NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Ledipasvir-sofosbuvir for treating chronic hepatitis C

Specification for manufacturer/sponsor submission of evidence

Submitted on 21st October 2014

Contents

List of Tables 3
List of Figures 6
Abbreviations 9
Executive summary 11
Section A – Decision problem 16
1 Description of technology under assessment 16
2 Context 21
3 Equality 36
3.1 Identification of equality issues 36
4 Innovation 38
5 Statement of the decision problem 42
Section B – Clinical and cost-effectiveness 44
6 Clinical evidence 44
6.1 Identification of studies 44
6.2 Study selection 45
6.3 Summary of methodology of relevant non-RCTs 53
6.4 Critical appraisal of relevant non-RCTs 76
6.5 Results of the relevant non-RCTs 77
6.6 Meta-analysis 111
6.7 Indirect and mixed treatment comparisons 112
6.8 Non-RCT evidence 122
6.9 Adverse events 122
6.10 Interpretation of clinical evidence 130
7 Cost-effectiveness 142
7.1 Published cost-effectiveness evaluations 142
7.2 De novo analysis 151
7.3 Clinical parameters and variables 159
7.4 Measurement and valuation of health effects 176
7.5 Resource identification, measurement and valuation 184
7.6 Sensitivity analysis 197
7.7 Results 198
7.8 Validation 251
7.9 Subgroup analysis 251
7.10 Interpretation of economic evidence 254
Section C – Implementation 258
8 Assessment of factors relevant to the NHS and other parties 258
References 264

List of Tables

Table 1: Summary of base-case cost-effectiveness results (ICER for LDV/SOF±RBV against each comparator: £/QALY) 15
Table 2: Summary of ongoing LDV/SOF studies 17
Table 3: Unit costs of technology being appraised 19
Table 4: NICE technology appraisal guidance in CHC 24
Table 5: Summary of EASL recommendations and UK consensus guidelines treatment options for hepatitis C 30
Table 6: Side effect profile of telaprevir and boceprevir 32
Table 7: LDV/SOF step-change innovation 38
Table 8: Eligibility criteria used in search strategy 45
Table 9: List of relevant LDV/SOF Phase II and III non-RCTs 49
Table 10: Comparative summary of methodology of the Phase III non-RCTs 54
Table 11: Summary eligibility criteria of the Phase III non-RCTs 58
Table 12: Eligibility criteria in the Phase III non-RCTs 59
Table 13: Characteristics of participants in ION-1 and across randomised groups 63
Table 14: Characteristics of participants in ION-3 across randomised groups 64
Table 15: Characteristics of participants in ION-2 across randomised groups 65
Table 16: Outcomes investigated in ION-1, ION-3, and ION-2 66
Table 17: Summary of statistical analyses in ION-1, ION-3, and ION-2 69
Table 18: Reasons for premature discontinuation of study treatment in ION-1 73
Table 19: Reasons for premature discontinuation of study treatment in ION-3 75
Table 20: Reasons for premature discontinuation of study treatment in ION-2 76
Table 21: Quality assessment results for Phase III trials 77
Table 22: Summary of response during and after treatment in ION-1 (FAS) 78
Table 23: Summary of HRQL outcomes (ION-1) 82
Table 24: Summary of response during and after treatment in ION-3 (FAS 84
Table 25: Differences in proportions of patients with SVR12 between treatment groups (FAS) 85
Table 26: Summary of HRQL outcomes (ION-3) 88
Table 27: Relapse rates by baseline viral load in ION-3, virologic failure population‡ 89
Table 28: Summary of response during and after treatment in ION-2 (FAS) 90
Table 29: SVR12 rate categorised by prior HCV therapy and presence of cirrhosis in ION-2 (FAS) 93
Table 30: Summary of HRQL outcomes (ION-2) 96
Table 31: Patient demographics and baseline characteristics in ELECTRON-2 100
Table 32: Prior sofosbuvir-treated GT1 patients in ELECTRON-2 101
Table 33: Summary of efficacy results in ELECTRON-2 101
Table 34: Patient demographics and baseline characteristics in ERADICATE 103

Table 35: SVR12 rates in ARV naïve and ARV treated patients – ERADICATE 104
Table 36: Summary of response after treatment in SOLAR-1 (FAS) 106
Table 37: SIRIUS subject disposition (safety analysis set) 108
Table 38: Study design for all relevant studies used in base case economic evaluation 113
Table 39: Patient characteristics, GT1 treatment naïve studies 118
Table 40: Patient characteristics, GT1 treatment experienced studies 119
Table 41: Patient characteristics, GT3 treatment naïve studies 120
Table 42: Patient characteristics, GT3 treatment experienced studies 121
Table 43: Safety summary in ION-1 (safety analysis set) 123
Table 44: Safety summary in ION-3 (safety analysis set) 125
Table 45: Safety summary in ION-2 (safety analysis set) 126
Table 46: Safety summary in SIRIUS (safety analysis set) 128
Table 47: Key data supporting licensed treatment regimens for LDV/SOF in GT1, GT4 or GT3 CHC 131
Table 48: Rationale for modelled treatment regimens and durations 139
Table 49 Eligibility criteria for cost-effectiveness studies 143
Table 50 Overview of the studies assessing cost-effectiveness of different treatment 147
Table 51: Model states 154
Table 52: Conversion between Fibrotest®, Fibroscan® and METAVIR scores 154
Table 53: Key features of analysis 156
Table 54: Treatment strategies per indication 157
Table 55 Clinical data implemented in the economic models 159
Table 56: Patient characteristics 163
Table 57: Transition probabilities 164
Table 58: GT1 TN: SVR 165
Table 59: GT1 TN: Treatment duration 167
Table 60: GT1 TN: Grade 3/4 AEs 168
Table 61: GT4 TN: SVR 168
Table 62: GT4 TN: Treatment duration 169
Table 63: GT1 and GT4 TE: SVR 170
Table 64: GT1 and GT4 TE: Treatment duration 171
Table 65:GT1 and GT4 TE: Grade 3/4 AEs 172
Table 66: GT3 TN: SVR 172
Table 67: GT3 TN: Treatment duration 173
Table 68: GT3 TN: Grade 3/4 AEs 173
Table 69: GT3 TE: SVR 174
Table 70: GT3 TE: Treatment duration 174
Table 71: GT3 TE: Grade 3/4 AEs 174
Table 72: Quality-of-life values 180

Table 73: GT1 and GT4 TN: Treatment-specific quality of life 182
Table 74:GT1 and GT4 TE: Treatment-specific quality of life 182
Table 75: GT3 TN: Treatment-specific quality of life 182
Table 76: GT3 TE: Treatment-specific quality of life 183
Table 77: Treatment unit costs 186
Table 78: Resource use unit costs 187
Table 79: Costs summary by monitoring phase and treatment 189
Table 80: Monitoring costs: summary by indication 191
Table 81: Health state costs 192
Table 82: Adverse event unit costs 193
Table 83: Adverse event treatment dosing and duration 194
Table 84: Other adverse event costs: Outpatient costs 195
Table 85: Other adverse event costs: Registrar costs 195
Table 86: Other adverse event costs: Specialist costs 196
Table 87: Model outputs by outcome 199
Table 88: Model outputs by outcome 199
Table 89: Model outputs by outcome 199
Table 90: Model outputs by outcome 200
Table 91: Model outputs by outcome (cirrhotic patients only) 200
Table 92: Model outputs by outcome 200
Table 93: Model outputs by outcome (cirrhotic patients only) 201
Table 94: Summary of base-case cost-effectiveness results (ICER for LDV/SOF±RBV against each comparator: £/QALY) 203
Table 95: Cost-effectiveness results, GT1 treatment naïve 204
Table 96: Cost-effectiveness results, GT4 treatment naive 205
Table 97: Cost-effectiveness results, GT1/GT4 treatment experienced† 206
Table 98: Cost-effectiveness results, GT3 treatment naive 207
Table 99: Cost-effectiveness results, GT3 treatment naïve with compensated cirrhosis 208
Table 100: Cost-effectiveness results, GT3 treatment experienced IFN ineligible 209
Table 101: Cost-effectiveness results, GT3 treatment experienced IFN ineligible with compensated cirrhosis 209
Table 102: Weighted costs and QALYs for LDV/SOF versus current treatment options 210
Table 103: GT1 TN: LDV/SOF vs SOF+PEG-IFN2a+RBV 211
Table 104: GT1 TN: LDV/SOF vs SMV+ PEG-IFN2a+RBV 212
Table 105: GT1 TN: LDV/SOF vs PEG-IFN2a+RBV 213
Table 106: GT1 TN: LDV/SOF vs TVR+PEG-IFN2a+RBV 214
Table 107: GT1 TN: LDV/SOF vs BOC+PEG-IFN2a+RBV 216
Table 108: GT1 TN: LDV/SOF vs no treatment 217
Table 109: GT4 TN: LDV/SOF vs SOF+PEG-IFN2a+RBV 218

Table 110: GT4 TN: LDV/SOF vs SMV+PEG-IFN2a+RBV 220
Table 111: GT4 TN: LDV/SOF vs PEG-IFN2a+RBV 221
Table 112: GT4 TN: LDV/SOF vs no treatment 222
Table 113: GT1/4 TE: LDV/SOF vs SOF+PEG-IFN2a+RBV 224
Table 114: GT1/4 TE: LDV/SOF vs SMV+PEG-IFN2a+RBV 225
Table 115: GT1/4 TE: LDV/SOF vs PEG-IFN2a+RBV 226
Table 116: GT1/4 TE: LDV/SOF vs TVR+PEG-IFN2a+RBV 227
Table 117: GT1/4 TE: LDV/SOF vs BOC+PEG-IFN2a+RBV 229
Table 118: GT1/4 TE: LDV/SOF vs no treatment 230
Table 119: GT3 TN: LDV/SOF+RBV vs PEG-IFN2a+RBV 232
Table 120: GT3 TN: LDV/SOF+RBV vs no treatment 233
Table 121: GT3 TN CC: LDV/SOF+RBV vs SOF+PEG-IFN2a+RBV 235
Table 122: GT3 TN CC: LDV/SOF+RBV vs SOF+RBV 236
Table 123: GT3 TE: LDV/SOF+RBV vs no treatment 238
Table 124: GT3 TE CC: LDV/SOF+RBV vs SOF+RBV 239
Table 125: Cost-effectiveness results, GT1/GT4 treatment experienced† 245
Table 126: Cost-effectiveness results, GT4 treatment naive 246
Table 127: Cost-effectiveness results, GT4 treatment experienced† 246
Table 128: Cost-effectiveness results, GT1 treatment naïve 247
Table 129: Cost-effectiveness results, GT4 treatment naive 248
Table 130: Cost-effectiveness results, GT1/GT4 treatment experienced† 248
Table 131: GT4 TN and GT1/4 TE DSA results with a net benefit<£0 (ICER >£20,000) 249
Table 132: Summary of base-case cost-effectiveness results (ICER for LDV/SOF±RBV against each comparator: £/QALY) 252
Table 133: Estimation of GT1 and 4 patients eligible for treatment 258
Table 134: Estimation of GT3 patients eligible for treatment 258
Table 135: Estimation of uptake of LDV/SOF regimens 259
Table 136: LDV/SOF comparator for each HCV genotype 259
Table 137: LDV/SOF comparator displacement 260
Table 138: Budget impact for GT1 and GT4 262
Table 139: Budget impact for GT3 262

List of Figures

Figure 1: Hepatitis C disease progression 21
[redacted] 37
Figure 3: Consort flow diagram of the systematic review 46
Figure 4: Patient disposition in ION-1 73
Figure 5: Patient disposition in ION-3 74
Figure 6: Patient disposition in ION-2 75

Figure 7: SVR by patient characteristics in ION-1 (FAS) 80
Figure 8: SVR12 rates according to subgroup in ION-3 (FAS) 85
Figure 9: SVR12 rates according to subgroup in ION-2 (FAS) 92
Figure 10 Flow-chart for economic systematic review (for the original review and Update 1) 145
Figure 11 Flow-chart for economic systematic review (for Update 2) 146
Figure 12: Markov model schematic for chronic hepatitis C 153
Figure 13: Cost-effectiveness frontier in GT1 treatment naïve 204
Figure 14: Cost-effectiveness frontier in GT4 treatment naïve 205
Figure 15: Cost-effectiveness frontier in GT1/GT4 treatment experienced 206
Figure 16: Cost-effectiveness frontier in GT3 treatment naïve 207
Figure 17: Cost effectiveness in GT3 frontier treatment naïve with compensated cirrhosis 208
Figure 18: Cost-effectiveness frontier in GT3 treatment experienced 209
Figure 19: Cost-effectiveness frontier in GT3 treatment experienced with compensated cirrhosis 210
Figure 20: Tornado diagram (GT1 TN: LDV/SOF vs SOF+PEG-IFN2a+RBV) 212
Figure 21: Tornado diagram (GT1 TN: LDV/SOF vs SMV+ PEG-IFN2a+RBV) 213
Figure 22: Tornado diagram (GT1 TN: LDV/SOF vs PEG-IFN2a+RBV) 214
Figure 23: Tornado diagram (GT1 TN: LDV/SOF vs TVR+PEG-IFN2a+RBV) 215
Figure 24: Tornado diagram (GT1 TN: LDV/SOF vs BOC+PEG-IFN2a+RBV) 216
Figure 25: Tornado diagram (GT1 TN: LDV/SOF vs no treatment) 218
Figure 26: Tornado diagram (GT4 TN: LDV/SOF vs SOF+PEG-IFN2a+RBV) 219
Figure 27: Tornado diagram (GT4 TN: LDV/SOF vs SMV+PEG-IFN2a+RBV) 220
Figure 28: Tornado diagram (GT4 TN: LDV/SOF vs PEG-IFN2a+RBV) 222
Figure 29: Tornado diagram (GT4 TN: LDV/SOF vs no treatment) 223
Figure 30: Tornado diagram (GT1/4 TE: LDV/SOF vs SOF+PEG-IFN2a+RBV) 224
Figure 31: Tornado diagram (GT1/4 TE: LDV/SOF vs SMV+PEG-IFN2a+RBV) 226
Figure 32: Tornado diagram (GT1/4 TE: LDV/SOF vs PEG-IFN2a+RBV) 227
Figure 33: Tornado diagram (GT1/4 TE: LDV/SOF vs TVR+PEG-IFN2a+RBV) 228
Figure 34: Tornado diagram (GT1/4 TE: LDV/SOF vs BOC+PEG-IFN2a+RBV) 229
Figure 35: Tornado diagram (GT1/4 TE: LDV/SOF vs no treatment) 231
Figure 36: Tornado diagram (GT3 TN: LDV/SOF+RBV vs PEG-IFN2a+RBV) 232
Figure 37: Tornado diagram (GT3 TN: LDV/SOF+RBV vs no treatment) 234
Figure 38: Tornado diagram (GT3 TN CC: LDV/SOF+RBV vs SOF+PEG-IFN2a+RBV) 236
Figure 39: Tornado diagram (GT3 TN CC: LDV/SOF+RBV vs SOF+RBV) 237
Figure 40: Tornado diagram (GT3 TE: LDV/SOF+RBV vs no treatment) 238
Figure 41: Tornado diagram (GT3 TE CC: LDV/SOF+RBV vs SOF+RBV) 240
Figure 42: Multiple CEACs for GT1 treatment naïve 241
Figure 43: Multiple CEAC for GT4 treatment naïve 241
Figure 44: CEAC for GT1/GT4 treatment experienced 242

Figure 45: CEAC for GT3 treatment naïve 243
Figure 46: CEAC for GT3 treatment naïve with compensated cirrhosis 243
Figure 47: CEAC for GT3 IFN ineligible treatment experienced 244
Figure 48: CEAC for GT3 treatment experienced IFN ineligible with compensated cirrhosis 244

Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ARV	Antiretroviral
BMI	Body mass index
BOC	Boceprevir
CHC	Chronic hepatitis C
CLDQ-HCV	Chronic Liver Disease Questionnaire-Hepatitis C virus
CPT	Child Pugh Turcotte
CSR	Clinical study report
DCV	Daclatasvir
DRESS	Drug rash with eosinophilia and systemic symptoms
DSA	Deterministic sensitivity analysis
EASL	European Association for the Study of the Liver
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FDC	Fixed dose combination
GT	Genotype
HAI	Histologic activity index
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQL	Health Related Quality of Life
IFN	Interferon
ITT	Intention-to-treat
IU	International unit
IWRS	Interactive web response system
IXRS	Interactive web and voice system
LDV	Ledipasvir
LLOQ	Lower limit of quantitation
NEJM	New England Journal of Medicine
NS5A	Non-structural protein 5A
PEG-IFN	Pegylated interferon
PI	Protease inhibitor

PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QoL	Quality of life
RBV	Ribavirin
RCT	Randomised controlled trial
RNA	Ribonucleic acid
SAE	Serious adverse event
SF-36	Short Form Health Survey
SMV	Simeprevir
SOF	Sofosbuvir
STR	Single tablet regimen
SVR	Sustained virologic response
TVR	Telaprevir
ULN	Upper limit of the normal range
WPAI: Hep C	Work Productivity and Activity Impairment: Hepatitis C

Executive summary

Burden of disease and unmet need

The primary goal of chronic hepatitis C (CHC) treatment is to cure the infection by eradicating the hepatitis C virus (HCV), denoted by achieving a sustained virologic response (SVR) at week 12 post-treatment. The treatment landscape in CHC, especially for genotype (GT) 1, has evolved rapidly with the recent regulatory approvals of sofosbuvir (SOF) and simeprevir (SMV). These medicines result in SVR rates of >90% with 12 weeks of SOF or >80% with 12 weeks of SMV, when combined with pegylated-interferon (PEG-IFN) and ribavirin (RBV) for 12 or 24–48 weeks respectively (1;2). Regimens containing SOF or SMV represent the preferred treatment options for CHC GT1, GT3 (SOF-based regimes only) and GT4, based on the most recent UK and European guidelines (3;4). In addition, some patients can benefit from interferon (IFN)-free regimens containing SOF plus either RBV or SMV. However, the majority of patients in England and Wales are currently treated with an IFN-containing option as there are no IFN-free options recommended by NICE for GT1 and GT4 patients, or GT3 patients who are non-cirrhotic.

The primary limitation of PEG-IFN+RBV containing regimens is the association with severe and often intolerable side effects including influenza-like symptoms, fatigue, psychiatric disorders, skin reactions, bone marrow suppression and anaemia (5). The need for safety and efficacy monitoring and support (4), long duration of treatment (up to 48 weeks) and weekly injections (6;7) has made HCV therapy difficult for many patients (4). A number of these side effects are associated with RBV (rash, nausea, anaemia (8)), and therefore new regimens that provide any reduction in the proportion of patients requiring either PEG-IFN or RBV would be desirable.

Thus, there is a clear medical need for IFN-free and RBV-free treatments with a higher likelihood of cure than existing treatments. Simpler once daily regimens with shorter treatment durations and improved tolerability will allow treatment to be expanded into important settings such as substance misuse clinics and prisons, which will ultimately be critical to stemming the HCV epidemic in England and Wales.

Ledipasvir-sofosbuvir (Harvoni®)

Ledipasvir (LDV) and SOF are potent and selective inhibitors of HCV replication, working via different mechanisms of action; LDV targets the HCV NS5A protein and SOF targets the HCV NS5B RNA-dependent RNA polymerase. Marketing authorisation is anticipated end-November 2014 for the fixed-dose combination tablet of 90mg LDV and 400mg SOF, for the treatment of chronic hepatis C in adults. It is anticipated that the SPC will recommend LDV/SOF as a single tablet regimen for the majority of patients with GT1 and GT4 CHC, with the addition of RBV recommended for GT3 patients, decompensated cirrhosis and pre- and post-liver transplant patients. These populations comprise approximately 94% of the CHC population in England and Wales.

LDV/SOF tablets will be available in one pack size containing 28 tablets (4 weeks treatment), with a recommended dose of one tablet once daily.

The recommended course of treatment is 8 or 12 weeks with LDV/SOF for the majority of GT1 and GT4 treatment naïve and treatment experienced patients. Extending treatment to 24 weeks may provide additional beneftit for those patients with cirrhosis who are at increased risk of clinical progression and/or without re-treatment options (see Section 1.10 and 6.10.4). LDV/SOF+RBV for 24 weeks is recommended for GT1 and GT4 patients with decompensated cirrhosis or who are

pre-/post-liver transplant and for GT3 patients with cirrhosis and/or who are treatment experienced. Patients co-infected with HCV/HIV should be treated in the same way as patients with HCV mono-infection.

The anticipated list price for 28 tablets is £12,993.33, which equates to £25,987, £38,980 and £77,960 for 8, 12 and 24 weeks treatment, respectively.

Clinical evidence supporting the efficacy and safety of LDV/SOF regimens comes from three pivotal Phase III studies (ION-1, ION-2 and ION-3), and several Phase II studies. The three ION studies were designed as uncontrolled randomised trials. The EMA and US FDA have agreed that new all-oral treatments for HCV do not need a controlled trial design given the significant reductions in treatment duration, improved safety profile and removal of an injectable drug from the regimen. However, in line with regulatory direction the studies were powered to enable analysis of statistical superiority versus historical controls based upon the registrational data for the protease inhibitors (PIs) (telaprevir [TVR] and boceprevir [BOC]). Furthermore, NICE has recently acknowledged the appropriateness of this, having issued preliminary guidance accepting the use of sofosbuvir (with restrictions) on the basis of similar evidence.

Phase III clinical evidence (ION-1, ION-2 and ION-3) shows that with LDV/SOF (8–24 weeks) cure rates of 94-99% are achieved in GT1 patients. Populations assessed included patients naïve to HCV treatment and patients who had failed prior therapy with an IFN-based regimen, including those who failed treatment with an HCV PI. Patients with compensated cirrhosis were enrolled in ION-1 and ION-2.

Of the 1,952 patients in the three Phase III ION trials, 96.7% (1,888) were cured of their HCV, 1.8% (36) experienced virologic relapse after treatment, 0.1% (2) experienced on-treatment breakthrough following a period of non-compliance and 1.3% (26) were lost to follow-up or withdrew consent.

Although limited data currently exist in GT4, all patients with available data (n=16) have achieved an SVR. GT4 and GT1 infections are recognised to respond in a similar way to HCV treatments and it is therefore recommended in the SPC that GT1 and GT4 infections are treated similarly with LDV/SOF.

For treatment naïve GT1 non-cirrhotic patients (comprising the majority of GT1 patients in England and Wales) LDV/SOF treatment can be completed in 8 weeks, with the majority of remaining GT1 and GT4 patients able to complete LDV/SOF treatment in 12 weeks (see Section 1.10 and 6.10.4). For a relatively small number of patients at high risk of clinical progression and/or with limited re-treatment options (estimated at 5% of the GT1 and GT4 population), extending treatment duration to 24 weeks (±RBV) is conservatively recommended as it is thought to reduce the likelihood of relapse after treatment.

In GT3 patients, treatment with LDV/SOF+RBV for 12 weeks resulted in 100% (26/26) cure rates in treatment naïve patients, including those with compensated cirrhosis (based on Phase II data from ELECTRON-2). In treatment experienced non-cirrhotic and cirrhotic patients, SVR4 rates were achieved in 89% (25/28) and 77% (17/22) of patients, respectively (based on preliminary data from the treatment experienced arm of ELECTRON-2; trial is ongoing).

For treatment naïve GT3 non-cirrhotic patients LDV/SOF+RBV treatment can be completed in 12 weeks, providing high cure rates without the need for IFN (ELECTRON-2; see section 5.1 SPC). Although the available data for all GT3 patients is for 12 weeks treatment, on the basis of the favourable tolerability profile of LDV/SOF, the regulators have recommended that selected GT3 patients – those with cirrhosis and/or treatment experienced – should be treated for 24 weeks. These selected patients represent populations for which there is a significant unmet need.

LDV/SOF provides a favourable safety profile with only fatigue and headache identified as more common in patients treated with LDV/SOF than patients given placebo. Discontinuation rates due to adverse events (AEs) from trials were low (≤1% discontinuing on LDV/SOF and ≤2% on LDV/SOF+RBV).

Economic analyses

A Markov state-transition model was adapted from previous economic models developed by the Southampton Health Technology Assessment Centre (SHTAC) for NICE (9;10), and based on the model submitted to NICE for the appraisal for sofosbuvir (11). Patients entered the model in non-cirrhotic (including mild and moderate CHC) or compensated cirrhosis health states. Patients who achieve SVR after treatment are considered to be virologically cured and those not achieving SVR either remain in their current health state or progress to more advanced stages of the disease, including decompensated cirrhosis, HCC or liver transplant.

The model was used to assess the cost-effectiveness of LDV/SOF±RBV within its licensed indication compared with the following treatments, as defined in the scope, from the perspective of the NHS and PSS in England and Wales:

- PEG-IFNα+RBV
- TVR+PEG-IFNα+RBV (GT1 only)
- BOC+PEG-IFNα+RBV (GT1 only)
- SOF+RBV±PEG-IFNα
- SMV+PEG-IFNα+RBV (GT1 and GT4 only)
- SMV+SOF (GT1 and GT4 only)
- Best supportive care (no treatment)

The populations included in the economic analyses were: GT1 and GT4 treatment naïve and treatment experienced; GT3 treatment naïve; GT3 treatment experienced IFN ineligible. For the GT3 treatment experienced population, only IFN ineligible patients were modelled on the basis that the licence recommends that all GT3 treatment experienced patients should be treated with LDV/SOF+RBV for 24 weeks. This approach would not be cost-effective versus the anticipated standard of care, SOF+PEG-IFN+RBV for 12 weeks for those eligible to receive IFN. Therefore in the interests of simplicity, for GT3 treatment experienced patients only IFN ineligible populations have been modelled. HCV/HIV co-infection has not been modelled separately on the basis that the licence recommends that these patients should be treated in the same way as HCV mono-infected patients, consistent with previous NICE submissions for other HCV medicines and as validated by KOLs.

Following the decision by the regulators that GT1 and GT4 should be treated similarly, and due to limited availability of data for GT4 patients, GT1 and GT4 were modelled as a single population using GT1 clinical data. This approach was validated based on KOL agreement that GT1 clinical data is generalisable to GT4. However, as there is currently no data on the 8-week LDV/SOF regimen in GT4 patients, only the 12 week regimen has been considered when treating the GT4 treatment naïve non-cirrhotic population.

Due to preliminary NICE recommendations restricting SOF+RBV and SOF+PEG-IFN+RBV to cirrhotic GT3 populations, analyses against these comparators in GT3 patients were restricted to cirrhotic patients only.

A summary of all base case ICERs is provided in Table 1. LDV/SOF was found to be dominant or cost-effective when compared with all comparators across GT1 and GT4 patient populations, with

ICERs <£14,000. LDV/SOF+RBV was cost-effective in the majority of GT3 patient populations, with ICERs <£20,000 in three out of six comparisons and between £20,000 and £30,000 in two further comparisons. LDV/SOF was not cost-effective compared with SOF+PEG-IFN+RBV in GT3 treatment naive patients with cirrhosis primarly diven by a difference in treatment cost due to the longer treatment duration for LDV/SOF (12 vs 24 weeks).

Extensive deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were undertaken to assess the uncertainty around the base case ICERs. In GT1 and GT4 patients LDV/SOF remained cost-effective in the majority of scenarios tested in the DSA. In the PSA, LDV/SOF had an 88-100% probability of being cost-effective versus all comparators at a threshold of £20,000. For GT3 treatment naive patients, the probability that LDV/SOF+RBV is the most cost-effective option versus PEG-IFN2a+RBV and no treatment at a threshold of £30,000 per QALY is 68%. For GT3 treatment experienced IFN ineligible patients, the probability that LDV/SOF is the most cost-effective option at a threshold of £20,000 per QALY versus SOF+RBV (the only active treatment) is 78%.

Conclusion

LDV/SOF, an oral, once daily, single tablet regimen, provides a well tolerated, short duration treatment that offers the opportunity of cure for the majority of GT1 and GT4 patients with CHC. For GT3 patients, the addition of RBV to the regimen is recommended. LDV/SOF is highly effective and cost-effective compared with all currently available CHC treatment options, and removes the need for IFN which is a major concern for physicans and patients when considering treatment. LDV/SOF should therefore be recommended as a treatment option for patients with CHC GT1, GT3 and GT4 in England and Wales, providing many more HCV infected patients with an opportunity for a cure.

Table 1: Summary of base-case cost-effectiveness results (ICER for LDV/SOF±RBV against each comparator: £/QALY)

Indication	LDV/SOF regimen	Comparator							
		SOF+ PEG-IFN2a +RBV	SMV+ PEG-IFN2a +RBV	PEG-IFN2a +RBV	TVR+ PEG-IFN2a +RBV	BOC+ PEG-IFN2a +RBV	SOF+RBV	NT	SMV+SOF
GT1 treatment naïve	LDV/SOF	LDV/SOF dominates	LDV/SOF dominates	£7,985	LDV/SOF dominates	LDV/SOF dominates	-	£7,458	LDV/SOF dominates
GT4 treatment naïve	LDV/SOF	£3,869	£12,399	£12,715	-	-	-	£10,468	LDV/SOF dominates
GT1/GT4 treatment experienced†	LDV/SOF	£5,497	£9,984	£12,491	£9,144	£3,551	-	£13,527	LDV/SOF dominates
GT3 treatment naïve‡	LDV/SOF+RBV	£46,691‡	-	£26,491	-	-	£19,013‡	£11,235	-
GT3 treatment experienced IFN ineligible‡	LDV/SOF+RBV	-	-	-	-	-	£6,210‡	£28,048	-

Abbreviations: BOC, boceprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; NT, no treatment; PEG-IFN, pegylated interferon; QALY; quality adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

† TVR+PEG-IFN2a+RBV and BOC+PEG-IFN2a+RBV are relevant for GT1 CHC only as they are not licensed for the treatment of GT4 CHC.

‡ In GT3 patients some comparisons have been restricted to cirrhotic patients only in line with preliminary NICE recommendations for particular comparators. All other scenarios include a mixed cohort of non-cirrhotic and cirrhotic patients.

Section A – Decision problem

1 Description of technology under assessment

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

Generic name: ledipasvir/sofosbuvir (LDV/SOF)

Approved name: Harvoni®

Therapeutic class: Hepatitis C virus (HCV) non-structural protein (NS) 5A inhibitor (LDV). Uridine nucleotide analogue NS5B polymerase inhibitor (SOF).

A copy of the draft SPC will be provided in the appendix, Section **Error! Reference source not found.**.

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

LDV is a HCV inhibitor targeting the HCV NS5A protein, which is essential for both ribonucleic acid (RNA) replication and the assembly of HCV virions. Biochemical confirmation of NS5A inhibition by LDV is not currently possible as NS5A has no enzymatic function. *In vitro* resistance selection and cross-resistance studies indicate ledipasvir targets NS5A as its mode of action.

SOF is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analogue triphosphate (GS-461203), which, when incorporated into HCV RNA by the NS5B polymerase, acts as a chain terminator. GS-461203 (the active metabolite of sofosbuvir) is neither an inhibitor of human deoxyribonucleic acid (DNA) and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.

1.3 ***Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).***

Regulatory submission to EMA: February 2014

CHMP positive opinion: 26th September 2014

Marketing authorisation: anticipated end-November 2014

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

The EPAR is anticipated and will be provided once available.

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

Harvoni is indicated for the treatment of chronic hepatitis C (CHC) in adults.

The licensed indication for LDV/SOF covers CHC as a whole, with recommended treatment regimens in genotype (GT) 1 and 4 included in the SPC (See SPC in appendix, section **Error! Reference source not found.**). Recommendations are also included in the SPC for certain GT3 populations (those with cirrhosis and/or prior treatment failure) and these populations are included in the submission. In addition, as per the SPC, data are available for treatment naïve non-cirrhotic

GT3 patients and therefore this group is included in the submission. [redacted]There are no clinical data available to date for the other genotypes: 2, 5 and 6. As such these populations are not included in this submission.

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

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

Table 2: Summary of ongoing LDV/SOF studies

Study number	Details	Estimated date final results will be available
GS-US-337-0113 (Japanese Phase IIIb)	• LDV/SOF±RBV for 12 weeks • Japanese patients • Treatment naïve and treatment experienced • HCV GT1 • No cirrhosis and compensated cirrhosis	[redacted]
GS-US-337-0123 (SOLAR-1)	• LDV/SOF+RBV for 12 or 24 weeks • HCV GT1 • Advanced liver disease or are post-liver transplant	[redacted]
CO-US-337-0117 (SYNERGY)	• LDV/SOF for 12 weeks • HCV GT1 and GT4 • Treatment naïve • Treatment experienced (including GT1 prior SOF/RBV treatment failures) • No cirrhosis and compensated cirrhosis	[redacted]
GS-US-337-0122 (ELECTRON-2)	• LDV/SOF+RBV for 12 weeks • HCV GT3 and GT6 • Treatment experienced and, for GT6 only, treatment naïve patients • No cirrhosis and compensated cirrhosis	[redacted]
GS-US-337-0121 SIRIUS	• LDV/SOF+RBV for 12 weeks • LDV/SOF for 24 weeks • HCV GT1 • Treatment experienced PI failure patients with compensated cirrhosis	[redacted]
GS-US-337-0115 (ION-4)	• LDV/SOF for 12 weeks • HCV GT1 or GT4 • HIV co-infection • No cirrhosis and compensated cirrhosis	[redacted]
GS-US-337-1118 (SOF re-treatment)	• LDV/SOF±RBV for 12 or 24 weeks • GT1 • SOF-experienced patients	[redacted]
GS-US-337-0124 SOLAR-2	• LDV/SOF+RBV for 12 or 24 weeks • HCV GT1 and GT4	[redacted]

	• Advanced liver disease or are post-liver transplant	
GS-US-337-1119 (GT4 and GT5 French study)	• LDV/SOF • HCV GT4 and GT5 • Treatment naïve and treatment experienced • No cirrhosis and compensated cirrhosis	[redacted]

Abbreviations: GT, genotype; HCV, hepatitis C; HIV, human immunodeficiency virus; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

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

Date of UK availability: end-November 2014, in line with Marketing Authorisation

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

Harvoni gained FDA approval in the United States on October 10th 2014, and was granted a Notice of Compliance by Health Canada on October 16th 2014.

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

A submission to the SMC was made on 6th October 2014. Advice is expected to be published 9th March 2015.

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

Table 3: Unit costs of technology being appraised

Pharmaceutical formulation	Film-coated tablet
Acquisition cost (excluding VAT)	28 day pack £12,993.33
Method of administration	Oral
Doses	90mg LDV and 400mg SOF as a single tablet
Dosing frequency	Once a day
Average length of a course of treatment*	The anticipated use of LDV/SOF regimens and treatment durations is summarised in the table below, dependent on genotype, prior treatment experience and cirrhosis status. Detailed rationale supporting the proportion of patients in each group is provided in Table 48.

Subgroup	Patient population	Regimen	Duration, weeks	% by treatment duration
GT1 and GT4				
Treatment naïve	without cirrhosis	LDV/SOF	8	79% (GT1 only)
		LDV/SOF	12	21% (GT1 only) 100% (GT4 only)
	with compensated cirrhosis	LDV/SOF	12†	95%
		LDV/SOF	24	5%
Treatment experienced	without cirrhosis	LDV/SOF	12	95%
		LDV/SOF	24‡	5%
	with compensated cirrhosis	LDV/SOF	12†	75%
		LDV/SOF	24	25%
Decompensated cirrhosis or who are pre-/post-liver transplant		LDV/SOF+RBV	24	100%
GT3				
Treatment naïve	without cirrhosis	LDV/SOF+RBV	12	100%
	with compensated cirrhosis	LDV/SOF+RBV	24	100%
Treatment experienced	without cirrhosis	LDV/SOF+RBV	24	100%
	with compensated cirrhosis	LDV/SOF+RBV	24	100%

Abbreviations: GT, genotype; NC, non-cirrhotic; TN, treatment naïve.
† for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options.
‡ for patients without subsequent retreatment options.

Average cost of a course of treatment (LDV/SOF only)	Ledipasvir/sofosbuvir only 8 week course=£25,986.67 12 week course=£38,980.00 24 week course=£77,960.00
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	Dose reduction is not recommended

Abbreviations: GT, genotype, HCV, hepatitis C virus; LDV, ledipasvir; RBV, ribavirin, SOF, sofosbuvir.
*Includes patients co-infected with HIV.

1.11 ***For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.***

N/A

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

No tests or investigations are required in addition to current routine hepatitis tests.

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

Less monitoring is required with LDV/SOF compared with currently available regimens:

- There is no requirement for response-guided therapy (RGT) with LDV/SOF.
  - Patients treated with pegylated interferon (PEG-IFN) or first generation protease inhibitor (PI)-based regimens are managed using a complex RGT approach, where virologic response measured at specific time points is used to determine the on-treatment response, likelihood of sustained virologic response (SVR) and the required treatment duration (6;7;12;13).
  - In comparison to PEG-IFN or PI-based regimens, with LDV/SOF a very high proportion of patients achieve a rapid virologic response (after 4 weeks of treatment) and an end of treatment response (99-100%). In addition, due to SOF's very high barrier to resistance, non-response and on-treatment breakthrough due to resistance have not been observed in the LDV/SOF clinical trials. As a result, monitoring associated with early stopping rules is not required. This should simplify patient management considerably relative to current standards of care and also reduce the need for frequent on-treatment viral load monitoring and clinic visits.
- PEG-IFN, PIs and RBV all require careful AE monitoring during treatment, including haematological monitoring (6-8;12;13), for progression/resolution of rashes (TVR, SMV (2;12)), or for signs or symptoms of psychiatric disorders, central nervous system effects, hepatic decompensation, development of gout, and dental and periodontal disorders (RBV (8)). With LDV/SOF there is no specific requirement for haematological monitoring and only fatigue and headache were identified as more common in patients treated with LDV/SOF compared with placebo. This safety profile for LDV/SOF should reduce monitoring and AE

costs versus PEG-IFN, PI and RBV containing therapies while on treatment. Although it is recommended that LDV/SOF is taken in combination with RBV in some patients, many patients can be effectively treated with LDV/SOF alone, without the addition of RBV.

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

RBV will be used in combination with LDV/SOF in CHC GT1 patients with decompensated cirrhosis, CHC GT1 patients who are pre-/post-liver transplant and in CHC GT3 patients (Table 3).

2 Context

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

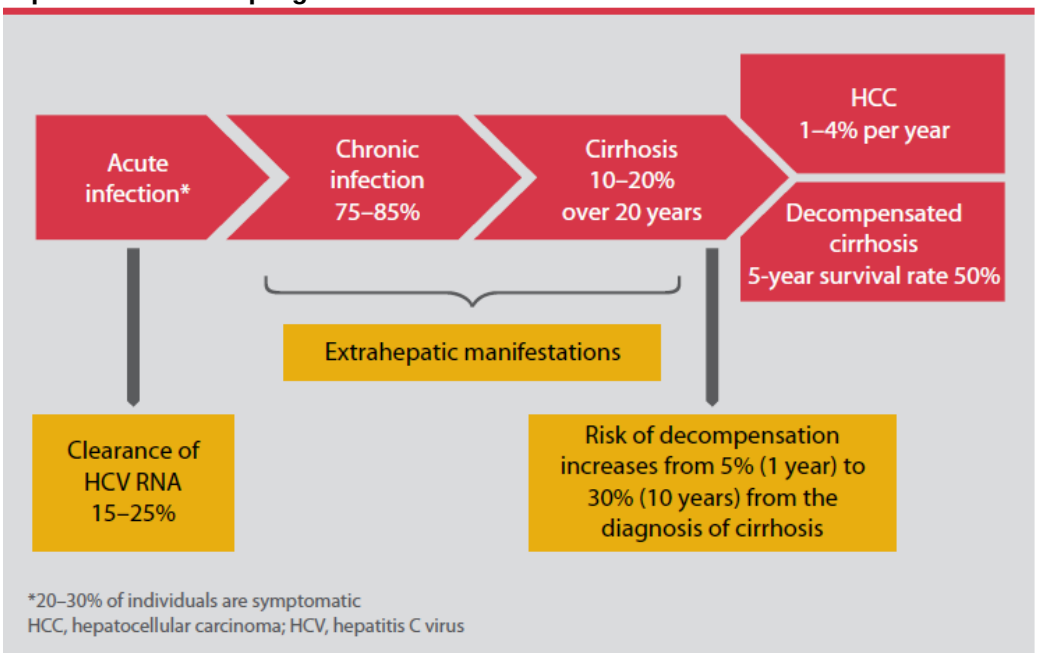
Hepatitis C is a progressive disease associated with significant morbidity, mortality and economic burden. It is caused by infection of the liver by HCV.

Acute infection is generally asymptomatic and 15–25% of acutely affected individuals will show a gradual decrease in virus levels (14). The remaining 75–85% will go on to develop CHC, defined as persistent, detectable serum HCV RNA for a period greater than 6 months (Figure 1) (14).

If left untreated, patients with CHC are at progressive risk of liver fibrosis, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC) and death (14), as well as extrahepatic diseases including circulatory diseases, renal diseases, autoimmune disorders, cutaneous manifestations and non-liver cancers (15;16).

An estimated 10–20% of patients with CHC will go on to develop cirrhosis over a 20-year period and once cirrhosis is established, HCC develops at a rate of 1–4% per year (14). Compensated cirrhosis is associated with a 5-year survival rate of 91%, whereas once decompensated cirrhosis occurs, the 5-year survival rate drops dramatically to 50% (14). HCC is associated with a 1-year survival rate of 67% (5). CHC is the most common cause of liver cirrhosis and the most common indication for liver transplantation in Europe (17).

Figure 1: Hepatitis C disease progression



Adapted from Chen and Morgan, 2006 (14)

The rate at which liver disease progresses is unpredictable and related to a range of environmental and host factors, including alcohol consumption, age at infection, sex, the presence of co-morbidities such as obesity or insulin resistance, and co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV) (17). Progression to cirrhosis is often clinically silent, apart from non-specific symptoms such as fatigue, upper right quadrant pain or, sometimes, arthralgia and myalgia (17). Some patients are not known to have CHC until they present with the complications of end-stage liver disease or HCC (14).

HCV has also been found in sites outside the liver, including bone marrow, the central nervous system, endocrine glands, lymphatic tissue and skin cells. This can result in a host of extrahepatic manifestations, including autoimmune disease, skin reactions, renal injury and neuropathy (17); it is estimated that up to 76% of patients with CHC experience at least one such manifestation (16). These extrahepatic manifestations contribute considerably to the overall disease burden in CHC patients (15).

In addition to the health burden, a patient's quality of life (QoL) can be significantly impaired, in terms of both their physical and mental health (18;19). Patients also have to manage with the social stigma associated with CHC (20).

There are six major HCV RNA genotypes (GT1–6) and multiple subtypes (labelled a, b, c, etc.) characterised by high RNA sequence heterogeneity; genotype and subtype sequences differ by approximately 30% and 20%, respectively (5). In England, sentinel surveillance data from 2009 to 2013 show GT1 (45%) and GT3 (45%) predominating with other genotypes, including GT4, comprising just 10% of infections (21). The choice of therapy, response to treatment and rate of disease progression is strongly influenced by HCV genotype (5;22).

CHC is associated with a considerable health burden with an estimated 214,000 individuals chronically infected with hepatitis C in the UK including 160,000 people in England (21). There has been a more than five-fold increase in the number of laboratory confirmed reports of HCV in England between 1996 and 2013 with 11,051 infections reported in 2013 (21).

