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# Glecaprevir-pibrentasvir for treating chronic hepatitis C


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**Rider on responsibility for report**
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Isaac Corro Ramos, Nasuh Büyükkaramikli, Nigel Armstrong and Steve Ryder acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter, Ciara Keenan, Stephanie Swift, Vanesa Huertas Carrera and Piet Portegijs acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Shelley de Kock critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

**Abbreviations**

| | |
|---|---|
| AE | Adverse events |
| AIDS | Acquired immune deficiency syndrome |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| ART | Anti-retroviral treatment |
| BI | Budget impact |
| BNF | British National Formulary |
| BOC | Boceprevir |
| BSC | Best supportive care |
| C | Cirrhotic |
| CADTH | Canadian Agency for Drugs and Technologies in Health |
| CC | Compensated cirrhosis |
| CE | Cost effectiveness |
| CEA | Cost effectiveness analysis |
| CEAC | Cost effectiveness acceptability curve |
| CHC | Chronic hepatitis C |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence interval |
| CKD | Chronic kidney disease |
| CMU | Commercial medicines unit |
| CRD | Centre for Reviews and Dissemination |
| CrI | Credible interval |
| CSR | Clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CUA | Cost utility analysis |
| DAA | Direct-acting antivirals |
| DAE | Discontinuation due to adverse events |
| DCC | Decompensated cirrhosis |
| DCV | Daclatasvir |
| DCV/RBV/IFN | Daclatasvir in combination with pegylated-interferon alfa and ribavirin |
| DCV/SOF | Daclatasvir in combination with sofosbuvir |
| DCV/SOF/RBV | Daclatasvir in combination with sofosbuvir, with ribavirin |
| DoH | Department of Health |
| EASL | European Association for the Study of Liver |
| EBR/GZR | Elbasvir/grazoprevir |
| EBR/GZR + RBV | Elbasvir/grazoprevir with ribavirin |
| ECG | Electrocardiogram |
| eGFR | Estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| EODBT | End of double-blinded treatment |
| EOT | End of treatment |
| EPAR | European public assessment report |
| EQ-5D | European Quality of Life-5 Dimensions |
| EQ-5D-3L | European Quality of Life-5 Dimensions, three-level scale |
| EQ-5D-5L | European Quality of Life-5 Dimensions, five-level scale |
| ERG | Evidence Review Group |

| | |
|---|---|
| eRVR | Extended rapid viral response |
| ESLD | End-stage liver disease |
| ESRD | End stage renal disease |
| EUR | Erasmus University Rotterdam |
| EVR | Early viral response |
| FAD | Final appraisal determination |
| FDA | Food and Drug Administration |
| FIB | Fibrosis |
| FSS | Fatigue Severity Scale |
| G/P | Glecaprevir in combination with pibrentasvir |
| GT | Genotype |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| HCHS | Hospital and Community Health Service |
| HCV | Hepatitis C virus |
| HCVTSat | Chronic HCV treatment satisfaction instrument |
| HIV/HIV-1 | Human immunodeficiency virus |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| HTA | Health Technology Assessment |
| HUI3 | Health Utilities Index Mark 3 |
| ICD | International Classification of Diseases |
| ICER | Incremental cost effectiveness ratio |
| IFN | Pegylated-interferon alpha |
| IFN + RBV | Pegylated-interferon alpha in combination with ribavirin |
| ITC | Indirect treatment comparison |
| ITT | Intention to treat |
| ITT-MS | ITT mono-infected HCV GT1 population |
| ITT-PS | ITT mono-infected GT1 DAA-naïve |
| ITT-PS-PP | Per-protocol ITT-PS population |
| KSR | Kleijnen Systematic Reviews |
| LDV | Ledipasvir |
| LDV/SOF | Ledipasvir in combination with sofosbuvir |
| LDV/SOF/RBV | Ledipasvir in combination with sofosbuvir, with ribavirin |
| LFT | Liver function test |
| LLOQ | Lower limit of quantitation |
| LSMD | Least squares mean difference |
| LT | Liver transplant |
| LYS | Life year saved |
| MAIC | Matching-adjusted indirect comparison |
| MCMC | Markov Chain Monte Carlo |
| MeSH | Medical subject headings |
| MCS | Mental component summary |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| MRI | Magnetic resonance imaging |
| MRU | Medical resources utilisation |
| MTC | Mixed treatment comparison |
| NA | Not applicable |

| | |
|---|---|
| NC | Non-cirrhotic |
| NHS | National Health Services |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health Research |
| NMA | Network meta-analysis |
| NR | Not reported |
| NS5A | Non-structural protein 5A |
| OAE | Overall adverse events |
| OBV/PTV/RTV | Ombitasvir–paritaprevir–ritonavir |
| OBV/PTV/RTV + DSV | Ombitasvir–paritaprevir–ritonavir with dasabuvir |
| OBV/PTV/RTV + RBV | Ombitasvir–paritaprevir–ritonavir with ribavirin |
| OBV/PTV/RTV + DSV + RBV | Ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin |
| OD | Once-daily |
| OL | Open label |
| ONS | Office of National Statistics |
| OS | Overall survival |
| PAS | Patient access scheme |
| PCR | Polymerase chain reaction |
| PPI | Proton pump inhibitor |
| PRESS | Peer Review of Electronic Search Strategies |
| PRO | Patient-reported outcome |
| PSA | Probabilistic sensitivity analyses |
| PSS | Personal Social Services |
| PWIDs | People who inject drugs |
| QALY(s) | Quality-adjusted life year(s) |
| QoL | Quality of life |
| RAVs | Resistance-associated variants |
| RBV | Ribavirin |
| RCT | Randomised controlled trial |
| RNA | Ribonucleic acid |
| RR | Relative risk; risk ratio |
| SAE | Serious adverse events |
| SC | Subcutaneous |
| ScHARR | School of Health and Related Research |
| SD | Standard deviation |
| SE | Standard error |
| SF-36 | Short form 36 |
| SF-6D | Short-Form Six-Dimension |
| SHTAC | Southampton Health Technology Assessments Centre |
| SIGN | Scottish Intercollegiate Guidelines Network |
| SLR | Systematic literature review |
| SMC | Scottish Medicines Consortium |
| SmPC | Summary of product characteristics |
| SMV | Simeprevir |
| SMV/SOF | Simeprevir in combination with sofosbuvir |
| SoC | Standard of care |
| SOF | Sofosbuvir |
| SOF/RBV | Sofosbuvir in combination with ribavirin |

| | |
|---|---|
| SOF/RBV/IFN | Sofosbuvir in combination with ribavirin, with pegylated-interferon alfa |
| SOF/VEL | Sofosbuvir–velpatasvir |
| STA | Single technology appraisal |
| SVR | Sustained virologic response |
| TE | Treatment-experienced |
| TE-PR | TE with regimens containing peg-IFN/RBV |
| TE-PRS | TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN |
| TN | Treatment-naïve |
| TVR | Telaprevir |
| UK | United Kingdom |
| UMC | University Medical Centre |
| VAS | Visual analogue scale |
| WHO | World Health Organisation |
| WPAI-HCV | Work Productivity Activity Impairment Hepatitis C Specific Instrument |
| WTP | Willingness to pay |

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# 1. SUMMARY

## *1.1 Critique of the decision problem in the company's submission*

The company's submission (CS) presents an evaluation of the clinical effectiveness and cost effectiveness of glecaprevir-pibrentasvir (G/P) for the treatment of chronic hepatitis C (CHC). The decision problem addressed by the CS was not completely in line with the final scope issued by the National Institute for Health and Care Excellence (NICE) with respect to the comparators. In particular, daclatasvir (DCV) in combination with sofosbuvir (SOF) (for GT1 and GT4); pegylated-interferon alfa (IFN) with RBV and SOF in combination with RBV (for GT1 and GT4) were not included in the decision problem. The rationale for these omissions, as supplied by the company, states that these treatment regimens are not used in current NHS practice.

The company's model does not include the development of resistance to G/P and other comparators based on the assumption that this outcome does not impact the cost effectiveness of G/P. Also, separate subgroup analyses for patients who are co-infected with HIV, previous treatment received (with or without DAA-containing regimens), people who have received treatment before liver transplantation, and those who have received it after liver transplantation, response to previous treatment (non-response, partial response, relapsed), and people with and without renal impairment were not presented, as it was deemed infeasible by the company.

## *1.2 Summary of clinical effectiveness evidence submitted by the company*

Eighty-one publications (reporting on 79 studies) were identified as meeting the eligibility criteria. Fourteen of these publications, representing seven studies, involved G/P. In addition, information on four further clinical studies of G/P in patients with CHC are mentioned in the company submission. These studies were conducted in special populations of patients with HIV co-infection, renal impairment, failure on prior DAAs and a post-transplant population. Finally, the company mentioned two trials in Japanese patients with CHC: CERTAIN-1 and CERTAIN-2. These trials are only minimally discussed in the CS and not included in the economic model. According to the company, this exclusion was because "these two trials were conducted entirely in Japanese patients" which "precludes their generalisability to the UK patient population and subsequently their use in the economic model". Apart from these two trials in Japanese patients, none of the included studies presented comparative data for the licensed treatment duration of G/P with any of the comparators.

The G/P studies included patients with all genotypes; treatment-naïve and treatment-experienced patient populations; and patients with 'no cirrhosis or compensated cirrhosis'.

When split by cirrhosis status and previous treatment (naïve or experienced), SVR rates were consistently above 90% for all genotypes, except for GT2/TE/NC ([redacted] in SURVEYOR-II, Part 4; but [redacted] in SURVEYOR-II, Parts 1 and 2), GT3/TE/CC ([redacted] in SURVEYOR-II, Part 2; but [redacted] in SURVEYOR-II, Part 3) and GT6/TN/NC ([redacted] in SURVEYOR-II, Part 4).

[redacted] In studies without a comparator, many treatment arms [redacted]

According to the company, G/P had a favourable safety profile that was similar to placebo and SOF/DCV, and that was similar across treatment durations of 8, 12, and 16 weeks. G/P was well

tolerated across a broad and diverse population of patients, including patients with CC, HIV co-infection, and CKD Stage 4/5. Common study adverse drug reactions (ADRs) occurring in ≥5% of patients were headache, fatigue, and nausea. Adverse drug reactions were mostly Grade 1 (mild) in severity. Serious ADRs and ADRs leading to premature study drug discontinuation were rare (≤0.1%).

### *1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted*

The company submission (CS) and response to clarification provided sufficient detail for the ERG to appraise the searches for eligible trials. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4 using a good range of databases. Additional searches of conference proceedings were conducted but no separate literature searches were undertaken to identify adverse events data, non-randomised and non-controlled evidence.

The conclusion from the G/P studies is that G/P has high SVR rates in all genotypes. In addition, G/P has a relative favourable safety and tolerability profile. However, patient numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each group. Only three out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC and GT2/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

The main concern regarding clinical effectiveness is that data (for SVR12 and AEs) for G/P and comparators were taken from single arms. Therefore, the comparisons for SVR12 rates and AEs between G/P and comparators relies on a naïve indirect comparison. The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how response and adverse events for comparator studies were selected and whether all possible sources were used. In most cases the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C). Therefore, the same critique as for TA430 applies: these methods increase the chance of bias and cherry-picking.

### *1.4 Summary of cost effectiveness submitted evidence by the company*

The company developed a de novo cost effectiveness model to assess the cost effectiveness of G/P compared to nine different comparators: BSC-watchful waiting, DCV/SOF, DCV/SOF/RBV, EBR/GZR, LDV/SOF, OBV/PTV/DSV+DSV ± RBV, PR, SOF/PR, SOF/RBV and SOF/VEL. The cost effectiveness analyses performed by the company are in line with previous STAs for HCV treatments. The population considered in the cost effectiveness analyses was sub-divided into 26 different subgroups, where patients were stratified by genotypes (GT1, GT2, GT3, GT4, GT5 and GT6), treatment experience (treatment-naïve and treatment-experienced patients), cirrhosis status (cirrhotic and non-cirrhotic patients) and IFN-eligibility (only for GT2 TN patients). Full incremental cost effectiveness results were presented for all subgroups. A National Health Service (NHS) and Personal and Social Services (PSS) perspective was adopted with a lifetime time horizon. A 3.5% discount rate was used for both costs and quality-adjusted life years (QALYs).

The cost effectiveness model developed for this submission was a Markov model which consists of 13 health states. Non-cirrhotic patients start from states F0-F3, and cirrhotic patients start from F4. All treatment related outcomes (achieving SVR, treatment related adverse events and discontinuation) occur within the first year of the model. Patients who do not achieve SVR are at risk of progressing to more severe states. Patients who reach F4 can progress to DC and HCC states, which may lead to liver transplantation and liver-related death. The liver transplantation state was divided into two categories (first year and later years).

Treatment effectiveness was modelled as the probability of achieving SVR. Other treatment-specific parameters included adverse event rates, treatment duration, and treatment-related utility adjustments. All these parameter estimates were based on naïve indirect comparison of clinical trials assessing the efficacy of G/P and its comparators in the relevant subgroups.

The model uses health state based utilities from the literature (utilities that were used in Wright et al. 2006 and Ratcliffe et al. 2002) in line with previous STAs for HCV treatments. A utility increment due to SVR is applied based on Shepherd et al. 2007 and Hartwell et al. 2011. Treatment-related health utility changes were applied to adjust for the impact on HRQoL of treatment, e.g. due to adverse events.

List prices were used as treatment costs for G/P and the comparator treatments in the cost effectiveness analysis. Health state costs (disease management costs based on disease stage) and other costs for adverse events were based on literature, expert opinion, UK reference costs and previous appraisals for HCV (especially TA430).

The base-case cost effectiveness results showed that for non-cirrhotic patients, G/P was always cost effective except for two subgroups: GT2 treatment-naïve IFN-eligible patients and GT3 treatment-experienced patients. For the subgroups of non-cirrhotic patients for which G/P was cost effective, the relevant comparator was always no treatment, which resulted in very low ICERs (always below £5,000 per QALY). For patients with compensated cirrhosis, G/P was only cost effective for GT1 treatment-naïve and GT3 treatment-naïve patients. For some of the subgroups where G/P was not considered cost effective, the reason was that at least one of the comparators, which was considered cost effective, produced the same amount of QALYs at a lower cost. Thus, although G/P was dominated, it can be considered as equally effective as these comparators. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was as effective as at least one cost effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above cost effectiveness threshold).

Additionally, the company conducted probabilistic, deterministic and scenario analyses. Probabilistic results were reported as the probability that G/P is cost effective against one single comparator for each subgroup at £20,000 and £30,000 thresholds. The comparator was selected as the one against which G/P had the lowest incremental net monetary benefit when valuing a QALY at £20,000. The result of the deterministic sensitivity analyses showed that in general the ICER was most sensitive to changes in SVR rates. Two scenario analyses conducted by the company first demonstrated how the cost effectiveness of G/P might change after the CMU price agreement (when comparators from other companies were based on list prices). Second, it was shown that using trial-based utilities increased total QALY estimates compared to the base-case when literature-based utilities were used as input.



### *1.5 Summary of the ERG's critique of cost effectiveness evidence submitted*

The CS and response to clarification provided sufficient detail for the ERG to appraise the cost effectiveness searches. Searches were well documented but not all searches were reproducible in line with the NICE guide to the methods of technology appraisal. However, a good range of databases were searched and additional searches of conference proceedings were also undertaken.

The following treatments were not included in the cost effectiveness analyses because, according to the company, these are not used in current NHS practice: 1) DCV in combination with SOF, with or without RBV (for specific people with GT1 or GT4; as recommended by NICE); 2) IFN with RBV (for GT1–6; except in GT2 non-cirrhotic treatment-naïve patients); 3) SOF in combination with RBV, with or without IFN (for specific people with GT1 and GT4; as recommended by NICE). The IFN eligibility

was only considered for GT2, however it was not clear why there was no IFN containing regimen as a comparator for the GT2 TN CC (IFN-eligible) subgroup.

Despite being included in the final scope, the company did not perform subgroup analyses for patients who are co-infected with HIV and post-liver transplantation. The subgroup of patients who are intolerant to or ineligible for interferon treatment were only considered for GT2 TN patients. Since these excluded groups (e.g. HIV co-infected patients) were also not taken into consideration while deriving some of the model input estimates (e.g. utility), transferability of the current results for these groups is disputable. Furthermore, heterogeneity of the treatment-experienced population was not taken into account. (e.g. whether a patient is intolerant or an inadequate responder to the previous therapy, or has already received a DAA treatment or maybe is DAA naïve, may all impact the effectiveness of G/P).

Onward transmission is not included in the economic model. Incorporating onward transmission would require a dynamic transmission model to capture an ongoing risk of infection for individuals in a population, and therefore could not be incorporated into the current modelling framework. Similarly, the company assumed a zero-reinfection probability after reaching SVR and assumed that no natural recovery takes place, despite contrary evidence reported in the clinical literature.

SVR rates, adverse event rates, treatment duration, and treatment-related utility adjustments were based on naïve indirect comparisons of clinical trials assessing the efficacy of G/P and its comparators in the relevant subgroups. The ERG has concerns on the plausibility of this approach, which is not in line with evidence synthesis best practices and is susceptible to bias. Furthermore, some of the SVR rates were either derived from very small sample sizes or the effectiveness in a subgroup was assumed to hold in another subgroup. Since SVR rates are the main driver of costs and effectiveness, all these assumptions create a substantial uncertainty on the cost effectiveness of G/P.

Furthermore, it was not clear to the ERG why age-dependent transition probabilities were not updated every year.

The health state utilities from RCTs could have been used by the company in their cost effectiveness analysis instead of the utilities from the literature. The ERG questions to what extent utility values published in 2006 (originating from EQ-5D questionnaires completed in 2002), i.e. before the DAA-era, can be seen as representative of UK patients currently suffering with CHC. Similarly, the RCT-based utility values show a difference in utility with or without SVR ranging from 0.025 to 0.029, substantially lower than the increment of 0.05 applied by the company based on Wright et al. 2016 thus raising doubt about the validity of the latter value.

The ERG was unsure about the completeness of the health state cost estimates used in the model, as items such as GP visits and home care costs are not included.

The ERG is concerned over the validation status of the cost effectiveness analysis by the company. The tests conducted for the technical verification of the model were not presented and the only validation effort was the external validation of the model estimates of the cirrhosis risk in 20 years from the clinical literature.

Despite the several uncertainties present in the CS base-case, the ERG did not produce an alternative base-case, since it was not clear that any alternative base-case assumptions would be properly justified, as in most situations the assumptions made by the company were reasonable and in line with previous appraisal. Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses.

There are two major flaws in the probabilistic analyses presented by the company. The first is considering a single comparator instead of all possible comparators in the analyses. The second is the failure to include a large number of SVR and AE rates (i.e. all that have a value of 100% and 0%) in the probabilistic analyses. As a consequence, the ERG considers the PSA results in the CS unreliable. Given the time constraints and the model complexity, the ERG could not produce detailed (corrected) PSA results for all subgroups, only for a few example subgroups. If it is judged that the analysis of uncertainty is a major concern for this submission, the PSA analyses should be repeated after tackling the issues discussed in this report.

### *1.6 ERG commentary on the robustness of evidence submitted by the company*

#### 1.6.1 Strengths

The majority of searches for eligible studies in the CS were well documented. Searches were carried out in a good range of databases and strategies utilised study design filters. In response to clarification questions, a number of searches were repeated to ensure all relevant evidence had been included. Supplementary searches of conference proceedings were also undertaken.

The company's submitted evidence on clinical effectiveness broadly covered the final scope set out by NICE. The review of G/P studies included all relevant studies in which G/P had been used. Reviews for other treatments were likely to have identified the majority of trials of other relevant treatments. The submission covers the key clinical outcomes, including SVR rates, adverse events and mortality.

The structure of the economic model developed by the company is in line with previous models presented in appraisals for HCV submitted to NICE. Thus, the model structure (not necessarily inputs) reflects the main aspects of the chronic HCV disease. The model also includes relevant adverse events, utilities and costs.

#### 1.6.2 Weaknesses and areas of uncertainty

Clinical effectiveness searches were re-run in response to clarification questions but did not include a number of comparators from the original search. Conference searches also did not look for the intervention of interest in addition to some comparator interventions. Cost effectiveness searches that were re-run in response to clarification questions added a restrictive UK country filter, which may have resulted in relevant evidence being missed. There is also concern about the effectiveness of the Embase search for health-related quality of life as the company did not present the full set of records that they claimed to have screened. Some searches were also not reproducible in line with NICE guide to the methods of technology appraisal. There were no searches for adverse events data, non-randomised and non-controlled evidence.

The main concern regarding clinical effectiveness is that data (for SVR12 and AEs) for G/P and comparators were taken from single arms. Therefore, the comparisons for SVR12 rates and AEs between G/P and comparators rely on a naïve indirect comparison. The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how responses and adverse events for comparator studies were selected and whether all possible sources were used. In most cases, the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C). Therefore, the same critique as for TA430 applies: these methods increase the chance of bias and cherry-picking.

In addition, patient numbers for most GT4, GT5 and GT6 populations in G/P studies are very low, often less than 10 patients in each subgroup. Only three out of the 24 subgroups included more than 100

patients (GT1/TN/NC, GT1/TE/NC and GT2/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

Since the key parameters in the cost effectiveness analyses (SVR rates) were based on the treatment effectiveness data, all health economic analyses suffer from the uncertainty of clinical effectiveness (i.e. comparative SVR rates). Furthermore, all analyses were conducted on list prices, which may not reflect the actual costs of the treatments to the NHS. Both probabilistic and sensitivity analyses presented by the company were performed incorrectly. As a consequence, the ERG considers the sensitivity analysis results in the CS unreliable. If it is judged that the analysis of uncertainty is a major concern for this submission, these analyses should be repeated after tackling the issues discussed in this report. The company submission would also benefit from a more transparent electronic model.

### *1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG*

The ERG has not presented an alternative base-case, since it was not clear that any alternative base-case assumptions would be properly justified, as in most situations the assumptions made by the company were reasonable and in line with previous appraisals. Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses. In the scenario analyses assumptions surrounding the utility gain due to SVR, impact of the treatment on utility, impact of age on utility were challenged. In addition, alternative inputs for transition probabilities between fibrosis stages and re-infection rates were explored. Even though these scenarios changed the total costs and/or total QALYs estimates, the impact on incremental results was minimal. The cost effectiveness of G/P in each subgroup did not change, hence the cost effectiveness results of the base-case seem to be robust to changes in utility and treatment-unrelated clinical model inputs.

Additionally, the exploratory PSA analyses conducted by the ERG showed that that the inclusion of parameter uncertainty around all SVR and AE rates (which was not included in the company's base-case when rates were 100% or 0%) can have a major impact on the G/P cost effectiveness probability for certain subgroups; but also that this impact can go in either direction (although more frequently it decreases the G/P cost effectiveness probability). This was especially striking for GT5 TN NC patients, for whom the company might have overestimated the probability of G/P being cost effectiveness by 66 percent. Furthermore, the ERG showed that the PSA outcomes were enormously scattered over the CE plane quadrants for a number of subgroups, which illustrates the main limitation of presenting cost effectiveness probabilities alone (as in the CS).

## 2. BACKGROUND

This report provides an appraisal of the evidence submitted by Abbvie in support of Glecaprevir/Pibrentasvir (G/P) (tradename: Maviret®) for the treatment of chronic hepatitis C virus (HCV) infection in both treatment-naïve (TN) and treatment-experienced (TE) populations. Maviret is a fixed dose combination of two directly-acting anti-viral agents (DAAs) that interfere with viral replication: Glecaprevir, an NS3/4a protease inhibitor, and Pibrentasvir, an NS5a inhibitor. The EMA granted G/P full market authorisation on 26 July 2017.[1] In this section, we outline and critique the company's description of the underlying health problem and the overview of current service provision. The information is taken mainly from section B1.3 of the company submission (CS) and the references to support this section of the submission have also been examined.

### *2.1 Critique of company's description of underlying health problem*

The target disease in this appraisal is chronic hepatitis C infection. The CS states that in approximately 15 to 25% of patients with acute HCV infection the disease is resolved, whilst the remaining 75 to 85% of patients progress to chronic HCV infection, defined as the presence of HCV RNA in the serum for >6 months.

The CS states that HCV prevalence levels correspond to a chronically infected worldwide population of approximately 170 million people, with 3 to 4 million new cases of HCV infection globally each year. The company adds that, in the UK, *it has been suggested that 86% of individuals infected with the virus are unaware they have been infected*,[2] which presents an issue for heightened risk of onward transmission. The CS further states that *the burden of HCV infection in England and Wales is largely carried by current and ex-PWIDs*.[2]

The CS explains that six major genotypes (GT1–6) and 67 subtypes of HCV have currently been identified. The CS describes that in England, HCV genotypes GT1 and GT3 are most prevalent, accounting for 47% and 44% of HCV infection cases, respectively, with other genotypes contributing the remaining 9%.[3]

**ERG comment:**

The company submission includes an appropriate description of the disease. However, several details are sparsely reported. For example, there is no discussion in the CS of the proportion of people who fail to respond to current treatments or develop treatment resistance (specifically to DAA therapies).

The ERG would like to add the following:

- Certain subgroups of patients are at a higher risk of progressing to chronic hepatitis C (CHC) i.e. African-Americans, HIV-infected individuals, men and those >25 years of age, since this provides a rationale for some of the sub-group analyses proposed in the scope of this submission.[4]
- The CS does not include prevalence data on HCV in England. Recent estimates are that approximately 160,000 people have chronic hepatitis C in England.[5]
- Aetiology and routes of infection are only briefly mentioned in the CS. Injection drug use continues to be the most important risk factor for HCV infection, as supported by approximately 90% of all reports where risk factors have been disclosed.[5]

The company discuss the risks and associated burdens of HCV. The CS states that, depending on whether co-factors are present (e.g. alcohol consumption), 10 to 20% of patients progress to cirrhosis

over 20 to 30 years. They highlight that infection with HCV GT3 is associated with the highest risk of developing cirrhosis and hepatocellular carcinoma (HCC).

The CS states that *once cirrhosis has developed, patients have a 1 - 5% annual risk of progression to decompensated cirrhosis (DCC).*[2]

The CS adds that *CHC is also associated with several extra-hepatic manifestations, including the development of mixed cryoglobulinaemia and its sequelae (ranging from cutaneous and visceral vasculitis to glomerulonephritis and B-cell non-Hodgkin's lymphoma), as well as increased rates of insulin resistance, diabetes, and atherosclerosis, which may lead to increased cardiovascular morbidity and mortality.*[6] *Neurological manifestations of HCV infection include fatigue and cognitive impairment.*[6]

The CS explains that health-related quality of life is lower in individuals suffering from CHC compared to the general population. They further state that current treatment options may also pose a considerable burden on HRQoL for some patient subgroups. As an example they state that *treatment with peg-IFNa plus RBV is associated with a variety of toxic side-effects.*[2]

The company cite evidence that in the UK, mortality rates among HCV-infected patients have been shown to be three times higher than expected relative to the general population of England. However they state that *the introduction of new direct-acting anti-viral (DAA) drugs may be starting to have an impact on HCV-related mortality, with a fall of 8% in HCV-related ESLD and HCC deaths in 2015.*[3]

**ERG comment:**

The risks and burdens of HCV have been appropriately discussed. The ERG noted the following:

- The risk of progression to decompensated cirrhosis is 3 to 6% according to the reference cited in the CS.[7] The quoted 1 to 5% annual risk values pertain to the risk of progression to *hepatocellular carcinoma*.[7]
- The study of UK mortality rates among HCV-infected patients used in the CS is considered to be reliable. However, whilst this study was relatively large, it only recruited patients from the Trent region of England, and there is clear evidence that regional disparities exist in the UK in terms of HCV prevalence and HCV-associated mortality.[8]

### *2.2 Critique of company's overview of current service provision*

The company presents a matrix of NICE-recommended therapies according to genotype, presence of cirrhosis and previous treatment. This matrix is duplicated below.

The CS states that there is *no NICE clinical guideline for hepatitis C to then distinguish which of the NICE-recommended therapies might represent standard of care*.[2]

The company claims that a number of NICE-approved therapies do not form part of clinical practice in England. This was based on expert clinical opinion and on a review of the European Association for the Study of the Liver (EASL) guidelines.[9]

- In particular, the CS highlights that the use of peginterferon and ribavirin (RBV) alone is reducing in clinical practice. This is due in part, to the adverse effects associated with interferon. They also state that *it is assumed that there will be no patients receiving peg-IFNa + RBV across any genotype and subgroup in which SOF / VEL is recommended by NICE*.[2]
- Secondly, the CS states that daclatasvir (DCV) in combination with sofosbuvir (SOF) with/without RBV is not used in clinical practice in England for patients with GT1 and GT4.

DCV in combination with SOF without RBV is only considered in the submission as a comparator to G/P for GT3 patients.

- Thirdly, the CS states that SOF in combination with RBV with / without peg-IFNa is not used in clinical practice in England for patients with GT1 and GT4. This combination is only considered a comparator to G/P in the appraisal for GT2, GT3, GT5 and GT6 patients.

The CS stresses that currently the only direct-acting antiviral (DAA) regimen suitable for all six genotypes, and without RBV and IFN, is SOF/VEL. However, they discuss some limitations with this drug: *'in GT2, SOF/VEL is only recommended for TN non-cirrhotic (NC) patients who cannot tolerate IFN-based treatments'*.[2]

The positioning of G/P is across all the genotypes of HCV. The company state that a large proportion of patients (TN NC (non-cirrhotic)) would be able to receive a short treatment (eight weeks). There would be the potential to remove the requirement to genotype any TN NC patients. This in turn would mean that the intervention could be delivered in the community which would improve access to treatment for difficult to engage populations. The company also highlights the specific populations who might benefit including those with severe renal impairment and specific TE GT 3 patients.

**ERG comment**:

- The complexity of the changing treatment landscape is appropriately outlined by the company.
- The reduction of peg-IFNα and RBV use in the HCV population and the adverse events associated with IFN-based regimes is appropriately outlined.
- Our clinical expert supported that the three regimes highlighted in the bullet points above are no longer relevant to clinical practice.
- Our clinician advises us that the statement '*in GT2 SOF/VEL is only recommended for TN non-cirrhotic (NC) patients who cannot tolerate IFN-based treatments'* is incorrect and that oral therapy is now recommended and funded for G2 NC patients.
- Within this report the role of G/P will be evaluated by genotype, prior treatment experience and presence of cirrhosis as presented by the company. Any changes to the clinical pathway such as removal of the need to genotype or intervention setting in relation to treatment-naïve non-cirrhotic patients would depend on approval for all genotypes.

**Table 2.1: Matrix of NICE-recommended therapies for chronic hepatitis C**

| Geno-type | Treatment (duration in weeks) | | | |
|---|---|---|---|---|
| | **TN-NC** | **TN-C** | **TE-NC** | **TE-C** |
| 1 | • SOF/VEL (12)<br>• *SOF + peg-IFN + RBV (12)*<br>• *Peg-IFN + RBV (24/48)*<br>• EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV<br>• SOF/LDV (8)<br>• OBV/PTV/RTV + DSV (12), 1a: + RBV<br>• *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (24), or peg-IFN + RBV (4) then BOC + peg-IFN + RBV (32) then peg-IFN + RBV (12)*<br>• *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (12), or TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)*<br>• Best supportive care (watchful waiting)<br>Treatments only recommended for patients with significant fibrosis[c]:<br>• SOF + DCV (12) | • SOF/VEL$^{+}$ (12)<br>• *SOF + peg-IFN + RBV (12)*<br>• *Peg-IFN + RBV (24/48)*<br>• EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV<br>• *SOF/LDV (12)<br>• *OBV/PTV/RTV + DSV + RBV (12), 1a: (24)[b]<br>• *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (44)*<br>• *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)*<br>• Best supportive care (watchful waiting)<br>Treatments only recommended for IFN-ineligible patients:<br>• *SOF + DCV ± RBV (24) | • SOF/VEL (12)<br>• *SOF + peg-IFN + RBV (12)*<br>• *Peg-IFN + RBV (48)*<br>• EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV<br>• SOF/LDV (12)<br>• OBV/PTV/RTV + DSV (12), 1a: + RBV<br>• *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (32) then peg-IFN + RBV (12), or peg-IFN + RBV (4) then BOC + peg-IFN + RBV (44)*<br>• *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (12), or TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)*<br>• Best supportive care (watchful waiting)<br>Treatments only recommended for patients with significant fibrosis[c]:<br>• SOF + DCV (12) | • SOF/VEL$^{+}$ (12)<br>• *SOF + peg-IFN + RBV (12)*<br>• *Peg-IFN + RBV (48)*<br>• EBR/GZR (12), 1a: + RBV (16) depending on viral titre or NS5A RAV<br>• *SOF/LDV[a] (12)<br>• *OBV/PTV/RTV + DSV + RBV (12), 1a: (24)[b]<br>• *Peg-IFN + RBV (4) then BOC + peg-IFN + RBV (44)*<br>• *TVR + peg-IFN + RBV (12) then peg-IFN + RBV (36)*<br>• Best supportive care (watchful waiting)<br>Treatments only recommended for IFN-ineligible patients:<br>• *SOF + DCV ± RBV (24) |
| 2 | • Peg-IFN + RBV (24)<br>• Best supportive care (watchful waiting) | • SOF/VEL$^{+}$ (12)<br>• *Peg-IFN + RBV (24)*<br>• Best supportive care (watchful waiting) | • SOF/VEL$^{+}$ (12)<br>• SOF + RBV (12)<br>• *Peg-IFN + RBV (24)*<br>• Best supportive care (watchful waiting) | • SOF/VEL$^{+}$ (12)<br>• SOF + RBV (12)<br>• *Peg-IFN + RBV (24)*<br>• Best supportive care (watchful waiting) |

| Geno-type | Treatment (duration in weeks) | | | |
|---|---|---|---|---|
| | **TN-NC** | **TN-C** | **TE-NC** | **TE-C** |
| | Treatments only recommended for IFN-ineligible patients:<br>• SOF/VEL (12)<br>• SOF + RBV (12) | Treatments only recommended for IFN-ineligible patients:<br>• SOF + RBV (12) | | |
| 3 | • SOF/VEL (12)<br>• Peg-IFN + RBV (24)<br>• Best supportive care (watchful waiting)<br>Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]:<br>• SOF + DCV (12) | • SOF/VEL[+] ± RBV (12)<br>• SOF + peg-IFN + RBV (12)<br>• *Peg-IFN + RBV (24)*<br>• Best supportive care (watchful waiting)<br>Treatments only recommended for IFN-ineligible patients:<br>• SOF + RBV (24)<br>• *SOF + DCV + RBV (24) | • SOF/VEL (12)<br>• SOF + peg-IFN + RBV (12)<br>• *Peg-IFN + RBV (24)*<br>• Best supportive care (watchful waiting)<br>Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]:<br>• SOF + DCV (12) | • SOF/VEL[+] ± RBV (12)<br>• SOF + peg-IFN + RBV (12)<br>• *Peg-IFN + RBV (24)*<br>• Best supportive care (watchful waiting)<br>Treatments only recommended for IFN-ineligible patients:<br>• SOF + RBV (24)<br>• *SOF + DCV + RBV (24) |
| 4 | • SOF/VEL (12)<br>• *Peg-IFN + RBV (24/48)*<br>• EBR/GZR (12) or + RBV (16) depending on viral titre<br>• OBV/PTV/RTV + RBV (12)<br>• *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12)*<br>• Best supportive care (watchful waiting) | • SOF/VEL[+] (12)<br>• *SOF + peg-IFN + RBV (12)*<br>• *Peg-IFN + RBV (24/48)*<br>• EBR/GZR (12) or + RBV (16) depending on viral titre<br>• *SOF/LDV (12)<br>• OBV/PTV/RTV + RBV (24)[b]<br>• *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12)*<br>• *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)*<br>• Best supportive care (watchful waiting) | • SOF/VEL (12)<br>• *Peg-IFN + RBV (48)*<br>• EBR/GZR (12) or + RBV (16) depending on viral titre<br>• SOF/LDV (12)<br>• OBV/PTV/RTV + RBV (12)<br>• *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12/36)*<br>• Best supportive care (watchful waiting) | • SOF/VEL[+] (12)<br>• *SOF + peg-IFN + RBV (12)*<br>• *Peg-IFN + RBV (48)*<br>• EBR/GZR (12) or + RBV (16) depending on viral titre<br>• *SOF/LDV[a] (12)<br>• OBV/PTV/RTV + RBV (24)[b]<br>• *SMV + peg-IFN + RBV (12) then peg-IFN + RBV (12/36)*<br>• *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)*<br>• Best supportive care (watchful waiting) |

| Geno-type | Treatment (duration in weeks) | | | |
|---|---|---|---|---|
| | **TN-NC** | **TN-C** | **TE-NC** | **TE-C** |
| | Treatments only recommended for patients with significant fibrosis[c]:<br>• *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)*<br><br>Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]:<br>• *SOF + DCV (12)* | Treatments only recommended for IFN-ineligible patients:<br>• **SOF + DCV ± RBV (24)* | Treatments only recommended for patients with significant fibrosis[c]:<br>• *DCV + peg-IFN + RBV (24) ± peg-IFN + RBV (24)*<br><br>Treatments only recommended for IFN-ineligible patients with significant fibrosis[c]:<br>• *SOF + DCV (12)* | Treatments only recommended for IFN-ineligible patients:<br>• **SOF + DCV ± RBV (24)* |
| 5 or 6 | • SOF/VEL (12)<br><br>• *Peg-IFN + RBV (24)*<br>• Best supportive care (watchful waiting) | • SOF/VEL[+] (12)<br>• SOF + peg-IFN + RBV (12)<br>• *Peg-IFN + RBV (24)*<br>• Best supportive care (watchful waiting) | • SOF/VEL (12)<br><br>• *Peg-IFN + RBV (24)*<br>• Best supportive care (watchful waiting) | • SOF/VEL[+] (12)<br>• SOF + peg-IFN + RBV (12)<br>• *Peg-IFN + RBV (24)*<br>• Best supportive care (watchful waiting) |

Source: CS, section B1.4, Table 4, pages 27-30[2]

*CC only (i.e. not recommended for DCC)

[+] + RBV if DCC

[a]Recommended only if all the following criteria are met: Child-Pugh class A, platelet count of 75,000/mm$^3$ or more, no features of portal hypertension, no history of HCV-associated decompensation episode and not previously treated with an NS5A inhibitor; [b]TA365 for OBV/PTV/RTV ± DSV was published before the results from TURQUOISE-III and AGATE-I became available and the NICE recommendation therefore stipulates the use of OBV/PTV/RTV ± DSV with RBV for GT1b patients with CC, and OBV/PTV/RTV + RBV for GT4 CC patients for 24 weeks. Subsequently, TURQUOISE-III demonstrated the efficacy of treatment with OBV/PTV/RTV + DSV for 12 weeks without RBV in GT1b patients with CC,[27] and AGATE-I demonstrated the efficacy of OBV/PTV/RTV + RBV for 12 weeks in GT4 patients with CC.[28] The licence for OBV/PTV/RTV ± DSV now reflects this. Therefore OBV/PTV/RTV + DSV without RBV for 12 weeks is used as the comparator in the economic analysis of this submission for GT1b patients with CC, and OBV/PTV/RTV + RBV for 24 weeks is used for GT4 CC patients; [c]Significant fibrosis is defined as METAVIR fibrosis stage F3 and F4.

BOC = boceprevir; C = cirrhotic; CC = compensated cirrhosis; DCC = decompensated cirrhosis; DCV = daclatasvir; DSV = dasabuvir; EBR = elbasvir; GZR = grazoprevir; IFN = interferon; LDV = ledipasvir; OBV = ombitasvir; peg-IFN = pegylated-IFN; PTV = paritaprevir; RAV = resistance associated variant; RBV = ribavirin; RTV = ritonavir; SMV = simeprevir; SOF = sofosbuvir; TVR = telaprevir; TN = treatment-naïve; TE = treatment-experienced; VEL = velpatasvir

Therapies highlighted in *italics* represent therapies that, although associated with a positive NICE recommendation for use in the NHS, no longer form part of current clinical practice according to the company and are therefore not considered as comparators to G/P in this submission.

## 3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

**Table 3.1: Statement of the decision problem (as presented by the company)**

| | Final scope issued by NICE | Decision problem addressed in the company submission and rationale | ERG comments |
|---|---|---|---|
| **Population** | Adults with CHC:<br>• who have not had treatment for CHC before (TN)<br>• who have had treatment for CHC before (TE) | Per final scope | This is in accordance with the scope. |
| **Intervention** | Glecaprevir/pibrentasvir; referred to in this submission as G/P | Per final scope | This is in accordance with the scope. |
| **Comparator(s)** | • Best supportive care (no active pharmacological treatment) (GT1-6)<br>• DCV in combination with SOF, with or without RBV (for specific people with GT1, GT3 or GT4; as recommended by NICE)<br>• EBR/GZR (for GT1 or GT4)<br>• SOF/LDV (for specific people with GT1 or GT4; as recommended by NICE)<br>• OBV/PTV/RTV with or without DSV or RBV (for GT1 or GT4)<br>• IFN with RBV (for GT1– 6)<br>• SOF in combination with RBV, with or without pegIFNα (for specific people with GT1–6; as recommended by NICE)<br>• SOF/VEL (for specific people with GT1–6; as recommended by NICE) | • Best supportive care (no active pharmacological treatment) (GT1–6)<br>• DCV in combination with SOF without RBV (for GT3 only, as recommended by NICE)<br>• EBR/GZR (for GT1 or GT4)<br>• SOF/LDV (for specific people with GT1 or GT4; as recommended by NICE)<br>• OBV/PTV/RTV with or without DSV or RBV (for GT1 or GT4)<br>• IFN with RBV for GT2 non-cirrhotic treatment-naïve patients only<br>• SOF in combination with RBV, with or without pegIFNα (for specific people with GT2, GT3, GT5 and GT6, as recommended by NICE)<br>• SOF/VEL (for specific people with GT1–6; as recommended by NICE) | Mostly in line with the final scope, albeit with some discrepancies (see Section 3.3). The company notes that "best supportive care" is defined as watchful waiting/no treatment in their submission.<br>In addition, the following treatments are not included in the CS because these treatment regimens are not used in current NHS practice according to the company:<br>• DCV in combination with SOF, with or without RBV (for specific people with GT1 or GT4; as recommended by NICE)<br>• IFN with RBV (for GT1–6; except in GT2 non-cirrhotic treatment-naïve patients)<br>• SOF in combination with RBV, with or without IFN (for specific |

| | Final scope issued by NICE | Decision problem addressed in the company submission and rationale | ERG comments |
|---|---|---|---|
| | | | people with GT1 and GT4; as recommended by NICE) |
| **Outcomes** | The outcome measures to be considered include:<br>• mortality<br>• SVR<br>• development of resistance to treatment<br>• adverse effects of treatment<br>• HRQoL | Per final scope | Mostly in line with the final scope. The development of resistance to G/P treatment (as well as to other comparators) was not incorporated to the electronic model, assuming it has limited impact on the cost effectiveness of G/P. |
| **Subgroups to be considered** | If the evidence allows the following subgroups will be considered:<br>• Genotype<br>• Co-infection with HIV<br>• People with and without cirrhosis<br>• Previous treatment received (with or without DAA-containing regimens)<br>• People who have received treatment before liver transplantation, and those who have received it after liver transplantation<br>• Response to previous treatment (non-response, partial response, relapsed)<br>• People who are intolerant to or ineligible for interferon treatment<br>• People with and without renal impairment | Clinical evidence for these subgroups is presented where this is available.<br>The economic analyses are stratified by genotype, cirrhosis status and previous treatment history (naïve or experienced), in line with recent prior NICE appraisals. Separate comparators for IFN-eligible and IFN-ineligible subgroups were also considered in line with NICE guidance.<br>Patients co-infected with HCV/HIV-1 are modelled as the same as those with HCV mono-infection. This is consistent with the approach taken in TA430.[1]<br>The analyses split patients into TN and TE, where the TE group was defined as patients who have not adequately responded to prior IFN/RBV-based treatment with or without SOF, in line with the clinical trial programme for G/P and its anticipated licence.<br>Separate economic subgroup analyses are not performed for TE patients stratified by previous treatment response. This is in line with the fact that neither NICE TA guidance nor the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1) provides distinct treatment recommendations on the basis of | In line with the final scope.<br>The company's submitted model evaluates costs and health gains (reported as incremental costs per quality-adjusted life year) from the perspective of the NHS and Personal Social Services (PSS) over a lifetime horizon.<br>Separate subgroup analyses are not presented for patients who are co-infected with HIV and those with post-liver transplantation. In addition, separate subgroup analyses are not presented for people who are intolerant to or ineligible for interferon treatment, except for GT2 treatment-naïve patients. |

| | Final scope issued by NICE | Decision problem addressed in the company submission and rationale | ERG comments |
|---|---|---|---|
| | | different previous treatment response.[2] Subgroup analyses were not performed in patients who had previously received treatment with NS3/4A- or NS5A inhibitors as G/P is currently not anticipated to be licensed in these patients.<br>Separate economic subgroup analyses were also not performed for patients who have received a liver transplant or for patients with renal impairment. The submission already considers an extensive number of subgroups subdivided by genotype, treatment history and cirrhosis status. Further subgroup analyses were therefore not performed, in order to focus the decision problem on the subgroups defined by genotype, treatment experience and cirrhosis status around which NICE treatment recommendations are based. | |
| **Special considerations including issues related to equity or equality** | If the evidence allows, the impact of treatment on reduced onward HCV transmission will also be considered. | Onward transmission is not included in the economic model.<br>Incorporating onward transmission would require a dynamic transmission model to capture an ongoing risk of infection for individuals in a population, and therefore could not be incorporated into the current modelling framework. | |

Source: Table 1, Section B.1.1 of the CS.[2]

Abbreviations: CHC = chronic hepatitis C; DAA = directly-acting antiviral; DCV = daclatasvir; DSV = dasabuvir; EBR = elbasvir; G/P = glecaprevir/pibrentasvir; GZR = grazoprevir; GT = genotype; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; IFN = interferon; LDV = ledipasvir; N/A = not applicable; OBV = ombitasvir; Peg-IFN = pegylated-interferon alfa; PTV = paritaprevir; QALY = quality adjusted life year; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; SVR = sustained virologic response; TA = technology appraisal; TE = treatment-experienced; TN = treatment-naïve; VEL = velpatasvir

### *3.1 Population*

The patient population described in the final scope are: people with chronic hepatitis C who have not had treatment for chronic hepatitis C before (treatment-naïve) or who have had treatment for chronic hepatitis C before (treatment-experienced).

On 22 June 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Maviret, (glecaprevir/pibrentasvir) intended for the treatment of chronic hepatitis C in adults.[10]

The population is in line with the NICE scope.

### *3.2 Intervention*

The intervention described in the final scope is glecaprevir/pibrentasvir (G/P). According to the CHMP, Maviret is a fixed dose combination of two direct acting-antivirals (DAA), glecaprevir and pibrentasvir. It will be available as film-coated tablets containing 100 mg glecaprevir and 40 mg pibrentasvir. Glecaprevir is an inhibitor of the HCV NS3/4A protease, while pibrentasvir is an inhibitor of the HCV NS5A protein. Both proteins are essential for HCV replication.[10]

The recommended dose of glecaprevir/pibrentasvir is 300 mg/120 mg (three 100 mg/40 mg tablets), taken orally, once daily with food. The recommended glecaprevir/pibrentasvir treatment durations for patients without prior HCV therapy is eight weeks for patients without cirrhosis and 12 weeks for patients with cirrhosis. Similarly, for patients with genotype 1, 2, 4, 5, or 6 who have failed prior therapy with IFN+RBV +/- SOF or SOF+RBV, the recommended glecaprevir/pibrentasvir treatment duration is eight weeks for patients without cirrhosis and 12 weeks for patients with cirrhosis. For patients with genotype 3 who have failed prior therapy with IFN+RBV +/- SOF, or SOF+RBV, the recommended glecaprevir/pibrentasvir treatment duration is 16 weeks (with or without cirrhosis).[11]

G/P is not recommended for the re-treatment of patients with prior exposure to NS3/4A- and/or NS5A-inhibitors. G/P is contraindicated for patients with severe hepatic impairment (Child-Pugh C).

G/P is subject to additional monitoring to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.[11]

### *3.3 Comparators*

The comparators described in the final scope are as follows:

- Best supportive care (no active pharmacological treatment) (GT1-6)
- DCV in combination with SOF, with or without RBV (for specific people with GT1, GT3 or GT4; as recommended by NICE)
- EBR/GZR (for GT1 or GT4)
- SOF/LDV (for specific people with GT1 or GT4; as recommended by NICE)
- OBV/PTV/RTV with or without DSV or RBV (for GT1 or GT4)
- IFN with RBV (for GT1– 6)
- SOF in combination with RBV, with or without IFN (for specific people with GT1–6; as recommended by NICE)
- SOF/VEL (for specific people with GT1–6; as recommended by NICE)

The company made the following changes to the final scope:

- DCV in combination with SOF, with or without RBV was assessed for GT3 only;

- IFN with RBV was assessed for GT2 treatment-naïve patients without cirrhosis only; and
- SOF in combination with RBV, with or without IFN was excluded from the decision problem.

These changes were made based on the company's rationale that these treatment regimens are no longer used in current NHS practice.

**ERG comment:** The ERG's clinical expert agreed that indeed these treatment regimens were no longer used in NHS clinical practice.

### *3.4 Outcomes*

The CS[2] includes the following outcomes, all of which are specified in the final NICE scope[12]:

- Mortality
- SVR
- Development of resistance to treatment
- Adverse effects of treatment
- HRQoL

The economic model does not include development of resistance to treatment, stating that this outcome does not impact the cost effectiveness of G/P, i.e. it has no impact on cost or QALYs. Clinical advice received by the ERG suggests that this end point reflects treatment failure other than that from not taking pills. Given the high SVR rates this outcome may therefore be less relevant.