Statistical modelling estimates that nearly 10,850 individuals are currently living with HCV related cirrhosis or HCC in England. Predictions are that if current treatment levels are maintained the number of patients with severe HCV related disease will continue to increase (13,590 cases by 2025), representing a substantial future burden on healthcare resources (21;23). By increasing treatment uptake and introducing more effective treatments rapidly it is estimated that the number of people living with HCV-related cirrhosis and HCC in 2025 could be dramatically reduced by 8,340, to 5,250 (21). Public Health England recommends that the availability, access and uptake of approved treatment in primary and secondary care, drug treatment services, prisons and other settings needs to be considered (21) so that this can be achieved.

The primary goal of treatment for CHC is to cure the infection by eradicating the HCV virus. In this regard, treatment efficacy is measured as the proportion of patients in whom the virus is undetectable at a defined time point, typically 12 or 24 weeks following treatment cessation; this is referred to as an SVR (3;24). Achieving SVR, and therefore being cured of CHC, is associated with a wide range of benefits, including regression of fibrosis and cirrhosis, and has been associated with a reduced rate of hepatic decompensation, a reduced risk for HCC and both a reduced rate of liver and non-liver related mortality (25-29). In addition, patients experience improved QoL (18;19), require reduced healthcare utilisation (30), and importantly, the patient is no longer at risk of transmitting HCV.

Details on the current treatment options including related NICE guidance and current unmet need are provided in Sections 2.4 and 2.5.

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

The estimated number of patients in England and Wales who will be eligible for treatment with LDV/SOF is 15,240. This figure is based on the following:

- There are approximately 16,300 patients with CHC under treater care in England and Wales.
- Based upon a commissioned analysis of the Public Health England sentinel survey data, approximately 94% of patients in England and Wales are infected with HCV GT1, GT3 or GT4 (31).

At present, approximately 3% of the total estimated chronically infected are treated per year, based upon around 28,000 treatments taking place between 2006 and 2011 (21). This equates to approximately 6,000 patients with GT1, GT3 or GT4 treated per year. However, it is anticipated that there will be an increase in the number HCV patients treated per year due to the high SVR rates demonstrated with the recently licensed treatments for CHC, the removal of IFN, and the potential for a reduction in treatment duration and in the burden of treatment management.

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

While there are data clearly demonstrating that CHC is associated with increased morbidity and mortality, published data on the actual life expectancy of people with CHC are limited and dependent on the degree of liver fibrosis and ongoing addictive behaviour, especially alcohol (32).

A cohort study conducted in England compared the death rates of 2,286 patients with HCV infection to that seen in an age- and sex-matched English population and found that standardised mortality rates were three times higher than those expected in the general population (32).

Data on patients with liver disease, from the British Society of Gastroenterology, highlight that the average age of someone dying with liver disease is 59 years compared to 82−84 years for heart and lung disease and stroke (33).

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

A NICE clinical guideline (Hepatitis C: Diagnosis and management of hepatitis C) is in development; this process has been suspended pending the publication of ongoing technology appraisals for individual treatments for hepatitis C. Recommendations from NICE technology appraisals are summarised in Table 4. Preliminary recommendations for SOF and simeprevir (SMV) have also been provided. NICE are currently reviewing ombitasvir/paritaprevir/ritonavir with or without dasabuvir (anticipated publication date June 2015) and daclatasvir (anticipated publication date to be confirmed) in the technology appraisal programme.

Table 4: NICE technology appraisal guidance in CHC

Guidance number/ Issue date	Title	Guidance recommendations (wording is as per guidance documents including any reference to other sections in those guidance documents)
ID 668 (Guidance in development for SMV)	Hepatitis C (chronic) – simeprevir	**Preliminary recommendations** 1.1 Simeprevir, in combination with PEG-IFN alfa and RBV, is recommended within its marketing authorisation as an option for treating genotype 1 chronic hepatitis C. 1.2 The Committee is minded not to recommend simeprevir, in combination with PEG-IFN alfa and RBV, for treating genotype 4 chronic hepatitis C. The Committee recommends that NICE requests a detailed rationale from the company about whether the clinical effectiveness in people with genotype 1 hepatitis C virus (HCV) can be generalised to people with genotype 4 HCV. 1.3 Simeprevir, in combination with sofosbuvir (with or without RBV) is not recommended within its marketing authorisation for treating genotype 1 or 4 chronic hepatitis C. 1.4 NICE recommends that clinical data, including genotype and sustained virological response at 12 weeks, is collected for all people treated with simeprevir in the NHS. 1.5 People currently receiving treatment initiated within the NHS with simeprevir that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop
ID654 (Guidance in development for SOF) (34)	Hepatitis C (chronic) - sofosbuvir	**Preliminary recommendations** Sofosbuvir in combination with PEG-IFN alfa and RBV 1.1 Sofosbuvir, in combination with PEG-IFN alfa and RBV, is recommended as an option for treating genotype 1 chronic hepatitis C in adults. 1.2 Sofosbuvir, in combination with PEG-IFN alfa and RBV, is recommended as an option for treating genotype 3 chronic hepatitis C in adults with cirrhosis. 1.3 Sofosbuvir, in combination with PEG-IFN alfa and RBV, is recommended as an option for treating genotype 3 chronic hepatitis C in adults without cirrhosis, only if they had treatment for hepatitis C before. 1.4 Sofosbuvir, in combination with PEG-IFN alfa and RBV, is not recommended for treating genotype 4, 5 and 6 chronic hepatitis C in adults Sofosbuvir in combination with RBV alone 1.5 Sofosbuvir, in combination with RBV alone is not recommended for treating adults with genotype 1, 4, 5 and 6 chronic hepatitis C. 1.6 Sofosbuvir, in combination with RBV, is recommended as an option for treating genotype 2 chronic hepatitis C in adults only if they: • have not had treatment for chronic hepatitis C before and are intolerant to or ineligible for interferon therapy or • have had treatment for chronic hepatitis C before,

Guidance number/ Issue date	Title	Guidance recommendations (wording is as per guidance documents including any reference to other sections in those guidance documents)
		regardless of interferon eligibility. 1.7 Sofosbuvir, in combination with RBV, is recommended as an option for treating genotype 3 chronic hepatitis C only in adults with cirrhosis. 1.8 People currently receiving treatment initiated within the NHS with sofosbuvir that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
TA253/April 2012 (35)	Boceprevir for the treatment of genotype 1 chronic hepatitis C	1.1 BOC in combination with PEG-IFN alfa and RBV is recommended as an option for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease: • who are previously untreated or • in whom previous treatment has failed.
TA252/April 2012 (36)	Telaprevir for the treatment of genotype 1 chronic hepatitis C	1.1 TVR in combination with PEG-IFN alfa and RBV is recommended as an option for the treatment of genotype 1 chronic hepatitis C in adults with compensated liver disease: • who are previously untreated or • in whom previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with RBV has failed, including people whose condition has relapsed, has partially responded or did not respond.
TA200/September 2010 (37)	Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C	1.1 Combination therapy with PEG-IFN alfa (2a or 2b) and RBV is recommended as a treatment option for adults with chronic hepatitis C: • who have been treated previously with PEG-IFN alfa (2a or 2b) and RBV in combination, or with PEG-IFN alfa monotherapy, and whose condition either did not respond to treatment or responded initially to treatment but subsequently relapsed or • who are co-infected with HIV. 1.2 Shortened courses of combination therapy with PEG-IFN alfa (2a or 2b) and RBV are recommended for the treatment of adults with chronic hepatitis C who: • have a rapid virological response to treatment at week 4 that is identified by a highly sensitive test and • are considered suitable for a shortened course of treatment. 1.3 When deciding on the duration of combination therapy, clinicians should take into account the licensed indication of the chosen drug (PEG-IFN alfa-2a or PEG-IFN alfa-2b), the genotype of the hepatitis C virus, the viral load at the start of treatment and the response to treatment (as indicated by the viral load).
TA106/August 2006 (38)	Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. This is an	1.1 Combination therapy, comprising PEG-IFN alfa-2a and RBV or PEG-IFN alfa-2b and RBV, is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C. 1.2 Monotherapy with PEG-IFN alfa-2a or PEG-IFN alfa-2b is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C for people who are unable to tolerate RBV, or for whom RBV is contraindicated. 1.3 The decision on whether a person with mild chronic hepatitis C

Guidance number/ Issue date	Title	Guidance recommendations (wording is as per guidance documents including any reference to other sections in those guidance documents)
	extension of the guidance given in NICE technology appraisal guidance 75	should be treated immediately or should wait until the disease has reached a moderate stage ('watchful waiting') should be made by the person after fully informed consultation with the responsible clinician. The decision to treat need not depend on a liver biopsy to determine the stage of the disease if treatment is initiated immediately. However, a biopsy may be recommended by the clinician for other reasons or if a strategy of watchful waiting is chosen. 1.4 This recommendation has been updated and replaced by NICE technology appraisal guidance 200 1.5 This recommendation has been updated and replaced by NICE technology appraisal guidance 200 1.6 There is insufficient evidence to recommend combination therapy or monotherapy with PEG-IFN alfa for people who have had a liver transplant.
TA75/January 2004 (39)	Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C This guidance is a review and extension of Technology Appraisal Guidance No. 14 issued in October 2000	1.1 Combination therapy with PEG-IFN alfa and RBV is recommended within its licensed indications for the treatment of people aged 18 years and over with moderate to severe chronic hepatitis C (CHC), defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation. 1.2 People with moderate to severe CHC are suitable for treatment if they have: • not previously been treated with interferon alfa or PEG-IFN alfa, or • been treated previously with interferon alfa (as monotherapy or in combination therapy), and/or 1.3 People currently being treated with interferon alfa, either as combination therapy or monotherapy, may be switched to the corresponding therapy with PEG-IFN alfa. 1.4 Treatment for the groups identified in Sections 1.1 and 1.2 should be as follows. • People infected with hepatitis C virus (HCV) of genotype 2 and/or 3 should be treated for 24 weeks. • For people infected with HCV of genotype 1, 4, 5 or 6, initial treatment should be for 12 weeks. Only people showing, at 12 weeks, a reduction in viral load to less than 1% of its level at the start of treatment (at least a 2-log reduction, see Section 4.1.2.5) should continue treatment until 48 weeks. For people in whom viral load at 12 weeks exceeds 1% of its level at the start of treatment, treatment should be discontinued. • People infected with more than one genotype that includes one or more of genotypes 1, 4, 5, or 6 should be treated as for genotype 1. (Recommendation 1.4 still applies for people who are treated with standard courses of combination therapy, but has been replaced by NICE technology appraisal guidance 200 [TA200] for people who are eligible for shortened courses of combination therapy [as described in recommendation 1.2 of TA200]) 1.5 People satisfying the conditions in Sections 1.1 and 1.2 but for whom RBV is contraindicated or is not tolerated should be treated with PEG-IFN alfa monotherapy. Regardless of

Guidance number/ Issue date	Title	Guidance recommendations (wording is as per guidance documents including any reference to other sections in those guidance documents)
		genotype, individuals should be tested for viral load at 12 weeks, and if the viral load has reduced to less than 1% of its level at the start of treatment, treatment should be continued for a total of 48 weeks. If viral load has not fallen to this extent, treatment should stop at 12 weeks. 1.6 People for whom liver biopsy poses a substantial risk (such as those with haemophilia, or those who have experienced an adverse event after undergoing a previous liver biopsy), and people with symptoms of extra-hepatic HCV infection sufficient to impair quality of life, may be treated on clinical grounds without prior histological classification. 1.7 There is insufficient evidence to recommend combination therapy using PEG-IFN alfa or interferon alfa in people who: • this part-recommendation has been updated and replaced by NICE technology appraisal guidance 200 • this part-recommendation has been updated and replaced by NICE technology appraisal guidance 300 • have had a liver transplantation. Treatment of CHC recurrence after liver transplantation (whether or not the person had been treated with IFN alfa or PEG-IFN alfa therapy at any time before transplantation) should be considered as experimental and carried out only in the context of a clinical trial.

Abbreviations: BOC, boceprevir; CHC, chronic hepatitis C; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PEG-IFN, pegylated interferon; RBV, ribavirin; TVR, telaprevir.

In addition, NICE has published the following public health guidance *'Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection'* (40). This guidance provides recommendations covering:

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

This guidance does not provide detail on treatments for hepatitis C that are covered by the technology appraisals detailed in Table 4.

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

The current clinical pathway of care takes into account the European Association for the Study of the Liver (EASL) recommendations on treatment of hepatitis C 2014 (April) guidelines (3) and the 2014 UK consensus guidelines-hepatitis C management and direct-acting anti-viral therapy (4) (Table 5).

Current treatment options include established treatments, such as PEG-IFN, TVR, and BOC, which have all been recommended by NICE (Table 4), and new options that are currently under review by NICE and have been recently licensed (SOF, SMV, DCV) or expect marketing authorisation early in 2015 (ombitasvir/paritaprevir/ritonavir with or without dasabuvir). Recent EASL guidelines and UK consensus guidelines recommend these new treatment options, and are reflective of preferred clinical practice, whereas their widespread use in England and Wales is reliant on approval from NICE. Of the four treatments under NICE review, preliminary recommendations for SOF and SMV have been provided (Table 4). SOF+PEG-IFN+RBV has preliminary recommendations for use in CHC GT1 patients, CHC GT3 patients with cirrhosis and CHC GT3 treatment experienced patients without cirrhosis. In genotypes of relevance to this submission SOF+RBV has a preliminary recommendation for use in GT3 patients with cirrhosis. NICE preliminary recommendations for SMV+PEG-IFN+RBV are in GT1 patients only, while the committee is minded not to recommend its use in GT4 patients, and to not recommend SMV+SOF in GT1 or GT4.

Treatment efficacy, and hence decisions around the choice of treatments is influenced by HCV genotype, the stage of liver disease – absence or presence of cirrhosis – and whether a patient has received treatment for the condition previously – HCV treatment naïve or treatment experienced (3).

The EASL 2014 guidelines outline several options of treatment for the genotypes of relevance to this submission – GT1, GT3, and GT4 (Table 5). Each of the regimens outlined in these guidelines, with the exception of SOF-based and DCV-based regimens require regular monitoring of treatment efficacy based on repeated measurements of HCV RNA in order to guide treatment duration (response-guided therapy; RGT). The UK consensus guidelines from April 2014 (4) are broadly in line with the EASL guidelines (Table 5).

In addition, EASL guidelines also provide the following recommendations for the following special populations (3):

- In patients with compensated cirrhosis IFN-free combination regimens should be preferred.
- In patients with decompensated cirrhosis (Child Pugh Turcotte [CPT] B and C) awaiting liver transplantation should be treated with SOF+RBV. IFN is contraindicated in these patients. As the only treatment option currently available, SOF-based regimens (in combination with LDV or DCV) already represent the standard of care in patients with decompensated cirrhosis in England, based on the interim commissioning policy from NHS England published in April 2014 (41).
- Indications for HCV treatment in HCV/HIV co-infected persons and in those with bleeding disorders are identical to those in patients with HCV mono-infection or those without bleeding disorders.

Ledipasvir-sofosbuvir

The single tablet regimen (STR) of LDV (90 mg) and SOF (400 mg) provides a simple, all oral, once-daily, IFN-, RBV- and PI-free treatment option for the majority of adult patients with GT1 and GT4 CHC, with improved efficacy and tolerability profile following 8-24 weeks of therapy. In addition, by adding RBV to the regimen, high cure rates can be achieved in GT1 or GT4 patients with decompensated cirrhosis or who are pre-/post-liver transplant, and in patients with GT3 infection. For GT1 treatment naïve non-cirrhotic patients, LDV/SOF can be completed in 8 weeks offering the shortest complete treatment course in CHC therapy.

It is anticipated that in CHC GT1, GT3 and GT4, LDV/SOF regimens will be preferred to IFN-containing regimens, including established treatments (PEG-IFN, TVR, BOC regimens), as well as those that are expecting approval in the near future, including SOF+PEG-IFN+RBV and SMV+PEG-IFN+RBV.

In addition, LDV/SOF will provide the first IFN-free option for the majority of patients unsuitable for IFN-based regimens, as SOF+RBV is currently limited to GT3 patients with cirrhosis (based on preliminary guidance for SOF and SMV-based regimens).

Table 5: Summary of EASL recommendations and UK consensus guidelines treatment options for hepatitis C

Genotype	EASL April 2014 Recommendations (3)	UK Consensus Guidelines (4)
GT1[†]	• **Option 1: 12 weeks SOF+PEG-IFN+RBV:** The most efficacious and easiest to use IFN-containing option, without the risk of selecting resistant viruses in case of treatment failure. • **Option 2: 12 weeks SMV+PEG-IFN+RBV (RGT)** ○ with additional 12 weeks of PEG-IFN+RBV in treatment naïve and treatment experienced prior relapse patients, including cirrhotics ○ with additional 36 weeks of PEG-IFN+RBV in treatment experienced prior partial and null responders, including cirrhotics. • **Option 3: 12 weeks DCV+PEG-IFN+RBV (RGT):** recommended for HCV GT1b only ○ extend treatment duration for an additional 12 weeks in patients who do not achieve HCV RNA <25 IU/mL at week 4 and undetectable at week 10. ○ PEG-IFN+RBV should be continued alone between week 12 and 24 in patients who achieve HCV RNA <25 IU/mL at week 4 and undetectable at week 10. • **Option 4: 24 weeks SOF+RBV** in patients who are IFN-intolerant or IFN-ineligible and when no other IFN-free option is available. • **Option 5: 12 weeks SMV+SOF:** The current most attractive licensed IFN-free combination. ○ RBV should be included in this option for patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. • **Option 6: 12 weeks SOF+DCV** in treatment naïve patients ○ extend treatment duration for an additional 12 weeks in treatment experienced, including those who failed on a triple combination of TVR+PEG-IFN+RBV or BOC+PEG-IFN+RBV ○ RBV should be included in this option for patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. • **PEG-IFN+RBV+TVR** and **PEG-IFN+RBV+BOC:** Remain acceptable in settings for which none of the above options are available.	• **Treatment naïve:** ○ 12 weeks SOF+PEG-IFN+RBV ○ 12 weeks SMV, 24 weeks PEG-IFN+RBV • **Treatment experienced:** ○ 12 weeks SMV, 24 or 48 weeks PEG-IFN+RBV (RGT) ○ 12 weeks SOF+PEG-IFN+RBV • **Cirrhotic patients:** ○ 12 weeks SOF+PEG-IFN+RBV
GT3	• **Option 1: 12 weeks SOF+PEG-IFN+RBV:** More efficacious with a shorter duration than SOF+RBV. • **Option 2: 24 weeks SOF+RBV:** Suboptimal in patients with cirrhosis and who have previously failed treatment with IFN and RBV. • **Option 3: 12 weeks SOF+daclatasvir** in treatment naïve patients ○ With an additional 12 weeks in treatment experienced patients	• **Treatment naïve:** ○ 12 weeks SOF+PEG-IFN+RBV ○ 24 weeks PEG-IFN+RBV ○ 24 weeks SOF+RBV

Genotype	EASL April 2014 Recommendations (3)	UK Consensus Guidelines (4)
	○ Addition of RBV should be considered for patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis • **PEG-IFN+RBV:** Remains acceptable in cases for which none of the above options are available.	• **Treatment experienced:** ○ 12 weeks SOF+PEG-IFN+RBV ○ 24 weeks SOF+RBV • **Cirrhotic patients:** ○ 24 weeks SOF+RBV ○ 12 weeks SOF+PEG-IFN+RBV
GT4‡	• **Option 1: 12 weeks SOF+PEG-IFN+RBV:** The most efficacious and easiest to use IFN-containing option, without the risk of selecting resistant viruses in case of treatment failure. • **Option 2: 12 weeks SMV+PEG-IFN+RBV (RGT)** ○ with an additional 12 weeks of PEG-IFN+RBV in treatment naïve and prior relapser patients, including cirrhotics ○ with an additional 36 weeks of PEG-IFN+RBV in prior partial and null responders, including cirrhotics. • **Option 3: 12 weeks DCV+PEG-IFN+RBV (RGT)** ○ extend treatment duration for an additional 12 weeks in patients who do not achieve HCV RNA <25 IU/mL at week 4 and undetectable at week 10. ○ PEG-IFN+RBV should be continued alone between week 12 and 24 in patients who achieve HCV RNA <25 IU/ml at week 4 and undetectable at week 10. • **Option 4: 24 weeks SOF+RBV:** for patients who are IFN-intolerant or ineligible. • **Option 5: 12 weeks SMV+SOF;** addition of RBV should be considered for patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. • **Option 6: 12 weeks SOF+DCV** in treatment naïve patients ○ with an additional 12 weeks in treatment experienced patients ○ RBV should be included in this option for patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. • **PEG-IFN+RBV:** Remains acceptable in settings for which none of the above options are available.	• **Treatment naïve:** ○ 12 weeks SOF+PEG-IFN+RBV ○ 12 weeks SMV, 24 or 48 weeks PEG-IFN+RBV (RGT) • **Treatment experienced:** ○ 12 weeks SOF+PEG-IFN+RBV ○ 12 weeks SMV, 24 or 48 weeks PEG-IFN+RBV (RGT) • **Cirrhotic patients:** ○ 12 weeks SOF+PEG-IFN+RBV

Abbreviations: BOC, boceprevir; DCV, daclatasvir; EASL, European Association for the Study of the Liver; GT, genotype; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RBV, ribavirin; RGT, response guided therapy; RNA, ribonucleic acid; SMV, simeprevir; SOF, sofosbuvir, TVR, telaprevir.
† The UK consensus guidelines also make reference to faldeprevir regimens in HCV GT1 infected treatment naïve patients. However, this product is not licensed for use in the UK.
‡ The treatments recommended for CHC GT4 in the UK consensus guidelines are also recommended for CHC GT5 and GT6.
.

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

Although CHC is a curable disease, and despite recent advances in treatment such as with the introduction of SOF, SMV, and DCV, there remains a significant unmet need with regards to treatment. While established current treatment options such as TVR, BOC and PEG-IFN+RBV provide a cure for some patients, they are not successful in a substantial proportion (5) and are associated with significant limitations. These include long and complicated treatment regimens, weekly PEG-IFN injections, intolerable side-effects and the development of treatment-resistant viral mutations, all of which can lead to treatment failure (42).

In addition, some patients with HCV remain untreated as a result of intolerance or contraindications to the established IFN-based treatments, such as hepatic decompensation, autoimmune disease and psychiatric illness (43), and therefore are currently without a viable treatment option. Current NICE recommendations (including preliminary recommendations for SOF and SMV-based regimens) mean that among patients with CHC GT1, GT3 and GT4, only GT3 patients with cirrhosis are eligible for IFN-free treatment (SOF+RBV (44)).

Treatment efficacy is influenced by genotype, stage of liver disease (e.g. presence of cirrhosis) and the patient's prior treatment status (5). For those patients who have been treated previously and do not achieve SVR, re-treatment can be associated with a low chance of success and should only be offered to patients who have an urgent indication for therapy, and/or if there is evidence of inadequate prior exposure to either PEG-IFN or RBV (5). As such, treatment experienced patients represent another important group of patients that contribute to the unmet need in HCV, given their limited treatment options and risk of long term complications of HCV infection.

2.6.1 *Telaprevir/boceprevir triple therapy*

In patients infected with CHC GT1, triple therapy of TVR or BOC in combination with PEG-IFN+RBV has resulted in improved cure rates versus PEG-IFN+RBV dual therapy and, in some patients, has shortened treatment duration. However, it is associated with a number of disadvantages. These include an increase in side effects and high discontinuation rates, a complicated treatment regimen (high pill burden, thrice daily dosing, and the need for a high fat diet), association with a number of clinically significant drug interactions and emergence of drug-resistant variants (12;13;35;36;45;46).

Triple therapy with both TVR and BOC is associated with an increase in AEs over and above those seen with PEG-IFN+RBV dual therapy (Table 6).

Table 6: Side effect profile of telaprevir and boceprevir

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

Abbreviations: DRESS, drug rash with eosinophilia and systemic symptoms.
† Most common side effects.

In addition to the common side effects of TVR, drug rash with eosinophilia and systemic symptoms (DRESS) and Steven Johnson syndrome (a life-threatening skin condition) may also be observed in some patients. A 'black box' warning for toxic epidermal necrosis, another life-threatening skin

condition, associated with TVR therapy was announced by the FDA in 2012 (42). These AEs may have a negative impact on adherence to, and tolerability of, the triple therapy regimens.

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

An additional limitation is the high pill burden with both TVR (two or three 375 mg tablets, twice or three times daily) and BOC (four 200 mg capsules, three times daily), and the need to take each medication with food (12;13), which may adversely affect adherence to therapy (46). The complexity of treatment regimens with TVR and BOC (e.g. the need for lead-in treatment or extended treatment with PEG-IFN/RBV depending on response) and the need for response-guided therapy also complicate treatment (12;13). Overall, the total length of treatment with TVR and BOC-based triple therapy ranges between 24 and 48 weeks, depending on baseline factors (e.g. cirrhosis), prior treatment history and on-treatment virologic response (12;13).

Both TVR and BOC are substrates and inhibitors of the hepatic enzyme cytochrome P450 3A and the drug transporter P-glycoprotein, which predisposes them to a wide range of drug-drug interactions (46). Interactions with drugs such as immunosuppressants and antiretrovirals mean that the combination of such agents with either drug should be avoided or only considered with caution in special populations such as liver transplant recipients and HCV/HIV co-infected (46).

A further and important consideration with BOC and TVR is a low barrier to resistance. Initial studies of TVR and BOC showed rapid emergence of resistant mutants and complete replacement of wild-type virus with drug resistant variants in patients with breakthrough viraemia (45). Overall, in Phase III TVR and BOC triple therapy trials in treatment naive patients, resistant variants were detected in 50–75% of patients not achieving an SVR, and in 90% of those with virologic failure (45). Moreover, such variants arising in response to either agent confer cross-resistance to the other drugs from the same class (45).

2.6.2 *PEG-IFN+RBV dual therapy*

Although PEG-IFN+RBV used to be the standard of care in CHC treatment the long treatment duration (up to 48 weeks) and the low cure rates, particularly in GT1 infection have seen it surpassed with other shorter and more effective treatments, including SOF and the PIs (1;2;5;6). PEG-IFN+RBV treatment is also associated with severe and often intolerable side effects. These include influenza-like symptoms, fatigue, depression, skin reactions and haematological events (anaemia, thrombocytopenia and neutropenia) (5). This has made treatment difficult for many patients, limiting the proportion that start or complete IFN-based therapy (4).

PEG-IFN is absolutely contraindicated in a significant proportion of patients, including: patients with uncontrolled depression, psychosis or epilepsy; patients with uncontrolled autoimmune diseases; pregnant women or couples unwilling to comply with adequate contraception; patients with severe concurrent medical disease, such as poorly controlled hypertension, heart failure, poorly controlled diabetes, and chronic obstructive pulmonary disease (5). In clinical practice, evidence suggests that only around 20% of patients are considered treatment eligible for PEG-IFN therapy and receive treatment (47). Medical ineligibility (predominantly substance use disorders, psychiatric disorders and medical comorbidities) along with patient attitudes and preferences, are the most commonly cited barriers to treatment in HCV-infected patients (47).

2.6.3 *Sofosbuvir-based regimens*

The recent introduction of SOF-based regimens (+RBV+/-PEG-IFN) has provided a therapy with the potential to provide higher cure rates, and simpler and shorter treatment duration than the established treatment options. In patients with GT1, GT3 and GT4 infection the primary regimen is the IFN-containing regimen of SOF+PEG-IFN+RBV for 12 weeks, and involves taking three separate drugs at different times, via oral and subcutaneous routes. The side effect profile of SOF+PEG-IFN+RBV is consistent with the expected safety profile of PEG-IFN or RBV treatment (1); given the issues around side effects experienced by patients on PEG-IFN+RBV regimens as described in Section 2.6.2 the goal is to develop IFN-free treatment options. Although the introduction of SOF-based regimens allows some patients to benefit from an all oral, IFN-free regimen, preliminary NICE guidance recommends the SOF+RBV 24 week regimen in only a relatively small subset of GT3 patients (cirrhotic only) and not at all in GT1 or GT4 patients (44).

2.6.4 *Simeprevir-based regimens*

SMV, a new NS3/4A PI, is indicated in combination with PEG-IFN+RBV or SOF±RBV for the treatment of CHC GT1 or GT4 in adults (2) but recommended only in CHC GT1 patients by NICE (preliminary recommendations). The IFN-containing SMV-regimen is relatively complex with a requirement to take three different drugs at different times, via oral and subcutaneous routes as well as having a need for treatment stopping rules. In addition, it fails to provide the IFN-free treatment option that is the target for new drug development in CHC.

Furthermore, SMV-based regimens have longer durations of treatment. In treatment naïve and prior relapse patients, SMV+PEG-IFN+RBV is administered for 12 weeks followed by an additional 12 weeks of PEG-IFN+RBV. In prior non-responder patients (including partial and null responders), 12 weeks of SMV+PEG-IFN+RBV is followed by an additional 36 weeks of PEG-IFN+RBV, totalling 48 weeks of treatment (2). Although SMV+SOF±RBV is recommended for 12 weeks, it is limited to the relatively small subset of patients who are IFN-intolerant or ineligible in urgent need of treatment (2).

Phase III trials demonstrated SVR12 rates of 80% in TN CHC GT1 patients (QUEST-1 and QUEST-2 pooled analysis) and 79%, in prior relapsed CHC GT1 patients (PROMISE) (48;49). These SVR12 rates still mean that one fifth of patients would remain without a cure. The AE profile of SMV is better than that of TVR or BOC triple therapy, and similar to the AE profile of PEG-IFN+RBV dual therapy (49).

2.6.5 *Unmet need*

The limitations of established regimens such as the PIs and PEG-IFN±RBV therapy have left the majority of diagnosed patients without suitable treatment options. Real-world studies suggest that only around 20% of HCV patients have been considered eligible for and have received treatment, and only 3–4% achieved an SVR (47).

Recent advances have seen the emergence of new therapies such as SOF+PEG-IFN+RBV and SMV+PEG-IFN+RBV. EASL guidelines and UK consensus guidelines recommend these new therapies; they reflect preferred clinical practice and, following the publication of final NICE guidance, will be considered the new standards of care in treating CHC. Despite providing greater treatment options, the primary SOF and SMV regimens are still IFN-based. Although licensed, the IFN-free option of SOF+RBV for 24 weeks is only recommended by NICE in a relatively small subset of patients with GT3 infection and cirrhosis. Furthermore, options for GT4 patients are still very limited with NICE not recommending SOF and SMV regimens for these patients (recommendations still to be finalised).

Treatment experienced GT1 and treatment experienced cirrhotic GT3 patients are recognised by clinicians in the UK as being groups of particular unmet need. No data are currently available providing evidence for the efficacy of SOF+RBV±PEG-IFN in treatment experienced GT1 patients, whilst regimens containing the PIs (TVR, BOC and SMV) (50-52) have been shown to have reduced efficacy in GT1 prior non-responders. For GT3, the limited data that currently exist for the treatment of cirrhotic treatment experienced patients with SOF+PEG-IFN+RBV and SOF+RBV suggest a reduction in efficacy compared with other populations (1). Given the lack of activity of PIs against the HCV GT3 virus, new treatments for this population are urgently needed.

Despite recent advances there is still a clear medical need for new treatments that can provide more effective and tolerable regimens with a higher likelihood of a cure, while also providing simpler and shorter options for patients. Treatments with a high barrier to resistance, few drug-to-drug interactions and that are effective for HCV treatment naïve and experienced patients are also necessary. IFN-free treatment options can minimise the limitations associated with long-term IFN use and avoid contraindications, opening up the possibility of cure to a broader population of patients.

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

The main comparators are listed below, in line with the scope for this appraisal. TVR, BOC and PEG-IFN regimens represent established therapies that are recommended by NICE and represent current clinical practice. Inclusion of SOF-based regimens and SMV-based regimens is in line with preliminary NICE guidance, recent EASL guidelines, UK consensus guidelines and clinical opinion. SOF and SMV-based regimens are reflective of preferred clinical practice in CHC and, following the publication of final NICE guidance, are expected to displace TVR, BOC, and PEG+RBV only regimens.

For a significant proportion of patients there are no alternative treatment options that are NICE recommended (i.e. patients who are medically ineligible for IFN, are IFN-intolerant, or unwilling to take IFN). For such patients, where SOF+RBV or SMV+SOF is not recommended, the alternative is a ‘best supportive care’ (no treatment) comparator.

- PEG-IFN+RBV (GT1, GT3 and GT4)
- TVR+PEG-IFN+RBV (GT1 only)
- BOC+PEG-IFN+RBV (GT1 only)
- SOF+RBV±PEG-IFN (GT, GT3 and GT4; subject to ongoing NICE appraisal ID654)
- SMV+PEG-IFN+RBV (GT1 or GT4 subject to ongoing NICE appraisal ID668)
- SMV+SOF (for patients with GT1 or GT4 disease and are ineligible for or intolerant to IFN treatment; subject to ongoing NICE appraisal ID668)
- Best supportive care (no treatment; GT1, GT3 and GT4)

NICE preliminary guidance has not recommended SMV+SOF for GT1 and GT4 patients who are IFN-ineligble. However, it has been included in this appraisal to deomonstrate the cost-effectiveness of LDV/SOF compared to another IFN-free medicine for the treatment of GT1 and GT4 patients.

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

In clinical studies, fatigue and headache were more common in patients treated with LDV/SOF than patients given placebo. Discontinuation rates due to AEs from trials were low (≤1%

discontinuing on LDV/SOF and ≤2% on LDV/SOF+RBV). It is not anticipated that there will be any need to administer other therapies to manage AEs when LDV/SOF is taken.

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

LDV/SOF is administered orally. No costs are associated with administration of LDV/SOF and, as the treatment duration is reduced for the majority of patients and response-guided therapy is not required, it is anticipated that monitoring costs will be reduced.

The improved tolerability profile compared with established treatments such as the PIs and PEG-IFN+RBV may also reduce associated healthcare costs.

Further details on costs will be provided in Section 7.

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

No. On the contrary, given that treatment duration is reduced for most patients, response-guided therapy is not required and AEs may be reduced with LDV/SOF, it is expected that pressures on the current infrastructure will be reduced.

3 Equality

3.1 *Identification of equality issues*

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

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

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

During the consultation on the second ACD for the NICE appraisal of sofosbuvir, a potential inequality issue was raised regarding the GT4 population in the UK. Further investigation suggested that some ethnic minorities, and the HCV/HIV co-infected population, are disproportionately represented in the GT4 population compared to other genotypes. These comparisons are primarily made with GT1, GT2 and GT3, which account for approximately 93.5% of the UK CHC population. A summary of the issues and data to support them is provided below.

Genotype and Ethnicity

The distribution of genotype and ethnicity are taken from a HCV genotype surveillance report provided to Gilead Sciences Ltd by the Immunisation Department within Public Health England[†]. The sentinel surveillance system collects information on all testing undertaken for hepatitis as well within a network of 24 laboratories across the UK.

[redacted]

Figure removed

[redacted]

HCV/HIV co-infection

Information provided from the UK Collaborative HIV Cohort (CHIC) database (data on file SOFUK 1405) recorded the genotype for [redacted] individuals (53). [redacted]

3.1.2 *How has the analysis addressed these issues?*

N/A

4 Innovation

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

As with the introduction of SOF, LDV/SOF offers a step-change in efficacy, safety, and tolerability for the treatment of patients with HCV making successful HCV cure a realistic probability for an even higher proportion of patients, including those who currently have no or limited treatment options.

LDV/SOF meets the five criteria for step-change innovation as laid out in the Kennedy Report 2009 (54) (Table 7).

Table 7: LDV/SOF step-change innovation

Kennedy report criteria	LDV/SOF
The product significantly and substantially improved the way that a current need is met	LDV/SOF (±RBV) demonstrates very high cure rates in patients with HCV GT1, with additional data to support high cure rates in GT3 and GT4 infection. By eliminating IFN from the regimen and being formulated as a single tablet, LDV/SOF simplifies treatment into an all-oral, once daily IFN- and PI-free therapy. LDV/SOF is a highly efficacious treatment option, even for those who are ineligible or intolerant to IFN and thus currently have limited or no treatment options. Many patients will be able to benefit from reduced treatment duration of 8 weeks (GT1 treatment naïve non-cirrhotic), the shortest complete course of therapy in HCV treatment.
The need met is one which the NHS has identified as being important	The NHS Outcomes Framework 2014–2015 (55) reflects the government commitment to reducing mortality due to liver disease in patients under 75 years of age. By providing a cure for the majority of patients, treatment with LDV/SOF has the potential to reduce HCV related liver disease and associated mortality.
Where appropriate, research on stratification has identified the population(s) in which the product is effective	LDV/SOF regimens are supported by a robust evidence base in both Phase II and III trials. The clinical trial programme demonstrated very high effectiveness in patients with HCV GT1, with additional data to support high efficacy in GT3 or GT4 infection, including clinical subgroups relevant to the UK HCV population.
The product has been shown to have an appropriate level of effectiveness	LDV/SOF regimens provide the opportunity of a cure for the vast majority of patients. It provides

	a simple treatment option for a broader patient population than are eligible for the currently established treatment options.
The product has marketing authorisation for the particular indication	Marketing authorisation for LDV/SOF is expected end-November 2014.

Abbreviations: HCV, hepatitis C virus; LDV, ledipasvir, NHS, National Health Service; SOF, sofosbuvir.

LDV/SOF represents a breakthrough HCV treatment for patients and clinicians with the following innovative qualities:

- A simple, PI-free, IFN-free, once daily tablet with few dosing restrictions. The safety profile of IFN-based regimens has historically made treatment difficult for many patients, significantly limiting the proportion that start or complete IFN-based therapy (4). In spite of recent advances in therapy, the established regimens for all patients except GT2 still contain IFN. Although some patients can benefit from a 24 week IFN-free SOF+RBV regimen, preliminary NICE guidance recommends this option in only a relatively small subset of GT3 patients (cirrhotic only) and not at all in GT1 patients (44). Therefore, the option of treatment with LDV/SOF is a significant advance especially for patients who are ineligible or intolerant to IFN and currently have very limited or no treatment options.
- A treatment which allows more patients the opportunity of a cure:
  - Cure rates of 94–99% were achieved in all CHC GT1 treatment naïve patients and treatment experienced non-cirrhotic patients, dependent upon treatment duration and prior treatment experience.
  - Cure rates of 86–100% were achieved in CHC GT1 treatment experienced patients with compensated cirrhosis, including those who have failed previous PI treatment.
  - Although limited data currently exist for LDV/SOF in GT4, [redacted].
  - In CHC GT1 patients with decompensated cirrhosis (CPT B and C) and post-liver transplant patients SVR4 rates of [redacted] have been achieved (preliminary Phase II data with LDV/SOF+RBV).
  - 100% cure rate was achieved in CHC GT3 treatment naïve patients, including those with compensated cirrhosis (Phase II data with LDV/SOF+RBV).
  - In CHC GT3 treatment experienced non-cirrhotic and cirrhotic patients SVR4 rates of 89% and 77%, respectively have been achieved (preliminary Phase II data with LDV/SOF+RBV).
  - 98% cure rate was achieved in CHC GT1 treatment naïve patients co-infected with HIV.
- Shorter treatment duration of 8 to 12 weeks (for the majority of GT1 and GT4 patients) compared with 24 to 48 weeks for established treatment options (PEG-IFN, TVR or BOC based regimens), 12 to 24 weeks for SOF-based regimens or 12 to 48 weeks for SMV-based regimens.
- LDV/SOF provides a favourable safety profile with only fatigue and headache identified as more common in patients treated with LDV/SOF than patients given placebo. Discontinuation rates due to AEs from trials were low (≤1% discontinuing on LDV/SOF and ≤2% on LDV/SOF+RBV). This could have a significant impact on patients' experience while on treatment, in addition to reduced monitoring and AEs costs.

- The lack of significant drug interactions with immunosuppressant drugs and multiple antiretroviral regimens means that LDV/SOF can be used safely in liver transplant patients and patients with decompensated cirrhosis (including CPT B and C) or co-infected with HIV. These populations represent groups for which current treatment options are very limited and who are in urgent need of treatment.

It should be noted that the EMA accepted an accelerated regulatory process for LDV/SOF, a designation only granted to those medicines of major public health interest.

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

Health-related benefits that are not included in the QALY calculation in Section 7 include:

- those associated with a reduction in onward transmission of HCV through rapid clearance of the virus from the body due to effective treatment
- the potential for regression of liver fibrosis once cured of HCV
- potential impact on relationships with family members and impact on employment, including a reduction in absenteeism.

By improving cure rates, LDV/SOF can lead to an increase in numbers of treated patients experiencing regression of liver fibrosis. In addition, by increasing the number of patients treated and treating them more effectively, onward transmission may be reduced. As a result, LDV/SOF has the potential to positively impact on public health, QoL and reduce the long-term burden of HCV to the NHS.

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

Reduction of onward transmission:

LDV/SOF regimens lead to rapid reduction in HCV RNA to <LLOQ; 99-100% of patients achieved HCV RNA <LLOQ by on-treatment week 4, which was sustained post-treatment in the majority of patients (see Section 6). Public health information regarding transmission from individuals infected with HCV suggests that rapid reduction of the virus through treatment can reduce onward transmission. Specifically, patients who inject drugs represent the main source of HCV transmission and the risk of transmission remains high even when there is high coverage of prevention interventions, such as needle and syringe programs and opioid substitution treatment (21;56). Injecting drug users tend not to be treated for their HCV infection because of the risk of re-infection; however modelling analyses by Martin et al suggest that HCV treatment can have an important role in preventing transmission in these populations and that this approach can be a cost-effective policy (56-58). The introduction of a simple, once daily regimen with shorter treatment duration may make it easier for patients who inject drugs to take and benefit from HCV treatment.

Regression of liver fibrosis and reduction in risk of HCC:

A published evidence review from Ng et al identified several studies showing that an SVR can lead to regression of fibrosis and cirrhosis and that these effects are seen in patients with varying degrees of fibrosis (27). The evidence showed that an SVR reduces liver-related mortality among

patients with CHC by 3.3- to 25-fold, reduces the incidence of HCC by 1.7- to 4.2-fold, and reduces the incidence of hepatic decompensation by 2.7- to 17.4-fold (27).

Impact on relationships and in the workplace:

Miller et al highlight the strain that living with hepatitis C can put on family relationships and also on disclosure of hepatitis C infection leading to discrimination in the workplace (19).

5 Statement of the decision problem

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with CHC • who have not had treatment for CHC before (treatment naïve) • who have had treatment for CHC before (treatment experienced)	While it is anticipated that no genotype specificity will be included within the licensed indication, the majority of data for LDV/SOF is for GT1 with some additional data for GT3 and GT4. This submission will focus solely on these three subgroups as there are very limited or no data for GT2, GT5 and GT6.	See previous column
Intervention	LDV/SOF with or without RBV	As per final scope	
Comparator(s)	• PEG-IFN+RBV (GT1–6) • TVR+PEG-IFN+RBV (GT1 only) • BOC+PEG-IFN+RBV (GT1 only) • SOF+RBV±PEG-IFN (GT1–6; subject to ongoing NICE appraisal ID654 • SMV+PEG-IFN+RBV (GT1 or GT4 subject to ongoing NICE appraisal ID668) • SMV+SOF (for patients with GT1 or GT4 disease and are ineligible for or intolerant to IFN treatment; subject to ongoing NICE appraisal ID668) • Best supportive care (watchful waiting; GT1–6)	As per final scope. “Best supportive care” is defined as no treatment in this submission	
Outcomes	The outcome measures to be considered include: • SVR • Development of resistance to LDV/SOF • Mortality • Adverse effects of treatment • HRQL	As per final scope. The development of resistance to LDV/SOF is discussed only in section 6 as this outcome does not impact the cost-effectiveness of LDV/SOF i.e. it has not impact on cost or QALYs.	
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per final scope. The time horizon for the modelling is a lifetime.	
Subgroups to be considered	If evidence allows the following subgroups will be considered:	As per final scope. Evidence allowed subgroup analyses including:	See section 7.9

Key parameter	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	• Genotype • Co-infection with HIV • People with and without cirrhosis • People who have received treatment pre- and post-liver transplantation • Response to previous treatment (non-response, partial response, relapsed) • People who are intolerant to or ineligible for IFN-treatment If evidence allows the impact of treatment on reduced onward HCV transmission will be considered. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	• Genotype • People with and without cirrhosis • People who are intolerant to or ineligible for IFN-treatment	
Special considerations, including issues related to equity or equality	CHC GT4 patients are characterised by a disproportionaly higher number of patients from ethnic minorities and who are HCV/HIV co-infected	As per final scope	

Abbreviations: BOC, boceprevir; CHC, chronic hepatitis C; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQL, health related quality of life; LDV, ledipasvir; NHS, National Health Service; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; TVR, telaprevir.

Section B – Clinical and cost-effectiveness

6 Clinical evidence

6.1 *Identification of studies*

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

A full systematic review has been carried out to identify clinical trials assessing LDV and SOF with or without ribavirin in patients with CHC. The search strategies are similar to those conducted for SOF and full details are provided in Section **Error! Reference source not found.**.

Databases searched included:

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

The following conference proceedings were specifically searched:

- American Association for the Study of Liver Disease (AASLD) 2013
- European Association for the Study of the Liver (EASL) 2014

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

Implementation and reporting of the systematic review followed the recommendations and standards required by NICE and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

Citations were first screened based on the title and abstract supplied with each citation. Each citation was screened by two independent reviewers, and any discrepancies between reviewers were reconciled by a third independent reviewer. Citations that did not match the eligibility criteria were excluded at this ‘first pass,’ and when unclear, citations were included. Duplicates of citations (due to overlap in the coverage of the databases) were also excluded and full-text copies of all references that could potentially meet the eligibility criteria were ordered at this stage.

Following this, the eligibility criteria were applied to full-text citations. Each full text article was screened by two independent reviewers, and any discrepancies between reviewers were reconciled by a third independent reviewer. Data presented in the studies included at this stage were extracted in parallel by two independent reviewers, with reconciliation of any differences by a third independent reviewer. Where more than one publication describing a single trial was identified, the data were compiled into a single entry in the data extraction table to avoid double counting of patients.

6.2 *Study selection*

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

Table 8: Eligibility criteria used in search strategy

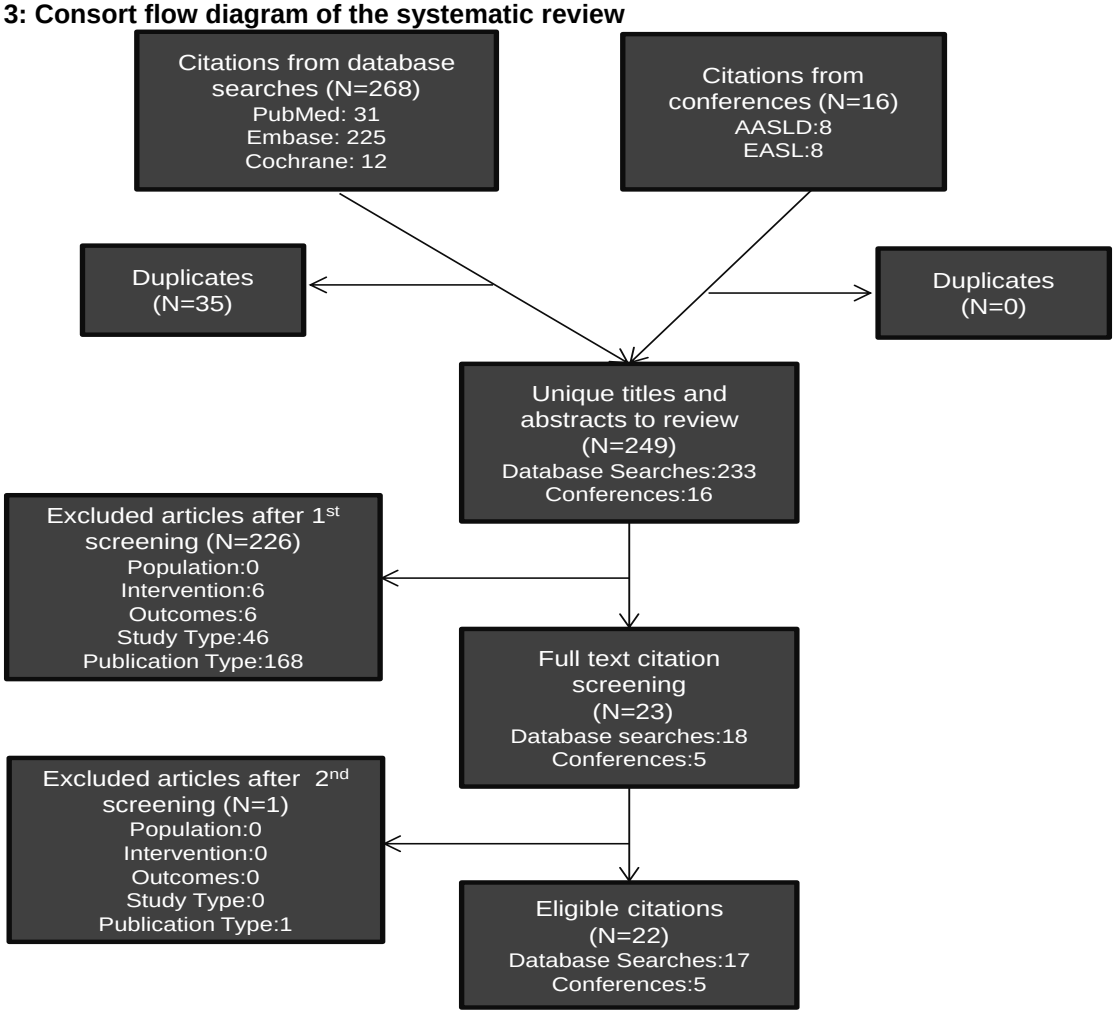
Inclusion criterion	Inclusion Criteria	Details	Comments
1	Patient population	Chronic hepatitis C patients	In line with the draft scope
2	Intervention	Ledipasvir	
3	Comparison therapy	Any comparison therapy	Single-arm studies were included
4	Patient relevant outcomes	SVR12, SVR24	Sustained virologic response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

SVR12, sustained virologic response at 12 weeks; SVR24, sustained virologic response at 24 weeks; RCT, randomised controlled trials

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

The systematic review identified 22 eligible citations covering 10 clinical studies (Figure 3).

Figure 3: Consort flow diagram of the systematic review



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

Not applicable. No RCTs are available. See section 6.2.7 for further details.

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

Not applicable.

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

Not applicable

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

Not applicable

List of relevant non-RCTs

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

The systematic review of clinical evidence identified seven non-RCTs (ION-1, ION-2, ION-3, ELECTRON, ELECTRON-2, SYNERGY, LONESTAR; 19 citations) for LDV/SOF in the populations of interest to this submission for which evidence has been published (Table 9). In addition to these seven studies, on-going studies have also been included for which evidence is either not yet published, or for which abstracts are available and data will be presented at the upcoming AASLD conference in November 2014. For all studies the relevant study protocol or clinical study report was used to provide additional information.

Two further studies (Wyles et al, 2014 (59) and Thompson et al, 2013 (60;60;61;61)) were identified via the systematic review that assessed LDV containing regimens. These are excluded from further discussion as none of the arms considered LDV and SOF in combination.

The clinical trials of relevance, and presented further in this submission, are therefore:

- Three pivotal randomised, multicentre Phase III studies providing evidence in CHC GT1:
  - ION-1: Treatment naïve including cirrhosis 12 vs 24 weeks treatment
  - ION-3: Treatment naïve without cirrhosis 8 vs 12 weeks treatment
  - ION-2: Treatment experienced including cirrhosis 12 vs 24 weeks treatment
- Phase II studies that provide supporting data for these pivotal studies:
  - ELECTRON-2; ELECTRON; LONESTAR; SIRIUS; SYNERGY.
- Data from two studies in patients with CHC GT4:
  - ION-1 and SYNERGY
- Data from one study in patients with CHC GT3:
  - ELECTRON-2
- Phase II studies in specific populations:
  - ERADICATE: GT1 HCV/HIV co-infection
  - SOLAR-1: GT1 with decompensated liver cirrhosis, and post-liver transplant (LDV/SOF+RBV)

All clinical trials submitted in support of the regulatory submission for LDV/SOF were designed as uncontrolled randomised trials (i.e. non-RCTs); similar to the approach for SOF they compare various LDV/SOF regimens (randomised) but do not contain classical control arms (i.e. placebo or active comparator arms). However, they have been designed with the rigour expected from a high-

quality RCT, and the Phase III ION trials have been published in the New England Journal of Medicine. In addition, ION-1-3 were designed to test the hypothesis that the primary efficacy outcome for LDV/SOF treated patients would be superior to a historical control based on previously reported data for the protease inhibitors TVR and BOC, in a trial population of cirrhotic and non-cirrhotic GT1 infected patients.

All LDV/SOF trials are reported in detail in sections 6.3–6.5.

Table 9: List of relevant LDV/SOF Phase II and III non-RCTs

Trial no. (acronym)	Interventions	Population characteristics	Primary study refs.	Refs identified but not used further	Justification for inclusion/exclusion
Pivotal Phase III studies					
GS-US-337-0102 (ION-1)	• LDV/SOF for 12 weeks • LDV/SOF+RBV for 12 weeks • LDV/SOF for 24 weeks • LDV/SOF+RBV for 24 weeks	• Treatment naïve • HCV GT1 • No cirrhosis and compensated cirrhosis	Afdhal NEJM 2014 (62) Supporting information from CSRs (63;64)	Jacobson 2014 (65) Mangia 2014 (66) Younossi 2014 (67)	Pivotal Phase III study in GT1 treatment naïve
GS-US-337-0108 (ION-3)	• LDV/SOF for 8 weeks • LDV/SOF+RBV for 8 weeks • LDV/SOF for 12 weeks	• Treatment naïve • HCV GT1 • No cirrhosis	Kowdley NEJM 2014 (68) Supporting information from CSRs (69;70)	Kowdley 2014 (71)	Pivotal Phase III study in GT1 treatment naïve
GS-US-337-0109 (ION-2)	• LDV/SOF for 12 weeks • LDV/SOF+RBV for 12 weeks • LDV/SOF for 24 weeks • LDV/SOF+RBV for 24 weeks	• Treatment experienced (included patients who had not achieved SVR12 with either PEG-IFN+RBV or PI+PEG-IFN+RBV). • HCV GT1 • No cirrhosis and compensated cirrhosis	Afdhal NEJM 2014 (72) Supporting information from CSRs (73;74)	Afdhal 2014 (75)	Pivotal Phase III study in GT1 treatment experienced
Supporting studies					
GS-US-337-0122 (ELECTRON-2)	• LDV/SOF for 12 weeks • LDV/SOF+RBV for 12 weeks	• Treatment experienced (HCV GT1, no cirrhosis, prior SOF-based treatment failures) • Treatment naïve (HCV GT1, decompensated cirrhosis) • Treatment naïve (HCV GT3, no cirrhosis and compensated cirrhosis) • Treatment experienced (HCV GT3, no cirrhosis and compensated cirrhosis)	Gane EASL 2014 (76) Interim synoptic CSR for GT3 treatment naïve patients, 2014 (77) Gane AASLD 2014 (78)	Gane 2014 (79)	Included: Pivotal Phase II study for GT3 data. Supporting data for decompensated cirrhosis and GT1

Trial no. (acronym)	Interventions	Population characteristics	Primary study refs.	Refs identified but not used further	Justification for inclusion/exclusion
CO-US-337-0116 (ERADICATE)	• LDV/SOF for 12 weeks	• Treatment naïve • HCV GT1 • No cirrhosis and compensated cirrhosis • HCV/HIV co-infection	Interim abbreviated CSR, 2014 (80) Osinusi 2014; (submitted manuscript, not yet published). (81)		Included: Pivotal Phase II study for HIV co-infection
GS-US-337-0123 (SOLAR-1)	• LDV/SOF+RBV for 12 or 24 weeks	• HCV GT1 • Moderate hepatic impairment (CPT class B; 7-9 points) • Severe hepatic impairment (CPT class C; 10-15 points) • Post-transplant subjects with fibrosis (F2-F4) no decompensation • Post-transplant subjects with mild hepatic impairment (CPT class A; 5-6 points) • Post-transplant subjects with moderate hepatic impairment (CPT class B; 7-9 points) • Post-transplant subjects with severe hepatic impairment (CPT class C; 10-15 points) • Post-transplant subjects with fibrosing cholestatic hepatitis	Clinical study protocol (82) and SPC Reddy AASLD; 2014 (83) Flamm AASLD 2014 (84)		Included: Pivotal Phase II study providing data on experienced cirrhotic, decompensated, and post-liver transplant patients in GT1
P7977-0523 (ELECTRON)	• LDV/SOF for 12 weeks • LDV/SOF+RBV for 12 weeks • LDV/SOF+RBV for 6 weeks • LDV+SOF†+RBV for 12 weeks ELECTRON also included other regimens; however any arm that assessed regimens that did not include SOF and LDV together have not been reported here.	• HCV GT1 • Treatment naïve (no cirrhosis) • Treatment experienced (no cirrhosis) • Treatment experienced (compensated cirrhosis) • Treatment naïve and treatment experienced with inherited blood disorders	Gane 2014 (85) Stedman APASL 2014 (86) Final synoptic CSR, 2014 (87)	Gane 2013 (88) Gane 2014 (89)	Included: Supporting Phase II study, including data on treatment of patients with inherited blood disorders and treatment duration assessment

Trial no. (acronym)	Interventions	Population characteristics	Primary study refs.	Refs identified but not used further	Justification for inclusion/exclusion
GS-US-337-0118 (LONESTAR)	• LDV/SOF for 8 weeks; • LDV/SOF+RBV for 8 weeks; • LDV/SOF for 12 weeks • LDV/SOF+RBV for 12 weeks	• HCV GT 1 • Treatment naïve non-cirrhotic • Treatment experienced PI-failures (50% cirrhotic)	Lawitz Lancet 2014 (90)	Lawitz 2014 (91) Lawitz 2013 (92)	Included: Supporting Phase II study for treatment duration assessment
GS-US-337-0121 (SIRIUS)	• LDV/SOF+RBV for 12 • LDV/SOF for 24 weeks	• HCV GT1 • Treatment experienced PI failures • Compensated cirrhosis	Bourlière AASLD 2014; (93)		Included: Supporting Phase II study providing data on GT1 treatment experienced patients with compensated cirrhosis, who have previously failed both PEG-IFN+RBV and PI+PEG-FIN+RBV therapy.
CO-US-337-0117 (SYNERGY)	• LDV/SOF for 12 weeks SYNERGY also included LDV/SOF in combination with other direct-acting antiviral agents; however as these are not licensed they have not been reported here	• HCV GT1 and GT4 • Treatment naïve • Treatment experienced (including GT1 prior SOF/RBV treatment failures) • No cirrhosis and compensated cirrhosis	Kohli CROI 2014 (94) Kapoor AASLD 2014 (95)	Kohli 2013 (96) Osinusi 2014 (97)	Included: Supporting Phase II study providing data on treatment naïve patients, GT1 prior SOF+RBV failures and GT4 patients
GS-US-337-1119 (French GT4/5 study)	• LDV/SOF	• HCV GT4 and GT5 • Treatment naïve and treatment experienced • No cirrhosis and compensated cirrhosis	Active and not yet published		Excluded: Study ongoing. Does not inform the licence
GS-US-337-0115 (ION-4 HIV co-infected Phase III)	• LDV/SOF for 12 weeks • LDV/SOF+RBV for 24 weeks	• Treatment naïve • Treatment experienced • HCV GT1 and GT4 • No cirrhosis and compensated cirrhosis	N/A		Excluded: Study enrolling and no data available to date

Trial no. (acronym)	Interventions	Population characteristics	Primary study refs.	Refs identified but not used further	Justification for inclusion/exclusion
GS-US-337-0113 (Japanese Phase III)	• LDV/SOF for 12 weeks • LDV/SOF+RBV for 12 weeks	• Treatment naïve • Treatment experienced • HCV GT1 • No cirrhosis and compensated cirrhosis		Mizokami AASLD 2014 abstract #1929	Excluded: Study ongoing. Does not inform the licence
GS-US-337-0124 (SOLAR-2)	• LDV/SOF±RBV for 12 or 24 weeks	• HCV GT1 and GT4 • Advanced liver disease • Post-liver transplant	Active and not yet published		Excluded: Study ongoing. Does not inform the licence

Abbreviations: AASLD, American Association for the Study of Liver Diseases: APASL, Asian Pacific Association for the Study of the Liver; CPT, Child Pugh Turcotte; CROI, Conference on Retroviruses and Opportunistic Infections; CSR, clinical study report; EASL, European Association for the Study of the Liver; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; NEJM, New England Journal of Medicine; PEG-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; RCT, randomised clinical trial; SOF, sofosbuvir; SR, systematic review; SVR, sustained virologic response.
†LDV+SOF denotes where LDV and SOF were given as single agents.

6.3 *Summary of methodology of relevant non-RCTs*

6.3.1 ***As a minimum, the summary should include information on the non-RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one non-RCT, the information should be tabulated.***

Methods

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

Information for ION-1 has been taken from The New England Journal of Medicine (NEJM) article and supplementary materials by Afdhal et al, 2014 (62), with supporting information from the clinical study reports (CSRs) (63;64).

Information for ION-3 has been taken from the NEJM article and supplementary materials by Kowdley et al, 2014 (68), with supporting information from the CSRs (69;70).

Information for ION-2 has been taken from the NEJM article and supplementary materials by Afdhal et al, 2014 (72), with supporting information from the CSRs (73;74).

The methodologies of the completed Phase III LDV/SOF clinical trials, ION-1, ION-3, and ION-2 are summarised in Table 10. ION-1 and ION-3 both enrolled HCV treatment-naïve patients, and hence are presented in sequence, whereas ION-2 enrolled HCV treatment-experienced patients, and is presented last.

Table 10: Comparative summary of methodology of the Phase III non-RCTs

Trial no. (acronym)	GS-US-337-0102 (ION-1) HCV GT1 treatment naïve patients	GS-US-337-0108 (ION-3) HCV GT1 treatment naïve non-cirrhotic patients	GS-US-337-0109 (ION-2) HCV GT1 treatment experienced patients
Study objective	To assess the efficacy and safety of 12 or 24 weeks of a FDC of LDV and SOF with or without RBV in treatment naïve patients with chronic HCV GT1 infection, including those with compensated cirrhosis.	To assess the efficacy and safety of 8 weeks of a FDC of LDV and SOF with or without RBV compared with 12 weeks of FDC of LDV and SOF alone in treatment naïve patients with chronic HCV GT1 infection without cirrhosis.	To assess the efficacy and safety of 12 or 24 weeks of a FDC of LDV and SOF with or without RBV in treatment experienced patients with chronic HCV GT1 infection, including those with compensated cirrhosis.
Location	99 sites in the United States and Europe 7 sites in England, none in Scotland, Wales, or Ireland.	59 sites in the United States.	64 sites in the United States.
Design	Multicentre randomised, open-label, Phase III.	Multicentre randomised, open-label, Phase III.	Multicentre randomised, open-label, Phase III.
Duration of study	Treatment duration: 12 or 24 weeks Follow-up: 24 weeks	Treatment duration: 8 or 12 weeks Follow-up: 24 weeks	Treatment duration: 12 or 24 weeks Follow-up: 24 weeks
Method of randomisation	An IXRS was employed to manage patient randomisation and treatment assignment. Randomisation was stratified by: • HCV GT1 subtype (1a or 1b) • Presence or absence of cirrhosis	An IWRS was employed to manage patient randomisation and treatment assignment. Randomisation was stratified by HCV GT1 subtype (1a or 1b).	An IWRS was employed to manage patient randomisation and treatment assignment. Randomisation was stratified by: • HCV GT1 subtype (1a or 1b) • Presence or absence of cirrhosis • Response to prior therapy (relapse or virologic breakthrough vs no response)
Method of blinding (care provider, patient and outcome assessor)	Study was open-label. Post-treatment HCV RNA results were blinded to the investigator and sponsor	Study was open-label. Post-treatment HCV RNA results were blinded to the investigator.	Study was open-label. Post-treatment HCV RNA results were blinded to the investigator.
Intervention(s) (n=) and comparator(s) (n=)	• LDV/SOF for 12 weeks (n=214) • LDV/SOF+RBV for 12 weeks (n=217) (Not licensed) • LDV/SOF for 24 weeks (n=217) • LDV/SOF+RBV for 24 weeks (n=217)	• LDV/SOF for 8 weeks (n=215) • LDV/SOF+RBV for 8 weeks (n=216) (Not licensed) • LDV/SOF for 12 weeks (n=216)	• LDV/SOF for 12 weeks (n=109) • LDV/SOF+RBV for 12 weeks (n=111) (Not licensed) • LDV/SOF for 24 weeks (n=109) • LDV/SOF+RBV for 24 weeks (n=111)

Trial no. (acronym)	GS-US-337-0102 (ION-1) HCV GT1 treatment naïve patients	GS-US-337-0108 (ION-3) HCV GT1 treatment naïve non-cirrhotic patients	GS-US-337-0109 (ION-2) HCV GT1 treatment experienced patients
	• Patients received a single tablet containing 90 mg of LDV and 400 mg of SOF, administered orally once daily. For patients who were also receiving RBV, RBV was administered orally twice daily, with the dose determined according to body weight (1,000 mg daily in patients with a body weight <75 kg, and 1,200 mg daily in patients with a body weight ≥75kg).	• Patients received a single tablet containing 90 mg of LDV and 400 mg of SOF, administered orally once daily. For patients who were also receiving RBV, RBV was administered orally twice daily, with the dose determined according to body weight (1,000 mg daily in patients with a body weight <75 kg, and 1,200 mg daily in patients with a body weight ≥75kg).	• Patients received a single tablet containing 90 mg of LDV and 400 mg of SOF, administered orally once daily. For patients who were also receiving RBV, RBV was administered orally twice daily, with the dose determined according to body weight (1,000 mg daily in patients with a body weight <75 kg, and 1,200 mg daily in patients with a body weight ≥75kg).

Permitted and disallowed concomitant medications	Concomitant medications taken within 30 days of screening through to 4 weeks following end of treatment were recorded.
	The following medications were prohibited from 28 days prior to the baseline visit through to the end of treatment:
	• Haematologic stimulating agents (e.g. ESAs, GCSF, TPO mimetics)
	• Chronic systemic immunosuppressants including:
	  ○ Corticosteroids (prednisone equivalent of >10 mg/day for >2 weeks)
	  ○ Azathioprine
	  ○ Monoclonal antibodies (e.g. infliximab)
	• Investigational agents or devices for any indication
	• Drugs disallowed according to prescribing information of RBV
	• Use of medications or herbal/natural supplements (inhibitors or inducers of drug transporters i.e. P-glycoprotein) which may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drug(s).		

Assessments performed	All patients had to complete screening, baseline, on-treatment, and post-treatment assessments. Screening assessments were to be completed within 28 days (42 days if liver biopsy required) of the baseline/Day 1 visit. All patients had to complete post-treatment week 4 and week 12 assessments. Patients with HCV RNA<LLOQ (25 IU/mL) at post-treatment week 12 had to complete post-treatment week 24 assessments unless confirmed viral relapse occurred. Assessments: • Complete physical examination (screening, baseline, weeks 12 and 24 [if applicable]) • Body weight (screening, baseline, weeks 12 and 24 [if applicable], post-treatment weeks 12 and 24) • IL28B genotyping (screening)		

Trial no. (acronym)	GS-US-337-0102 (ION-1) HCV GT1 treatment naïve patients	GS-US-337-0108 (ION-3) HCV GT1 treatment naïve non-cirrhotic patients	GS-US-337-0109 (ION-2) HCV GT1 treatment experienced patients
	• 12-lead ECG (screening, baseline, weeks 1, 12 and 24 [if applicable]) • Four HRQL† surveys (baseline, weeks 2, 4, 8, 12 and 24 [if applicable], post-treatment weeks 4, 12 and 24) • Vital signs‡ (every visit) • Serum HCV RNA (every visit) • AEs and concomitant medications (every visit) • Viral RNA sequencing and phenotyping (every visit)		
Primary outcomes (including scoring methods and timings of assessments)	SVR12, defined as HCV RNA<lower limit of quantitation (LLOQ), 12 weeks after the end of treatment, in the FAS population. The LLOQ was 25 IU/mL.		
Secondary outcomes (including scoring methods and timings of assessments)	• Non-inferiority of 8 weeks of LDV/SOF to the other treatment regimens (ION-3 only) • Proportion of patients with SVR (HCV RNA<LLOQ) at 4 weeks and 24 weeks after end of treatment (SVR4 and SVR24) • The proportion of patients with HCV RNA<LLOQ on treatment • HCV RNA change from baseline • Proportion of patients with virologic failure. On-treatment virologic failure is breakthrough, rebound, or non-response. Relapse, after achieving a response at the end of treatment is also virologic failure. • Development of resistance: Deep sequencing of the NS5A and NS5B regions of the HCV RNA was performed in all patients at baseline and at time of virologic failure in those that had virologic failure. The resulting sequences were compared to detect resistance –associated variants that emerged during treatment. Only variants present in >1% of sequence reads were reported. • ALT normalisation • HRQL†		

Abbreviations: AE, adverse event; CLDQ, Chronic Liver Disease Questionnaire ECG, electrocardiogram; ESA, erythropoiesis-stimulating agent; FACIT-F, Fatigue Index; FDC, fixed-dose combination; GCSF, granulocyte colony stimulating factor; GT, genotype; HCV, hepatitis C virus; HRQL, Health Related Quality of Life; IWRS, interactive web response system; IXRS, interactive web and voice response system; LDV, ledipasvir; LLOQ, lower limit of quantitation; RBV, ribavirin; RNA, ribonucleic acid; SF-36, 36-Item Short-Form Survey; SOF, sofosbuvir; SVR, sustained virologic response; TPO, thrombopoietin; WPAI, Work Productivity and Activity Impairment.
† HRQL surveys were SF-36, CLDQ-HCV, FACIT-F and WPAI; ‡ Vital signs include resting blood pressure pulse, respiratory rate and temperature.

Participants

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

Summary details of the eligibility criteria for ION-1, ION-3 and ION-2 are presented in Table 11 and further details are presented in Table 12. The key differences in terms of inclusion/exclusion criteria relate to prior treatment experience and percentage of patients with cirrhosis. All three trials enrolled patients with CHC GT1.

Table 11: Summary eligibility criteria of the Phase III non-RCTs

Trial no. (acronym)	GS-US-337-0102 (ION-1) GT1 treatment naïve patients	GS-US-337-0108 (ION-3) GT1 treatment naïve patients	GS-US-337-0109 (ION-2) GT1 treatment experienced patients
Genotype	GT1	GT1	GT1
Treatment experience	HCV treatment naïve • No prior exposure to any IFN, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent • Study includes patients with relative or absolute contraindications to interferon treatment ("IFN ineligible"), as determined by the Investigator	HCV treatment naïve • No prior exposure to any IFN, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent • Study includes patients with relative or absolute contraindications to interferon treatment ("IFN ineligible"), as determined by the Investigator	HCV treatment experienced • Prior virologic failure after treatment with an NS3/4A PI plus PEG-IFN and RBV, or those who have failed treatment with a PEG-IFN/RBV regimen. Patients must not have discontinued prior therapy due to an AE.
Cirrhosis permitted	Up to 20%	Absence of cirrhosis	Up to 20%
General inclusion criteria	Aged ≥18 years; BMI≥18 kg/m^2; HCV RNA≥10^4 IU/mL at screening; confirmation of chronic HCV infection by positive anti-HCV, positive HCV RNA or positive HCV genotyping ≥6 months prior to baseline or liver biopsy with evidence of CHC.		
Exclusion criteria	Co-infection with HBV or HIV; any other chronic liver disease; current or history of decompensated liver disease; current or history of major organ transplant; clinically relevant drug abuse; alcohol misuse. Women who were pregnant or nursing or men whose partners were pregnant.		

Abbreviations: AE, adverse event; BMI, body mass index; CHC, chronic hepatitis C; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; GT, genotype; IFN interferon; NS, non-structural protein; PEG-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin.

Table 12: Eligibility criteria in the Phase III non-RCTs

Trial no. (acronym)	GS-US-337-0102 (ION-1) GT1 treatment naïve patients	GS-US-337-0108 (ION-3) GT1 treatment naïve patients	GS-US-337-0109 (ION-2) GT1 treatment experienced patients
Inclusion criteria			
Treatment experience	• **HCV treatment naïve** No prior exposure to any IFN, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent **Study includes patients with relative or absolute contraindications to interferon treatment ("IFN ineligible"), as determined by the Investigator**	• **HCV treatment naïve** No prior exposure to any IFN, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent **Study includes patients with relative or absolute contraindications to interferon treatment ("IFN ineligible"), as determined by the Investigator**	• **HCV treatment experienced** Prior virologic failure after treatment with an NS3/4A PI plus PEG-IFN and RBV, or those who have failed treatment with a PEG-IFN/RBV regimen. Patients must not have discontinued prior therapy due to an AE. The patient's medical records must include sufficient detail of prior virologic failure to allow categorisation of prior response, as either: ○ non-responder: patient did not achieve undetectable HCV RNA levels (HCV RNA≥LLOQ) while on treatment, or ○ relapse/breakthrough: patients achieved undetectable HCV RNA levels (HCV RNA<LLOQ) during treatment or within 4 weeks of the end treatment but did not achieve SVR.
Cirrhosis permitted	• **Presence of cirrhosis in up to 20% of patients** ○ Cirrhosis was defined as any one of the following: ▪ Liver biopsy showing cirrhosis (Metavir score=4 or Ishak score ≥5) ▪ Fibroscan† showing cirrhosis or results >12.5 kPa ▪ FibroTest® score of 0.75 and an AST: platelet ratio index (APRI) of >2 during screening ○ Absence of cirrhosis was defined as any one of the following: ▪ Liver biopsy within 2 years of	• **Absence of cirrhosis** ○ Absence of cirrhosis was defined as any one of the following: ▪ Liver biopsy within 2 years of screening showing absence of cirrhosis ▪ Fibroscan† within 6 months of baseline visit with a result of ≤12.5 kPa ▪ FibroTest® score of ≤0.48 and APRI of ≤1 during screening ○ Cirrhosis was defined as any one of the following: ▪ Liver biopsy showing cirrhosis (Metavir	• **Presence of cirrhosis in up to 20% of patients** ○ Cirrhosis was defined as any one of the following: ▪ Liver biopsy showing cirrhosis (Metavir score=4 or Ishak score ≥5) ▪ FibroTest® score of > 0.75 and an ratio index (APRI) of >2 during screening ○ Absence of cirrhosis was defined as any one of the following: ▪ Liver biopsy within 2 years of screening absence of cirrhosis ▪ FibroTest® score of ≤0.48 and APRI of

Trial no. (acronym)	GS-US-337-0102 (ION-1) GT1 treatment naïve patients	GS-US-337-0108 (ION-3) GT1 treatment naïve patients	GS-US-337-0109 (ION-2) GT1 treatment experienced patients
	screening absence of cirrhosis ▪ Fibroscan‡ within 6 months of baseline visit with a result of ≤12.5 kPa ▪ FibroTest® score of ≤0.48 and APRI of ≤1 during screening ○ A liver biopsy was required in the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria. Liver biopsy results superseded any imaging or blood test results and were considered definitive • **Liver imaging within 6 months of baseline visit was required in cirrhotic patients to exclude HCC**	score=4 or Ishak score ≥5) ▪ Fibroscan‡ showing cirrhosis or results >12.5 kPa ▪ FibroTest® score of >0.75 and an ratio index (APRI) of >2 during screening ○ A liver biopsy was required in the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria. Liver biopsy results superseded any imaging or blood test results and were considered definitive	≤1 during screening ○ A liver biopsy was required in the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria. Liver biopsy results superseded any imaging or blood test results and were considered definitive • **Liver imaging within 6 months of baseline visit was required in cirrhotic patients to exclude HCC**
General inclusion criteria	• Willing and able to provide written informed consent • Aged ≥18 years • BMI≥18 kg/m^2 • HCV RNA≥10^4 IU/mL at screening • HCV genotype 1a, 1b, or mixed 1a/1b at screening • Confirmation of chronic HCV infection documented by either: ○ A positive anti-HCV antibody test or positive HCV RNA or positive HCV genotyping test ≥6 months prior to the baseline visit ○ A liver biopsy performed prior to the baseline visit with evidence of chronic HCV infection • ECG at screening without clinically significant abnormalities • Laboratory parameters at screening: ○ ALT≤10 x ULN ○ AST≤10 x ULN ○ Direct bilirubin ≤1.5 x ULN ○ Platelets >50,000 (>90,000 for ION-3) ○ HbA_{1c} ≤8.5% ○ CL_{cr} ≥60 mL/min ○ Haemoglobin ≥11 g/dL for female patients; ≥12 g/dL for male patients		

Trial no. (acronym)	GS-US-337-0102 (ION-1) GT1 treatment naïve patients	GS-US-337-0108 (ION-3) GT1 treatment naïve patients	GS-US-337-0109 (ION-2) GT1 treatment experienced patients
	○ Albumin ≥3 g/dL ○ INR≤1.5 x ULN unless patient had known haemophilia or was stable on an anticoagulant regimen affecting INR • Not been treated with any investigational drug or device within 30 days of the screening visit (not defined for ION-3) • Female patients that were not pregnant or nursing, of non-childbearing potential, or of childbearing potential but abstaining from intercourse or using adequate methods of birth control from a defined list • Male patients using adequate methods of birth control (female partners also needed to be using adequate methods of birth control from a defined list) • Male patients refrained from sperm donation from the screening date until ≥90 days after the last dose of study drug or 7 months after the last dose or RBV • General good health, with the exception of chronic HCV infection, as determined by the investigator • Able to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments		
Exclusion criteria			
Specific exclusion criteria	• Donation or loss of >400 mL blood within 2 months prior to baseline • Use of any prohibited concomitant medications within 28 days of the baseline visit	• Presence of cirrhosis • Use of any prohibited concomitant medications within 21 days of the baseline visit	• Prior exposure to approved or experimental HCV-specific direct-acting antiviral agent(s), other than a NS3/4A PI. • Use of any prohibited concomitant medications within 21 days of the baseline visit
General exclusion criteria	• Current or prior history of any of the following: ○ Clinically significant illness (other than HCV) or any other major medical disorder that may interfere with patient treatment assessment or compliance with the protocol; patients under evaluation for a potentially clinically significant illness (other than HCV) were also excluded ○ Gastrointestinal disorder or post-operative condition that could interfere with absorption of the study drug ○ Difficulty with blood collection and/or poor venous access for the purposes of phlebotomy ○ Clinical hepatic decompensation ○ Solid organ transplantation ○ Significant pulmonary disease, significant cardiac disease, or porphyria ○ Psychiatric hospitalisation, suicide attempt, and/or a period of disability as a result of psychiatric illness within the last 5 years. Patients with psychiatric illness that was well-controlled on a stable treatment regimen for ≥12 months prior to randomisation or had not required medication in the last 12 months could be included. ○ Malignancy diagnosed or treated within 5 years (recent localised treatment of squamous or non-invasive basal cell skin cancers was permitted; cervical carcinoma *in situ* was allowed if appropriately treated prior to screening); patients under evaluation for malignancy were		

Trial no. (acronym)	GS-US-337-0102 (ION-1) GT1 treatment naïve patients	GS-US-337-0108 (ION-3) GT1 treatment naïve patients	GS-US-337-0109 (ION-2) GT1 treatment experienced patients
	not eligible ○ Significant drug allergy (e.g. anaphylaxis or hepatotoxicity) • Pregnant or nursing female or male with pregnant female partner • Chronic liver disease of a non-HCV aetiology (e.g. hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, cholangitis). • Infection with HBV or HIV • Clinically-relevant drug abuse within 12 months of screening. A positive drug screen excluded patients unless it was explained by a prescribed medication. • Alcohol misuse, defined by an AUDIT score ≥8 • Contraindication to RBV therapy, including significant history of clinically significant haemoglobinopathy (e.g. sickle cell disease, thalassemia) • Chronic use of systemically administered immunosuppressive agents (e.g. prednisone equivalent >10 mg/day) • Known hypersensitivity to RBV, LDV, SOF, or formulation recipients		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; APRI, ratio index; AST, aspartate aminotransferase; AUDIT, BMI, body mass index; CL_{cr}, creatinine clearance; ECG, electrocardiogram; GT, genotype; HbA_{1c}, haemoglobin A_{1c}; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus, IFN, interferon; INR, International Normalised Ratio of prothrombin time; IUD, intrauterine device; LDV, ledipasvir; LLOQ, lower limit of quantitation; NS, non-structural protein; PEG-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; ULN, upper limit of the normal range.
† Fibroscan in countries where it is locally approved.

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

Patient characteristics at baseline are summarised in Table 13, Table 14 and Table 15 for the trials, ION-1, ION-3, and ION-2, respectively. Within each trial there were no significant differences between groups regarding gender, BMI, race, ethnic group, HCV genotype, HCV RNA levels, IL28B genotype, or ALT levels (using the Kruskal-Wallis test for the overall difference across treatment groups for continuous variables and the Cochran–Mantel–Haenszel test for the overall difference across treatment groups for categorical variables). The mean age and proportion of patients eligible for IFN treatment did not differ between the groups in ION-1 and ION-3. In ION-2, there was a significant difference (p=0.02) in age between treatment groups. Prior treatment and response were not tested in ION-2.

Table 13: Characteristics of participants in ION-1 and across randomised groups

Baseline characteristics	12 week		24 week	
	LDV/SOF (n=214)	LDV/SOF+RBV (n=217)	LDV/SOF (n=217)	LDV/SOF+RBV (n=217)
Mean age (range), years	52 (18–75)	52 (18–78)	53 (22–80)	53 (24–77)
Male, n (%)	127 (59)	128 (59)	139 (64)	119 (55)
Mean BMI (range), kg/m^2 †	27 (18–41)	27 (18–42)	27 (18–48)	26 (18–48)
Race, n (%)‡				
White	187 (87)	188 (87)	177 (82)	183 (84)
Black	24 (11)	26 (12)	32 (15)	26 (12)
Asian	1 (<1)	0	5 (2)	5 (2)
Other	2 (1)	3 (1)	3 (1)	3 (1)
Ethnic group, n (%)‡				
Hispanic	26 (12)	20 (9)	29 (13)	26 (12)
Non-Hispanic	187 (87)	197 (91)	188 (87)	190 (88)
Not disclosed	1 (<1)	0	0	1 (<1)
Region, n (%)				
US	125 (58)	118 (54)	132 (61)	137 (63)
Europe	89 (42)	99 (46)	85 (39)	80 (37)
HCV genotype, n (%)§				
1a	144 (67)	148 (68)	146 (67)	143 (66)
1b	66 (31)	68 (31)	68 (31)	71 (33)
Other	4 (2)	1 (<1)	3 (1)	3 (1)
Mean HCV RNA±SD, $\log_{10}$ IU/mL	6.4±0.69	6.4±0.64	6.3±0.68	6.3±0.65
HCV RNA≥800,000 IU/mL, n (%)	169 (79)	173 (80)	168 (77)	173 (80)
IL28B genotype, n (%)				
CC	55 (26)	76 (35)	52 (24)	73 (34)
CT	113 (53)	107 (49)	119 (55)	112 (52)
TT	46 (21)	34 (16)	46 (21)	32 (15)
Cirrhosis, n (%)	34 (16)	33 (15)	33 (15)	36 (17)

Baseline characteristics	12 week		24 week	
	LDV/SOF	LDV/SOF+RBV	LDV/SOF	LDV/SOF+RBV
ALT>1.5 x ULN, n (%)	120 (56)	119 (55)	109 (50)	112 (52)
IFN eligibility status, n (%)				
Eligible	200 (93)	197 (91)	198 (91)	203 (94)
Ineligible	14 (7)	20 (9)	19 (9)	14 (6)

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; HCV, hepatitis C virus, IFN, interferon; IU, international unit; LDV, ledipasvir; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir; ULN, upper limit of the normal range.
† BMI is the weight in kilograms divided by the square of the height in metres; ‡ Race and ethnic group were self-reported; § Four patients had an unconfirmed HCV genotype (one patient in each group), two had HCV GT4 (one in the 12 week LDV/SOF group and one in the 24 week LDV/SOF+RBV group), and there were five patients with missing data (two in the 12 week LDV/SOF group, two in the 24 week LDV/SOF group and one in the 24 week LDV/SOF+RBV group).

Table 14: Characteristics of participants in ION-3 across randomised groups

Baseline characteristics	8 week regimen		12 week regimen
	LDV/SOF (n=215)	LDV/SOF+RBV (n=216)	LDV/SOF (n=216)
Mean age (range), years	53 (22–75)	51 (21–71)	53 (20–71)
Male, n (%)	130 (60)	117 (54)	128 (59)
Mean BMI (range), kg/m^2 †	28 (18–43)	28 (18–56)	28 (19–45)
Race, n (%)‡			
White	164 (76)	176 (81)	167 (77)
Black	45 (21)	36 (17)	42 (19)
Other	6 (3)	4 (2)	7 (3)
Ethnic group, n (%)‡			
Hispanic	13 (6)	12 (6)	14 (6)
Non-Hispanic	200 (93)	204 (94)	202 (94)
Not disclosed	2 (1)	0	0
HCV genotype, n (%)			
1a	171 (80)	172 (80)	172 (80)
1b	43 (20)	44 (20)	44 (20)
1 without confirmed subtype	1 (<1)	0	0
Mean HCV RNA±SD, log_{10} IU/mL§	6.5±0.8	6.4±0.7	6.4±0.8
HCV RNA≥800,000 IU/mL, n (%)	181 (84)	171 (79)	172 (80)
IL28B genotype, n (%)			
CC	56 (26)	60 (28)	56 (26)
CT	120 (56)	128 (59)	124 (57)
TT	39 (18)	28 (13)	36 (17)
ALT>1.5 x ULN, n (%)	87 (40)	95 (44)	99 (46)
Fibrosis score, n (%)			
F0–F2	127 (59)	108 (50)	127 (59)

Baseline characteristics	8 week regimen		12 week regimen
	LDV/SOF	LDV/SOF+RBV	LDV/SOF
F3	29 (13)	28 (13)	29 (13)
IFN eligibility status, n (%)			
Eligible	202 (94)	203 (94)	203 (94)
Ineligible	13 (6)	13 (6)	15 (7)

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; HCV, hepatitis C virus, IFN, interferon; IU, international unit; LDV, ledipasvir; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir; ULN, upper limit of the normal range.
† BMI is the weight in kilograms divided by the square of the height in metres; ‡ Race and ethnic group were self-reported.