### *3.5 Other relevant factors*

The decision problem addressed by the CS[2] includes consideration of the following subgroups, all of which were specified in the final NICE scope[12]:

- Genotype
- People with and without cirrhosis
- Previous treatment history (naïve or treatment-experienced)

In addition, the company considered separate comparators for IFN-eligible and IFN-ineligible subgroups.

Separate subgroup analyses are not presented for patients who are: co-infected with HIV, previous treatment received (with or without DAA-containing regimens), people who have received treatment before liver transplantation, and those who have received it after liver transplantation, response to previous treatment (non-response, partial response, relapsed), and people with and without renal impairment. The company stated that '*it is not considered feasible to perform subgroup analyses in these special patient populations, given the existing need to stratify all analyses by genotype, cirrhosis status and treatment history, the criteria around which previous NICE treatment recommendations are based.*'[13]

Under 'special considerations including issues related to equity or equality', the company mentioned that the impact of treatment on reduced onward HCV transmission would also be considered if the evidence allowed. However, onward transmission is not included in the economic model because this would require a dynamic transmission model to capture an ongoing risk of infection for individuals in a population, and therefore could not be incorporated into the current modelling framework.

The company is negotiating a pricing agreement with the CMU such that the total regimen cost of G/P is [redacted]

[redacted]. This is pending acceptance at the time of submission. This is not a PAS but represents a negotiated confidential pricing agreement.

# 4. CLINICAL EFFECTIVENESS

## *4.1 Critique of the methods of review(s)*

### 4.1.1 Searches

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.[14] The submission was also checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[15]

The CS stated that systematic review searches were undertaken in April 2017.[2] Searches were reported in detail in Appendix D for the following databases: PubMed, Embase, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Trials (CENTRAL).[16] In response to clarification, the company reran Embase, PubMed and Cochrane Library searches in August 2017.[17]

Additional searches of the following conference proceedings were reported for the last two years: American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), The Viral Hepatitis Congress and Asian Pacific Association for the Study of the Liver.

**ERG comment:**

- The database searches were clearly structured (population, intervention, study design), using a combination of subject heading indexing and free text terms, with synonyms, adjacency operators and truncation. Publication year was limited from 2004 onwards and there were no language limits.
- The original clinical effectiveness search undertaken in Embase was limited to results with "clinical trial" in the title and abstract only. To correct this, the company repeated the search but did not include a number of comparators in the updated search that had been included in the original search, specifically RBV and peg-IFN alpha, as per the decision problem addressed in the CS.[2] The omission of these comparators in the updated search and the "clinical trial" limitation in the first search may mean that relevant information has been missed.
- In response to the clarification letter, the company reported the search strategy undertaken for the conference searches. However, the conference searches did not include terms for G/P (the intervention of interest) or a number of comparators indicated in the decision problem: RBV, peg-IFN alpha and RTV. It is a possibility that relevant evidence has therefore been missed.
- In response to a typographical error in the original PubMed searches, the company reran the hepatitis C search terms to include the MeSH heading "hepacvirus". Unfortunately, the company did not rerun the original hepatitis C search terms to compare against, so were unable to detect any additional articles which may have been found with the corrected MeSH heading for "hepacvirus". The ERG did not recognise the search syntax used in the updated PubMed search, so were not able to replicate the search to ensure nothing had been missed.
- In response to the ERG's concern that study design filters had been applied to searches in the Cochrane Library, which is a study design-specific resource, the company reran the searches to disregard the clinical trials filter. The additional records retrieved were screened but did not yield anything significant.

### 4.1.2 Inclusion criteria

The company used one set of inclusion criteria for intervention trials and comparator trials. The inclusion criteria are outlined in Table 4.1 (see CS Appendix D, Table 121, page 14).

**Table 4.1: Eligibility criteria used in the search strategy**

| PICOS | Inclusion and exclusion criteria |
|---|---|
| Population | • Adult patients (≥18 years of age) of any race and gender<br>• Patients were chronically infected with HCV GT1–6<br>• Studies which assessed mixed populations were included only if outcomes were reported for the relevant population<br>• Studies in which patients were not chronically infected with HCV GT1–6 were excluded<br>• Studies with renal, transplant or HCV-HIV co-infected patients were excluded |
| Interventions | • IFN-free regimens, including: G/P, SOF/VEL, EBR/GZR ± RBV, SOF/LDV ± RBV, OBV/PTV/RTV ± DSV ± RBV, SOF + DCV ± RBV, SOF + RBV<br>• IFN-containing regimens: DCV + peg-IFN + RBV, SMV + peg-IFN + RBV, SOF + peg-IFN + RBV<br>• Interventions using other DAA combinations, with or without peg-IFN and RBV were excluded, as well as studies which assessed only peg-IFN and/or RBV and other experimental DAAs not listed in the inclusion criteria. |
| Comparator(s) | All |
| Outcomes | SVR12, SVR24, DAE, OAE, safety outcomes (including but not limited to: anaemia, pruritus, nausea, neutropaenia, rash and thrombocytopenia) |
| Study design | • Randomised controlled trials and controlled trials with at least one arm assessing an intervention of interest<br>• Non-randomised clinical trials, including single-arm prospective clinical trials assessing an intervention of interest<br>• Comments, editorials or review articles were excluded, as well as Meta-analysis, Phase I studies or *in vitro* studies and Observational or retrospective studies |
| Language restrictions | • Only articles in the English language were included |

Source: Table 121 of the CS appendix, page 14
DAA = direct-acting antiviral; DAE = discontinuations relating to adverse events; DCV = daclatasvir; DSV = dasabuvir; EBR/GZR = elbasvir/grazoprevir; G/P = glecaprevir/pibrentasvir; GT = genotype; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IFN = interferon; LDV = ledipasvir; OAE = overall adverse events; OBV/PTV/RTV = ombitasvir/paritaprevir/ritonavir; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; VEL = velpatasvir

**ERG comment:** These inclusion criteria match the decision problem set out within the final NICE scope[12] in terms of the population and the intervention. A major limitation is that there is a language restriction: only English language publications are included.

The company did not mention in the eligibility criteria that a 2004 date cut-off was applied. This is mentioned on page 4 of the CS, Appendix D (search strategy).

The inclusion criteria state that randomised clinical trials and non-randomised clinical trials, including single-arm prospective clinical trials assessing an intervention of interest, were included. This is appropriate as the company performed a naïve comparison using individual arms of studies. However, the company used a trial filter in their search strategy which may well have excluded most single arm studies. For the proposed analysis, limiting the inclusion criteria to randomised trials only makes no sense. Therefore, for the naïve comparison, relevant studies may have been missed.

The study selection process was provided in a flow diagram of study selection (see CS Appendix D, Figure 17, page 15) that indicates that 81 publications (reporting on 79 studies) were identified as meeting the eligibility criteria. Fourteen of these publications, representing seven studies, involved G/P.[18-30]

In addition, information on four further clinical studies of G/P in patients with CHC are included in the company submission (EXPEDITION-2, EXPEDITION-4, MAGELLAN-I, MAGELLAN-II). These studies were conducted in special populations of patients with HIV co-infection, renal impairment, failure on prior DAAs and a post-transplant population, respectively. The company clarified that these trials were undertaken by AbbVie and identified from company records of the clinical development programme. The company considered that these trials would provide supportive data on the efficacy of G/P. The results from these studies have been published,[31-37] but were not identified by the SLR, since trials in special populations were excluded under the SLR eligibility criteria (see above). This means no comparative data are presented in the CS for these populations.

Finally, the company mentions two trials in Japanese patients with CHC: CERTAIN-1 and CERTAIN-2. These trials are only minimally discussed in the CS and not included in the economic model because "*these two trials were conducted entirely in Japanese patients*" which "*precludes their generalisability to the UK patient population and subsequently their use in the economic model*", according to the company.

A summary of the studies providing evidence for G/P is provided in Table 4.2 below.

**Table 4.2: Clinical effectiveness evidence: G/P studies**

| Study acronym | Intervention(s) | Comparator(s) | Population | Notes |
|---|---|---|---|---|
| ***ENDURANCE studies*** | | | | |
| ENDURANCE-1[18, 38, 39] | G/P (300 mg/120 mg OD) for 8 or 12 weeks | None | • GT1<br>• TN or TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN (TE-PRS)<br>• NC<br>• With or without HIV-1 co-infection | |
| ENDURANCE-2[19, 40, 41] | G/P (300 mg/120 mg OD) for 12 weeks | Placebo | • GT2<br>• TN or TE-PRS<br>• NC | Not used in economic model. Treatment duration not in line with anticipated licence for NC patients. |

| Study acronym | Intervention(s) | Comparator(s) | Population | Notes |
|---|---|---|---|---|
| ENDURANCE-3[20, 42, 43] | G/P (300 mg/120 mg OD) for 8 or 12 weeks | SOF + DCV for 12 weeks | • GT3<br>• TN<br>• NC | Multicentre, randomised, open-label, active-controlled, Phase III |
| ENDURANCE-4[21, 44, 45] | G/P (300 mg/120 mg OD) for: 12 weeks | None | • GT4, GT5 or GT6<br>• TN or TE-PRS<br>• NC | Not used in economic model. Treatment duration not in line with anticipated licence for NC patients. |
| ***EXPEDITION-1 and SURVEYOR-II, Parts 2 and 3*** | | | | |
| EXPEDITION-1)[46, 47] | G/P (300 mg/120 mg OD) for 12 weeks | None | • GT1, GT2, GT4, GT5 or GT6<br>• TN or TE-PRS<br>• CC | |
| SURVEYOR-II, Part 2[22, 23, 48-52] | G/P (300 mg/120 mg OD) for 8 or 12 weeks ± RBV | None | • GT2, GT3<br>• TN or TE with regimens containing peg-IFN/RBV (TE-PR)<br>• NC or CC (GT3 CC were TN only[a]; GT2 were NC only) | |
| SURVEYOR-II, Part 3[24, 48, 51, 52] | G/P (300 mg/120 mg OD) for 12 or 16 weeks | None | • GT3<br>• TN CC<br>• TE-PRS NC CC | |
| ***SURVEYOR-I, Part 2 and SURVEYOR-II, Parts 1 and 4 studies*** | | | | |
| SURVEYOR-I, Part 2[23, 49, 53-55] | G/P (300 mg/120 mg OD) for 8 or 12 weeks | None | • GT1, GT4, GT5 or GT6<br>• TN or TE-PR<br>• GT1 NC and CC; GT4, GT5 and GT6 NC only | Not used in economic model. Data from larger trials were available. |
| SURVEYOR-II, Part 1[48, 49, 51, 52, 56] | G/P (300 mg/120 mg OD or 200mg/120 mg OD) for 12 weeks ± RBV | None | • GT2, GT3<br>• TN or TE-PR<br>• NC | |
| SURVEYOR-II, Part 4[48, 51, 52, 57] | G/P (300 mg/120 mg OD) for 8 weeks | None | • GT2, GT4, GT5 or GT6<br>• TN or TE-PRS<br>• NC | |

| Study acronym | Intervention(s) | Comparator(s) | Population | Notes |
|---|---|---|---|---|
| ***EXPEDITION-2 and 4 and MAGELLAN studies*** | | | | |
| EXPEDITION-2[32, 58] | G/P (300 mg/120 mg OD) for 8 (NC, n=137)) or 12 (CC, n=16) weeks | None | • GT1, GT2, GT3, GT4, GT5 or GT6<br>• TN or TE<br>• NC or CC<br>• With HIV co-infection | Not used in economic model.<br>Only limited details are presented; trial has only recently been completed |
| EXPEDITION-4[34, 59, 60] | G/P (300 mg/120 mg OD) for 12 weeks | None | • GT1, GT2, GT3, GT4, GT5 or GT6<br>• TN (all genotypes) or TE-PRS (GT1, GT2, GT4, GT5 or GT6)<br>• NC or CC<br>• Who had severe renal impairment or end-stage renal disease (including those on dialysis) | Not used in economic model.<br>A subgroup analysis for patients with severe renal impairment was not performed |
| MAGELLAN-I, Part 1[31, 35, 61, 62] | G/P (300 mg/120 mg OD) for 12 weeks ± RBV | None | • GT1<br>• TE-DAA<br>• NC | Not used in economic model. Population is not within the anticipated licence for G/P |
| MAGELLAN-I, Part 2)[31, 36, 37, 61, 62] | G/P (300 mg/120 mg OD) for 12 or 16 weeks | None | • GT1, GT4, GT5 or GT6<br>• TE-DAA<br>• NC or CC | Not used in economic model. |
| MAGELLAN-II[33, 62, 63] | G/P (300 mg/120 mg OD) for 12 weeks | None | • GT1, GT2, GT3, GT4, GT5 or GT6<br>• TN or TE<br>• NC<br>• Patients who had received a liver or renal transplant. | Not used in economic model.<br>Only limited details are presented; trial has only recently been completed. |
| ***CERTAIN studies*** | | | | |
| CERTAIN-1, part 1[64-66] | G/P (300 mg/120 mg OD) for 8 weeks | OBV/PTV/RTV | • GT1<br>• NR<br>• NC | Not used in economic model.<br>Japanese adults with CHC<br>Part 1: All patients with Y93H polymorphisms received 8 weeks G/P |
| CERTAIN-1, part 2[64-66] | G/P (300 mg/120 mg OD) for 8 or 12 weeks | None | • GT1, GT2, GT3, GT4, GT5, GT6<br>• TE-DAA<br>• CC or NC | |

| Study acronym | Intervention(s) | Comparator(s) | Population | Notes |
|---|---|---|---|---|
| | | | • Patients with severe renal impairment and CC | |
| CERTAIN-2[64, 67-69] | G/P (300 mg/120 mg OD) for 8 weeks | SOF + RBV for 12 weeks | • GT2<br>• DAA-TN<br>• NC<br>• Patients with severe renal impairment and CC | Not used in economic model.<br>Japanese adults with CHC |

Source: CS, Tables 6-9, pages 38-44.

CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; IFN, interferon; NC, non-cirrhotic; OD, once daily; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-DAA = TE with regimens containing DAAs; TE-PRS = TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve.

[a]When SURVEYOR-II, Part 2 enrolment was initiated, both TN and TE-PR CC GT3-infected patients were eligible for enrolment, but after 7 TE-PR CC GT3-infected patients were enrolled, enrolment was halted for these patients based on feedback from the United States Food and Drug Administration.

### 4.1.3 Critique of data extraction

The data extraction process was not described and it is not stated how many reviewers were involved in the data extraction process.

**ERG comment:** The involvement of two reviewers in the data extraction of included studies helps to reduce the potential for bias and error. It is usual to report data extraction methods including details of how many reviewers were involved and processes for resolving discrepancies. Without this detail, it is impossible to exclude the risk of bias in the review.

### 4.1.4 Quality assessment

Tables 133 to 140 in the CS, Appendix D.2 (pages 88-99) provided an overview of the quality assessment of the G/P studies. For randomised controlled trials, quality assessment was performed using the quality assessment tool based on the CRD's guidance for undertaking reviews in healthcare, as recommended by NICE. For non-RCTs, the Downs and Black checklist was used.[70]

**ERG comment:** Using different quality assessment tools for RCTs and non-RCTs is unusual in this case, as only single arms from studies were included in the CS. Therefore, the distinction between RCTs (usually the gold standard) and other study designs is irrelevant. Observational data from included studies were used for comparative analyses between studies. These types of data are not suitable for comparative purposes. Therefore, the quality of all included studies is poor.

### 4.1.5 Evidence synthesis

Regarding evidence synthesis of G/P evidence, the company states that (CS, Section B2.9, page 130): "As the G/P trials presented do not provide direct evidence in comparison to all the relevant comparators in this submission, meta-analyses are not presented and the approach taken to comparative effectiveness is detailed in Section B.2.10."

**ERG comment:** The ERG agrees that a meta-analysis of G/P studies is not feasible. For a critique of the 'approach taken to comparative effectiveness', please see Section 4.4 of this report.

### *4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)*

As explained in Section 4.1.2 of this report, seven G/P studies were identified through the search strategy and four further clinical trials of G/P in patients with CHC are included in the company submission. We will describe those G/P studies that had treatment durations that were in line with the anticipated licence indication for the population included in the study and were used in the economic model (see Table 4.3). Trial methodology for these studies is reported in Tables 4.4 and 4.5 and baseline characteristics are reported in Table 4.6.

Only one of these studies included an active comparator: ENDURANCE-3. However, ENDURANCE-3 included three arms (G/P-12w, SOF+DCV-12w and G/P-8w) and patients were only randomised to two of the three arms: G/P-12w versus SOF+DCV-12w. After enrolment in these two arms was complete, new patients were assigned to receive G/P for eight weeks. Therefore, G/P-8w is not part of the randomised comparison and G/P-12w is not in line with the anticipated licence for patients in this trial. This means there is no direct comparative evidence for G/P versus any of the comparators mentioned in the scope, apart from the two CERTAIN trials. Since the CERTAIN trials were in Japanese patients only, these were considered by the company as not generalisable to the UK population.

**ERG comment:** We asked our clinical experts whether it was reasonable to exclude the CERTAIN studies and the response was mixed. On the one hand, there is no reason to assume that the relative effectiveness of G/P versus other active comparators would be different in a Japanese population; on the other hand, given the SVR rates reported in the CERTAIN studies, including these would probably not make any difference. Therefore, we have not reported the CERTAIN studies in the main part of our report; however, we have reported a summary of both studies in Section 4.5.

**Table 4.3: G/P studies with data used in the economic model**

| Trial no. (acronym) | Intervention(s) | Comparator(s) | Population |
|---|---|---|---|
| ***ENDURANCE studies*** | | | |
| ENDURANCE-1[18, 38, 39] | G/P (300 mg/120 mg OD) for 8 or 12 weeks | None | • GT1<br>• TN or TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN (TE-PRS)<br>• NC<br>• With or without HIV-1 co-infection |
| ENDURANCE-3[20, 42, 43] | G/P (300 mg/120 mg OD) for 8 or 12 weeks | SOF + DCV for 12 weeks | • GT3<br>• TN<br>• NC |
| ***EXPEDITION-1 and SURVEYOR-II studies*** | | | |
| EXPEDITION-1)[46, 47] | G/P (300 mg/120 mg OD) for 12 weeks | None | • GT1, GT2, GT4, GT5 or GT6<br>• TN or TE-PRS<br>• CC |
| SURVEYOR-II, Part 1[48, 49, 51, 52, 56] | G/P (300 mg/120 mg OD or 200mg/120 mg OD) for 12 weeks ± RBV | None | • GT2, GT3<br>• TN or TE-PR<br>• NC |

| Trial no. (acronym) | Intervention(s) | Comparator(s) | Population |
|---|---|---|---|
| SURVEYOR-II, Part 2[22, 23, 48-52] | G/P (300 mg/120 mg OD) for 8 or 12 weeks ± RBV | None | • GT2, GT3<br>• TN or TE with regimens containing peg-IFN/RBV (TE-PR)<br>• NC or CC (GT3 CC were TN only[a]; GT2 were NC only) |
| SURVEYOR-II, Part 3[24, 48, 51, 52] | G/P (300 mg/120 mg OD) for 12 or 16 weeks | None | • GT3<br>• TN CC<br>• TE-PRS NC CC |
| SURVEYOR-II, Part 4[48, 51, 52, 57] | G/P (300 mg/120 mg OD) for 8 weeks | None | • GT2, GT4, GT5 or GT6<br>• TN or TE-PRS<br>• NC |

Source: CS, Tables 6-9, pages 38-44.

CC, compensated cirrhosis; G/P, glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; IFN, interferon; NC, non-cirrhotic; OD, once daily; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TE-DAA = TE with regimens containing DAAs; TE-PRS = TE with regimens containing IFN, peg-IFN ± RBV, SOF + RBV ± peg-IFN; TN, treatment-naïve.

[a]When SURVEYOR-II, Part 2 enrolment was initiated, both TN and TE-PR CC GT3-infected patients were eligible for enrolment, but after 7 TE-PR CC GT3-infected patients were enrolled, enrolment was halted for these patients based on feedback from the United States Food and Drug Administration.

**Table 4.4: Summary of trial methodology for relevant G/P studies (ENDURANCE and EXPEDITION)**

| Trial acronym | ENDURANCE-1[18, 38, 39] | ENDURANCE-3[20, 42, 43] | EXPEDITION-1[46, 47] |
|---|---|---|---|
| **Clinicaltrials.gov identifier** | NCT02604017 | NCT02640157 | NCT02642432 |
| **Study population** | GT1, TN or TE-PRS, NC<br>G/P treatment length: 8 or 12 weeks With or without HIV-1 co-infection | GT3, TN, NC<br>G/P treatment length: 8 or 12 weeks | GT1, GT2, GT4-6, TN or TE-PRS, CC<br>G/P treatment length: 12 weeks |
| **Study objective** | To compare the efficacy of 8- versus 12-week treatment with G/P. | To compare the efficacy of 12-week treatment with G/P versus 12-week treatment with SOF + DCV and versus 8-week treatment with G/P. | To evaluate the efficacy of 12-week treatment with G/P. |
| **Location** | 110 study locations in the United States, Australia, Austria Belgium, Canada, Chile, France, Germany, Hungary, Israel, Italy, Korea, Lithuania, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, Spain, Sweden, Switzerland and Taiwan, and 6 sites (28 patients) in the United Kingdom | 69 study locations in the United States, Australia, Canada, France, Germany, New Zealand, Sweden and Switzerland, and 9 sites (81 patients) in the United Kingdom | 40 study locations in the United States, Belgium, Canada, Germany, South Africa and Spain |
| **Trial design** | Multicentre, randomised, open-label, Phase III | Multicentre, partially randomised, open-label, active-controlled, Phase III | Multicentre, open-label, single-arm, Phase III |
| **Duration of study** | Treatment duration: 8 or 12 weeks depending on treatment assignment<br>Follow-up: up to 24 weeks post-treatment | Treatment duration: 8 or 12 weeks depending on treatment assignment<br>Follow-up: up to 24 weeks post-treatment | Treatment duration: 12 weeks<br>Follow-up: up to 24 weeks post-treatment |
| **Intervention(s) (n=) and comparators(s) (n=)** | Patients receiving G/P received three fixed-dose combination tablets containing 100 mg of GLE and 40 mg of PIB OD<br>Patients were randomised in a 1:1 ratio to:<br>G/P for 12 weeks (n=352)<br>G/P for 8 weeks (n=351) | Patients were randomised in a 2:1 ratio to:<br>G/P for 12 weeks (n=233)<br>SOF + DCV for 12 weeks (n=115) | G/P for 12 weeks (n=146) |

| Trial acronym | ENDURANCE-1[18, 38, 39] | ENDURANCE-3[20, 42, 43] | EXPEDITION-1[46, 47] |
|---|---|---|---|
| | | After enrolment in these two arms was complete, new patients were assigned to receive G/P for 8 weeks (n=157)<br><br>Patients receiving SOF + DCV received one 400 mg tablet of SOF and one 60 mg tablet of DCV OD | |
| **Permitted and disallowed concomitant medication** | Patients were on a stable dose of concomitant medications, which were confirmed to be safely administered with study drugs, for at least 2 weeks prior to initiation of study drugs. Patients were required to discontinue the prohibited medications and supplements listed below at least 2 weeks or 10 half-lives (whichever was longer) prior to the first dose of any study drug, and were not allowed to use these during the treatment period and for 30 days following discontinuation of study drugs<br>Any herbal supplements (including milk thistle), red yeast rice (monacolin K), St. John's Wort<br>Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin<br>Atorvastatin, lovastatin, simvastatin<br>Astemizole, cisapride, terfenadine<br>Ethinyl estradiol containing oral contraceptives and systemic immunosuppressants<br>Patients were allowed to resume previously prohibited medications/supplements or revert to pre-study doses, 30 days following discontinuation of study drugs | | |
| **Primary outcomes (including scoring methods and timings of assessments)** | SVR12 is defined as HCV RNA <LLOQ at 12 weeks after EOT<br><br>Non-inferiority of the percentage of patients achieving SVR12 in the 12-week arm ITT mono-infected GT1 DAA-naïve (ITT-PS) population compared to the historical efficacy established by current approved SoC regimens for this patient population (OBV/PTV/RTV + DSV ± RBV or SOF/LDV for 12 weeks)<br>Non-inferiority of the percentage of patients achieving SVR12 in the 8-week arm compared to the 12-week arm in the per | Non-inferiority of the percentage of patients in the ITT population achieving SVR12 in the G/P 12-week arm compared to the SOF + DCV 12-week arm<br>Non-inferiority of the percentage of patients in the ITT population achieving SVR12 in the G/P 8-week arm compared to the G/P 12-week arm<br>Safety | Percentage of patients in the ITT population achieving SVR12, as defined as HCV RNA <LLOQ at 12 weeks after EOT<br>Safety |

| Trial acronym | ENDURANCE-1[18, 38, 39] | ENDURANCE-3[20, 42, 43] | EXPEDITION-1[46, 47] |
|---|---|---|---|
| | protocol ITT mono-infected GT1 DAA-naïve (ITT-PS-PP) population<br>Non-inferiority of the percentage of patients achieving SVR12 in the 8-week arm compared to the 12-week arm in ITT mono-infected GT1 DAA-naïve (ITT-PS) population | | |
| **Pre-planned subgroups** | When study arms were not divided by patient characteristics such as treatment or cirrhosis status, post-hoc analyses were performed to examine the results in these subgroups | | When study arms were not divided by patient characteristics such as treatment or cirrhosis status, post-hoc analyses were performed to examine the results in these subgroups |

Source: CS, Table 11 and 12, page 53-59

DAA = direct-acting antiviral; DB = double-blind; DCV = daclatasvir; DSV = dasabuvir; EOT = end of treatment; EQ-5D-3L = EuroQol-5 Dimensions-three Level; FSS = Fatigue Severity Scale; G/P = glecaprevir/pibrentasvir; GLE = glecaprevir; GT = genotype; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IFN = interferon; IRT = interactive response technology; ITT = intention-to-treat; ITT-MS = ITT mono-infected HCV GT1 population; ITT-PS = ITT mono-infected GT1 DAA-naïve; ITT-PS-PP = per-protocol ITT-PS; IU = infectious unit; LLOQ = lower limit of quantitation; NC = non-cirrhotic; NGS = next generation sequencing; OBV = ombitasvir; OD = once-daily; OL = open-label; peg-IFN = pegylated IFN; PIB = pibrentasvir; PRO = patient reported outcome; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SF-36v2 = SF-36 version 2; SoC = standard of care; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TE-PRS = treatment-experienced with regimens containing IFN = peg-IFN ± RBV = SOF + RBV ± peg-IFN; TN = treatment-naïve; WPAI-HCV = Work Productivity Activity Impairment Hepatitis C Specific Instrument

**Table 4.5: Summary of trial methodology for relevant G/P studies (SURVEYOR-II)**

| Trial acronym | SURVEYOR-II, Part 1[48, 49, 51, 52, 56] | SURVEYOR-II, Part 2[22, 23, 48-52] | SURVEYOR-II, Part 3[24, 48, 51, 52] | SURVEYOR-II, Part 4[48, 51, 52, 57] |
|---|---|---|---|---|
| **Clinicaltrials.gov identifier** | NCT02243293 | | | |
| **Study population** | GT2, GT3 TN or TE-PRS, NC<br>G/P treatment length: 12 weeks ± RBV | GT2, GT3, TN or TE-PR, NC or CC<br>G/P treatment length: 8 or 12 weeks ± RBV | GT3, TN CC, TE-PRS NC or CC<br>G/P treatment length: 12 or 16 weeks | GT2, GT4-6, TN or TE-PRS, NC<br>G/P treatment length: 8 weeks |
| **Study objective** | To evaluate the efficacy of 12-week G/P treatment | To evaluate the efficacy of 8- or 12-week G/P treatment | To evaluate the efficacy of 12- or 16-week G/P treatment | To compare the efficacy of 8-week treatment with G/P versus the historical efficacy of 12-week treatment with SOF + RBV |
| **Location** | For whole SURVEYOR-II study: 78 study locations in the United States, Australia, Canada, France, Korea, New Zealand and Taiwan, and 3 sites in the United Kingdom | | | |
| | No patients in the UK were enrolled in Part 1 | 4 patients in the UK were enrolled in Part 2 | 5 patients in the UK were enrolled in Part 3 | No patients in the UK were enrolled in Part 4 |
| **Trial design** | Multicentre, randomised, open-label, Phase II | Multicentre, partially-randomised open-label, Phase II | | Multicentre, open-label, single-arm, Phase II |
| **Duration of study** | Treatment duration: 12 weeks<br>Follow-up: up to 24 weeks post-treatment | Treatment duration: 8 or 12 weeks depending on treatment assignment<br>Follow-up: up to 24 weeks post-treatment | Treatment duration: 12 or 16 weeks depending on treatment assignment<br>Follow-up: up to 24 weeks post-treatment | Treatment duration: 8 weeks<br>Follow-up: up to 24 weeks post-treatment |
| **Intervention(s) (n=) and comparators(s) (n=)** | Patients receiving G/P received three 100 mg tablets of GLE and three 40 mg tablets of PIB OD unless otherwise stated | | | |
| | GT2 NC patients were randomised in a 1:1:1 ratio to:<br>G/P (300 mg/120 mg) for 12 weeks (n=25) | In this trial patients receiving G/P received three 100 mg tablets of GLE and three 40 mg tablets of PIB OD | TE-PRS patients without cirrhosis were randomised at a 1:1 ratio to:<br>G/P for 12 weeks (n=22) | Patients in this study received three fixed-dose combination tablets containing 100 mg of GLE and 40 mg of PIB OD<br>G/P for 8 weeks |

| Trial acronym | SURVEYOR-II, Part 1[48, 49, 51, 52, 56] | SURVEYOR-II, Part 2[22, 23, 48-52] | SURVEYOR-II, Part 3[24, 48, 51, 52] | SURVEYOR-II, Part 4[48, 51, 52, 57] |
|---|---|---|---|---|
| | G/P (200 mg/120 mg) for 12 weeks (n=24)<br>G/P (200 mg/120 mg) + RBV for 12 weeks (n=25)<br>Patients receiving RBV received 1,000 mg or 1,200 mg (weight based) divided twice daily<br><br>GT3 NC patients were randomised in a 1:1:1:1 ratio to:<br>G/P (300 mg/120 mg) for 12 weeks (n=30)<br>G/P (200 mg/120 mg) for 12 weeks (n=31)<br>G/P (200 mg/120 mg) + RBV for 12 weeks (n=31)<br>G/P (200 mg/40 mg) for 12 weeks (n=30) | GT2 NC patients were enrolled to receive G/P for 8 weeks (n=54)<br><br>GT3 NC patients were enrolled to receive G/P for 8 (TN) or 12 (TE-PR) weeks (n=53)<br><br>GT3 TN CC patients were randomised in a 1:1 ratio to:<br>G/P for 12 weeks (n=28)[a]<br>G/P + RBV for 12 weeks (n=27)[a]<br>Patients receiving RBV received 800 mg OD | G/P for 16 weeks (n=22)<br><br>TN patients with cirrhosis were only enrolled to receive G/P for 12 weeks (n=40)<br><br>TE-PRS patients with cirrhosis were only enrolled to receive G/P for 16 weeks (n=47) | GT2 (n=145)<br>GT4, GT5 or GT6 (n=58) |
| **Permitted and disallowed concomitant medication** | Patients were on a stable dose of concomitant medications, which were confirmed to be safely administered with study drugs, for at least 2 weeks prior to initiation of study drugs. Patients were required to discontinue the prohibited medications and supplements listed below at least 2 weeks or 10 half-lives (whichever was longer) prior to the first dose of any study drug, and were not allowed to use these during the treatment period and for 30 days following discontinuation of study drugs<br>• Any herbal supplements (including milk thistle), red yeast rice (monacolin K), St. John's Wort<br>• Carbamazepine, phenytoin, pentobarbital, phenobarbital, primidone, rifabutin, rifampin<br>• Atorvastatin, lovastatin, simvastatin<br>• Astemizole, cisapride, terfenadine<br>• Ethinyl estradiol containing oral contraceptives and systemic immunosuppressants | | | |

| Trial acronym | SURVEYOR-II, Part 1[48, 49, 51, 52, 56] | SURVEYOR-II, Part 2[22, 23, 48-52] | SURVEYOR-II, Part 3[24, 48, 51, 52] | SURVEYOR-II, Part 4[48, 51, 52, 57] |
|---|---|---|---|---|
| | • Patients were allowed to resume previously prohibited medications/supplements or revert to pre-study doses, 30 days following discontinuation of study drugs | | | |
| **Primary outcomes (including scoring methods and timings of assessments)** | Percentage of patients in the ITT population achieving SVR12. SVR12 is defined as HCV RNA <LLOQ at 12 weeks after EOT<br>***SURVEYOR-II, Part 4 only:*** Non-inferiority of the percentage of GT2 DAA-TN NC patients in the ITT population achieving SVR12 compared to the historical efficacy (SVR12 95%) of 12-week treatment with SOF + RBV<br>Safety | | | |
| **Pre-planned subgroups** | When study arms were not divided by patient characteristics such as treatment or cirrhosis status, post-hoc analyses were performed to examine the results in these subgroups | | | |

Source: CS, Table 12 and 13, page 59-67

CC = compensated cirrhosis; DAA = direct-acting antiviral; DB = double-blind; DCV = daclatasvir; DSV = dasabuvir; EOT = end of treatment; EQ-5D-3L = EuroQol-5 Dimensions-three Level; EQ-5D-5L = EuroQol-5 Dimensions-five Level; FSS = Fatigue Severity Scale; G/P = glecaprevir/pibrentasvir; GLE = glecaprevir; GT = genotype; HCV = hepatitis C virus; HCVTSat = chronic HCV treatment satisfaction instrument; HIV = human immunodeficiency virus; IFN = interferon; IRT = interactive response technology; ITT = intention-to-treat; ITT-MS = ITT mono-infected HCV GT1 population; ITT-PS = ITT mono-infected GT1 DAA-naïve; ITT-PS-PP = per-protocol ITT-PS; IU = infectious unit; LLOQ = lower limit of quantitation; NC = non-cirrhotic; NGS = next generation sequencing; OBV = ombitasvir; OD = once-daily; OL = open-label; peg-IFN = pegylated IFN; PIB = pibrentasvir; PRO = patient reported outcome; PTV = paritaprevir; RBV = ribavirin; RNA = ribonucleic acid; RTV = ritonavir; SF-36v2 = SF-36 version 2; SoC = standard of care; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TE-PR = treatment-experienced with regimens containing peg-IFN/RBV; TE-PRS = treatment-experienced with regimens containing IFN = peg-IFN ± RBV = SOF + RBV ± peg-IFN; TN = treatment-naïve; WPAI-HCV = Work Productivity Activity Impairment Hepatitis C Specific Instrument

**Table 4.6: Baseline characteristics for relevant G/P studies (ENDURANCE and EXPEDITION)**

| | ENDURANCE-1[18, 39] | ENDURANCE-3[20, 43] | EXPEDITION-1[47] |
|---|---|---|---|
| Baseline characteristics, n (%) | G/P 8 weeks (N=351) | G/P 8 weeks (N=157) | G/P 12 weeks (N=146) |
| Age (years) | | | |
| Category 1: <65 | 309 (88.0) | [redacted] | [redacted] |
| Category 1: ≥65 | 42 (12.0) | [redacted] | [redacted] |
| Category 2: <75 | 346 (98.6) | [redacted] | [redacted] |
| Category 2: ≥75 | 5 (1.4) | [redacted] | [redacted] |
| Male | 167 (47.6) | 92 (58.6) | 90 (61.6) |
| BMI (kg/m$^2$) <30 | 300 (85.5) | [redacted] | [redacted] |
| BMI (kg/m$^2$) ≥30 | 51 (14.5) | [redacted] | [redacted] |
| Race | | | |
| White | 289 (82.3) | 134 (85.4) | 120 (82.2) |
| Black | 14 (4.0) | [redacted] | [redacted] |
| Asian | 44 (12.5) | [redacted] | [redacted] |
| Other | 4 (1.2) | [redacted] | [redacted] |
| Baseline fibrosis stage | | | |
| F0–F1 | 296 (85.1) | 122 (77.7) | - |
| F2 | 22 (6.3) | 8 (5.1) | - |
| F3 | 30 (8.6) | 27 (17.2) | - |
| F4 | 0 | 0 | - |
| Missing | 3 | - | - |
| Baseline Child-Pugh score | | | |
| 5 | - | - | [redacted] |
| 6 | - | - | [redacted] |
| >6 | - | - | [redacted] |

| | **ENDURANCE-1[18, 39]** | **ENDURANCE-3[20, 43]** | **EXPEDITION-1[47]** |
|---|---|---|---|
| Baseline characteristics, n (%) | G/P 8 weeks (N=351) | G/P 8 weeks (N=157) | G/P 12 weeks (N=146) |
| Missing | - | - | [redacted] |
| Prior HCV treatment history | | | |
| Naïve | 219 (62.4) | 157 (100) | 110 (75.3) |
| Experienced | 132 (37.6) | N/A | 36 (24.7) |
| Type of previous regimen | | | |
| IFN-based | 131 (37.3) | N/A | [redacted] |
| SOF-based | 1 (0.3) | N/A | [redacted] |
| Response to previous HCV treatment | | | |
| Breakthrough/on-treatment non-responder | [redacted] | N/A | [redacted] |
| Post-treatment relapse | [redacted] | N/A | [redacted] |
| Unknown/other | [redacted] | N/A | [redacted] |
| IL28B genotype | | | |
| CC | 102 (29.1) | [redacted] | [redacted] |
| CT | 197 (56.1) | [redacted] | [redacted] |
| TT | 52 (14.8) | [redacted] | - |
| Baseline HCV RNA level (IU/mL) | | | |
| Category 1: <6,000,000 | 302 (86.0) | [redacted] | - |
| Category 1: ≥6,000,000 | 49 (14.0) | [redacted] | - |
| Category 2: <10,000,000 | 335 (95.4) | [redacted] | - |
| Category 2: ≥10,000,000 | 16 (4.6) | [redacted] | - |
| Other characteristics | | | |
| HCV mono-infected | 336 (95.7) | 157 (100) | - |
| HCV/HIV-1 co-infected | 15 (4.3) | - | - |

| | **ENDURANCE-1[18, 39]** | **ENDURANCE-3[20, 43]** | **EXPEDITION-1[47]** |
|---|---|---|---|
| Baseline characteristics, n (%) | G/P 8 weeks (N=351) | G/P 8 weeks (N=157) | G/P 12 weeks (N=146) |
| HCV genotype | | | |
| 1 (total) | [redacted] | - | 87 (59.6) |
| 1a | 152 (43.3) | - | [redacted] |
| 1b | [redacted] | - | [redacted] |
| 2 (total) | - | - | 34 (23.3) |
| 3 (total) | - | 115 (100) | - |
| 4 (total) | - | - | 16 (11.0) |
| 5 (total) | - | - | 2 (1.4) |
| 6 (total) | - | - | 7 (4.8) |

Source: CS, Tables 16, 17, 20 and 21, pages 75-89.
CC = compensated cirrhosis; DCV = daclatasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; SOF = sofosbuvir; HCV = hepatitis C virus; NC = non-cirrhotic; RBV = ribavirin

**Table 4.7: Baseline characteristics for relevant G/P studies (SURVEYOR-II)**

| | **SURVEYOR-II, Part 1[48, 49, 52, 56]** | | **SURVEYOR-II, Part 2[23, 49, 53, 55]** | | **SURVEYOR-II, Part 3[24, 48, 52]** | | **SURVEYOR-II, Part 4[24, 48, 52]** |
|---|---|---|---|---|---|---|---|
| Baseline characteristics, n (%) | GT2 G/P (300 mg/120 mg) 12 weeks, N=25 | GT3 G/P (300 mg/120 mg) 12 weeks, N=30 | GT2 G/P 8 weeks, N=54 | GT3 G/P 12 or 16 weeks, N=28 | TN CC G/P 12 weeks, N=40 | TE-PRS CC G/P 16 weeks, N=47 | GT2 G/P 8 weeks, N=145[a] |
| Age (years) | | | | | | | |
| Category 1: <65 | 21 (84.0) | 28 (93.3) | 44 (81.5) | [redacted] | 38 (95.0) | 39 (83.0) | 128 (88.3) |
| Category 1: ≥65 | 4 (16.0) | 2 (6.7) | 10 (18.5) | [redacted] | 2 (5.0) | 8 (17.0) | 17 (11.7) |
| Category 2: <75 | - | - | - | - | - | - | - |
| Category 2: ≥75 | - | - | - | - | - | - | - |
| Male | 16 (64.0) | 19 (63.3) | 33 (61.1) | 15 (53.6) | 24 (60.0) | 36 (76.6) | 61 (42.1) |
| BMI (kg/m$^2$) <30 | 15 (60.0) | 24 (80.0) | 43 (79.6) | [redacted] | 25 (62.5) | 34 (72.3) | 100 (69.0) |
| BMI (kg/m$^2$) ≥30 | 10 (40.0) | 6 (20.0) | 11 (20.4) | [redacted] | 15 (37.5) | 13 (27.7) | 45 (31.0) |
| Race | | | | | | | |
| White | 22 (88.0) | 29 (96.7) | 51 (94.4) | [redacted] | 37 (92.5) | 42 (89.4) | 120 (82.8) |
| Black | 2 (8.0) | 1 (3.3) | 1 (1.9) | [redacted] | 0 | 0 | 11 (7.6) |
| Asian | 1 (4.0) | 0 | 0 | [redacted] | 1 (2.5) | 3 (6.4) | 10 (6.9) |
| Other | 0 | 0 | 2 (3.7) | [redacted] | 2 (5) | 2 (4.2) | 4 (2.8) |
| Baseline fibrosis stage | | | | | | | |
| F0–F1 | 16 (64.0) | 18 (60.0) | 45 (83.3) | [redacted] | 0 | 0 | 123 (84.8) |
| F2 | 6 (24.0) | 6 (20.0) | 6 (11.1) | [redacted] | 0 | 0 | 9 (6.2) |
| F3 | 3 (12.0) | 6 (20.0) | 3 (5.6) | [redacted] | 0 | 0 | 13 (9.0) |
| F4 | 0 | 0 | 0 | [redacted] | 40 (100) | 47 (100) | 0 |
| Missing | - | - | - | - | - | - | - |
| Baseline Child-Pugh score | | | | | | | |
| 5 | - | - | - | [redacted] | [redacted] | [redacted] | - |

| | **SURVEYOR-II, Part 1**[48, 49, 52, 56] | | **SURVEYOR-II, Part 2**[23, 49, 53, 55] | | **SURVEYOR-II, Part 3**[24, 48, 52] | | **SURVEYOR-II, Part 4**[24, 48, 52] |
|---|---|---|---|---|---|---|---|
| Baseline characteristics, n (%) | GT2 G/P (300 mg/120 mg) 12 weeks, N=25 | GT3 G/P (300 mg/120 mg) 12 weeks, N=30 | GT2 G/P 8 weeks, N=54 | GT3 G/P 12 or 16 weeks, N=28 | TN CC G/P 12 weeks, N=40 | TE-PRS CC G/P 16 weeks, N=47 | GT2 G/P 8 weeks, N=145[a] |
| 6 | - | - | - | [redacted] | [redacted] | [redacted] | - |
| >6 | - | - | - | - | - | - | - |
| Missing | - | - | 54 | - | [redacted] | [redacted] | - |
| Prior HCV treatment history | | | | | | | |
| Naïve | 22 (88.0) | 27 (90.0) | 47 (87.0) | [redacted] | 40 (100) | 0 | 127 (87.6) |
| Experienced | 3 (12.0) | 3 (10.0) | 7 (13.0) | [redacted] | 0 | 47 (100) | 18 (12.4) |
| Type of previous regimen | | | | | | | |
| IFN-based | - | - | - | - | 0 | 22 (46.8) | 12 (8.3) |
| SOF-based | - | - | - | - | 0 | 25 (53.2) | 6 (4.1) |
| IL28B genotype | | | | | | | |
| CC | 13 (52.0) | 10 (33.3) | 22 (40.7) | [redacted] | 10 (22.7) | 20 (50.0) | 69 (47.6) |
| CT | 9 (36.0) | 18 (60.0) | 24 (44.4) | [redacted] | 27 (61.4) | 18 (45.0) | 56 (38.6) |
| TT | 3 (12.0) | 2 (6.7) | - | - | - | - | 20 (13.8) |
| Baseline HCV RNA level (IU/mL) | | | | | | | |
| <6,000,000 | 9 (36.0) | 13 (43.3) | 23 (42.6) | [redacted] | 36 (90.0) | 37 (78.7) | 83 (57.2) |
| ≥6,000,000 | 16 (64.0) | 17 (56.7) | 31 (57.4) | [redacted] | 4 (10.0) | 10 (21.3) | 62 (42.8) |
| <10,000,000 | 12 (48.0) | 18 (60.0) | 37 (68.5) | [redacted] | 39 (97.5) | 43 (91.5) | 107 (73.8) |
| ≥10,000,000 | 13 (52.0) | 12 (40.0) | 17 (31.5) | [redacted] | 1 (2.5) | 4 (8.5) | 38 (26.2) |
| HCV genotype | | | | | | | |
| 1 (total) | - | - | - | - | - | - | - |
| 1a | - | - | - | - | - | - | - |
| 1b | - | - | - | - | - | - | - |

| | **SURVEYOR-II, Part 1[48, 49, 52, 56]** | | **SURVEYOR-II, Part 2[23, 49, 53, 55]** | | **SURVEYOR-II, Part 3[24, 48, 52]** | | **SURVEYOR-II, Part 4[24, 48, 52]** |
|---|---|---|---|---|---|---|---|
| Baseline characteristics, n (%) | GT2 G/P (300 mg/120 mg) 12 weeks, N=25 | GT3 G/P (300 mg/120 mg) 12 weeks, N=30 | GT2 G/P 8 weeks, N=54 | GT3 G/P 12 or 16 weeks, N=28 | TN CC G/P 12 weeks, N=40 | TE-PRS CC G/P 16 weeks, N=47 | GT2 G/P 8 weeks, N=145[a] |
| 2 (total) | 25 (100) | - | 54 (100) | - | - | - | 145 (100) |
| 3 (total) | - | 30 (100) | - | [redacted] | [redacted] | [redacted] | - |
| 4 (total) | - | - | - | - | - | - | - |
| 5 (total) | - | - | - | - | - | - | - |
| 6 (total) | - | - | - | - | - | - | - |

Source: CS, Table 18, 19, 20 and 21, pages 79-89.

CC = compensated cirrhosis; DCV = daclatasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; SOF = sofosbuvir; HCV = hepatitis C virus; NC = non-cirrhotic; RBV = ribavirin

[a]) Two GT2-infected patients were later determined as GT1 by phylogenetic analysis. These patients were included in the ITT analysis, but were excluded for the comparison to historical threshold.

[b]) At screening, this patient was assessed by the investigator as having cirrhosis but did not end up having qualifying results for cirrhosis per protocol prior to enrolment. The patient did have a historical FibroScan result of 14.0 kPa (F3).

**ERG comment**

- Although baseline characteristics from the G/P trials are supplied, in most cases baseline characteristics for G/P studies are not reported for the specific population used to compare effectiveness between regimes. It is therefore not possible to ascertain whether the patients in the specific comparisons made are comparable or whether they are representative of those in clinical practice.

### 4.2.1 Results

The CS reports clinical effectiveness results according to the primary objective (SVR12) for each of the included G/P studies. Here, we will only report results for the studies that had treatment durations that were in line with the anticipated licence indication for the population included in the study and were used in the economic model (see Table 4.3).

In the table below, SVR12 rates for G/P regimens corresponding to the (anticipated) licensed dose and treatment duration are reported. The SVR12 rates from each trial are reported whenever possible from ITT patient subpopulations defined by genotype, treatment history and cirrhosis status.

**Table 4.8: Results for relevant G/P studies**

| Genotype | Subgroup | Study | Regimen | SVR12 |
|---|---|---|---|---|
| GT1 | TN NC | ENDURANCE-1[18, 39] | G/P 8 weeks | [redacted] |
| | | SURVEYOR-I, Part 2 | G/P 8 weeks | 96.6% (28/29) |
| | TN CC | EXPEDITION-1[47] | G/P 12 weeks | [redacted] |
| | TE NC | ENDURANCE-1[18, 39] | G/P 8 weeks | [redacted] |
| | | SURVEYOR-I, Part 2 | G/P 8 weeks | 100% (5/5) |
| | TE CC | EXPEDITION-1[47] | G/P 12 weeks | [redacted] |
| GT2 | TN NC | SURVEYOR-II, Part 4[24, 48, 52] | G/P 8 weeks | [redacted] |
| | | SURVEYOR-II, Parts 1 and 2[22, 23, 48-50, 52, 56] | G/P 8 weeks | [redacted] |
| | TN CC | EXPEDITION-1[47] | G/P 12 weeks | [redacted] |
| | TE NC | SURVEYOR-II, Part 4[24, 48, 52] | G/P 8 weeks | [redacted] |
| | | SURVEYOR-II, Parts 1 and 2[22, 23, 48-50, 52, 56] | G/P 8 weeks | [redacted] |
| | TE CC | EXPEDITION-1[47] | G/P 12 weeks | [redacted] |
| GT3 | TN NC | ENDURANCE-3[25, 43] | G/P 8 weeks | 94.9% (149/157) |
| | TN CC | SURVEYOR-II, Part 2[22, 23, 48-50, 52, 56] | G/P 12 weeks | 100% (24/24) |
| | | SURVEYOR-II, Part 3[24, 52] | G/P 12 weeks | [redacted] |
| | TE NC | SURVEYOR-II, Part 3[24, 52] | G/P 16 weeks | [redacted] |
| | TE CC | SURVEYOR-II, Part 2[22, 23, 48-50, 52] | G/P 16 weeks | [redacted] |

| Genotype | Subgroup | Study | Regimen | SVR12 |
|---|---|---|---|---|
| | | SURVEYOR-II, Part 3[24, 52] | G/P 16 weeks: | [redacted] |
| GT4–6 | TN NC | GT4: SURVEYOR-II, Part 4[52] | G/P 8 weeks | [redacted] |
| | | GT5: SURVEYOR-II, Part 4[52] | G/P 8 weeks | [redacted] |
| | | GT6: SURVEYOR-II, Part 4[52] | G/P 8 weeks | [redacted] |
| | TN CC | GT4: EXPEDITION-1[47] | G/P 12 weeks | [redacted] |
| | | GT5: EXPEDITION-1[47] | G/P 12 weeks | [redacted] |
| | | GT6: EXPEDITION-1[47] | G/P 12 weeks | [redacted] |
| | TE NC | GT4–6: SURVEYOR-II, Part 4[52] | G/P 8 weeks | [redacted] |
| | TE CC | GT4–6: EXPEDITION-1[47] | G/P 12 weeks | [redacted] |
| Source: CS, section B2.7.1, page 108<br>*ITT population excluding prior SOF+ RBV ± peg-IFN failures | | | | |



**ERG comment:** As can be seen from Table 4.8, numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each group. Only three out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC and GT2/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

### 4.2.2 Health-related quality of life

[redacted]In ENDURANCE-1, '[redacted]' (G/P vs Placebo) and in ENDURANCE-3 '[redacted]' (G/P vs SOF/DCV). [redacted], according to the company.