Table 15: Characteristics of participants in ION-2 across randomised groups

Baseline characteristics	12 week regimen		24 week regimen	
	LDV/SOF (n=109)	LDV/SOF+RBV (n=111)	LDV/SOF (n=109)	LDV/SOF+RBV (n=111)
Mean age (range), years	56 (24–67)	57 (27–75)	56 (25–68)	55 (28–70)
Male, n (%)	74 (68)	71 (64)	74 (68)	68 (61)
Mean BMI (range), kg/m^2 †	29 (19–47)	28 (19–45)	28 (19–41)	28 (19–50)
Race, n (%)‡				
White	84 (77)	94 (85)	91 (83)	89 (80)
Black	24 (22)	16 (14)	17 (16)	20 (18)
Asian	1 (1)	0	0	0
Hawaiian or Pacific Islander	0	1 (1)	0	1 (1)
Other	0	0	1 (1)	1 (1)
Ethnic group, n (%)‡				
Hispanic	7 (6)	12 (11)	11 (10)	11 (10)
Non-Hispanic	100 (92)	99 (89)	98 (90)	99 (89)
Not disclosed	2 (2)	0	0	1 (1)
HCV genotype, n (%)				
1a	86 (79)	88 (79)	85 (78)	88 (79)
1b	23 (21)	23 (21)	24 (22)	23 (21)
Mean HCV RNA±SD, log_{10} IU/mL	6.5±0.44	6.4±0.54	6.4±0.57	6.5±0.60
HCV RNA≥6 log_{10} IU/mL, n (%)	96 (88)	94 (85)	86 (79)	91 (82)
IL28B genotype, n (%)				
CC	10 (9)	11 (10)	16 (15)	18 (16)
CT	70 (64)	77 (69)	68 (62)	68 (61)
TT	29 (27)	23 (21)	25 (23)	25 (23)
Cirrhosis, n (%)	22 (20)	22 (20)	22 (20)	22 (20)
ALT>1.5 x ULN, n (%)	53 (49)	51 (46)	60 (55)	49 (44)
Prior treatment				

Baseline characteristics	12 week regimen		24 week regimen	
	LDV/SOF	LDV/SOF+RBV	LDV/SOF	LDV/SOF+RBV
PEG-IFN or IFN, + RBV, n (%)	43 (39)	47 (42)	59 (54)	60 (54)
PI regimen, n (%)	66 (61)	64 (58)	50 (46)	51 (46)
Prior response to treatment, n (%)				
Relapse or virologic breakthrough	60 (55)	65 (59)	60 (55)	60 (54)
No response	49 (45)	46 (41)	49 (45)	51 (46)

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; HCV, hepatitis C virus, IFN, interferon; IU, international unit; LDV, ledipasvir; PEG-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; RNA, ribonucleic acid; SD, standard deviation; SOF, sofosbuvir; ULN, upper limit of the normal range.
† BMI is the weight in kilograms divided by the square of the height in metres; ‡ Race and ethnic group were self-reported.

Outcomes

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

The same primary and secondary outcomes were investigated in ION-1, ION-3, and ION-2. The outcomes and their relevance to the decision problem are presented in Table 16.

Table 16: Outcomes investigated in ION-1, ION-3, and ION-2

Outcomes and measures	Included in NICE scope	Reliability/validity/current use in clinical practice
Primary outcome		
SVR12, defined as HCV RNA<LLOQ† 12 weeks after the end of treatment in the FAS population	Yes	SVR is the primary aim of treatment in clinical practice. SVR12 is the established appropriate endpoint for regulatory approval and is accepted by the EMA and FDA.
Secondary outcomes		
The proportion of patients with HCV RNA<LLOQ at 4 weeks and 24 weeks after the end of treatment (SVR4 and SVR24)	Yes	Historically, SVR24 has been used as an endpoint for HCV studies to determine efficacy. However, SVR12 has been shown to have high concordance with SVR24 rates, based on clinical trial data of various treatment regimens and durations. SVR12 is now used as standard by regulatory authorities.
The proportion of patients with HCV RNA<LLOQ on treatment	No	The kinetics of circulating HCV RNA during treatment forms part of routine clinical practice with current treatments (PEG-IFN, RBV, BOC and TVR) and is used to monitor and guide treatment (referred to as response guided therapy). On-treatment viral kinetics do not inform treatment duration with sofosbuvir-based regimens.
HCV RNA change from baseline		

Outcomes and measures	Included in NICE scope	Reliability/validity/current use in clinical practice
The proportion of subjects with virologic failure	No	This outcome provides a measure of treatment failure either on-treatment – by way of viral breakthrough, rebound, or non-response – or in the post-treatment phase (relapse). For patients receiving a PEG-IFN+RBV regimen the mechanism of treatment failure (non-response vs relapse) is a good predictor of future response to a PEG-IFN–based regimen.
Deep sequencing of NS5A and NS5B regions of HCV RNA to detect resistance-associated variants that emerged during treatment	Yes	Deep sequencing refers to the number of times a nucleotide position in the HCV genome is read during the sequencing process. Sequencing accuracy is increased by sequencing individual HCV genomes a large number of times to identify low-frequency mutations. It is accepted by the regulatory authorities as a valid method for characterising low frequency mutations. It is not in use in clinical practice.
Other outcomes of interest		
ALT normalisation	No	In clinical practice, ALT is an important laboratory test marker for monitoring HCV disease activity. Treatment induced reductions in HCV viral load, and eradication of HCV from the patient, often lead to a normalisation of ALT levels, indicating a reduction in ongoing liver damage.
HRQL outcomes	Yes	The following questionnaires were used to assess patients' HRQL. • SF-36 • CLDQ-HCV • FACIT-F • WPAI:Hep C All HRQL questionnaires are recognised and validated questionnaires

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; CLDQ-HCV, Chronic Liver Disease Questionnaire-Hepatitis C Virus; EMA, European Medicines Agency; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FAS, full analysis set; FDA, Food and Drug Administration; HCV, hepatitis C virus; HRQL, health related quality of life; LDV, ledipasvir; LLOQ, lower limit of quantitation; NS, non-structural; PEG-IFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SF-36, Short Form Health Survey; SVR, sustained virologic response; WPAI: Hep C, Work Productivity and Activity Impairment: Hepatitis C.
† LLOQ=25 IU/mL.

Statistical analysis and definition of study groups

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

Analysis sets

The following are the analysis sets used in ION-1, ION-3, and ION-2.

Full analysis set (FAS): Patients who were randomised into the study and received at least one dose of the study drug.

Modified FAS (mFAS): Patients who were randomised into the study and received at least one dose of the study drug, but excluding those lost to follow up or who withdrew consent (ION-1 sub-group analysis only).

Safety analysis set: Patients who were randomised into the study and received at least one dose of the study drug.

Table 17: Summary of statistical analyses in ION-1, ION-3, and ION-2

Trial no. (acronym)	GS-US-337-0102 (ION-1)	GS-US-337-0108 (ION-3)	GS-US-337-0109 (ION-2)
Hypothesis objective	The SVR12 rates in each treatment group would be higher than the adjusted historical SVR null rate of 60%, as accepted by regulatory bodies and derived from: 1. A historical SVR rate of ~65% was calculated from the TVR (ADVANCE) study and BOC (SPRINT2) study data after adjusting for the expected proportion of patients with cirrhosis in ION-1 (~20%). The weighted average of the TVR and BOC data was estimated to be ~70% in non-cirrhotic patients and ~44% in cirrhotic patients. The SVR rate for the historical control in ION-1 (80% non-cirrhotic patients and 20% cirrhotic patients) was then calculated to be ~65% (i.e. 0.8 x 70% + 0.2 x 44%). 2. The 60% null SVR rate was obtained after allowing for a 5% trade-off in efficacy exchanged for an improved safety profile and shorter treatment duration.	The SVR12 rates in each treatment group would be higher than the adjusted historical SVR null rate of 60%, as accepted by regulatory bodies and derived from: 1. A historical SVR rate of ~65% was calculated from the TVR (ADVANCE) study and BOC (SPRINT2) study data. The weighted average of the TVR and BOC data was estimated to be ~70% in non-cirrhotic patients. With an estimated minimum of 8% of patients being IFN ineligible (based on enrolment data from ION-1) and assuming a 5% response rate in these patients, the SVR rate for the historical control in ION-3 was then calculated to be ~65% (i.e. 0.92 x 70% + 0.08 x 5%). 2. The 60% null SVR rate was obtained after allowing for a 5% trade-off in efficacy exchanged for an improved safety profile and shorter treatment duration.	The SVR12 rates in each treatment group would be higher than the adjusted historical SVR null rate of 25%, as accepted by regulatory bodies and derived from: 1. A historical SVR rate of ~65% was calculated from the TVR (REALIZE) study and BOC (RESPOND-2) study data after adjusting for the expected proportion of patients with cirrhosis in ION-2 (~20%). The weighted average of the TVR and BOC data was estimated to be ~69% in non-cirrhotic patients and 50% in cirrhotic patients. The retreatment SVR rate for the historical control in ION-2 (80% non-cirrhotic patients and 20% cirrhotic patients) was then calculated to be ~65% (i.e. 0.8 x 69% + 0.2 x 50%). 2. There is currently a lack of retreatment options for patients who have failed treatment with PI+PEG-IFN+RBV, therefore, a conservative retreatment SVR rate of 5% was used. In ION-2, ~50% of patients were expected to have had prior treatment with a PI+PEG-IFN+RBV. A 35% null SVR rate was obtained after averaging a 65% retreatment SVR control rate for treatment experienced (e.g. PEG-IFN+RBV) patients being retreated with PI+PEG-IFN+RBV, and a 5% SVR control rate for patients who failed prior treatment of a PI+PEG-IFN+RBV, if retreated with a PI+PEG-IFN+RBV. 3. The final 25% null SVR rate was obtained after allowing for a further 10% trade-off in efficacy exchanged for an improved safety

Trial no. (acronym)	GS-US-337-0102 (ION-1)	GS-US-337-0108 (ION-3)	GS-US-337-0109 (ION-2)
			profile and shorter treatment duration.
Statistical analysis of primary endpoint	**Primary analysis of the primary endpoint:** A two-sided one-sample binomial test was used to test the statistical hypotheses. The two-sided 95% exact CI based on the Clopper-Pearson method was provided for the SVR12 rate in each treatment group. **Subgroup analysis of the primary endpoint** The point estimates and 95% exact CIs based on the Clopper-Pearson method were provided for each subgroup in each treatment group.	**Primary analysis of the primary endpoint:** A two-sided one-sample binomial test was used to test the statistical hypotheses. **Additional analyses of the primary endpoint:** In addition, non-inferiority between the groups was assessed with the use of the conventional confidence-interval approach and a non-inferiority margin of 12%. The two-sided 95% exact CI based on the Clopper Pearson method was provided for the SVR12 rate in each treatment group. **Subgroup analysis of the primary endpoint** The point estimates and 95% exact CIs based on the Clopper-Pearson method were provided for each subgroup in each treatment group.	**Primary analysis of the primary endpoint:** A two-sided one-sample binomial test was used to test the statistical hypotheses. The two-sided 95% exact CI based on the Clopper Pearson method was provided for the SVR12 rate in each treatment group. **Subgroup analysis of the primary endpoint** The point estimates and 95% exact CIs based on the Clopper-Pearson method were provided for each subgroup in each treatment group.
Statistical analysis of secondary efficacy endpoints	• HCV RNA <LLOQ by study visit: Two-sided 95% exact CI based on the Clopper-Pearson method was provided for the proportion of patients with HCV RNA <LLOQ in each treatment group. • HCV RNA absolute values and change from baseline through week 8: Summary statistics were presented by treatment and study visit. Plots of the mean±SD and median (Q1, Q3) HCV RNA absolute values and change from baseline through week 8 were presented. • Virologic failure: Descriptively summarised as “on-treatment virologic failure” and “relapse.” Patients who did not achieve SVR12 and did not meet criteria for virologic failure were categorised as “other”. Point estimates and 95% Clopper-Pearson exact confidence intervals will be presented for the overall virologic failure. • Virologic resistance ION-1): Results for the HCV drug resistance-associated variants at baseline for all treatment groups were reported. Additionally, results for HCV drug resistance substitutions through post-treatment week 24 for the patients who had viral relapse, on-treatment breakthrough, or early discontinuation were summarised. • Virologic resistance (ION-2 and ION-3): Results for the HCV drug resistance-associated variants at baseline, during study drug dosing, and after study drug dosing were reported. Results for HCV drug resistance substitutions through post-treatment week 12 were summarised.		
Sample size, power	A sample size of 200 patients in each treatment group was calculated to provide over 91% power to detect ≥13% improvement in SVR12	A sample size of 200 patients in each treatment group was calculated to provide over 90% power to detect ≥30% improvement in SVR12	A sample size of 100 patients in each treatment group was calculated to provide over 99% power to detect ≥45% improvement in SVR12

Trial no. (acronym)	GS-US-337-0102 (ION-1)	GS-US-337-0108 (ION-3)	GS-US-337-0109 (ION-2)
calculation	rate from the adjusted historical null rate of 60% using a two-sided one-sample binomial test at significant level of 0.0125 based on a Bonferroni correction	rate from the adjusted historical null rate of 60% using a two-sided one-sample binomial test at significant level of 0.025.	rate from the adjusted historical null rate of 25% using a two-sided one-sample binomial test at significant level of 0.0125 based on a Bonferroni correction.
Data management, patient withdrawals	Values for missing data were not imputed for any outcomes except HCV RNA and HRQL data. For categorical HCV RNA data, if a data point was missing and was preceded and followed by values that were a success (<LLOQ TND and/or <LLOQ detected) then the missing data point was termed a bracketed success; otherwise the data point was termed a bracketed failure (≥LLOQ detected). Patients with missing data due to premature discontinuation of the study had missing data imputed up to the time of their last dose (if last dose was on-treatment). If study day associated with the last dose was ≥the lower bound of a visit window, and the value at visit was missing, then the value was imputed. If the study day associated with the last dose was <the lower bound of the visit window, then the on-treatment value at that visit remained missing. If HCV RNA values after the last dose of study drug were missing, the patient was considered a treatment failure for SVR outcomes. However, patients who achieved SVR12 and had no further HCV RNA measurements were counted as having achieved SVR24 due to the high correlation between SVR12 and SVR24. For continuous HCV RNA efficacy data, missing values in a visit window which were bracketed by values that were a success were set to 24 IU/mL. No other imputations were performed for continuous data. For HRQL data, missing data at on-treatment visits and post-treatment week 4 visit were not imputed. The last post-treatment observation carried forward was used for imputation of missing data at post-treatment visits after post-treatment week 4.		

Abbreviations: CI, confidence interval; GT, genotype; H_0, null hypothesis; H_1, alternative hypothesis; HCV, hepatitis C virus; HRQL, health related quality of life; IU, international unit; LDV, ledipasvir; LLOQ, lower limit of quantitation; MH, Mantel-Haenszel; PEG-IFN, pegylated-interferon; PI, protease inhibitor; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; TND, target not detected.

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

Pre-planned subgroup analyses of SVR12 were performed for various pre-planned demographic and baseline characteristics. These included, age (<65, ≥65 years), sex at birth (male, female), race (black, non-black), ethnicity (Hispanic/Latino, not Hispanic/Latino), HCV genotype (1a, 1b, other), baseline HCV RNA (<800,000, ≥800,000), baseline BMI (<30, ≥30), baseline ALT (≤1.5 x ULN, >1.5 x ULN), and IL28b (CC, CT, TT) in ION-1, ION-3, and ION-2.

In addition study specific subgroup analyses included:

- Region (US, Europe) – ION-1
- Cirrhosis (no, yes) – ION-1 and ION-2
- IFN eligibility (eligible, ineligible) – ION-1 and ION-3.
  - Patients may be IFN ineligible due to medical conditions such as substance use disorders, psychiatric disorders and medical comorbidities.

The patients in ION-2 were treatment experienced so additional pre-planned sub-group analyses in this study alone included response to prior HCV therapy (relapse, non-responder), prior HCV therapy (PI+PEG-IFN+RBV, PEG-IFN+RBV), and cirrhosis by prior therapy. A pre-planned exact logistic-regression analysis was also performed to identify baseline factors associated with SVR in ION-2.

Pre-planned analyses of SVR12 rates were also performed based on the randomisation strata for each study based on the Clopper-Pearson method.

A post-hoc analysis of patients from the ION-3 study was undertaken to investigate factors that might be predictive of relapse following 8 weeks treatment with LDV/SOF.

Participant flow

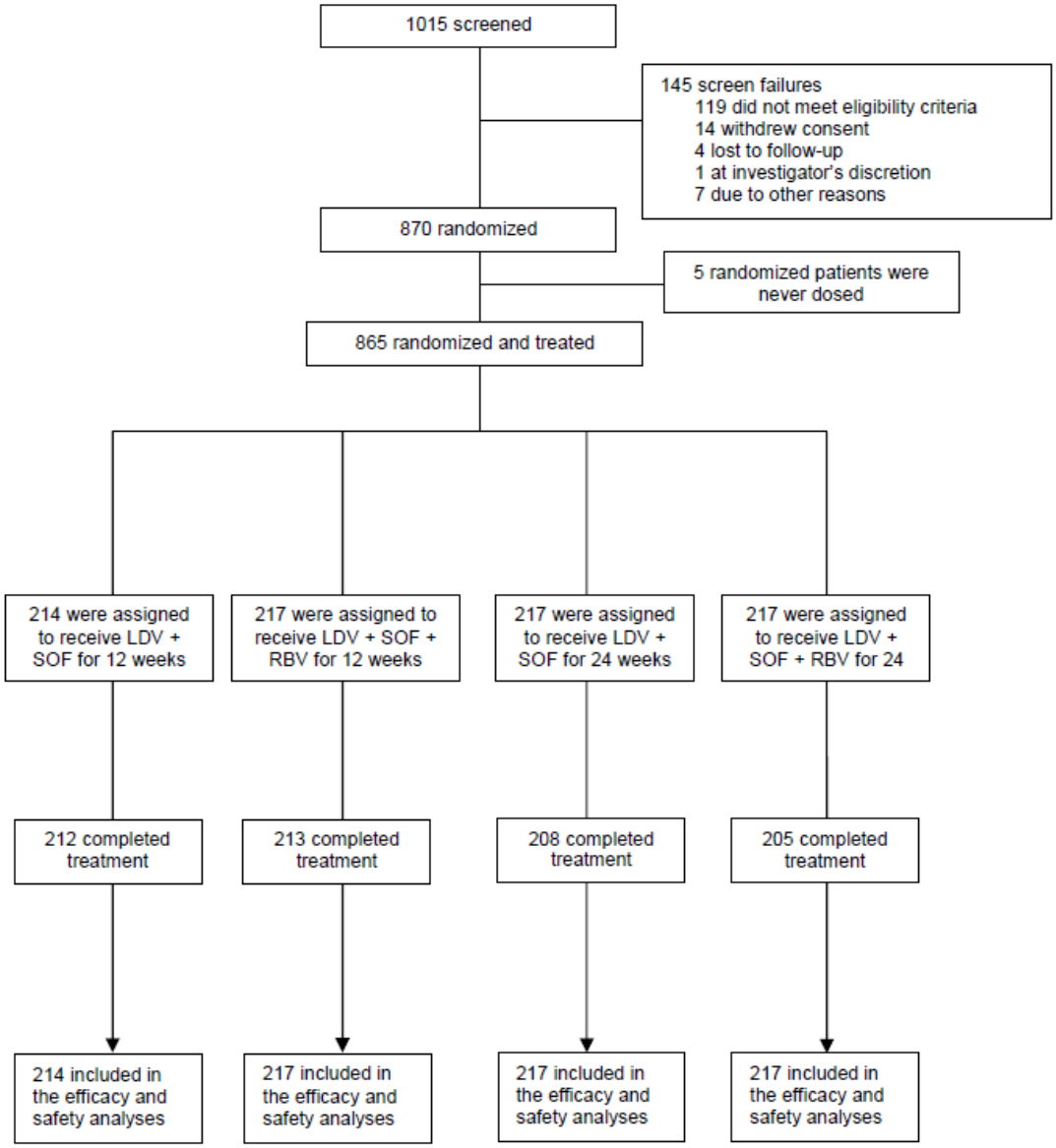
6.3.8 *Provide details of the numbers of patients who were eligible to enter the non-RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the non-RCT. This information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

CONSORT flow charts for ION-1, ION-3, and ION-2 are presented in Figure 4, Figure 5 and Figure 6, respectively. The primary analyses in all three ION trials were based on the FAS.

- In ION-1, 870 patients were randomised and 865 received at least one dose of the study drug, representing the FAS.
- In ION-3, 647 patients were randomised and all 647 received at least one dose of the study drug (FAS).
- In ION-2, 441 patients were randomised and 440 received at least one dose of the study drug (FAS).

Reasons for premature discontinuations in ION-1, ION-3 and ION-2 are presented in Table 18, Table 19 and Table 20, respectively.

Figure 4: Patient disposition in ION-1



Abbreviations: LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

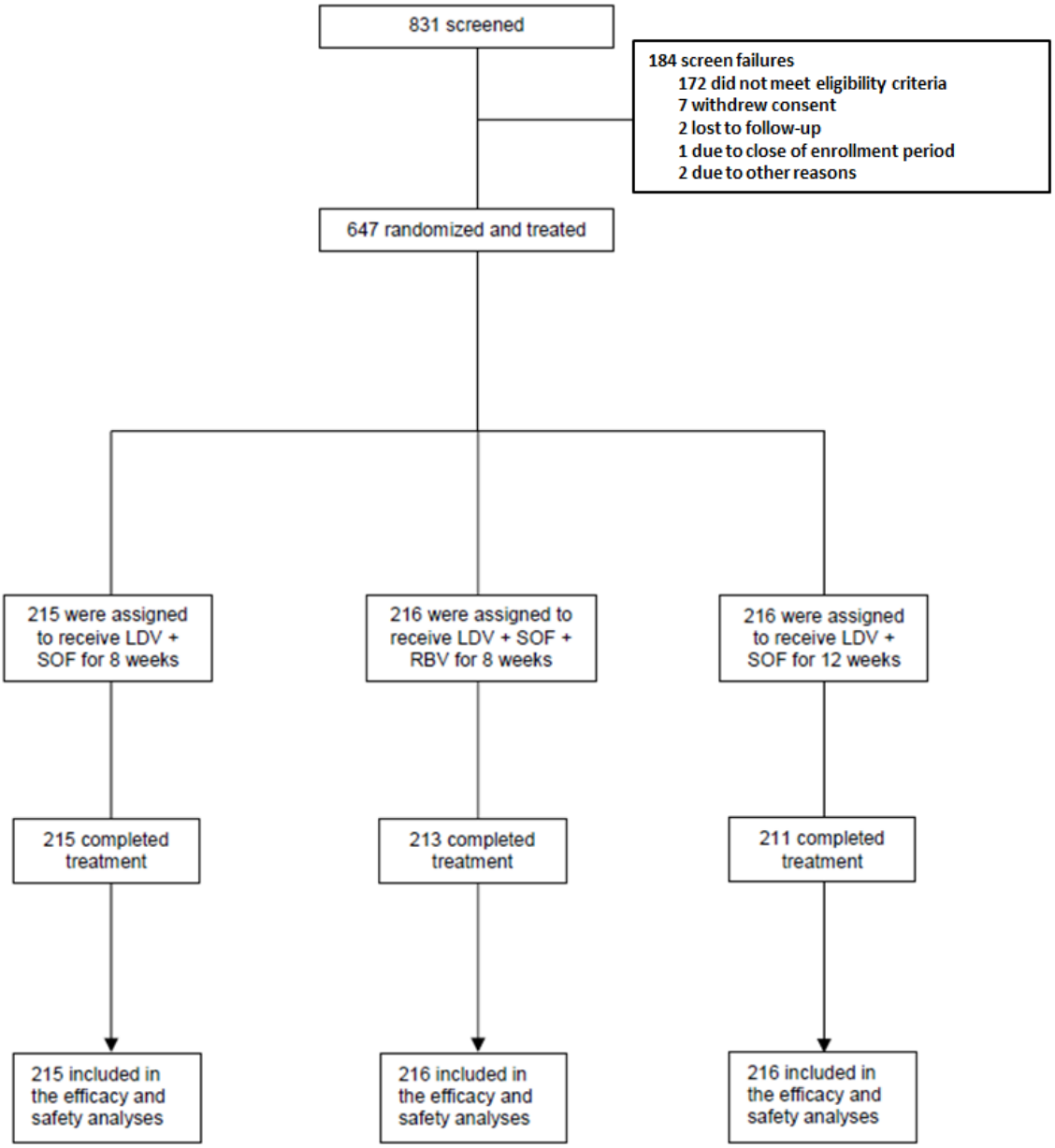
Table 18: Reasons for premature discontinuation of study treatment in ION-1

	12 week		24 week		Total
	LDV/SOF	LDV/SOF+RBV	LDV/SOF	LDV/SOF+RBV	
Total no. (%) of premature discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for premature discontinuation					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	12 week		24 week		Total
	LDV/SOF	LDV/SOF+RBV	LDV/SOF	LDV/SOF+RBV	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir

Figure 5: Patient disposition in ION-3



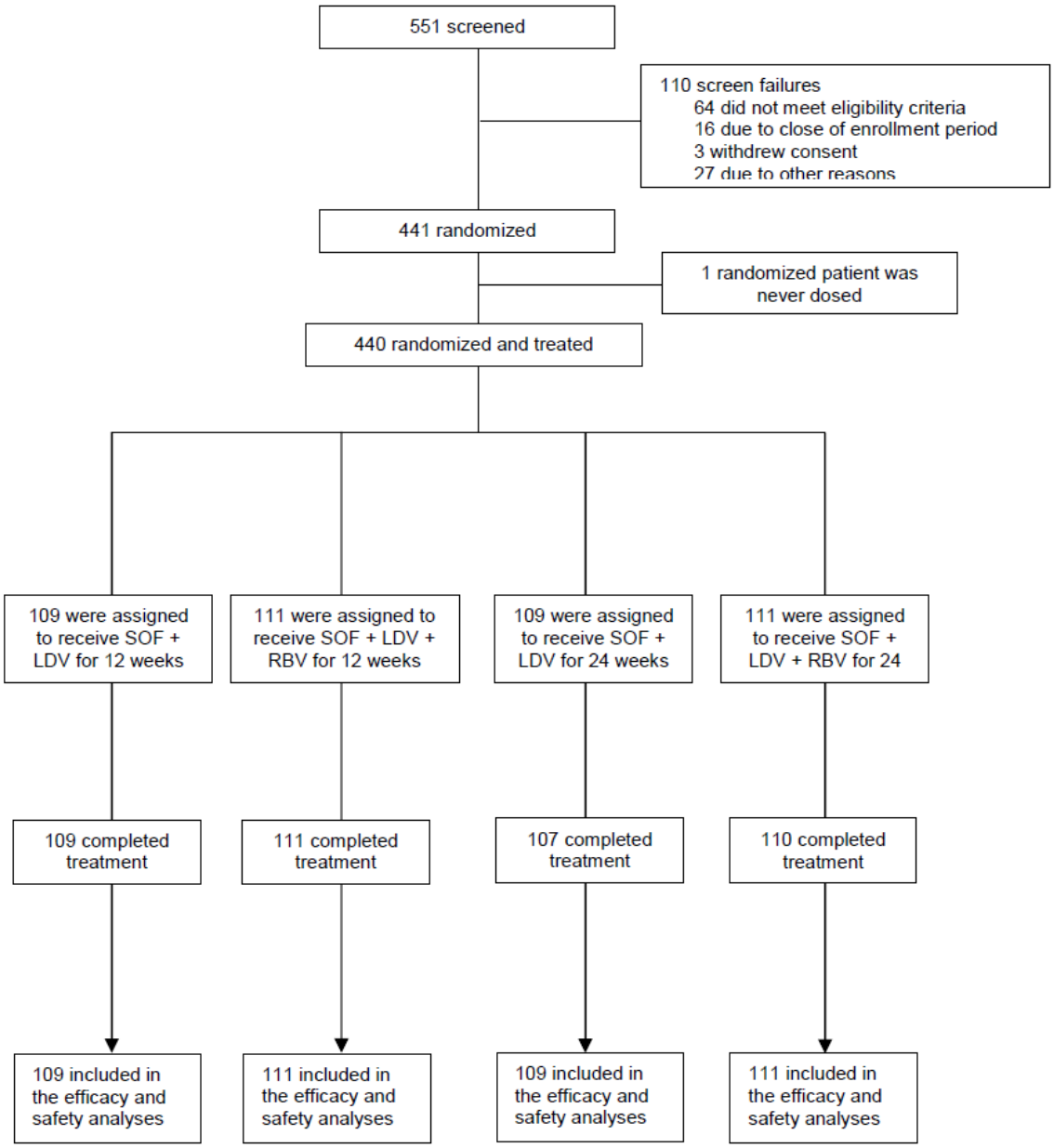
Abbreviations: LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

Table 19: Reasons for premature discontinuation of study treatment in ION-3

	8 week		12 week	Total
	LDV/SOF (N=215)	LDV/SOF+RBV (N=216)	LDV/SOF (N=216)	
Total no. (%) of premature discontinuations	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for premature discontinuation				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir

Figure 6: Patient disposition in ION-2



Abbreviatio

ns: LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

Table 20: Reasons for premature discontinuation of study treatment in ION-2

	12 week		24 week		Total
	LDV/SOF	LDV/SOF+RBV	LDV/SOF	LDV/SOF+RBV	
Total no. (%) of premature discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for premature discontinuation					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir

[redacted]

6.4 *Critical appraisal of relevant non-RCTs*

6.4.1 ***The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in non-RCTs, but the list is not exhaustive.***

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

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

A complete quality assessment for each Phase III trial is provided in **Error! Reference source not found.**.

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

A summary of the quality assessment results for the Phase III trials, ION-1, ION-3, and ION-2 is presented in Table 21.

Table 21: Quality assessment results for Phase III trials

	GS-US-337-0102 (ION-1)	GS-US-337-0108 (ION-3)	GS-US-337-0109 (ION-2)
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	N/A	N/A	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	There were no significant differences among the treatment groups except for age (p=0.02).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Study was open-label. Post-treatment HCV RNA results were blinded to the investigator and sponsor.	Study was open-label. Post-treatment HCV RNA results were blinded to the investigator.	Study was open-label. Post-treatment HCV RNA results were blinded to the investigator.
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No The analyses assessed the patients that were randomised and received at least one dose of study drug (FAS). Appropriate methods were used to account for missing data (see Table 17)	No The analyses assessed the patients that were randomised and received at least one dose of study drug (FAS). Appropriate methods were used to account for missing data (see Table 17)	No The analyses assessed the patients that were randomised and received at least one dose of study drug (FAS). Appropriate methods were used to account for missing data (see Table 17)

Abbreviations: N/A, not applicable.

6.5 *Results of the relevant non-RCTs*

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

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

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

- ***The unit of measurement.***

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

6.5.4 *Study GS-US-337-0102 (ION-1): HCV GT1 treatment naive*

Primary and secondary efficacy results for ION-1 are summarised in Table 22.

Results presented are from the final CSR. They differ from the NEJM publication because of one patient for whom the post-treatment week 12 visit was pending and therefore they were considered to have not achieved SVR12 at the time of publication and were categorised as lost to follow-up. In the final analysis, the patient had HCV <LLOQ at the post-treatment week 12 and 24 visits.

Table 22: Summary of response during and after treatment in ION-1 (FAS)

Response	12 week		24 week	
	LDV/SOF (N=214)	LDV/SOF+RBV (N=217)	LDV/SOF (N=217)	LDV/SOF+RBV (N=217)
HCV RNA<LLOQ				
During treatment, n/N (%)[†]				
At week 2	174/213 (82)	181/217 (83)	179/216 (83)	180/217 (83)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
At week 4	213/213 (100)	215/217 (99)	216/216 (100)	217/217 (100)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
At week 12	213/213 (100)	214/214 (100)	213/214 (>99)	216/216 (100)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment, n (%)				
At week 4 (SVR4)	211 (99)	213 (98)	215 (99)	215 (99)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
At week 12 (SVR12)	211 (99)	211 (97)	213 (98)	215 (99)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
SVR12 in specific subgroups, n/N (%)				
Non-cirrhotic patients	179/180 (99.4)	178/184 (96.7)	181/184 (98.4)	179/181 (98.9)

Response	12 week		24 week	
	LDV/SOF (N=214)	LDV/SOF+RBV (N=217)	LDV/SOF (N=217)	LDV/SOF+RBV (N=217)
95% CI	96.9–100	93.0–98.8	95.3–99.7	96.1–99.9
Cirrhotic patients 95% CI	32/34 (94.1) 80.3–99.3	33/33 (100) 89.4–100	32/33 (97.0) 84.2–99.9	36/36 (100) 90.3–100
Virologic failure during treatment, relapse, lost to follow up or consent withdrawals				
Virologic failure during treatment, n (%)	0	0	1 (0.5)	0
Relapse, n (%)	1 (0.5)	0	1 (0.5)	0
Lost to follow-up, n (%)	2 (0.9)	4 (1.8)	1 (0.5)	2 (0.9)
Withdrew consent, n (%)	0	2 (0.9)	1 (0.5)	0

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; LLOQ, lower limit of quantitation; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response.
† Data are shown for patients for whom HCV RNA results were available.

Primary efficacy results: SVR12

Primary analysis

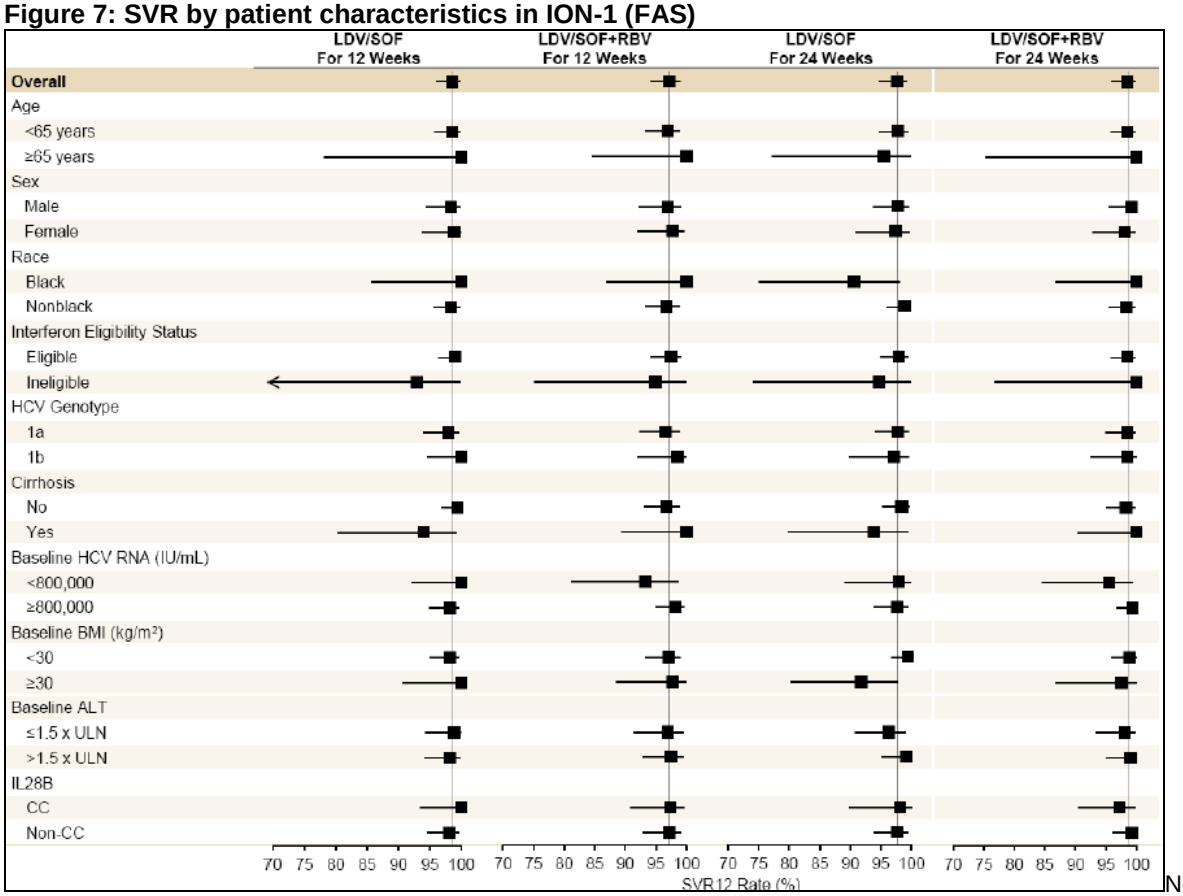
The SVR12 rates in all four treatment groups in ION-1 ranged from 97–99% (Table 22) and were superior to the historical rate of 60% ($p<0.001$ for all comparisons). No additional benefit was observed with the addition of RBV to the LDV/SOF regimen or with extension of treatment duration from 12 to 24 weeks.

Subgroup analysis

In the subgroup analysis including patients with characteristics historically associated with a poor response to treatment, high SVR12 rates were observed. These rates were similar to those patients without these characteristics (Figure 7). The SVR12 rates in the four treatment groups ranged from 94 to 100% among patient with cirrhosis, 97 to 99% among patients with HCV GT1a infection, 97 to 100% among patients with HCV GT1b infection, 97 to 99% among patients with a non-CC IL28B allele, and 91 to 100% among black patients. Based on SVR12 rate (Table 22), the majority of patients with compensated cirrhosis can be cured with 12 weeks treatment (SVR12 94%) with minimal additional benefit from extending treatment to 24 weeks (SVR12 97%).

Of the 865 patients in the FAS (randomised and received at least one dose of study drug), 850 achieved SVR12. Of the 15 patients that did not achieve SVR12, only two relapsed following completion of therapy (one cirrhotic patient receiving 12 weeks LDV/SOF and one cirrhotic patient receiving 24 weeks LDV/SOF), one experienced virologic failure on treatment (associated with a period of non-compliance), three withdrew consent and 9 were lost to follow-up. In an mFAS analysis, patients who withdrew consent or were lost to follow-up were excluded. The results observed in the mFAS analysis were similar to the results observed in the FAS analysis (Figure 7).

Figure 7: SVR by patient characteristics in ION-1 (FAS)



Note: The position of the square indicates the SVR12 in each subgroup; the horizontal lines indicate 95% CI; the vertical lines represent the overall SVR12 rate in each treatment group.
Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CI, confidence intervals; HCV, hepatitis C virus; IU, international unit; LDV, ledipasvir; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response; ULN, upper limit of the normal range.

Secondary efficacy results

Proportion of patients with SVR4 and SVR24

The SVR4 rates ranged from 98–99% across all four treatment groups. SVR24 rates ranged from 97–99% across all four treatment groups (Table 22). All patients who achieved an SVR12 also achieved an SVR24.

Proportion of patients with HCV RNA<LLOQ on treatment

A summary of the proportion of patients with HCV<LLOQ on treatment at weeks 2, 4, and 12 in ION-1 is presented in Table 22. As early as week 2, >80% of patients in each treatment group had achieved HCV RNA<LLOQ, indicating a very rapid virologic response to the study drugs.

HCV RNA change from baseline

HCV RNA levels declined rapidly in all four treatment groups and were similar across groups, irrespective of RBV inclusion in the treatment regimen. After 1 week, mean (SD) changes from baseline ranged from [redacted] $\log_{10}$ IU/mL across all groups. The decreases in HCV RNA levels were maintained from week 2 through to week 8 with mean changes from baseline ranging from [redacted] $\log_{10}$ IU/mL.

Proportion of patients with virologic failure

Only three patients had virologic failure during or after finishing treatment in ION-1 (Table 22). The plasma concentrations of LDV and GS-331007 (the main circulating metabolite of SOF) in one of these patients suggested non-compliance to the treatment regimen (LDV/SOF 24 weeks) as a possible cause of on-treatment virologic failure. The remaining two patients had virologic relapse after finishing treatment; one was a 56 year old white man with HCV GT1a infection who received 12 weeks LDV/SOF and had a relapse by post-treatment week 4, and the other was a 65 year old black man with GT1b infection who received 24 weeks LDV/SOF and had relapse between post-treatment week 4 and 12. Both of these patients had cirrhosis.

Development of resistance

At baseline, variants associated with resistance to NS5A inhibitors were detected by deep sequencing in 140 of 861 (16%) patients, 136 (97%) of whom achieved SVR12. This demonstrates that the presence of NS5A resistance-associated variants at baseline does not affect response to treatment with LDV/SOF.

Of the three patients with virologic failure, the two who relapsed had NS5A-resistant variants at baseline. At the time of virologic failure viral samples from all three patients had NS5A-resistant variants; L31M variant in the patient with HCV GT1a infection and Y93H variant in the two patients with HCV GT1b infection. None of the samples from patients with virologic failure showed evidence of mutations conferring resistance to sofosbuvir

Other endpoints of interest

ALT normalisation

The proportion of patients with ALT>ULN at [redacted] in the four treatment groups [redacted] Normalisation of ALT (defined as ALT≤ULN at each visit) was observed in most of these patients by the end of treatment (12 week: [redacted]% and [redacted]% in LDV/SOF and LDV/SOF+RBV groups, respectively; 24 weeks: [redacted]% and [redacted]%), coincident with suppression of viral replication.

HRQL

Four HRQL questionnaires were used in ION-1: SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C. At the time of post-treatment questionnaire completion, patients were unaware of whether they had achieved SVR or not. A summary of the HRQL outcomes are presented in Table 23.

Overall results from the HRQL questionnaires indicated that the LDV/SOF groups did not experience a statistically significant worsening in HRQL between baseline and end of treatment for most responses for the SF-36, FACIT-F and WPAI:Hep C questionnaires. In contrast, a statistically significant ($p<0.05$) worsening in HRQL was observed with the LDV/SOF+RBV groups while on treatment. The mean scores for all scales improved from end of treatment to 12 and 24 weeks post-treatment.

Table 23: Summary of HRQL outcomes (ION-1)

Instrument	BL Mean (SD)	EOT Mean (SD)	PT Week 12 Mean (SD)	BL Mean (SD)	EOT Mean (SD)	PT Week 12 Mean (SD)	BL Mean (SD)	EOT Mean (SD)	PT Week 12 Mean (SD)	BL Mean (SD)	EOT Mean (SD)	PT Week 12 Mean (SD)
	LDV+SOF 12 weeks (N=162)			LDV/SOF+RBV 12 weeks (N=165)			LDV/SOF 24 weeks (n=165)			LDV/SOF+RBV 24 weeks (n=166)		
SF-36, Physical component	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36, Mental component	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LDV+SOF 12 weeks (N=214)			LDV/SOF+RBV 12 weeks (N=217)			LDV/SOF 24 weeks (n=217)			LDV/SOF+RBV 24 weeks (n=217)		
CLDQ-HCV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACIT-F Total score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI, percentage of overall work impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI, percentage of activity impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BL, baseline; CLDQ-HCV, Chronic Liver Disease Questionnaire-Hepatitis C Virus; EOT, end of treatment; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HRQL, health related quality of life; LDV, ledipasvir; PT, post-treatment; RBV, ribavirin; SD, standard deviation; SF-36, Short Form Health Survey; SOF, sofosbuvir; WPAI, Work Productivity and Activity Impairment.

[redacted]

Note: For SF-36, CLDQ-HCV, and FACIT-F total score: a higher value indicates better quality of life outcome. For WPAI, percentage of overall work impairment and WPAI, percentage of activity impairment: a lower value indicated better quality of life

Conclusion (ION-1)

LDV/SOF, administered as an STR once daily for 12 weeks to HCV GT1 treatment naïve patients resulted in consistently high SVR12 rates (94–99%), irrespective of presence or absence of cirrhosis.

Overall, no additional benefit was observed with the addition of RBV or with the extension of treatment duration to 24 weeks.

Treatment with LDV/SOF led to all patients achieving undetectable HCV RNA on-treatment.

Of 865 patients in the FAS, 15 patients did not achieve SVR12; of those the majority were actually lost to follow up (n=9) or withdrew consent (n=3), with only one experiencing virologic failure on treatment and two relapsing following completion of therapy. All three of the patients with virologic failure had NS5A resistance-associated variants at the time of virologic failure. However, the presence of NS5A resistance-associated variants at baseline did not affect response to treatment with LDV/SOF. There was no evidence of mutations conferring resistance to sofosbuvir.