### 4.2.3 Subgroup analyses

Subgroup analyses are described in section B2.8 (pages 128-129) of the CS and Appendix E (CS Appendix, pages 385-392). Basic results presented above are already reported by genotype, for people with and without cirrhosis and based on previous treatment (naïve or experienced). Additional subgroups mentioned in the scope are:

- co-infection with HIV
- previous treatment received (with or without DAA-containing regimens)

- people who have received treatment before liver transplantation, and those who have received it after liver transplantation
- response to previous treatment (non-response, partial response, relapsed)
- people who are intolerant to or ineligible for interferon treatment
- people with and without renal impairment

From these subgroups, the company provided results for people co-infected with HIV (ENDURANCE-1 - GT1/NC/TN+TE). No results are provided for any of the other subgroups that were used in the economic model.

### 4.2.4 Adverse events

The summary of the safety profile for G/P in the SmPC[11] shows that in patients treated for eight, 12 or 16 weeks with compensated liver disease (with or without cirrhosis), based on Phase 2 and 3 studies which evaluated approximately 2,300 patients, the most commonly reported adverse reactions (incidence ≥ 10%) were headache and fatigue. Less than 0.1% of patients treated with G/P had serious adverse reactions (transient ischaemic attack). The proportion of patients treated with G/P who permanently discontinued treatment due to adverse reactions was 0.1%. The type and severity of adverse reactions in patients with cirrhosis were overall comparable to those seen in patients without cirrhosis.[11]

The most commonly reported adverse reactions identified in patients treated with G/P are reported in Table 4.9. The adverse reactions are listed below by body system organ class and frequency.

**Table 4.9: Adverse reactions identified with G/P**

| Frequency | Adverse reactions |
|---|---|
| *Nervous system disorders* | |
| Very common | headache |
| *Gastrointestinal disorders* | |
| Common | diarrhoea, nausea |
| *General disorders and administration site conditions* | |
| Very common | fatigue |
| Common | asthenia |
| Source: Glecaprevir & Pibrentasvir (Maviret) Draft SPC_26-06-2017[11]<br>Very common: ≥ 1/10), common: ≥ 1/100 to < 1/10) | |

Adverse events (AEs) in the CS are reported in four groups. First, AEs from a placebo-controlled study (ENDURANCE-2); second, AEs from an active-controlled study (ENDURANCE-3); third, AEs from all randomised patients from 21 arms of the Phase II/III studies who received at least one dose of G/P 300 mg/120 mg OD without RBV; and fourth, AEs from a study including patients with chronic kidney disease (CKD Stage 4/5; EXPEDITION-4).

**Placebo-controlled study: ENDURANCE-2**

In the placebo-controlled analysis set, 302 (202 G/P, 100 placebo) patients received at least one dose of study drug in ENDURANCE-2. Patients were genotype GT2, NC, TN or TE with IFN, peg-IFN ± RBV, or SOF + RBV ± peg-IFN. Treatment was 12 weeks of G/P at a dose of 300 mg/120 mg. Adverse events from ENDURANCE-2 are reported in Table 4.10.

**Table 4.10: ENDURANCE-2 and ENDURANCE-3 adverse events summaries**

| Adverse events, n (%) | ENDURANCE-2 | | ENDURANCE-3 | |
|---|---|---|---|---|
| | G/P (300 mg/ 120 mg), 12 weeks (N=202) | Placebo 12 weeks (N=100) | G/P (300 mg/ 120 mg) 12 weeks (N=233) | SOF + DCV 12 weeks (N=115) |
| ≥1 AE | 131 (64.9) | 58 (58.0) | 177 (76.0) | 80 (69.6) |
| ≥1 treatment-related AE | [redacted] | [redacted] | 112 (48.1) | 50 (43.5) |
| Grade 3 or 4 AE | [redacted] | [redacted] | [redacted] | [redacted] |
| **Grade 3/4 AEs** | | | | |
| Alanine aminotransferase increased | [redacted] | [redacted] | NR | NR |
| Ankle fracture | [redacted] | [redacted] | NR | NR |
| Aspartate aminotransferase increased[a] | [redacted] | [redacted] | NR | NR |
| Bile duct stone[c] | [redacted] | [redacted] | NR | NR |
| Gamma-glutamyltransferase increased[a] | [redacted] | [redacted] | NR | NR |
| Haemorrhoids | [redacted] | [redacted] | NR | NR |
| Joint dislocation[b] | [redacted] | [redacted] | NR | NR |
| Pulmonary pain | [redacted] | [redacted] | NR | NR |
| Neutropaenia | [redacted] | [redacted] | NR | NR |
| ≥1 treatment-related SAE | NR | NR | NR | NR |
| Deaths | NR | NR | NR | NR |
| Discontinuation due to AEs | NR | NR | 1 | NR |
| **Common AEs[†]** | | | | |
| Headache | 24 (11.9) | 12 (12.0) | 60 (25.8) | 23 (20.0) |
| Fatigue | 23 (11.4) | 10 (10.0) | 44 (18.9) | 16 (13.9) |
| Insomnia | NR | NR | NR | NR |
| Nausea | [redacted] | [redacted] | 32 (13.7) | 15 (13.0) |
| Oropharingeal pain | [redacted] | [redacted] | NR | NR |
| Nasopharyngitis | NR | NR | [redacted] | [redacted] |
| Upper respiratory infection | NR | NR | [redacted] | [redacted] |
| Irritability | NR | NR | NR | NR |
| Cough | NR | NR | NR | NR |
| Pruritus | [redacted] | [redacted] | NR | NR |
| Dyspepsia | NR | NR | NR | NR |
| Back pain | NR | NR | NR | NR |
| Asthenia | [redacted] | [redacted] | [redacted] | [redacted] |
| Diarrhoea | [redacted] | [redacted] | [redacted] | [redacted] |
| Dizziness | [redacted] | [redacted] | NR | NR |
| Constipation | NR | NR | NR | NR |

| Adverse events, n (%) | ENDURANCE-2 | | ENDURANCE-3 | |
|---|---|---|---|---|
| | G/P (300 mg/ 120 mg), 12 weeks (N=202) | Placebo 12 weeks (N=100) | G/P (300 mg/ 120 mg) 12 weeks (N=233) | SOF + DCV 12 weeks (N=115) |
| Arthralgia | NR | NR | NR | NR |
| Dyspnoea | NR | NR | NR | NR |
| Abdominal pain | NR | NR | NR | NR |
| Muscle spasms | NR | NR | NR | NR |
| Rash | NR | NR | NR | NR |
| Anxiety | NR | NR | NR | NR |
| Vomiting | NR | NR | NR | NR |
| Dry skin | NR | NR | NR | NR |
| Anaemia | NR | NR | NR | NR |
| Myalgia | NR | NR | NR | NR |
| Sleep disorder | NR | NR | NR | NR |
| Dyspnoea exertional | NR | NR | NR | NR |
| Decreased appetite | NR | NR | NR | NR |
| Disturbance in attention | NR | NR | NR | NR |
| Pyrexia | NR | NR | NR | NR |
| Source: CS, Tables 197 and 199, pages 158-159.<br>AE = adverse event<br>†Common AEs were those that occurred in ≥5% of patients in any treatment group. | | | | |

The risk difference (G/P versus placebo) [redacted]

[redacted] G/P patients ([redacted]%) experienced [redacted] ([redacted]%) AEs of Grade ≥3 in severity compared to [redacted] ([redacted]%) for placebo patients.

**Active-controlled study: ENDURANCE-3**

In the active-controlled analysis set, 233 patients were randomised and received G/P 300 mg/120 mg for 12 weeks and 115 patients received SOF + DCV (2:1 randomisation ratio) in ENDURANCE-3 (GT3-infected patients without cirrhosis). Adverse events from ENDURANCE-3 are reported in Table 4.10.

[redacted].

**Uncontrolled Phase II/III studies**

The Phase II and III analysis set, included 2,265 patients who received at least one dose of co-administered or co-formulated G/P 300 mg/120 mg OD (any duration) without RBV (see Table 4.11).

**Table 4.11: AEs reported for ≥5.0% of patients (Phase II and III analysis set)**

| Preferred term | Phase II and III analysis set, (N=2265), n (%) | |
|---|---|---|
| | All AEs | Study drug-related AEs[a] |
| Any AE | 1,529 (67.5) | [redacted] |
| Headache | 410 (18.1) | [redacted] |
| Fatigue | 330 (14.6) | [redacted] |
| Nausea | [redacted] | [redacted] |
| Diarrhoea | [redacted] | [redacted] |

[a]Investigator assessment; AE = adverse event

[redacted] ([redacted]) of patients with AEs experienced AEs that were Grade ≥3 (severe) in maximum severity. Of the [redacted] patients who experienced an AE of Grade ≥3 severity, [redacted] patients had AEs considered study drug-related ([redacted] patient each with [redacted]; and [redacted] patient with [redacted]).

Seven deaths were reported in the Phase II and III analysis set (N = [redacted]). [redacted].

**Patients with chronic kidney disease: EXPEDITION-4**

EXPEDITION-4 is a single arm study, including TN patients of all genotypes and TE-PRS for GT1, GT2, GT4, GT5 and GT6; patients were NC or CC and had severe renal impairment or end-stage renal disease (including those on dialysis). Treatment duration was 12 weeks. The aim of the study was to evaluate the efficacy of 12-week treatment with G/P in TN or TE-PRS NC and CC patients with or without stage 4 or 5 CKD, as measured by the proportion of patients with SVR12 and to evaluate the safety and tolerability of the treatment regimen. Patients were recruited from 28 study locations in the United States, Australia, Belgium, Canada, France, Greece, Italy and New Zealand, and two sites (seven patients) in the United Kingdom.

Patients enrolled in EXPEDITION-4 had CKD Stage 4/5, and the majority were on dialysis. Given the severity of the underlying renal disease and its associated comorbidities, the frequency and severity of the AEs in patients enrolled in this study were expected to be higher than in patients enrolled in the other registrational studies. Therefore, adverse events in this study are reported separately.

[redacted] (see Table 4.12).

**Table 4.12: Overview of AEs (EXPEDITION-4)**

| | EXPEDITION-4, n (%) (N=104) |
|---|---|
| Any AE | 74 (71.2) |
| Any DAA-related AE[a,b] | [redacted] |
| An AE Grade ≥3 | [redacted] |
| Any DAA-related AE Grade ≥3[a,b] | [redacted] |
| Any SAE | 25 (24.0) |
| Any DAA-related SAE[a,b] | 0 |
| Discontinuation of study drug due to: | |
| Any AE | 4 (3.8) |
| Any DAA-related AE[a,b] | [redacted] |
| Any fatal AE | [redacted] |
| All deaths[c] | 1 (1.0) |

Source: CS Appendix F, Table 206, page 165
[a]DAAs = GLE, PIB, or G/P; [b]Investigator assessment; [c]Includes nontreatment-emergent deaths
AE = adverse event; DAA = direct-acting antiviral agent; G/P = glecaprevir/pibrentasvir; GLE = glecaprevir; PIB = pibrentasvir; SAE = serious adverse event



Among patients in EXPEDITION-4, the most frequently reported (≥10.0% of patients) AEs were pruritus, fatigue, and nausea (see Table 4.13).

**Table 4.13: Treatment-emergent adverse events reported in ≥ 5.0% of patients**

| MedDRA 19.0 Preferred Term | EXPEDITION-4, (N = 104), n (%) |
|---|---|
| Any adverse event | [redacted] |
| Pruritus | [redacted] |
| Fatigue | [redacted] |
| Nausea | [redacted] |
| Asthenia | [redacted] |
| Diarrhoea | [redacted] |
| Decreased appetite | [redacted] |
| Headache | [redacted] |
| Vomiting | [redacted] |
| Dizziness | [redacted] |
| Dyspnoea | [redacted] |

Source: CSR, Table 25, page 138[59]
EXPEDITION-4: G/P, 300 mg/120 mg QD for 12 weeks
MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily

Of the patients in EXPEDITION-4 experiencing DAA-related events (N=[redacted]), [redacted] ([redacted]%) had events of maximum severity of Grade 1 (mild), [redacted] ([redacted]%) had a maximum severity of Grade 2, and [redacted] ([redacted]%) had a maximum severity of Grade 3.

[redacted]

[redacted]

[redacted] (See Table 4.14). [redacted] In the subset of patients who were not receiving dialysis (N=[redacted]), [redacted] patients had Grade 3 or 4 creatinine values and [redacted] patients had Grade 3 or 4 creatinine clearance values. [redacted].

**Table 4.14: Number (%) of patients with CTCAE Grade 3/4 laboratory values increasing in grade from baseline during the treatment period (EXPEDITION-4)**

| Variable (criterion) | EXPEDITION-4, (N=104), n/N* (%) |
|---|---|
| Haemoglobin (<80 g/L) | 5/104 (4.8) |
| Platelet count (<50 × $10^9$/L) | [redacted] |
| Leukocytes (<2.0–1.0 × $10^9$/L) | [redacted] |
| Total neutrophils (<1 × $10^9$/L) | [redacted] |
| INR (>2.5 × ULN) | [redacted] |
| ALT (>5 × ULN) | [redacted] |
| AST (>5 × ULN) | [redacted] |
| GGT (>5 × ULN) | [redacted] |
| Alkaline phosphatase (>5 × ULN) | [redacted] |
| Total bilirubin (>3 × ULN) | [redacted] |
| Creatinine clearance, calculated (<30 mL/min) | [redacted] |
| Albumin (<20 g/L) | [redacted] |
| Cholesterol (>10.34 mmol/L) | [redacted] |
| Glucose (>13.9 mmol/L) | [redacted] |
| Creatinine (>3 × ULN) | [redacted] |
| Sodium (<130 mmol/L) | [redacted] |
| Potassium (>6.0 mmol/L) | [redacted] |
| Triglycerides (>5.7 mmol/L) | [redacted] |

Source: CS Appendix F, Table 207, page 166

Note: n/N* indicates the number of patients with postbaseline values for the respective parameter meeting the criteria; grade must have been more extreme than baseline; Of note, no patients in EXPEDITION-4 met criteria for potential hepatotoxicity based on results for a single laboratory parameter (ALT or total bilirubin) or based on results for both ALT and total bilirubin. ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GGT = gamma-glutamyl transferase; INR = international normalized ratio; ULN = upper limit of normal.

[redacted] patients experienced an i[redacted] in the EXPEDITION-4 study. [redacted]

[redacted]

### *4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison*

As described in section 4.2.1 of this report, 81 publications (reporting on 79 studies) were identified as meeting the eligibility criteria. Fourteen of these publications, representing seven studies, involved G/P. Therefore, the remaining 67 publications, representing 72 studies, involved comparators.

Most of these comparator studies are not mentioned in the clinical effectiveness section of the CS. Only a few are briefly mentioned in section B.2.10 of the CS to explain that it is not feasible to form any network between G/P and any relevant comparator therapies.

The only place these studies are mentioned is in Tables 63 to 78, describing the sources for inputs in the economic model. No further details of the comparator studies are reported in the main CS. In Appendix D, the company presents an overview of comparator studies (see CS, Appendix D, Table 123, page 17-34 and Table 4.15 below). Baseline characteristics for the comparator studies are presented in Table 124 (CS, Appendix D, page 34). However, because results used in the economic model are mostly from subgroups of patients in these studies (based on genotype, treatment experience and cirrhosis status), baseline characteristics for the total population of each study cannot be used to assess whether populations are comparable to those from G/P studies. In most cases baseline characteristics for G/P studies are not reported for the specific population used for effectiveness data. Therefore, the ERG was unable to assess differences in patient populations between G/P studies and comparator studies.

A list of SVR rates for comparators used in the economic model are presented in Tables 65 and 66 of the CS (CS, pages 158-163). We have summarised these two tables in Table 4.16 below, and we have added SVR rates from G/P studies in the relevant populations.

**Table 4.15: Overview of studies of comparator DAAs identified by the SLR**

| No. | Trial | Trial design | Population | Intervention | Comparator(s) | Reference(s) |
|---|---|---|---|---|---|---|
| **OBV/PTV/RTV + DSV** | | | | | | |
| 1 | GARNET | Single-arm, open-label study | Patients with CHC GT1b whose treatment status was not reported and were NC | OBV/PTV/RTV + DSV | | Welzel 2017[71] |
| 2 | Arama et al (2017) | Cohort study (limited details in abstract) | Patients with CHC GT1 whose treatment status was not reported and who had CC | OBV/PTV/RTV + DSV and RBV | | Arama 2017[72] |
| 3 | AGATE-I | Randomised, open-label trial | Patients with CHC GT4 whose treatment status was not reported and had CC | OBV (25 mg)/PTV (150 mg)/RTV (100 mg) once daily with weight-based RBV for 12 (Arm A) or 16 weeks (Arm B) | | Asselah 2016[73] |
| 4 | PEARL-I | Randomised, open-label study | Patients with CHC GT1b/4 who were treatment-naïve and TE and were NC or had CC | OBV (25 mg)/PTV (150 mg)/RTV (100 mg) once daily for 12 or 24 weeks<br>OBV (25 mg)/PTV (150 mg)/RTV (100 mg) once daily and weight-based RBV for 12 weeks | | Hézode 2015b[74] |
| 5 | PEARL-II | Randomised, open-label study | Patients with CHC GT1b who were TE and NC | OBV/PTV/RTV + DSV | OBV/PTV/RTV + DSV + RBV | Andreone 2014[75] |
| 6 | PEARL-III | Randomised, double blind study | Patients with CHC GT1b who were TN and NC | OBV/PTV/RTV + DSV + RBV | OBV/PTV/RTV + DSV + Placebo RBV | Ferenci 2014[76] |
| 7 | PEARL-IV | Randomised, double blind study | Patients with CHC GT1a who were TN and NC | OBV/PTV/RTV + DSV + RBV | OBV/PTV/RTV + DSV +Placebo RBV | Ferenci 2014[76] |
| 8 | TURQUOISE-II | Randomised, open-label study | Patients with CHC GT1 whose TN or TE status was not reported and had CC | OBV/PTV/RTV + DSV+ RBV for 12 weeks | OBV/PTV/RTV + DSV + RBV for 24 weeks | Poordad 2014[77] |

| No. | Trial | Trial design | Population | Intervention | Comparator(s) | Reference(s) |
|---|---|---|---|---|---|---|
| 9 | TURQUOISE-III | Single-arm, open-label study | Patients with CHC GT1b who were TN and TE and had CC | OBV/PTV/RTV + DSV for 12 weeks | | Feld 2016[78] |
| 10 | Navigator | Non-randomised, open-label study | Patients with CHC GT1/2/3 who were TN and NC | OBV/PTV/RTV + RBV in GT1-3<br>OBV/PTV/RTV in GT1-3 | | Lawitz 2015c[79] |
| 11 | SAPPHIRE-I | Randomised, double blind study | Patients with CHC GT1 who were TN and NC | OBV/PTV/RTV + DSV + RBV | Placebo followed by OBV/PTV/RTV + DSV + RBV | Feld 2014[80] |
| 12 | SAPPHIRE-II | Randomised, double blind study | Patients with CHC GT1 who were TE and NC | OBV/PTV/RTV + DSV + RBV | Placebo followed by OBV/PTV/RTV + DSV + RBV | Zeuzem 2014b[81] |
| 13 | Kowdley (2014) | Randomised, open-label study | Patients with CHC GT1 who were treatment-naïve and TE and NC | OBV (25mg)/PTV (100/150/200 mg)/RTV (100 mg) once daily +/- DSV (400 mg) twice daily +/- RBV dosed by weight, twice daily for 8, 12 or 24 weeks | | Kowdley 2014b[82] |
| 14 | MALACHITE I | Randomised, open-label study | Patients with CHC GT1 who were TN and NC | OBV/PTV/RTV + DSV + RBV in GT1a and GT1b<br>OBV/PTV/RTV + DSV in GT1b | TVR + IFN + RBV in GT1a and GT1b. | Dore 2016[83] |
| 15 | MALACHITE II | Randomised, open-label study | Patients with CHC GT1 who were TE and were NC | OBV (25mg)/PTV (150 mg)/RTV (100 mg) once daily + DSV (250 mg) twice daily plus weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks | TVR co-administered with IFN and weight-based RBV for 12 weeks, followed by IFN and weight-based RBV for either 12 or 36 weeks, per local prescribing information. | Dore 2016[83] |
| EBR/GZR | | | | | | |

| No. | Trial | Trial design | Population | Intervention | Comparator(s) | Reference(s) |
|---|---|---|---|---|---|---|
| 16 | MK-5172-035/C-WORTHY | Randomised, double blind study | Patients with CHC GT1 who were TN and TE, with or without cirrhosis | EBR (20/50 mg)/GZR (100 mg) +/- RBV for 8, 12 or 18 weeks | | Lawitz 2015b[84] |
| 17 | C-EDGE TE | Randomised, open-label study | Patients with CHC GT1/4/6 who were TE and were with or without cirrhosis | EBR/GZR for 12 weeks<br>EBR/GZR + RBV for 12 or 16 weeks | | Kwo 2017[85] |
| 18 | MK-5172-077 | Randomised, open-label study | Patients with CHC GT1/4 who were TN and TE and were with or without cirrhosis | EBR/GZR for 12 weeks | SOF + IFN + RBV for 12 weeks | Sperl 2016[86] |
| 19 | C-ISLE (no trial ID) | Randomised, open-label study | Patients with CHC GT3 who were TN and TE | EBR/GZR + SOF ± RBV for 8 or 12 weeks (five arms) | | Foster 2017[87] |
| 20 | C-EDGE TN | Phase II, randomised clinical trial | Patients with CHC GT1/4/6 who were TN | EBR (50 mg)/GZR (100 mg) FDC | Placebo for 12 weeks, followed by the intervention | Zeuzem 2015[88] |
| SOF/LDV | | | | | | |
| 21 | Gane (2015) | Phase II, randomised, open-label study | Patients with CHC GT1/2/3/6 who were TN and TE, with or without cirrhosis | SOF/LDV +/- RBV for 12 or 24 weeks<br>SOF + IFN + RBV for 12 weeks<br>SOF/VEL (25/100mg) +/- RBV for 8 weeks | | Gane 2015[89] |
| 22 | ELECTRON | Randomised, open-label study | Patients with CHC GT2/3 who were TN and whose cirrhosis status was not reported | SOF + RBV for 8 or 12 weeks<br>SOF + RBV for 12 weeks + IFN for 4 or 8 weeks<br>SOF + IFN + RBV for 8 or 12 weeks<br>SOF for 12 weeks<br>SOF/LDV +/- RBV for 6 or 12 weeks | | Gane 2014[90] |

| No. | Trial | Trial design | Population | Intervention | Comparator(s) | Reference(s) |
|---|---|---|---|---|---|---|
| 23 | ION-1 | Randomised, open-label study | Patients with CHC GT1 who were TN and were with or without cirrhosis | SOF/LDV for 12 weeks<br>SOF/LDV for 24 weeks | SOF/LDV + RBV for 24 weeks<br>SOF/LDV + RBV for 12 weeks | Afdhal 2014b[91] |
| 24 | ION-2 | Randomised, open-label study | Patients with CHC GT1 who were TE and were with or without cirrhosis | SOF/LDV for 12 weeks<br>SOF/LDV for 24 weeks | SOF/LDV + RBV for 12 weeks<br>SOF/LDV + RBV for 24 weeks | Afdhal 2014a[92] |
| 25 | ION-3 | Randomised, open-label study | Patients with CHC GT1 who were TN and NC | SOF/LDV +/- RBV for 8 weeks | SOF/LDV for 12 weeks | Kowdley 2014a[93] |
| 26 | Study 1119 | Phase II, non-randomised, open-label study | Patients with CHC GT4/5 who were treatment-naïve and TE and were with or without cirrhosis | SOF/LDV for up to 12 weeks in GT4 and GT5 | | Abergel 2016[94] |
| 27 | SIRIUS | Randomised, double blind study | Patients with CHC GT1 who were TE and were cirrhotics only | SOF/LDV | SOF/LDV + RBV | Bourlière 2015[95] |
| 28 | Kohli (2015) | Phase II, non-randomised, open-label study | Patients with CHC GT1/4 who were TN and TE and were with or without cirrhosis | SOF/LDV for 12 weeks<br>SOF/LDV/GS-9669 for 4, 6 or 12 weeks | N/A | Kohli 2015[96] |
| SOF/VEL | | | | | | |
| 21 | Gane (2015) – | see details above | | | | |
| 29 | ASTRAL-1 | Randomised, double blind study | Patients with CHC GT1/2/4/5/6 who were TN and TE and were with or without cirrhosis | SOF/VEL for 12 weeks | Placebo | Feld 2015[97] |
| 30 | ASTRAL-2 | Randomised, open-label study | Patients with CHC GT2 who were TN and TE and | SOF/VEL fixed dose combination for 12 weeks | SOF + RBV for 12 weeks | Foster 2015b[98] |

| No. | Trial | Trial design | Population | Intervention | Comparator(s) | Reference(s) |
|---|---|---|---|---|---|---|
| | | | were with or without cirrhosis | | | |
| 31 | ASTRAL-3 | Randomised, open-label study | Patients with CHC GT3 who were TN and TE and were with or without cirrhosis | SOF/VEL 12 weeks | SOF + RBV for 24 weeks | Foster 2015b[98] |
| 32 | ASTRAL-4 | Randomised, open-label study | Patients with CHC GT1/2/3/4/5/6 who were TN and TE and had DCC | SOF/VEL for 12 weeks<br>SOF/VEL + RBV for 12 weeks | SOF/VEL for 24 weeks | Curry 2015[99] |
| 33 | Pianko (2015) | Phase II, randomised, open-label study | Patients with CHC GT1/3 who were TE and were with or without cirrhosis | SOF/VEL (25/100mg) +/- RBV | N/A | Pianko 2015[100] |
| 34 | Everson (2015) | Phase II, randomised, open-label study | Patients with CHC GT1/2/3/4/5/6 who were TN and NC | SOF/VEL (25/100 mg) +/- RBV for 8 or 12 weeks | N/A | Everson 2015[101] |
| SOF | | | | | | |
| 22 | ELECTRON - | see details above | | | | |
| 30 | ASTRAL-2 - | see details above | | | | |
| 31 | ASTRAL-3 - | see details above | | | | |
| 35 | Wehmeyer (2015) | Prospective study (open or blind not reported) | Patients with CHC GT4 who were TN and TE and were NC or CC | SOF + IFN + RBV<br>IFN + RBV | | Wehmeyer 2015[102] |
| 36 | BOSON | Randomised, open-label study | Patients with CHC GT2/3 who were TN and TE and had CC | SOF + RBV for 16 weeks<br>SOF + RBV for 24 weeks<br>SOF + IFN + RBV for 12 weeks | | Foster 2015a[103] |
| 37 | Lawitz (2015) | Non-randomised, open-label study | Patients with CHC GT2/3 who were TE and were cirrhotics only | SOF + IFN + RBV for 12 weeks | N/A | Lawitz 2015a[104] |

| No. | Trial | Trial design | Population | Intervention | Comparator(s) | Reference(s) |
|---|---|---|---|---|---|---|
| 38 | ATOMIC | Randomised, open-label study | Patients with CHC GT1/4/5/6 who were TN and had no history of any other clinically significant chronic liver disease | SOF + IFN + RBV for 12 weeks<br>SOF + IFN + RBV for 24 weeks | SOF + IFN + RBV for 12 weeks | Lawitz 2014a[105] |
| 39 | Rodriguez-Torres (2013) | Phase II, randomised, double blind study | Patients with CHC GT1 who were TN and cirrhosis status was not reported | SOF (100 mg) + IFN + RBV<br>SOF (200 mg) + IFN + RBV<br>SOF (400 mg) + IFN + RBV | Placebo + IFN + RBV | Rodriguez-Torres 2013[106] |
| 40 | VALENCE | Randomised, double blind study | Patients with CHC GT2/3 who were treatment-naïve and TE and were with or without cirrhosis | SOF for 12 weeks in GT2/3<br>SOF for 24 weeks in GT3 | N/A | Zeuzem 2014a[107] |
| 41 | FUSION | Randomised, double blind study | Patients with CHC GT3 who were TE and were with or without cirrhosis | SOF + RBV for 16 weeks | SOF + RBV for 12 weeks followed by placebo for 4 weeks | Jacobson 2013[108] |
| 42 | POSITRON | Randomised, double blind study | Patients with CHC GT2/3 who were IFN intolerant or ineligible and were with or without cirrhosis | SOF + RBV for 12 weeks | Placebo | Jacobson 2013[108] |
| 43 | NEUTRINO | Single-arm, open-label study | Patients with CHC GT1/4/5/6 who were TN and were with or without cirrhosis | SOF + IFN + RBV | N/A | Lawitz 2013a[109] |
| 44 | FISSION | Randomised, open-label study | Patients with CHC GT2/3 who were TN and had no hepatic decompensation | SOF + RBV for 12 weeks | IFN + RBV for 24 weeks. | Lawitz 2013a[109] |
| 45 | PROTON | Randomised, double blind study | Patients with CHC GT1/2/3 who were TN and were NC | SOF (200 mg) in GT1<br>SOF (400 mg) in GT1<br>SOF (400 mg) in GT2/3 | Placebo (GT 1). Participants with GT 1 HCV infection were | Lawitz 2013b[110] |

| No. | Trial | Trial design | Population | Intervention | Comparator(s) | Reference(s) |
|---|---|---|---|---|---|---|
| | | | | | randomised to receive placebo to match SOF (4 tablets) + IFN + RBV for 12 weeks followed by IFN + RBV for up to an additional 36 weeks. | |
| SOF/DCV* | | | | | | |
| 46 | ALLY -3+ | Randomised, open-label study | Patients with CHC GT3 who were TN and TE and had advanced fibrosis or CC | 1: SOF/DCV + RBV for 12 weeks | 2: SOF/DCV + RBV for 16 weeks | Leroy 2016[111] |
| 47 | ALLY3 | Non-randomised, open-label study | Patients with CHC GT3 who were TN and TE and had no decompensated liver disease | A1: SOF/DCV in TN | A2: SOF/DCV in TE | Nelson 2015[112] |
| 48 | Hézode (2017b) | Single-arm, open-label study | Patients with CHC GT 3 who were TN | SOF/DCV for 8 weeks | | Hézode 2017b[113] |
| 49 | AI444040 | Randomised, open-label study | Patients with CHC GT1/2/3 who were TN and were NC | SOF/DCV +/- RBV | | Sulkowski 2014[114] |
| SMV/SOF | | | | | | |
| 50 | PLUTO | Single-arm, open-label study | Patients with CHC GT4 who were TN and TE and were NC or CC | SMV (150 mg)/SOF (400 mg) | | Buti 2017[115] |
| 51 | SMV-SOF | Randomised, open-label study | | SMV/SOF | IFNα-2b + RBV + SOF for 12 weeks | Pearlman 2015[116] |
| 52 | OPTIMIST 2 | Single-arm, open-label study | Patients with CHC GT1 who were TN and TE and had cirrhosis only | SMV/SOF | | Lawitz 2016[117] |

| No. | Trial | Trial design | Population | Intervention | Comparator(s) | Reference(s) |
|---|---|---|---|---|---|---|
| 53 | COSMOS | Randomised, open-label study | Patients with CHC GT1 who were TN and NR and had no hepatic decompensation | SMV/SOF for 24 weeks<br>SMV/SOF for 12 weeks | SMV/SOF+ RBV for 12 or 24 weeks | Lawitz 2014b[118] |
| DCV | | | | | | |
| 54 | Pol (2012) | Phase II, randomised, double blind study | Patients with CHC GT1 who were TN and were NC | A: DCV + IFNα-2a + RBV<br>B: DCV + IFNα-2a + RBV<br>C: DCV + IFNα-2a + RBV | Placebo, IFNα-2a, RBV<br>(D) Interventions: Drug: Placebo Drug: IFNα-2a Drug: RBV | Pol 2012[119] |
| 55 | Rodriguez-Torres (2016) | Phase III, single-arm open-label study | Patients with CHC GT1 who were TN, compensated cirrhotics were capped at approximately 25% | DCV + IFN + RBV | N/A | Rodriguez-Torres 2016[120] |
| 56 | COMMAND-1 | Randomised, double blind study | Patients with CHC GT1/4 who were TN and were NC | DCV+IFNα-2a + RBV (20 mg)<br>DCV+IFNα-2a + RBV (60 mg) | Placebo+IFNα-2a+ RBV | Hézode 2015a[121] |
| 57 | COMMAND-4 | Randomised, double blind study | Patients with CHC GT1 who were TN and were NC | DCV + IFNα-2a + RBV | Placebo Comparator: Placebo matching DCV + IFNα-2a + RBV | Hézode 2015c[122] |
| 58 | A1444-031 | Randomised, double blind study | Patients with CHC GT2/3 who were TN and had no DC | DCV + IFNα-2a + RBV for 12 weeks<br>DCV + IFNα-2a + RBV for 12 weeks | Control Placebo + IFNα-2a + RBV | Dore 2015[123] |
| SMV/DCV | | | | | | |
| 59 | LEAGUE-1 | Randomised, open-label study | Patients with CHC GT1 who were TN and TE, patients with CC were permitted | SMV/DCV +/- RBV | | Zeuzem 2016[124] |

| No. | Trial | Trial design | Population | Intervention | Comparator(s) | Reference(s) |
|---|---|---|---|---|---|---|
| 60 | Hézode et al (2017a) | Single-arm, open-label study | Patients with CHC GT1b who were TN and were NC or CC | SMV/DCV for 12 or 24 weeks | | Hézode 2017a[125] |
| GZR | | | | | | |
| 61 | MK-5172-038 | Randomised, double blind study | Patients with CHC GT1 who were TN and were NC | GZR (25 mg) + IFN + RBV<br>GZR (50 mg) + IFN + RBV<br>GZR (100 mg) + IFN + RBV | N/A | Lagging 2016[126] |
| 62 | MK-5172-003 or Manns (2014) | Randomised, double blind study | Patients with CHC GT1 who were TN CC patients were allowed | GZR (100/200/400/800 mg) + IFN + RBV for 12 weeks followed by 12 or 36 weeks of IFN RBV, based on response guided therapy<br>As the result of an interim analysis, participants assigned to the GZR (400/800 mg) group were unblinded and transitioned to GZR (100 mg) once daily + IFN + RBV | BOC (800 mg) in TN NC participants start a 4 week lead-in with IFN + RBV, then receive BOC (800 mg) + IFN + RBV for 24 weeks followed by 0 or 20 weeks of IFN + RBV, based on response guided therapy. | Manns 2014a[127] |
| PTV/RTV+DSV | | | | | | |
| 63 | Poordad (2013) | Phase II, non-randomised, open-label study | Patients with CHC GT1 who were TN and NR, and NC | PTV (150/250 mg)/RTV (100 mg) + DSV + RBV | | Poordad 2013[128] |
| SMV | | | | | | |
| 64 | QUEST-1 | Randomised, double blind study | Patients with CHC GT1 who were TN and had no hepatic decompensation | SMV (150 mg) once daily for 12 weeks + IFN + RBV for 24 or 48 weeks | IFN + RBV + Placebo for 48 weeks | Jacobson 2014[129] |
| 65 | QUEST-2 | Randomised, double blind study | Patients with CHC GT1 who were TN and had no hepatic decompensation | SMV (150 mg) once daily for 12 weeks + IFN + RBV for 24 or 48 weeks | IFN + RBV + Placebo for 48 weeks | Manns 2014b[130] |
| 66 | RESTORE | Single-arm, open-label study | Patients with CHC GT4 who were TN and TE and | SMV | N/A | Moreno 2015[131] |

| No. | Trial | Trial design | Population | Intervention | Comparator(s) | Reference(s) |
|---|---|---|---|---|---|---|
| | | | had no hepatic decompensation | | | |
| 67 | PILLAR | Randomised, double blind study | Patients with CHC GT1 who were TN and NC | SMV (75/150 mg) for 12 or 24 weeks + IFN + RBV 24/48 | | Fried 2013[132] |
| 68 | OPERA-1 | Randomised, double blind study | Patients with CHC GT1 who were TN and TE, and NC | SMV (25/75/150/200 mg) | | Manns 2011[133] |
| 69 | ASPIRE | Randomised, double blind study | Patients with CHC GT1 who were TE, cirrhosis status was not reported | SMV (100/150 mg) for 12, 24 or 48 weeks + IFN + RBV for 48 weeks | | Zeuzem 2014c[134] |
| 70 | PROMISE | Randomised, double blind study | Patients with CHC GT1 who were TE and had no hepatic decompensation | SMV (150 mg) once daily for 12 weeks + IFN + RBV for 24 or 48 weeks | IFN + RBV + Placebo for 48 weeks | Forns 2014[135] |
| ASV/DCV | | | | | | |
| 71 | Hallmark QUAD | Single-arm, open-label study | Patients with CHC GT1 who were TE, patients with CC were permitted | ASV/DCV + IFNα-2a + RBV for 24 weeks | N/A | Jensen 2015[136] |
| 72 | Everson (2014) | Randomised, open-label study | Patients with CHC GT1/4 who were TN and NC | ASV (200 mg)/DCV (30/60 mg) + BMS-791325 (75/150mg) +/- RBV | | Everson 2014[137] |

Source: CS Appendix D, Table 123, page 16.

ASV = asunaprevir; CC = compensated cirrhosis; DCV = daclatasvir; DSV = dasabuvir; EBR = elbasvir; FDC = fixed dose comparison; GT = genotype; GZR = grazoprevir; IFN = interferon; LDV = ledipasvir; NC = non-cirrhotic; NR = non-responder = OBV = ombitasvir; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SC = subcutaneously; SMV = simeprevir = SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naïve; TVR = telaprevir; VEL = velpatasvir

**Table 4.16: SVR12 rates for all included treatments**

| Geno -type | Treatment (duration in weeks) | | | |
|---|---|---|---|---|
| | TN | | TE | |
| | NC | CC | NC | CC |
| 1 | • G/P (8): [redacted]<br>• SOF/VEL (12): 98.4% (251/255)[e]<br>• EBR/GZR[a] (12[d]): 93.2%[c]<br>• SOF/LDV (8): F0–F1: 95.2% (80/84); F2–F3: 94.4% (68/72)<br>• OBV/PTV/RTV + DSV ± RBV(12): [redacted][c]<br>• Best supportive care (watchful waiting): 0%* | • G/P (12): [redacted]<br>• SOF/VEL (12): 98.6% (72/73)[e]<br>• EBR/GZR[a] (12[d]): 95.9%[c]<br>• SOF/LDV (12): 94.1% (32/34)<br>• OBV/PTV/RTV + DSV ± RBV (12/24): 96.4%[c]<br>• Best supportive care (watchful waiting); 0%* | • G/P (8): [redacted]<br>• SOF/VEL (12): 98.4% (251/255)[e]<br>• EBR/GZR[a] (12): 93.4%[c]<br>• SOF/LDV (12): 95.4% (83/87)<br>• OBV/PTV/RTV + DSV ± RBV (12): 97.4%[c,i]<br>• Best supportive care (watchful waiting): 0%* | • G/P (12): [redacted]<br>• SOF/VEL (12): 98.6% (72/73)[e]<br>• EBR/GZR[a] (12): 93.2%[c]<br>• SOF/LDV (12): 86.4% (19/22)<br>• OBV/PTV/RTV + DSV ± RBV (12/24): 98.5%[c,i]<br>• Best supportive care (watchful waiting): 0%* |
| 2 | • G/P (8): [redacted]<br>**Comparators for IFN-eligible patients:**<br>• Peg-IFN + RBV (24): 81.5% (44/54)<br>• Best supportive care (watchful waiting): 0%*<br>**Comparators for IFN-ineligible patients:**<br>• SOF/VEL (12): 99.0% (99/100)[e]<br>• SOF + RBV (12): 96.3% (180/187)<br>• Best supportive care (watchful waiting): 0%* | • G/P (12): [redacted]<br>**Comparators for IFN-eligible patients:**<br>• SOF/VEL (12): 100.0% (15/15)[e]<br>• Best supportive care (watchful waiting): 0%*<br>**Comparators for IFN-ineligible patients:**<br>• SOF/VEL (12): 100.0% (15/15)[e]<br>• SOF + RBV (12): 89.7% (26/29)<br>• Best supportive care (watchful waiting): 0%* | • G/P (8): [redacted]<br>• SOF/VEL (12): 100.0% (15/15)[e]<br>• SOF + RBV (12): 88.5% (69/78)<br>• Best supportive care (watchful waiting): 0%* | • G/P (12): [redacted]<br>• SOF/VEL (12): 100.0% (4/4)[e]<br>• SOF + RBV (12): 77.3%<br>• Best supportive care (watchful waiting): 0%* |
| 3 | • G/P (8): 94.9% (149/157)<br>• SOF/VEL (12): 98.2% (160/163)<br>• SOF + DCV (12): 96.8% (184/190) | • G/P (12): [redacted]<br>• SOF/VEL (12): 96.7% (116/120)<br>• SOF + DCV + RBV (24): 100% (5/5) | • G/P (8): 95.5% (21/22)<br>• SOF/VEL (12): 91.2% (31/34)<br>• SOF + DCV (12): 94.1% (32/34) | • G/P (12): [redacted]<br>• SOF/VEL (12): 89.9% (62/69)<br>• SOF + DCV + RBV (24): 100% (5/5)[k] |

| Geno -type | Treatment (duration in weeks) | | | |
|---|---|---|---|---|
| | TN | | TE | |
| | NC | CC | NC | CC |
| | • Best supportive care (watchful waiting): 0%* | • SOF + peg-IFN + RBV (12): 91.3% (21/23)<br>• SOF + RBV (24): 77.6% (45/58)<br>• Best supportive care (watchful waiting): 0%* | • SOF + peg-IFN + RBV (12); NR<br>• Best supportive care (watchful waiting): 0%* | • SOF + peg-IFN + RBV (12): 85.7% (30/35)<br>• SOF + RBV (24): 59.0% (49/83)<br>• Best supportive care (watchful waiting): 0%* |
| **4** | • G/P (8): [redacted]<br>• SOF/VEL (12): 100.0% (89/89)[e]<br>• EBR/GZR[a] (12[d]): 100.0% (16.71/16.71)[g]<br>• OBV/PTV/RTV + RBV (12): 100.0% (42/42)[c, f]<br>• Best supportive care (watchful waiting): 0%* | • G/P (12): [redacted]<br>• SOF/VEL (12): 100.0% (27/27)[e]<br>• EBR/GZR[a] (12[d]): 100.0 (1.29/1.29)[g]<br>• SOF/LDV (12): 100.0% (1/1)<br>• OBV/PTV/RTV + RBV (12)[b]: 96.7% (29/30)[c]<br>• Best supportive care (watchful waiting): 0%* | • G/P (8): [redacted][l]<br>• SOF/VEL (12): 100.0% (89/89)[e]<br>• EBR/GZR[a] (12) 100.0% (3/3)[g]<br>• SOF/LDV (12): 84.6% (11/13)<br>• OBV/PTV/RTV + RBV (12): 100.0% (49/49)[c, i]<br>• Best supportive care (watchful waiting): 0%* | • G/P (12): [redacted][l]<br>• SOF/VEL (12): 100.0% (27/27)[e]<br>• EBR/GZR[a] (12) 66.7% (4/6)[g]<br>• SOF/LDV (12): 100.0% (9/9)<br>• OBV/PTV/RTV + RBV (12): 98.2% (N=29)[c, i, m]<br>• Best supportive care (watchful waiting): 0%* |
| **5** | • G/P (8): [redacted]<br>• SOF/VEL (12): 96.6% (28/29)[e]<br>• Best supportive care (watchful waiting): 0%* | • G/P (12): [redacted]<br>• SOF/VEL (12): 100.0% (5/5)[e]<br>• SOF + peg-IFN + RBV (12): 50% (1/2)[h]<br>• Best supportive care (watchful waiting): 0%* | • G/P (8): [redacted][l]<br>• SOF/VEL (12): 100.0% (11/11)[e]<br>• Best supportive care (watchful waiting): 0%* | • G/P (12): [redacted][l]<br>• SOF/VEL (12): 100.0% (11/11)[e]<br>• SOF + peg-IFN + RBV (12): 50% (1/2)[n]<br>• Best supportive care (watchful waiting): 0%* |
| **6** | • G/P (8): [redacted]<br>• SOF/VEL (12): 100.0% (35/35)[e]<br>• Best supportive care (watchful waiting): 0%* | • G/P (12): [redacted]<br>• SOF/VEL (12): 100.0% (6/6)[e]<br>• SOF + peg-IFN + RBV (12) 50% (1/2)[h]<br>• Best supportive care (watchful waiting): 0%* | • G/P (8): [redacted][l]<br>• SOF/VEL (12): 100.0% (35/35)[e]<br>• Best supportive care (watchful waiting): 0%* | • G/P (12): [redacted][l]<br>• SOF/VEL (12): 100.0% (6/6)[e]<br>• SOF + peg-IFN + RBV (12): 50% (1/2)[n]<br>• Best supportive care (watchful waiting): 0%* |

Source: CS, Tables 59, 65 and 66, pages 148-163.
*) For best supportive care (no treatment), the SVR rate is assumed to be 0% (CS, Page 156)

| Geno -type | Treatment (duration in weeks) | | | |
|---|---|---|---|---|
| | TN | | TE | |
| | NC | CC | NC | CC |

[a]For the sake of simplicity the model assumes all patients receive a 12 week treatment duration without RBV; [b]TA365 for OBV/PTV/RTV ± DSV was published before the results from TURQUOISE-III and AGATE-I became available and the NICE recommendation therefore stipulates the use of OBV/PTV/RTV ± DSV with RBV for GT1b patients with CC, and OBV/PTV/RTV + RBV for GT4 CC patients for 24 weeks. Subsequently, TURQUOISE-III demonstrated the efficacy of treatment with OBV/PTV/RTV + DSV for 12 weeks without RBV in GT1b patients with CC,[78] and AGATE-I demonstrated the efficacy of OBV/PTV/RTV + RBV for 12 weeks in GT4 patients with CC.[73] The licence for OBV/PTV/RTV ± DSV now reflects this. Therefore OBV/PTV/RTV + DSV without RBV for 12 weeks is used as the comparator in the economic analysis of this submission for GT1b patients with CC, and OBV/PTV/RTV + RBV for 24 weeks is used for GT4 CC patients; [c]SVR in GT1 patients is calculated using a weighted average of SVRs in GT1a and GT1b patients, and n/N is not reported; [d]For simplicity, the model assumes all patients receive EBR/GZR for 12 weeks; [e]Data available included the following: (i) SVR data stratified by cirrhosis status for TN and TE patients combined and (ii) overall SVR data stratified by TN and TE patients. The former were used and it was assumed that TN=TE; [f]'RBV-eligible' patients; [g]The number of GT4 NC and CC patients was calculated, assuming the percentage of CC patients was the same between GT4 and GT6 patients. The percentage of CC patients among GT4 and GT6 patients was calculated from the percentage of patients among the GT1, GT4 and GT6 patient population available in the trial publication[85, 88] and the percentage of patients among the GT1 population available in the US package insert.[138] The calculated n/N is reported to 2 decimal places; [h]Data for overall GT4, GT5 and GT6 population; [i]Data are weighted among null response, partial response and prior relapse patients; [k]Assumed to be the same as for TN; [l]There were low numbers of GT4, GT5 and GT6 TE patients recruited, so pooled results from GT4-, GT5- and GT6-infected patients were used; [m]In GT4 F4 where SVR≠100%, only the consolidated 'N' is reported; [n]Assumed to be the same as TN (data for overall GT4, GT5 and GT6 population), same assumption as TA430.[139]

CC = compensated cirrhosis; CSR = clinical study report; DAA = direct-acting antiviral; DCV = daclatasvir; DSV = dasabuvir; EBR = elbasvir; G/P = glecaprevir/ pibrentasvir (300 mg/120 mg); GT = genotype; GZR = grazoprevir; IFN = interferon; ITT = intention-to-treat; ITT-PS = ITT mono-infected GT1 DAA-naïve; LDV = ledipasvir; NC = non-cirrhotic; OBV = ombitasvir; Peg-IFN = pegylated-IFN; PTV = paritaprevir; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; SVR = sustained virologic response; TE = treatment-experienced; TN = treatment-naïve; VEL = velpatasvir.

### *4.4 Critique of the indirect comparison and/or multiple treatment comparison*

The company concludes that it is not feasible to form any network between G/P and any relevant comparator therapies; therefore, an indirect treatment comparison is not possible. The company then suggests the use of matching-adjusted indirect comparison (MAIC). However, this was not considered useful because most active interventions achieve SVR12 rates approaching 100%, requiring large sample sizes to detect any statistically significant differences in SVR12 rates; and because many baseline characteristics, necessary for adjusting response rates, are not available for comparators at subgroup levels.

Ultimately, the company uses naïve indirect comparisons to inform treatment effect estimates. The company acknowledges that this is associated with limitations, but does not describe any of these limitations. In fact, the section in the CS describing the uncertainties in the indirect and mixed treatment comparisons consists of two words: "Not applicable".

The company does not present any information about how response and adverse events for comparator studies were selected; whether all possible sources were used or how results were combined when multiple sources were available. In addition, no results for any of the comparator interventions are described in section B.2 (Clinical Effectiveness). Results of comparator interventions are only reported as inputs for the economic model (Section B3.3 Clinical parameters and variables); here, results for SVR (CS, Tables 65 and 66) and AEs (Tables 68 and 69) are reported without any references to differences between studies, apart from the main subgroup (genotype, TE vs TN, and NC vs CC). In most cases, the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C[139]); in fact the company presents two tables describing inputs that are different from TA430 (CS, Table 64 for SVR rates, and Table 67 for AE rates).

Therefore, the same critique[140] applies as for TA430:

1. The company selected one source for each intervention and population. Choices were often arbitrary and selecting results from a single arm of a study means that results are open to all the risks of bias associated with observational studies.
2. SVR rates are selected from a pool of RCTs retrieved through the company's original search. However, other study designs should have been included in the searches (uncontrolled studies, case series, etc.) because data are taken from individual study arms.
3. Sometimes multiple SVR rates are presented within a study; the choice of one particular SVR rate within a study is arbitrary and therefore subject to bias.

In addition, as described above, the company uses naïve indirect comparisons to inform treatment effect estimates in the economic model. Effect estimates are taken from single arms of included studies. This naïve indirect comparison is not adjusted for any differences between studies because the majority of publications do not provide the breakdown of baseline patient characteristics at the subgroup level (i.e. by genotype, treatment experience and cirrhosis status).

Although the ERG agrees that it is not feasible to form any network between G/P and any relevant comparator therapies and that the limited availability of baseline characteristics for comparator studies precludes an adjusted analysis, it should be taken into account that the results of these naïve indirect comparisons are unreliable.

The DSU describes the recommended methods for population-adjusted indirect comparisons in submissions to NICE in their report NICE DSU TSD 18.[141] On page 56 of TSD 18, the DSU states: '*The size of this systematic error can certainly be reduced, and probably substantially, by appropriate*

*use of MAIC or STC. Much of the literature on unanchored MAIC and STC acknowledges the possibility of residual bias due to unobserved prognostic variables and effect modifiers; however, it is not made clear that the accuracy of the resulting estimates is entirely unknown, because there is no analysis of the potential magnitude of residual bias, and hence no idea of the degree of error in the unanchored estimates. It is, of course, most unlikely that systematic error has been eliminated. Hoaglin,[142, 143] in a series of letters critiquing an unanchored comparison by Di Lorenzo et al.[144] based upon a matching approach similar to MAIC, remarked that, without providing evidence that the adjustment compensates for the missing common comparator arms and the resulting systematic error, the ensuing results 'are not worthy of consideration'.'*[141]

If the results of a poorly performed adjusted simulated treatment comparison based on single arm studies (unanchored) are 'not worthy of consideration', surely the results of a naïve comparison without any attempt at adjustment are even less worthy of consideration.

### *4.5 Additional work on clinical effectiveness undertaken by the ERG*

An ideal approach would be to present results separately for head-to-head comparisons with other active comparators. However, only one of the studies used in the economic model included an active comparator: the ENDURANCE-3 trial. However, ENDURANCE-3 included three arms (G/P-12w, SOF+DCV-12w and G/P-8w) and patients were randomised to two of the three arms: G/P-12w versus SOF+DCV-12w. After enrolment in these two arms was complete, new patients were assigned to receive G/P for eight weeks. Therefore, G/P-8w is not part of the randomised comparison and G/P-12w is not in line with the anticipated licence for patients in this trial. This means there is no direct comparative evidence for G/P versus any of the comparators mentioned in the scope, apart from the two CERTAIN trials. Since these trials were in Japanese patients only, these were not considered by the company to be generalisable to the UK population.

As explained in Section 4.2, we will present a summary of the two CERTAIN studies in this section.

#### 4.5.1 CERTAIN-1

The CERTAIN-1 trial (NCT02707952) was a Phase III, partially-randomised, open-label, multicentre study to evaluate the efficacy of G/P in Japanese adults with CHC, composed of two sub-studies.[64-66] The objectives of the study were to determine the safety and efficacy of G/P treatment in CHC.

Sub-study 1 was a randomised study in GT1-infected NC patients. Patients without Y93H polymorphisms were randomised at a 2:1 ratio to receive either eight weeks of treatment with G/P (300 mg/120 mg) or 12 weeks of treatment with OBV/PTV/RTV. All patients with Y93H polymorphisms were enrolled to receive eight weeks of treatment with G/P (300 mg/120 mg).

Sub-study 2 was a non-randomised study in GT1- or GT2-infected CC patients; GT3-, GT4-, GT5-, or GT6-infected NC and CC patients; GT1- or GT2-infected NC and CC patients who had failed prior DAA treatments; and GT1- or GT2-infected patients with severe renal impairment and CC. All patients were enrolled to receive G/P (300 mg/120 mg) for 12 weeks. Finally, GT1- or GT2-infected NC patients with severe renal impairment received G/P (300 mg/120 mg) for eight weeks.

Two hundred and ninety-five patients were enrolled. The primary efficacy endpoint tested the non-inferiority of the SVR12 rate in the eight-week G/P arm to the 12-week OBV/PTV/RTV arm in sub-study 1. The secondary efficacy endpoints were in line with the studies in the previous Section (SVR12 rate in each study arm, percentage of patients with on-treatment virologic failure and post-treatment relapse). Additional outcomes included safety, resistance, and patient reported outcomes (PROs).

In CERTAIN-1, the primary efficacy analysis was the percentage of GT1-infected NC patients in the ITT population of sub-study 1 without Y93H polymorphisms who achieved SVR12. This was 99.1% (two-sided 95% CI 97.2% to 100.0%) following eight weeks of treatment with G/P, and 100% [redacted] following 12 weeks of treatment with OBV/PTV/RTV. Further results for this study are not reported in the company submission. The CSR shows that a SVR12 rate of [redacted] was achieved in HCV GT3-infected patients with compensated cirrhosis or without cirrhosis and with or without prior pegylated IFN/ribavirin experience who were treated with 12 weeks of G/P.[64] This was [redacted].

The fixed-dose combination of G/P 300 mg/120 mg QD administered for eight and 12 weeks was well tolerated by Japanese patients including those without cirrhosis, with compensated cirrhosis, and with severe renal impairment, including those on dialysis. A similar safety profile was observed between HCV GT1-infected, DAA treatment-naïve, Japanese patients treated with either G/P 300 mg/120 mg QD administered for eight weeks or OBV/PTV/RTV QD for 12 weeks. Overall, among patients treated with G/P, the most common (≥ 5.0% of patients) TEAEs were nasopharyngitis, pruritus, and headache.[64]



### 4.5.2 CERTAIN-2

The CERTAIN-2 trial (NCT02723084) was a Phase III, randomised, open-label, multicentre study to evaluate the efficacy of G/P in Japanese NC adults with chronic GT2 HCV infection.[64, 67-69] The objectives of the study were to determine the safety and efficacy of G/P treatment.

GT2-infected NC DAA-TN patients were randomised at a 2:1 ratio to receive G/P (300 mg/120 mg) for eight weeks or SOF + RBV for 12 weeks. 136 patients were enrolled. The primary efficacy endpoint tested the non-inferiority of the SVR12 rate in the eight-week G/P arm to the 12-week SOF + RBV arm. The secondary efficacy endpoints were in line with CERTAIN-1.

In CERTAIN-2, the SVR rate among GT2-infected DAA-TN patients without cirrhosis 12 weeks after treatment with G/P for eight weeks was 97.8% (two-sided 95% CI 94.7% to 100.0%), and 93.5% [redacted] with SOF + RBV for 12 weeks. Further results for this study are not reported in the company submission.

The fixed dose combination of G/P 300 mg/120 mg QD administered for eight weeks was well tolerated by Japanese patients with HCV GT2 infection without cirrhosis. Patients treated with G/P treatment had fewer overall TEAEs and TEAEs related to treatment compared to SOF + RBV treatment. Patients treated with SOF + RBV had higher rates of anemia, hyperbilirubinemia, and hyperuricemia. Overall among patients treated with G/P, the most common (≥ 5% of patients) TEAEs were nasopharyngitis, headache, and malaise. No TEAE related to treatment was reported in > 5% of patients treated with G/P. The most common (≥ 5% of patients) TEAEs reported among patients receiving SOF + RBV were anemia, blood bilirubin increased, malaise, nasopharyngitis, nausea, stomatitis, and hyperuricemia. TEAEs related to SOF + RBV reported in > 5% of patients included anemia and blood bilirubin increased. The higher rates of these events related to SOF + RBV are likely due to the effect of RBV.[69]

## *4.6 Conclusions of the clinical effectiveness section*

The conclusion from the G/P studies is that G/P has high SVR rates in all genotypes. In addition, G/P has a relative favourable safety and tolerability profile. However, patient numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each subgroup. Only three out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC and GT2/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

The main concern regarding clinical effectiveness is that data (for SVR12 and AEs) for G/P and comparators were taken from single arms. Therefore, the comparisons for SVR12 rates and AEs between G/P and comparators relies on a naïve indirect comparison. The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how response and adverse events for comparator studies were selected and whether all possible sources were used. In most cases, the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C[139]). Therefore, the same critique as for TA430 applies: these methods increase the chance of bias and cherry-picking.

# 5. COST EFFECTIVENESS

## *5.1 ERG comment on company's review of cost effectiveness evidence*

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the CS: measurement and evaluation of health effects; and cost and healthcare resource identification, measurement and valuation.

### 5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the CS.

**Searches for cost effectiveness analysis review**

A systematic literature review was conducted to identify evidence to support the cost and cost effectiveness of novel DAAs for HCV. The systematic literature review was undertaken in April 2017 and was an update to the systematic literature review performed for TA430.[139] No date limits were indicated in the search strategies, but it was stated in Appendix G that databases were searched from 2016 to present.[16] There were no language limits. Searches were carried out in PubMed, Embase, Tufts Cost Effectiveness Analysis (CEA) Registry, HTA database, NHS EED and EconLit. In addition, supplementary searches were undertaken from 2016 to present in AASLD, EASL, ISPOR, The Viral Hepatitis Congress and the Asian Pacific Association for the Study of the Liver.

**ERG comment:** In response to a clarification question about the correct PRISMA figures for the cost effectiveness Embase search, the company confirmed that an incorrect search strategy had been submitted in error and the correct strategy was consequently presented.

The ERG noted that a UK country search filter had been added to the updated Embase and PubMed strategies, and were concerned that a number of relevant records may have been missed as the filter was not sufficiently comprehensive to have picked up all UK records. The ERG also noted that the updated Embase search strategy continued to make ineffective use of parentheses and lacked relevant EMTREE terms. It is therefore possible that relevant evidence has still been missed.

The ERG commented that PubMed searches may have used wildcard symbols which were not supported by PubMed and therefore results may have been compromised. In response the company re-ran searches but no new records were identified.

The ERG felt the use of a cost filter was unnecessarily restrictive to be applied in the Cochrane Library which is a study design specific resource. Consequently, the company re-ran searches in the HTA database and NHS EED without a cost filter. This resulted in two new records, neither of which were relevant.

**Measurement and valuation of health effects**

A separate systematic literature search was conducted for health-related quality-of-life benefits of DAAs for HCV and was reported in detail in Appendix H.[16] Searches were undertaken in PubMed, Embase, EconLit, CDSR, DARE, CENTRAL, HTA database and NHS EED from 2016 to April 2017. As before, this systematic literature review was an update of TA430.[139] In addition, supplementary searches for conference proceedings from 2016 to present were conducted in AASLD, EASL, ISPOR, The Viral Hepatitis Congress and the Asian Pacific Association for the Study of the Liver.

**ERG comment:** The ERG raised an issue in the clarification letter that findings in Embase searches in Appendix H for health-related quality of life studies were unexpectedly low (n=321) and that this was most likely the result of a Boolean NOT operator being applied inappropriately.[13] The company explained that this number was a test set and that screening was done on a full set.[17] However, the PRISMA flowchart indicates that 321 Embase results were screened for health-related quality of life studies and the response to clarification did not provide further evidence or additional numbers for the full set of Embase results. The ERG remains unconvinced that this search was run adequately and it therefore remains possible that evidence has been missed.

**Cost and healthcare resource identification, measurement and valuation**

A systematic literature review was conducted on resource use of novel DAAs for HCV from 2016 to April 2017 on PubMed, Embase, EconLit, CDSR, DARE, CENTRAL, HTA database and NHS EED. As with previous sections, supplementary searches for conference proceedings were undertaken from 2016 to present in AASLD, EASL, ISPOR, The Viral Hepatitis Congress and the Asian Pacific Association for the Study of the Liver. The searches were an update of TA430 as the research question was the same for both appraisals.[16, 139]

**ERG comment:** In response to queries about the use of wildcard characters which are not supported in PubMed, the company re-ran PubMed searches in Medline (Ovid). A more comprehensive UK country filter was applied in this search and the ERG was satisfied that most UK records were likely to have been found. An English language limit was also applied and, although this is not recommended practice, the company was looking specifically for UK records, so it is likely that no relevant records were missed with this limit.

### 5.1.2 Inclusion/exclusion criteria used in the study selection

The eligibility criteria for the economic systematic literature review were summarised in Table 213 from the Appendix G of the company submission.[16] The eligibility criteria for inclusion/exclusion can be classified into six main classes as below:

- Language: only studies in English language are included.
- Study design: cost-consequence, cost-minimisation, cost effectiveness, cost-utility and cost-benefit studies are included. Review studies, letters to the editors or other comments are excluded.
- Population: studies with chronically infected HCV adult patients (older than 18 years old) with genotypes 1 to 6 are included.
- Interventions: Following IFN free regimens: G/P, SOF/VEL, EBR/GZR (with or without RBV), LDV/SOF (with or without RBV), OBV/PTV/RTV (with or without RBV), OBV/PTV/RTV+DSV (with or without RBV), DCV/SOF (with or without RBV), SOF/RBV and following IFN-containing regimens are included: DCV/PR, SMV/PR, SOF/PR and PR. Other DAA combinations, with or without PR are excluded.
- Outcomes: no exclusion based on outcomes
- Comparators: no exclusion based on comparators

**ERG Comments:** The ERG considers the eligibility criteria suitable for the objective of the company literature review.

### 5.1.3 Included/excluded studies in the cost effectiveness review

Seven studies were identified from the electronic database and conference proceeding abstract search described in Section 5.1.1. The number of excluded studies and their reasons of exclusion were summarised in the PRISMA diagram given in Figure 32 (Appendix G of the CS). Two recent NICE TAs, TA430 and TA413 were also included, which resulted in nine cost effectiveness studies published after 2016.[139, 145-152]

The summary and quality assessment of these nine studies, together with the studies identified by the SLR performed for TA430, were provided in Table 214 and in Table 215 from the Appendix G of the CS. None of these identified studies evaluated the cost effectiveness of G/P. Due to the lack of studies on the cost effectiveness of G/P, the company suggested that a de novo analysis was required.

Also, even though they were not identified in the SLR, the company provided a brief summary for the following three UK based cost effectiveness studies: Wright et al. (2006), Shepherd et al. (2007) and Hartwell et al. (2011).[153-155] These studies guided the company in the development of model structure and selection of inputs.

**ERG comment:** The cost effectiveness literature review in this submission was conducted as an update of the systematic literature review (SLR) conducted in TA430. This approach is based on a full reliance on the SLR results in TA430, not only in terms of search strategy but also the review process and reviewers. The ERG considers that this approach might be prone to missing/excluding potentially relevant articles that were missed/excluded in TA430.

Furthermore, it was not clear to the ERG how the three UK based cost effectiveness studies (Wright et al. 2006, Shepherd et al. 2007 and Hartwell et al. 2011) were identified.[153-155] The ERG has doubts if these were the only UK based cost effectiveness analyses that could have informed the CS model structure/choice of inputs and considers that the selection of these studies could have been based on a systematic, reproducible procedure.

### 5.1.4 Conclusions of the cost effectiveness review

No specific conclusions from the economic review were provided in the CS. The ERG considers that the identified studies might contain valuable information regarding costs, utilities and model structure, but that they do not negate the necessity of developing a de novo model for the current comparison.

## *5.2 Summary and critique of company's submitted economic evaluation by the ERG*

Table 5.1 presents a summary of the *de novo* economic model developed by the company.

**Table 5.1: Summary of the company submission economic evaluation**

| | Approach | Source/Justification | Signpost (location in CS) |
|---|---|---|---|
| **Model** | A cost effectiveness model that consist of a Markov cohort model describing the long-term disease progression of chronic HCV. The model takes into account the main efficacy outcome SVR12, as evaluated in the clinical trials. The same model structure is used for all subpopulations. Patients initiated treatment at the start of the first year. | The economic model aimed to reflect the clinical pathway of care for patients with chronic HCV. The modelling approach is in line with the modelling approaches in previous NICE technology assessments. [145, 156] | Section B.3.2.2 |
| **Sub populations** | Twenty-six subpopulation groups were considered based on categories below:<br>• genotypes: GT1, GT2, GT3, GT4, GT5 and GT6<br>• treatment-naïve (TN) and treatment-experienced (TE).<br>• cirrhotic (C) and non-cirrhotic (NC)<br>• IFN eligibility (only for GT2 and TN patients)<br>This categorisation resulted in the following subpopulations:<br>1. GT1, TN, C<br>2. GT1, TN, NC<br>3. GT1, TE, C<br>4. GT1, TE, NC<br>5. GT2, TN, C, IFN eligible<br>6. GT2, TN, C, IFN ineligible<br>7. GT2, TN, NC, IFN eligible<br>8. GT2, TN, NC, IFN ineligible<br>9. GT2, TE, C<br>10. GT2, TE, NC<br>11. GT3, TN, C<br>12. GT3, TN, NC<br>13. GT3, TE, C<br>14. GT3, TE, NC<br>15. GT4, TN, C<br>16. GT4, TN, NC<br>17. GT4, TE, C | These subgroups were considered because of the differences in effectiveness and treatment duration of G/P between these subgroups, as well as the list of comparators and their effectiveness for each subgroup. | Section B.3.2.1 |

| | Approach | Source/Justification | Signpost (location in CS) |
|---|---|---|---|
| | 18. GT4, TE, NC<br>19. GT5, TN, C<br>20. GT5, TN, NC<br>21. GT5, TE, C<br>22. GT5, TE, NC<br>23. GT6, TN, C<br>24. GT6, TN, NC<br>25. GT6, TE, C<br>26. GT6, TE, NC | | |
| **States and events** | The model consists of 13 health states. F0-F3 are noncirrhotic states and F4 was considered as cirrhotic state.<br>• No HCV<br>• F0: no fibrosis<br>• F1: portal fibrosis without septa<br>• F2: portal fibrosis with septa<br>• F3: portal fibrosis with numerous septa<br>• F4: compensated cirrhosis<br>• SVR, history of mild fibrosis (F0-F1)<br>• SVR, history of moderate fibrosis (F2-F3)<br>• SVR history of compensated cirrhosis (F4)<br>• DC: decompensated cirrhosis<br>• HCC: Hepatocellular carcinoma<br>• LT: Liver transplant (differentiated to first and subsequent years)<br>• LV-Death: Liver related death associated with DC, HCC or liver transplantation<br>• LV unrelated death<br>Non-cirrhotic patients start from states F0-F3, and cirrhotic patients start from F4. All treatment related outcomes (achieving SVR, treatment related adverse events and discontinuation) occur within the first year of the model. Patients who do not achieve SVR are at risk of progressing to more severe states. Patients who reached F4 can progress to DC and HCC states, which may lead to liver transplantation and liver related death. | Health states were based upon disease severity and treatment effect. The treatment determines the SVR, adverse event and discontinuation probabilities. | Section B.3.2.2 |

| | Approach | Source/Justification | Signpost (location in CS) |
|---|---|---|---|
| | Liver transplantation state was divided into two categories (first year and later years). | | |
| **Comparators** | Comparators differ for each of the subpopulation.<br>EBR/GZR (EBR and GZR 12w; subpopulations 1-4, 15-18)<br>BSC-watchful waiting (subpopulations: 1-26)<br>SOF/VEL (12 w, subpopulations: 1-6,8-26)<br>LDV/SOF (8w, subpopulation 2; 12w, subpopulations 1, 3, 4, 15, 17 and 18)<br>OBV/PTV/DSV+DSV ± RBV (12 w or 24w, subpopulations 1-4 and 15-18)<br>PR (24 w, subpopulation 7)<br>SOF/RBV: (12w, subpopulations: 6 and 8-10; 24w, subpopulations 11 and 13)<br>DCV/SOF: (12w, subpopulations 12 and 14)<br>DCV/SOF/RBV (24 w, subpopulations 11 and 13)<br>SOF/PR (12w, subpopulations 11, 13 and 14) | They are mainly based on licensed indications and NICE recommendations, however in the submission not all comparators mentioned in the final scope were included. Some of the comparators in the NICE final scope (e.g. PR) were excluded based on expert advice from English clinicians as well as the June 2017 Eastern Liver Network Hepatitis C Guidelines (v8.1).[157] | Section B.3.2.3 |
| **Natural history** | Natural history is based on how disease progresses when a patient does not reach SVR. | The progression rates between F0 and F4 were based on Thein et al. 2008, which is a systematic review and meta-analysis providing state specific progression rates.[158] GT specific hazard ratios from Kanwal et al. 2014 were applied.[159] Transition probabilities after DC are based on Cardoso et al. 2010 (transition to HCC from the recovered state) and Fattovich et al. 1997 (for all other transitions).[160] | Section B.3.3.3 |
| **Treatment effectiveness** | Treatment influences the probability of reaching SVR, adverse events and discontinuation. | SVR, adverse event and discontinuation probabilities were based on naïve indirect comparison of clinical trials assessing the | Section B.3.3.2 |

| | Approach | Source/Justification | Signpost (location in CS) |
|---|---|---|---|
| | | efficacy of G/P and its comparators in the relevant subgroups. | |
| **Adverse events** | The adverse events considered in the economic model were anaemia, neutropaenia, rash, depression and thrombocytopenia. Only the cost consequences of these events were modelled. | These adverse events were selected by the company according to their frequency and impact on costs. | Section B.3.5.3 |
| **Health-related QoL** | The model uses state based utilities from the literature (utilities that were used in Wright et al. and Ratcliffe et al. 2002).[161] A utility increment due to SVR is applied based on Shepherd et al. 2007 and Hartwell et al. 2011.[154]<br>Treatment-related health utility changes were applied to adjust for the impact on HRQoL of treatment, e.g. due to adverse events. | Those state-based health utility values were used in previous submissions. | Section B.3.4 |
| **Resource utilisation and costs** | Treatment cost (e.g. technology acquisition and administration costs of G/P and other comparators, monitoring costs and tests) and health state costs (disease management costs based on disease stage) and other costs for adverse events. | Based on literature, expert opinion and UK reference costs and previous appraisals (especially TA430). | Section B.3.5 |
| **Discount rates** | A 3.5% discount rate was used for both costs and effects. | According to NICE reference case. | Section B.3.2.2 |
| **Sensitivity analysis** | One-way deterministic sensitivity analysis, scenario analyses and probabilistic sensitivity analysis | Ranges based on observed confidence intervals and assumptions. | Section B.3.8 |

AE: Adverse event; BSC: best supportive care; C: cirrhosis; DC: Decompensated cirrhosis; DCV: daclatasvir; EBR: Elbasvir; F: Fibrosis; GT: genotype; GZR: grazoprevir; HCC: Hepatocellular carcinoma; HCV: hepatitis C virus; LDV: ledipasvir; LT: liver transplantation; NC: non-cirrhosis; NHS: National Health Services; PLT: post-liver transplantation; PR: pegylated interferon and ribavirin; SOF: sofosbuvir; SVR: sustained virological response; TE, treatment-experienced; TN, treatment-naïve; w: week; WTP, willingness to pay; CS = Company submission; NICE = National Institute for Health and Care Excellence; QALY = National Institute for Health and Care Excellence; TA = Technology Appraisal; UK = United Kingdom.

### 5.2.1 NICE reference case checklist (TABLE ONLY)

**Table 5.2: Comparison of company submission model to the NICE reference case**

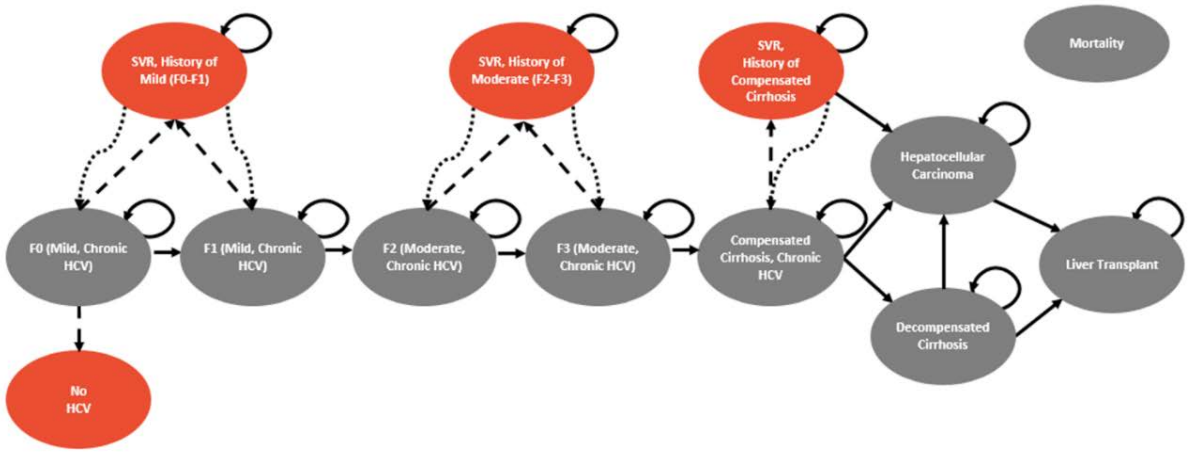
| Elements of the economic evaluation | Reference Case | Included in submission | Comment on whether de novo evaluation meets requirements of NICE reference case |
|---|---|---|---|
| **Comparator(s)** | Therapies routinely used in the NHS, including technologies regarded as current best practice | No | Some of the treatments specified in the final scope were excluded based on clinic experts and Eastern Liver Network Hepatitis C Guidelines (v8.1).[157] |
| **Type of economic evaluation** | Cost effectiveness analysis | Yes | Half-cycle correction not considered in the analysis. |
| **Perspective on costs** | NHS and PSS | Yes | |
| **Perspective on outcomes** | All health effects on individuals | Yes | |
| **Time horizon** | Sufficient to capture differences in costs and outcomes | Yes | |
| **Synthesis of evidence in outcomes** | Systematic review | Yes/partially | Most parameters were based on systematic review; however, comparative effectiveness is based on naïve indirect comparison. Some parameters were identified by a non-systematic search (referring to previous appraisals). |
| **Measure of health effects** | QALYs | Yes | |
| **Source of data for measurement HRQoL** | Reported directly by patients and/or carers. | Yes | |
| **Source of preference data for valuation of changes in HRQoL** | Sample of public | Yes | |
| **Discount rate** | Annual rate of 3.5% on costs and health effects | Yes | |
| **Equity weighting** | No special weighting | Yes | |
| **Sensitivity analysis** | Probabilistic sensitivity analysis | Yes | |

HRQoL = Health-related Quality of Life; NHS = National Health Services; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = Quality-adjusted Life Year

### 5.2.2 Model structure

A cohort Markov state-transition model was developed for this submission. The structure of the model relied on published models of the natural history of HCV infection, including a model previously developed by the company for 2D or 3D for the NICE technology appraisal TA365.[145, 155, 156, 162] The model structure is depicted in Figure 5.1, where "recovered" health states are represented by red ellipses, "non-recovered" health states by grey ellipses, solid arrows represent transitions between health states, hashed arrows depict the possibility of achieving SVR, and dotted arrows depict a potential re-infection. However, as explained below, not all potential transitions depicted in Figure 5.1 are possible in practice.

**Figure 5.1: Post-treatment, natural disease progression phase schematic**




DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; HCV = hepatitis C Virus; LT = liver transplant; SVR = sustained virologic response. Source: Figure 15 in the CS.[2]

Further assumptions made by the company regarding the economic model's structure are summarised below.

#### Treatment phase

In the initial treatment phase of the model, the efficacy of the initial antiviral treatments is captured by estimating the proportion of patients who achieve SVR. The model distinguishes between non-cirrhotic (NC) and cirrhotic patients. NC patients are further stratified by fibrosis severity (F0– F3). The model assumes that all cirrhotic patients in the treatment phase have compensated cirrhosis (CC). This is because G/P is not licensed for use in patients with decompensated cirrhosis (DCC). Initially, all patients are on treatment for the first cycle (one year) of the model. Since the duration of all HCV treatments is short (e.g. 8–16 weeks for G/P), it is assumed that all direct treatment-related costs and effects are captured within the first cycle. The company's model also assumes that patients cannot progress or die in the weeks while on treatment. This is in line with previous HCV models.[147, 156] Patients for whom treatment is deemed successful are assumed to achieve SVR. Otherwise, they are assumed to be at risk of progressive liver disease as if they were untreated.[153]

#### Natural history phase

The natural history phase of the model considers the lifetime disease progression of patients with HCV. The company assumed that spontaneous remission of HCV was not possible. Thus, the transition probability from F0 to "no HCV" is zero in the model. This assumption was justified on page 144 in the CS due to the "*low probability of spontaneous clearance of HCV infection*".[2] The model also assumes that patients achieving SVR enter one of three possible "recovered" health states, depending

on their fibrosis history (SVR with history of mild [F0–F1] fibrosis, SVR with history of moderate [F2–F3] fibrosis, or SVR with history of CC [F4]). Patients who enter the mild or moderate "recovered" health states are assumed to remain there until they die (i.e. the re-infection probability is assumed zero). Thus, patients who achieve SVR with a history of mild or moderate CHC cannot progress to more severe liver disease health states. This assumption is supported by clinical data.[163-168] However, patients with a history of CC, even after achieving SVR, can still transition to the HCC health state. This assumption is also based on clinical evidence.[167-172] Patients who do not achieve SVR are considered as if they were untreated and can remain in the ("non-recovered") health states (defined by their fibrosis history) or progress to more severe disease health states (DCC, HCC, and liver transplant [LT]). Finally, death is also included as a health state in the model and it can be reached from any other health state. It is defined by general mortality rates based on national life tables.[173] In addition, liver-related death is possible from the DCC, HCC and LT health states only, as these states are considered to have increased mortality risks.[154, 155, 174, 175]

**Re-infection and onward transmission**

The company's model does not include the probability of re-infection (dotted arrows in Figure 5.1) and the risk of onward transmission. This approach was previously accepted by NICE.[176]

**ERG comment:** The model structure in the CS is in line with the clinical pathway of care for CHC. Deviations from this, such as not modelling subsequent lines of treatment, have been explained by the company. It is also in line with previous economic models submitted to NICE (TA364 and TA413),[147, 177] where four mild/moderate fibrosis health states of increasing METAVIR scores, CC, DCC, HCC, LT and death are included in the model structure.

Patients who do not achieve SVR are considered as if they were untreated,[153] although in clinical practice these patients may receive further lines of treatment. The company claimed on page 144 of the CS that the "*re-treatment pathway is not well-defined*" and the assumptions required to model re-treatment would result in additional uncertainty to the model results.[2] The ERG considers the first part of the sentence unclear and, while agreeing with the second part, additional uncertainty should be captured in the probabilistic analyses. The company also mentions that, since the success rates of treatment are high, the proportion of patients who experience treatment failure is low. Therefore, the company does not expect this to have a major impact on the model results. While the ERG agrees with this, it should be emphasised that this applies to the deterministic results. Not including further lines of treatments is likely to underestimate the overall uncertainty in the company's model. In the context of cost effectiveness analyses with multiple comparators this might have significant consequences on the probabilistic results. Nevertheless, the assumption of not modelling further lines of treatment is consistent with economic models that have been previously appraised by NICE.[139, 147, 156]

Patients who do not achieve SVR can progress to more severe disease health states (DCC, HCC, and liver transplant [LT]). In line with previous models, DCC is modelled as a single health state,[145, 155, 162, 178] although the company acknowledged in their submission (page 144) that "*DCC can present simultaneously in multiple forms in any individual patient*".[2] This is a limitation of the current modelling approach, which does not account for patient heterogeneity. Two separate health states are considered for HCC: one for the first year and one for subsequent years. However, the input parameters associated to these health states are the same in all economic analyses. Therefore, in practice there is no distinction between the two health states. Patients with DCC or HCC may transition to LT. The LT probability of death is different for the first year and for subsequent years and it is modelled as two different health states.

In line with previous approaches accepted by NICE,[176] the company did not include onward transmission and the probability of re-infection in their cost effectiveness model. The ERG agrees with the company that modelling onward transmission would not fit into a common Markov model. However, re-infection probabilities have been excluded from the model without any proper justification. The company claims (on page 145 in the CS) that including onward transmission in the model is likely to result in lower ICERs for active treatments,[2] in particular, for those that are most effective and for which onward transmission would be most reduced. In contrast, re-infection is likely to result in higher ICERs for active treatments since patients who achieved SVR would be in risk of advancing to more severe health states without the possibility of re-achieving SVR (given that subsequent therapies are not included in the model). The company also refers to Madin-Warburton et al. 2016 where it is shown that "*there is a net positive impact on cost effectiveness in a dynamic transmission model for treatment of HCV infection of incorporating both re-infection and onward transmission*".[179] Based on these, the company concluded (on page 145 in the CS) that their model "*may represent a conservative approach that under-estimates the cost effectiveness of active treatments including G/P*".[2] While this conclusion might be correct, the ERG considers that it is not possible to determine the extent to what this approach is indeed conservative or not.



### 5.2.3 Population

The patient population considered in the company's economic analyses was adults with CHC. Results are presented for 26 different subgroups, which are characterised by HCV genotype, treatment history and fibrosis status. There are six different HCV genotypes (GT1-GT6), each with different characteristics (see also Section 2 of this report). Treatment history distinguishes between treatment-naïve and treatment-experienced patients where the latter are defined as patients who have not adequately responded to prior IFN/RBV-based treatment with or without SOF. This is in line with the clinical trial programme of G/P (see Section B.2 in the CS).[2] Fibrosis status considers non-cirrhotic patients (i.e. patients with METAVIR score F0-F3) and patients with compensated cirrhosis (i.e. patients with METAVIR score F4). Analyses for IFN-ineligible versus IFN-eligible patients are conducted for GT2 treatment-naïve patients only. However, it should be noted that the only differences between the IFN-eligible and IFN-ineligible patients are the comparators considered for the economic analyses, i.e. the SVR or AE rates are not adjusted according to IFN-eligibility. Furthermore, GT1a and GT1b subgroups are not differentiated in the company's model. A summary of the subgroups included in the CS is presented in Table 5.3.

**Table 5.3: Population subgroups considered in the company's economic analyses**

| HCV genotype | Treatment-naïve | | Treatment-experienced | |
|---|---|---|---|---|
| | Non-cirrhotic | Compensated cirrhosis | Non-cirrhotic | Compensated cirrhosis |
| GT1 | ✓ | ✓ | ✓ | ✓ |
| GT2 | IFN-eligible: ✓<br>IFN-ineligible: ✓ | IFN-eligible: ✓<br>IFN-ineligible: ✓ | ✓ | ✓ |
| GT3 | ✓ | ✓ | ✓ | ✓ |
| GT4 | ✓ | ✓ | ✓ | ✓ |
| GT5 | ✓ | ✓ | ✓ | ✓ |
| GT6 | ✓ | ✓ | ✓ | ✓ |

Source: Table 56 in the CS.[2]
GT = genotype; IFN = interferon

The baseline characteristics used in the base-case health economic analyses were obtained from the Adelphi Chart Tracking Study, a market research performed amongst 75 specialist healthcare professionals in the UK.[180] The results of the study are summarised in Table 5.4.

**Table 5.4: Baseline characteristics**

| Variable | Treatment-naïve | | Treatment-experienced | | Source |
|---|---|---|---|---|---|
| | Non-cirrhotic | Compensated cirrhosis | Non-cirrhotic | Compensated cirrhosis | |
| Age (years) | 43 | | 45 | | Adelphi Research UK (2017)[180] |
| Male (%) | 66 | | 71 | | |
| F0 (%) | 35.9 | 0 | 32.1 | 0 | |
| F1 (%) | 45.7 | 0 | 33.6 | 0 | |
| F2 (%) | 14.7 | 0 | 23.2 | 0 | |
| F3 (%) | 3.8 | 0 | 11.1 | 0 | |
| F4 (%) | 0 | 100 | 0 | 100 | |

Source: Table 61 and 62 in the CS.[2]
F = fibrosis severity (METAVIR score)

**ERG comment:** The population considered in the company's economic analyses is in line with the NICE scope. The rationale for including (or excluding) subgroups in the analyses is described in Section 3.5 of this report.

Distinction based on IFN-eligibility was only considered for GT2 TN patients. This was because GT2 is the genotype in which the SOF/VEL recommendation is restricted on the basis of IFN-eligibility. Therefore, the company considered that GT2 is the genotype for which the question of IFN-eligibility remains a key consideration. However, treatment and patient characteristics and costs are assumed to be the same regardless of IFN-eligibility. The only difference in the economic analyses was the comparators included in the analysis. Furthermore, the clinical trials for G/P did not stratify patients by IFN-eligibility.

The company did not distinguish GT1 patients by subtype (1a and 1b). The company considered that since GT1a and GT1b patients are treated similarly with G/P, and the difference in response between GT1a and GT1b is small, it is unlikely that this becomes a major issue from both a clinical and cost effectiveness perspective. This assumption represents a pragmatic approach, and it has been previously considered acceptable by Evidence Review Groups (ERGs) as part of NICE appraisals in this indication.[176] Moreover, this assumption is also in line with G/P licence.

### 5.2.4 Interventions and comparators

The intervention considered in the company's economic model is G/P, which recently received marketing authorisation from the EMA. The licensed dose is 300 mg/120 mg OD, with the recommended treatment durations shown in Table 5.5. Thus, the intervention is in line with the scope.

**Table 5.5: Treatment duration for licence**

| Patient population | 8 weeks for all genotypes | CC |
|---|---|---|
| TN | GT1,2, 4–6: 8 weeks<br><br>GT3: 16 weeks | 12 weeks for all genotypes |
| TE, previously treated with:<br>Peg-IFN + RBV<br>SOF + peg-IFN + RBV<br>SOF + RBV | 8 weeks for all genotypes | GT1, 2, 4–6: 12 weeks<br><br>GT3: 16 weeks |
| Source: Table 58 in CS.[2]<br>CC, compensated cirrhosis; GT, genotype; NC, non-cirrhotic; peg-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve | | |

The company determined the comparators included in the economic analyses based on "*consideration of NICE-approved treatments for CHC, expert advice from English clinicians, and the June 2017 Eastern Liver Network Hepatitis C Guidelines (v 8.1)*".[157] These comparators were included in the model as per their marketing authorisations and licensed doses (as recommended by NICE). The comparators considered in the CS are summarised by subgroup genotype in Table 5.6. The included comparators are in line with the scope; however, some of the comparators mentioned in the scope are excluded from the economic analyses.

**Table 5.6: Comparator treatments per subgroup**

| Genotype | Treatment (duration in weeks) | | | |
|---|---|---|---|---|
| | TN | | TE | |
| | NC | CC | NC | CC |
| 1 | SOF/VEL (12)<br>EBR/GZR[a] (12)<br>SOF/LDV (8)<br>OBV/PTV/RTV + DSV (12), 1a: + RBV<br>Best supportive care (watchful waiting) | SOF/VEL (12)<br>EBR/GZR[a] (12)<br>SOF/LDV (12)<br>OBV/PTV/RTV + DSV (12), 1a: (24) + RBV[b]<br>Best supportive care (watchful waiting) | SOF/VEL (12)<br>EBR/GZR[a] (12)<br>SOF/LDV (12)<br>OBV/PTV/RTV + DSV (12), 1a: + RBV<br>Best supportive care (watchful waiting) | SOF/VEL (12)<br>EBR/GZR[a] (12)<br>SOF/LDV (12)<br>OBV/PTV/RTV + DSV (12), 1a: (24) + RBV[b]<br>Best supportive care (watchful waiting) |
| 2 | Comparators for IFN-eligible patients:<br>Peg-IFN + RBV (24)<br>Best supportive care (watchful waiting)<br><br>Comparators for IFN-ineligible patients: | Comparators for IFN-eligible patients:<br>SOF/VEL (12)<br>Best supportive care (watchful waiting)<br><br>Comparators for IFN-ineligible patients:<br>SOF/VEL (12)<br>SOF + RBV (12) | SOF/VEL (12)<br>SOF + RBV (12)<br>Best supportive care (watchful waiting) | SOF/VEL (12)<br>SOF + RBV (12)<br>Best supportive care (watchful waiting) |

| Genotype | Treatment (duration in weeks) | | | |
|---|---|---|---|---|
| | TN | | TE | |
| | NC | CC | NC | CC |
| | SOF/VEL (12)<br>SOF + RBV (12)<br>Best supportive care (watchful waiting) | Best supportive care (watchful waiting) | | |
| 3 | SOF/VEL (12)<br>SOF + DCV (12)<br>Best supportive care (watchful waiting) | SOF/VEL (12)<br>SOF + DCV + RBV (24)<br>SOF + peg-IFN + RBV (12)<br>SOF + RBV (24)<br>Best supportive care (watchful waiting) | SOF/VEL (12)<br>SOF + DCV (12)<br>SOF + peg-IFN + RBV (12)<br>Best supportive care (watchful waiting) | SOF/VEL (12)<br>SOF + DCV + RBV (24)<br>SOF + peg-IFN + RBV (12)<br>SOF + RBV (24)<br>Best supportive care (watchful waiting) |
| 4 | SOF/VEL (12)<br>EBR/GZR[a] (12)<br>OBV/PTV/RTV + RBV (12)<br>Best supportive care (watchful waiting) | SOF/VEL (12)<br>EBR/GZR[a] (12)<br>SOF/LDV (12)<br>OBV/PTV/RTV + RBV (12)[b]<br>Best supportive care (watchful waiting) | SOF/VEL (12)<br>EBR/GZR[a] (12)<br>SOF/LDV (12)<br>OBV/PTV/RTV + RBV (12)<br>Best supportive care (watchful waiting) | SOF/VEL (12)<br>EBR/GZR[a] (12)<br>SOF/LDV (12)<br>OBV/PTV/RTV + RBV (12)[b]<br>Best supportive care (watchful waiting) |
| 5 or 6 | SOF/VEL (12)<br>Best supportive care (watchful waiting) | SOF/VEL (12)<br>SOF + peg-IFN + RBV (12)<br>Best supportive care (watchful waiting) | SOF/VEL (12)<br>Best supportive care (watchful waiting) | SOF/VEL (12)<br>SOF + peg-IFN + RBV (12)<br>Best supportive care (watchful waiting) |

Source: Table 59 in CS.[2]

[a] For the sake of simplicity the model assumes all patients receive a 12 week treatment duration without RBV.

[b] TA365 for OBV/PTV/RTV ± DSV was published before the results from TURQUOISE-III and AGATE-I became available and the NICE recommendation therefore stipulates the use of OBV/PTV/RTV ± DSV with RBV for GT1b patients with CC, and OBV/PTV/RTV + RBV for GT4 CC patients for 24 weeks. Subsequently, TURQUOISE-III demonstrated the efficacy of treatment with OBV/PTV/RTV + DSV for 12 weeks without RBV in GT1b patients with CC,[78] and AGATE-I demonstrated the efficacy of OBV/PTV/RTV + RBV for 12 weeks in GT4 patients with CC.[73] The licence for OBV/PTV/RTV ± DSV now reflects this. Therefore OBV/PTV/RTV + DSV without RBV for 12 weeks is used as the comparator in the economic analysis of this submission for GT1b patients with CC, and OBV/PTV/RTV + RBV for 24 weeks is used for GT4 CC patients.

CC, compensated cirrhosis; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GZR, grazoprevir; IFN, interferon; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; Peg-IFN, pegylated-IFN; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; VEL, velpatasvir

**ERG comment:** The comparators included in the cost effectiveness analyses were mostly in line with the final scope. Discrepancies and excluded comparators were described in Section 3.3 of this report.

The company did not consider any treatment continuation rules for G/P or any relevant comparators. Although NICE guidance recommends SOF + DCV for GT3 NC patients with significant fibrosis only, the company took a pragmatic approach and included this treatment as a comparator for all GT3 NC patients.

### 5.2.5 Perspective, time horizon and discounting

The cost effectiveness analyses performed by the company adopted the perspective of the NHS/PSS. A discount rate of 3.5% was applied for both costs and utilities. A 70-year time horizon with an annual cycle length was assumed in the cost effectiveness model.

### 5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness parameters for the model were derived from the trial data described throughout Section 4 of this report. As explained in Section 5.2.2, two main types of transition probabilities can be distinguished in the model: SVR rates and natural disease progression transition probabilities. These are discussed in more detail below.



**Sustained virologic response rates**

SVR rates were obtained from clinical trial data. These were used to estimate the transition probabilities from baseline health states (mild fibrosis, moderate fibrosis or CC) to the corresponding "recovered" health state after successful treatment. In particular, the SVR rates (defined as HCV RNA <LLOQ) observed at 12 weeks after the end of treatment on the ITT population (denoted by SVR12) from the company and comparator clinical trials were used directly in the model. These are presented in Table 4.16 of this report. SVR rates are further stratified by fibrosis severity (NC [F0–F3] and CC [F4]) and HCV genotype (GT1 to GT6). Since in most of cases available data did not report different SVR rates for mild (F0-F1) and moderate (F2-F3) fibrosis, the available NC SVR rate was applied for both the mild and moderate fibrosis health states. Only for SOF/LDV in GT1 TN patients, SVR rates were obtained separately for patients with mild and moderate fibrosis.

**ERG comment:** The model uses the SVR12 rates obtained in RCTs with the various treatment options as model input for treatment effectiveness. As also discussed in Section 4 of this report the main concern is that data for SVR12 were taken from single arms. Therefore, the comparisons for SVR12 rates between G/P and comparators rely on a naïve indirect comparison. The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how response and adverse events for comparator studies were selected and whether all possible sources were used. The limitations of this input data necessarily lead to non-robust cost effectiveness outcomes.

In addition, patient numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each subgroup. Only three out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC and GT2/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

**Natural disease progression transition probabilities**

Natural disease progression transition probabilities were derived from the literature. These were categorised in four different groups: fibrosis progression, non-fibrosis progression, liver transplantation and liver-related mortality. A brief description of each category and a summary of the annual transition probabilities used in the economic model are given below.

*Fibrosis progression*

The company considered a two-step approach where fibrosis progression transition probabilities for GT1 were calculated first using equations from Thein et al. 2008.[158] Subsequently, different literature-based hazard ratios were applied to obtain the transition probabilities for the genotypes GT2 to GT6.

The regression equations presented by Thein et al. 2008 were used to calculate stage-specific fibrosis progression rates as a function of the following covariates: duration of HCV infection (in years), age at infection (in years), gender (% male), genotype (% GT1), source of infection (intravenous drug use [IDU] or blood transfusion), excessive alcohol consumption (at least more than 20 g/day in the 12 months prior to study entry) and study design (cross-sectional/retrospective = 1; retrospective-prospective = 0).[158] These equations can be seen in Table 5.7 below.

**Table 5.7: Equations to estimate fibrosis progression rates for GT1**

| Progression rate | Equation | Source |
|---|---|---|
| F0 to F1 | $\exp(-\beta 1 + \beta 2 \times duration + \beta 3 \times design + \beta 4 \times male + \beta 5 \times genotype)$ | Thein et al. (2008)[158] |
| F1 to F2 | $\exp(-\beta 1 - \beta 2 \times duration + \beta 3 \times excess\ alcohol)$ | |
| F2 to F3 | $\exp(-\beta 1 + \beta 2 \times age - \beta 3 \times duration + \beta 4 \times excess\ alcohol)$ | |
| F3 to F4 | $\exp(-\beta 1 + \beta 2 \times age - \beta 3 \times duration + \beta 4 \times injecting\ drug\ users + \beta 5 \times blood\ transfusion + \beta 6 \times genotype)$ | |
| Source: Page 177 in the CS.[2]<br>exp = Exponential | | |

In order to estimate fibrosis progression rates for GT1, the equations above were populated with the patient baseline characteristics and the regression coefficients used in the base-case for TA364 (as reported in Table 72 and Table 73 in the CS, respectively).[2] The estimated fibrosis progression rates were converted to transition probabilities for GT1 by applying the following formula: transition probability = 1 – exp (rate). The hazard ratios used to obtain the transition probabilities for the genotypes GT2 to GT6 were based on Kanwal et al. 2014.[159] Despite being a non-UK study, the company used these hazard ratios since the applicability of this study to a UK setting was accepted by clinical experts in TA430.[139] The company further assumed that, in the absence of hazard ratios for GT5 and GT6, the GT4 hazard ratio would apply to GT5 and GT6.