HRQL was assessed using the SF-36, CLDQ-HCV, FACIT-F and WPAI: Hep C questionnaires. Patients treated with LDV/SOF experienced no decrements in HRQL while on treatment and the mean scores of all scales improved from the end of treatment to post-treatment week 12 and 24.

6.5.5 *Study GS-US-337-0108 (ION-3): HCV GT1 treatment naïve non-cirrhotic*

Primary and secondary efficacy results for ION-3 are summarised in Table 24. Results presented are from the final CSR. They differ from the NEJM publication because of two patients for whom the post-treatment week 12 visit was pending and therefore they were considered to have not achieved SVR12 at the time of publication and were categorised as lost to follow-up. In the final analysis, both of these patients had HCV <LLOQ at the post-treatment week 12 and 24 visits.

Table 24: Summary of response during and after treatment in ION-3 (FAS

Response	8 week		12 week
	LDV/SOF (N=215)	LDV/SOF+RBV (N=216)	LDV/SOF (N=216)
HCV RNA<LLOQ			
During treatment, n/N (%)†			
At week 2	190/215 (88)	195/214 (91)	197/216 (91)
95% CI	[redacted]	[redacted]	[redacted]
At week 4	215/215 (100)	211/213 (99)	216/216 (100)
95% CI	[redacted]	[redacted]	[redacted]
Post-treatment, n (%)			
At week 4 (SVR4)	207 (96.3)	205 (94.9)	208 (96.3)
95% CI	[redacted]	[redacted]	[redacted]
At week 12 (SVR12)	202 (94.0)	201 (93.1)	208 (96.3)
95% CI	89.9–96.7	88.8–96.1	92.8–98.4
Virologic failure during treatment, relapse, lost to follow up or consent withdrawals			
Virologic failure during treatment, n	0	0	0
Relapse, n (%)	11 (5)	9 (4)	3 (1)
Lost to follow-up, n	1 (0.5)	5 (2.3)	5 (2.3)
Withdrew consent, n	1 (0.5)	1 (0.5)	0

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; LLOQ, lower limit of quantitation; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response
† Data are shown for patients for whom HCV RNA results were available.

Primary efficacy results: SVR12

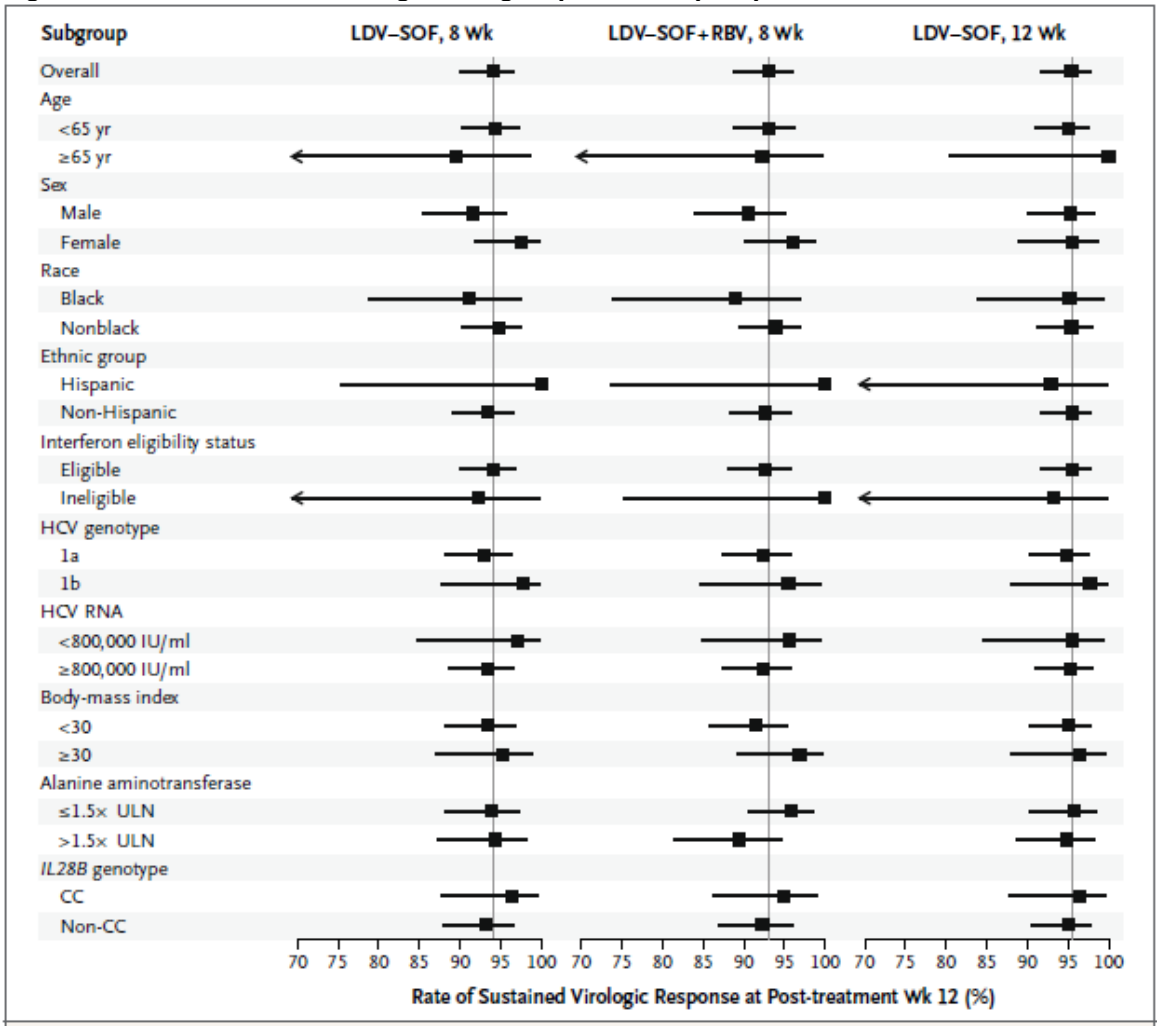
Primary analysis

The SVR12 rates in all three treatment groups in ION-3 ranged from 93–96% (Table 24) and were statistically significant and superior to the historical rate of 60% (p<0.001 for all comparisons).

Subgroup analysis

The rates of SVR12 in pre-specified subgroups across the three treatment groups were similar to those observed in the overall population. Patients with characteristics historically associated with poor response to IFN-based treatment had SVR12 rates similar to patients without these characteristics. The SVR12 rates in patients who received 8 weeks of LDV/SOF ranged from 89–100% in all subgroups.

Figure 8: SVR12 rates according to subgroup in ION-3 (FAS)



Note: The position of the square indicates the SVR12 in each subgroup; the horizontal lines indicate 95% CI; the vertical lines represent the overall SVR12 rate in each treatment group.
Abbreviations: HCV, hepatitis C virus; LDV, ledipasvir; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; ULN, upper limit of the normal range.

Secondary efficacy results

Inter-group comparison of SVR12

The SVR12 rate among patients who received 8 weeks of LDV/SOF was non-inferior to the SVR12 rates among patients in the other two treatment groups (Table 25).

Table 25: Differences in proportions of patients with SVR12 between treatment groups (FAS)

	p-value	Proportion difference, % (CI)
LDV/SOF+RBV 8 weeks vs SOF/LDV 12 weeks	[redacted]	[redacted]
LDV/SOF 8 weeks vs LDV/SOF 12 weeks	[redacted]	[redacted]
LDV/SOF 8 weeks vs LDV/SOF+RBV 8 weeks	[redacted]	[redacted]

Abbreviations: CI, confidence interval; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.
† 97.5% CI; ‡ 95% CI.

Proportion of patients with SVR4 and SVR24

SVR4 rates ranged from 95–96% across the three treatment groups (Table 24). SVR24 was achieved by 93–96% of patients across the three treatment groups. All patients who achieved an SVR12 also achieved an SVR24.

Proportion of patients with HCV RNA<LLOQ on treatment

A summary of the proportion of patients with HCV<LLOQ on treatment at weeks 2 and 4 in ION-3 is presented in Table 24. As early as week 2, >88% of patients in each treatment group had achieved HCV RNA<LLOQ indicating a very rapid virologic response to the study drugs.

HCV RNA change from baseline

HCV RNA levels declined rapidly in all three treatment groups and were similar across groups, irrespective of RBV inclusion in the treatment regimen. After 1 week, mean (SD) changes from baseline ranged from [redacted] log_{10} IU/mL across all groups. The decreases in HCV RNA levels were maintained from week 2 through to week 8 with mean changes from baseline ranging from [redacted] log_{10} IU/mL.

Proportion of patients with virologic failure

Overall, there were no virologic failures on treatment whilst 23 patients had a virologic relapse after the end of treatment (Table 24). The remaining 13 patients who did not achieve SVR12 were either lost to follow up (n=11) or withdrew consent (n=2).

Development of resistance

At baseline, NS5A resistance-associated variants were detected by deep sequencing in 116 (18%) of the 647 patients. Of these, 104 (90%) achieved SVR12. Of the 23 patients who had a relapse, 15 had NS5A resistance-associated variants at the time of relapse and eight did not. Of the 15 that had NS5A resistance-associated variants at relapse, nine had the variants at baseline and six did not.

The NS5B S282T variant, which is associated with reduced susceptibility to sofosbuvir, was not detected in any patient at baseline or at the time of virologic failure.

Other endpoints of interest

ALT normalisation

The proportion of patients with ALT>ULN [redacted] in the three treatment groups [redacted]Normalisation of ALT (defined as ALT≤ULN at each visit) was observed in most of these patients by the end of treatment [redacted]coincident with suppression of viral replication.

HRQL

Four HRQL questionnaires were used in ION-3: SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C. A summary of the outcomes are presented in Table 26.

Overall results indicated that the LDV/SOF groups did not experience a statistically significant worsening in HRQL for most responses for the SF-36, FACIT F and WPAI: Hep C questionnaires between baseline and end of treatment. In contrast, a statistically significant ($p<0.05$) worsening in HRQL was observed with the LDV/SOF+RBV groups while on-treatment. The mean scores for most scales improved from end of treatment to 12 and 24 weeks post-treatment.

In addition, persistent statistically significant between-treatment differences in mean changes from baseline for the SF-36 mental component score were observed between the LDV/SOF 8 week and LDV/SOF+RBV 8 week treatment groups at post-treatment week 4 and 12, although this was not maintained to week 24. These results should be interpreted with caution as multiple endpoints were tested and the study was not powered to test these exploratory endpoints.

Table 26: Summary of HRQL outcomes (ION-3)

	LDV+SOF 8 weeks (N=215)			LDV/SOF+RBV 8 weeks (N=216)			LDV/SOF 12 weeks (N=216)		
Instrument	**BL Mean (SD)**	**EOT Mean (SD)**	**PT Week 12 Mean (SD)**	**BL Mean (SD)**	**EOT Mean (SD)**	**PT Week 12 Mean (SD)**	**BL Mean (SD)**	**EOT Mean (SD)**	**PT Week 12 Mean (SD)**
SF-36, Physical component	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36, Mental component	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CLDQ-HCV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACIT-F Total score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI, percentage of overall work impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI, percentage of activity impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BL, baseline; CLDQ-HCV, Chronic Liver Disease Questionnaire-Hepatitis C Virus; EOT, end of treatment; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HRQL, health related quality of life; LDV, ledipasvir; PT, post-treatment; RBV, ribavirin; SD, standard deviation; SF-36, Short Form Health Survey; SOF, sofosbuvir; WPAI, Work Productivity and Activity Impairment.

[redacted]

Note: For SF-36, CLDQ-HCV, and FACIT-F total score: a higher value indicates better quality of life outcome. For WPAI, percentage of overall work impairment and WPAI, percentage of activity impairment: a lower value indicated better quality of life

Analysis of factors associated with relapse

A post-hoc analysis of patients from the ION-3 study was undertaken to investigate factors that might be predictive of relapse following 8 weeks treatment with LDV/SOF. With 8 weeks LDV/SOF a relapse rate of 2% was observed for patients with a baseline HCV RNA of <6 million IU/mL. The corresponding SVR was 97% (119/123), compared with 96% (126/131) with 12 weeks LDV/SOF for those with baseline HCV RNA of <6 million IU/mL. For patients with baseline HCV RNA ≥6 million IU/mL, a relapse rate of 10% was observed with 8 weeks LDV/SOF and 1% with 12 weeks LDV/SOF (Table 27). These data support the use of 8 weeks of treatment for non-cirrhotic naïve GT1 patients with a baseline viral load of <6 million IU/mL.

Table 27: Relapse rates by baseline viral load in ION-3, virologic failure population‡

	LDV/SOF 8 weeks (n=213)	**LDV/SOF+RBV 8 weeks (n=210)**	**LDV/SOF 12 weeks (n=211)**
Relapse rates by baseline HCV RNA, n/N (%)†			
HCV RNA < 6 million IU/mL	2/121 (2)	3/136 (2)	2/128 (2)
HCV RNA ≥ 6 million IU/mL	9/92 (10)	6/74 (8)	1/83 (1)

Abbreviations: HCV, hepatitis C virus; LDV, ledipasvir; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir.
† HCV RNA values were determined using the Roche TaqMan Assay; a patient's HCV RNA may vary from visit to visit.
‡ Patients lost to follow up or who withdrew consent excluded.

Conclusion (ION-3)

LDV/SOF, administered as an STR once daily for 8 weeks to HCV GT1 treatment naive patients without cirrhosis, resulted in high SVR12 rates (94%).

The addition of RBV to the treatment regimen or extending treatment duration to 12 weeks did not increase the observed SVR12 rate overall. However, in a post hoc analysis the baseline viral load was analysed to determine risk of relapse with the 8 week versus the 12 week regimen. The analysis showed that in patients with a viral load of <6 million IU/ml, relapse rates were comparable for 8 and 12 week regimen, at ~2%. However with viral load of >6 million the relapse rate was higher with 8 weeks regimen compared with 12 weeks (10 vs 1%). This analysis thus supports the use of 8 weeks LDV/SOF for GT1 treatment naïve patients without cirrhosis who have a baseline viral load of <6 million IU/mL, and 12 weeks LDV/SOF in those with a baseline viral load ≥6 million IU/mL.

LDV/SOF treatment led to a very rapid virologic response, with all patients achieving an on-treatment response.

In total, 23 out of 647 patients had virologic relapse and 15 of them had NS5A resistance-associated variants at the time of relapse. However, 104 (90%) of the 116 in whom NS5A resistance-associated variants were detected achieved SVR12, indicating that presence of NS5A resistance-associated variants at baseline did not affect response to LDV/SOF treatment. There was no evidence of mutations conferring resistance to sofosbuvir.

HRQL was assessed using the SF-36, CLDQ-HCV, FACIT-F and WPAI: Hep C questionnaires. Patients treated with LDV/SOF experienced no decrements in HRQL while on treatment and the mean scores of most scales improved from the end of treatment to post-treatment week 12 and 24.

6.5.6 *Study GS-US-337-0109 (ION-2): HCV GT1 treatment experienced*

Primary and secondary efficacy results for ION-2 are summarised in Table 28.

Table 28: Summary of response during and after treatment in ION-2 (FAS)

Response	12 week		24 week	
	LDV/SOF (N=109)	LDV/SOF+RBV (N=111)	LDV/SOF (N=109)	LDV/SOF+RBV (N=111)
HCV RNA<LLOQ				
During treatment, n/N (%)				
At week 2	89/109 (82)	92/111 (83)	89/109 (82)	93/111 (84)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
At week 4	109/109 (100)	110/111 (99)	108/109 (99)	110/111 (99)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
At week 12	108/109 (99)	111/111 (100)	109/109 (100)	110/110 (100)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Post-treatment, n (%)				
At week 4 (SVR4)	103 (94.5)	107 (96.4)	109 (100)	110 (99.1)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
At week 12 (SVR12)	102 (93.6)	107 (96.4)	108 (99.1)†	110 (99.1)
95% CI	87.2–97.4	91.0–99.0	95.0–100	95.1–100
SVR12 in specific subgroups, n/N (%)				
Non-cirrhotic patients	83/87 (95.4)	89/89 (100)	86/87 (98.9)	88/89 (98.9)
95% CI	88.6–98.7	95.9–100	93.8–100	93.9–100
Cirrhotic patients	19/22 (86.4)	18/22 (81.8)	22/22 (100)	22/22 (100)
95% CI	65.1–97.1	59.7–94.8	84.6–100	84.6–100
PEG-IFN+RBV failures	40/43 (93.0)	45/47 (95.7)	58/58 (100)	58/59 (98.3)
95% CI	80.9–98.5	85.5–99.5	93.8–100	90.9–100
PI+PEG-IFN+RBV failures	62/66 (93.9)	62/64 (96.9)	49/50 (98.0)	51/51 (100)
95% CI	85.2–98.3	89.2–99.6	89.4–99.9	93.0–100
Virologic failure during treatment, relapse, lost to follow up or consent withdrawals				
Virologic failure during treatment, n (%)	0	0	0	1 (1)‡
Relapse, n (%)	7 (6)	4 (4)	0	0
Withdrew consent	0	0	1 (1)	0

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; LLOQ, lower limit of quantitation; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir; SVR, sustained virologic response.
† One of the 109 patients who received 24 weeks of LDV/SOF withdrew consent after the post-treatment week 4 visit; at this visit, HCV RNA <25 IU/mL
‡ This patient did not adhere to the study treatment as indicated by plasma concentrations of LDV and GS-331007 (the predominant circulating metabolite of SOF) that were below or near the LLOQ at weeks 2, 4, and 6 during treatment.

Primary efficacy results: SVR12

Primary analysis

The SVR12 rates in all four treatment groups in ION-2 ranged from 93.6–99.1% (Table 28) and were superior to the historical rate of 25% (p<0.001 for all comparisons). Addition of RBV did not appreciably enhance the observed SVR12 rates. [redacted]

Subgroup analysis

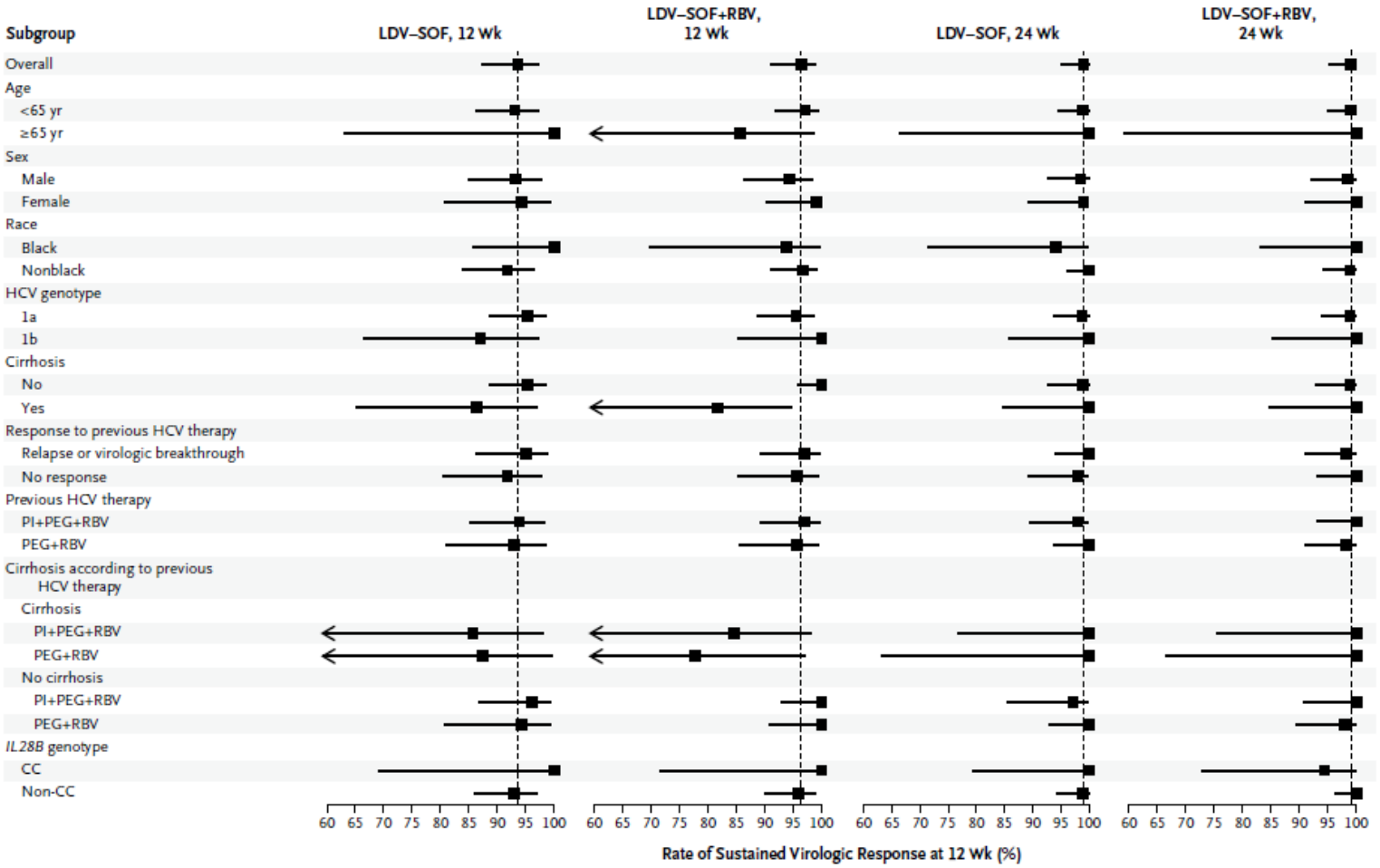
SVR12 rates were similar in all four treatment groups among patients infected with HCV GT1a (95.3–98.9%) and those with HCV GT1b (87.0–100%), and among patients who had no response to prior treatment (91.8–100%) and those who had prior virologic relapse or breakthrough (95.0–100%; Figure 9).

SVR12 rates were also similar among patients who had been previously treated with PEG-IFN+RBV (93.0–100%) and those who had previously been treated with PI+PEG-IFN+RBV (93.9–100%) (Table 28).

In patients with cirrhosis there was a significant difference (p=0.007) in SVR12 rates between the 12-week (82-86% SVR12) and 24-week (100% SVR12) treatment regimen groups. However, this observation is preliminary, since the study was not powered for intergroup comparisons. Based on multivariate exact logistic-regression analysis the absence of cirrhosis was the only baseline factor associated with a significant increase in SVR12 rates.

With 12 weeks LDV/SOF, the SVR12 rate was 85.7% for previous PI+PEG-IFN+RBV failures with cirrhosis and 87.5% for previous PEG-IFN+RBV failures with cirrhosis (Table 29). For both populations, 100% SVR12 was achieved with 24 weeks LDV/SOF.

Figure 9: SVR12 rates according to subgroup in ION-2 (FAS)



Note: The position of the square indicates the SVR12 in each subgroup; the horizontal lines indicate 95% CI; dashed vertical lines represent the overall SVR12 rate in each treatment group.
Abbreviations: HCV, hepatitis C virus; LDV, ledipasvir; PEG, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; SOF, sofosbuvir.

Table 29: SVR12 rate categorised by prior HCV therapy and presence of cirrhosis in ION-2 (FAS)

Cirrhosis	Prior HCV therapy	12 week		24 week	
		LDV/SOF	LDV/SOF+RBV	LDV/SOF	LDV/SOF+RBV
No, n/N (%; 95% CI)	PEG-IFN+RBV	33/35 (94.3; 80.8–99.3)	38/38 (100; 90.7–100)	50/50 (100; 92.9–100)	49/50 (98.0; 89.4–99.9)
	PI+PEG-IFN+RBV	50/52 (96.2; 86.8–99.5)	51/51 (100; 93.0–100)	35/36 (97.2; 85.5–99.9)	38/38 (100; 90.7–100)
Yes, n/N (%; 95% CI)	PEG-IFN+RBV	7/8 (87.5; 47.3–99.7)	7/9 (77.8; 40.0–97.2)	8/8 (100; 63.1–100)	9/9 (100; 66.4–100)
	PI+PEG-IFN+RBV	12/14 (85.7; 57.2–98.2)	11/13 (84.6; 54.6–98.1)	14/14 (100; 76.8–100)	13/13 (100; 75.3–100)

Abbreviations: CI, confidence interval; FAS, full analysis set; HCV, hepatitis C virus; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir

Secondary efficacy results

Proportion of patients with SVR4 and SVR24

SVR4 rates ranged from 94.5–100% across all four treatment groups (Table 28). All the patients that had SVR at post-treatment week 12 also had SVR at post-treatment week 24.

Proportion of patients with HCV RNA<LLOQ on treatment

A summary of the proportion of patients with HCV<LLOQ on treatment at weeks 2, 4, and 12 in ION-2 is presented in Table 28. As early as week 2, >80% of patients in each treatment group had achieved HCV RNA<LLOQ indicating a very rapid virologic response to the study drugs.

HCV RNA change from baseline

HCV RNA levels declined rapidly in all four treatment groups and were similar across groups, irrespective of RBV inclusion in the treatment regimen. After 1 week, mean (SD) changes from baseline ranged from [redacted] $\log_{10}$ IU/mL across all groups. The decreases in HCV RNA levels were maintained from week 2 through to week 8 with mean changes from baseline ranging from [redacted] $\log_{10}$ IU/mL.

Proportion of patients with virologic failure

Overall, 11 of the 440 (2%) patients had a virologic relapse after the end of treatment, all of whom were in the 12 week treatment groups (Table 28); 10 had a relapse by post-treatment week 4 and one had a relapse between post-treatment weeks 4 and 12.

Two patients in the 24 week treatment groups did not achieve SVR12. One patient had virologic rebound during treatment. This patient had low-to-undetectable plasma concentrations of LDV and GS-331007 (circulating metabolite of SOF) at weeks 2, 4, and 6, which suggested non-compliance to the study regimen. The other patient withdrew consent after the post-treatment week 4 visit; HCV RNA was <25 IU/mL at this visit, indicative of SVR4.

Development of resistance

Variants associated with resistance to NS5A were detected at baseline in 62 of 439 (14%) patients; 55 (89%) of them had SVR12. Variants associated with resistance to NS3/4A PIs were detected at baseline in 163 of 228 (71%) patients who underwent successful sequencing and had prior treatment with a PI regimen; 159 (98%) of them had SVR12.

Four (57%) of the seven patients who experienced relapse following 12 weeks LDV/SOF had NS5A resistant variants at baseline. Two (50%) of the four patients who experienced relapse following 12 weeks LDV/SOF+RBV also had NS5A resistant variants at baseline. All 11 patients who had a relapse had detectable levels of NS5A resistant variants at the time of relapse.

The NS5B-resistant variant S282T, which reduces susceptibility to sofosbuvir, was not detected in any patient at baseline or at any time thereafter, confirming the high genetic barrier to the development of resistance that has been observed in previous studies of sofosbuvir.

Other endpoints of interest

ALT normalisation

The proportion of patients with ALT>ULN [redacted] in the four treatment groups [redacted] Normalisation of ALT (defined as ALT≤ULN at each visit) was observed in most of these patients by the end of treatment [redacted]

[redacted] coincident with suppression of viral replication.

HRQL

Four HRQL questionnaires were used in ION-1: SF-36, CLDQ-HCV, FACIT-F, and WPAI: Hep C. A summary of the outcomes are presented in Table 30.

Overall results from the HRQL questionnaires indicated that the LDV/SOF groups did not experience a statistically significant worsening in HRQL (SF-36 domains of physical functioning, role physical, vitality, social functioning [24 Week group only], role emotional, and mental component [24 week group only] and the FACIT-F trial outcome index [24 week group only]) between baseline and end of treatment. In contrast, a statistically significant ($p<0.05$) worsening in HRQL was observed with the LDV/SOF+RBV groups while on-treatment. The mean scores for most scales improved from end of treatment to 24 weeks post-treatment.

Table 30: Summary of HRQL outcomes (ION-2)

	LDV+SOF 12 weeks (N=109)			LDV/SOF+RBV 12 weeks (N=111)			LDV/SOF 24 weeks (N=109)			LDV/SOF+RBV 24 weeks (N=111)		
Instrument	**BL Mean (SD)**	**EOT Mean (SD)**	**PT Week 12 Mean (SD)**	**BL Mean (SD)**	**EOT Mean (SD)**	**PT Week 12 Mean (SD)**	**BL Mean (SD)**	**EOT Mean (SD)**	**PT Week 12 Mean (SD)**	**BL Mean (SD)**	**EOT Mean (SD)**	**PT Week 12 Mean (SD)**
SF-36, Physical component	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SF-36, Mental component	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CLDQ-HCV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FACIT-F Total score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI, percentage of overall work impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WPAI, percentage of activity impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BL, baseline; CLDQ-HCV, Chronic Liver Disease Questionnaire-Hepatitis C Virus; EOT, end of treatment; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HRQL, health related quality of life; LDV, ledipasvir; PT, post-treatment; RBV, ribavirin; SD, standard deviation; SF-36, Short Form Health Survey; SOF, sofosbuvir; WPAI, Work Productivity and Activity Impairment.

[redacted]

Note: For SF-36, CLDQ-HCV, and FACIT-F total score: a higher value indicates better quality of life outcome. For WPAI, percentage of overall work impairment and WPAI, percentage of activity impairment: a lower value indicated better quality of life

Conclusion (ION-2)

LDV/SOF, administered as a once daily STR for 12 weeks to HCV GT1 treatment experienced patients, including those who had previously failed the existing PI-based standard of care, resulted in a high SVR12 rate (94%) irrespective of HCV GT1 subtype.

The SVR12 rates were similar, with widely overlapping confidence intervals, between patients who received 12 weeks of treatment and those who received 24 weeks; and also between those that received LDV/SOF and those receiving LDV/SOF+RBV.

SVR12 rates were similar between the LDV/SOF 12 and 24 week regimens, irrespective of previous treatment (PEG-IFN+RBV or PI+PEG-IFN+RBV).

[redacted] Although the SVR12 rate was lower among patients with cirrhosis when treated with 12 weeks versus 24 weeks, the majority of patients with cirrhosis achieved SVR12 (19/22) after 12 weeks of treatment.

LDV/SOF for 12 weeks led to a very rapid virologic response, with all patients achieving undetectable HCV RNA on-treatment.

In total, 12 patients had virologic failure and 11 of them had NS5A resistance-associated variants at the time of failure. The presence of NS5A resistance-associated variants at baseline did not affect response to treatment with LDV/SOF. There was no evidence of mutations conferring resistance to sofosbuvir.

HRQL was assessed using the SF-36, CLDQ-HCV, FACIT-F and WPAI: Hep C questionnaires. Patients treated with LDV/SOF experienced no decrements in HRQL while on treatment and the mean scores of most scales improved from the end of treatment to post-treatment week 24.

6.5.7 *Supporting studies*

6.5.7.1 HCV GT4

Data are available from two studies to support the use of LDV/SOF in GT4 patients. This is an updated analysis to the data presented within the SPC.

Two patients with GT4 HCV infection were enrolled into the ION-1 study. One patient received LDV/SOF for 12 weeks; another patient received LDV/SOF+RBV for 24 weeks. Both achieved SVR12 (see SPC). In SYNERGY, an ongoing Phase II study evaluating LDV/SOF for 12 weeks (See Section 6.5.7.8 for description of other arms from SYNERGY), 21 GT4 patients are being treated. Post-treatment week 12 data are available for [redacted] patients: [redacted] have achieved SVR12; [redacted] (data due to be reported at AASLD Nov 2014, abstract accepted (95)).

6.5.7.2 Study GS-US-337-0122 (ELECTRON-2): HCV GT1 treatment experienced (SOF failures), HCV GT1 decompensated cirrhosis, HCV GT3 treatment naïve and treatment experienced, HCV GT6 treatment naïve and treatment experienced

Methods (ELECTRON-2)

Citation	Gane et al, 2014 (76). Additional information taken from the interim synoptic CSR for GT3 treatment naïve (77), AASLD 2014 abstract (78)and clinical study protocol (98).
Objectives	To evaluate the safety and efficacy of LDV/SOF±RBV for 12 weeks in difficult-to-treat patient populations. Populations included were those who had previously failed treatment with a sofosbuvir-based regimen, those with decompensated cirrhosis, and those with HCV GT3 or GT6 infection.
Location	2 centres in New Zealand
Design	Ongoing, open-label Phase II study. Only the GT3 treatment naïve arms were randomised. Treatment groups: • LDV/SOF+RBV (n=19): Treatment experienced, HCV GT1 infected patients who were previously treated with SOF regimens but failed to achieve SVR12 • LDV/SOF (n=20): Treatment naïve, HCV GT1 infected patients with decompensated cirrhosis (CPT class B) • LDV/SOF (n=25): Treatment naïve, HCV GT3 infected patients. • LDV/SOF+RBV (n=26): Treatment naïve, HCV GT3 infected patients. • LDV/SOF+RBV (n=50): Treatment experienced, HCV GT3 infected patients. • LDV/SOF+RBV (n=25): Treatment naïve and treatment experienced, HCV GT6 infected patients (data for this arm of the study is not presented in this submission).
Treatment period	12 weeks for all treatment groups.
Key inclusion criteria and exclusion criteria for all patients	[redacted]

	[redacted]
Additional inclusion and exclusion criteria for each group	[redacted]

	[redacted]
Efficacy outcomes	Primary endpoint: SVR12. Secondary endpoints: • The proportion of patients with HCV RNA <LLOQ while on-treatment and at 2, 4, 8, 16 and 24 weeks after discontinuation of therapy. • The proportion of subjects with on-treatment virologic failure and relapse. Additional efficacy endpoints of interest include HCV RNA change from baseline and ALT normalisation.
Populations analysed	The analysis set for antiviral activity analyses was the FAS, which included patients who were randomised into the study and received at least one dose of study drugs.
Statistical information	SVR12 rates calculated with the 2-sided 95% exact CI using the binomial distribution. No statistical hypothesis testing was performed. Patients for whom no HCV RNA values were obtained after the last dose of study drug were considered treatment failures for the SVR12 endpoint.

Patient disposition, demographics and baseline characteristics (ELECTRON-2)

Data describing the 50 HCV GT3 treatment experienced patients are still being analysed and should be available in November.

As patients with HCV GT6 are not included in this submission, the GT6 treatment arm, containing 25 patients, is not discussed further.

Ninety patients were enrolled in the HCV GT1 and GT3 treatment naïve arms. One patient with HCV GT3 infection (treatment naïve) discontinued due to AEs in the LDV/SOF group. Patient demographics and baseline characteristics are presented in Table 31.

Table 31: Patient demographics and baseline characteristics in ELECTRON-2

	GT1, prior SOF	GT1, CPT class B	GT3 treatment naïve	
	LDV/SOF+RBV n=19	LDV/SOF n=20	LDV/SOF n=25	LDV/SOF+RBV n=26
Mean age (range), years	55 (39–65)	56 (47–72)	43 (22–63)	48 (28–64)
Male, n (%)	13 (68)	17 (85)	13 (52)	11 (42)
White, n (%)	18 (95)	17 (85)	22 (88)	23 (88)
Mean BMI (range), kg/m^2	27 (19–38)	31 (20–50)	27 (19–37)	28 (18–42)
Cirrhosis	0	20 (100)	3 (12)	5 (19)
IL28B CC, n (%)	4 (21)	7 (35)	9 (36)	15 (58)
GT, n (%)				

	GT1, prior SOF	GT1, CPT class B	GT3 treatment naïve	
	LDV/SOF+RBV n=19	LDV/SOF n=20	LDV/SOF n=25	LDV/SOF+RBV n=26
1a	17 (89)	18 (90)	0	0
1b	2 (11)	2 (10)	0	0
3a	0	0	25 (100)	26 (100)
Mean HCV RNA (range), log10 IU/mL	6.3 (4.8–7.0)	6.0 (4.9–6.7)	6.3 (4.0–7.3)	6.3 (4.3–7.6)

Abbreviations: BMI, body mass index; CPT, Child Pugh Turcotte; GT, genotype; HCV, hepatitis C virus; LDV, ledipasvir; RBV, ribavirin; RNA, ribonucleic acid; SOF, sofosbuvir.

In the prior SOF-regimen failures group, all 19 patients had relapsed on prior SOF-therapy. Thirteen of the relapsed patients were treatment naïve prior to the previous SOF therapy; six were treatment experienced and were null responders to a previous therapy (Table 32). Of note, eight of the prior treatment naïve patients had received 6 weeks LDV/SOF+RBV as their first SOF-based regimen and were therefore being re-treated with the identical regimen, but for a longer duration, in this study (Table 32).

Table 32: Prior sofosbuvir-treated GT1 patients in ELECTRON-2

Treatment status prior to previous SOF regimen	Previous SOF regimen	n (%)
Treatment naive	LDV/SOF+RBV 6 weeks	8 (42)
	SOF+RBV 12 weeks	4 (21)
	GS-9669+SOF+RBV 12 week	1 (5)
Null responders	SOF+RBV 12 week	6 (32)

Abbreviations: LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

Efficacy results (ELECTRON-2)

SVR12 rates across the HCV GT1 and GT3 treatment naïve difficult-to-treat patient populations in this study ranged between 64-100% (Table 33).

- The 100% SVR12 rate in HCV GT1 prior SOF failures demonstrated that patients can be re-treated with a SOF-based regimen and achieve a cure.
- Patients with decompensated cirrhosis (CPT class B) currently have no effective treatment option; in this group 13/20 patients (65%) achieved SVR12 following treatment with LDV/SOF for 12 weeks.
- SVR12 rate in treatment naïve patients with HCV GT3 infection was 64% (n=16) when treated with LDV/SOF for 12 weeks. Of the nine patients in this group that did not achieve an SVR, eight relapsed and one discontinued due to AEs. Addition of RBV to the LDV/SOF regimen allowed an SVR12 rate of 100% to be achieved.

Table 33: Summary of efficacy results in ELECTRON-2

	GT1, prior SOF	GT1, CPT class B	GT3 treatment naïve	
	LDV/SOF+RBV n=19	LDV/SOF n=20	LDV/SOF n=25	LDV/SOF+RBV n=26
SVR12 rate, n (%)	19 (100)	13 (65)	16 (64)	26 (100)
95% CI	[redacted]	[redacted]	[redacted]	[redacted]

Relapse, n (%)	0	7 (35)	8 (32)	0
Discontinued due to AEs, n (%)	0	0	1 (4)	0

Abbreviations: AE, adverse events; CI, confidence interval; CPT, Child Pugh Turcotte; GT, genotype; HCV, hepatitis C virus; LDV, ledipasvir; NA, not available, RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response.

- An interim analysis has been undertaken for the 50 HCV GT3 treatment experienced patients enrolled in this ongoing study. SVR4 rates of 89% (25/28) and 77% (17/22) have been achieved in the non-cirrhotic and cirrhotic patients respectively.

Conclusion (ELECTRON-2)

LDV/SOF regimens for 12 weeks are safe and effective IFN-free treatments for difficult-to-treat patient populations.

- In treatment naïve GT3 patients, LDV/SOF+RBV for 12 weeks resulted in a 100% SVR12 rate.
- LDV/SOF+RBV resulted in an SVR12 rate of 100% in previously SOF-treated GT1 patients, demonstrating that patients can be re-treated with, and achieve benefit from, a SOF-based regimen. The study specifically provides proof of concept that patients receiving a short course of LDV/SOF-based regimen (6 weeks) could be successfully re-treated with a longer duration LDV/SOF-based regimen (12 weeks).
- In patients with decompensated cirrhosis, for whom no effective treatment is available and who would normally go on to require a liver transplant, LDV/SOF for 12 weeks provided a cure (SVR12) in 65% of patients.
- In treatment experienced GT3 patients, SVR4 rates of 89% and 77% have been observed for those without, and with cirrhosis, respectively.

6.5.7.3 Study CO-US-337-0116 (ERADICATE): HCV GT1/HIV co-infected

Methods (ERADICATE)

Citation	Interim abbreviated CSR (80), [redacted] (81)
Objectives	The primary objective of the study was to assess the safety, tolerability, and efficacy of an FDC of LDV/SOF tablets for 12 weeks in HIV/HCV GT1 co-infected patients who were HCV treatment naïve.
Location	1 centre in USA
Design	Ongoing, open-label, non-randomised Phase IIb study. Treatment groups: • LDV/SOF in HCV treatment naïve, antiretroviral (ARV) untreated patients (n=13) • LDV/SOF in HCV treatment naïve, ARV treated patients (n=37)
Treatment period	12 weeks in all treatment groups
Key inclusion criteria and exclusion criteria	Eligible patients were infected with HCV GT1, naïve to HCV treatment, with stable HIV disease. Patients could be ARV therapy naïve with a CD4 T-lymphocyte count ≥500 cells/mL, stable CD4 count with HIV viral load <500 copies/mL or on ARVs with HIV RNA values of ≤50 copies/mL with a CD4 T-lymphocyte count ≥100 cells/µL. Patients on ARVs were required to have

	been receiving a stable treatment regimen for at least 8 weeks before screening. Acceptable ARVs were emtricitabine/tenofovir in combination with efavirenz, raltegravir, or rilpivirine. Patients with cirrhosis were excluded from this study.
Efficacy outcomes	Primary efficacy endpoint: SVR12 Secondary endpoints: Proportion of patients with unquantifiable HCV viral load at specified time points during and after treatment discontinuations due to AEs, safety laboratory changes and evaluation of HCV resistance mutations in the patient who relapsed. The trial is ongoing.
Populations analysed	All 50 patients that were enrolled in the study were included in the efficacy analysis.
Statistical information	In the primary efficacy analysis the SVR12 rate was compared to the assumed spontaneous rate of 5% using two-sided exact one-sample binomial test at a significance level of 0.05.

Patient disposition, demographics and baseline characteristics (ERADICATE)

Fifty HCV GT1 treatment naïve patients were enrolled. Patient demographics and baseline characteristics are presented in Table 34.

Table 34: Patient demographics and baseline characteristics in ERADICATE

	ARV untreated n=13	**ARV treated n=37**
Median age (IQR), years	59 [redacted]	58 [redacted]
Male, n (%)	7 (54)	30 (81)
Median BMI (IQR), kg/m^2	26 [redacted]	26 [redacted]
BMI ≥30, n (%)	[redacted]	[redacted]
Race or ethnicity, n (%)		
White	3 (13)	4 (11)
Black	10 (77)	32 (86)
Hispanic	0	1 (3)
Knodell HAI Fibrosis, n (%)		
0–2	8 (62)	29 (78)
3–4	5 (38)	8 (22)
HCV GT1 subtype, n (%)		
1a	9 (75)	30 (81)
1b	3 (25)	7 (19)
IL28B genotype, n (%)		
CC	[redacted]	[redacted]
CT	[redacted]	[redacted]
TT	[redacted]	[redacted]
Median baseline HCV RNA (IQR), $\log_{10}$ IU/mL	6.1 [redacted]	6.0 [redacted]
HCV RNA >800,000 IU/mL, n (%)	[redacted]	[redacted]
Median Baseline CD4 (IQR)	[redacted]	[redacted]

	ARV untreated n=13	ARV treated n=37
Antiretroviral use	0	37 (100)
Tenofovir/emtricitabine plus:		
Efavirenz	NA	15 (41)
Raltegravir	NA	10 (27)
Rilpivirine	NA	8 (21)
Raltegravir/rilpivirine	NA	3 (8)
Raltegravir/efavirenz	NA	1 (3)

Abbreviations: ARV, antiretroviral, BMI, body mass index; GT, genotype; HAI, histologic activity index, HCV, hepatitis C virus; NA, not applicable; RNA, ribonucleic acid.