**ERG comment:** Fibrosis progression was modelled using the equations by Thein et al. 2008,[158] which is the approach taken in TA253 and TA364.[177, 181] In Section 5.3, the ERG explored the scenario where the fibrosis progression was modelled using the equations from Grischchenko et al. 2009.[178]

TA430 did not distinguish between different non-cirrhotic fibrosis health states, and transition probabilities from fibrosis to CC were calculated from Kanwal et al. 2014.[2, 159]

*Non-fibrosis progression*

Non-fibrosis progression transition probabilities considered in the company's model include transition to the HCC health state from the corresponding "recovered" health state (i.e. SVR with history of CC) and the possible transitions between the CC, DCC and HCC health states, as depicted in Figure 5.1. Transition to HCC from the "recovered" health state was sourced from Cardoso et al. 2010,[182] while transitions between CC, DCC and HCC were taken from Fattovich et al. 1997.[160] These two sources

have been previously used in cost effectiveness analyses of HCV therapies in the UK.[153-155] However, the economic analyses in TA430 used Cardoso et al. 2010[182] to estimate the transition probabilities between CC, DCC and HCC. Both sources have been used previously in economic models in NICE submissions, and it has been concluded that both are generalisable to UK clinical practice and that the true value lies somewhere between.[176] Another deviation from TA430 is that the company's model considers a GT-specific hazard ratio which is applied to the transition probabilities from CC and DCC to HCC. These, as in the case of fibrosis progression transition probabilities, were sourced from Kanwal et al. 2014.[159]

*Liver transplantation*

The transition probability from DCC to LT was estimated from Siebert et al. 2003.[155, 183] This was done in TA430 and in other previous UK cost effectiveness models.[139, 153-155, 175] Unlike in TA430,[139] the company's model allows the transition from HCC to LT. The company argues that this is in line with current UK clinical practice.[184] The same transition probability used to model progression from DCC to LT was assumed for HCC to LT progression. This is in line with previous UK cost effectiveness models.[153, 155]

*Liver-related mortality*

Liver-related mortality risks for the DCC and HCC health states were obtained from Fattovich et al. 1997.[160] Mortality risks after liver transplantation are assumed to differ between the first and subsequent years after transplantation. For the year following liver transplantation (LT – first year) this was sourced from a survival analysis of UK registry data on liver transplantation, which was used in previous UK cost effectiveness studies.[154, 155, 175] For subsequent years, this was obtained from Bennett et al. 1997.[185]

**ERG comment:** The transition probabilities for DCC and HCC to liver death are in line with the models presented by Wright et al. (2006), Shepherd et al. (2007) and Hartwell et al. (2011).[153-155] The transition probability for HCC to liver death is the same as the one used in TA430.[139]

The value for the probability of death in the year following liver transplantation (LT – first year) has been used in UK cost effectiveness studies including Grieve et al. (2006), Shepherd et al. (2007), and Hartwell et al. (2011).[154, 155, 175] The transition probability from LT (subsequent year) to liver death was sourced from Bennett et al. (1997),[185] which was in line with the models presented in Shepherd et al. (2007) and Hartwell et al. (2011).[154, 155] In TA430, a single transition probability for liver transplant to death was used from Bennett et al (1997),[185] which is higher than those used in this model. However, the value used in this model is consistent with other models submitted recently to NICE such as TA365 and TA364.[156, 177, 186]

Note also that the transition probabilities used in the base-case do not change with age except for the transition probability to death from all causes and the age-dependent fibrosis stage-specific transition rates.

*Summary of annual transition probabilities*

**Table 5.8: Annual transition probabilities**

| Variable | Base-case value | Source | TA430 value and reference [139] |
|---|---|---|---|
| GT1 fibrosis progression | | | |
| F0-F1 | 0.110 | Equations from Thein et al. (2008)[158] and patient characteristics from TA364[177] | Model did not distinguish between non-cirrhotic fibrosis health states |
| F1-F2 | 0.088 | | |
| F2-F3 | 0.176 | | |
| F3-CC | 0.143 | | See below in the table |
| GT-specific fibrosis progression multipliers | | | |
| GT2 | 0.68 | Kanwal et al. (2014)[159] (adjusted hazard ratio) | F3-CC genotype-specific transition probabilities were calculated from Kanwal et al. (2014)[159]; GT1 0.0213, GT2 0.0165, GT3 0.0296, GT4 0.0202, GT5 0.0202, GT6 0.0202 |
| GT3[a] | 1.30 | | |
| GT4 | 0.94 | | |
| GT5 | 0.94 | Assume same as GT4 | |
| GT6 | 0.94 | | |
| Non-fibrosis disease progression | | | |
| SVR, history of CC (F4) to HCC | 0.012 | Cardoso et al. (2010)[182] | Same value and reference |
| CC to DCC | 0.039 | Fattovich et al. (1997)[160] | 0.0438 Cardoso et al. (2010) [182] |
| CC to HCC; GT1 | 0.014 | | 0.0631 Cardoso et al. (2010) [182] |
| DCC to HCC; GT1 | 0.014 | | 0.0631 Cardoso et al. (2010) [182] |
| GT-specific non-fibrosis transition rate multipliers | | | |
| *CC to HCC multiplier* | | | |
| GT2 | 0.62 | Kanwal et al. (2014)[159] | Not applied |
| GT3 | 1.44 | | |
| GT4 | 0.96 | | |
| GT5 | 0.96 | Assumed same as GT4 | |
| GT6 | 0.96 | | |
| *DCC to HCC multiplier* | | | |
| GT2 | 0.62 | Assumed same as CC to HCC multiplier | Not applied |
| GT3 | 1.44 | | |
| GT4 | 0.96 | | |
| GT5 | 0.96 | | |
| GT6 | 0.96 | | |
| LT | | | |
| DCC to LT (first year) | 0.020[b] | Siebert et al. (2003)[183] | 0.022 Siebert et al. (2005)[187] |

| Variable | Base-case value | Source | TA430 value and reference [139] |
|---|---|---|---|
| HCC to LT (first year) | 0.020[b] | | Transition not allowed in model |
| Liver-related mortality | | | |
| DCC to liver death | 0.130 | Fattovich et al. (1997)[160] | 0.24 EAP data (EASL 2016) [186] |
| LT first year to liver death | 0.150 | Grieve et al. (2006)[175] | 0.2100 Bennett et al (1997) [185] |
| LT subsequent year to liver death | 0.057 | Bennett et al. (1997)[185] | |
| HCC to liver death | 0.430 | Fattovich et al. (1997) [160] | Same value and reference |
| Spontaneous remission from F0 | 0.000 | Assumption (see Section B.3.2.2.3 in the CS)[2] | Same assumption |
| Background age- and gender-adjusted probability of death | Variable | ONS (2016)[173] | Same value and reference |

Source: Table 75 in CS.[2]

[a] the inputs are based on Table 2 from Kanwal et al. (2014).[159] Note that there is a discrepancy in the publication for the GT3 fibrosis progression multiplier. In the introduction and the results section, the text mentions 1.31, but the results in Table 2 shows 1.30;

[b] For the transition probability form DCC to LT, Siebert et al. (2003)[183] actually use 0.022; Shepherd et al. (2011), and Wright et al. (2006) and Hartwell et al. (2011) use 0.02, so the model presented here has aligned with these other UK models.[153-155]

CC, compensated cirrhosis; DCC, decompensated cirrhosis; GT, genotype; HCC, hepatocellular carcinoma; LT, liver transplant; ONS, Office of National Statistics; SVR, sustained virologic response

### 5.2.7 Adverse events

Relevant adverse events (AEs) are included in the company's cost effectiveness model, which are assumed to impact both costs and health-related quality of life (HRQoL). However, the way AEs are implemented in the model differs for costs and HRQoL.

Costs associated to AEs are calculated in the model using AE rates observed in clinical trials. These AE rates are presented in Table 5.9 and Table 5.10 for treatment-naïve and treatment-experienced patients (and the corresponding genotype, treatment received and cirrhosis status), respectively. In particular, the following five AEs were included in the company's model: anaemia, depression, rash, Grade 3/4 neutropaenia and Grade 3/4 thrombocytopaenia. Other CHC-related AEs like nausea, vomiting, diarrhoea and pruritus were assumed to have a minor impact on the overall costs and therefore, these were not included in the company's model. Furthermore, the company assumed that, when AE rates were not reported separately for NC patients and CC patients, the same AE rates were applied for these two subgroups. Finally, for best supportive care (i.e. no treatment), the company assumed a 0% AE rate for all AEs.

**Table 5.9: Inputs for AEs in TN patients using clinical trial data**

| Patient population (TN) | Regimen | Cirrhosis status | Anaemia | Rash | Depression | Grade 3/4 neutropaenia | Grade 3/4 thrombocy-topaenia | Reference |
|---|---|---|---|---|---|---|---|---|
| GT1 | G/P | NC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | ENDURANCE-1[39] |
| | | CC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | EXPEDITION-1[47] |
| | OBV/PTV/RTV + DSV ± RBV | NC | 3.84% | 7.88% | 0.00% | 0.15% | 0.15% | Pooled data from SAPPHIRE-I[80]and PEARL-IV[76]; weighted average with PEARL-III[76] |
| | | CC | 7.13% | 10.96% | 4.75% | 1.19% | 1.06% | TURQUOISE-II[77] |
| | EBR/GZR | NC | 2.85% | 0.00% | 0.00% | 0.32% | 0.00% | C-EDGE TN[88] |
| | | CC | 2.85% | 0.00% | 0.00% | 0.32% | 0.00% | |
| | SOF/LDV | NC | 0.93% | 1.40% | 0.00% | 0.00% | 0.00% | ION-3[93] |
| | | CC | 0.47% | 4.88% | 0.00% | 0.47% | 0.23% | ION-1[91] |
| | SOF/VEL | NC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | ASTRAL-1[97] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | |
| GT2 | G/P | NC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | SURVEYOR-II, pooled data from Parts 2 and 4[52] |
| | | CC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | EXPEDITION-1[47] |
| | SOF/VEL | NC | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | ASTRAL-2[98] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | |

| Patient population (TN) | Regimen | Cirrhosis status | Anaemia | Rash | Depression | Grade 3/4 neutropaenia | Grade 3/4 thrombocy-topaenia | Reference |
|---|---|---|---|---|---|---|---|---|
| | SOF + RBV | NC | 4.24% | 4.87% | 3.18% | 0.21% | 0.00% | Pooled data from FISSION,[108] VALENCE[107] and ASTRAL-2[108] |
| | | CC | 4.24% | 4.87% | 3.18% | 0.21% | 0.00% | |
| | Peg-IFN + RBV | NC | 11.52% | 17.70% | 13.99% | 14.81% | 7.41% | FISSION[109] |
| GT3 | G/P | NC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | ENDURANCE-3[25] |
| | | CC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | SURVEYOR-II, pooled data from Parts 2 and 3[52] |
| | SOF/VEL | NC | 0.00% | 0.00% | 0.00% | 0.26% | 0.52% | Pooled data from ASTRAL-3[98] and POLARIS-3[188, 189] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.26% | 0.52% | |
| | SOF + DCV ± RBV | NC | 0.00% | 0.75% | 0.00% | 0.00% | 0.75% | Pooled data from ENDURANCE-3[25] and ALLY-3[112] |
| | | CC | 7.14% | 0.00% | 14.29% | 0.00% | 0.00% | A1444040[114] |
| | SOF + RBV | CC | 0.00% | 0.00% | 0.19% | 0.00% | 0.76% | Pooled data from VALENCE[107]and ASTRAL-3[98] |
| | SOF + peg-IFN + RBV | CC | 0.00% | 19.80% | 0.51% | 15.74% | 4.57% | BOSON[103] |
| GT4 | G/P | NC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | SURVEYOR-II, Part 4[52] |

| Patient population (TN) | Regimen | Cirrhosis status | Anaemia | Rash | Depression | Grade 3/4 neutropaenia | Grade 3/4 thrombocy-topaenia | Reference |
|---|---|---|---|---|---|---|---|---|
| | | CC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | EXPEDITION-1[47] |
| | OBV/PTV/RTV + RBV | NC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | PEARL-I (CSR)[190] |
| | | CC[d] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | AGATE-I (CSR)[191] |
| | EBR/GZR | NC | 2.85% | 0.00% | 0.00% | 0.32% | 0.00% | C-EDGE TN[88] |
| | | CC | 2.85% | 0.00% | 0.00% | 0.32% | 0.00% | |
| | SOF/LDV | CC | 0.00% | 0.00% | 0.00% | 0.00% | 4.55% | Study 1119[192] |
| | SOF/VEL | NC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | ASTRAL-1[97] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | |
| GT5 | G/P | NC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | SURVEYOR-II, Part 4[52] |
| | | CC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | EXPEDITION-1[47] |
| | SOF/VEL | NC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | ASTRAL-1[97] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | |
| | SOF + peg-IFN + RBV | CC | 20.80% | 18.04% | 9.48% | 20.18% | 0.31% | NEUTRINO[110] |
| GT6 | G/P | NC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | SURVEYOR-II, Part 4[52] |
| | | CC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | EXPEDITION-1[47] |
| | SOF/VEL | NC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | ASTRAL-1[97] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | |

| Patient population (TN) | Regimen | Cirrhosis status | Anaemia | Rash | Depression | Grade 3/4 neutropaenia | Grade 3/4 thrombocy-topaenia | Reference |
|---|---|---|---|---|---|---|---|---|
| | SOF + peg-IFN + RBV | CC | 20.80% | 18.04% | 9.48% | 20.18% | 0.31% | NEUTRINO[110] |

Source: Table 68 in CS.[2]

Note: For published references, if AEs were not reported (for example because only AEs affecting >5% of patients were reported), these were assumed to have a frequency of 0.

AEs, adverse events; CC, compensated cirrhosis; CSR, clinical study report; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir (300 mg/120 mg); GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TN, treatment-naïve; VEL, velpatasvir

**Table 5.10: Inputs for AEs in TE patients using clinical trial data**

| Patient population (TE) | Regimen | Cirrhosis status | Anaemia | Rash | Depression | Grade 3/4 neutropaenia | Grade 3/4 thrombocy-topaenia | Reference |
|---|---|---|---|---|---|---|---|---|
| GT1 | G/P | NC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | ENDURANCE-1[39] |
| | | CC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | EXPEDITION-1[47] |
| | OBV/PTV/RTV + DSV ± RBV | NC | 3.67% | 6.30% | 0.00% | 0.00% | 0.00% | Weighted average of PEARL-II[75] and SAPPHIRE-II[81] |
| | | CC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | TURQUOISE-III (Feld et al. [2016][78] and CSR[193]) |
| | EBR/GZR | NC | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | C-EDGE TE[85] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | |
| | SOF/LDV | NC | 0.00% | 1.83% | 0.00% | 0.00% | 0.92% | ION-2[92] |
| | | CC | 0.00% | 1.83% | 0.00% | 0.00% | 0.92% | |
| | SOF/VEL | NC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | ASTRAL-1[97] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | |
| GT2 | G/P | NC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | SURVEYOR-II, pooled data from Parts 2 and 4[52] |
| | | CC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | EXPEDITION-1[47] |
| | SOF/VEL | NC | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | ASTRAL-2[98] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | |

| Patient population (TE) | Regimen | Cirrhosis status | Anaemia | Rash | Depression | Grade 3/4 neutropaenia | Grade 3/4 thrombocy-topaenia | Reference |
|---|---|---|---|---|---|---|---|---|
| | SOF + RBV | NC | 3.45% | 2.19% | 2.19% | 0.63% | 0.63% | Pooled data from FUSION,[108] VALENCE[107] and ASTRAL-2[108] |
| | | CC | 3.45% | 2.19% | 2.19% | 0.63% | 0.63% | |
| GT3 | G/P | NC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | SURVEYOR-II, Part 3[52] |
| | | CC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | SURVEYOR-II, pooled data from Parts 2 and 3[52] |
| | SOF/VEL | NC | 0.00% | 0.00% | 0.00% | 0.26% | 0.52% | Pooled data from ASTRAL-3[98] and POLARIS-3[188, 189] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.26% | 0.52% | |
| | SOF + DCV ± RBV | NC | 0.00% | 0.00% | 0.00% | 0.00% | 1.32% | ALLY-3[112] |
| | | CC | 7.14% | 0.00% | 14.29% | 0.00% | 0.00% | A1444040[114] |
| | SOF + RBV | CC | 0.00% | 0.00% | 0.19% | 0.00% | 0.76% | Pooled data from VALENCE[107]and ASTRAL-3[98] |
| | SOF + peg-IFN + RBV | CC | 0.00% | 19.80% | 0.51% | 15.74% | 4.57% | BOSON[103] |
| GT4 | G/P | NC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | SURVEYOR-II, Part 4[52] |
| | | CC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | EXPEDITION-1[47] |
| | OBV/PTV/RTV + RBV | NCc | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | PEARL-I(CSR)[190] |

| Patient population (TE) | Regimen | Cirrhosis status | Anaemia | Rash | Depression | Grade 3/4 neutropaenia | Grade 3/4 thrombocy-topaenia | Reference |
|---|---|---|---|---|---|---|---|---|
| | | CCd | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | AGATE-I (CSR)[191] |
| | EBR/GZR | NC | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | C-EDGE TE[85] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.00% | 0.00% | |
| | SOF/LDV | NC | 0.00% | 0.00% | 0.00% | 0.00% | 4.55% | Study 1119[192] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.00% | 4.55% | |
| | SOF/VEL | NC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | ASTRAL-1[97] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | |
| GT5 | G/P | NC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | SURVEYOR-II, Part 4[52] |
| | | CC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | EXPEDITION-1[47] |
| | SOF/VEL | NC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | ASTRAL-1[97] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | |
| | SOF + peg-IFN + RBV | CC | 20.80% | 18.04% | 9.48% | 20.18% | 0.31% | NEUTRINO[110] |
| GT6 | G/P | NC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | SURVEYOR-II, Part 4[52] |
| | | CC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | EXPEDITION-1[47] |
| | SOF/VEL | NC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | ASTRAL-1[97] |
| | | CC | 0.00% | 0.00% | 0.00% | 0.64% | 0.16% | |
| | SOF + peg-IFN + RBV | CC | 20.80% | 18.04% | 9.48% | 20.18% | 0.31% | NEUTRINO[110] |

Source: Table 69 in CS.[2]

| Patient population (TE) | Regimen | Cirrhosis status | Anaemia | Rash | Depression | Grade 3/4 neutropaenia | Grade 3/4 thrombocy-topaenia | Reference |
|---|---|---|---|---|---|---|---|---|
| Note: For published references, if AEs were not reported (for example because only AEs affecting >5% of patients were reported), these were assumed to have a frequency of 0.<br>AEs, adverse events; CC, compensated cirrhosis; CSR, clinical study report; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; VEL, velpatasvir | | | | | | | | |

The company implemented the effect of AEs on HRQoL using treatment-related change in health utility (based on PROs). With this approach, the company aimed to capture the impact of all treatment-related AEs, not only those related to the AEs listed in Table 5.9 and Table 5.10. The operationalisation of HRQoL changes due to adverse events in the model are further described in Section 5.2.8 of this report.

**ERG comment:** The AE rates used in the model suffer from the same strong limitations as the SVR rates, i.e. the rates are based on single arms from various RCTs without any consideration of the comparability of these RCTs and for some subgroups the AE rates are based on very few patients.

As the impact of AEs is only explicitly incorporated for the costs outcome, the company argues that various AE that were previously included in TA430 (e.g. nausea, vomiting, diarrhoea and pruritus) could be excluded in the current model, due to their low associated costs. However, the validity of this reasoning depends not just on the associated costs, but also on the incidence of the AE. If low cost AEs occur in many patients, they may still have an impact on the outcomes. Thus, without an overview of all adverse events with their rates of occurrence, it is impossible to judge the validity of the current selection made by the company.

Note that the company has opted not to model the AE-related disutility explicitly, but instead has chosen to apply a treatment-related change in utility for all treatments for the duration of the treatment. Hence, the exact selection of AEs to include in the model can only impact the cost outcome, not the QALY outcome.

### 5.2.8 Health-related quality of life

As UK patients represented only a small percentage of the total enrolled patient sample in the various G/P studies, it was felt that the utilities collected from them would not be representative of the UK patients suffering with CHC. Furthermore, the trials for G/P did not enrol patients with DCC, HCC, or LTs. Thus, it was decided to use health state utilities identified from the literature, derived from UK patients. These utility values were all used in previous NICE submissions.[147, 156]

The base-case health utility values used for health states F0-F4 and SVR F0-F4 in the cost effectiveness model were derived from the study by Wright et al. 2006.[153] Utility values for more advanced liver disease (DCC, HCC, LT) and PLT were derived from Ratcliffe et al. 2002.[161] These values are presented in Table 5.11.

In a scenario analysis the company explored the impact of using trial-based utility values for health states F0-F3 and CC plus the SVR states associated with these five health states. It was considered more appropriate to use the literature-derived health-state utility values in the base-case for consistency with previous appraisals in chronic HCV.

In the CS, a utility increment of 0.05 for achieving SVR for patients with mild and moderate fibrosis and CC is assumed, occurring from the second cycle of the model onwards. This utility gain was based on data collected in the UK trial on mild HCV by Wright et al. 2006 and used to calculate the health state utility value for SVR with a history of mild (F0–F1) or moderate (F2–F3) fibrosis by Wright et al. 2006; the +0.05 increment was applied to the health state utility value for SVR with a history of CC by Shepherd et al. 2007 and Hartwell et al. 2011, and by previous NICE TAs.[147, 153-156] The SVR utility increment applied in this CS is different from that in TA430; in TA430 an SVR utility increment of +0.04 from Vera-Llonche et al. 2013 was applied.[194]

**Table 5.11: Health state utilities used in the cost effectiveness model**

| Health state | Base-case value | Source | TA430 value and reference[1] |
|---|---|---|---|
| F0 | 0.77 | Wright et al. 2006[153] | 0.750 Wright et al. 2006[153] |
| F1 | 0.77 | | |
| F2 | 0.66 | | |
| F3 | 0.66 | | |
| CC | 0.55 | | Same value and reference |
| SVR, history of mild fibrosis (F0, F1) | 0.82 | +0.05 added to mild fibrosis health state; Wright et al. 2006[153] and aligned with Shepherd et al. 2007 and Hartwell et al. 2011[154, 155] | 0.790 (calculated from SVR utility increment of +0.04 from Vera-Llonche et al. 2013[194] |
| SVR, history of moderate fibrosis (F2, F3) | 0.71 | +0.05 added to moderate fibrosis health state[a] | |
| SVR, history of CC (F4) | 0.60 | +0.05 added to CC health state. Utility aligned with Shepherd et al. 2007 and Hartwell et al. 2011[154, 155] | 0.590 (calculated; ERG: 0.55) |
| DCC | 0.45 | Ratcliffe et al. 2002[161] | Same value and reference |
| HCC | 0.45 | | |
| LT (first year) | 0.45 | | |
| LT (subsequent) | 0.67 | | |

Source: Table 77 in CS.[2]

[a]This value (0.71) is consistent with previous appraisals using a +0.05 utility increment for achieving SVR (e.g. TA413 and TA365),[147, 156] however, Hartwell et al. (2011), Shepherd et al.(2007) and Wright et al (2006) (referenced in these appraisals) used a value of 0.72.[153-155] The value of 0.71 has been used here to prioritise consistency with previous appraisals.

CC, compensated cirrhosis; DCC, decompensated cirrhosis; ERG, Evidence Review Group; F0: no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplant; SVR, sustained virologic response

Treatment-related health utility changes were applied to adjust for the impact on HRQoL of treatment, e.g. due to adverse events. For comparator treatments, these (dis)utilities were derived from previous NICE submissions.[26, 66, 195, 196] For most treatments, a disutility was found ranging from -0.05 to -0.001. The mean overall utility change for EBR/GZR and SOF/LDV was 0 (i.e. no utility change), and for G/P, SOF/VEL, and OBV/PTV/RTV ± RBV (except for the TN NC subgroup) a utility increment was applied. The treatment-related health utility changes per the expected regimen duration were annualised (for example, a 12-week change would be reweighted by multiplying it by 12/52), and then applied to baseline utilities from Wright et al. 2006 in cycle 1 of the model,[153] in which treatment is received. For best supportive care (no treatment), the treatment-related change in health utility is 0. Annualised treatment-related health utility changes by treatment and patient population are summarised in Table 5.12. Finally, it should be noted that the methodology for calculating and applying treatment-related utilities in the CS is different from that of TA430.[139] In TA430 the manufacturer applied treatment-specific (multiplicative) utility increments for DAA therapies whilst utility decrements were applied for each AE. In the current company model no utility decrements are applied for individual AEs as this

may lead to double-counting, as the effect of treatment-related AEs on HRQoL would be captured in the treatment-related utility adjustment.

**Table 5.12: Annualised treatment-related health utility changes by treatment and patient population**

| Regimen (duration in weeks) and patient population | | | Annualised change in treatment-related health utility |
|---|---|---|---|
| G/P (8) | | | [redacted] |
| G/P (12) | | | [redacted] |
| G/P (16) | | | [redacted] |
| OBV/PTV/RTV + DSV ± RBV | GT1, TN | NC (12) | [redacted] |
| | | CC (12 or 24) | [redacted] |
| | GT1, TE | NC (12) | [redacted] |
| | | CC (12) | [redacted] |
| OBV/PTV/RTV ± RBV[b] (12) | GT4, TN | NC | [redacted] |
| | | CC | [redacted] |
| | GT4, TE | NC | [redacted] |
| | | CC | [redacted] |
| EBR/GZR (12)[a] | | | 0 |
| SOF/LDV (12) | | | 0 |
| SOF/VEL (12)[b] | | | 0.007 |
| SOF + DCV ± RBV (12) | TN | NC | -0.002 |
| | | CC | -0.027 |
| | TE | NC | -0.008 |
| | | CC | -0.027 |
| SOF + peg-IFN + RBV (12) | | | -0.034 |
| SOF + RBV (12) | GT2, TN | NC | -0.001 |
| | | CC | -0.001 |
| | GT2, TE | NC | -0.006 |
| | | CC | -0.006 |
| SOF + RBV (24) | GT3, TN | CC | -0.024 |
| | GT3, TE | CC | -0.024 |
| Peg-IFN + RBV (24) | GT2, TN | NC | -0.050 |

Source: Table 78 CS.[2]

[a]EQ-5D data was extracted from TA413 for C-EDGE TN.[147] It was assumed conservatively that the on-treatment change in health utility also applies to TE patients; [b]The ASTRAL trials did not collect EQ-5D data. The same treatment-related change in health utility as G/P (12 weeks) was assumed.

CC, compensated cirrhosis; CSR, clinical study report; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GT, genotype; GZR, grazoprevir; LDV, ledipasvir; NC, non-cirrhotic; OBV, ombitasvir; peg-IFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TN, treatment-naïve VEL, velpatasvir

**ERG comment:** Using utilities derived from the literature[153] is consistent with the approach used in previous STAs.[25, 26, 195, 197] However, it also means that in this STA, as well as some of the previous STAs, utilities derived from RCTs have not been taken into account in the base-case. In the CS it is argued that UK patients represented only a small percentage of the total enrolled patient sample in the various G/P RCTs and that it was therefore felt that these utilities would not be representative of the UK patients suffering with CHC. A similar justification was given in the STA of EBR/GZR.[147] However, the ERG questions to what extend utility values published in 2006 (originating from EQ-5D questionnaires completed in 2002),[153] i.e. before the DAA-era, can be seen as representative of UK patients currently suffering with CHC.

As the RCT-based utilities are higher than those observed in Wright et al. 2006,[153] with smaller differences between F0-F1, F2-F3, and F4, and smaller differences between states with and without a SVR, it is relevant to assess the impact of changing the source of the health state utility values. This scenario analysis has been provided in the CS, and the results are presented in Section 5.3. There it can be seen that these RCT utility values lead to a higher number of QALYs per treatment, without really altering the conclusions regarding cost effectiveness.

From the RCT-based utility values as presented in Table 117 from the CS,[2] it can be seen that the difference in utility of a health state with or without SVR ranges from 0.025 to 0.029, substantially lower than the increment of 0.05 applied by the company.[153] This raises the question if the utility gain observed in Wright et al. 2006 can still be considered as a valid estimate.[153] The ERG therefore requested in their clarification letter (question B11) that the company would perform a scenario analysis with the SVR-gain set to 0, as an extreme scenario. [13] Although the company explained how to do such scenario analysis in the electronic model, they did not provide the results of that scenario analysis. Hence, the ERG ran the scenario and its results are presented in Section 5.3, showing only a minimal impact on the results.

The impact of receiving treatment on health-related quality of life was taken into account in the company model using utility increments and decrements. Note that these changes in utility were only applied while patients are on treatment but not through the whole model's time horizon. Conceptually, the ERG agrees with this approach as it takes into account both the impact of a quick response to treatment and the impact of adverse events. However, most of these adjustment estimates were based on the same studies as the estimates of SVR rates and AE rates, implying that all comments regarding those (see Section 4.6) apply here as well. Therefore, the ERG requested in their clarification letter (question B11) that the company would perform a (worst case) scenario analysis in which no utility adjustments would be applied.[13] However, the company opted not to provide the results of such analysis and instead only described which changes had to be made to run the analysis. In Section 5.3 the results of the scenario analysis as run by the ERG are presented.

### 5.2.9 Resources and costs

In the CS the costs for the clinical management of CHC are made up of two main components: 1) Health state costs and 2) treatment-related costs.

Health state costs capture the average medical costs in a specific health state. Costs include those associated with the management of progressive liver disease (in patients who do not respond to treatment) and with post-treatment surveillance following treatment cessation and achievement of SVR.

Treatment-related costs consist of drug acquisition costs multiplied by the mean treatment duration from trials, costs associated with on-treatment monitoring for response, and costs of treating adverse events to treatment.

#### 5.2.9.1 Treatment-related costs

The CS presents a list price for G/P of £464.06 per day. List prices were also used for comparator products; Table 5.13 presents daily medication costs. Table 80 in the CS shows in detail how these costs per day have been derived from pack prices and treatment duration.[2]

**Table 5.13: Treatment regime costs per day**

| Therapy | Regimen costs (per day, list price 2016 £) | Source | Comparison to TA430[1] |
|---|---|---|---|
| G/P (list price, indicative) | £464.06 | AbbVie | Regimen costs were sourced from the BNF |
| OBV/PTV/RTV + DSV | £416.67 | BNF 2016[198] | |
| OBV/PTV/RTV | £383.33 | | |
| EBR/GZR | £434.52 | | |
| SOF/LDV | £464.05 | | |
| SOF/VEL | £464.05 | | |
| SOF | £416.46 | | |
| DCV | £291.88 | | |
| RBV | £13.21 | | |
| IFN | £17.77 | | |

Source: Table 79 in the CS.[2]
BNF, British National Formulary; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; G/P, glecaprevir/pibrentasvir; GZR, grazoprevir; IFN, pegylated interferon, LDV, ledipasvir; OBV, ombitasvir; PTV, paritaprevir; RBV, ribavirin; RTV, ritonavir; SOF, sofosbuvir; VEL, velpatasvir

The CS used information on the frequency of monitoring of patients (outpatient appointments, inpatient care, tests and investigations) whilst being treated with INF from Shepherd et al. 2007,[154] as was previously done in Hartwell et al. 2011[155] and in NICE submissions, including TA430.[156, 176] The values were adapted for DAA regimens. Costs were inflated to 2015/2016 values.[199] Estimations of monitoring costs per treatment duration are described in Table 5.14. Unlike TA430, the company did not stratify monitoring costs by cirrhosis status, and there are no monitoring costs for untreated patients.[139] These assumptions are consistent with the economic model submitted previously by the company for OBV/PTV/RTV ± DSV (TA365).[156]

**Table 5.14: Monitoring costs during treatment**

| Duration therapy | Monitoring costs (2015/2016 £) (See also CS Table 81) | Source | Comparison to TA430 |
|---|---|---|---|
| 8 weeks – all-oral therapy | £303 | Shepherd et al. (2007)[154] costs inflated to 2015/2016 values[199] | Monitoring costs were also based on Shepherd et al. 2007[154] |
| 12 weeks – all-oral therapy | £420 | | |
| 16 weeks – all-oral therapy | £477 | Assume equal to 12 weeks monitoring costs + week 8 assessment (£57.52) | |
| 24 weeks – all-oral therapy | £840 | Assume proportional to 12 weeks | |

Source: Table 79 in the CS.[2]

Frequencies of AEs for each treatment were previously described in Section 5.2.7. The company used data from Thorlund et al. 2012 to obtain resource use and unit cost for anaemia and rash (costs were inflated to 2015/2016 values).[199, 200] For depression, the company obtained assumptions used to inform the cost of treatment and monitoring from NICE GC 90: Depression in adults.[201] These inputs are in line with TA365 (OBV/PTV/RTV ± DSV).[156] Finally, the estimate of resource use for neutropaenia and thrombocytopaenia were based on NICE TA430.[139] A detailed breakdown of the resource use used to calculate the AE costs are described in Table 83 of the CS. Table 84 of the CS shows the differences between the AE costs in this model compared to TA430. A summary of the AE-related costs included in the economic model is presented in Table 5.15.

**Table 5.15: Costs of treating adverse events**

| Treatment-related adverse event | costs (2015/2016 £) | Source | Comparison to TA430 |
|---|---|---|---|
| Anaemia | £486 | Thorlund et al. (2012)[200] | See Table 84 in the CS[2] |
| Rash | £160 | | |
| Depression | £490 | NICE CG90 (2009)[201] | |
| Grade 3/4 neutropaenia | £1,334 | TA430[139] | |
| Grade 3/4 thrombocytopenia | £1,902 | | |
| Source: Table 79 in the CS.[2] | | | |

#### 5.2.9.2 Health state unit costs and resource use

Health-state unit costs were derived from previous publications and inflated to 2014/15 values.[54, 60, 167] The same costs were applied to all genotypes and all subgroups.

Table 5.16 presents the cost estimates associated with each health state. The company used data from two studies, i.e. Hartwell et al. 2011 and Backx et al. 2014.[155, 202] The study by Backx et al. 2014 is a retrospective analysis of health resource usage and costs by patients in the East Midland region of the UK. It captured data for different disease states (e.g. fibrosis versus cirrhosis) and the data was evaluated according to response to treatment (SVR or non-SVR).[202] Therefore, values from this study were used in the CS for SVR health states and F2–F4 health states. In the CS it is conservatively assumed that all recovered patients require life-long monitoring post achieving an SVR, irrespective of their initial fibrosis stage.

In the absence of more recent or relevant sources, costs for F0 and F1 health states and those for more advanced liver disease (DCC, HCC, LT) were sourced by the company from Hartwell et al. 2011.[155] Costs were inflated to 2015/2016 values.[199] Compared to TA430, this model uses more recent inputs whenever possible from Backx et al. 2014,[202] in line with TA365,[156] whereas the majority of inputs for TA430 are from Wright et al. 2006.[153]

**Table 5.16: Summary of health state costs**

| Health state | Costs per event (2015/2016 £) | Source | TA430 value and reference (2014/2015 £) |
|---|---|---|---|
| F0 | £164 | Hartwell et al. 2011[155] | £327 Calculation: 83%,17% split[a] Wright et al. 2006 [153] Mild: £189 (inflated) Moderate: £1,001 (inflated) |
| F1 | £164 | | |
| F2 | £609 | Backx et al. 2014 [202] | |
| F3 | £609 | | |
| CC | £945 | | £1,561 Wright et al. 2006 [153] |

| Health state | Costs per event (2015/2016 £) | Source | TA430 value and reference (2014/2015 £) |
|---|---|---|---|
| SVR, history of mild fibrosis(F0–F1) | £60 | Backx et al. 2014 [202] | £246 Calculation: 83%,17% split[a] Grishchenko et al. 2009 [202] SVR, mild: £237 (inflated) SVR, moderate: £290 (inflated) |
| SVR, history of moderate fibrosis (F2–F3) | £60 | | |
| SVR, history of CC | £606 | | £513 Grishchenko et al. 2009 [178] |
| DCC | £12,670 | Hartwell et al. 2011[155] | £12,510 Wright et al. 2006 [153] |
| HCC | £11,291 | | £11,147 Wright et al. 2006 [153] |
| LT (first year) | £51,108 | | 1st year LT: £85,191; 1st year post LT 0-12 months: £28,067; subsequent year £4,194 (12-24 months). From Singh/Longworth et al. 2014 [203] split between post-liver transplant year 1 and year 2 cost based on Wright et al. 2006 [153] |
| LT (subsequent year) | £1,924 | | |

Source: Table 82 in the CS.[2]
[a]Based on 83% F0-F2 (mild) and 17% F3 (moderate), derived from HCV TherapyWatch market research data.
AE, adverse event; CC, compensated cirrhosis; DCC, decompensated cirrhosis; F0: no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplant; SVR, sustained virologic response

**ERG comment:** Overall the ERG has few comments to make to the company's approach to including costs in the cost effectiveness analysis. It should be noted that Table 5.16 shows that for the health states F0, F1, DCC, HCC and LT estimates were obtained from a publication by Hartwell et al. 2011.[155] However, the paper by Hartwell et al. refers in turn to the study by Wright et al. 2006,[153] which was also used in TA430. Hence, though it appears that the current submission uses a different source for the cost estimates, in fact it uses the same as TA430 for F0, F1, DCC, HCC and LT.

In the health state cost estimates neither allied health care nor GP visits or home care have been included. Whilst it might be reasonable to assume that GP costs and allied health care costs will be relative small compared to hospital admissions and outpatient visits, this is less clear for home care, especially for patients with hepatocellular carcinoma or decompensated cirrhosis. Unfortunately, none of the cost studies identified by the manufacturer (CS Appendix I) reported these types of resource use, so no data was available for the ERG to add these.[16] However, the tornado diagrams reporting the DSA (CS appendix L.1.3) show that even when health state costs are changed by 50% this does not alter the conclusions, and for most subgroups the impact is extremely small.[16]

The determination of AE cost estimates is somewhat confusing to the ERG. For anaemia and rash the company favours the study by Thorlund et al. 2012,[200] in which experts were consulted, over the estimates from TA430, which were based on expert opinion. However, Thorlund also present an estimate for neutropaenia (of £25) which is only a small fraction of the cost estimate used both in this model and in TA430. A potential explanation could be that the estimate in Thorlund et al. refers to all grades of neutropaenia, whereas in the current model only grade 3 and 4 neutropaenia is included.

Observational data regarding resource use for adverse events would be needed to reduce the uncertainty that currently exists. However, from the lack of mentioning of AE costs in the tornado diagrams reporting the DSA (CS Appendix L.1.3) it can be deducted that even when adverse event costs are altered by 50%, they have an almost negligible impact on the results.[16]

### 5.2.10 Cost effectiveness results

Cost effectiveness results were presented incrementally including all relevant comparators for the different subgroups considered in the analyses. Subgroups were characterised by genotype (GT1 – GT6), treatment history (treatment-naïve or treatment-experienced) and cirrhosis status (non-cirrhotic or compensated cirrhosis). Furthermore, GT2 treatment-naïve patients were also subdivided by IFN-eligibility. This resulted in 26 subgroups in total as reported in Table 5.3 in Section 5.2.3.

**Base-case incremental cost effectiveness analysis results**

The results summarised in this section are sourced from Appendix B14 in the clarification responses.[17] These were provided by the company after it was discovered during the clarification phase (Question B14 in the clarification letter[17]), that the results reported in the CS did not match those obtained from the submitted economic model. In these analyses, list prices were used for G/P and all comparators.

Table 5.17 below provides an overview of the (list price) base-case cost effectiveness results per subgroup. In the CS, results often refer to both the £20,000 and £30,000 cost per QALY threshold, which might be leading to some confusion, given the vast amounts of results that need to be presented. Given the high level of uncertainty associated with the input parameters of the model, the ERG chose to describe the cost effectiveness results in this section based on the £20,000 threshold.

It was observed that, for non-cirrhotic patients, G/P was always cost effective except for the following two subgroups: GT2 treatment-naïve IFN-eligible patients and GT3 treatment-experienced patients. For the subgroups of non-cirrhotic patients for which G/P was cost effective, the relevant comparator was always no treatment, which resulted in very low ICERs (always below £5,000 per QALY). For patients with compensated cirrhosis, G/P was only cost effective for GT1 treatment-naïve and GT3 treatment-naïve patients. For some of the subgroups where G/P was not considered cost effective, the reason was that at least one of the comparators, which was considered cost effective, produced the same amount of QALYs at a lower cost. Thus, although G/P was dominated, it can be considered as equally effective as these comparators. This is indicated with shaded cells in Table 5.17. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was as effective as at least one cost effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above cost effectiveness threshold).

**Table 5.17: G/P cost effectiveness per subgroup (based on list price deterministic full incremental results)**

| HCV genotype | Treatment-naïve | | Treatment-experienced | |
|---|---|---|---|---|
| | **Non-cirrhotic** | **Compensated cirrhosis** | **Non-cirrhotic** | **Compensated cirrhosis** |
| GT1 | G/P cost effective<br>2nd lowest total costs<br>highest QALYs<br>(out of 6 interventions) | G/P cost effective<br>3rd lowest total costs<br>highest QALYs<br>(out of 6 interventions) | G/P cost effective<br>2nd lowest total costs<br>highest QALYs<br>(out of 6 interventions) | G/P not cost effective<br>4th lowest total costs<br>3rd highest QALYs<br>(out of 6 interventions) |
| GT2 | IFN-eligible:<br>G/P not cost effective<br>3rd lowest total costs<br>highest QALYs<br>(out of 3 interventions) | IFN-eligible:<br>G/P not cost effective<br>3rd lowest total costs<br>highest QALYs<br>(together with SOF/VEL)<br>(out of 3 interventions) | G/P cost effective<br>2nd lowest total costs<br>2nd highest QALYs<br>(out of 4 interventions) | G/P not cost effective<br>3rd lowest total costs<br>highest QALYs<br>(together with SOF/VEL)<br>(out of 4 interventions) |
| | IFN-ineligible:<br>G/P cost effective<br>2nd lowest total costs<br>2nd highest QALYs<br>(out of 4 interventions) | IFN-ineligible:<br>G/P not cost effective<br>4th lowest total costs<br>highest QALYs<br>(together with SOF/VEL)<br>(out of 4 interventions) | | |
| GT3 | G/P cost effective<br>2nd lowest total costs<br>3rd highest QALYs<br>(out of 4 interventions) | G/P cost effective<br>lowest total costs<br>G/P cost effective<br>2nd lowest total costs<br>2nd highest QALYs<br>(out of 6 interventions) | G/P not cost effective<br>4th lowest total costs<br>highest QALYs<br>(out of 5 interventions) | G/P not cost effective<br>4th lowest total costs<br>2nd highest QALYs<br>(out of 6 interventions) |
| GT4 | G/P cost effective<br>2nd lowest total costs<br>4th highest QALYs<br>(out of 5 interventions) | G/P not cost effective<br>5th lowest total costs<br>highest QALYs<br>(together with SOF/VEL)<br>(out of 6 interventions) | G/P cost effective<br>2nd lowest total costs<br>2nd highest QALYs<br>(out of 6 interventions) | G/P not cost effective<br>4th lowest total costs<br>highest QALYs<br>(together with SOF/VEL)<br>(out of 6 interventions) |
| GT5 | G/P cost effective | G/P not cost effective | G/P cost effective | G/P not cost effective |

| HCV genotype | Treatment-naïve | | Treatment-experienced | |
|---|---|---|---|---|
| | **Non-cirrhotic** | **Compensated cirrhosis** | **Non-cirrhotic** | **Compensated cirrhosis** |
| | 2nd lowest total costs<br>highest QALYs<br>(out of 3 interventions) | 3rd lowest total costs<br>highest QALYs (together with SOF/VEL)<br>(out of 4 interventions) | 2nd lowest total costs<br>2nd highest QALYs<br>(out of 3 interventions) | 3rd lowest total costs<br>highest QALYs (together with SOF/VEL)<br>(out of 4 interventions) |
| GT6 | G/P cost effective<br>2nd lowest total costs<br>2nd highest QALYs<br>(out of 3 interventions) | G/P not cost effective<br>3rd lowest total costs<br>highest QALYs (together with SOF/VEL)<br>(out of 4 interventions) | G/P cost effective<br>2nd lowest total costs<br>2nd highest QALYs<br>(out of 3 interventions) | G/P not cost effective<br>3rd lowest total costs<br>highest QALYs (together with SOF/VEL)<br>(out of 4 interventions) |
| Source: Electronic model.[204]<br>GT = genotype; IFN = interferon; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); QALY = quality-adjusted life year; SOF = sofosbuvir; VEL = velpatasvir; | | | | |

A more detailed description of the cost effectiveness results per genotype is given below.

*GT1 patients*

The results of the base-case cost effectiveness analysis for GT1 non-cirrhotic patients showed that G/P dominated all its comparators, with the exception of no treatment, regardless of treatment history. Thus, for treatment-naïve patients G/P resulted in a total cost of £27,657, 16.30 QALYs and an ICER compared to no treatment of £2,239, while for treatment-experienced patients the total costs, total QALYs and ICER compared to no treatment were £27,604, 15.49 and £1,855, respectively. Therefore, at a threshold of £20,000 per QALY gained, G/P can be considered a cost effective treatment option for these subgroups.

For patients with compensated cirrhosis, different results were observed depending on the treatment history. Thus, for treatment-naïve patients G/P dominated all its comparators except EBR/GZR and no treatment, and resulted in a total cost of £55,208, 10.49 QALYs and an ICER compared to EBR/GZR of £10,633. For treatment-experienced patients G/P resulted in a total cost of £56,016 and 10.11 QALYs but it was dominated by SOF/VEL (produced more QALYs at lower costs), which presented an ICER of £6,144 compared to EBR/GZR.

*GT2 patients*

GT2 treatment-naïve patients were further subdivided based on IFN eligibility. For non-cirrhotic patients, G/P was cost effective depending on IFN eligibility. Thus, for IFN-eligible patients, G/P resulted in a total cost of £27,557, 16.30 QALYs and an ICER of £32,704 compared to PR. For IFN-ineligible patients G/P resulted in the same total costs and QALYs as in the IFN-eligible subgroup (the only difference between these two subgroups are the comparators included in the analysis) and an ICER of £4,433 compared to no treatment. For patients with compensated cirrhosis, the only difference between IFN-eligible and IFN-ineligible was that in the latter subgroup, SOF/RBV was added as an

additional comparator. However, SOF/RBV was extendedly dominated; thus, the results for G/P in GT2 treatment-naïve cirrhotic patients were the same regardless of IFN eligibility. In both cases G/P resulted in a total cost of £55,208 and 10.49 QALYs but it was dominated by SOF/VEL (produced same QALYs at lower costs), which presented an ICER of £3,498 compared to no treatment.

For GT2 treatment-experienced non-cirrhotic patients, G/P was the least expensive option, with the exception of no treatment, and resulted in a total cost of £28,745, 15.28 QALYs and an ICER compared to no treatment of £4,550. For patients with compensated cirrhosis, G/P resulted in a total cost of £54,832 and 10.25 QALYs but it was dominated by SOF/VEL (produced same QALYs at lower costs), which presented an ICER of £3,804 compared to no treatment.

*GT3 patients*

The results of the base-case cost effectiveness analysis for GT3 treatment-naïve patients showed that G/P was the least expensive option, with the exception of no treatment, regardless of cirrhosis status. Thus, for non-cirrhotic patients G/P resulted in a total cost of £28,619, 16.11 QALYs and an ICER compared to no treatment of £1,475, while for patients with compensated cirrhosis the total costs, total QALYs and ICER compared to no treatment were £55,604, 10.43 and £3,703, respectively.

For GT3 treatment-experienced, G/P was not cost effective, regardless of cirrhosis status. Thus, for non-cirrhotic patients G/P resulted in a total cost of £54,675, 15.33 QALYs and an ICER compared to SOF/PR of £157,141, while for patients with compensated cirrhosis the total costs, total QALYs and ICER compared to SOF/VEL were £69,411, 10.03 and £81,897, respectively.

*GT4 patients*

The results of the base-case cost effectiveness analysis for GT4 non-cirrhotic patients showed that G/P was the least expensive option, with the exception of no treatment, regardless of treatment history. Thus, for treatment-naïve patients G/P resulted in a total cost of £28,657, 16.06 QALYs and an ICER compared to no treatment of £3,033, while for treatment-experienced patients the total costs, total QALYs and ICER compared to no treatment were £27,271, 15.52 and £2,005, respectively.

For patients with compensated cirrhosis, G/P was dominated by SOF/VEL (produced same QALYs at lower costs) regardless treatment history. SOF/VEL was not cost effective in these subgroups. For treatment-naïve patients G/P resulted in a total cost of £55,208 and 10.49 QALYs, and for treatment-experienced patients these were £54,832 and 10.25, respectively.

*GT5 patients*

The results of the base-case cost effectiveness analysis for GT5 non-cirrhotic patients showed that G/P was the least expensive option, with the exception of no treatment, regardless of treatment history. Thus, for treatment-naïve patients G/P resulted in a total cost of £27,306, 16.33 QALYs and an ICER compared to no treatment of £2,417, while for treatment-experienced patients the results were the same as in GT4.

For patients with compensated cirrhosis, the results for G/P were the same as in GT4.

*GT6 patients*

The results of the base-case cost effectiveness analysis for GT6 non-cirrhotic patients showed that G/P was the least expensive option, with the exception of no treatment, regardless of treatment history. Thus, for treatment-naïve patients G/P resulted in a total cost of £29,501, 15.89 QALYs and an ICER compared to no treatment of £3,473, while for treatment-experienced patients the results were the same as in GT4.

For patients with compensated cirrhosis, the results for G/P were the same as in GT4.

### 5.2.11 Sensitivity analyses

Sensitivity analyses were undertaken in the 26 patient subgroups described in Section 5.2.3 of this report. Due to the large number of subgroups and comparators within each subgroup, the company judged it unfeasible to perform PSA/DSA for all treatment comparisons in all patient subgroups (cf. pp. 217 and 219 in the CS).[2] Thus, for each subgroup a comparison of G/P to a single comparator treatment was chosen. The comparator was selected as the one against which G/P had the lowest incremental net monetary benefit when valuing a QALY at £20,000. The comparators used by the company in the PSA/DSA are summarised per subgroup in Table 5.18.

**Table 5.18: Comparators used for PSA/DSA analyses**

| HCV genotype | Treatment-naïve | | Treatment-experienced | |
|---|---|---|---|---|
| | Non-cirrhotic | Compensated cirrhosis | Non-cirrhotic | Compensated cirrhosis |
| GT1 | SOF/LDV | EBR/GZR | OBV/PTV/RTV + DSV | SOF/VEL |
| GT2 | IFN-eligible: peg-IFN + RBV<br>IFN-ineligible: SOF + RBV | IFN-eligible: SOF/VEL<br>IFN-ineligible: SOF/VEL | SOF/VEL | SOF/VEL |
| GT3 | SOF/VEL | SOF/VEL | SOF + peg-IFN + RBV | SOF/VEL |
| GT4 | OBV/PTV/RTV | OBV/PTV/RTV | OBV/PTV/RTV | OBV/PTV/RTV |
| GT5 | SOF/VEL | SOF/VEL | SOF/VEL | SOF/VEL |
| GT6 | SOF/VEL | SOF/VEL | SOF/VEL | SOF/VEL |

Source: Table 113 in the CS.[2]
DSA = deterministic sensitivity analysis; DSV = dasabuvir; EBR = elbasvir; GT = genotype; GZR = grazoprevir; IFN = interferon; LDV = ledipasvir; OBV = ombitasvir; PSA = probabilistic sensitivity analysis; PTV = paritaprevir; peg-IFN = pegylated IFN; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; VEL = velpatasvir

**ERG comment:** The ERG considers that choosing a single comparator is methodologically incorrect and the interpretation of the results can be potentially misleading. In general, when more than two treatments have a positive cost effectiveness probability at a certain cost effectiveness threshold, restricting the analysis to two treatments only is likely to overestimate the cost effectiveness probability of the most cost effective treatment. Therefore, PSA with multiple comparators should have been performed.

**Probabilistic sensitivity analysis**

The company distinguished between treatment-specific and non-treatment specific input parameters. The first group included SVR rates, AE rates and treatment-related utility change. Treatment-specific input parameters were varied when possible using the 95% confidence intervals observed in the clinical trials. This was the case for SVR and AE rates, which were assumed to follow a Beta distribution, with the input parameters given by the trial subgroup sample size and percentage of patients achieving SVR or with an AE in that subgroup. SVR rates were summarised in Table 4.16 and AE rates in Table 5.9 and 5.10. Due to the lack of data, only for G/P was the treatment-related utility change (see Table 5.12)

included in the PSA, which was assumed to follow a Normal distribution. The non-treatment-specific input parameters included disease progression transition probabilities, health state costs and utilities and AE-related costs, and health utilities. A full list of the non-treatment-specific parameters with their corresponding lower and upper limits and assumed probability distributions can be found in Appendix 2. Other model input parameters (like treatment costs) were considered fixed and therefore not included in the PSA.

The company presented PSA results based on 500 model iterations. Results were reported as the probability that G/P is cost effective against the comparator chosen for each subgroup at £20,000 and £30,000 thresholds. As mentioned in Section 5.2.10, the ERG considered that reporting results for both thresholds might be confusing and given the high level of uncertainty associated with the input parameters of the model, only the results based on the £20,000 threshold are reported in this section. These probabilities can be seen in Table 5.19. For extensive PSA results, including cost effectiveness probabilities at the £30,000 threshold, we refer to Appendix 2. The model developed by the company can also produce scatter plots of the PSA outcomes on the cost effectiveness (CE) plane, a cost effectiveness acceptability curve (CEAC) and a cost effectiveness acceptability frontier (CEAF). However, these plots were not included in the CS.

**Table 5.19: G/P cost effectiveness probability (%) at £20,000 threshold (against a single comparator)**

| HCV genotype | Treatment-naïve | | Treatment-experienced | |
|---|---|---|---|---|
| | Non-cirrhotic | Compensated cirrhosis | Non-cirrhotic | Compensated cirrhosis |
| GT1 | 99.4% (SOF/LDV) | 60.8% (EBR/GZR) | 100% (OBV/PTV/RTV + DSV) | 12.0% (SOF/VEL) |
| GT2 | IFN-eligible: 2.4% (peg-IFN + RBV) | IFN-eligible: 43.8% (SOF/VEL) | 99.8% (SOF/VEL) | 37.6% (SOF/VEL) |
| | IFN-ineligible: 100% (SOF + RBV) | IFN-ineligible: 43.8% (SOF/VEL) | | |
| GT3 | 100% (SOF/VEL) | 74.0% (SOF/VEL) | 0.0% (SOF + peg-IFN + RBV) | 0.2% (SOF/VEL) |
| GT4 | 67.6% (OBV/PTV/RTV) | 14.4% (OBV/PTV/RTV) | 100% (OBV/PTV/RTV) | 1.6% (OBV/PTV/RTV) |
| GT5 | 100% (SOF/VEL) | 48.6% (SOF/VEL) | 100% (SOF/VEL) | 37.6% (SOF/VEL) |
| GT6 | 70.4% (SOF/VEL) | 46.6% (SOF/VEL) | 100% (SOF/VEL) | 45.4% (SOF/VEL) |

Source: Table 53 in the CS.[2]
DSV = dasabuvir; EBR = elbasvir; GT = genotype; GZR = grazoprevir; IFN = interferon; LDV = ledipasvir; OBV = ombitasvir; PSA = probabilistic sensitivity analysis; PTV = paritaprevir; peg-IFN = pegylated IFN; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; VEL = velpatasvir

**ERG comment:** There are two major flaws in the PSA results presented by the company. The first one was considering a single comparator instead of all possible comparators in the analyses. The second one was not including a large number of SVR and AE rates in the PSA. The impact of these two issues

separately on the PSA results is explained below. As a consequence, the ERG considers the PSA results in the CS unreliable.

Despite being judged unfeasible by the company, the ERG was able to run all PSAs including all treatment comparisons in all patient subgroups. Detailed results of these PSAs are presented in Appendix 2. The ERG observed that for all subgroups consisting of non-cirrhotic patients, only G/P and the comparator chosen by the company for the PSA (see Table 5.18 above), had a positive cost effectiveness probability at the £20,000 threshold. Therefore, Table 5.19 reports the appropriate cost effectiveness probabilities for G/P at the £20,000 threshold for non-cirrhotic patients. However, this was not the case for the subgroups considering patients with compensated cirrhosis. In all of these 13 subgroups, there were at least two comparators with a positive cost effectiveness probability at the selected threshold. Table 5.20 shows the G/P cost effectiveness probability at the £20,000 threshold for patients with compensated cirrhosis when G/P is compared against only one comparator (as chosen by the company) and when G/P is compared with all the relevant comparators for each of the subgroups (Table 5.6). Whereas in most of the subgroups the difference in cost effectiveness probability can be deemed minor, for GT1, GT3 and GT4 treatment-naïve cirrhotic patients, the company overestimated the cost effectiveness probability of G/P by at least 10%.

**Table 5.20: G/P cost effectiveness probability (%) at £20,000 threshold for patients with compensated cirrhosis in the company submission (against only one comparator) and with multiple comparators**

| HCV genotype | Treatment-naïve | | Treatment-experienced | |
|---|---|---|---|---|
| | One comparator* | All comparators** | One comparator* | All comparators** |
| GT1 | 60.8% | 50.2% | 12.0% | 9.0% |
| GT2 | IFN-eligible*: 43.8% | IFN-eligible: 40.0% | 37.6% | 38.6% |
| | IFN-ineligible*: 43.8% | IFN-ineligible: 40.6% | | |
| GT3 | 74.0% | 61.6% | 0.2% | 1.0% |
| GT4 | 14.4% | 0.6% | 1.6% | 1.8% |
| GT5 | 48.6% | 45.0% | 37.6% | 40.0% |
| GT6 | 46.6% | 46.0% | 45.4% | 42.4% |

GT = genotype; IFN = interferon
*Comparators in Table 5.18; **Comparators in Table 5.6.
Note: shaded cells indicate a difference of at least 10% in the cost effectiveness probability of G/P vs. one or all relevant comparators for each subgroup.

It should be emphasised that, even when all relevant comparators are included in the PSA, the resulting uncertainty associated with the PSA results was considerably underestimated in certain subgroups. This was mainly caused by a programming error made by the company. The company modelled SVR and AE rates based on the actual number of observed events in the trials. While in principle this is methodologically correct, in many cases these observed rates were 100% or 0%, mostly due to a very low number of patients in a subgroup where all of them achieved SVR or none of them had AEs. In that situation, the estimated mean SVR or AE rate would be 100% or 0% but the estimated standard deviation would be zero. In order to account for the uncertainty around these extreme rates, some

adjustments need to be made in the model. In the company's electronic model, it is explicitly mentioned that when an SVR or AE rate "*was equal to 0% or 100%, a solution have been implemented to allow variation when running the PSA based on Briggs et al. More specifically, +1 was added to the denominator of all SVR rates and +1 was added in the numerator and denominator of all AE rates. Otherwise, PSA variation was not possible and was therefore assumed to remain at the same level*" (cf. electronic model – e.g. sheet 'Inputs – AbbVie GP' cell AD209).[204] However, this correction was not applied in the PSA performed by the company. Consequently, many of these rates were kept fixed in the analyses and were not included in the PSA. This produced invalid results since SVR or AE rates of 100% or 0%, respectively, were most often found in subgroups with a very limited number of observed patients (for one subgroup going as low as n=2) and these were now associated with low uncertainty whereas the opposite should be expected. The number of parameters not included in the PSA, and therefore, the uncertainty associated to its results, varies per subgroup. Table 5.21 shows the probability that G/P is cost effective against all relevant comparators chosen for each subgroup at a £20,000 threshold when all SVR and AE rates were included in the PSA and the difference in probability with respect to the PSA not including all relevant SVR and AE rates. Shaded cells indicate a difference of at least 10% absolute difference in the cost effectiveness probability of G/P against all relevant comparators for each subgroup. It is clear from Table 5.21 that the inclusion of parameter uncertainty around all SVR and AE rates can have a major impact on the G/P cost effectiveness probability for certain subgroups; but also that this impact can go in either direction (although more frequently it decreases the G/P cost effectiveness probability). This is especially striking for GT5 TN NC patients, for whom the company might have overestimated the cost effectiveness probability of G/P by 66 percent.

**Table 5.21: G/P cost effectiveness probability (%) at £20,000 threshold against all comparators and including SVR and AE rates in PSA (difference with respect to PSA excluding SVR and AE rates in PSA)**

| HCV genotype | Treatment-naïve | | Treatment-experienced | |
|---|---|---|---|---|
| | Non-cirrhotic | Compensated cirrhosis | Non-cirrhotic | Compensated cirrhosis |
| GT1 | 100% (0%) | 57.0% (+7%) | 100% (0%) | 3.4% (-6%) |
| GT2 | IFN-eligible: 3.8% (+1%) | IFN-eligible: 56.2% (-16%) | 99.8% (0%) | 61.2% (+24%) |
| | IFN-ineligible: 100% (0%) | IFN-ineligible: 47.6% (+7%) | | |
| GT3 | 100% (0%) | 59.4% (-2%) | 0.0% (0%) | 1.0% (0%) |
| GT4 | 62.8% (-5%) | 9.4% (+9%) | 84.6% (-15%) | 2.4% (+1%) |
| GT5 | 34.4% (-66%) | 26.8% (-18%) | 99.6% (0%) | 20.0% (-20%) |
| GT6 | 41.2% (-29%) | 46.0% (0%) | 93.6% (-6%) | 37.8% (-4%) |

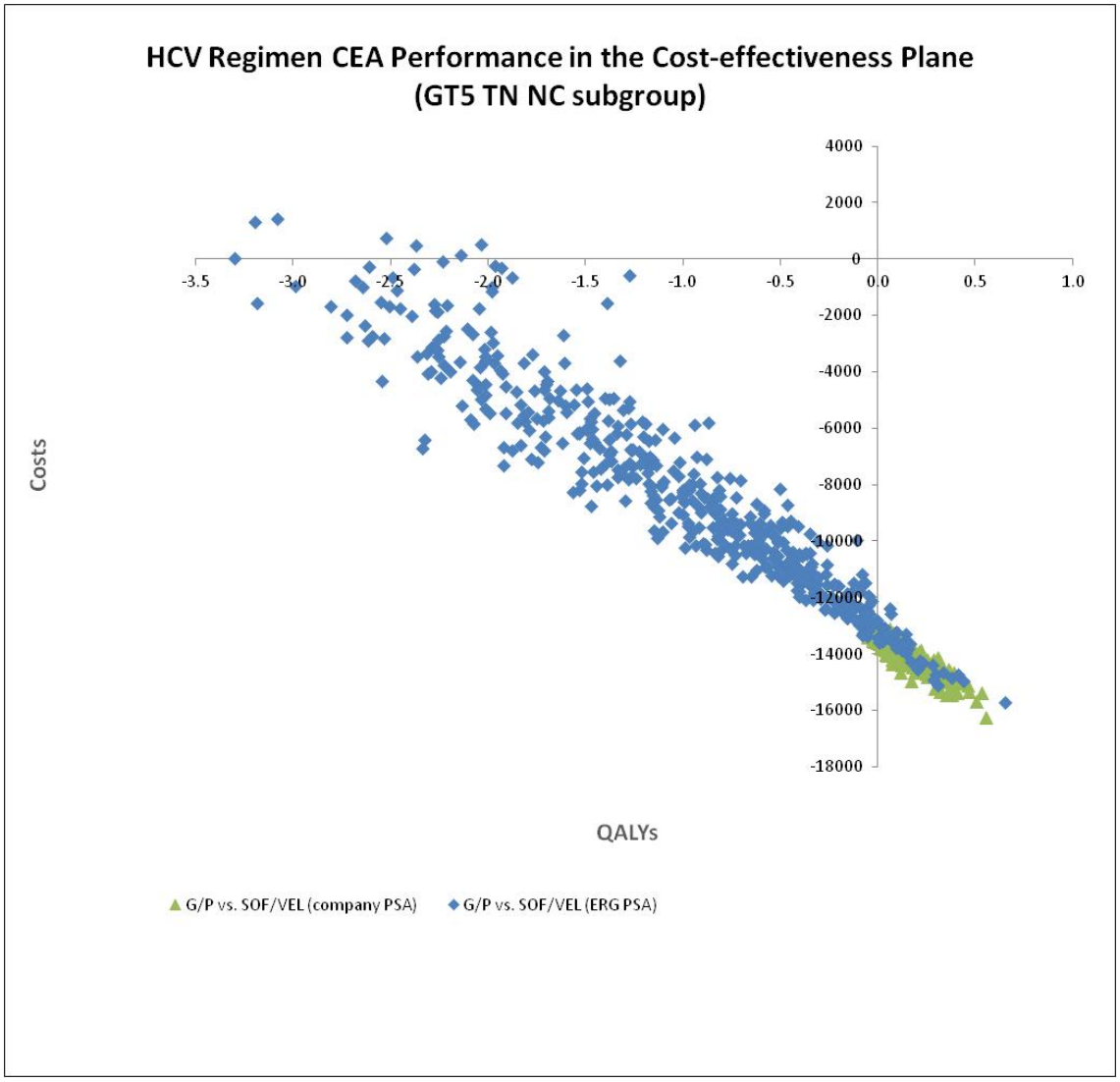
Source: Electronic model.[204]
GT = genotype; IFN = interferon; PSA = probabilistic sensitivity analysis

It should also be noted that a well-known feature of the cost effectiveness probability is that it only captures the probability of making the wrong decision, but not the consequences of making a wrong decision (as determined in a value of information analysis). For that reason, when reporting PSA results, it is considered insufficient to report only the cost effectiveness probability in any of its forms (table,

CEAC/CEAF) and a more detailed description of the PSA results should have been included in the CS (e.g. through plots of the PSA results on the CE-plane), especially for those subgroups for which high uncertainty was expected. This is illustrated below for GT5 TN NC and GT6 TN CC patients.

It was observed in Table 5.21 that the inclusion of all relevant SVR and AE rates reduced the cost effectiveness probability of G/P for GT5 TN NC patients by 66 percent. This can also be observed in Figure 5.2, where PSA results of G/P vs. SOF/VEL obtained with the company and ERG approaches were plotted on the cost effectiveness plane. This plot shows the great uncertainty (and skewness) of the ERG PSA results for this subgroup, which is intuitively credible when realising that the SVR rate of G/P was based on 2/2 patients, whereas the SVR rate for SOF/VEL was based on 28/29 patients.

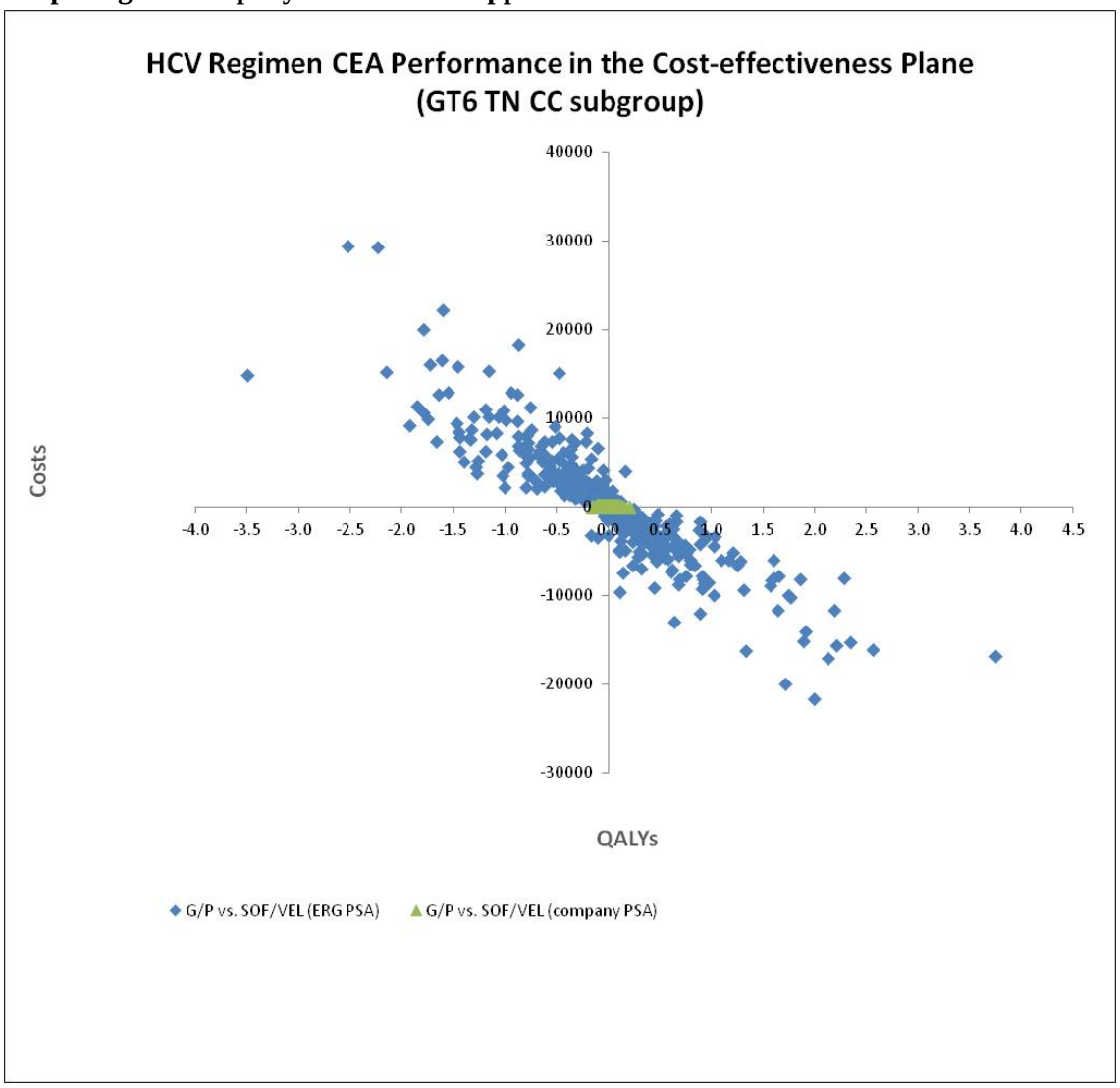
**Figure 5.2: Cost effectiveness plane with G/P vs. SOF/VEL PSA results for GT5 TN NC patients comparing the company and the ERG approaches**




Another interesting situation occurred for the GT6 TN CC subgroup. In Table 5.21, it was observed that the inclusion of all relevant SVR and AE rates did not change the cost effectiveness probability of G/P for these patients since it was 46% in both cases. However, by plotting the PSA results of G/P (SVR 6/6) vs. SOF/VEL (SVR 6/6) obtained with the company and ERG approaches on the cost effectiveness plane, it can be observed how different these two scenarios are. The plot in Figure 5.3 shows that although the number of PSA outcomes in the NW and SE quadrant might be comparable in both cases,

the ERG PSA outcomes are enormously scattered over these quadrants compared to the company's PSA outcomes. This scenario illustrates very clearly the main limitation of presenting cost effectiveness probabilities only. It shows two scenarios where these probabilities are comparable but the difference in decision uncertainty (e.g. in the consequences of making a wrong decision) is extremely large.

**Figure 5.3: Cost effectiveness plane with G/P vs. SOF/VEL PSA results for GT6 TN CC patients comparing the company and the ERG approaches**




Given the time constraints and the model complexity, the ERG could not produce detailed (corrected) PSA results for all subgroups. Nevertheless, it is considered that with the examples provided above, the major flaws in the PSA results presented by the company are properly explained. If it is judged that the analysis of uncertainty is a major concern for this submission, the PSA analyses should be repeated after tackling the issues presented in this section.

**Deterministic sensitivity analysis**

In response to the clarification letter,[17] the company presented tornado diagrams based on the INMB of G/P against one relevant comparator for all subgroups. These tornado diagrams were different from those presented in the original submission and they can also be found in Appendix 2. In Table 5.22 below, we indicate (based on the provided tornado diagrams) only those parameters for which the INMB changes its sign (from positive to negative or vice versa) since only these parameters are considered to

have the potential of reversing a cost effectiveness decision. For example, for the subgroup of GT1 non-cirrhotic treatment-naïve patients, the base-case INMB of G/P vs. SOF/LDV was positive. Therefore, in that case, G/P can be considered cost effective compared to SOF/LDV. The INMB remained positive for all the input parameters considered in the DSA except for the comparator SVR rates, which for high values resulted in a negative INMB. Thus, based on the DSA results for this subgroup, it can be concluded that only changes on the comparator SVR rates have the potential to make G/P not being considered cost effective. Overall, cost effectiveness based on INMB was not sensitive to changes on the input parameters considered in the DSA for 16 subgroups. For the other 10 subgroups, the INMB was most sensitive to changes in SVR rates for both intervention and comparator and for some utilities associated to the "recovered" health states.

**Table 5.22: Input parameters which might influence the cost effectiveness results according to DSA (against comparator)**

| HCV genotype | Treatment-naïve | | Treatment-experienced | |
|---|---|---|---|---|
| | **Non-cirrhotic** | **Compensated cirrhosis** | **Non-cirrhotic** | **Compensated cirrhosis** |
| GT1 | SVR rates comparator (SOF/LDV) | SVR rates comparator<br>Utility – SVR history of severe cirrhosis (EBR/GZR) | None (OBV/PTV/RTV + DSV) | SVR rates intervention (SOF/VEL) |
| GT2 | IFN-eligible: Utility – SVR history of mild fibrosis<br>SVR rates comparator (peg-IFN + RBV) | IFN-eligible: None (SOF/VEL) | SVR rates intervention (SOF/VEL) | None (SOF/VEL) |
| | IFN-ineligible: None (SOF + RBV) | IFN-ineligible: None (SOF/VEL) | | |
| GT3 | None (SOF/VEL) | SVR rates comparator<br>SVR rates intervention (SOF/VEL) | SVR rates comparator<br>Utility – SVR history of mild fibrosis (SOF + peg-IFN + RBV) | None (SOF/VEL) |
| GT4 | SVR rates intervention<br>Utility – SVR history of mild fibrosis<br>Utility – F1 (OBV/PTV/RTV) | SVR rates comparator (OBV/PTV/RTV) | None (OBV/PTV/RTV) | None (OBV/PTV/RTV) |
| GT5 | None (SOF/VEL) | None (SOF/VEL) | None (SOF/VEL) | None (SOF/VEL) |

| HCV genotype | Treatment-naïve | | Treatment-experienced | |
|---|---|---|---|---|
| | Non-cirrhotic | Compensated cirrhosis | Non-cirrhotic | Compensated cirrhosis |
| GT6 | SVR rates intervention<br>Utility – SVR history of mild fibrosis<br>Utility – F1 (SOF/VEL) | None (SOF/VEL) | None (SOF/VEL) | None (SOF/VEL) |

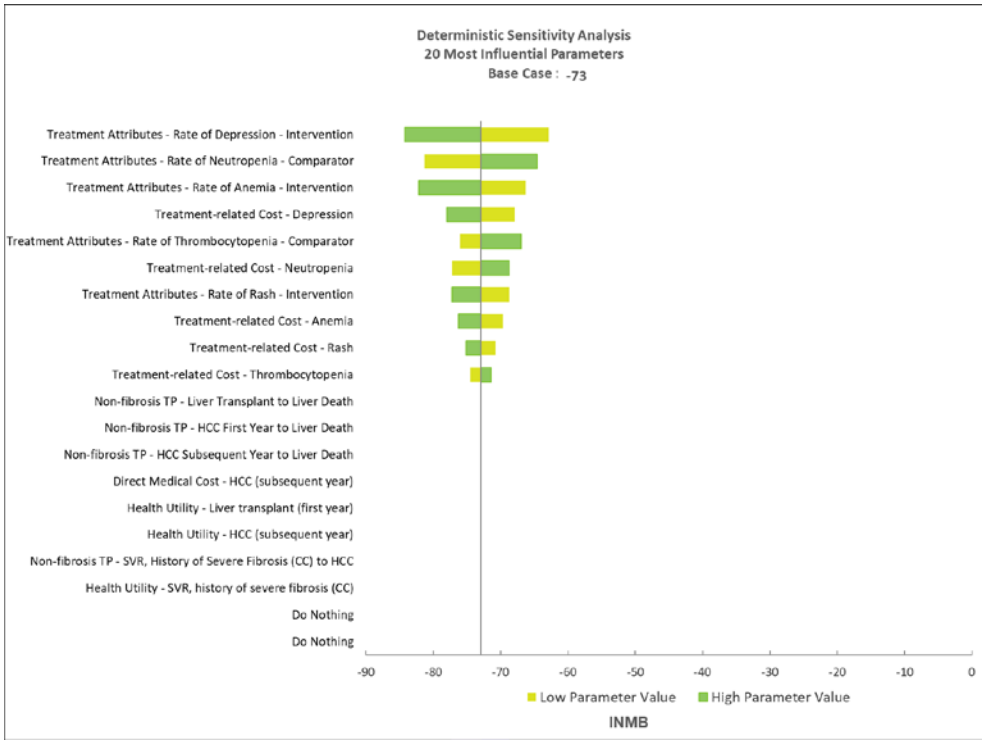
DSA = deterministic sensitivity analysis; DSV = dasabuvir; EBR = elbasvir; GT = genotype; GZR = grazoprevir; IFN = interferon; LDV = ledipasvir; OBV = ombitasvir; PSA = probabilistic sensitivity analysis; PTV = paritaprevir; peg-IFN = pegylated IFN; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; VEL = velpatasvir

Note: shaded cells indicate that the INMB of G/P vs. the corresponding comparator is positive and therefore, G/P can be considered cost effective in those cases.

**ERG comment:** Results were provided for G/P compared to a single comparator in each subgroup. Unlike PSAs, the ERG considers that this can be considered a pragmatic approach to DSA since an alternative methodology involving all comparators seems difficult to perform in practice. In any case, the DSA results should be interpreted with caution since the choice of a single comparator might produce biased results. If an indication of the degree of importance of individual parameters on the cost effectiveness results (including all comparators) is sought, then the expected value of partial perfect information seems a more reliable technique. This can be performed for example with the assistance of the SAVI tool.[205]

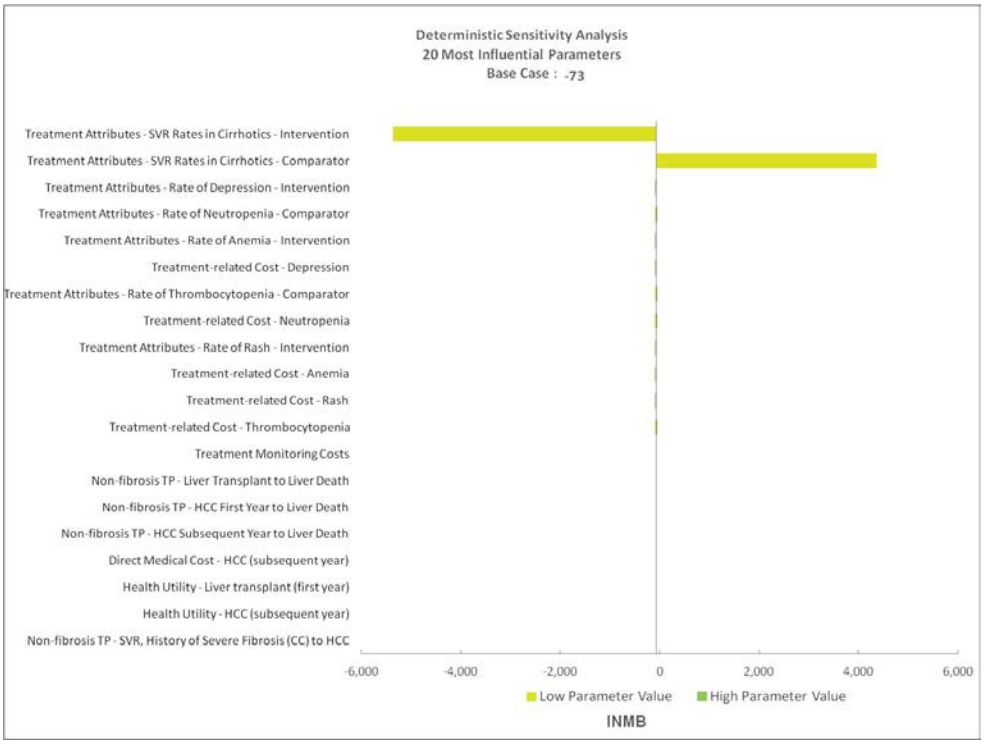
As explained in the PSA section, due to a programming error made by the company, many SVR and AE rates were not included in the DSA. This might produce misleading results since it can give the wrong impression that for subgroups based on a small number of patients the uncertainty is low, where the opposite should be expected. This is illustrated with Figure 5.4 and Figure 5.5. The first figure shows the tornado diagram provided by the company in response to the clarification letter for the subgroup of GT6 TE CC patients. Given the low number of patients in this subgroup used to estimate SVR rates (SVR rates for G/P based on five patients – cf. Table 4.16), one should expect high uncertainty associated to these parameters. However, these were not included in the DSA since they were assumed to be 100%. When lower limits for SVR rates were considered, Figure 5.5 shows that SVR rates are the parameters for which the INMB is most sensitive to changes. In fact, the difference in change in INMB with respect to the other parameters is so large that all the other parameters can be considered irrelevant. Given that these extreme rates often occur in subgroups with very few observations, it is not surprising that, when included in the DSA, these SVR rates are the parameters for which the model results are most sensitive. It should be noted though that this might have been a reporting error made by the company when presenting updated results after clarification. In all cases where a rate of 100% or 0% occurs, the model includes functionality to make sure that still a lower or upper boundary can be defined for the DSA. In Appendix L.1.3 of the CS, the tornado diagrams are based on this functionality. However, in the new set of results that was provided in their response to the clarification letter, the company did not invoke this functionality. Due to time constraints, the ERG could not correct this for all subgroups. The example shown here should be considered for illustrative purposes only and to indicate that the DSA results reported by the company (as presented in Appendix 2) can be unreliable for some subgroups.

**Figure 5.4: Tornado diagram: GT6 TE CC, G/P vs. SOF/VEL**




Source: response to clarification letter Appendix F.[17]

**Figure 5.5: Tornado diagram including lower limits for SVR rates: GT6 TE CC, G/P vs. SOF/VEL**




Source: Electronic model.[204]

### 5.2.12 Model validation and face validity check

In the CS (on page 222), it was mentioned that both technical/internal validation and external validation steps were undertaken.[2] In terms of technical validation, it was mentioned that two experienced, independent modellers reviewed the model structure and parameters and the software programme was checked and cleaned for potential programming errors by applying different routine tests. Furthermore, it was mentioned that the model's predictions were compared with the data that was used in the model, as part of the internal validation. The details and results of these validation efforts (technical/internal validation) were not reported.

As part of the external validation, the model's CC estimates for untreated mild-no fibrosis (F0) GT1 patients with specific baseline patient characteristics in line with Thein et al. 2008 were generated, and the 20-year post-infection CC rate from the model (21.3%) was compared with the cirrhosis estimates from other sources (Freeman et al. 2001, Alter and Seeff 2000, Seeff 2009 and Brady et al. 2007).[158, 206-209]

Freeman et al. 2001 reported a systematic review of 57 epidemiological studies.[207] The published studies were divided into four categories: liver clinic series, post-transfusion, blood donor and community-based studies. The mean prevalence of CC after 20 years of infection with HCV varied substantially among these four categories: 21.9% in the liver clinic series (N=492), 23.8 in the post-transfusion cohorts (N=72), 3.7% in the blood donor series (N=65) and 6.5% for the community based cohorts.

In Alter and Seeff 2000, the risk of progression to a severe clinical outcome at 20 years (defined as CC or HCC) was estimated to be approximately 20% from twelve studies examined adult patients with HCV.[208]

In a follow-up study by Seeff 2009, CC risk after 20 years from HCV infection was found to be 16%. This estimation varied substantially among different type of designs (18% for cross-sectional, 7% for retrospective-prospective studies, 18% for studies conducted in clinical setting and 7% for studies conducted in non-clinical setting).[209]

In Brady et al. 2007, in which an economic model was developed for the economic evaluation of PR for CHC treatment, a validation analysis was conducted and CC risk at 20 years was estimated to be around 19% for untreated patients.[206] This figure was in line with the review they conducted, which suggested a 20% risk of CC progression at 20 years for mild CHC patients.

**ERG comment:** In the CS, the details and the results of the technical and internal validation efforts were not reported. Upon ERG's request, more details on the model audit procedure was presented (Appendix B. 17 from the Response to the Clarification Letter).[17] Even though the description of the model auditing process gave a better overview of the technical validation efforts, the ERG considered that these efforts were mainly focused on the functionality of the drop-down menus or the VBA macros. In the description provided by the company, the types of the stress tests were lacking.

The ERG noticed several aspects of the model implementation that did not facilitate the technical validation of the model. For example, a number of hidden rows, which were active in the model's calculations, were controlled by a macro which made it unnecessarily complicated un-hiding them in order to check their values and references to other cells of the model. Activating an important functionality of the model as the one that includes estimates of lower or upper boundaries for SVR rates of 100% or AE rates of 0% was not straightforward. The PSA size is set within a macro but the sheet where this macro is recording the PSA outcomes is not prepared for a sample size larger than the default. While all these issues alone might be deemed as minor in other circumstances, given the large number

of subgroups included in the economic analyses, the adjustments that needs to be made for each of them (e.g. selecting the appropriate comparators) and the lack of time, the ERG considered that the aspects mentioned above could have been corrected in the model to facilitate its validation and to avoid an unnecessary burden on the ERG.

### *5.3 Exploratory and sensitivity analyses undertaken by the ERG*

In this section, the ERG conducted additional scenario analyses on the company base-case to explore the uncertainty around the assumptions taken in the company's base-case analysis. The ERG refrained from setting a preferred base-case, due to the concerns about the uncertainty surrounding SVR rates for the intervention and its comparators, which are caused by small sample sizes for some groups (e.g. n=2) as well as the method used to compare the effectiveness between treatments (naïve indirect comparison). Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses.

The following exploratory scenarios were conducted:

- No utility gain in SVR
- No treatment effect in utility
- Age based utility decrement
- Alternative transition probability inputs for fibrosis states
- Non-zero re-infection rates



#### 5.3.1 Scenario-1: No utility gain in SVR

In this scenario, it was assumed that after SVR, there is no additional gain in health utility, whereas in the base-case a utility gain of 0.05 was assumed. In this scenario, it was assumed that after SVR, there is no utility gain, whilst in the base-case a utility gain of 0.05 was assumed. The removal of this utility gain has no impact on the ranking of G/P regarding cost effectiveness (yes or no in a subgroup), total costs, and total QALYs; these remain the same as presented in Table 5.17.

#### 5.3.2 Scenario-2: No treatment specific health utility change

In this scenario, it was assumed that there is no treatment-related health utility change whilst on treatment. In the base-case, the values given in Table 5.12 were applied. Removing these utility adjustments had only an impact on the QALY ranking for GT4, GT5 and GT6, for TE NC patients. It had no impact on the ranking of G/P regarding cost effectiveness and total costs.

**Table 5.23: G/P cost effectiveness per subgroup, without a treatment-related utility adjustment (based on list price deterministic full incremental results)**

| HCV genotype | Treatment-naïve | | Treatment-experienced | |
|---|---|---|---|---|
| | Non-cirrhotic | Compensated cirrhosis | Non-cirrhotic | Compensated cirrhosis |
| GT1 | same as Table 5.17 | same as Table 5.17 | same as Table 5.17 | same as Table 5.17 |
| GT2 | IFN-ineligible: same as Table 5.17 | IFN-eligible: same as Table 5.17 | same as Table 5.17 | same as Table 5.17 |
| | IFN-ineligible: same as Table 5.17 | IFN-ineligible: same as Table 5.17 | | |
| GT3 | same as Table 5.17 | same as Table 5.17 | same as Table 5.17 | same as Table 5.17 |
| GT4 | same as Table 5.17 | same as Table 5.17 | G/P cost effective 2nd lowest total costs | G/P not cost effective |

| HCV genotype | Treatment-naïve | | Treatment-experienced | |
|---|---|---|---|---|
| | Non-cirrhotic | Compensated cirrhosis | Non-cirrhotic | Compensated cirrhosis |
| | | | *highest QALYs (together with SOF/VEL, EBR/GZR and OBV/PTV/RTV + DSV ± RBV)* | 4th lowest total costs<br>highest QALYs (together with SOF/VEL and *LDV/SOF*) |
| GT5 | same as Table 5.17 | same as Table 5.17 | G/P cost effective<br>2nd lowest total costs<br>*highest QALYs (together with SOF/VEL)* | same as Table 5.17 |
| GT6 | same as Table 5.17 | same as Table 5.17 | G/P cost effective<br>2nd lowest total costs<br>*highest QALYs (together with SOF/VEL)* | same as Table 5.17 |

Source: Electronic model.[204]
GT = genotype; IFN = interferon; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); QALY = quality-adjusted life year; SOF = sofosbuvir; VEL = velpatasvir; DSV = dasabuvir; EBR = elbasvir; GZR = grazoprevir; LDV = ledipasvir; OBV = ombitasvir; PTV = paritaprevir; RTV = ritonavir; RBV = ribavirin;



### 5.3.3 Scenario-3: Age-based utility decrement

In this scenario, age based utility decrements derived from Ara and Brazier 2010[210] were applied. In the base-case, no age based utility decrements were applied. The addition of these age based utility decrements has no impact on the ranking of G/P regarding cost effectiveness, total costs, and total QALYs; these remain the same as presented in Table 5.17.

### 5.3.4 Scenario-4: Alternative transition probabilities for the fibrosis states

In this scenario, alternative transition probabilities from Grischenko et al. 2009 were applied for the transitions between the fibrosis states.[178] In the base-case transition probabilities from Thein et al. 2008 were used.[158] When compared with the base-case results, the addition of these alternative transition probabilities has no impact on the ranking of G/P regarding cost effectiveness, total costs, and total QALYs; these remain the same as presented in Table 5.17.

### 5.3.5 Scenario-5: Non-zero re-infection rates

In this scenario, alternative probabilities for re-infection from SVR states were incorporated. The re-infection probability estimate of 0.0033 from Simmons et al. 2016[211] was assumed. In the base-case re-infection probability was assumed to be zero. The addition of these re-infection probabilities has no impact on the ranking of G/P regarding cost effectiveness, total costs, and total QALYs; these remain the same as presented in Table 5.17.

### *5.4 Conclusions of the cost effectiveness section*

The ERG considered that the economic model described in the CS meets the NICE reference case to a reasonable extent. While the economic model is in line with the decision problem formulated by the company, it is only partially in line with the scope. Intervention and comparators included in the company's economic analysis were also included in the scope. However, other relevant comparators listed in the NICE scope [1) DCV in combination with SOF, with or without RBV (for specific people with GT1 or GT4; as recommended by NICE); 2) IFN with RBV (for GT1–6; except in GT2 non-cirrhotic treatment-naïve patients); 3) SOF in combination with RBV, with or without IFN (for specific people with GT1 and GT4; as recommended by NICE)] were not included in the company's cost effectiveness analysis because, according to the company, these are not used in current NHS practice. Furthermore, despite being included in the scope, the company did not perform subgroup analyses for patients who are co-infected with HIV and post-liver transplantation. The subgroup of patients who are intolerant to or ineligible for interferon treatment were only considered for GT2 TN patients.

The ERG assessment indicated that the model was presented and reported appropriately except for the sensitivity analyses. The company developed a de novo cost effectiveness model to assess the cost effectiveness of G/P compared to nine different comparators: BSC-watchful waiting, DCV/SOF, DCV/SOF/RBV, EBR/GZR, LDV/SOF, OBV/PTV/DSV+DSV ± RBV, PR, SOF/PR, SOF/RBV and SOF/VEL.

The cost effectiveness analyses performed by the company are in line with previous STAs for HCV treatments. The population considered in the cost effectiveness analyses was sub-divided into 26 different subgroups, where patients were stratified by genotypes (GT1, GT2, GT3, GT4, GT5 and GT6), treatment experience (treatment-naïve and treatment-experienced patients), cirrhosis status (cirrhotic and non-cirrhotic patients) and IFN-eligibility (only for GT2 TN patients).

The cost effectiveness model developed for this submission was a Markov model which consists of 13 health states. Non-cirrhotic patients start from states F0-F3, and cirrhotic patients start from F4. All treatment related outcomes (achieving SVR, treatment related adverse events and discontinuation) occur within the first year of the model. Patients who do not achieve SVR are at risk of progressing to more severe states. Patients who reached F4 can progress to DC and HCC states, which may lead to liver transplantation and liver related death. Liver transplantation state was divided into two categories (first year and later years).

The model uses health state based utilities from the literature (utilities that were used in Wright et al. 2006[153] and Ratcliffe et al. 2002[161]) in line with previous STAs for HCV treatments. A utility increment of 0.05 due to SVR is applied based on Shepherd et al. 2007[154] and Hartwell et al. 2011[155]. Treatment-related health utility changes were applied to adjust for the impact on HRQoL of treatment, e.g. due to adverse events.

List prices were used as treatment costs for G/P and the comparator treatments in the cost effectiveness analysis. Health state costs (disease management costs based on disease stage) and other costs for adverse events were based on literature, expert opinion, UK reference costs and previous appraisals for HCV (especially TA430).

It should be noted that while the current model structure does not allow for sequential treatments, in clinical practice, patients who do not achieve SVR (who do not respond to the therapy or discontinue due to adverse events) or who were re-infected after SVR may receive further lines of treatments.

Onward transmission was not included in the economic model. Incorporating onward transmission would require a dynamic transmission model to capture an ongoing risk of infection for individuals in a population, and therefore could not be incorporated into the current modelling framework. Similarly, the company assumed a zero-reinfection probability after reaching SVR and assumed that no natural recovery takes place, despite contrary evidence reported in the clinical literature.

Treatment effectiveness was modelled as the probability of achieving SVR. Other treatment-specific parameters included adverse event rates, treatment duration, and treatment-related utility adjustments. All these parameter estimates were based on naïve indirect comparison of clinical trials assessing the efficacy of G/P and its comparators in the relevant subgroups. The ERG has concerns on the plausibility of this approach, which is not in line with the evidence synthesis best practices and susceptible to bias. Furthermore, some of the SVR rates were derived from very small sample sizes or the effectiveness in a subgroup was assumed to hold in another subgroup. Since SVR probability is the main driver of costs and effectiveness, all these assumptions create a substantial uncertainty on the cost effectiveness of G/P.

Furthermore, it was not clear to the ERG why age-dependent transition probabilities were not updated every year.

The health state utilities from RCTs could have been used by the company in their cost effectiveness analysis instead of the utilities from the literature. The ERG questions to what extend utility values published in 2006 (originating from EQ-5D questionnaires completed in 2002),[153] i.e. before the DAA-era, can be seen as representative of UK patients currently suffering with CHC. Similarly, the RCT-based utility values show a difference in utility with or without SVR ranging from 0.025 to 0.029, substantially lower than the increment of 0.05 applied by the company based on Wright et al. 2006[153] thus raising doubt about the validity of the latter value.

The impact of receiving treatment on QoL during treatment was taken into account in the company model using utility increments and decrements. However, most of these adjustment estimates were based on the same studies as the estimates of SVR rates and AE rates, implying that all comments regarding those (see Section 4.6) apply here as well.

The ERG was unsure about the completeness of the health state cost estimates used in the model, as items such as GP visits and home care costs are not included.

The base-case cost effectiveness results showed that, for non-cirrhotic patients, G/P was always cost effective except for the following two subgroups: GT2 treatment-naïve IFN-eligible patients and GT3 treatment-experienced patients. For the subgroups of non-cirrhotic patients for which G/P was cost effective, the relevant comparator was always no treatment, which resulted in very low ICERs (always below £5,000 per QALY). For patients with compensated cirrhosis, G/P was only cost effective for GT1 treatment-naïve and GT3 treatment-naïve patients. For some of the subgroups where G/P was not considered cost effective, the reason was that at least one of the comparators, which was considered cost effective, produced the same amount of QALYs at a lower cost. Thus, although G/P was dominated, it can be considered as equally effective as these comparators. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was as effective as at least one cost effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above cost effectiveness threshold).

Additionally, the company conducted probabilistic, deterministic and scenario analyses. Probabilistic results were reported as the probability that G/P is cost effective against one single comparator for each

subgroup at £20,000 and £30,000 thresholds. The comparator was selected as the one against which G/P had the lowest incremental net monetary benefit when valuing a QALY at £20,000. The result of the deterministic sensitivity analyses showed that in general the ICER was most sensitive to changes in SVR rates. Two scenario analyses conducted by the company first demonstrated how the cost effectiveness of G/P might change after the CMU price agreement (when comparators from other companies were based on list prices). Second, it was shown that using trial based utilities increased total QALY estimates compared to the base-case when literature based utilities were used as input.

There are two major flaws in the probabilistic analyses presented by the company. The first one was considering a single comparator instead of all possible comparators in the analyses. The second one was not including a large number of SVR and AE rates (those that were 100% or 0%) in the probabilistic analyses. As a consequence, the ERG considers the PSA results in the CS unreliable. Given the time constraints and the model complexity, the ERG could not produce detailed (corrected) PSA results for all subgroups. If it is judged that the analysis of uncertainty is a major concern for this submission, the PSA analyses should be repeated after taking care of the issues discussed in this report.

The ERG is concerned over the validation status of the cost effectiveness analysis by the company. The tests conducted for the technical verification of the model were not presented and the only validation effort was the external validation of the model estimates of the cirrhosis risk in 20 years from the clinical literature. The company submission would also benefit from a more transparent electronic model.

The ERG did not present an alternative base-case, since it was not clear that any alternative base-case assumptions would be properly justified, as in most situations the assumptions made by the company were reasonable and in line with previous appraisals. Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses. In the scenario analyses assumptions surrounding the utility gain due to SVR, impact of the treatment on utility, impact of age on utility were challenged. In addition alternative inputs for transition probabilities in between fibrosis stages and re-infection rates were explored. Even though these scenarios changed the total costs and/or total QALYs estimates, the impact on incremental results were minimal. The cost effectiveness of G/P in each subgroup did not change, hence the cost effectiveness results of the base-case seem to be robust to changes in utility and treatment unrelated clinical model inputs.

In addition, the exploratory PSA analyses conducted by the ERG showed that that the inclusion of parameter uncertainty around all SVR and AE rates (which was not included in the company’s base-case) can have a major impact on the G/P cost effectiveness probability for certain subgroups; but also that this impact can go in either direction (although more frequently it decreases the G/P cost effectiveness probability). This was especially striking for GT5 TN NC patients, for whom the company might have overestimated the cost effectiveness probability of G/P by 66 percent. Furthermore, the ERG showed that the PSA outcomes were enormously scattered over the CE plane quadrants for a number of subgroups and illustrated the main limitation of presenting cost effectiveness probabilities only (as in the CS).

## 6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG has not presented an alternative base-case, since it was not clear that any alternative base-case assumptions would be properly justified, as in most situations the assumptions made by the company were reasonable and in line with previous appraisals. Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses in Section 5.3.

# 7. OVERALL CONCLUSIONS

## *7.1 Statement of principal findings*

Eighty-one publications (reporting on 79 studies) were identified as meeting the eligibility criteria. Fourteen of these publications, representing seven studies, involved G/P. In addition, information on four further clinical studies of G/P in patients with CHC are included in the company submission. These studies were conducted in special populations of patients with HIV co-infection, renal impairment, failure on prior DAAs and a post-transplant population. Finally, the company mentions two trials in Japanese patients with CHC: CERTAIN-1 and CERTAIN-2. These trials are only minimally discussed in the CS and not included in the economic model because "*these two trials were conducted entirely in Japanese patients*" which "*precludes their generalisability to the UK patient population and subsequently their use in the economic model*", according to the company.[2] Apart from these two trials in Japanese patients, none of the included studies presented comparative data for the licensed treatment duration of G/P with any of the comparators.