Efficacy results (ERADICATE)

SVR12 was achieved in 98% (49/50) of HCV/HIV co-infected patients enrolled in the study. All (13/13) ARV naïve patients achieved SVR12 (Table 35). In ARV treated patients an SVR12 rate of 97% (36/37) was achieved, with one patient relapsing prior to post-treatment week 4, having had undetectable plasma HCV RNA at end of treatment. [redacted]

LDV/SOF for 12 weeks led to a rapid virologic response, with 100% of patients in both ARV treated and untreated groups achieving HCV<LLOQ by on-treatment week 4.

Table 35: SVR12 rates in ARV naïve and ARV treated patients – ERADICATE

	ARV naïve (n=13)	ARV treated (n=37)
SVR12, n/N (%; 95% CI)	13/13 (100; 75–100)	36/37 (97; 89–100)†

Abbreviations: ARV, antiretroviral, NR, not reported; SVR, sustained virologic response
† 1 patient had undetectable HCV RNA at the end of treatment but relapsed prior to post-treatment week 4.

Conclusion (ERADICATE)

LDV/SOF treatment for 12 weeks in HIV/HCV co-infected patients resulted in 98% (49/50) SVR12 overall: 100% SVR12 rate in ARV untreated patients and 97% SVR12 in ARV treated patients. This study shows that the STR of LDV/SOF can result in high rates of SVR in HIV/HCV co-infected patients, achieving similar results to those in mono-infected patients treated with the same regimen.

6.5.7.4 Study GS-US-337-0123 (SOLAR-1): Advanced liver disease/Post-liver transplant

This study is on-going and further data should be available in November.

Methods (SOLAR-1)

Citation	Information for SOLAR-1 has been taken from the clinical study protocol (82), two AASLD 2014 abstracts (83;84) and the SPC (99).
Objectives	Primary objectives: • To explore the antiviral efficacy of combination therapy with SOF/LDV + RBV for 12 or

	24 weeks in patients with advanced liver disease (either pre-liver transplant or not currently wait-listed) and post-liver transplant HCV patients, as measured by SVR12. • To evaluate the safety and tolerability of SOF/LDV + RBV administered for 12 or 24 weeks in each patient population.
Location	Approximately 30 centres in the US (planned).
Design	Multi-centre open label randomised study
Treatment period	12 and 24 weeks
Key inclusion criteria and exclusion criteria	[redacted]
Efficacy outcomes	[redacted]
Populations analysed	[redacted]
Statistical information	[redacted]

Preliminary efficacy results (SOLAR-1)

Preliminary data from the SOLAR-1 study are presented in Table 36. [redacted]

Table 36: Summary of response after treatment in SOLAR-1 (FAS)

	LDV/SOF+RBV 12 weeks [redacted]		**LDV/SOF+RBV 24 weeks** [redacted]	
	SVR4	SVR12	SVR4	SVR12
Pre-transplant				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-transplant				
METAVIR fibrosis F0-F3	96% (53/55)	96% (53/55)	[redacted]	[redacted]
CPT A†	96% (25/26)	96% (25/26)	[redacted]	[redacted]
CPT B†	[redacted]	[redacted]	[redacted]	[redacted]
CPT C†	100% (5/5)	60% (3/5)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations:CPT, Child Pugh Turcotte FAS, full analysis set; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response.

[redacted]

In patients treated pre-transplant, an SVR4 rate of [redacted] was achieved with LDV/SOF+RBV in patients with decompensated cirrhosis (CPT B or C) for both treatment durations studied (12 or 24 weeks), with an overall SVR12 rate of approximately [redacted] in those receiving 12 weeks LDV/SOF+RBV. [redacted] In post-liver transplant patients without decompensated liver disease, SVR4 rates were [redacted] for both treatment durations studied (12 or 24 weeks) and SVR12 rates with 12 weeks LDV/SOF+RBV were 96%. [redacted] In post-liver transplant patients with decompensated liver disease SVR4 rates were [redacted] for both treatment durations studied and the overall SVR12 rate with 12 weeks LDV/SOF+RBV is [redacted]

Conclusion (SOLAR-1)

Preliminary data shows that LDV/SOF+RBV (12 and 24 weeks) is highly effective in:

- patients with decompensated cirrhosis [redacted] patients who are post-liver transplant without decompensated cirrhosis_[redacted] patients who are post-liver transplant with decompensated cirrhosis_[redacted]

6.5.7.5 Study P7977-0523 (ELECTRON): HCV GT1 treatment naïve and GT1 treatment experienced, HCV GT1 patients with inherited blood disorders,

Data presented are from Gane et al, 2014 (85) and Stedman et al, 2014 (86), with additional information from the final synoptic CSR (87).

ELECTRON is a Phase II, multicentre, open-label, exploratory 12-week study to investigate the safety, tolerability, and pharmacokinetics/pharmacodynamics following oral administration of SOF in various combinations with established agents, including PEG-IFN and RBV) and investigational agents, including LDV. Note that in some arms LDV and SOF were administered as an FDC (LDV/SOF) and in others as single agents (LDV+SOF).

Various arms of the study have been reported to date, including several treatment arms of LDV+SOF+RBV or LDV/SOF±RBV for 12 weeks (85). These arms with smaller patient numbers support the evidence from the larger, pivotal Phase III ION studies reported in Sections 6.5.4–6.5.6. In summary, these arms demonstrate high cure rates (SVR12) with 12 week regimens in:

- GT1 treatment naive patients:
  - 100% (25/25) with LDV+SOF+RBV 12 weeks
- GT1 treatment experienced patients:
  - 100% (9/9) with LDV+SOF+RBV 12 weeks
- GT1 treatment experienced patients with cirrhosis:
  - 70% (7/10) with LDV/SOF 12 weeks
  - 100% (9/9) with LDV/SOF+RBV 12 weeks

A 6-week regimen of LDV/SOF+RBV in GT1 treatment naïve patients was also studied (providing an SVR12 of 68%) but this treatment duration does not form part of the marketing authorisation for LDV/SOF and so is not discussed further.

In addition, the ELECTRON study provides proof-of-concept data on a sub-group of patients with inherited blood disorders, a patient group known to be disproportionately affected by HCV (Stedman). Fourteen patients were enrolled and received LDV/SOF+RBV for 12 weeks. The mean age of patients was 54 years, mean BMI 27 kg/m^2, mean HCV RNA 6.5 $\log_{10}$ IU/mL, 86% of patients were male, 86% were white, 29% had IL28B CC, 71% were infected with GT1a, 7% had cirrhosis, and 21% were treatment experienced.

The primary endpoint, SVR12, was achieved by 14/14 patients (100%), demonstrating that HCV GT1 patients with an inherited bleeding disorder can successfully be treated with LDV/SOF+RBV for 12 weeks. All 14 patients achieved HCV RNA<LLOQ as early as week 4 of treatment, indicating a rapid response to treatment, which was maintained through to the end of treatment.

Conclusion (ELECTRON)

- 70% cure rate was achieved in CHC GT1 treatment experienced patients with cirrhosis following 12 weeks treatment with LDV/SOF.
- 100% cure rate was achieved in CHC GT1 patients with inherited blood disorders following 12 weeks treatment with LDV/SOF+RBV.

6.5.7.6 Study GS-US-337-0118 (LONESTAR): HCV GT1 treatment naïve and treatment experienced

Data presented are from Lawitz et al 2014 (90).

LONESTAR is a Phase II study providing initial data on treatment duration assessment (8 or 12 weeks) for LDV/SOF regimens in GT1 treatment naïve and treatment experienced patients. The larger, pivotal Phase III ION studies reported in sections 6.5.4–6.5.6 provide the key data in these populations and hence LONESTAR has not been reported in any detail in this submission. However, the study did show that overall 97 out of 100 patients achieved SVR12; 95–100% of GT1 treatment naïve patients without cirrhosis treated with LDV/SOF for 8 or 12 weeks or LDV/SOF+RBV for 8 weeks; 95–100% of GT1 treatment experienced (50% cirrhosis) patients who previously failed on a PI-based regimen, treated with LDV/SOF or LDV/SOF+RBV for 12 weeks.

6.5.7.7 Study GS-US-337-0121 (SIRIUS): HCV GT1 treatment experienced, compensated cirrhosis

Data presented are from the NDA LDV/SOF FDC safety update (100) and the late breaking AASLD 2014 abstract (93).

This ongoing Phase II, randomised, multicentre, double-blind, placebo-controlled study is evaluating the efficacy and safety of LDV/SOF+RBV treatment for 12 weeks or LDV/SOF treatment for 24 weeks in treatment experienced, cirrhotic patients with GT1 HCV infection. To be eligible for the study, patients were required to have not achieved SVR following treatment with at least one PEG-IFN+RBV regimen followed by at least one PI+PEG-IFN+RBV regimen.

Following screening, 155 patients were randomised in a 1:1 ratio to the following treatment groups:

- Group 1: LDV/SOF + matched RBV placebo for 24 weeks.
- Group 2 (deferred treatment): matched LDV/SOF placebo + matched RBV placebo for 12 weeks, followed by LDV/SOF+RBV 12 weeks.

Randomisation was stratified by HCV genotype (1a, 1b; mixed or other GT1 results were stratified with GT1a) and response to prior HCV therapy (never achieved HCV RNA <LLOQ, achieved HCV RNA <LLOQ).

All patients were to have evidence of cirrhosis defined as any of the following: biopsy, transient elastography cirrhosis results >12.5 kPa, or Fibrotest score >0.75 together with an AST: platelet ration index (APRI) of >2 at screening.

Of the 155 patients who received at least one dose of study drug, all patients were continuing study drug treatment at week 12 with the exception of 1 patient (0.6%) in the placebo 12 week group, who discontinued study treatment early due to an AE (Table 37). Note that data in this table refers to the safety analysis set and is only available for patients from the time of first dose to week 12 (i.e. only data for LDV/SOF administered for 12 weeks and placebo administered for 12 weeks are presented).

Table 37: SIRIUS subject disposition (safety analysis set)

Subject Disposition	LDV/SOF 12 Weeks	Placebo 12 Weeks	Total
Subjects randomised	77	78	155
Subjects in safety analysis set	77	78	155
Study treatment status			
On study treatment	77 (100%)	77 (98.7%)	155 (99.4%)

Subject Disposition	LDV/SOF 12 Weeks	Placebo 12 Weeks	Total
Completed study treatment	0	0	0
Discontinued study treatment	0	1 (1.3%)	1 (0.6%)
Reasons for study treatment discontinuation			
Adverse event	0	1 (1.3%)	1 (0.6%)

Abbreviations: LDV, ledipasvir; SOF, sofosbuvir.

The mean age was 56 years (range: 23 to 77 years). Most patients were white (97.4%) and the majority of patients were male (73.5%); most patients were non-Hispanic/Latino (97.4%). The mean baseline BMI was 27.1 kg/m^2 and most patients (79.4%) had a baseline BMI <30 kg/m^2. The majority (63.2%) of patients had GT1a HCV infection. The mean baseline HCV RNA was 6.5 $\log_{10}$ IU/mL, with most patients (84.3%) having HCV RNA ≥ 800,000 IU/mL. Most patients had IL28B non-CC alleles (93.5%). Overall, all but one patient had compensated cirrhosis (99.4%); one patient was enrolled in violation of the protocol as the patient did not meet the protocol definition of cirrhosis. In these treatment experienced patients who did not achieve SVR following treatment with at least one PEG-IFN+RBV regimen followed by at least one PI+PEG-IFN+RBV regimen, [redacted] were prior non-responders, [redacted] had previously relapsed, [redacted] had previous breakthrough, and [redacted] had stopped due to an AE.

High cure rates (SVR12) were achieved in both treatment groups:

- 97% (75/77) was achieved in group 1 (LDV/SOF + matched RBV placebo for 24 weeks)
- 96% (74/77) in group 2 (matched LDV/SOF placebo + matched RBV placebo for 12 weeks, followed by LDV/SOF+RBV 12 weeks).

A total of five patients relapsed; two (3%) in group 1 and three (4%) in group 2. One patient discontinued therapy due to an SAE (sepsis) during the placebo phase of the study and was therefore excluded from the efficacy analysis per pre-specified criteria but included in the safety analysis.

Conclusion (SIRIUS)

- The results from SIRIUS demonstrate that HCV GT1 patients with compensated cirrhosis who have previously failed both PEG-IFN+RBV and PI+PEG-IFN+RBV regimens can be successfully treated with LDV/SOF+RBV for 12 weeks and LDV/SOF for 24 weeks.
- These results provide additional data for these difficult to treat patients and are consistent with the cure rates observed in the ION-2 trial (section 6.5.6).

6.5.7.8 Study CO-US-337-0117 (SYNERGY): HCV GT1 and GT4 treatment naïve and experienced (including GT1 SOF failures)

Data presented are from Osinusi et al, 2014 (101), Kohli et al, 2014 (94) and Kapoor et al (95)

SYNERGY is a Phase II, 12-week study to evaluate the efficacy of LDV/SOF regimens in HCV GT1 and GT4 patients. The study is ongoing and a full dataset in GT4 patients is not yet available (see Section 6.5.7.1 for available data from [redacted] patients).

In one arm of the study the objective was to assess the efficacy of LDV/SOF in treatment experienced GT1 patients who had relapsed following previous treatment with SOF/RBV. Fourteen patients were enrolled in this arm and received LDV/SOF as an FDC tablet for 12 weeks. Enrolled patients had previously been treated with, and relapsed following, 24 weeks of SOF/RBV in the NIAID SPARE study (102). The mean age of patients was 59.5 years, median BMI 28.5 kg/m^2, median HCV RNA 6.45 log_{10} IU/mL, 93% were male, 93% African-American, 86% had IL28B CT/TT, 57% were infected with GT1a, and 50% had Histologic activity index (HAI) stage 3-4 fibrosis. The primary endpoint, SVR12, was achieved by 14/14 patients (100%). One patient with detectable S282T mutation after relapse to SOF/RBV also achieved SVR12.

Three other arms were included with the objective of assessing the use of multiple direct-acting agents on reducing the duration of treatment in treatment naïve GT1 patients. In the LDV/SOF 12 week arm SVR12 was achieved by 100% (n=20) of patients, supporting the evidence from the ION studies in GT1 treatment naïve patients. The other two arms assessed LDV/SOF in combination with other unlicensed direct acting antiviral agents and hence the results have not been included.

The results from SYNERGY demonstrate that patients infected with GT1 HCV who fail SOF/RBV therapy can be successfully retreated with LDV/SOF for 12 weeks. In addition the results in GT1 treatment naïve patients are consistent with cure rates observed in the ION trials.

6.6 *Meta-analysis*

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

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

Not applicable

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

Not applicable

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

Not applicable

6.7 *Indirect and mixed treatment comparisons*

Similar to the situation with the SOF NICE submission, no network meta-analysis (NMA) was possible for LDV/SOF. As described in Section 6, the Phase III trial programme evaluated LDV/SOF regimens with and without RBV for different treatment durations without classical active control arms. In order to link LDV/SOF via a network to the currently recommended regimens for the treatment of CHC patients, a common comparator would be required. As described in Section 6.10.2, there were no appropriate comparators for the LDV/SOF trials and therefore they were uncontrolled (historical control) studies. For this reason, it was impossible to create a network to indirectly link LDV/SOF to other comparator regimens currently used for the treatment of CHC patients, and thus carry out a mixed-treatment comparison or an indirect comparison. Other statistical methods have been used previously to adjust for differences in non-RCT studies in order to provide comparative effectiveness estimates, such as matching-adjusted indirect comparisons. This would involve taking the patient level data for LDV/SOF studies and applying the inclusion/exclusion criteria used for the comparator studies and re-estimating the outcome of interest (SVR). Because the SVR rates were so close to 100% for LDV/SOF and the inclusion/exclusion criteria from the comparator trials would lead to the exclusion of the 'harder to treat' patients from the LDV/SOF trials, the SVR rates for LDV/SOF had little flexibility to show any differences due to changes in the inclusion/exclusion criteria. Therefore this approach was not considered appropriate.

A naïve comparison approach was taken to source efficacy data for comparators, with data derived from individual studies across all patient groups modelled in the economic evaluation (see Table 38 for summary of studies).

While the lack of a network meta-analysis may be considered a limitation, SVR is a hard and objective end point consistently measured across all trials, and is not subject to bias from the patient or investigator. In addition, the baseline characteristics of the trial populations, summarised in Table 39 and Table 42 show that the GT1 patient populations were similar except for a higher proportion of patients with cirrhosis and GT1a in the LDV/SOF trials, both of which are considered to be associated with numerically lower SVR rates. This means the naïve comparisons are likely to be conservative in favour of the comparators.

It should be noted that this overall approach is in line with the approach taken for SOF and accepted by HTA bodies as being an appropriate methodology given the available data.

SVR rates derived from these studies are presented in the economic section (Section 7.2) and represent subgroup analyses based on specific HCV genotype, cirrhotic status and treatment experience. For example, ION-1 provides data for LDV/SOF in two groups of treatment naïve patients – those with and those without cirrhosis.

Study selection

Table 38: Study design for all relevant studies used in base case economic evaluation

Main regimen	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition
GT1 treatment naïve (non-cirrhotic and cirrhotic)								
LDV/SOF 12w or 24w	ION-1	3	Randomised, multicentre	Open-label	HCV GT1 HCV RNA≥10^4 IU/mL at screening	Naïve	Cirrhosis allowed in ~20% of patients but decompensated cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ = 25 IU/mL
LDV/SOF 8w or 12w	ION-3	3	Randomised, multicentre	Open-label	HCV GT1 HCV RNA≥10^4 IU/mL at screening	Naïve	Cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ = 25 IU/mL
SOF+PEG-IFN+/RBV 12w	NEUTRINO (SPC and Lawitz 2013 (1;103))	3	Single arm	Open-label	HCV GT1/4/5/6, plasma HCV RNA >10^4 IU/mL at screening	Naïve	Cirrhosis allowed in ~20% of patients but decompensated cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ = 25 IU/mL
SMV+PEG-IFN+RBV 24w	QUEST (C208) (SPC and Jacobsen 2014 (2;104))	3	Randomised, multicentre, placebo-controlled	Double-blind	HCV GT1 HCV RNA≥10^4 IU/mL at screening	Naïve	Cirrhosis allowed if ultrasound ≤6 months showed no signs of HCC. Decompensated cirrhosis excluded	HCV RNA concentration of <25 IU/mL undetectable at EOT and <25 IU/mL detectable or undetectable 12 weeks after the planned EOT
	QUEST 2 (C216) (SPC and Manns 2014 (2;105))	3	Randomised, multicentre, placebo-controlled	Double-blind	HCV GT1 HCV RNA≥10^4 IU/mL at screening	Naïve	Cirrhosis allowed if ultrasound ≤6 months showed no signs of HCC. Decompensated cirrhosis excluded	HCV RNA concentration of <25 IU/mL undetectable at EOT and <25 IU/mL detectable or undetectable 12 weeks after the planned EOT

Main regimen	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition
SMV+SOF 12w	COSMOS (SPC, Lawitz 2014, (2;106))	2	Randomised, multicentre	Open-label	HCV GT1 HCV RNA≥10^4 IU/mL at screening	Cohort 1: Previous non-responders to PEG-IFN+RBV Cohort 2: Tx naïve or previous non-responders to PEG-IFN+RBV	Cohort 1: METAVIR F0-F2 Cohort 2: METAVIR F3-F4	SVR12 (HCV RNA titres <25 IU/mL)
TVR+PEG-IFN+RBV	ADVANCE (Study 108; Jacobson et al, 2011 (107), SPC (12))	3	Randomised, placebo-controlled	Double-blinded	Documented CHC GT1 infection	Naïve	Compensated cirrhosis allowed. Decompensated cirrhosis excluded	Undetectable HCV RNA 24 weeks after EOT LLOD = 10 IU/mL, LLOQ = 25 IU/mL
	ILLUMINATE (Study 111) (SPC (12))	3	Randomised	Open-label	Compensated liver disease, detectable HCV RNA and liver histopathology consistent with CHC. GT1 infection	Naïve	Compensated cirrhosis allowed	Undetectable HCV RNA as measured at the Week 72 visit LLOQ = 25 IU/mL
	Study C211 (SPC (12))	3	Randomised	Open-label	GT infection	Naïve	Compensated cirrhosis allowed	Undetectable HCV RNA 12 weeks after EOT LLOQ = 25 IU/mL
BOC+PEG-IFN+RBV	Poordad et al, 2013 (108)	3	Randomised	Open-label	Chronic HCV GT1, HCV RNA ≥ 10^4 IU/mL	Naïve	Decompensated liver disease excluded	Undetectable HCV RNA 24 weeks after EOT LLOD = 9.3 IU/mL, LLOQ = 25 IU/mL
PEG-IFN+RBV 48w	IDEAL; McHutchison et al, 2009 (109)	NR	Randomised, multicentre	Double-blinded	Detectable plasma HCV RNA level and chronic HCV GT1 infection	Naive	Compensated liver disease	Undetectable HCV RNA 24 weeks after EOT LLOD: 27 IU/ml

Main regimen	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition
GT1 treatment experienced (non-cirrhotic and cirrhotic)								
LDV/SOF 12w or 24w	ION-2	3	Randomised, multicentre	Open-label	HCV GT1 HCV RNA≥10^4 IU/mL at screening	Prior virologic failure after PI+PEG-IFN+ RBV, or failed PEG-IFN/RBV	Cirrhosis in 20% of patients but decompensated cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ = 25 IU/mL
SOF+PEG-IFN-RBV 12w	No study available. SVRs taken from FDA bridging analysis							
SMV+PEG-IFN+RBV 48w	PROMISE (HPC3007) (SPC and Forns 2014 (2;110))	3	Randomised, multicentre, placebo-controlled	Double-blind	HCV GT1 HCV RNA≥10^4 IU/mL at screening	Relapsed following ≥24 weeks IFN-based therapy	Bridging fibrosis (F3) or cirrhosis (F4) allowed if ultrasound performed ≤6months before screening with no findings suspicious for HCC. Decompensated cirrhosis excluded.	HCV RNA <25 IU/mL undetectable at actual EOT and HCV RNA<25 IU/mL
	ASPIRE (C206) (SPC (2))	2	Randomised, placebo-controlled	Double-blind	HCV GT1	Failed prior therapy with PEG-IFN+RBV (including prior relapsers, partial responders or null responders)	Cirrhosis was permitted	NR
SMV+SOF 12w	COSMOS (See GT1 TN)							
TVR+PEG-IFN+RBV	REALIZE (Study C216 (SPC (12))	3	Randomised, placebo-controlled	Double-blind	Compensated liver disease, detectable HCV RNA and liver histopathology consistent with CHC. GT1 infection	Prior relapsers and prior non-responders on PEG-IFN+RBV	Compensated cirrhosis allowed.	Undetectable HCV RNA as measured at the Week 72 visit LLOQ = 25 IU/mL

Main regimen	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition
BOC+PEG-IFN+RBV	RESPOND-2 (50)	3	Randomised	Open-label	Chronic HCV GT1 infection	Prior relapsers and prior non-responders on IFN	Compensated cirrhosis allowed. Decompensated cirrhosis excluded	Undetectable HCV RNA at Week 24 of follow up
PEG-IFN+RBV 48w	REALIZE (Study C216) (TVR SPC (12))	3	Randomised, placebo-controlled	Double-blind	Compensated liver disease, detectable HCV RNA and liver histopathology consistent with CHC. GT1 infection	Prior relapsers and prior non-responders on PEG-IFN+RBV	Compensated cirrhosis allowed.	Undetectable HCV RNA as measured at the Week 72 visit LLOQ = 25 IU/mL
GT3 treatment naïve (non-cirrhotic and cirrhotic)								
LDV/SOF+RBV 12w	ELECTRON-2	2	Randomised, multicentre	Open-label	HCV GT3 HCV RNA≥10^4 IU/mL at screening	Naïve	Cirrhosis allowed but decompensated cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ = 25 IU/mL
SOF+PEG-IFN+RBV 12 w	ELECTRON (SPC and Gane 2013 (1;111))	2	Randomised, multi-centre	Open-label	HCV GT2/3, plasma HCV RNA >50,000 IU/mL at screening	Naïve	Cirrhosis excluded	Undetectable HCV RNA 12 weeks after EOT LLOD = 15 IU/mL
SOF+PEG-IFN+RBV 12w	PROTON (SPC, Lawitz, 2013 and CSR (1;112;113))	2	Randomised, multi-centre, placebo-controlled	Open-label	HCV GT1–3, plasma HCV RNA >50,000 IU/mL at screening	Naïve	Cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOD = 15 IU/mL
SOF+PEG-IFN+RBV 12w	LONESTAR-2 (SPC, Lawitz 2013 and protocol (1;114;115))	2	Single-centre, single-arm	Open-label	HCV GT2/3, plasma HCV RNA >10^4 IU/mL at screening	Experienced: Virologic failure with prior IFN-based treatment (provides data in cirrhotic patients in absence of cirrhotic treatment naïve)	Cirrhosis in ~50% of patients but decompensated cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ = 25 IU/mL

Main regimen	Source	Phase	Design	Blinded?	HCV diagnosis	Treatment experience	Liver histology	SVR definition
SOF+RBV 24w	VALENCE (SPC and Zeuzem et al, 2014 (1;116))	3	Randomised, multi-centre, placebo-controlled	Double-blind	HCV GT2/3, plasma HCV RNA >10^4 IU/mL at screening	Naïve and experienced (either IFN intolerant or a treatment failure)	Cirrhosis in ~20% of patients but decompensated cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ = 25 IU/mL
PEG-IFN+RBV 24w	FISSION (SPC and Lawitz et al, 2013 (1;103))	3	Randomised, multi-centre	Open-label	HCV GT2/3, plasma HCV RNA >10^4 IU/mL at screening	Naive	Cirrhosis in ~20% of patients but decompensated cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ = 25 IU/mL
GT3 treatment experienced (non-cirrhotic and cirrhotic)								
LDV/SOF+RBV 24w	No data currently available							
SOF+RBV 24w	VALENCE (SPC and Zeuzem et al, 2014 (1;116))	3	Randomised, multi-centre, placebo-controlled	Double-blind	HCV GT2/3, plasma HCV RNA >10^4 IU/mL at screening	Naïve and experienced (either IFN intolerant or a treatment failure)	Cirrhosis in ~20% of patients but decompensated cirrhosis excluded	Undetectable HCV RNA 12 weeks and 24 weeks after EOT LLOQ = 25 IU/mL

Abbreviations: BOC, boceprevir; EOT, end of treatment; GT, genotype; LDV, ledipasvir; LLOD, lower limit of detection; NR, not reported; PEG IFN2a/2b, pegylated interferon 2a/2b; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

Table 39: Patient characteristics, GT1 treatment naïve studies

		ION-1		ION-3		NEUTRINO	QUEST	QUEST 2	COSMOS		ADVANCE (Study 108)	ILLUMINATE (Study 111)	Study C211	Poordad et al, 2013	IDEAL
		LDV/ SOF12	LDV/ SOF24	LDV/ SOF8	LDV/ SOF12	SOF+ PR12	SMV+PR 24	SMV+PR 24	SMV+SOF 12 Cohort1†	SMV+SOF 12 Cohort2†	TVR+PR	TVR+PR	TVR+PR	BOC+PR	PR48
N		214	217	215	216	327	264	257	14	14	363	540	371[§]	500[‡]	1,035
Age	**Mean**	52	53	53	53	52	48	46	56 (median)	58 (median)	49 (median)	51 (median)	51 (median)	50	48
Race	**White %**	87%	82%	76%	77%	79%	86%	92%	79%	86%	90%	NR	NR	77%	71%
	Black %	11%	15%	21%	19%	17%	10%	6%	21%	14%	7%	14%	5%	18%	19%
Viral load (RNA IU/mL)	**> 400,000**	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	91%	NR
	> 600,000	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NA	82%
	> 800,000	79%	77%	84%	80%	82%	83%	77%	NR	NR	77%	82%	85%	NA	NR
Advanced liver disease	**F3/4**	47%	49%	13% (F3)	13% (F3)	NR	29%	22%	0%	50% (F3)	NR	NR	NR	14%	11%
	Cirrhosis	16%	15%	0%	0%	17%	12% (F4)	7% (F4)	0%	50% (F4)	6%	11%	14%	10%	NR
Genotype	**% GT1**	98%	99%	100%	100%	89%	100%	99%	100%	100%	100%	NR	100%	100%	100%
	% GT1a	67%	67%	80%	80%	69%	56%	41%	71%	79%	59%	72%	57%	67%	61%
	% GT1b	31%	31%	20%	20%	20%	44%	58%	29%	21%	41%	27%	43%	29%	36%
BMI	**Median [Range] or (SD)**	27 (mean [18–41]	27 (mean) [18–48	28 (mean [18–43]	28 (mean [19–45]	29 (mean) [18–56]	26.6 [16.5–45.2]	25.8 [17.5–53.5]	28.3 [21.7–36.6]	31.6 [22.5–40.6]	26.2 [17-46]	NR	NR	28.1 (5.8)	NR
Weight	**Mean (SD)**	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	82.8 (16.6)

IL28B	**CC**	26%	24%	26%	26%	29%	29%	29%	100%	71%	NR	NR	29%	31%	NR
	CT	53%	55%	56%	57%	55%	57%	55%	0%	NR	NR	NR	56%	51%	NR
	TT	21%	21%	18%	17%	16%	14%	16%	0%	NR	NR	NR	15%	17%	NR

BMI, body mass index; BOC, boceprevir; GT, genotype; LDV, ledipasvir; NR, not reported; PR, pegylated interferon + ribavirin; RNA, ribonucleic acid; SD, standard deviation; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
† Cohort 1 did not comprise any treatment naïve patients, however is used to provide additional non-cirrhotic patients to the analysis. Cohort 2 comprised treatment naïve (n=7) and prior non-responders to PEG-IFN+RBV (n=7). Patient characteristics are shown for each full cohort.
‡ Poordad reports patient characteristics for a sub-group of 500 of 687 patients enrolled. These 500 patients were those that became anaemic during the study.
§ N number for arm treated with TVR 750 mg three times daily. Patient characteristics only available for whole study cohort treated with either TVR 750 mg three times daily or 1,125 mg twice daily.

Table 40: Patient characteristics, GT1 treatment experienced studies

		ION-2		**PROMISE**	**ASPIRE**	**COSMOS**		**REALIZE**	**RESPOND-2**	**REALIZE**
		LDV/ SOF12	**LDV/ SOF24**	**SMV+PR48**	**SMV+PR48‡**	**SMV+SOF12 Cohort1†**	**SMV+SOF12 Cohort2†**	**TVR+PR**	**BOC+PR**	**PR 48**
N		109	109	260	120	14	14	266‡‡	162	132‡‡
Age	**Mean**	56	56	52 (median)	50	56 (median)	58 (median)	51 (median)	52.9	51 (median)
Race	**White %**	77%	83%	93.5%	93%	79%	86%	NR	88%	NR
	Black %	22%	16%	2.7%	5%	21%	14%	5%	11%	5%
Viral load (RNA IU/mL)	**> 400,000**	NR	NR	NR	NR	NR	NR	NR	NR	NR
	> 600,000	NR	NR	NR	NR	NR	NR	NR	NR	NR
	> 800,000	88% (≥6 $\log_{10}$)	79% (≥6 $\log_{10}$)	NR	86%	NR	NR	89%	91%	89%
Advanced liver disease	**F3/4**	58%	58%	17.6% (F3)	19% (F3)	0%	50% (F3)	NR	20%	NR
	Cirrhosis	20%	20%	15.6% (F4)	18% (F4)	0%	50% (F4)	26%	10%	26%
Genotype	**% GT1**	100%	100%	100%	NR	100%	100%	100%	99%	100%
	% GT1a	79%	78%	42%	41%	71%	79%	54%	58%	54%
	% GT1b	21%	22%	58%	58%	29%	21%	46%	41%	46%
BMI	**Median [Range] or (SD)**	29 (mean [19–47]	28 (mean [19–41]	27.2 [14.3–47.7]	NR	28.3 [21.7–36.6]	31.6 [22.5–40.6]	NR	28.8 (mean)	NR
Weight	**Mean (SD)**	NR	NR	NR	NR	NR	NR	NR	NR	NR
IL28B	**CC**	9%	15%	24%	18%	100%	71%	NR	NR	NR

	CT	64%	62%	64%	65%	0%	NR	NR	NR	NR
	TT	27%	23%	12%	18%	0%	NR	NR	NR	NR
Previous therapy	**PR**	39%	54%	95%	100%§	100%¶	100% of TE pts¶	100%††	100%	100% of TE pts††
	PI	61%	46%	NR	NR	NR	NR	NR	NR	NR
	Other	NR	NR	5%	NR	NR	NR	NR	NR	NR

BMI, body mass index; BOC, boceprevir; GT, genotype; LDV, ledipasvir; NR, not reported; PI, protease inhibitor; PR, pegylated interferon + ribavirin; RNA, ribonucleic acid; SD, standard deviation; SMV, simeprevir; SOF, sofosbuvir; TE, treatment experienced; TVR, telaprevir.
† Cohort 1 comprised of prior non-responders to PEG-IFN+RBV. Cohort 2 comprised treatment naïve (n=7) and prior non-responders to PEG-IFN+RBV (n=7). Patient characteristics are shown for each full cohort.
‡ N shown for pooled 150 mg SMV for 12, 24 or 48 weeks with PEG-IFN+RBV for 48 weeks; patient characteristics shown for overall trial population.
§ Based on inclusion criteria of study (patients who had failed prior therapy with PEG-IFN+RBV).
¶ Based on inclusion criteria of study (non-responders to previous PEG-IFN+RBV).
†† Based on inclusion criteria of study (did not achieve SVR with prior treatment with PEG-IFN+RBV).
‡‡ N number for treatment arm, patient characteristics for overall study population.

Table 41: Patient characteristics, GT3 treatment naïve studies

		ELECTRON-2	**ELECTRON**	**PROTON**	**LONESTAR-2**	**VALENCE**	**FISSION**
		LDV/SOF+RBV12	**SOF+PR12**	**SOF+PR12**	**SOF+PR12‡**	**SOF+R24†**	**PR24**
N		26	11	25	47	250	243
Age	**Mean**	48	46	47	56	48	48
Race	**White %**	88%	82%	80%	96%	94%	87%
	Black %	0%	NR	16%	NR	0%	2%
Viral load (RNA IU/mL)	**> 400,000**	NR	NR	NA	NR	NR	NR
	> 600,000	NR	NR	NA	NR	NR	NR
	> 800,000	77%	NR	52%	NR	NR	65%
Advanced liver disease	**Cirrhosis**	19%	0%	0%	55%	23%	21%
Genotype	**% GT3**	100%	64%	40%	51%	100%	72%
BMI	**Median [Range] or (SD)**	28 (mean) [18–42]	24 (mean) [21-28]	29 (4.8)	31 [21-53]	25 [17-41]	28 [19-52]
IL28B	**CC**	58%	36%	28%	36%	34%	44%
	CT	23%	45%	68%	NR	52%	40%
	TT	19%	18%	4%	NR	13%	16%

BMI, body mass index; GT, genotype; LDV, ledipasvir; NR, not reported; PI, protease inhibitor; PR, pegylated interferon + ribavirin; R, ribavirin; RNA, ribonucleic acid; SD, standard deviation; SMV, simeprevir; SOF, sofosbuvir.
† SOF/R24 arm in VALENCE comprised 42% HCV treatment naïve, 58% treatment experienced. Patient characteristics are presented for the entire arm of the trial.
‡ LONESTAR-2 enrolled treatment experienced patients only. This study is used to provide data on cirrhotic patients in the GT3 treatment naïve population in the absence of this data in a treatment naïve population.

Table 42: Patient characteristics, GT3 treatment experienced studies

		VALENCE
		SOF+R24†
N		250
Age	**Mean**	48
Race	**White %**	94%
	Black %	0%
Viral load (RNA IU/mL)	**> 400,000**	NR
	> 600,000	NR
	> 800,000	NR
Advanced liver disease	**Cirrhosis**	23%
Genotype	**% GT2**	0%
	% GT3	100%
BMI	**Mean [Range] or (SD)**	25 [17-41]
IL28B	**CC**	34%
	CT	52%
	TT	13%
Previous therapy	**PR**	NR§
	PI	NR
	Other	NR

BMI, body mass index; GT, genotype; LDV, ledipasvir; NR, not reported; PI, protease inhibitor; PR, pegylated interferon + ribavirin; R, ribavirin; RNA, ribonucleic acid; SD, standard deviation; SMV, simeprevir; SOF, sofosbuvir.
† SOF/R24 arm in VALENCE comprised 42% HCV treatment naïve, 58% treatment experienced. Patient characteristics are presented for the entire arm of the trial.
§ Based on inclusion criteria of study, all treatment experienced patients were defined as IFN intolerant or a treatment failure on previous IFN-based therapy (IFN or PEG-IFN).

6.8 *Non-RCT evidence*

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

All studies are described in section 6.1 to section 6.5.

6.9 *Adverse events*

6.9.1 ***If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.***

The identification of clinical evidence is described in Sections 6.1 and 6.2. All trials relevant to this submission are listed in Section 6.2.7.

The trials reported herein were designed to primarily assess clinical efficacy. In each study the assessment of safety was a secondary objective and the results are reported in Section 6.9.2.

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

6.9.2.1 Study GS-US-337-0102 (ION-1): HCV GT1 treatment naive

ION-1 was designed to assess the efficacy and safety of 12 or 24 weeks of a FDC of LDV/SOF, with or without RBV, in treatment naïve patients with chronic HCV GT1 infection, including those with compensated cirrhosis (methods reported in Section 6.3). Safety results are summarised in Table 43.

Across all four treatment groups, 81–93% of patients had at least one AE. Of these, 94% had AEs that were mild to moderate in severity. The most common AEs were fatigue, headache, insomnia, and nausea. Patients in the groups that received LDV/SOF+RBV for 12 or 24 weeks had higher rates of AEs known to be associated with RBV treatment (fatigue, insomnia, asthenia, rash, cough, pruritus, and anaemia) compared with patients in the RBV-free treatment groups. A total of [redacted] patients had grade 3 (severe) AEs ([redacted] receiving LDV/SOF 12 weeks; [redacted] receiving LDV/SOF+RBV 12 weeks; [redacted] receiving LDV/SOF 24 weeks; [redacted] receiving LDV/SOF+RBV 24 weeks; see appendix, section **Error! Reference source not found.**). [redacted] grade 4 (life-threatening) AEs were reported.

In total, 33 patients experienced a serious adverse event (SAE) during treatment, of which the majority (18, 8.3%) were in the LDV/SOF 24 week group. The most common SAEs were cellulitis, chest pain, gastroenteritis, hand fracture, non-cardiac chest pain, and pneumonia; each occurred in 2 patients.

Of the 865 patients that were randomised and treated, no patients on the 12 week regimens discontinued treatment due to AEs. Ten patients on the 24 week regimens discontinued treatment due to AEs (4 [2%] in the LDV/SOF group and 6 [3%] in the LDV/SOF+RBV group; Table 43). All 10 achieved SVR12 and the shortest duration of therapy among these patients was 8 weeks

The mean change in haemoglobin levels from baseline to end of treatment was greater in patients who received LDV/SOF+RBV compared with patients who received LDV/SOF alone (LDV/SOF: −0.4 g/dL [12 weeks], −0.2 g/dL [24 weeks]; LDV/SOF+RBV: −2.2 g/dL [12 weeks], −1.9 g/dL [24 weeks]). Severe hyperbilirubinaemia (bilirubin level >2.5xULN) developed in nine (4%) and seven (3%) patients who received LDV/SOF+RBV for 12 and 24 weeks, respectively. Only one (<1%) patient, who had Gilbert's syndrome, developed hyperbilirubinaemia in the LDV/SOF 24 week group. The increased anaemia and hyperbilirubinaemia observed in the LDV/SOF+RBV arms correlate with the known haemolytic effect of ribavirin (8). Decreases from baseline in [redacted] and increases in [redacted] and [redacted] in subjects treated with LDV/SOF+RBV were [redacted] with the expected toxicity profile of [redacted]

The safety profile of the LDV/SOF+RBV regimen was consistent with that observed previously with the SOF+RBV regimen and that expected for RBV. Additionally, the type, frequency and severity of AEs observed in the LDV/SOF group in ION-1 were similar to those observed in the placebo group in a previous trial of SOF and RBV (117) in patients with HCV infection. No specific safety signal associated with LDV/SOF was identified.

Table 43: Safety summary in ION-1 (safety analysis set)

Adverse event	12 week		24 week	
	LDV/SOF (N=214)	LDV/SOF+RBV (N=217)	LDV/SOF (N=217)	LDV/SOF+RBV (N=217)
Duration of treatment in weeks, mean (SD)	12.1 (0.8)	12.0 (0.7)	23.6 (2.6)	23.7 (1.9)
≥1 AE, n (%)	173 (81)	187 (86)	178 (82)	202 (93)
Grade 3 or 4 AE†	4 (1.9)	14 (6.5)	21 (9.7)	12 (5.5)
≥1 SAE, n (%)	1 (<1)	7 (3)	18 (8)	7 (3)
Discontinuation of LDV/SOF due to AEs, n (%)	0	0	4 (2)	6 (3)
Common AEs, n (%)‡				
Fatigue	46 (22)	79 (36)	53 (24)	84 (39)
Headache	53 (25)	50 (23)	54 (25)	65 (30)
Insomnia	17 (8)	45 (21)	26 (12)	46 (21)
Nausea	24 (11)	37 (17)	29 (13)	32 (15)
Asthenia	14 (7)	23 (11)	20 (9)	26 (12)
Diarrhoea	24 (11)	18 (8)	24 (11)	14 (6)
Rash	16 (7)	21 (10)	16 (7)	26 (12)
Irritability	11 (5)	17 (8)	17 (8)	24 (11)
Cough	6 (3)	22 (10)	16 (7)	25 (12)

Adverse event	12 week		24 week	
	LDV/SOF (N=214)	LDV/SOF+RBV (N=217)	LDV/SOF (N=217)	LDV/SOF+RBV (N=217)
Pruritus	11 (5)	22 (10)	8 (4)	20 (9)
Anaemia	0	25 (12)	0	22 (10)
Haematologic abnormality, n (%)				
Decreased haemoglobin level				
<10 g/dL	0	20 (9)	0	16 (7)
<8.5 g/dL	0	1 (<1)	0	0
Lymphocyte count <350/mm^3	0	1 (<1)	0	0
Neutrophil count 500 to <750/mm^3	1 (<1)	0	3 (1)	0
Platelet count 25,000 to <50,000/mm^3	1 (<1)	0	1 (<1)	0

Abbreviations: AE, adverse event; LDV, ledipasvir; RBV, ribavirin; SAE, serious adverse event; SD, standard deviation; SOF, sofosbuvir.
† No grade 4 AEs were reported ‡ Common adverse events were those that occurred in ≥10% of the patients in any group.

6.9.2.2 Study GS-US-337-0108 (ION-3): HCV GT1 treatment naïve non cirrhotic

ION-3 was designed to assess the efficacy and safety of 8 weeks of a FDC of LDV and SOF with or without RBV compared with 12 weeks of a FDC of LDV and SOF alone, in treatment naïve patients with chronic HCV GT1 infection without cirrhosis (methods reported in 6.3). Safety results are summarised in Table 44.

The incidence of AEs was lower among patients receiving LDV/SOF alone (68% and 69% in the 8 and 12 weeks treatment groups, respectively) compared with LDV/SOF+RBV 8 weeks (77%). Patients in the group that received LDV/SOF+RBV had higher rates of AEs that are associated with RBV therapy (fatigue, headache, nausea, insomnia, irritability, rash, pruritus, cough, and anaemia) compared with patients who received LDV/SOF alone. The majority of AEs were mild or moderate in severity. A total of 17 patients had grade 3 (severe) or grade 4 (life-threatening) AEs (two receiving LDV/SOF 8 weeks; eight receiving LDV/SOF+RBV 8 weeks; seven receiving LDV/SOF 12 weeks; see the appendix, section **Error! Reference source not found.**).