The G/P studies included patients with all genotypes; treatment-naïve and experienced patient populations; and patients with 'no cirrhosis and compensated cirrhosis'.

When split by cirrhosis status and previous treatment (naïve or experienced), SVR rates were consistently above 90% for all genotypes, except for GT2/TE/NC ([redacted] in SURVEYOR-II, Part 4; but [redacted] in SURVEYOR-II, Parts 1 and 2), GT3/TE/CC ([redacted] in SURVEYOR-II, Part 2; but [redacted] in SURVEYOR-II, Part 3) and GT6/TN/NC ([redacted] in SURVEYOR-II, Part 4).

Health-related quality of life (HRQoL) questionnaires indicated [redacted] In studies without a comparator, many treatment arms [redacted]

According to the company, G/P has a favourable safety profile that was similar to placebo and SOF/DCV, and that was similar across durations of eight, 12, and 16 weeks. G/P was well tolerated across a broad and diverse population of patients, including patients with CC, HIV co-infection, and CKD Stage 4/5. Common study adverse drug reactions (ADRs) occurring in ≥5% of patients were headache, fatigue, and nausea. Adverse drug reactions were mostly Grade 1 (mild) in severity. Serious ADRs and ADRs leading to premature study drug discontinuation were rare (≤0.1%).

The results of the company's base-case showed that, for non-cirrhotic patients, G/P was always cost effective except for the following two subgroups: GT2 treatment-naïve IFN-eligible patients and GT3 treatment-experienced patients. For the subgroups of non-cirrhotic patients for which G/P was cost effective, the relevant comparator was always no treatment, which resulted in very low ICERs (always below £5,000 per QALY). For patients with compensated cirrhosis, G/P was only cost effective for GT1 treatment-naïve and GT3 treatment-naïve patients. For some of the subgroups where G/P was not considered cost effective, the reason was that at least one of the comparators, which was considered cost effective, produced the same amount of QALYs at a lower cost. Thus, although G/P was dominated, it can be considered as equally effective as these comparators. Thus, in summary, at a cost effectiveness threshold of £20,000 per QALY gained, G/P was considered cost effective in 13 of 26 subgroups. In seven of the 13 subgroups where G/P was not cost effective, G/P was as effective as at least one cost effective comparator. In the remaining six subgroups, G/P was clearly not cost effective (ICER above

cost effectiveness threshold). Probabilistic results were reported by the company as the probability that G/P is cost effective against one single comparator for each subgroup at £20,000 and £30,000 thresholds. However, the ERG showed that including all comparators in the PSA could substantially alter the probability that G/P would be cost effective. The result of the deterministic sensitivity analyses showed that in general the ICER was most sensitive to changes in SVR rates. Two scenario analyses conducted by the company first demonstrated how the cost effectiveness of G/P might change after the CMU price agreement (when comparators from other companies were based on list prices). Second, it was shown that using trial based utilities increased total QALY estimates compared to the base-case when literature based utilities were used as input, without really altering the conclusions from the base-case analyses.

The ERG did not present an alternative base-case, since it was not clear that any alternative base-case assumptions would be properly justified, as in most situations the assumptions made by the company were reasonable and in line with previous appraisals. Instead of setting a preferred base-case, the ERG conducted a number of exploratory scenario analyses.

In the scenario analyses assumptions surrounding the utility gain due to SVR, impact of the treatment on utility, impact of age on utility were challenged. In addition alternative inputs for transition probabilities in between fibrosis stages and re-infection rates were explored. Even though these scenarios changed the total costs and/or total QALYs estimates, the impact on incremental results were minimal. The cost effectiveness of G/P in each subgroup did not change, hence the cost effectiveness results of the base-case seem to be robust to changes in utility and treatment unrelated clinical model inputs.

The exploratory PSA analyses conducted by the ERG showed that that the inclusion of parameter uncertainty around all SVR and AE rates (which was not included in the company's base-case whenever rates were 100% or 0%) can have a major impact on the G/P cost effectiveness probability for certain subgroups; but also that this impact can go in either direction (although more frequently it decreases the G/P cost effectiveness probability). This was especially striking for GT5 TN NC patients, for whom the company might have overestimated the cost effectiveness probability of G/P by 66 percent. Furthermore, the ERG showed that the PSA outcomes were enormously scattered over the CE plane quadrants for a number of subgroups and illustrated the main limitation of presenting cost effectiveness probabilities only (as in the CS).

### *7.2 Strengths and limitations of the assessment*

The conclusion from the G/P studies is that G/P has high SVR rates in all genotypes. In addition, G/P has a relatively favourable safety and tolerability profile. However, patient numbers for most GT4, GT5 and GT6 populations are very low, often less than 10 patients in each group. Only three out of the 24 subgroups included more than 100 patients (GT1/TN/NC, GT1/TE/NC and GT2/TN/NC). Therefore, the uncertainty around SVR rates in most subgroups is considerable.

The main concern regarding clinical effectiveness is that data (for SVR12 and AEs) for G/P and comparators were taken from single arms. Therefore, the comparisons for SVR12 rates and AEs between G/P and comparators relies on a naïve indirect comparison. The company does not present any information about the comparability of populations between G/P studies and comparator studies; and about how response and adverse events for comparator studies were selected and whether all possible sources were used. In most cases the sources for SVR rates and AEs for comparators are the same as in TA430 (Sofosbuvir-velpatasvir for treating chronic hepatitis C). Therefore, the same critique as for TA430 applies: these methods increase the chance of bias and cherry-picking.

The main strength of the CS is that the structure of the economic model is in line with previous models presented in appraisals for HCV submitted to NICE and therefore, it reflects the main aspects of the chronic HCV disease. The model also includes relevant adverse events, utilities and costs.

The main limitation of the CS is that, since the key parameters in the cost effectiveness analyses (SVR rates) were based on the treatment effectiveness data, all health economic analyses suffered from the uncertainty of clinical effectiveness (comparative SVR rates). Furthermore, both probabilistic and deterministic sensitivity analyses presented by the company were performed incorrectly. As a consequence, the sensitivity analysis results in the CS are unreliable. If it is judged that the analysis of uncertainty is a major concern for this submission, these analyses should be repeated after tackling the issues discussed in this report. The company submission would also benefit from a more transparent electronic model.

### *7.3 Suggested research priorities*

Head to head trials of direct-acting antivirals (DAAs) are warranted in patients with HCV.

Clinical and cost effectiveness for the treatment sequences in HCV should be explored. Furthermore, subgroup analyses for the cost effectiveness of G/P in interferon ineligible/intolerant populations and patients co-infected with HIV should be conducted. The population level effects of new DAA treatments should be explored via a dynamical model. In the current landscape, a MTA of non-DAA, partly DAA and all-DAA treatment regimens would guide the decision makers and benefit the efficient use of resources of the UK healthcare system. Non-RCT based utility studies for HCV health states would help to understand the difference between the estimates in Wright et al. 2006[153] and utilities directly obtained from the DAA RCTs.

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**Appendix 1: Further critique of searches in the company submission**

- Using both American and UK spellings would have helped improve the thoroughness of searching. For example,"randomized controlled trial"[Title/Abstract] in the clinical effectiveness searches should have been "randomized controlled trial" or "randomised controlled trial" ; "cost AND minimization AND analysis" in Appendix A3 should have been: "cost AND minimization AND analysis" or "cost AND minimisation AND analysis"
- It is redundant to search for "random$"[Title/Abstract] and "randomization"[Title/Abstract] as the truncated random$ will find randomization. This is the same for "placebo$"[Title/Abstract] which will find both placebo and placebos.
- Searching for CAS numbers for drugs would have helped improve the thoroughness of the searching. For example 1365970-03-1 for glecaprevir.
- Additional synonyms could have also been added to searches for some of the drugs. For example hepcinat, hepcvir, sovihep and resof are all synonyms for sofosbuvir that could have been looked for.
- Time could have been saved by using a MeSH browser to find the correct MeSH headings. For example, there is no MeSH for "crossover procedure", "double-blind procedure" or "non a non be hepatitis" so no need to search for these using MeSH.
- Looking up the correct terms for EMTREE would also save time. For example, "hepatitis non A non B" is the correct EMTREE term and not "non a non b hepatitis" which was also searched for as an EMTREE term.
- There are also a number of EMTREE terms for the interventions of interest which were not looked for. For example, sofosbuvir, velpatasvir, elbasvir, ombitasvir, ledipasvir, daclatasvir, grazoprevir, simeprevir, paritaprevir, pibrentasvir and glecaprevir all have EMTREE headings.
- Parentheses were poorly applied in a number of Embase searches. For example:

| | | |
|---|---|---|
| #4 | (((**quality** AND **adjusted** AND **life** AND year$ OR qaly$ OR **life**) AND year$ AND **gained** OR **life**) AND year$ AND equivalent$ OR **incremental**) AND **cost** AND effective$ OR **icer** | **13800** |

A more faithful update of the original TA430 search would have been:

((quality adjusted life year$ OR qaly$) OR (life year$ gained) OR (life year$ equivalent$) OR (incremental cost effective$) OR (icer))

## Appendix 2: List price base-case incremental cost effectiveness results

This appendix presents the base-case incremental cost effectiveness results summarised as reported by the company in Appendix B14 in the clarification responses.[17] The cost effectiveness results in the CS, were obtained from an early version of the economic model which was acknowledged by the company as an (cf. response to Question B14 in the clarification letter).[17] The results presented below are based on list prices for G/P and all comparators.

### *GT1 patients*

**Table A.1: List price base-case incremental cost effectiveness analysis results for GT1 TN NC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 19,514 | 18.77 | 12.66 | NA |
| G/P | 27,657 | 20.40 | 16.30 | 2,239 |
| SOF/LDV | 28,437 | 20.34 | 16.15 | Dominated |
| 3D/2D | 37,718 | 20.38 | 16.23 | Dominated |
| EBR/GZR | 39,224 | 20.31 | 16.08 | Dominated |
| SOF/VEL | 40,860 | 20.39 | 16.28 | Dominated |

Source: Table 1 – Appendix B14 in response to the clarification letter.[17]
DSV = dasabuvir; EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LDV = ledipasvir; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

**Table A.2: List price base-case incremental cost effectiveness analysis results for GT1 TN CC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 43,322 | 13.35 | 7.13 | NA |
| EBR/GZR | 53,678 | 17.40 | 10.34 | 3,228 |
| G/P | 55,208 | 17.57 | 10.49 | 10,633 |
| SOF/VEL | 55,513 | 17.51 | 10.44 | Dominated |
| SOF/LDV | 56,509 | 17.32 | 10.28 | Dominated |
| 3D/2D | 76,663 | 17.42 | 10.35 | Dominated |

Source: Table 2 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis; DSV = dasabuvir; EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LDV = ledipasvir; LYG = life-years gained; N/A = not applicable; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

**Table A.3: List price base-case incremental cost effectiveness analysis results for GT1 TE NC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 20,977 | 17.99 | 11.92 | NA |
| G/P | 27,604 | 19.82 | 15.49 | 1,855 |
| 3D/2D | 37,695 | 19.79 | 15.42 | Dominated |
| EBR/GZR | 39,248 | 19.71 | 15.28 | Dominated |
| SOF/VEL | 40,849 | 19.81 | 15.47 | Dominated |
| SOF/LDV | 41,519 | 19.75 | 15.35 | Dominated |

Source: Table 3 – Appendix B14 in response to the clarification letter.[17]
DSV = dasabuvir; EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LDV = ledipasvir; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

**Table A.4: List price base-case incremental cost effectiveness analysis results for GT1 TE CC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 42,629 | 13.18 | 7.04 | NA |
| EBR/GZR | 54,017 | 16.89 | 10.02 | 3,824 |
| SOF/VEL | 55,132 | 17.11 | 10.20 | 6,144 |
| G/P | 56,016 | 16.99 | 10.11 | Dominated |
| SOF/LDV | 58,542 | 16.62 | 9.80 | Dominated |
| 3D/2D | 75,680 | 17.11 | 10.19 | Dominated |

Source: Table 4 – Appendix B14 in response to the clarification letter.[17]

CC = compensated cirrhosis; DSV = dasabuvir; EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LDV = ledipasvir; LYG = life-years gained; N/A = not applicable; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

***GT2 patients***

**Table A.5: List price base-case incremental cost effectiveness analysis results for GT2 TN NC patients (IFN-eligible)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| Peg-IFN + RBV | 9,847 | 20.25 | 15.76 | NA |
| No treatment | 15,238 | 19.49 | 13.52 | Dominated |
| G/P | 27,557 | 20.41 | 16.30 | 32,704 |

Source: Table 5 – Appendix B14 in response to the clarification letter.[17]
G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; Peg-IFN = pegylated IFN; QALY = quality-adjusted life year; RBV = ribavirin; TN = treatment-naïve

**Table A.6: List price base-case incremental cost effectiveness analysis results for GT2 TN NC patients (IFN-ineligible)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 15,238 | 19.49 | 13.52 | NA |
| G/P | 27,557 | 20.41 | 16.30 | 4,433 |
| SOF/RBV | 37,839 | 20.39 | 16.22 | Dominated |
| SOF/VEL | 40,619 | 20.41 | 16.31 | 1,710,917 |

Source: Table 6 – Appendix B14 in response to the clarification letter.[17]
G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naïve

**Table A.7: List price base-case incremental cost effectiveness analysis results for GT2 TN CC patients (IFN-eligible)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 44,514 | 13.98 | 7.48 | NA |
| SOF/VEL | 55,041 | 17.57 | 10.49 | 3,498 |
| G/P | 55,208 | 17.57 | 10.49 | Dominated |

Source: Table 7 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; QALY = quality-adjusted life year; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

**Table A.8: List price base-case incremental cost effectiveness analysis results for GT2 TN CC patients (IFN-ineligible)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 44,514 | 13.98 | 7.48 | NA |
| SOF/RBV | 54,848 | 17.20 | 10.17 | Extended dominance |
| SOF/VEL | 55,041 | 17.57 | 10.49 | 3,498 |
| G/P | 55,208 | 17.57 | 10.49 | Dominated |

Source: Table 8 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

**Table A.9: List price base-case incremental cost effectiveness analysis results for GT2 TE NC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 17,098 | 18.69 | 12.72 | NA |
| G/P | 28,745 | 19.74 | 15.28 | 4,550 |
| SOF/RBV | 39,472 | 19.70 | 15.19 | Dominated |
| SOF/VEL | 40,444 | 19.83 | 15.52 | 47,391 |

Source: Table 9 – Appendix B14 in response to the clarification letter.[17]
G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

**Table A.10: List price base-case incremental cost effectiveness analysis results for GT2 TE CC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 43,738 | 13.78 | 7.37 | NA |
| SOF/VEL | 54,665 | 17.17 | 10.25 | 3,804 |
| G/P | 54,832 | 17.17 | 10.25 | Dominated |
| SOF/RBV* | 58,295 | 16.40 | 9.58 | Dominated |

Source: Table 10 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir
* Reporting in the table provided by the company. Corrected based on the electronic model.

***GT3 patients***

**Table A.11: List price base-case incremental cost effectiveness analysis results for GT3 TN NC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 22,440 | 18.03 | 11.92 | NA |
| G/P | 28,619 | 20.30 | 16.11 | 1,475 |
| SOF/VEL | 40,826 | 20.38 | 16.26 | 83,021 |
| SOF/DCV | 61,608 | 20.35 | 16.19 | Dominated |

Source: Table 11 – Appendix B14 in response to the clarification letter.[17]
DCV = daclatasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

**Table A.12: List price base-case incremental cost effectiveness analysis results for GT3 TN CC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 42,077 | 12.69 | 6.78 | NA |
| G/P | 55,604 | 17.49 | 10.43 | 3,703 |
| SOF/VEL | 55,874 | 17.41 | 10.36 | Dominated |
| SOF/PR | 56,027 | 17.15 | 10.12 | Dominated |
| SOF/RBV | 93,001 | 16.48 | 9.62 | Dominated |
| SOF/DCV | 129,294 | 17.57 | 10.45 | 3,106,990 |

Source: Table 12 – Appendix B14 in response to the clarification letter.[17]
Abbreviations: CC = compensated cirrhosis; DCV = daclatasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; peg-IFN = pegylated IFN; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

**Table A.13: List price base-case incremental cost effectiveness analysis results for GT3 TE NC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 23,577 | 17.28 | 11.23 | NA |
| SOF/PR | 40,436 | 19.69 | 15.24 | 4,214 |
| SOF/VEL | 42,376 | 19.61 | 15.15 | Dominated |
| G/P | 54,675 | 19.72 | 15.33 | 157,141 |
| SOF/DCV | 62,256 | 19.68 | 15.26 | Dominated |

Source: Table 13 – Appendix B14 in response to the clarification letter.[17]
DCV = daclatasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; peg-IFN = pegylated IFN; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

**Table A.14: List price base-case incremental cost effectiveness analysis results for GT3 TE CC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 41,467 | 12.54 | 6.70 | NA |
| SOF/PR | 57,088 | 16.51 | 9.70 | Extended dominance |
| SOF/VEL | 57,265 | 16.70 | 9.89 | 4,952 |
| G/P | 69,411 | 16.89 | 10.03 | 81,987 |
| SOF/RBV | 97,406 | 15.27 | 8.76 | Dominated |
| SOF/DCV | 128,918 | 17.17 | 10.21 | 336,033 |

Source: Table 14 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis; DCV = daclatasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; peg-IFN = pegylated IFN; QALY = quality-adjusted life year; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

***GT4 patients***

**Table A.15: List price base-case incremental cost effectiveness analysis results for GT4 TN NC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 18,786 | 18.90 | 12.81 | NA |
| G/P | 28,657 | 20.30 | 16.06 | 3,033 |
| OBV/PTV/RTV | 35,017 | 20.42 | 16.33 | 23,580 |
| EBR/GZR | 37,989 | 20.42 | 16.33 | Dominated |
| SOF/VEL | 40,573 | 20.42 | 16.34 | 1,203,376 |

Source: Table 15 – Appendix B14 in response to the clarification letter.[17]
EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

**Table A.16: List price base-case incremental cost effectiveness analysis results for GT4 TN CC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 43,442 | 13.41 | 7.17 | NA |
| OBV/PTV/RTV | 49,957 | 17.43 | 10.38 | 2,031 |
| EBR/GZR | 52,551 | 17.57 | 10.48 | 25,133 |
| SOF/VEL | 55,135 | 17.57 | 10.49 | 373,179 |
| G/P | 55,208 | 17.57 | 10.49 | Dominated |
| SOF/LDV | 55,273 | 17.57 | 10.48 | Dominated |

Source: Table 16 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis; EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LDV = ledipasvir; LYG = life-years gained; N/A = not applicable; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

**Table A.17: List price base-case incremental cost effectiveness analysis results for GT4 TE NC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 20,320 | 18.11 | 12.05 | NA |
| G/P | 27,271 | 19.83 | 15.52 | 2,005 |
| OBV/PTV/RTV | 34,980 | 19.83 | 15.51 | Dominated |
| EBR/GZR | 37,935 | 19.83 | 15.52 | Dominated |
| SOF/VEL | 40,538 | 19.83 | 15.52 | 3,858,701 |
| SOF/LDV | 43,619 | 19.57 | 14.98 | Dominated |

Source: Table 17 – Appendix B14 in response to the clarification letter.[17]
EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LDV = ledipasvir; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

**Table A.18: List price base-case incremental cost effectiveness analysis results for GT4 TE CC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 42,741 | 13.24 | 7.08 | NA |
| OBV/PTV/RTV | 49,141 | 17.10 | 10.19 | 2,055 |
| SOF/VEL | 54,759 | 17.17 | 10.25 | 101,059 |
| G/P | 54,832 | 17.17 | 10.25 | Dominated |
| SOF/LDV | 54,897 | 17.17 | 10.24 | Dominated |
| EBR/GZR | 61,267 | 15.86 | 9.18 | Dominated |

Source: Table 18 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis; EBR = elbasvir; G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GZR = grazoprevir; GT = genotype; ICER = incremental cost effectiveness ratio; LDV = ledipasvir; LYG = life-years gained; N/A = not applicable; OBV = ombitasvir; PTV = paritaprevir; QALY = quality-adjusted life year; RTV = ritonavir; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

***GT5 patients***

**Table A.19: List price base-case incremental cost effectiveness analysis results for GT5 TN NC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 18,786 | 18.90 | 12.81 | NA |
| G/P | 27,306 | 20.42 | 16.33 | 2,417 |
| SOF/VEL | 41,179 | 20.37 | 16.22 | Dominated |

Source: Table 19 – Appendix B14 in response to the clarification letter.[17]
G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; QALY = quality-adjusted life year; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

**Table A.20: List price base-case incremental cost effectiveness analysis results for GT5 TN CC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 43,442 | 13.41 | 7.17 | NA |
| SOF/VEL | 55,135 | 17.57 | 10.49 | 3,524 |
| G/P | 55,208 | 17.57 | 10.49 | Dominated |
| SOF/PR | 67,669 | 15.49 | 8.79 | Dominated |

Source: Table 20 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis = G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; QALY = quality-adjusted life year; peg-IFN = pegylated IFN; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

**Table A.21: List price base-case incremental cost effectiveness analysis results for GT5 TE NC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 20,320 | 18.11 | 12.05 | NA |
| G/P | 27,271 | 19.83 | 15.52 | 2,005 |
| SOF/VEL | 40,538 | 19.83 | 15.52 | 3,858,701 |

Source: Table 21 – Appendix B14 in response to the clarification letter.[17]
G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; QALY = quality-adjusted life year; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

**Table A.22: List price base-case incremental cost effectiveness analysis results for GT5 TE CC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 42,741 | 13.24 | 7.08 | NA |
| SOF/VEL | 54,759 | 17.17 | 10.25 | 3,791 |
| G/P | 54,832 | 17.17 | 10.25 | Dominated |
| SOF/PR | 67,130 | 15.20 | 8.62 | Dominated |

Source: Table 22 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis = G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; QALY = quality-adjusted life year; peg-IFN = pegylated IFN; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

***GT6 patients***

**Table A.23: List price base-case incremental cost effectiveness analysis results for GT6 TN NC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 18,786 | 18.90 | 12.81 | NA |
| G/P | 29,501 | 20.23 | 15.89 | 3,473 |
| SOF/VEL | 40,573 | 20.42 | 16.34 | 24,958 |

Source: Table 23 – Appendix B14 in response to the clarification letter.[17]
G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; QALY = quality-adjusted life year; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

**Table A.24: List price base-case incremental cost effectiveness analysis results for GT6 TN CC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 43,442 | 13.41 | 7.17 | NA |
| SOF/VEL | 55,135 | 17.57 | 10.49 | 3,524 |
| G/P | 55,208 | 17.57 | 10.49 | Dominated |
| SOF/PR | 67,669 | 15.49 | 8.79 | Dominated |

Source: Table 24 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis = G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; QALY = quality-adjusted life year; peg-IFN = pegylated IFN; RBV = ribavirin; SOF = sofosbuvir; TN = treatment-naïve; VEL = velpatasvir

**Table A.25: List price base-case incremental cost effectiveness analysis results for GT6 TE NC patients**

| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 20,320 | 18.11 | 12.05 | NA |
| G/P | 27,271 | 19.83 | 15.52 | 2,005 |
| SOF/VEL | 40,538 | 19.83 | 15.52 | 3,858,701 |

Source: Table 25 – Appendix B14 in response to the clarification letter.[17]
G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; LYG = life-years gained; N/A = not applicable; NC = non-cirrhotic; QALY = quality-adjusted life year; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

**Table A.26: List price base-case incremental cost effectiveness analysis results for GT6 TE CC patients**

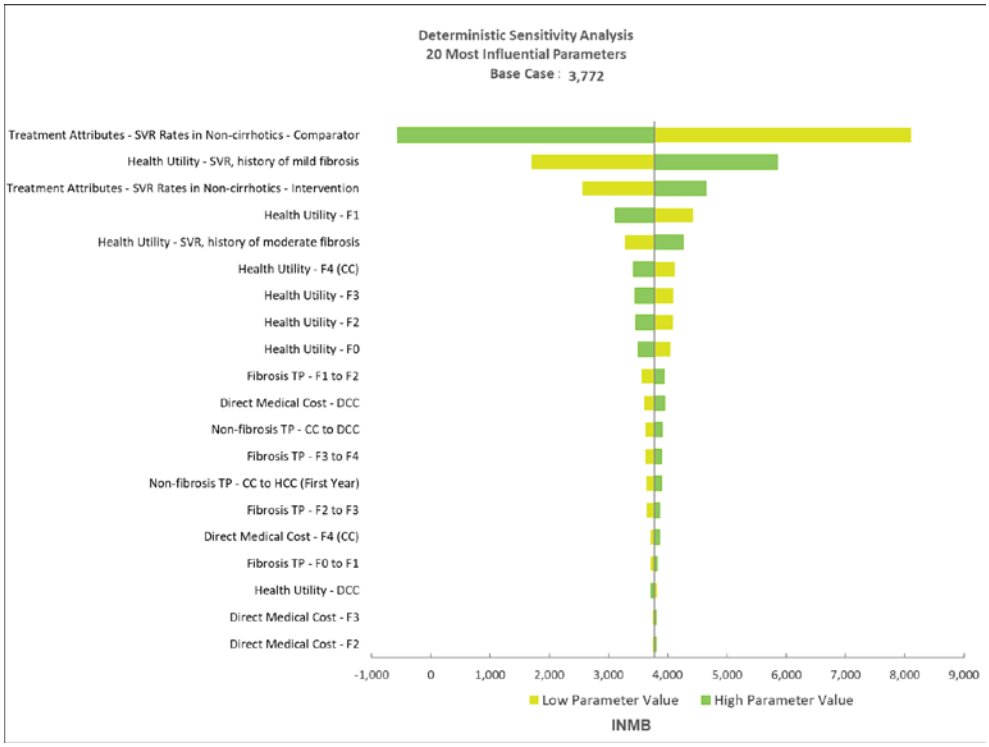
| Technologies | Total costs (£) | Total LYG | Total QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|
| No treatment | 42,741 | 13.24 | 7.08 | NA |
| SOF/VEL | 54,759 | 17.17 | 10.25 | 3,791 |
| G/P | 54,832 | 17.17 | 10.25 | Dominated |
| SOF/PR | 67,130 | 15.20 | 8.62 | Dominated |

Source: Table 26 – Appendix B14 in response to the clarification letter.[17]
CC = compensated cirrhosis = G/P = glecaprevir/pibrentasvir (300 mg/120 mg); GT = genotype; ICER = incremental cost effectiveness ratio; IFN = interferon; LYG = life-years gained; N/A = not applicable; QALY = quality-adjusted life year; peg-IFN = pegylated IFN; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; VEL = velpatasvir

***Deterministic sensitivity analysis***

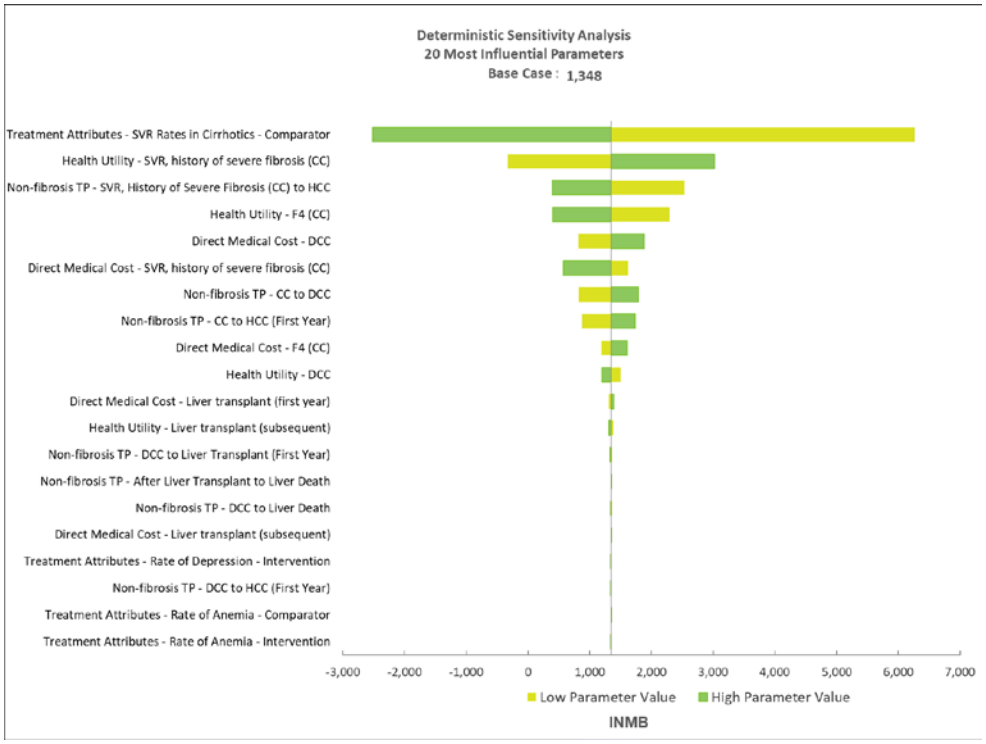
In this section, the tornado diagrams for the 26 patient subgroups described in Section 5.2.3 of this report are presented. These tornado diagrams were built by the company based on the INMB of G/P against one relevant comparator for each subgroup at a threshold of £20,000 per QALY. The diagrams were reported in response to the clarification letter in Appendix F.[17] The ERG noticed an inconsistency in one of the tornado diagrams reported by the company, which did not match the one produced by the electronic model. The ERG assumed that the diagram obtained from the model was the correct one and it is the one shown in this appendix. This was for the GT3 TN NC subgroup (Figure A.12 below).

**Figure A.1: Tornado diagram: GT1 TN NC, G/P vs. SOF/LDV**



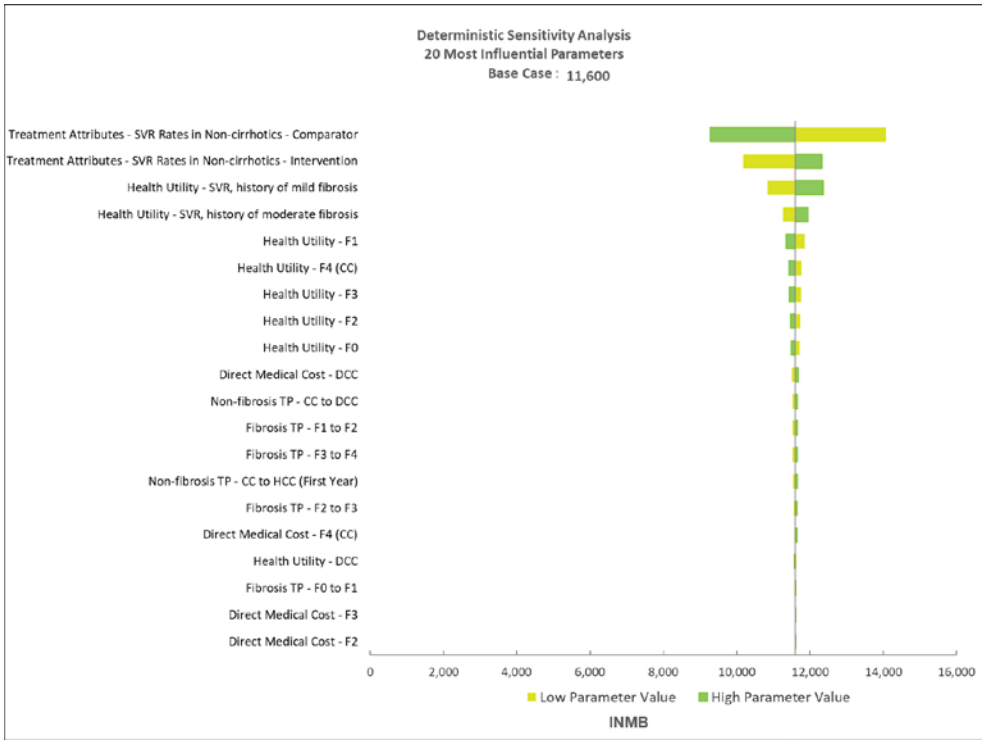

Source: response to clarification letter Appendix F.[17]

**Figure A.2: Tornado diagram: GT1 TN CC, G/P vs. EBR/GZR**



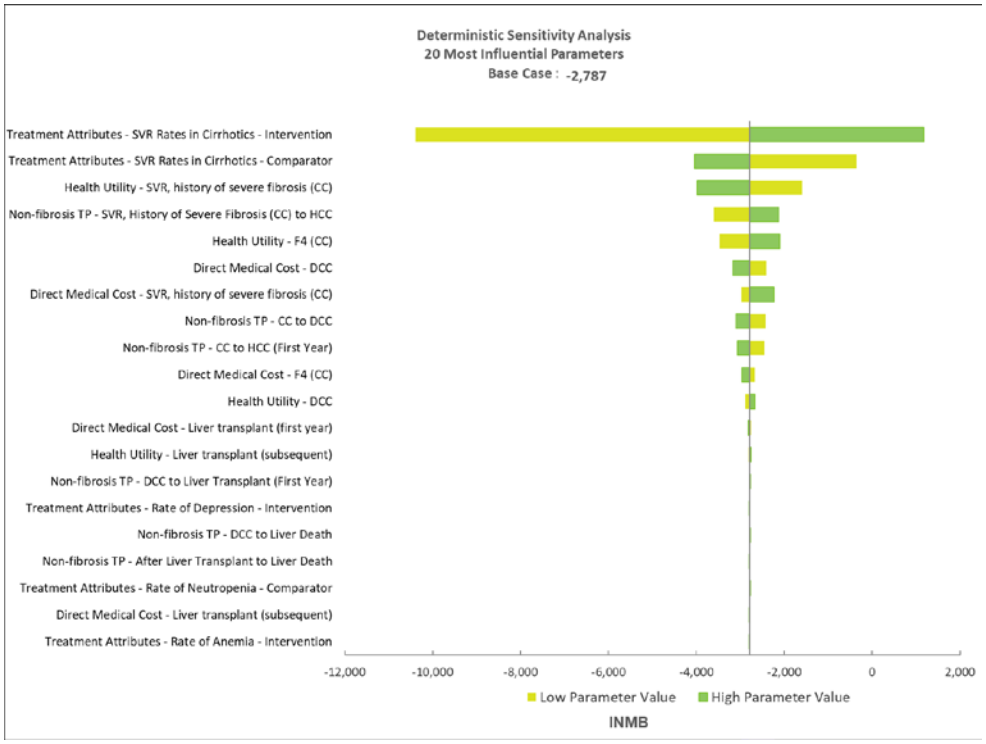

Source: response to clarification letter Appendix F.[17]

**Figure A.3: Tornado diagram: GT1 TE NC, G/P vs. OBV/PTV/RTV + DSV**



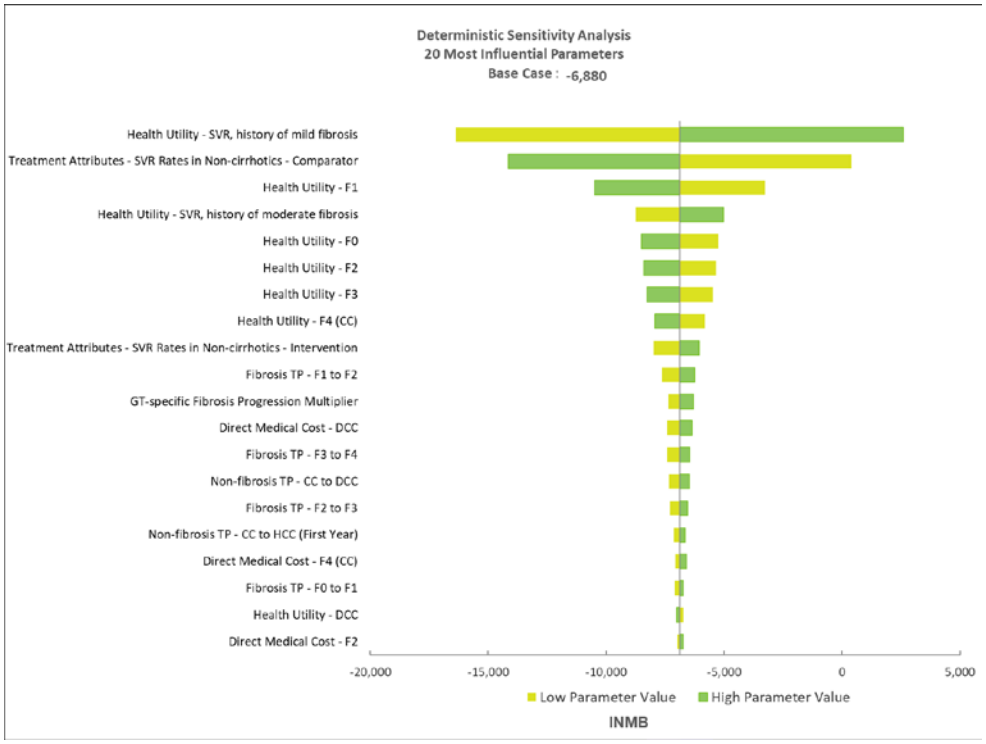

Source: response to clarification letter Appendix F.[17]

**Figure A.4: Tornado diagram: GT1 TE CC, G/P vs. SOF/VEL**



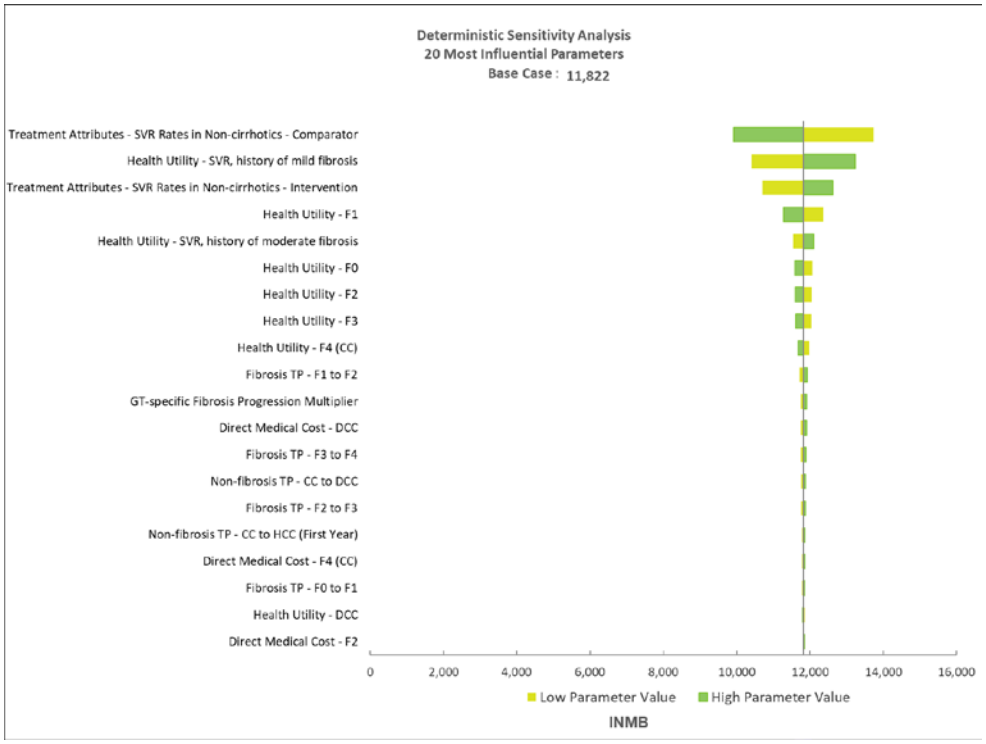

Source: response to clarification letter Appendix F.[17]

**Figure A.5: Tornado diagram: GT2 TN NC IFN-eligible, G/P vs. peg-IFN + RBV**



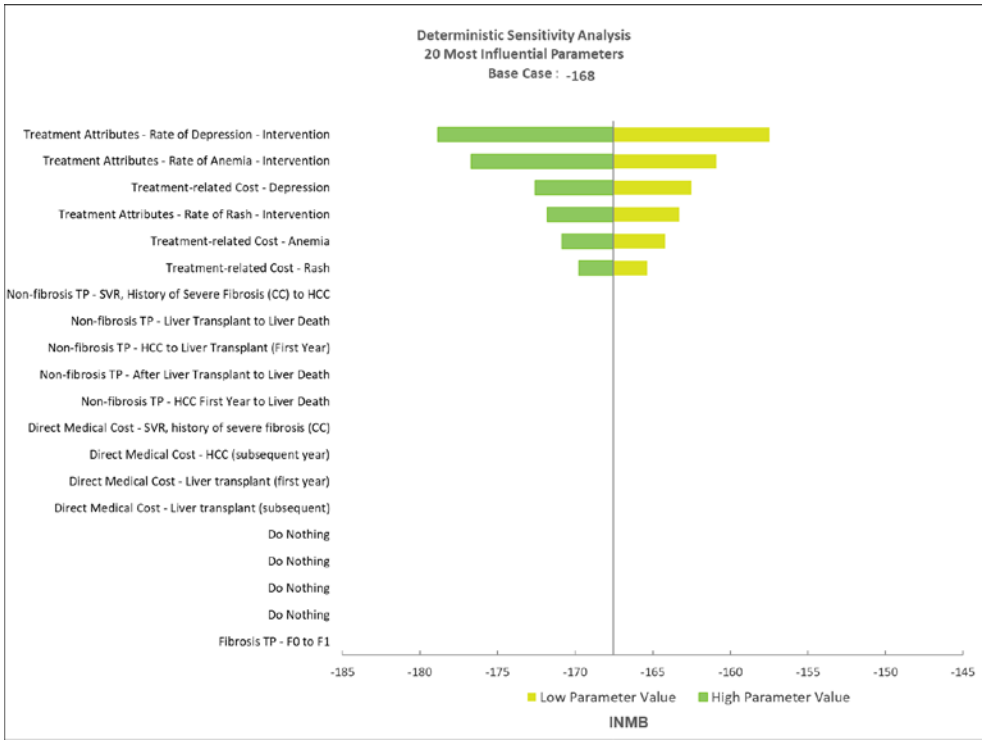

Source: response to clarification letter Appendix F.[17]

**Figure A.6: Tornado diagram: GT2 TN NC IFN-ineligible, G/P vs. SOF + RBV**



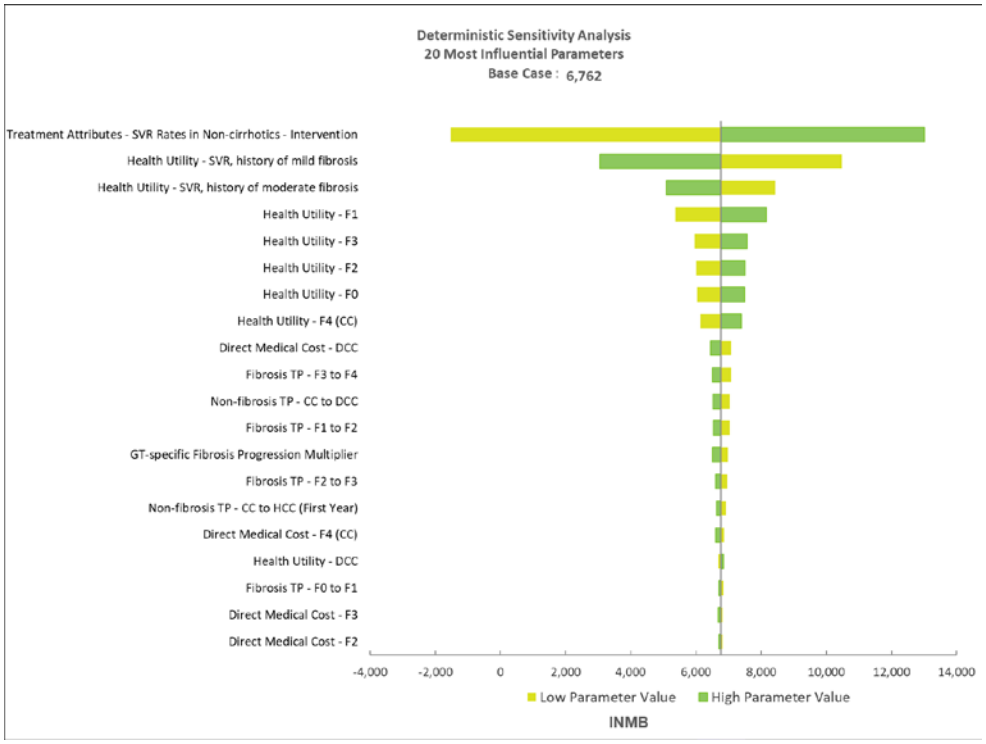

Source: response to clarification letter Appendix F.[17]

**Figure A.7: Tornado diagram: GT2 TN CC, G/P vs. SOF/VEL[a]**



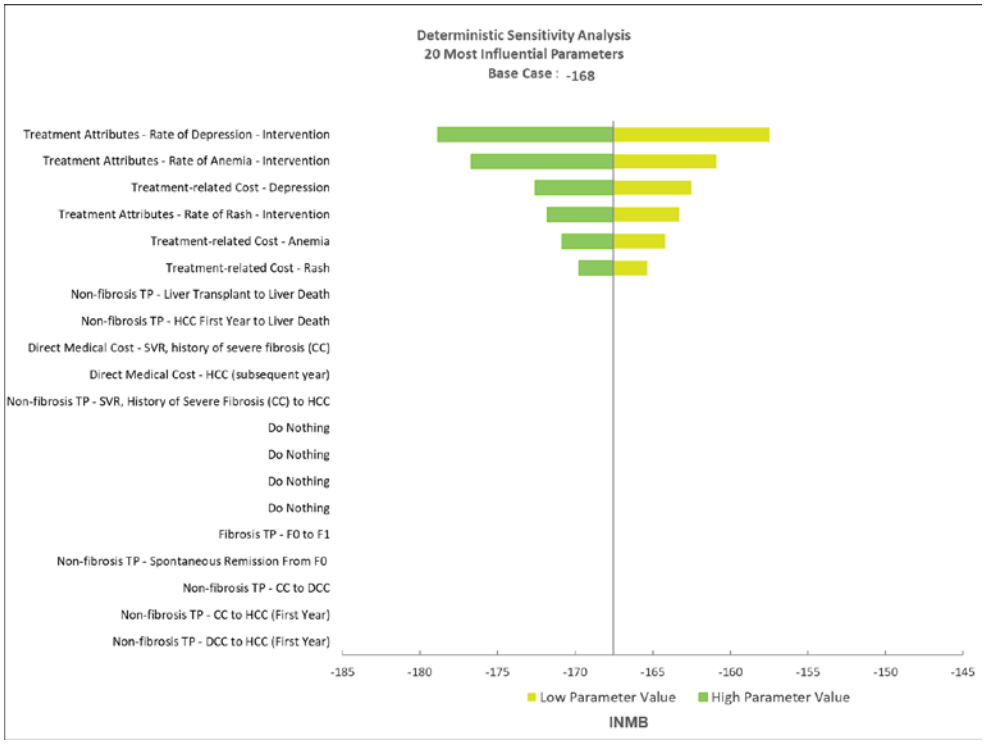

[a]As the comparator for DSA is the same in the GT2 TN CC IFN-eligible and IFN-ineligible subgroups, and there are no differences between the modelling of these two subgroups, the above tornado diagram applies to both groups. Source: response to clarification letter Appendix F.[17]

**Figure A.8: Tornado diagram: GT2 TE NC, G/P vs. SOF/VEL**



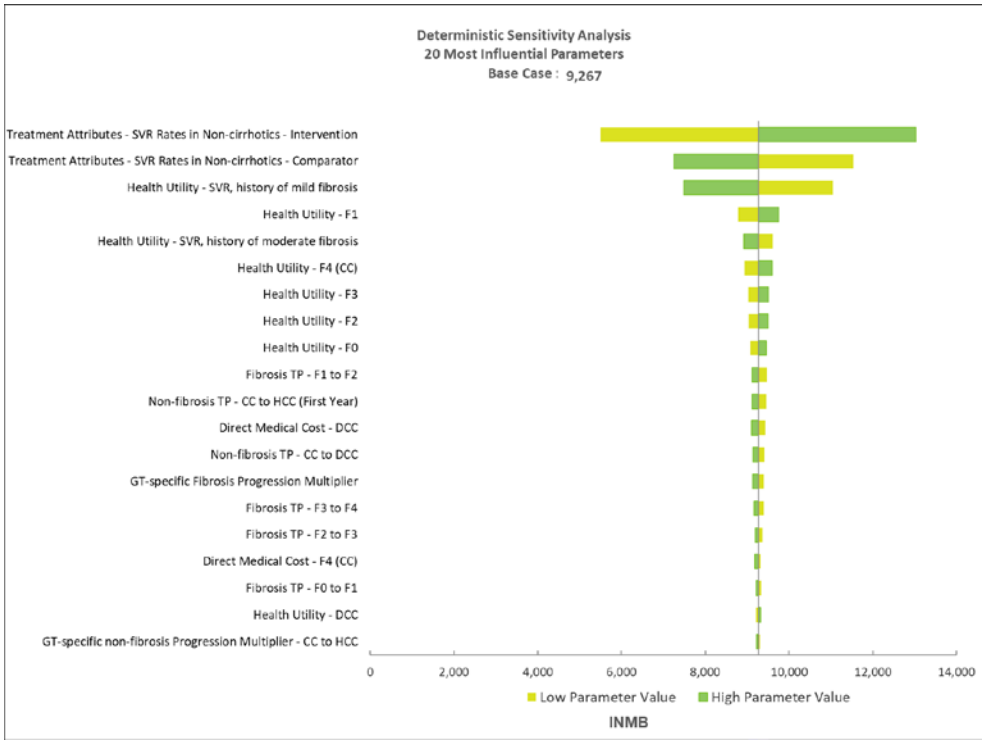

Source: response to clarification letter Appendix F.[17]

**Figure A.9: Tornado diagram: GT2 TE CC, G/P vs. SOF/VEL**



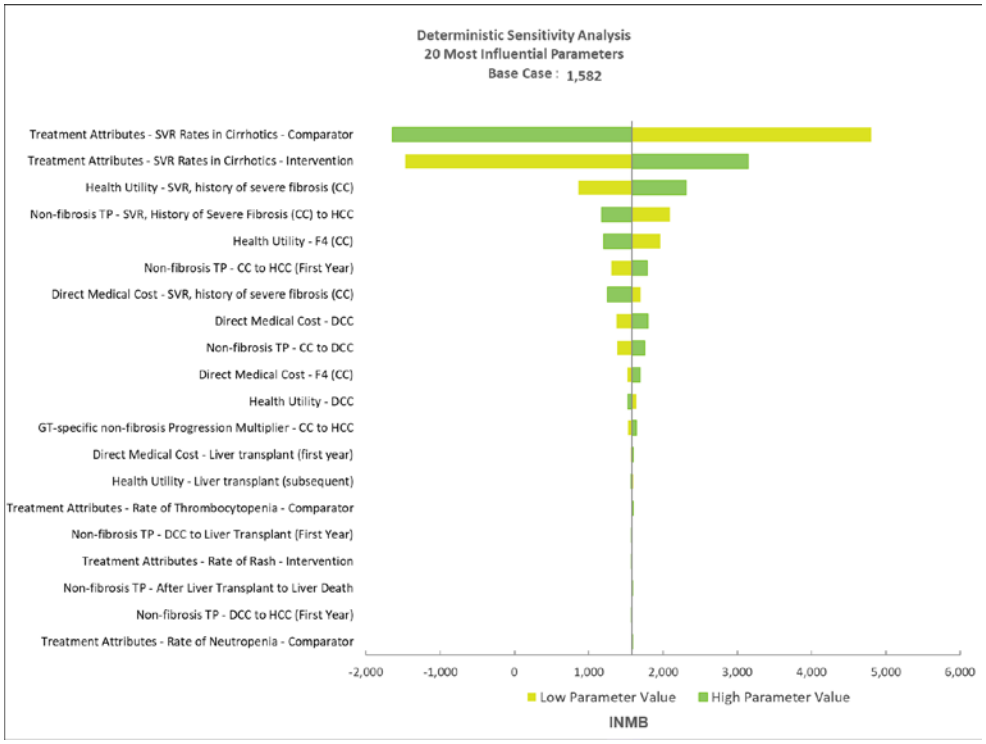

Source: response to clarification letter Appendix F.[17]

**Figure A.10: Tornado diagram: GT3 TN NC, G/P vs. SOF/VEL**



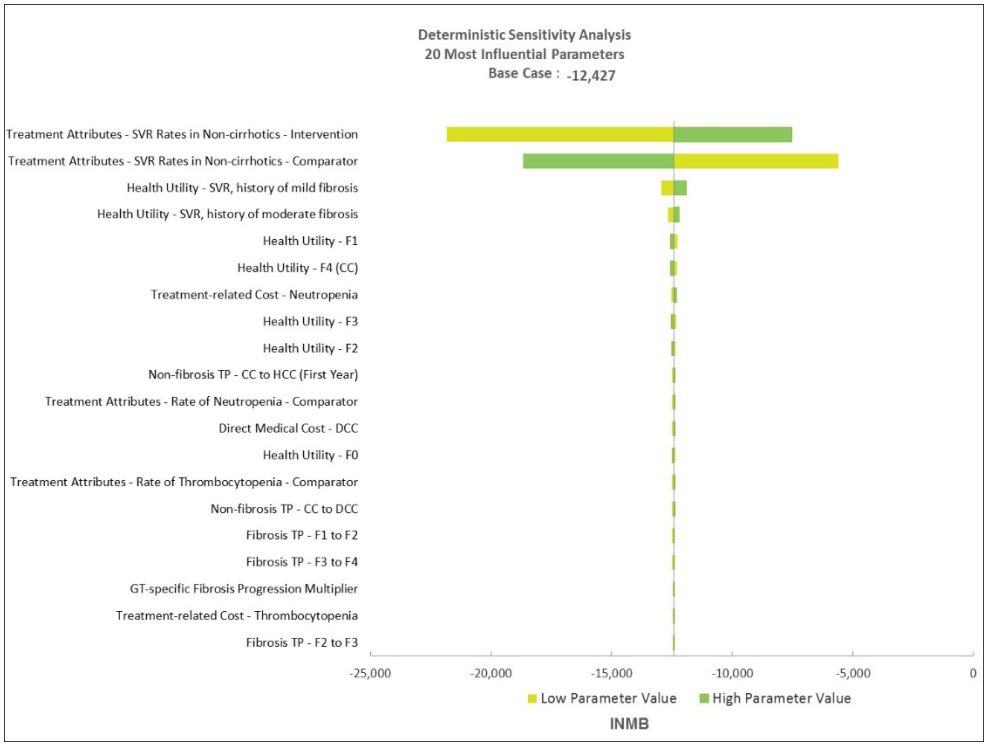

Source: response to clarification letter Appendix F.[17]

**Figure A.11: Tornado diagram: GT3 TN CC, G/P vs. SOF/VEL**



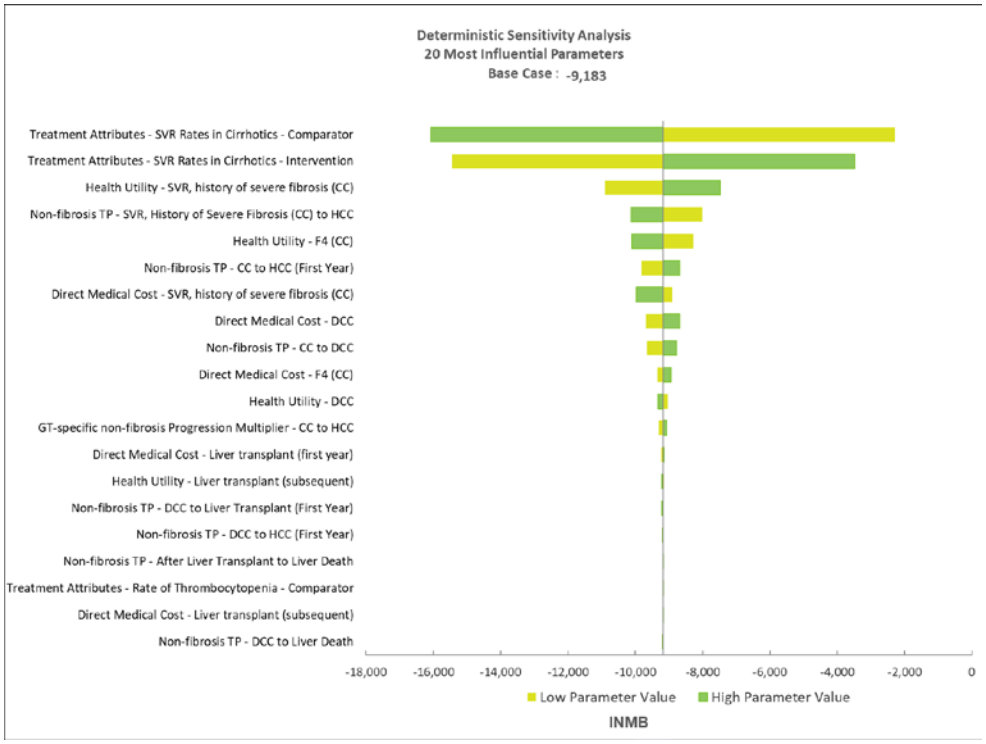

Source: response to clarification letter Appendix F.[17]

**Figure A.12: Tornado diagram: GT3 TE NC, G/P vs. SOF + peg-IFN + RBV**



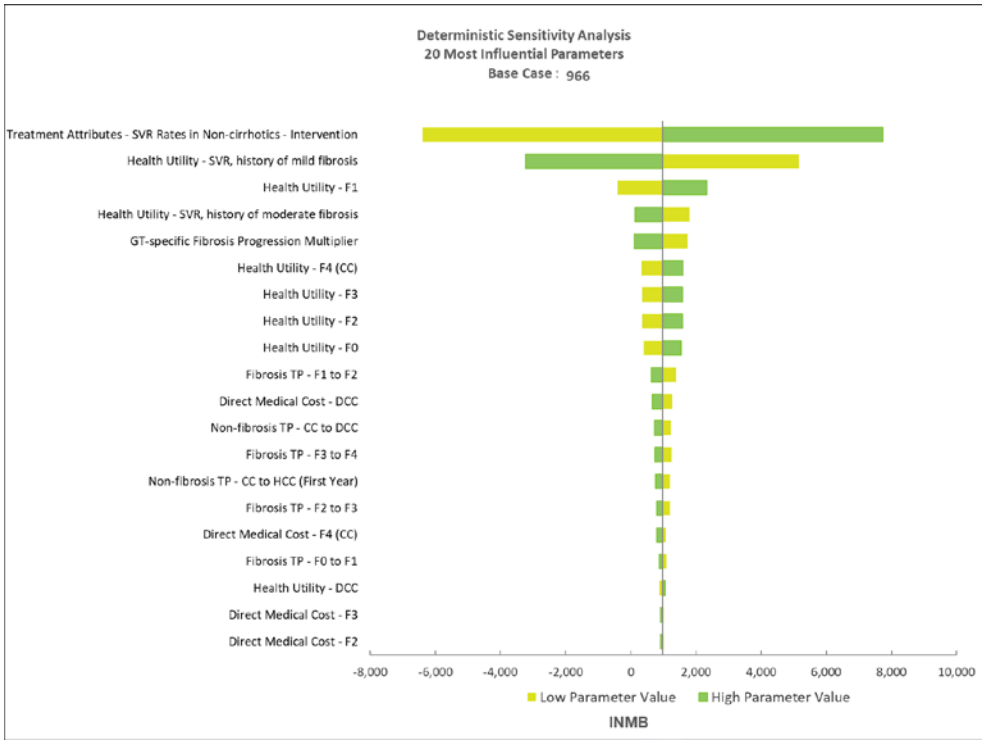

Source: Electronic model.[204]

**Figure A.13: Tornado diagram: GT3 TE CC, G/P vs. SOF/VEL**



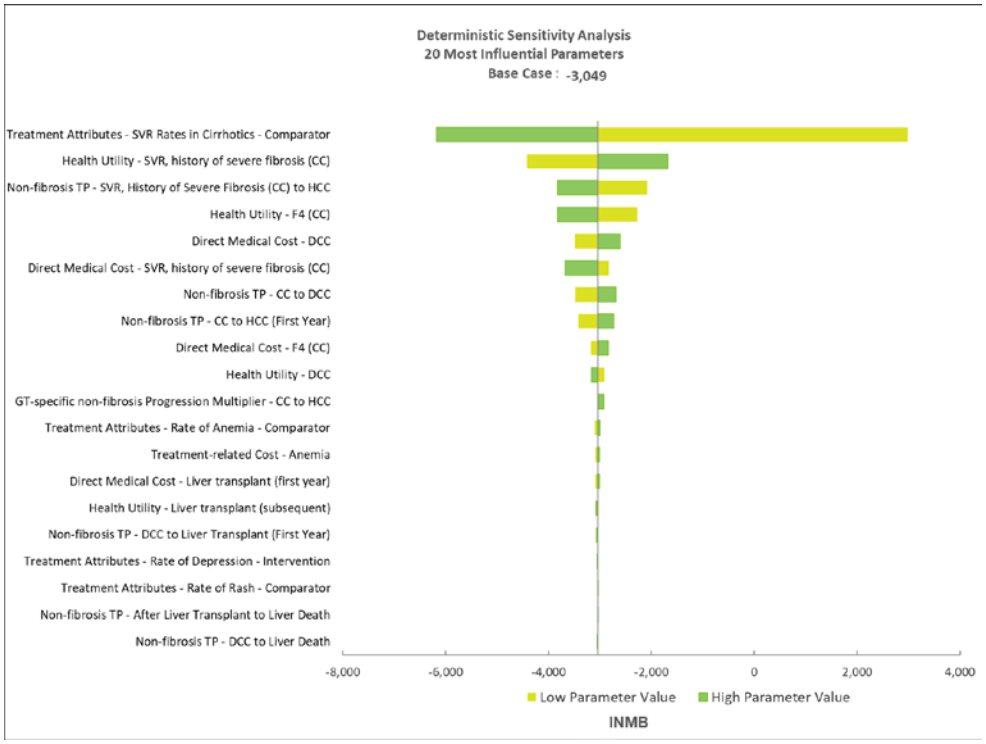

Source: response to clarification letter Appendix F.[17]

**Figure A.14: Tornado diagram: GT4 TN NC, G/P vs. OBV/PTV/RTV**



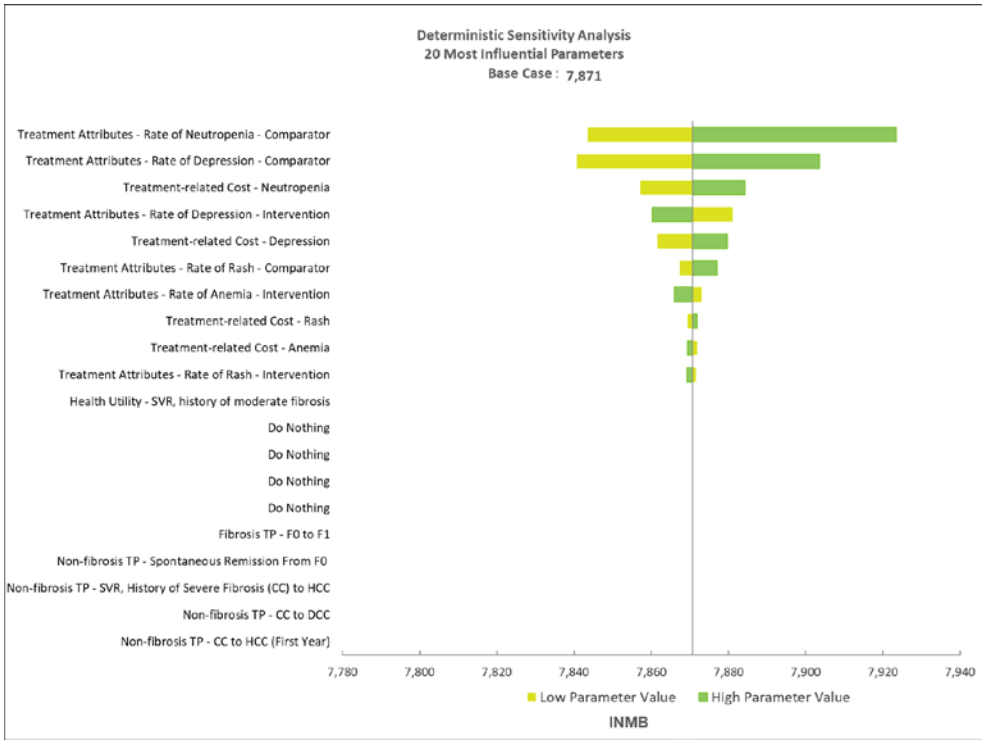

Source: response to clarification letter Appendix F.[17]

**Figure A.15: Tornado diagram: GT4 TN CC, G/P vs. OBV/PTV/RTV**



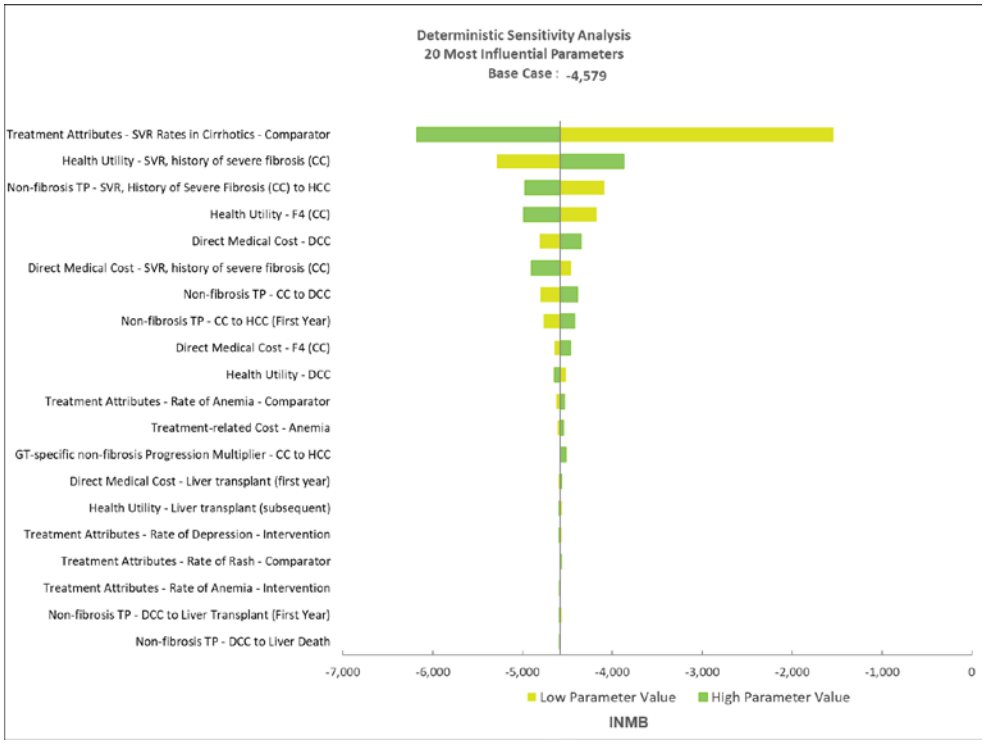

Source: response to clarification letter Appendix F.[17]

**Figure A.16: Tornado diagram: GT4 TE NC, G/P vs. OBV/PTV/RTV**



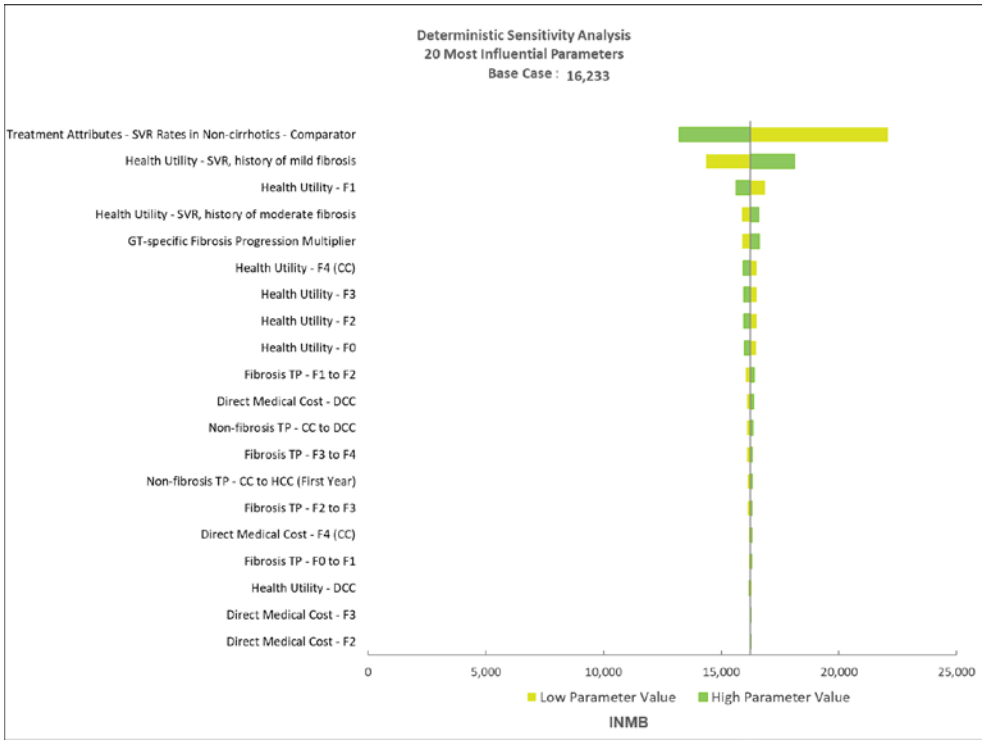

Source: response to clarification letter Appendix F.[17]

**Figure A.17: Tornado diagram: GT4 TE CC, G/P vs. OBV/PTV/RTV**



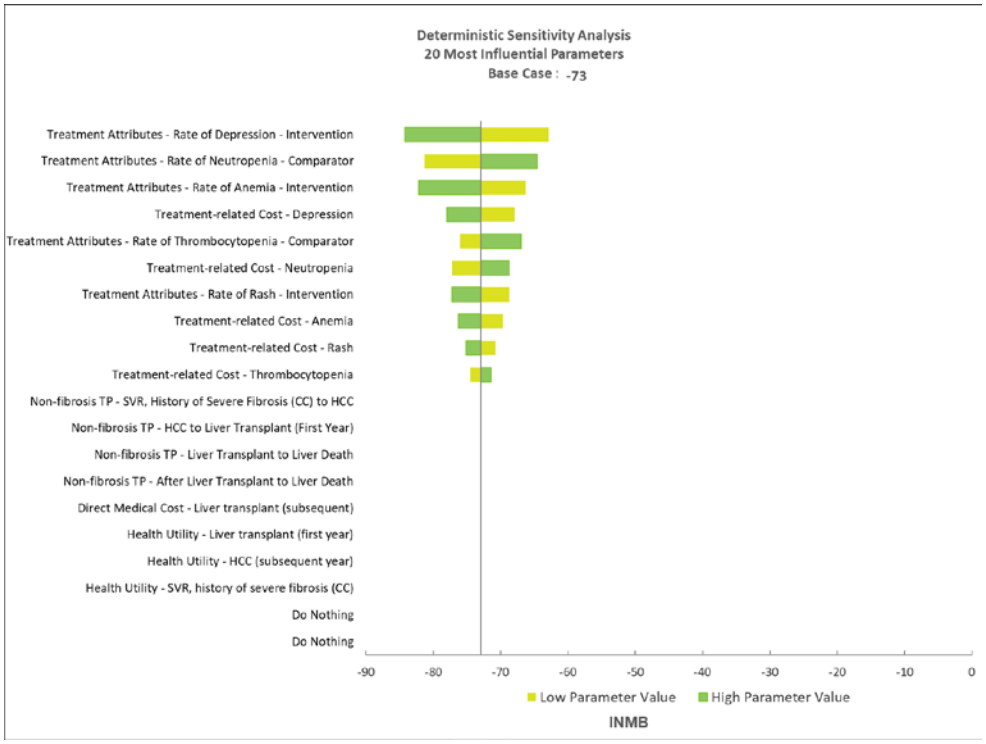

Source: response to clarification letter Appendix F.[17]

**Figure A.18: Tornado diagram: GT5 TN NC, G/P vs. SOF/VEL**



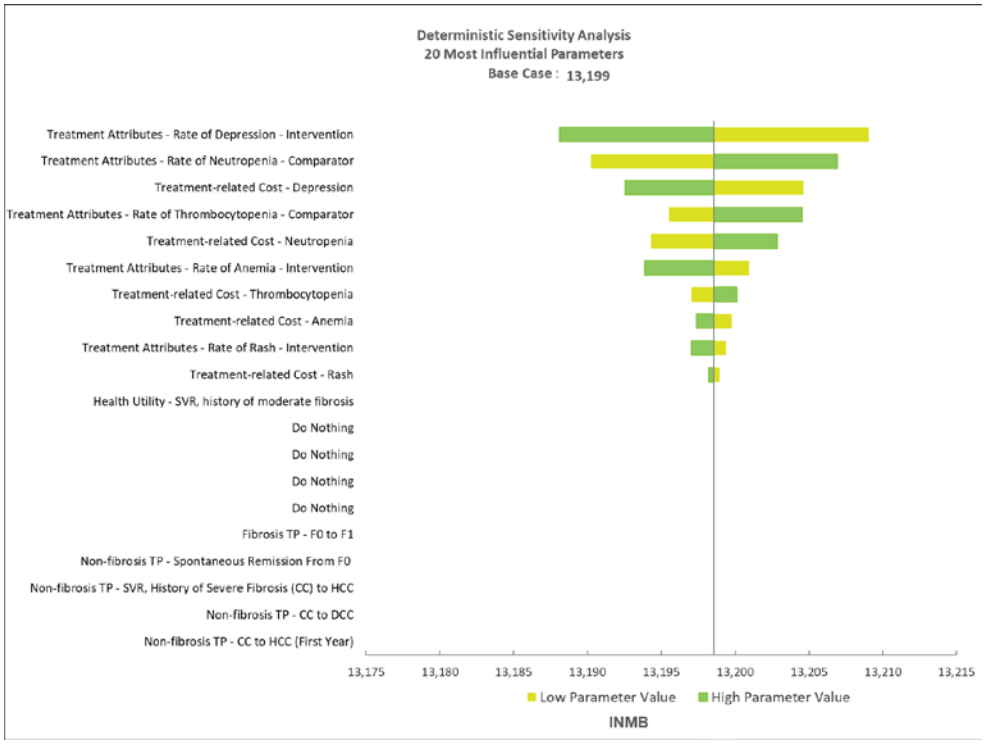

Source: response to clarification letter Appendix F.[17]

**Figure A.19: Tornado diagram: GT5 TN CC, G/P vs. SOF/VEL**



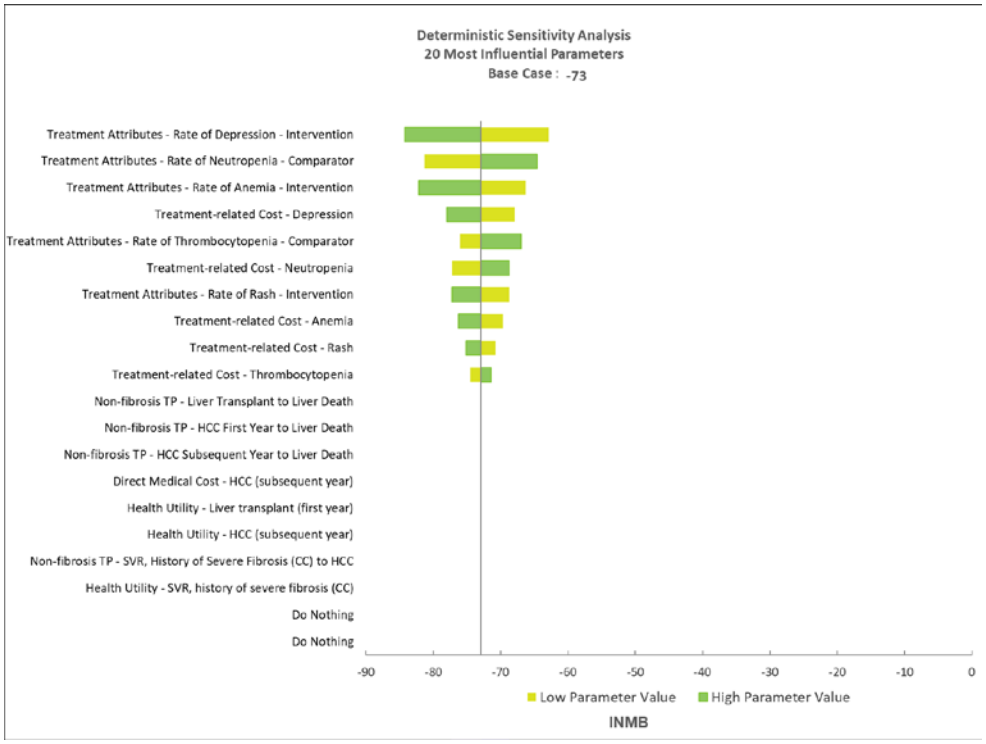

Source: response to clarification letter Appendix F.[17]

**Figure A.20: Tornado diagram: GT5 TE NC, G/P vs. SOF/VEL**



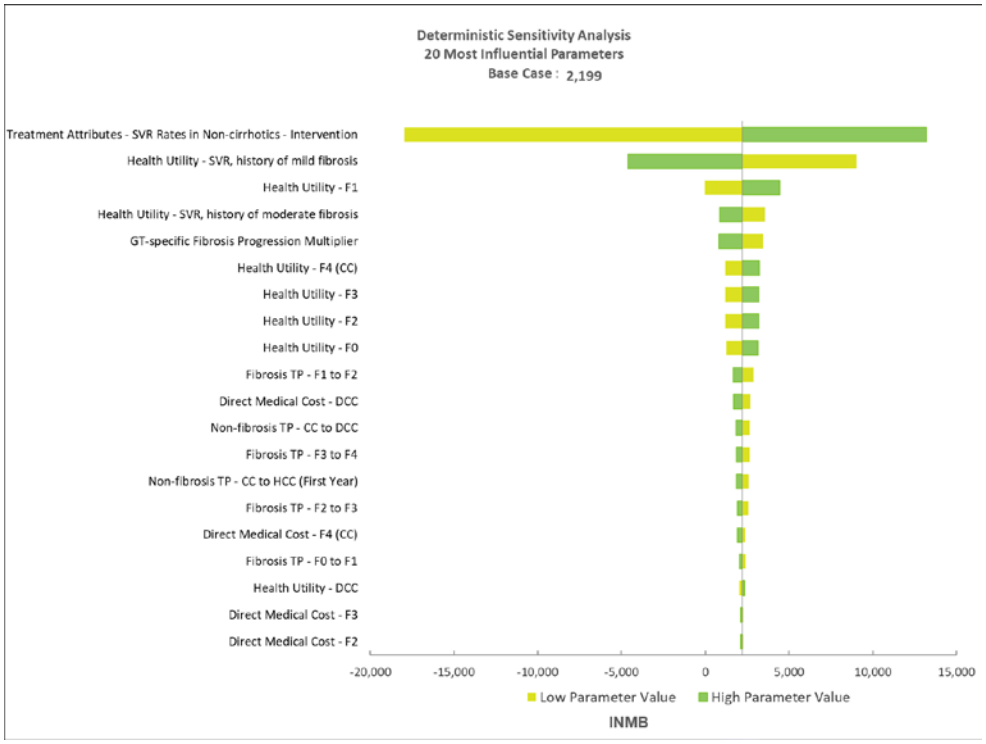

Source: response to clarification letter Appendix F.[17]

**Figure A.21: Tornado diagram: GT5 TE CC, G/P vs. SOF/VEL**



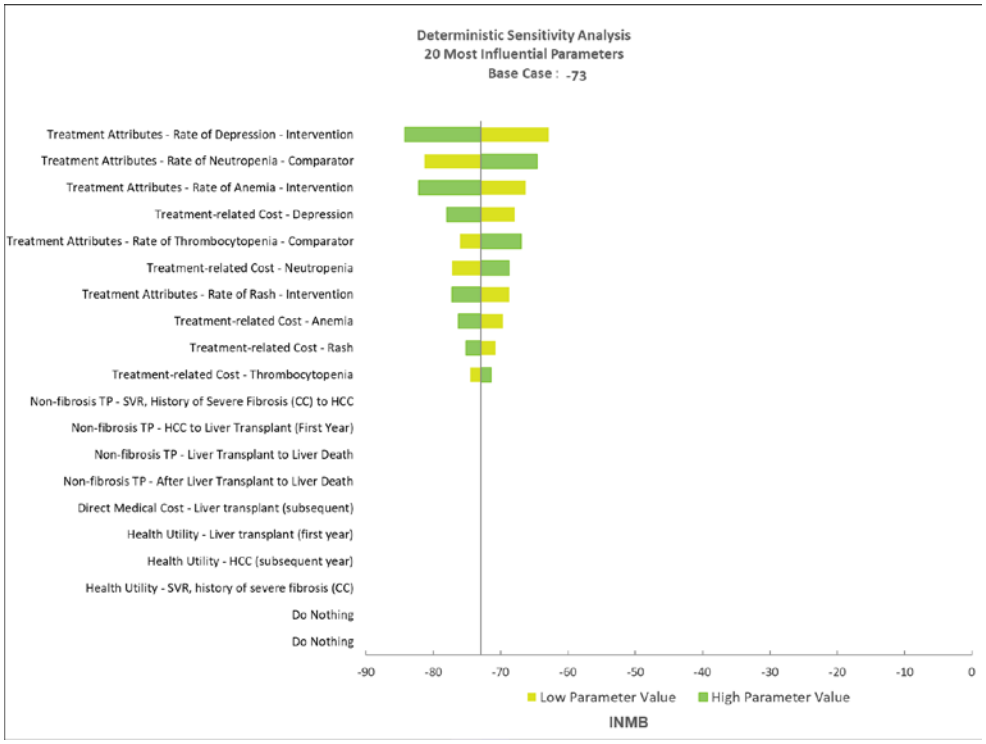

Source: response to clarification letter Appendix F.[17]

**Figure A.22: Tornado diagram: GT6 TN NC, G/P vs. SOF/VEL**



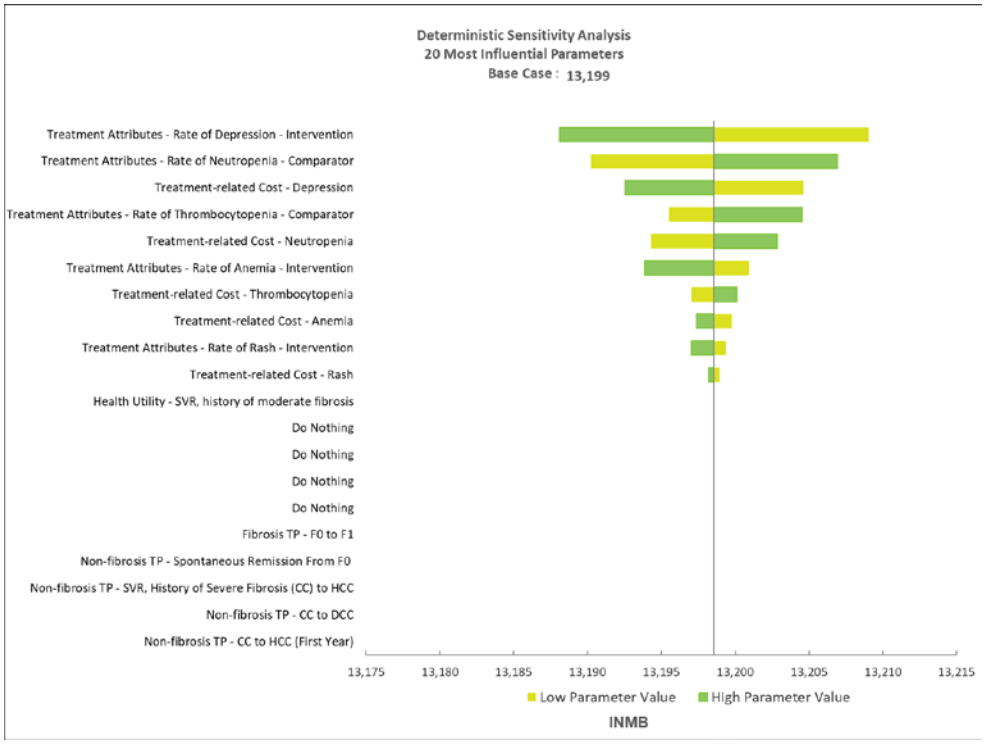

Source: response to clarification letter Appendix F.[17]

**Figure A.23: Tornado diagram: GT6 TN CC, G/P vs. SOF/VEL**



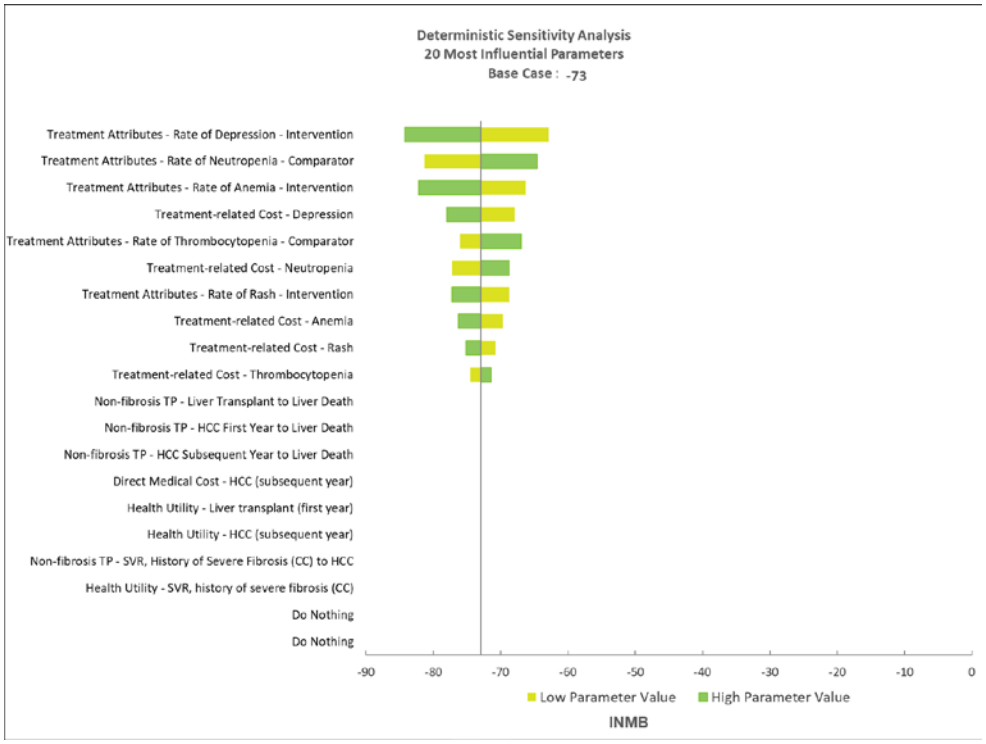

Source: response to clarification letter Appendix F.[17]

**Figure A.24: Tornado diagram: GT6 TE NC, G/P vs. SOF/VEL**




Source: response to clarification letter Appendix F.[17]

**Figure A.25: Tornado diagram: GT6 TE CC, G/P vs. SOF/VEL**




Source: response to clarification letter Appendix F.[17]

**Table A.27: Non-treatment-specific input parameters included in the probabilistic sensitivity analysis**

| Parameter | Base value | Low | High | Standard error | Distribution |
|---|---|---|---|---|---|
| Transitional probabilities (annual) | | | | | |
| *GT1 fibrosis progression* | | | | | |
| F0–F1 | 0.110 | 0.088 | 0.132 | 0.011 | BETA |
| F1–F2 | 0.088 | 0.070 | 0.105 | 0.009 | BETA |
| F2–F3 | 0.176 | 0.141 | 0.211 | 0.018 | BETA |
| F3–CC | 0.143 | 0.114 | 0.172 | 0.014 | BETA |
| *GT-specific fibrosis progression multiplier* | | | | | |
| GT2 | 0.68 | 0.64 | 0.73 | 0.026 | NORMAL |
| GT3 | 1.30 | 1.22 | 1.39 | 0.046 | NORMAL |
| GT4 | 0.94 | 0.78 | 1.14 | 0.102 | NORMAL |
| GT5 | 0.94 | 0.78 | 1.14 | 0.102 | NORMAL |
| GT6 | 0.94 | 0.78 | 1.14 | 0.102 | NORMAL |
| *Non-fibrosis disease progression* | | | | | |
| SVR, history of CC (F4) to HCC | 0.012 | 0.003 | 0.022 | 0.011 | BETA |
| CC to DCC | 0.039 | 0.029 | 0.049 | 0.010 | BETA |
| CC to HCC | 0.014 | 0.004 | 0.024 | 0.010 | BETA |
| LT | | | | | |
| DCC to LT (first year) | 0.020 | 0.016 | 0.024 | 0.002 | BETA |
| HCC to LT (first year) | 0.020 | 0.016 | 0.024 | 0.002 | BETA |
| *Liver-related mortality* | | | | | |
| DCC to liver death | 0.130 | 0.120 | 0.140 | 0.010 | BETA |
| LT (first year) to liver death | 0.150 | 0.120 | 0.180 | 0.015 | BETA |
| LT (subsequent year) to liver death | 0.057 | 0.046 | 0.068 | 0.006 | BETA |
| HCC to liver death | 0.430 | 0.400 | 0.460 | 0.030 | BETA |
| *GT-specific non-fibrosis transition rate multipliers* | | | | | |
| CC to HCC multiplier | | | | | |
| GT2 | 0.62 | 0.50 | 0.77 | 0.077 | NORMAL |
| GT3 | 1.44 | 1.23 | 1.68 | 0.122 | NORMAL |
| GT4 | 0.96 | 0.96 | 1.22 | 0.133 | NORMAL |
| GT5 | 0.96 | 0.96 | 1.22 | 0.133 | NORMAL |
| GT6 | 0.96 | 0.96 | 1.22 | 0.133 | NORMAL |
| DCC to HCC multiplier | | | | | |
| GT2 | 0.62 | 0.50 | 0.77 | 0.077 | NORMAL |

| Parameter | Base value | Low | High | Standard error | Distribution |
|---|---|---|---|---|---|
| GT3 | 1.44 | 1.23 | 1.68 | 0.122 | NORMAL |
| GT4 | 0.96 | 0.96 | 1.22 | 0.133 | NORMAL |
| GT5 | 0.96 | 0.96 | 1.22 | 0.133 | NORMAL |
| GT6 | 0.96 | 0.96 | 1.22 | 0.133 | NORMAL |
| Health state utilities[a] | | | | | |
| F0 | 0.77 | 0.62 | 0.92 | 0.077 | BETA |
| F1 | 0.77 | 0.62 | 0.92 | | |
| F2 | -0.11 | -0.18 | -0.04 | 0.035 | LOG-NORMAL |
| F3 | 0.66 | 0.53 | 0.79 | | |
| CC (F4) | -0.22 | -0.30 | -0.13 | 0.043 | LOG-NORMAL |
| SVR, history of mild fibrosis (F0, F1) | 0.82 | 0.66 | 0.98 | | |
| SVR, history of moderate fibrosis (F2, F3) | 0.71 | 0.57 | 0.85 | | |
| SVR, history of CC | 0.60 | 0.48 | 0.72 | | |
| DCC | 0.45 | 0.36 | 0.54 | 0.045 | BETA |
| HCC | 0.45 | 0.36 | 0.54 | 0.045 | BETA |
| LT (first year) | 0.45 | 0.36 | 0.54 | 0.045 | BETA |
| LT (subsequent) | 0.67 | 0.54 | 0.80 | 0.067 | BETA |
| Health state costs (2015/2016 £)[b] | | | | | |
| F0 | 164 | 82 | 246 | 45 | GAMMA |
| F1 | 164 | 82 | 246 | 45 | GAMMA |
| F2 | 609 | 431 | 861 | 100 | GAMMA |
| F3 | 609 | 431 | 861 | 100 | GAMMA |
| CC (F4) | 945 | 579 | 1,541 | 220 | GAMMA |
| SVR, history of mild fibrosis (F0–F1) | 60 | 47 | 78 | 10 | GAMMA |
| SVR, history of moderate fibrosis (F2–F3) | 60 | 47 | 78 | 10 | GAMMA |
| SVR, history of CC (F4) | 606 | 214 | 1,711 | 300 | GAMMA |
| DCC | 12,670 | 6,335 | 19,006 | 3,200 | GAMMA |
| HCC | 11,291 | 5,645 | 16,936 | 3,100 | GAMMA |
| LT (first year) | 51,108 | 25,554 | 76,662 | 13,000 | GAMMA |
| LT (subsequent year) | 1,924 | 962 | 2,886 | 500 | GAMMA |
| Treatment-related AE costs (2015/2016 £)[b] | | | | | |
| Anaemia | 486 | 243 | 729 | 150 | GAMMA |
| Rash | 160 | 80 | 240 | 40 | GAMMA |
| Depression | 490 | 245 | 735 | 150 | GAMMA |

| Parameter | Base value | Low | High | Standard error | Distribution |
|---|---|---|---|---|---|
| Grade 3/4 neutropaenia | 1,334 | 667 | 2,001 | 330 | GAMMA |
| Grade 3/4 thrombocytopoenia | 1,902 | 951 | 2,854 | 475 | GAMMA |

Source: Table 233 in Appendix L.1.2 in the CS.[16]
[a]1. Health utilities from Wright et al. (2006)[153] combine F0 and F1 into mild and F2 and F3 into moderate. Therefore, health utilities for F0 is drawn and used for F0 and F1 and health utilities for F2 is drawn and used for F2 and F3. 2. For moderate (F2) and F4, the Base/Low/High columns correspond to the difference vs. mild per Table 50 of Wright et al. (2006). One exception: the mean difference between mild and CC was reported as -0.21 whereas the difference between mild (0.77) and CC (0.55) is in fact -0.22. This is likely due to rounding issue. The correction has been made here for consistency. 3. Moderate (F2) and CC (F4) are not sampled from a Beta distribution. Rather, the relative difference (delta or ratio) between moderate/CC and mild was sampled from the log-normal distribution which was applied to obtain health utilities in moderate and CC at each simulation. 4. Recovered states are not sampled from a beta distribution. Rather, a fixed +0.05 increase (base-case value) from the initial fibrosis stage is assumed; [b]Gamma: Each standard error has been selected such that the 95% CI obtained through 500 simulations replicates as closely as possible the lower and upper bound of the parameter in question. 5. No HCV state is not sampled from a Beta distribution. Rather, the drawn value for SVR history of mild fibrosis is used (base-case assumption).
AE, adverse event; CC, compensated cirrhosis; CI, confidence interval; DCC, decompensated cirrhosis; DSA, deterministic sensitivity analysis; GT, genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplant; N/A: Not applicable; PSA, probabilistic sensitivity analysis; SVR, sustained virologic response

***Probabilistic sensitivity analysis - results at £30,000 threshold***

**Table A.28: G/P cost effectiveness probability (%) at £30,000 threshold (against the indicated comparator)**

| HCV genotype | Treatment-naïve | | Treatment-experienced | |
|---|---|---|---|---|
| | Non-cirrhotic | Compensated cirrhosis | Non-cirrhotic | Compensated cirrhosis |
| GT1 | 99.2% (SOF/LDV) | 71.0% (EBR/GZR) | 100% (OBV/PTV/RTV + DSV) | 13.4% (SOF/VEL) |
| GT2 | IFN-eligible: 36.6% (peg-IFN + RBV) | IFN-eligible: 45.5% (SOF/VEL) | 93.4% (SOF/VEL) | 41.2% (SOF/VEL) |
| | IFN-ineligible: 100% (SOF + RBV) | IFN-ineligible: 45.5% (SOF/VEL) | | |
| GT3 | 99% (SOF/VEL) | 74.4% (SOF/VEL) | 0.0% (SOF + peg-IFN + RBV) | 4.4% (SOF/VEL) |
| GT4 | 41.0% (OBV/PTV/RTV) | 23.8% (OBV/PTV/RTV) | 100% (OBV/PTV/RTV) | 6.2% (OBV/PTV/RTV) |
| GT5 | 100% (SOF/VEL) | 49.6% (SOF/VEL) | 100% (SOF/VEL) | 39.4% (SOF/VEL) |
| GT6 | 55.4% (SOF/VEL) | 47.0% (SOF/VEL) | 100% (SOF/VEL) | 46.8% (SOF/VEL) |

Source: Table 53 in the CS.[2]
DSV = dasabuvir; EBR = elbasvir; GT = genotype; GZR = grazoprevir; IFN = interferon; LDV = ledipasvir; OBV = ombitasvir; PSA = probabilistic sensitivity analysis; PTV = paritaprevir; peg-IFN = pegylated IFN; RBV = ribavirin; RTV = ritonavir; SOF = sofosbuvir; VEL = velpatasvir

**Table A.29: G/P cost effectiveness probability (%) at £30,000 threshold for patients with compensated cirrhosis in the company submission (against only one comparator) and with multiple comparators**

| HCV genotype | Treatment-naïve | | Treatment-experienced | |
|---|---|---|---|---|
| | One comparator* | All comparators** | One comparator* | All comparators** |
| GT1 | 71.0% | 57.8% | 13.4% | 11.2% |
| GT2 | IFN-eligible*: 45.5% | IFN-eligible: 43.0% | 41.2% | 41.4% |
| | IFN-ineligible*: 45.5% | IFN-ineligible: 45.2% | | |
| GT3 | 74.4% | 64.4% | 4.4% | 7.6% |
| GT4 | 23.8% | 4.2% | 6.2% | 5.2% |
| GT5 | 49.6% | 47.4% | 39.4% | 42.4% |

| | | | | |
|---|---|---|---|---|
| GT6 | 47.0% | 48.2% | 46.8% | 44.8% |

GT = genotype; IFN = interferon

*Comparators in Table 5.18. **Comparators in Table 5.6.

Note: shaded cells indicate a difference of at least 10% in the cost effectiveness probability of G/P vs. one or all relevant comparators for each subgroup.

**Table A.30: G/P cost effectiveness probability (%) at £30,000 threshold (against all comparators and including 100% SVR rates and 0% AE rates in the PSA)**

| HCV genotype | Treatment-naïve | | Treatment-experienced | |
|---|---|---|---|---|
| | Non-cirrhotic | Compensated cirrhosis | Non-cirrhotic | Compensated cirrhosis |
| GT1 | 100% | 60.8% | 100% | 3.8% |
| GT2 | IFN-eligible: 38.8% | IFN-eligible: 58.0% | 95.8% | 63.2% |
| | IFN-ineligible: 100% | IFN-ineligible: 50.4% | | |
| GT3 | 98.4% | 61.0% | 0.0% | 3.8% |
| GT4 | 40.0% | 11.2% | 61.6% | 2.8% |
| GT5 | 26.2% | 27.2% | 95.4% | 20.4% |
| GT6 | 26.0% | 47.8% | 80.2% | 39.8% |

Source: Electronic model.[204]

GT = genotype; IFN = interferon; PSA = probabilistic sensitivity analysis