Ten patients had SAEs; no single SAE occurred in more than one patient. Four patients in the LDV/SOF 8 week group experienced anaphylactic reaction, colitis, diabetes mellitus inadequate control, hypertension, and lower gastrointestinal haemorrhage; one patient in the LDV/SOF+RBV 8 week group had pituitary tumour; five patients in the LDV/SOF 12 week group had abdominal pain, bile duct stone, haemothorax, hypoglycaemia, intestinal perforation, jaundice, mental status changes, respiratory failure, rhabdomyolysis, road traffic accident, skeletal injury, and squamous cell carcinoma of the lung.

Out of 647 patients, three discontinued the study treatment due to AEs (one receiving LDV/SOF+RBV 8 weeks [owing to a road accident] and two receiving LDV/SOF 12 weeks (one owing to arthralgia and one to lung cancer).

The mean change in haemoglobin levels from baseline to end of treatment was greater in patients who received LDV/SOF+RBV for 8 weeks (−1.9 g/dL) compared with patients who received LDV/SOF alone (−0.2 g/dL and −0.4 g/dL for 8 and 12 weeks, respectively). Grade 3 hyperbilirubinaemia developed in three (1%) patients who received LDV/SOF+RBV for 8 weeks.

Decreases from baseline in [redacted] and [redacted], and increases in [redacted] and [redacted] in subjects treated with LDV/SOF+RBV were [redacted] with the expected toxicity profile of [redacted].

The safety profile of the LDV/SOF+RBV regimen was consistent with that observed previously with the SOF+RBV regimen and that expected for RBV. No specific safety signal associated with LDV/SOF was identified.

Table 44: Safety summary in ION-3 (safety analysis set)

Adverse event	8 week		12 week
	LDV/SOF (N=215)	LDV/SOF+RBV (N=216)	LDV/SOF (N=216)
Duration of treatment in weeks, mean (SD)	8.1 (0.2)	8.0 (0.9)	12.0 (0.9)
≥1 AE, n (%)	147 (68)	166 (77)	150 (69)
Grade 3 or 4 AE	2 (0.9)	8 (3.7)	7 (3.2)
≥1 SAE, n (%)	4 (2)	1 (<1)	5 (2)
Discontinuation of LDV/SOF due to AEs, n (%)	0	1 (<1)	2 (1)
Common AEs, n (%)†			
Fatigue	45 (21)	75 (35)	49 (23)
Headache	30 (14)	54 (25)	33 (15)
Nausea	15 (7)	38 (18)	24 (11)
Insomnia	11 (5)	26 (12)	15 (7)
Irritability	3 (1)	29 (13)	10 (5)
Diarrhoea	15 (7)	13 (6)	9 (4)
Arthralgia	9 (4)	12 (6)	16 (7)
Constipation	9 (4)	12 (6)	8 (4)
Dizziness	6 (3)	13 (6)	9 (4)
Rash	3 (1)	20 (9)	5 (2)
Pruritus	2 (1)	16 (7)	5 (2)
Cough	3 (1)	12 (6)	7 (3)
Anaemia	2 (1)	17 (8)	2 (1)
Muscle spasms	3 (1)	12 (6)	6 (3)
Dyspnoea	0	11 (5)	1 (<1)
Haematologic abnormality, n (%)			
Haemoglobin level <10 g/dL	0	11 (5)	1 (<1)
Lymphocyte count 350 to <500/mm^3	0	1 (<1)	0
Neutrophil count 500 to <750mm^3	0	1 (<1)	1 (<1)

Abbreviations: AE, adverse event; LDV, ledipasvir; RBV, ribavirin; SAE, serious adverse event; SD, standard deviation; SOF, sofosbuvir.
† Common adverse events were those that occurred in ≥10% of the patients in any group.

6.9.2.3 Study GS-US-337-0109 (ION-2): HCV GT1 treatment experienced

ION-2 was designed to assess the efficacy and safety of 12 or 24 weeks of a FDC of LDV/SOF with or without RBV in treatment experienced patients with chronic HCV GT1 infection, including

those with compensated cirrhosis (methods reported in Section 6.3). Safety results are summarised in Table 45.

At least one AE was experienced by 67-90% of patients in each treatment group. Most of the AEs were mild to moderate severity. Incidence rates of adverse events were higher in the LDV/SOF 24 week group compared with the LDV/SOF 12 week group (81% vs 67%). The incidence rates of AEs in the 2 groups receiving LDV/SOF+RBV were similar (86% and 90% in the 12 and 24 week group, respectively). Higher rates of AEs known to be associated with RBV therapy (fatigue, nausea, insomnia, arthralgia, cough, rash, irritability, dyspnoea, and anaemia) were observed among patients receiving RBV compared with patients receiving LDV/SOF alone. A total of 23 patients had grade 3 (severe) or grade 4 (life-threatening) AEs (2 receiving LDV/SOF 12 weeks; 3 receiving LDV/SOF+RBV 12 weeks; 10 receiving LDV/SOF 24 weeks; 8 receiving LDV/SOF+RBV 24 weeks; see the appendix, section **Error! Reference source not found.**).

Only patients in the 24 week treatment groups had SAEs (6% in the LDV/SOF group and 3% in the LDV/SOF+RBV group). Angina unstable, convulsion, hepatic encephalopathy, intervertebral disc protrusion, non-cardiac chest pain, spondylolisthesis, and upper gastrointestinal haemorrhage occurred in one patient each in the LDV/SOF 24 week group and cholecystitis, vaginal prolapse, and wound infection occurred in one patient each in the LDV/SOF+RBV 24 week group. No patient discontinued treatment due to AEs.

The mean change in haemoglobin levels from baseline to end of treatment was greater in patients who received LDV/SOF+RBV compared with patients who received LDV/SOF alone (LDV/SOF: −0.5 g/dL [12 weeks], −0.6 g/dL [24 weeks]; LDV/SOF+RBV: −2.5 g/dL [12 weeks], −2.4 g/dL [24 weeks]). Mild to moderate hyperbilirubinaemia developed in 32% and 41% patients who received LDV/SOF+RBV for 12 and 24 weeks, respectively. Two patients who received LDV/SOF+RBV developed grade 3 hyperbilirubinaemia. Decreases from baseline in haemoglobin and increases in reticulocytes and platelets observed in both RBV-containing groups for the duration of treatment, were consistent with the expected toxicity profile of RBV.

The safety profile of the LDV/SOF+RBV regimen was consistent with that observed previously with the SOF+RBV regimen and that expected for RBV. No specific safety signal associated with LDV/SOF was identified.

Table 45: Safety summary in ION-2 (safety analysis set)

Adverse event	**12 week**		**24 week**	
	LDV/SOF (N=109)	**LDV/SOF+RBV (N=111)**	**LDV/SOF (N=109)**	**LDV/SOF+RBV (N=111)**
Duration of treatment in weeks, mean (SD)	12.2 (0.2)	12.1 (0.2)	23.9 (1.6)	24.0 (1.7)
≥1 AE, n (%)	73 (67)	96 (86)	88 (81)	100 (90)
Grade 3 or 4 AE	2 (1.8)	3 (2.7)	10 (9.2)	8 (7.2)
≥1 SAE, n (%)	0	0	6 (6)	3 (3)
Treatment discontinuation due to AEs, n (%)	0	0	0	0
Common AEs, n (%)[†]				
Fatigue	23 (21)	45 (41)	26 (24)	50 (45)
Headache	28 (26)	26 (23)	25 (23)	35 (32)

Adverse event	12 week		24 week	
	LDV/SOF (N=109)	LDV/SOF+RBV (N=111)	LDV/SOF (N=109)	LDV/SOF+RBV (N=111)
Nausea	13 (12)	20 (18)	7 (6)	25 (23)
Insomnia	10 (9)	18 (16)	4 (4)	19 (17)
Arthralgia	7 (6)	13 (12)	7 (6)	17 (15)
Cough	5 (5)	16 (14)	5 (5)	16 (14)
Diarrhoea	7 (6)	5 (5)	9 (8)	17 (15)
Rash	2 (2)	11 (10)	6 (6)	16 (14)
Irritability	2 (2)	13 (12)	4 (4)	12 (11)
Dizziness	3 (3)	8 (7)	7 (6)	12 (11)
Upper respiratory tract infection	4 (4)	6 (5)	7 (6)	11 (10)
Dyspnoea	0	16 (14)	3 (3)	9 (8)
Muscle spasm	1 (1)	8 (7)	2 (2)	12 (11)
Anaemia	0	9 (8)	1 (1)	12 (11)
Dry skin	0	3 (3)	3 (3)	11 (10)
Haematologic abnormality, n (%)				
Decreased haemoglobin level				
<10 g/dL	0	2 (2)	0	9 (8)
< 8.5 g/dL	0	0	0	2 (2)
Decreased lymphocyte count				
350 to <500/mm^3	1 (1)	1 (1)	1 (1)	3 (3)
< 350/mm^3	0	1 (1)	0	1 (1)
Platelet count 25,000 to <50,000/mm^3	1 (1)	0	2 (2)	0

Abbreviations: AE, adverse event; LDV, ledipasvir; RBV, ribavirin; SAE, serious adverse event; SD, standard deviation; SOF, sofosbuvir.
† Common adverse events were those that occurred in ≥10% of the patients in any group.

6.9.3 *GS-US-337-0121 (SIRIUS)*

Data presented are from the NDA LDV/SOF FDC safety update (100) and the late breaking AASLD 2014 abstract (93). The methodology for SIRIUS is reported in detail in section 6.5.7.7. Briefly this is an ongoing Phase II, randomised, multicentre, double-blind, placebo-controlled study in treatment experienced, cirrhotic patients with GT1 HCV infection. Following screening, 155 patients were randomised in a 1:1 ratio to the following treatment groups:

- Group 1: LDV/SOF + matched RBV placebo for 24 weeks.
- Group 2 (deferred treatment): matched LDV/SOF placebo + matched RBV placebo for 12 weeks, followed by LDV/SOF+RBV 12 weeks.

To allow an evaluation of the safety of LDV/SOF compared to placebo, the safety data for patients in this study are reported from the time of first dose to week 12 (i.e. only data for LDV/SOF administered for 12 weeks and placebo administered for 12 weeks are presented).

Similar percentages of patients had at least one AE in the LDV/SOF 12 week group (84.4%) and placebo 12 week group (83.3%). Of these, a slightly higher percentage of patients had a treatment-

related AE in the LDV/SOF 12 week group (67.5%) vs the placebo 12 week group (61.5%). Three patients had a Grade 3 or 4 AE, two in the LDV/SOF 12 week group (both Grade 3; [redacted] and [redacted]) and one in the placebo 12 week group (Grade 4; hepatic decompensation considered unrelated to study drug by the investigator). No individual Grade 3 or 4 AE was reported in >1 patient.

Table 46: Safety summary in SIRIUS (safety analysis set)

Adverse event	LDV/SOF 12 Weeks (N=77)	Placebo 12 Weeks (n=78)
≥1 AE, n (%)	65 (84.4)	65 (83.3)
Grade 3 or 4 AE, n (%)	2 (2.6)	1 (1.3)
≥1 SAE, n (%)	3 (3.9)	1 (1.3)
Treatment discontinuation due to AEs, n (%)	0	1 (1.3)
Common AEs, n (%)†		
Asthenia	28 (36.4)	25 (32.1)
Headache	27 (35.1)	16 (20.5)
Insomnia	11 (14.3)	10 (12.8)
Pruritus	4 (5.2)	14 (17.9)
Fatigue	13 (16.9)	3 (3.8)
Nausea	7 (9.1)	8 (10.3)
Diarrhoea	7 (9.1)	4 (5.1)
Hypertension	7 (9.1)	4 (5.1)
Sleep disorder	7 (9.1)	4 (5.1)
Arthralgia	5 (6.5)	5 (6.4)
Dry skin	4 (5.2)	6 (7.7)
Irritability	8 (10.4)	2 (2.6)
Abdominal pain upper	4 (5.2)	5 (6.4)
Decreased appetite	5 (6.5)	4 (5.1)
Back pain	6 (7.8)	2 (2.6)
Cough	5 (6.5)	2 (2.6)
Influenza like illness	4 (5.2)	3 (3.8)
Myalgia	5 (6.5)	2 (2.6)
Constipation	4 (5.2)	2 (2.6)
Bronchitis	4 (5.2)	1 (1.3)
Rhinitis	1 (1.3)	4 (5.1)

Four patients had an SAE, three in the LDV/SOF 12 week group ([redacted]) and one in the placebo 12 week group (arthritis bacterial and hepatic cirrhosis). No individual SAE was reported in >1 patient and all

SAEs were considered unrelated to study drug by the investigator. No deaths or AEs leading to modification/interruption of study drug were reported in the study. Only one patient permanently discontinued any study drug due to an AE (placebo 12 week group). A total of [redacted] patients had Grade 4 laboratory abnormalities ([redacted] receiving placebo and [redacted]receiving LDV/SOF) and [redacted] patients had Grade 3 laboratory abnormalities. Nearly [redacted]patients in the placebo 12 week group had a Grade 3 laboratory abnormality compared with the LDV/SOF 12 week group ([redacted]). [redacted] patients met the criteria for liver-related laboratory abnormalities of interest ([redacted]).[redacted]The safety profile of the LDV/SOF regimen was consistent with that observed in the ION studies. The frequency of headache and fatigue was >10% greater in patients treated with LDV/SOF compared with placebo.

6.9.4 *Give a brief overview of the safety of the technology in relation to the decision problem*

Clinical trials demonstrate that LDV/SOF has a favourable safety profile with only fatigue and headache identified as being more common in patients treated with LDV/SOF compared with patients given placebo. When LDV/SOF was given in combination with RBV adverse drug recations were consistent with the known safety profile of RBV, without increasing the frequency or severity of the expected adverse adverse drug reactions. Discontinuation rates due to AEs from trials were low ([redacted] discontinuing on LDV/SOF and [redacted] on LDV/SOF+RBV).

In clinical practice the LDV/SOF tolerability profile has the potential to reduce the level of resource utilisation and free-up service capacity in HCV treatment relative to PEG-IFN containing regimens due to an expected reduction in treatment emergent AEs. In addition, it means that more patients may be willing to consider active treatment and it will improve patients' treatment experience compared with the established treatment options.

6.10 *Interpretation of clinical evidence*

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

Key efficacy data presented within the submission, and supporting the recommended treatment regimens and durations in CHC GT1, GT3 and GT4 patients, are summarised in Table 47 and described below. Outcomes measured in clinical trials for LDV/SOF included SVR, resistance development, adverse events and HRQL, in line with outcomes requested in the scope for this appraisal.

The evidence demonstrates that very high cure rates (SVR12) of 86–100% can be achieved in patients with CHC GT1 infection by treating with an STR of LDV/SOF for 8 to 24 weeks. The addition of RBV to the treatment regimen (12 weeks treatment) enables high cure rates (SVR12 100%) to be achieved in CHC GT3 treatment naïve patients.

The evidence base also supports the use of LDV/SOF regimens in populations with limited treatment options, such as those who previously failed a PI-based regimen, those who are treatment experienced and infected with GT3, those who have decompensated cirrhosis or who are pre- or post-liver transplant (GT1 and GT4 only), and those with HCV/HIV co-infection.

Across the Phase III clinical studies, treatment with LDV/SOF regimens resulted in a rapid, profound and sustained decline in HCV ribonucleic acid (RNA) levels, with [redacted]% of patients achieving a very rapid virologic response below the level of quantification after 2 weeks of treatment and ≥99% achieving this outcome after 4 weeks of treatment. This response negates the need for on-treatment monitoring of HCV RNA or response-guided therapy for LDV/SOF regimens and is in contrast to other therapies, such as PEG-IFN, and PI-based regimens.

Of the 1,952 patients enrolled into the three Phase III ION trials, 96.7% (1,888) were cured of their HCV, 1.8% (36) experienced virologic relapse after treatment, 0.1% (2) experienced on-treatment breakthrough following a period of non-compliance and 1.3% (26) were lost to follow-up or withdrew consent. Furthermore, 100% concordance has been observed between SVR12 and SVR24, with every patient achieving SVR12 going on to achieve SVR24. With such a high proportion of non-SVR patients coming from non-virologic failures (lost to follow up, withdrew consent, non-compliance) it is helpful to look at the relapse rates as well as the SVRs, as detailed in Table 47.

LDV/SOF has a high barrier to the development of treatment-resistant mutations. In the Phase III studies, comprehensive analyses showed that, of the [redacted] patients experiencing relapse, none had resistance to SOF and [redacted]) also did not have resistance to LDV, at virologic failure. Single-class resistance to LDV was observed in the remaining [redacted] cases ([redacted]). In addition, high SVR12 rates were achieved in the presence of baseline NS5A resistance associated variants, observed in [redacted]% of the subject population, irrespective of whether or not RBV was added to the SOF/LDV regimen. Thus, the presence of resistance associated variants at baseline has a poor predictive value for virologic failure when patients are treated with LDV/SOF.

The results from HRQL questionnaires from ION-1, ION-2, and ION-3 indicated no on-treatment decrements in HRQL in LDV/SOF treated patients whilst there was a significant worsening in HRQL of patients treated with LDV/SOF+RBV. There was an improvement in HRQL from the end of treatment to 12 and 24 weeks post-treatment.

The safety and tolerability data from clinical studies demonstrate that LDV/SOF is well tolerated with only fatigue and headache identified as AEs that were more common in patients receiving LDV/SOF than those receiving placebo.

Table 47: Key data supporting licensed treatment regimens for LDV/SOF in GT1, GT4 or GT3 CHC

Patient population	Sub-Group	Treatment	Duration, wks	Study	SVR12, % (n/N)	Relapsers, % (n/N)[§]	Section
GT1 or GT4 CHC patients without cirrhosis	Naïve with VL <6 million IU/mL	LDV/SOF	8	ION-3	96.7 (119/123)	1.6 (2/123)	6.5.5
	Naïve	LDV/SOF	12	ION-3	96.3 (208/216)	1.4 (3/216)	6.5.5
				ION-1	99.4 (179/180)	0 (0/180)	6.5.4
	Experienced[†]	LDV/SOF	12	ION-2	95.4 (83/87)	4.6 (4/87)	6.5.5
			24	ION-2	98.9 (86/87)	0 (0/87)	6.5.5
GT1 or GT4 CHC patients with compensated cirrhosis	Naïve	LDV/SOF	12	ION-1	94.1 (32/34)	2.9 (1/34)	6.5.4
			24	ION-1	97.0 (32/33)	3.0 (1/33)	6.5.4
	Experienced[†]	LDV/SOF	12	ION-2	86.4 (19/22)	13.6 (3/22)	6.5.5
			24	ION-2	100 (22/22)	0 (0/22)	6.5.5
				SIRIUS[‡‡]	97 (75/77)	4 (3/77)	6.5.7.7
Patients with decompensated cirrhosis		LDV/SOF+RBV	12	SOLAR-1	[redacted]	[‡]	6.5.7.4
		LDV/SOF+RBV	24	SOLAR-1	[redacted]	[‡]	6.5.7.4
Patients who are post-transplant without cirrhosis		LDV/SOF+RBV	12	SOLAR-1	[redacted]	[‡]	6.5.7.4
		LDV/SOF+RBV	24	SOLAR-1	[redacted]	[‡]	6.5.7.4
Patients who are post-transplant with compensated cirrhosis		LDV/SOF+RBV	12	SOLAR-1	[redacted]	[‡]	6.5.7.4
		LDV/SOF+RBV	24	SOLAR-1	[redacted]	[‡]	6.5.7.4
Patients who are post-transplant with decompensated cirrhosis or fibrosing cholestatic hepatitis		LDV/SOF+RBV	12	SOLAR-1	[redacted]	[‡]	6.5.7.4
		LDV/SOF+RBV	24	SOLAR-1	[redacted]	[‡]	6.5.7.4
GT3 CHC without cirrhosis	Naïve	LDV/SOF+RBV	12	ELECTRON-2	100 (21/21)	0 (0/21)	6.5.7.2
	Experienced	LDV/SOF+RBV	12[¶]	ELECTRON-2	SVR4: 89 (25/28)	[††]	6.5.7.2
GT3 CHC with compensated cirrhosis	Naïve	LDV/SOF+RBV	12[¶]	ELECTRON-2	100 (5/5)	0 (0/5)	6.5.7.2
	Experienced	LDV/SOF+RBV	24[¶]	ELECTRON-2	SVR4: 77 (17/22)	[††]	6.5.7.2

Abbreviations: CHC, chronic hepatitis C; CPT, Child Pugh Turcotte score; GT, genotype; HCV, hepatitis C virus; LDV, ledipasvir; PEG-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response, VL, viral load.

† Treatment experienced patients include those who have failed treatment with either PEG-IFN+RBV or an HCV PI+PEG-IFN+RBV.

‡ SOLAR-1 is ongoing. SVR12 and SVR4 data has been entered where available. Relapse rates are not yet available.

§ Reasons for not achieving SVR12 other than relapse include patients withdrawing consent, lost to follow-up and on-treatment virologic failure.

¶ Recommended duration of 24 weeks LDV/SOF+RBV is provided in SPC for GT3 patients with cirrhosis and/or prior treatment failure is 24 weeks.

†† ELECTRON-2 is ongoing; SVR4 rates are presented for GT3 treatment experienced patients without and with cirrhosis, respectively. Relapse rates are not yet available.
‡‡ SIRIUS also included an arm with patients treated with LDV/SOF+RBV for 12 weeks giving an SVR12 rate of 96% (74/77). This data became available after the SPC was finalised.

GT1 patients without cirrhosis

- Based on a post-hoc analysis of patients that relapsed in ION-3, patients with a baseline viral load <6 million IU/mL can achieve a cure rate of 96.7% with 8 weeks LDV/SOF. Based upon analysis of the HCV Research UK database, the majority of treatment naïve non-cirrhotic patients in clinical practice (see Table 48 in section 6.10.4) have viral load <6 million IU/mL and would therefore benefit from the 8-week regimen. The remainder of treatment naïve patients will be treated with LDV/SOF for 12 weeks; cure rates with 12 weeks treatment in non-cirrhotic patients range between 96.3–99.4% (ION-1/ION-3). Of the 396 non-cirrhotic patients treated for 12 weeks in ION-1 and ION-3 programme, <1% (n=3) were virologic failures (relapsers).
- In treatment experienced patients cure rates of 95.4% and 98.9% were achieved with LDV/SOF for 12 and 24 weeks, respectively (ION-2). The modest numerical increase in SVR12 with the 24-week regimen means that patients without subsequent retreatment options should be considered for 24 weeks therapy. This represents a small proportion of the GT1 population (validated through KOL opinion, see Table 48).

GT1 patients with compensated cirrhosis

- In treatment naïve patients with compensated cirrhosis, cure rates of 94.1% and 97.0% were achieved with LDV/SOF for 12 and 24 weeks, respectively (ION-1). However, the difference in SVR between 12 and 24 weeks is driven entirely by non-virologic failures (lost to follow up, withdrew consent) with only 2 relapsers across the entire study, one in the 12 week arm and one in the 24 week arm. There is therefore no evidence in this study to suggest that extending treatment duration from 12 to 24 weeks increases the SVR rate. However, on the basis of the favourable tolerability profile of the drug, the regulators have suggested that those patients at greater risk of clinical progression and/or who have limited re-treatment options should be considered for extended therapy. It is anticipated that the group of patients who would be treated with 24 weeks LDV/SOF would be a very small proportion of this overall patient group (validated through KOL opinion, see Table 48).
- In treatment experienced patients, including PI experienced patients, with compensated cirrhosis, cure rates of 86.4% and 100% were achieved with LDV/SOF for 12 and 24 weeks, respectively (ION-2). In this case there is a significant increase in response rate with 24 weeks treatment, albeit based upon a small number of patients in each ION-2 arm (SVR12: 19/22 with 12 weeks LDV/SOF and 22/22 with 24 weeks LDV/SOF). However, the high cure rates achieved following 12 weeks treatment supports the use of this shorter duration in patients who are at low risk of clinical disease progression and have re-treatment options (see Table 48). Additional data from SIRIUS provides an SVR12 of 97% (75/77) in treatment experienced PI-failure patients with compensated cirrhosis, when treated for 24 weeks. Of note, the 96% (74/77) SVR12 rate observed with 12 weeks LDV/SOF+RBV treatment in SIRIUS suggests that this regimen might provide an alternative to the extended treatment duration of 24 weeks.

GT1 patients with decompensated cirrhosis and pre-/post-liver transplant

- SVR rates at post-treatment week 4 (SVR4) of [redacted]% were achieved in patients with decompensated cirrhosis (CPT B and C) following LDV/SOF treatment for 12 and 24 weeks (SOLAR-1). With 12 weeks LDV/SOF+RBV the SVR12 rate to date is [redacted]%.
- In post-liver transplant patients without cirrhosis or with compensated cirrhosis, SVR4 of [redacted] was achieved (SOLAR-1) with both 12 and 24 weeks of treatment with LDV/SOF+RBV. With

12 weeks LDV/SOF+RBV the SVR12 rate to date is [redacted]% in patients without or with compensated cirrhosis.

- For post-liver transplant patients with decompensated cirrhosis SVR4 rates were [redacted]% for both treatment durations studied and the SVR12 rate with 12 weeks LDV/SOF+RBV is [redacted] to date. Among patients with fibrosing cholestatic hepatitis, [redacted] have achieved SVR4 to date. Both post-transplant decompensated and fibrosing cholestatic hepatitis groups of patients would likely benefit from treatment for 24 weeks with LDV/SOF+RBV.
- Data collection is still ongoing but LDV/SOF treatment is very valuable in these patient populations as alternative treatment options are limited.

GT4 patients

- Although limited data currently exist in GT4, [redacted] patients ([redacted]) with available data ([redacted] SYNERGY and ION-1) have achieved SVR12.
- GT4 and GT1 infections are recognised to respond equivalently and it is recommended in the SPC that GT1 and GT4 infections are treated similarly with LDV/SOF.
- Clinical trials for LDV/SOF in CHC GT4 patients are currently ongoing and will provide further data in this patient group (SYNERGY and GS-US-337-1119 [French study]).

GT3 patients

- In the ELECTRON-2 study, 100% (26/26) of treatment naïve CHC GT3 patients including those with compensated cirrhosis (5/5, 19%) were cured following 12 weeks of treatment with LDV/SOF+RBV. Given the limited data available, a recommended treatment duration for GT3 treatment naïve patients has not been provided in the licence. However, based upon the available data (as presented within Section 5.1 of LDV/SOF SPC) it is expected that non-cirrhotic treatment naïve patients would receive 12 weeks LDV/SOF+RBV (validated through KOL opinion).
- The GT3 treatment experienced arm of ELECTRON-2 trial is ongoing. SVR4 rates of 89% (25/28) and 77% (17/22) have been achieved in the non-cirrhotic and cirrhotic patients, respectively.
- Although the available data in GT3 patients is for LDV/SOF+RBV for 12 weeks, on the basis of the favourable tolerability profile of the drug, the regulators have recommended that specific GT3 patients – those with cirrhosis and/or treatment experienced – should be treated with LDV/SOF+RBV for 24 weeks.

HCV/HIV co-infected patients

- A cure rate of 98% (49/50) was achieved in HCV/HIV co-infected patients treated with LDV/SOF for 12 weeks (ERADICATE). Of the patients not treated with antiretroviral (ARV) drugs, 100% (13/13) achieved SVR12, whilst 97% (36/37) of ARV-treated patients achieved SVR12.
- In line with current clinical guidelines (3;4), the LDV/SOF SPC recommends that HCV/HIV co-infected patients are treated with the same treatment regimens and durations as HCV mono-infected patients.

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

Strengths:

- The efficacy and safety of LDV/SOF for the treatment of CHC in adults has been assessed in a comprehensive clinical trial programme, comprising:
    - Three pivotal randomised, multicentre Phase III studies, ION-1, ION-2, and ION-3 in CHC GT1.
    - One pivotal Phase II study providing evidence in CHC GT4 (SYNERGY).
    - One pivotal Phase II study providing evidence in CHC GT3 (ELECTRON-2).
    - A number of additional Phase II and III studies that provide supporting data for these pivotal studies, as well as key evidence in special populations with limited treatment options, such as those with decompensated cirrhosis or who are pre- or post-liver transplant (GT1 only), those with inherited blood disorders (GT1 only), and patients with HIV co-infection.

  This evidence base supports the use of LDV/SOF regimens in CHC GT1, GT3 and GT4, in treatment naïve and treatment experienced patients, with or without cirrhosis.

- The Phase III studies, ION-1, ION-2, and ION-3 were multicentre studies with recognised clinically valid endpoints and have been published in the NEJM. Seven of the sites in the ION-1 study were in England.
- A wide range of patient groups have been studied in LDV/SOF trials including substantial proportions of patients with characteristics that have historically been associated with lower rates of response to IFN-based treatment (68) and that reflect patient characteristics seen in clinical practice. These characteristics include presence of cirrhosis, both compensated and decompensated, previous treatment failure on PI+PEG-IFN+RBV therapy, high baseline HCV viral load, black race, older age, high BMI, CHC GT1a and a non-CC IL28B genotype. Sub-group analyses across ION-1, ION-2, and ION-3 showed that SVR12 rates with LDV/SOF regimens were not significantly affected by any predefined patient characteristic other than cirrhosis (ION-2). A post-hoc analysis of ION-3 data identified an additional benefit of treating GT1 treatment naïve patients without cirrhosis for 12 weeks (rather than 8 weeks) if baseline viral load was ≥6 million IU/mL.
- No resistance-associated on-treatment virologic breakthrough was observed in the Phase III trials.Two patients experienced virologic breakthrough associated with non-compliance.
- Studies are relevant to the final NICE scope and the licensed indication for LDV/SOF.

Limitations:

- All clinical trials supporting the regulatory submission for LDV/SOF were designed as uncontrolled randomised trials; they compare various LDV/SOF regimens but do not contain classical control arms (i.e. placebo or active comparator arms). However, they have been designed with the rigour expected from a high-quality RCT required to support marketing authorisation. The Phase III studies, ION-1, ION-2, and ION-3 were multicentre studies with recognised clinically valid endpoints and have been published in the NEJM.
    - EMA and US FDA have accepted that new treatments for CHC do not need an RCT design and that the most appropriate comparison to make in the ION studies was with a historical control, based on previously reported data for GT1 with the established PIs, TVR

and BOC. This is appropriate given the challenges associated with using IFN-based regimens as active controls and similar to the situation with SOF. Whereas LDV/SOF regimens are delivered orally, all established regimens contain PEG-IFN which requires administration intravenously, making blinding impossible, in addition to requiring much longer treatment duration for the control arms. PEG-IFN based regimens are also associated with well-documented adverse events that can lead to high discontinuation rates and limit enrolment in studies. As such, new all-oral regimens can not be compared directly against IFN-containing regimens in blinded trials and therefore, in the absence of an all-oral standard of care at the time of study initiation, the non-RCT design and historic control was deemed the most appropriate. (At the time of enrolment, SOF and SMV were not licensed and hence were not considered appropriate comparators). NICE has recently acknowledged this approach, having issued preliminary guidance accepting the use of sofosbuvir (with restrictions) on the basis of similar evidence.

- The Phase III trials were open-label, with only the post-treatment HCV RNA results being blinded to the investigator. However, as all the trials were comparing variations of LDV/SOF regimens, it was not considered necessary to blind them.
    - The clinical data for CHC GT4 are currently limited (data available for [redacted] patients, [redacted] achieved SVR12) with trials on-going (SYNERGY and a French study [GS-US-337-1119]). However, GT4 and GT1 infections are recognised to respond equivalently, (as shown previously for GT1 and GT4 patients treated with other HCV therapies) and it is recommended in the SPC that GT1 and GT4 infections are generally treated similarly with LDV/SOF (Table 3).
- The recommended treatment duration for GT3 patients is 24 weeks for those with cirrhosis and/or prior treatment failure, with no posology recommendation provided for non-cirrhotic treatment naïve patients (although available data is presented in Section 5.1 of the SPC). The clinical data for CHC GT3 are currently limited to LDV/SOF+RBV for 12 weeks in treatment naïve and treatment experienced patients, including those with cirrhosis (ELECTRON-2). In this study all treatment naïve patients achieved SVR12 (100%, n=26), including those with cirrhosis, suggesting that a 12 week regimen is likely to be of sufficient duration to result in cure for the majority of non-cirrhotic treatment naïve patients. The extended 24 week duration in the licence for those with cirrhosis and/or prior treatment failure is a reflection of the regulator's desire to maximise the chance of a cure with LDV/SOF+RBV.
- No UK specific studies have been performed; however, trials have been conducted in populations that can be considered as broadly representative of the UK population. In ION-1, 7 of the 99 sites were in England and across the four treatment groups, 37–46% of the patients enrolled were in Europe, with the remainder enrolled in the US. ION-2 and ION-3 were conducted in the US. However, age and gender demographics of HCV infected patients in the UK and the US are similar (118) and sub-group analyses showed that cure rates with LDV/SOF regimens were not significantly affected by any predefined patient characteristic other than cirrhosis (ION-2).

6.10.3 *Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.*

The evidence base presented herein reflects the evidence of relevance to the licensed indication for LDV/SOF and the decision problem. The patient populations included in the clinical trial programme represent a broad patient population, including difficult-to-treat patients, who are

representative of the real-world CHC population and would be eligible for treatment. The outcomes achieved within the clinical trials are therefore expected in real-world clinical practice.

The primary outcome of HCV treatment is to cure the infection, by eradicating detectable circulating virus in the blood in order to prevent progression of liver disease and the complications of HCV-related liver disease including fibrosis, cirrhosis, hepatocellular carcinoma (HCC), and death (119). The accepted endpoint of therapy is SVR, defined as the absence of detectable HCV RNA in the blood at a defined time point after treatment has been completed (119). SVR12 has been established as an appropriate primary endpoint for regulatory approval (119;120). In the Phase III trials – ION-1, ION-2, and ION-3 – there was 100% concordance between SVR12 and SVR24 confirming that SVR12 is an appropriate primary endpoint for LDV/SOF trials.

Achieving SVR, and therefore being cured of CHC, is associated with a wide range of benefits, including a reduced risk of hepatic decompensation, HCC and death (25-29). A cure is also associated with regression of fibrosis and cirrhosis (25-29) and improved QoL (18;19). From a healthcare perspective, patients who achieve SVR have significantly reduced healthcare utilisation compared with patients who fail to respond to treatment e.g. avoiding liver transplantation (30;119).

Through improving cure rates and therefore reducing onward transmission, LDV/SOF has the potential to positively impact public health by reducing the prevalence and incidence of CHC in UK and thus reducing the long-term burden that it causes to the NHS.

6.10.4 *Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?*

Demographic data from UK suggests that around two-thirds of patients with hepatitis C are male (21;118), with a mean age of 50 years (121). This is generally consistent with the age and sex distribution seen across the pivotal Phase III LDV/SOF studies, in which males accounted for 54-68% of patients and the mean age was between 51 and 57 years. Although the studies ION-2 and ION-3 were conducted at centres only in the US, gender and age demographics of HCV patients in the UK and the US are similar (118;119). The majority of patients were White (76–87%) or Black (11–22%), with other races accounting for ≤3% of treatment arms. Sub-group analyses have demonstrated that demographic factors including race and ethnic group, as well as age and sex, did not have a significant impact on the SVR12 rates achieved.

As described in section 6.10.2 sub-group analyses across ION-1, ION-2, and ION-3 showed that SVR12 rates with LDV/SOF regimens were not significantly affected by any predefined patient characteristic other than cirrhosis (ION-2) and viral load (ION-3).

All trials presented in this submission provide evidence to support the licensed dose (90 mg LDV/400 mg SOF). All trials include treatment arms that are relevant to the licensed regimens (LDV/SOF or LDV/SOF+RBV) and treatment durations (8, 12 or 24 weeks).

The data for LDV/SOF showed no safety or tolerability concerns when extending treatment duration up to 24 weeks. As a result, the regulators have taken a conservative approach of recommending 24 weeks treatment in some subgroups at risk of clinical disease progression and/or with limited re-treatment options, in order to maximise the likelihood of SVR. This recommendation is made despite only small (and in some cases no) improvements in efficacy being demonstrated in the trials. The wording in the SPC provides only general guidance on where

treatment should be extended, leaving the regimen selection to the treating physician. To aid applicability of the study results to patients in England and Wales, guidance is provided in Table 48 as to where it may be appropriate to extend treatment duration in GT1 and GT4 whilst minimising over-treatment of the majority of patients, which would otherwise result in a significant cost to the NHS. The proportion of patients who would likely be treated with each duration of LDV/SOF was validated with three English KOLs.

For GT3 treatment naïve non-cirrhotic patients no posology recommendation is given in the licence (although data from ELECTRON-2 are provided in Section 5.1 of the SPC), whilst for cirrhotic and/or treatment experienced GT3 patients 24 weeks is recommended. Based upon the data available it is assumed that all GT3 treatment naïve non-cirrhotic patients will receive 12 weeks LDV/SOF+RBV, an assumption confirmed by KOLs as appropriate.

To address the uncertainty in the estimates for treatment durations, they were tested in sensitivity analyses by varying the treatment costs for LDV/SOF.

In summary, the clinical trial programme, and thus corresponding study results, are broadly applicable to patients in routine clinical practice in England and Wales.

Table 48: Rationale for modelled treatment regimens and durations

Subgroup	Patient population	Study	SVR12, % (n/N)	Trial duration, weeks	% by licensed treatment duration‡	Rationale
GT1 & GT4						
Treatment naïve	Patients without cirrhosis	ION-3	96.7 (119/123) (patients with baseline viral load <6 million IU/mL)	8	79%	The SPC states "*8 weeks may be considered in previously untreated genotype 1-infected patients*". The overall SVR rate from ION-3 for 8 weeks was 94%, However, a post hoc analysis showed that in patients with viral load of >6 million IU/mL the relapse rate was higher with 8 weeks regimen compared with 12 weeks (10 vs 1%). This analysis supports the use of 8 weeks LDV/SOF for GT1 treatment naïve patients without cirrhosis who have a baseline viral load of <6 million IU/mL, and 12 weeks LDV/SOF in those with a baseline viral load ≥6 million IU/mL. Patient level data from the HCV Research UK database including 408 G1 non-cirrhotic patients in the UK showed 79% had a pre-treatment viral load <6million IU/mL. All GT4 patients should receive 12 weeks of treatment.
		ION-3	96.3 (208/216)	12	21%	
		ION-1	99.4 (179/180)			
	Patients with compensated cirrhosis	ION-1	94.1 (32/34)	12	95%	The SPC states "*12 weeks may be considered in patients deemed at low risk for clinical disease progression and who have subsequent retreatment options*". In the ION-1 study, only 2/67 patients relapsed, with "lost to follow-up" and "withdrawn consent" accounting for the remaining patients not achieving SVR. Both of the patients that relapsed were cirrhotic; one received LDV/SOF for 12 weeks and one LDV/SOF for 24 weeks. Thus, no benefit of extending treatment duration from 12 to 24 weeks was observed in treatment naïve patients treated in Phase III. It is assumed that all patients who are treatment naïve prior to LDV/SOF exposure and do not achieve an SVR are potential candidates for subsequent re-treatment with an IFN-free PI-based regimen. Based upon this rationale, a conservative estimation of 5% has been used in the economic analysis for treatment naïve cirrhotic patients who will be given 24 weeks treatment.
			97.0 (32/33)	24	5%	

Subgroup	Patient population	Study	SVR12, % (n/N)	Trial duration, weeks	% by licensed treatment duration‡	Rationale
Treatment Experienced	Patients without cirrhosis	ION-2	93.6 (102/109)	12	95%	The SPC states "*24 weeks should be considered for previously treated patients with uncertain subsequent retreatment options*". In the ION-2 study, 4/87 (4.6%) treatment experienced non-cirrhotic patients relapsed following 12 weeks LDV/SOF whilst 0/86 relapsed (1 patient withdrew consent and is therefore not included) following 24 weeks LDV/SOF. Patients that are PEG-IFN+RBV experienced have the potential re-treatment option of an IFN-free PI regimen, should they not achieve SVR with 12 weeks LDV/SOF. Given the lack of observed SOF resistance in the SOF and LDV/SOF Phase III trials, patients that are PI+PEG-IFN+RBV experienced have the potential re-treatment option of SOF+PEG-IFN+RBV (or SOF+RBV if intolerant to IFN), should they not achieve SVR with 12 weeks LDV/SOF. Thus, it is expected that there would be very few patients in England and Wales that would be considered as not having a re-treatment option following LDV/SOF. Based upon this rationale, a conservative estimate of 5% has been incorporated into the model for the population that will receive 24 weeks treatment.
			99.1 (108/109)	24	5%	
	Patients with compensated cirrhosis	ION-2	86.4 (19/22)	12	75%	The SPC states "*12 weeks may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options*" In the ION-2 study, 3/22 cirrhotic patients relapsed following 12 weeks LDV/SOF whilst 0/22 relapsed following 24 weeks LDV/SOF, suggesting a potential benefit of extending treatment duration from 12 to 24 weeks. As detailed for the treatment experienced non-cirrhotic patients, it is expected that a small number of patients in England / Wales would not have a subsequent re-treatment option should they not achieve SVR with LDV/SOF. Based upon this rationale, in this submission the assumption has been made that 25% of treatment experienced cirrhotic patients may be at risk of clinical progression.
		ION-2	100 (22/22)	24	25%	
		SIRIUS†	97 (75/77)			

Subgroup	Patient population	Study	SVR12, % (n/N)	Trial duration, weeks	% by licensed treatment duration‡	Rationale
GT3						
Treatment naive	Patients without cirrhosis	ELECTRON-2	100 (21/21)	12	12 wks: 100%	No recommended regimen is detailed in the SPC. The available data indicates that LDV/SOF+RBV for 12 weeks provides an IFN-free option with a high cure rate for this population. At present, no IFN-free regimen is approved for GT3 treatment naïve patients and thus LDV/SOF has the potential to fill this unmet need. A 12 week regimen has therefore been modelled in this submission.
	Patients with compensated cirrhosis	ELECTRON-2	100 (5/5)	12	24 wks: 100%	For GT3 patients with cirrhosis and/or prior treatment failure the SPC gives *24 weeks LDV/SOF+RBV* as the recommended regimen. An alternative, PEG-IFN -based 12-week regimen with high SVR rates is likely to be approved by NICE for these populations (SOF+PR). There is no evidence to suggest that a 24 week LDV/SOF+RBV regimen offers a benefit in SVR rate, but does incur a greater cost. Based upon this rationale, this submission models solely the treatment of IFN-ineligible GT3 patients with cirrhosis and/or prior treatment failure, as these patients are unlikely to have a NICE approved treatment option.
Treatment Experienced	Patients without cirrhosis	ELECTRON-2	SVR4: 89 (25/28)	12	24 wks: 100%	
	Patients with compensated cirrhosis	ELECTRON-2	SVR4: 77 (17/22)	12	24 wks: 100%	

Abbreviations: GT, genotype; LDV, ledipasvir; SOF, sofosbuvir; SVR, sustained virologic response;
† SIRIUS also included an arm with patients treated with LDV/SOF+RBV for 12 weeks giving an SVR12 rate of 96% (74/77). This data became available after the SPC was finalised.
‡ Validated with three English KOLs

7 Cost-effectiveness

7.1 *Published cost-effectiveness evaluations*

Identification of studies

7.1.1 ***Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in Section 10.10, appendix 10.***

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

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

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

Due to the breadth of literature and the changing nature of cost and cost-effectiveness over time, the search was limited to studies published in the last 10 years (i.e. 2002 to the literature search date in September 2012) in the original review. This search was further updated to include all studies published up to October 2013 (Update 1) and then in August 2014 (Update 2). All searches were designed to build on previous searches performed in systematic literature reviews by NICE and the Cochrane Collaboration. Detailed literature search strategies are provided in section **Error! Reference source not found.**. In addition, a manual search of the reference list from included systematic reviews published from 2010 onwards was conducted to ensure that no publications were overlooked.

Following the searches in the aforementioned databases, all potentially eligible references were imported into the Reference Manager software and any duplicates were removed. The titles and abstracts of the remaining references were reviewed by two independent reviewers based on the inclusion and exclusion criteria that were defined by the PICOS (Patient-Intervention-Comparator-Outcome-Study) methodology detailed in Table 49. In the instance of discrepancies between the two decisions, arbitration was carried out by an independent reviewer.

Table 49 Eligibility criteria for cost-effectiveness studies

Category	Inclusion Criteria	Exclusion Criteria
Disease and population	• Infection with Hepatitis C virus (HCV), genotypes 1, 3, 4 • Adults (> 18 years) • Treatment-naïve patients • Treatment-experienced patients: relapsers, non- partial- and null-responders • HIV co-infected patients	• Studies in children • Economic studies on following disease and population: • Not focussed on adults (> 18 years) • Studies on smaller population (< 10) • Acute HCV • Recurrent HCV • HCV/HBV co-infected • Renal dysfunction • Depression • Studies focussing on homeless populations and intravenous drug users (IDU)
Interventions	• HCV screening programmes* • HCV treatments (e.g., PEG-IFN, RBV, LDV, SOF, telaprevir, boceprevir, daclatasvir, asunaprevir, simeprevir, faldaprevir) • Watchful waiting	• Studies not reporting impact on economic outcomes
Outcomes	• Costs • Resource use • QALYs • LYG • Productivity losses	• Non-economic outcomes • Efficacy • Safety • QoL • HCV sequence
Study type	• Economic evaluations • Health technology assessments • Systematic reviews	• Studies not reporting impact on economic outcomes
Language	• Studies in English, French, German, Spanish Italian	• All other languages besides English, French, German, Spanish Italian

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

*Note: In the original review HCV screening programmes were considered a relevant comparator to provide data on another outcome (assess burden of illness) but were not included in the most recent update.

The full publication of any articles that were deemed relevant for full-text review was obtained. Two independent researchers reviewed each full-text article and, in the instance of any disagreement, a third party was consulted. A total of 182 articles were included after the full-text screening stage of

the review (53 articles in the original review, 59 articles in the Update 1, and 70 articles in the Update 2) and were then data extracted. The PRISMA flowcharts of the review are illustrated in Figure 10 (for the original review and Update 1) and Figure 11 (for Update 2).

Figure 10 Flow-chart for economic systematic review (for the original review and Update 1)

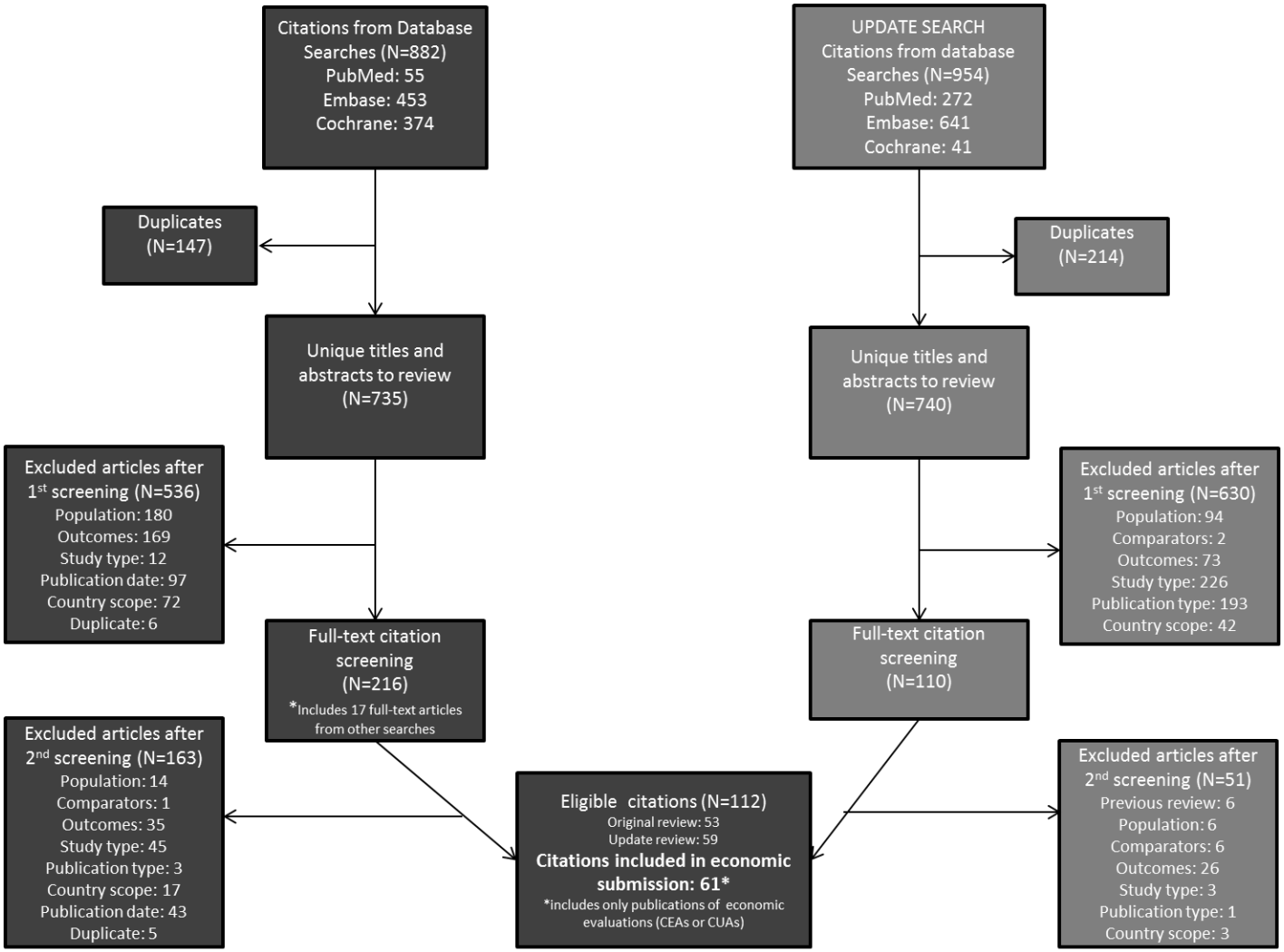
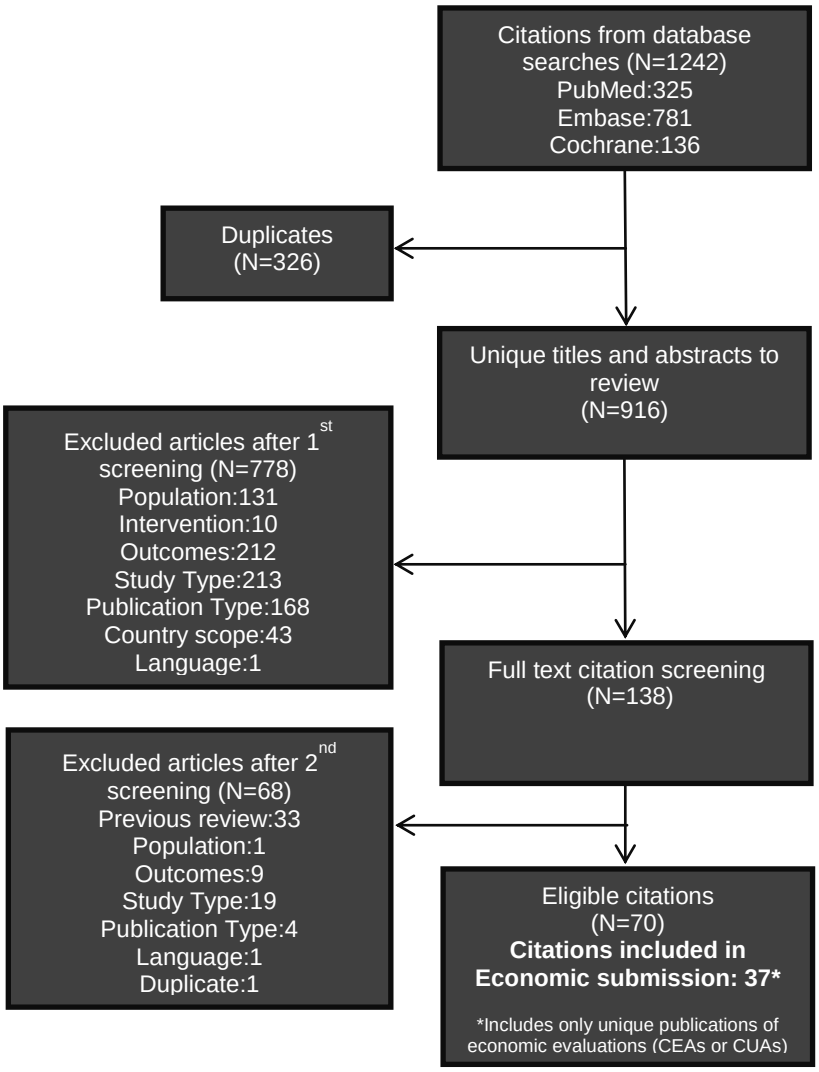


Figure 11 Flow-chart for economic systematic review (for Update 2)



The search in PubMed retrieved 652 results. The search in EMBASE retrieved 1,875 results. The search in CRD retrieved 551 results. A total of 3,078 articles were retrieved by the search (1,836 from original review and Update 1, and 1,242 from Update 2). After the duplicates were removed 2,391 abstracts were available to be reviewed against the criteria outlined in Table 49 and 1,944 papers were excluded. After the abstracts were reviewed, 326 articles from original review and Update 1 (17 articles were included from other searches) and 138 articles from Update 2 were ordered for full publication review. After the full publications were reviewed 182 articles (112 from original review and Update 1, and 70 from Update 2) met the inclusion criteria and data were extracted.

Description of identified studies

7.1.2 ***Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.***

Of the 182 articles that met the inclusion criteria, a total of 98 economic evaluations reporting results from decision analytic models, mathematical models and Monte Carlo simulations in HCV were identified and summarised. These comprised of one cost-minimisation analysis (CMA), 54 cost-effectiveness analyses (CEA) and 43 cost-utility analyses (CUA). A brief overview of all the included economic studies is provided in section **Error! Reference source not found.**.

Of the included studies, only one study (122) evaluated the cost-effectiveness of LDV/SOF fixed dose combination. Six (123-128) studies looked at the cost-effectiveness of screening programmes in HCV and one study (129) investigated the economic and clinical impact of an HCV surveillance strategy for cirrhotic HCV patients. Two (130;131) studies assessed the cost-effectiveness of IFN-based regimen vs. IFN-free regimen. And, two (132;133) studies assessed the cost-effectiveness of new DAA therapies compared with waiting for IFN-free regimen (hypothetical treatment assumed). Four CUAs (134-137) looked at the impact of initiating treatment at different disease stages on the cost-effectiveness of HCV treatment, one CEA (138) looked at the impact of initiating treatment immediately compared to the delayed treatment with a PI-based regimen, and another CEA (139) study assessed the cost-effectiveness of finding cases of HCV infection in the UK migrant populations. Fourteen studies (140-153) assessed the cost-effectiveness of different treatment regimens/strategies e.g. truncated therapy, response-guided therapy, biopsy-guided therapy, multidisciplinary support programme associated therapy, IL28B genotype guided therapy etc. Three other studies (154-156) looked at various methodologies of conducting economic evaluations in chronic HCV. Table 50 presents an overview of the remaining 64 studies (including one LDV/SOF study) comparing the cost-effectiveness of different treatments.

Table 50 Overview of the studies assessing cost-effectiveness of different treatment

Intervention	Number of studies assessing intervention	No. of studies where intervention was found cost-effective/dominant	References
BOC+PEG-IFN+RBV	23 studies	Vs. PEG-IFN+RBV: 18 studies	Becker et al, 2012(157), Elbasha et al, 2013(158), Northup et al, 2009(159), Ramachandran et al, 2012(160), Ferrante et al, 2011(161), Mendes et al, 2011(162), Nikoglou et al, 2011(163), Humphreys et al, 2012(164), Mernagh et al, 2012(165), Odhiambo et al,2012(166), Chan et al, 2013(167), de Ledinghen et al, 2012(168) Jalundhwala et al, 2014(169) Ivakhnenko et al, 2013(170) Mernagh et al, 2013(171) Ferrante et al, 2013(172) Ehlers et al, 2013(173) Athanasakis et al, 2013(174)

Intervention	Number of studies assessing intervention	No. of studies where intervention was found cost-effective/dominant	References
		Vs. PEG-IFN-2b+RBV: 3 studies	Ferrante et al, 2013(175), Chhatwal et al, 2013(176), Blazquez-Perez et al, 2013(177)
		Vs. TVR+PEG-IFN+RBV: 3 studies	Ramachandran et al, 2012(160), Fonseca et al, 2012(178), de Ledinghen et al, 2012(168)
		Vs. No treatment: 1 study	Camma et al, 2013(179)
		Vs. SMV+PEG-IFN+RBV: 1 study	Jalundhwala et al, 2014(169)
		Vs. SOF+PEG-IFN+RBV: 1 study	Jalundhwala et al, 2014(169)
TVR+PEG-IFN+RBV	28 studies	Vs. PEG-IFN+RBV: 21 studies	Cure et al, 2012(180), Northup et al, 2009(159), Ramachandran et al, 2012(160), Jones et al, 2011(181), Gellad et al, 2011(144), Lukac et al, 2012(182), Stahmeyer et al, 2012(183), Chan et al, 2013(167), Jacobson 2012(184), Bock et al, 2013(185), de Ledinghen et al, 2012(168) Brogan et al, 2014(186) Cure et al, 2014(187) Paveliu et al, 2013(188) Garcia et al, 2013(189) Garcia et al, 2013(190) Garcia et al, 2013(191) Buti et al, 2013(192) Morais et al, 2013(193) Kaczor et al, 2013(194)
		Vs. PEG-IFN-2a+RBV: 3 studies	Brogan et al, 2013(195), Cure et al, 2013(196), Said et al, 2012(197)
		Vs. PEG-IFN-2b+RBV: 1 study	Blazquez-Perez et al, 2013(177)
		Vs. BOC+PEG-IFN+RBV: 8 studies	Camma et al, 2013(179), Cure et al, 2013(196) Cure et al, 2014(187) Ruggeri et al, 2014(198) Hasan et al, 2014(199) Ariza et al, 2013(200) Garcia et al, 2013(189) Garcia et al, 2013(190) Garcia et al, 2013(191)
		Vs. No treatment: 1 study	Camma et al, 2013(179)
PEG-IFN+RBV+PI (BOC or TVR)	1 study	Vs. PEG-IFN+RBV	Liu et al, 2012(201)

Intervention	Number of studies assessing intervention	No. of studies where intervention was found cost-effective/dominant	References
PEG-IFN+RBV	7 studies	Vs. No treatment: 5 studies	Norris et al, 2009(202), Chan et al, 2013(167), Logge et al, 2013(203), Brady et al, 2007(204), Siebert et al, 2009a(156)
		Vs. IFN+RBV: 2 studies	Siebert et al, 2009b(205), Brady et al, 2007(204),
		Vs. BSC: 1 study	Hartwell et al, 2011(10)
PEG-IFN-2a+RBV	7 studies	Vs. PEG-IFN-2b+RBV: 5 studies	Ventayol-Bosch et al, 2010(206), Yeh et al, 2007(207) Barros et al, 2013(208) Turnes et al, 2013(209) Ryazhenov et al, 2013(210)
		Vs. No treatment: 2 studies	Yeh et al, 2007(207), Grishchenko et al, 2009(211)
		Vs. BSC: 1 study	Shepherd et al, 2007(9)
PEG-IFN-2b+RBV	2 studies	Vs. No treatment: 1 study	Yeh et al, 2007(207)
		Vs. BSC: 1 study	Shepherd et al, 2007(9)
PEG-IFN-2b	1 study	Vs. BSC	Shepherd et al, 2007(9)
SOF+SMV	1 Study	Vs. SOF/RBV	Hagan et al, 2014(212)
All oral IFN-free regimen	2 studies	Vs. SOC: 1 study	Hagan et al, 2013(213)
		Vs. PEG-IFN+RBV: 1 study	Rein et al, 2014(214)
		Vs. PEG-IFN+RBV+PI (TVR or BOC): 1 study	Rein et al, 2014(214)
		Vs. No treatment: 1 study	Rein et al, 2014(214)
SOF+LDV+RBV	1 study	Vs. No treatment	McGinnis et al, 2014(122)
		Vs. PEG-IFN+RBV+PI (TVR or BOC)	McGinnis et al, 2014(122)
SOF+PEG-IFN+RBV	1 study	Vs. PEG-IFN+RBV+PI (TVR or BOC)	Younossi et al, 2014(215)

BOC, Boceprevir; BSC, Best Supportive Care; IFN, Interferon; LDV, Ledipasvir; PEG-IFN, Pegylated interferon; PEG-IFN-2a, Pegylated interferon α - 2a; PEG-IFN-2b, Pegylated interferon α - 2b; PI, Protease inhibitors; RBV, Ribavirin; SMV, Simeprevir; SOC, Standard of Care; SOF, Sofosbuvir; TVR, Telaprevir.

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

Study Countries

The economic evaluations were conducted in Australia, Brazil, Columbia, Egypt, Peru, Russia, North America (Canada and US) and Europe (Austria, Belgium, Denmark, France, Germany, Greece, Hungary, Italy, Poland, Portugal, Romania, Slovakia, Spain, the UK), with the majority of models based in the US, the UK and France.

Model Structure

A variety of modelling techniques were used to assess the cost-effectiveness of different DAA regimens (including both IFN-based and IFN-free regimens) and standard of care (SOC) in HCV. These models were subject to substantial methodological and structural differences. The two key types of methodologies adopted were: decision trees and Markov models. Other modelling techniques adopted include discrete event simulations and mathematical modelling. Below is a brief overview of the adopted methodologies and structure across all the included economic studies.

Out of the 54 CEA studies, 41 used a Markov model for modelling the decision outcomes based on health states at any given time-point. Of these 41 studies, 24 did not report which Markov model was used, nine used decision analytic Markov model, four used semi-Markov and the remaining four used discrete event simulation model. Three of the CEA studies used a mathematical model, whereas one CEA study each used Monte-Carlo simulation model, decision tree model, Bayesian model and decision analysis model. Six remaining CEA studies did not state the type of modelling approach used. Among the 43 CUA studies, all except two studies have applied a Markov modelling approach. Of these, 32 studies did not report which Markov model was used, six studies used decision analytic Markov model, two studies used semi-Markov model and one study used stochastic decision tree Markov model. Of the remaining two CUA studies, one study used Monte Carlo simulation model and another used both decision tree and Markov model. The cost minimisation study included in the review applied decision tree modelling approach. Of the total economic evaluation studies (n=98), 41 studies used a newly constructed model and rest of the studies applied a previously validated and published model from the literature.

For any economic evaluation, the time horizon considered in the analysis should be long enough to capture the entire difference in costs and outcomes of the alternative strategies. Of the included studies, 70 were conducted over a lifetime horizon, 10 were conducted over 20 to 30 year time frame and one was conducted over treatment duration plus a six-month time horizon. The remaining 17 studies did not clearly state the time horizon for which the analyses were performed. Within the applied models in the reviewed studies, the majority (n=74) were assessed in solely the HCV genotype 1 population.

The perspective adopted within a study determines the different components of costs included and outcomes to be evaluated. Out of the overall identified economic evaluations, 46 studies adopted third party payer perspective (National health services or statutory health insurance services), 14 studies adopted health care system perspective, 11 studies adopted societal perspective, and one study adopted both healthcare and societal perspective. The remaining 26 studies did not clearly state the perspective adopted for the cost evaluation.

Utilities and transition probabilities

Health state utility values representing the HCV-related quality of health or life at different disease states were reported by most of the studies reviewed. Measures of health state utility were most commonly listed for mild to moderate disease consistent with METAVIR fibrosis stages F0 to F2, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplant year 1 and follow up, post liver transplant, SVR associated with cirrhotic and non-cirrhotic disease states and death. Treatment associated utility values were also listed in a few studies.

The speed at which patients move between the Markov states are defined as transitional probabilities. Disease state transitions widely adopted in the extracted studies were between the METAVIR fibrosis stages F0 to F4 sequentially, mild to moderate disease and transitions to advanced liver disease (decompensated cirrhosis, HCC), liver transplant, or liver-related death.

7.1.3 ***Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996 BMJ 313 (7052): 275–83), or Philips Z,* et al*. (2004 Health Technology Assessment 8: 36). For a suggested format based on Drummond and Jefferson (1996), please see Section 10.11, appendix 11.***

See Section **Error! Reference source not found.**, Appendix 11.

7.2 *De novo analysis*

Patients

7.2.1 ***What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in Sections 1.4 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.***

An economic evaluation was conducted to determine the cost-effectiveness of LDV/SOF treatment in chronically infected HCV patients (including patients with HCV/HIV co-infection). These patient groups are defined by HCV genotype including those with compensated cirrhosis and previous treatment (naïve or experienced):

- Genotype 1 and 4 (GT1 and GT4)
  - Treatment naïve patients
  - Treatment experienced patients
- Genotype 3 (GT3)
  - Treatment naïve patients
  - Treatment experienced patients (IFN-ineligible patients only)

These populations reflect both the licensed indications for LDV/SOF therapy as well as the patient populations recruited to the Phase II/III LDV/SOF studies.

GT4

Although limited data currently exist in GT4, [redacted] patients with available data [redacted] have achieved SVR12 (see section 6.5.7.2). GT4 and GT1 infections are known to respond in a similar way and it is recommended in the SPC that GT1 and GT4 infections are generally treated in the same way with LDV/SOF. KOLs agreed that GT1 data could be generalised to GT4 for the purposes of the economic evaluation (section 7.3.5), and hence the economic evaluation covers GT1 and GT4 populations together using clinical data for GT1. The exception is for the treatment naïve population, where the GT1 and GT4 populations are reported separately because the 8 week LDV/SOF treatment option is only recommended for the GT1 treatment naïve without cirrhosis population. In the absence of any GT4 specific data for 8 weeks of treatment, GT4 patients are treated with LDV/SOF for 12 weeks. For this population only the duration is altered and again uses clinical data for GT1.

Scenario analyses have been run applying GT4-specific SVR data for LDV/SOF and comparators where data exists.

GT3

In GT3, LDV/SOF SVR12 data are currently available in treatment naïve patients from ELECTRON-2, with preliminary SVR4 data available from an ongoing arm in this study in treatment-experienced patients. ICERs are provided for all relevant comparators in the treatment naïve population. In the treatment experienced population, comparisons focus only on those patients who are IFN ineligible, a population in whom treatment choices are limited to only SOF+RBV (cirrhotic patients only) or no treatment, and hence where there is the greatest unmet need. This GT3 treatment experienced population only includes IFN-ineligible patients as IFN eligible patients can be treated with SOF+PEG+RBV. As SOF+PEG+RBV is a 12 week treatment option versus the recommended duration of 24 weeks for LDV/SOF, in the interest of simplicity we have not included this comparison as it is highly unlikely that LDV/SOF would be shown to be cost-effective based on the higher treatment costs and no evidence of an additional benefit in efficacy.

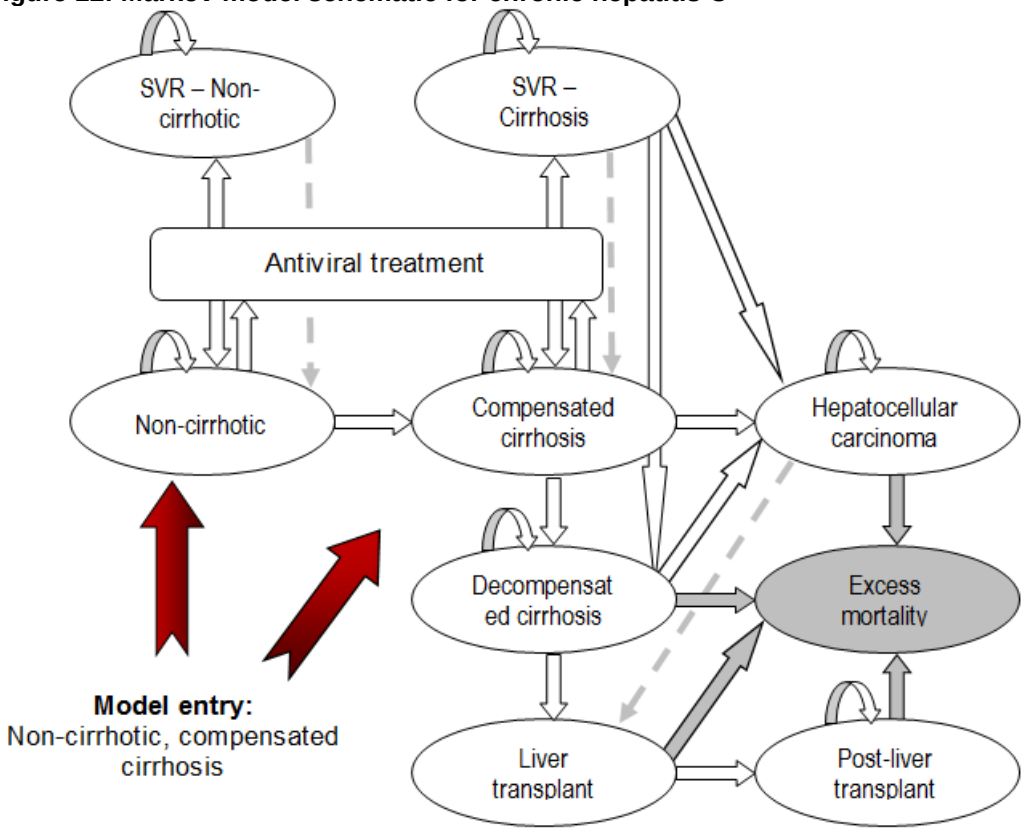
In addition, some comparisons have been restricted to cirrhotic patients only, to align with where the comparator has a NICE recommendation restricting its use to certain sub-populations. This is the case for SOF+PEG-IFN+RBV in GT3 treatment naïve patients with cirrhosis and SOF+RBV in IFN-ineligible GT3 patients with cirrhosis, irrespective of prior treatment experience (based on preliminary NICE recommendations). The exception to this is SMV+SOF, which has been included, despite not being recommended in preliminary NICE guidance, to allow for a comparison versus another medicine for GT1 and GT4 patients who are IFN ineligible.

Model structure

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

The model structure is shown in Figure 12; the same model structure is used for all patients irrespective of HCV genotype or treatment experience. The model consists of nine health states with transition between the states, and costs, mortality and morbidity associated with each state.

Figure 12: Markov model schematic for chronic hepatitis C



Abbreviations: SVR, sustained virologic response.
Notes: Patients can die in each health state.
The grey health state "excess mortality" represents the disease-specific mortality associated with having decompensated cirrhosis, liver transplant or hepatocellular carcinoma.
Dashed arrows represent health state transitions only investigated in sensitivity analysis.

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

A Markov state-transition model was adapted from the model by Dusheiko and Roberts, 1995 (216) to describe the progression of disease over the lifetime of a patient cohort. The rationale for using this model is for two reasons as described below.

Firstly, this model structure represents the natural history of chronic hepatitis C patients and has been widely used and adapted; the latest adaptations were developed by the Southampton Health Technology Assessment Centre (SHTAC) in the UK for NICE (Shepherd et al, 2007 (217) and Hartwell et al, 2011 (10)). This model has been further adapted, similar to the model submitted for the sofosbuvir appraisal, with the pre-compensated cirrhosis health states represented as a single health state (non-cirrhotic), rather than being into mild versus moderate or by METAVIR fibrosis score (F0-F4). As treatment decisions are determined on the presence or absence of cirrhosis, this model structure reflects current clinical practice.

Secondly, this structure offers the best fit for Gilead pivotal Phase III trials, in which patients were split between non-cirrhotic and cirrhotic defined as per the Fibrotest® and Fibroscan® scores. No liver biopsy was performed at study entry, which is used to determine the level of fibrosis with the non-cirrhotic state, which reflects the fact that an invasive liver biopsy is no longer undertaken as part of standard clinical practice in the UK. As such, liver fibrosis according to the METAVIR score

is not available. This model structure is justified in that it reflects clinical practice in the UK, and is therefore an improvement on the precedent model previously submitted to NICE.

For some patients, a liver biopsy had been performed within 2 years of screening (and the METAVIR scores for these patients at that time were recorded). However, as patients may have progressed from the time of the biopsy until trial entry and because data were not available for all patients, we could not base the model structure on this data.

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

Definitions of the individual health states are provided in Table 51.

Table 51: Model states

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

Abbreviations: APRI, aspartate aminotransferase to platelet ratio index; CHC, chronic hepatitis C; kPa, kilopascal; SVR, sustained virologic response.
†Source: Gilead clinical trial protocols
‡Major Symptomatic = encephalopathy, coagulopathy, variceal bleed.

In the pivotal LDV/SOF Phase III trials, the presence of cirrhosis was assessed using liver biopsy or Fibrotest® and Fibroscan® tools, as defined in Table 51. An alternative staging system – the METAVIR system – has been used in some comparator trials, and hence a conversion system is required to enable their use in the model. According to the conversion between Fibrotest®/Fibroscan® and the METAVIR scores provided, non-cirrhotic patients correspond to F0-F3 and cirrhotic patients to F4 in the METAVIR scores. The conversion between the Fibrotest®, Fibroscan® and METAVIR scores is displayed in Table 52.

Table 52: Conversion between Fibrotest®, Fibroscan® and METAVIR scores

METAVIR	Fibrotest®	Fibroscan®
F0 F0–F1 F1	0.00-0.21 0.22-0.27 0.28-0.31	2.4–7.1 kPa
F1–F2 F2	0.32-0.48 0.49-0.58	7.1–9.5 kPa

METAVIR	Fibrotest®	Fibroscan®
F2–F3 F3	0.49-0.58 0.59-0.72	9.5–12.5 kPa
F3–F4 F4	0.73-0.74 0.75-1.00	≥ 12.5 kPa

Abbreviations: kPa, kilopascal.

7.2.5 *How does the model structure capture the main aspects of the condition for patients and clinicians as identified in Section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to Section 2.1.*

The model captures two distinctive and critical aspects of the condition for patients and clinicians: the on-treatment phase (consisting of either active therapy or best supportive care) and the post-treatment phase. As shown in Figure 12, the on-treatment phase ("Antiviral treatment") directs patients in the model to either:

- SVR health states of either "SVR - Cirrhosis" or "SVR - Non-cirrhotic", or
- Disease health states representing non-cirrhotic CHC or CHC with compensated cirrhosis;
  - In these states, patients can either remain in their existing health state, or progress to a worse health state in the direction indicated by the white arrows.
  - These assumptions of disease progression have also been used by Grishchenko et al, 2009 (211), Hartwell et al, 2011 (10) and Shepherd et al, 2007 (217).

Non-cirrhotic and cirrhotic patients move to the SVR health state after completing treatment if they have undetectable HCV RNA 12 or 24 weeks after the end of treatment, otherwise referred to as a 'cure'.

A patient who started treatment in the non-cirrhotic state and was subsequently cured would not become symptomatic again. However, cirrhotic patients who achieved SVR are still exposed to a risk of moving to the decompensated cirrhotic and the hepatocellular carcinoma states.

Recurrence and re-infection of HCV are considered in sensitivity analysis for both non-cirrhotic and cirrhotic patients by allowing them to transition to their initial health state following the reappearance of HCV.

Although there is some evidence to suggest that antiviral treatment, even in the absence of a SVR, can delay disease progression, we made the simplifying assumption that treated patients who do not achieve SVR face an annual probability of progressing from no cirrhosis to compensated cirrhosis at the same rate as if they had not received antiviral treatment (218).

Patients in both compensated and decompensated cirrhosis stages can progress to hepatocellular carcinoma stage, with its associated costs and HRQL. Following liver transplantation, patients face a probability of dying or moving to the post-transplantation phase. In the post-transplantation phase patients remain at a higher risk of death compared with the general population.

For simplification, patients with HCC cannot transition to decompensated cirrhosis since this is expected to have little impact on results, and we have no clinical or economic data on the impact of developing decompensated cirrhosis among patients with HCC.

Although not represented on the transition diagram, age- and gender-specific general population mortality rates are applied to each health state in the model. The risk of death is however highest in the most severe states (i.e. decompensated cirrhosis, HCC, liver transplant, post-liver transplantation). The excess mortality associated with these health states is depicted by the grey coloured arrows in Figure 12.

7.2.6 *Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.*

Table 53: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (until patients reach 100 years of age)	As previous reflected in NICE HTAs, due to the nature of chronic HCV, lifetime horizon allows capturing the difference between LDV/SOF and the comparators in terms of long-term costs and health benefits. This is consistent with the NICE reference case which requires costs and effects to be measured over sufficient time horizon to fully capture the relative costs and benefits.	Hartwell et al, 2011(10) Shepherd et al, 2007 (217)
Cycle length	Monthly for the first 18 cycles, three-monthly thereafter until year 2 and yearly from year 3 until the end of the analysis	LDV/SOF is administered for either 2, 3 or 6 months (8, 12 or 24 weeks) which results in SVR12 measured at 5, 6 or 9 months. Shorter initial cycles also allowed modelling different treatment strategies with patients transiting to SVR12 or SVR24 in the same model at different cycles.	Hartwell et al, 2011(10) Grishchenko et al, 2009(211) Shepherd et al, 2007 (217) Grieve et al, 2006(219) Wright et al, 2006(218)
Half-cycle correction	Applied from year 3 onwards (yearly transitions)	Patients transition throughout the cycle and not only at the beginning/end of each cycle. This is also consistent with previous HTAs. Half-cycle correction applied from year 3 onwards since shorter cycle lengths were applied in years 1-2.	Hartwell et al, 2011(10) Shepherd et al, 2007 (217)
Were health effects measured in QALYs; if not, what was used?	QALYs	As per NICE reference case	NICE methods 2013 (220)
Discount of 3.5% for utilities and costs	3.5% for utilities and costs	As per NICE reference case	NICE methods 2013 (220)
Perspective (NHS/PSS)	NHS and PSS	As per NICE reference case	NICE methods 2013 (220)

Abbreviations: HCV, Hepatitis C Virus; HTA, Health Technology Assessment; NA, not applicable; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; PSS, Personal Social Services; QALY, Quality-Adjusted Life Year; SVR, Sustained Virologic Response

Technology

7.2.7 *Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in Sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?*

Treatment regimens are included as per their marketing authorisations and licensed doses, and are described in Table 54.

Previous guidelines on treatment for HCV have shown PEG-IFN2a to be clinically equivalent to PEG-IFN2b (119), an assumption previously accepted by NICE in the technology appraisals of TVR and SOF (221;222). Given their assumed equivalence, ICERs are only reported herein for comparisons with regimens incorporating PEG-IFN2a. This is a conservative approach in terms of costs as PEG-IFN2a is more expensive than PEG-IFN2b.

Table 54: Treatment strategies per indication

Indication	Active treatment	Comparator(s)
Genotype 1		
GT1 TN	LDV/SOF (90mg/400mg OD) for 8, 12 or 24 wks	SOF (400 mg OD) + PEG-IFN2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 12 wks SMV (150 mg OD) + PEG-IFN2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 24 wks TVR (750 mg q8h) + PEGIFN2a (180µg/wk) + weight-based RBV (15mg/kg OD) for 24 or 48 wks based in stopping rules and eRVR status BOC (800 mg TID) + PEGIFN2b (1.5µg/kg/wk) + weight-based RBV (15mg/kg OD) for 28 or 48 wks based on futility rules PEGIFN2a (180µg/wk) + weight-based RBV (15mg/kg OD) for 48 wks No treatment SMV (150 mg OD) + SOF (400 mg OD) for 12 weeks
GT1 TE	LDV/SOF (90mg/400mg OD) for 12 or 24 wks	SOF (400 mg OD) + PEG-IFN2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 12 wks SMV (150 mg OD) + PEG-IFN2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 48 wks TVR (750 mg q8h) + PEGIFN2a (180µg/wk) + weight-based RBV (15mg/kg OD) for 24 or 48 wks based in stopping rules and eRVR status BOC (800 mg TID) + PEGIFN2b (1.5µg/kg/wk) + weight-based RBV (15mg/kg OD) for 28 or 48 wks based on futility rules PEGIFN2a (180µg/wk) + weight-based RBV (15mg/kg OD) for 48 wks No treatment (PI failures) SMV (150 mg OD) + SOF (400 mg OD) for 12 wks
Genotype 4		

Indication	Active treatment	Comparator(s)
GT4 TN	LDV/SOF (90mg/400mg OD) for 12 or 24 wks	PEGIFN2a (180µg/wk) + weight-based RBV (15mg/kg OD) for 48 wks No treatment SOF (400 mg OD) + PEG-IFN2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 12 wks SMV (150 mg OD) + PEG-IFN2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 24 wks SMV (150 mg OD) + SOF (400 mg OD) for 12 weeks
GT4 TE	LDV/SOF (90mg/400mg OD) for 12 or 24 wks	No treatment (PI failures) PEGIFN2a (180µg/wk) + weight-based RBV (15mg/kg OD) for 48 wks SOF (400 mg OD) + PEG-IFN2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 12 wks SMV (150 mg OD) + PEG-IFN2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 48 wks SMV (150 mg OD) + SOF (400 mg OD) for 12 wks
Genotype 3		
GT3 TN	LDV/SOF (90mg/400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 12 or 24 wks	SOF (400 mg OD) + PEG-IFN2a (180 µg/wk) + weight-based RBV (1,000-1,200 mg OD) for 12 wks SOF (400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 24 wks PEG-IFN2a (180 µg/wk) + weight-based RBV (800 mg OD) for 24 wks No treatment
GT3 TE (IFN ineligible only)	LDV/SOF (90mg/400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 24 wks	SOF (400 mg OD) + weight-based RBV (1,000-1,200 mg OD) for 24 wks No treatment (SOF+PEG-IFN+RBV not included as per rationale provided in Section 7.2.1)

Abbreviations: µg, micrograms; GT, genotype; IFN, interferon; LDV, ledipasvir; PEG-IFN, pegylated interferon; PI, protease inhibitor; OD, once daily; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; wks, weeks; TE, treatment experienced; TN, treatment naïve.

7.2.8 ***Please note that the following question refers to clinical continuation rules and not patient access schemes. If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.***

- ***The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).***
- ***The robustness and plausibility of the endpoint on which the rule is based.***
- ***Whether the 'response' criteria defined in the rule can be reasonably achieved.***
- ***The appropriateness and robustness of the time at which response is measured.***
- ***Whether the rule can be incorporated into routine clinical practice.***
- ***Whether the rule is likely to predict those patients for whom the technology is particularly cost-effective.***
- ***Issues with respect to withdrawal of treatment from non-responders and other equity considerations.***

Treatment regimens and durations for LDV/SOF differ according to genotype, presence of cirrhosis and prior treatment experience. No stopping rules, lead-in phase, or additional treatment is considered for LDV/SOF, in line with what is detailed in the SPC and based upon the LDV/SOF clinical trials, in which 99-100% of patients achieved viral suppression 4 weeks post LDV/SOF treatment initiation. Treatment combinations and length of treatment, dependant on genotype, are listed in section 1.10.

7.3 *Clinical parameters and variables*

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

Key clinical data are listed in Table 55 and described further in the following sub sections.

Table 55 Clinical data implemented in the economic models

Characteristic	Data	Source
Patient characteristics	Mean age at treatment initiation Disease severity distribution (% cirrhotic patients) Weight Probability of death	HCV UK Research Database Published literature
Treatment characteristics	SVR rates Rates of AEs Treatment durations	LDV/SOF clinical trials and comparator published literature Expert opinion
Health related quality of life	Relative on-treatment decrements	LDV/SOF clinical trials and comparator published literature. Where necessary mapping from clinical trial data to SF-6D/EQ-5D was performed.

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

Patient characteristics

Patient characteristics impact on drug dosage, certain transition probabilities and mortality rates. The key patient characteristics, including the percentage of patients who are cirrhotic, mean age at treatment, and mean weight, are presented for each indication in Table 56.

The proportion of non-cirrhotic patients was defined as 100% minus the proportion of cirrhotic patients. In order to reflect real-life practice, the proportions were obtained from the HCV UK Research database querying 5,000 anonymised patient records in the UK (121). The proportion of non-cirrhotic and cirrhotic patients was varied in the deterministic sensitivity analysis (DSA) for all indications.

The mean age at treatment and weight are based on Hartwell et al, 2011 (10).

The annual and 3-month probability of death, by age group for England, was obtained from the Office of National Statistics (ONS) 2010-12 National Life Tables (223). A weighted annual probability rate was calculated by assuming population gender split of 61% men and 39% women (218).

Treatment characteristics

SVR rates directly determine health state progression probabilities. SVR rate inputs for LDV/SOF and comparators were obtained from relevant trials or SPCs and are described in Section 7.3.6 for each population of relevance. As described in Section 6.7, only naïve comparisons were possible due to the non-RCT trial design. LDV/SOF and the comparator regimens are varied in deterministic sensitivity analysis to address the uncertainty in this approach.

Rates of Grade 3 and 4 AEs for LDV/SOF and comparators were obtained from relevant trials or SPCs and are described in Section 7.3.6. Unit costs of treating adverse events were applied, as described in Section 7.5.7.

Treatment durations were used to estimate drug acquisition costs and on-treatment monitoring costs. If more than one treatment duration is recommended a weighted average was calculated. The proportion on a given treatment duration was based on data and/or clinical opinion.

HRQL

The impact of any AE during treatment was captured by monitoring the QoL of a patient across the treatment course and applying this as a utility decrement to baseline utility while on treatment.

Utility decrements are generally expressed as a percentage because a multiplicative approach was used to estimate on-treatment quality of life, which involved application of the treatment-related decrement to baseline utilities. However, in the case of SMV, an absolute treatment-related utility decrement was applied during the duration of treatment in line with data availability.

Utility decrements were either derived directly from the published literature or, where clinical trial HRQL data were used, this was mapped to the appropriate HRQL tool for modelling.

7.3.2 *Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.*

The transition probabilities (TPs) used in the model are reported in Table 57. In general, the TPs chosen were those used by the latest UK HTAs (such as Hartwell et al, 2011 (10) and Shepherd et al, 2007 (217)) and those used by Grishchenko et al, 2009 (211), which were taken from a large representative sample of UK cases centres.

Following the same approach as for the sofosbuvir model, for the non-cirrhotic to compensated cirrhosis transition, TPs were derived from Thompson, 2008 (224). Since these sources provided probabilities for transition between mild, moderate and cirrhotic stages of disease (224), the TPs had to be re-estimated for the non-cirrhotic (F0-F3) to compensated cirrhosis (F4) transition as described below:

1) TPs from mild to moderate, and moderate to cirrhotic disease stages were obtained from Thompson et al, 2008 (224).
2) A three-state Markov model was run for 10, 15 and 20 years where patients moved from mild to moderate and then from moderate to the cirrhotic stage, by applying these TPs. Based on a post-hoc weighted distribution of patients across the F0-F2 (mild) and F3 (moderate) stages of disease in the ION trials (based on conversion to METAVIR staging from Fibrotest®/Fibroscan® scores where available), 78% of patients started the Markov model in the mild state and 22% started the model in the moderate state. The total number of patients ending in the cirrhotic stage at the end of 10, 15 and 20 years was then estimated.
3) Another Markov model was developed that considered only the non-cirrhotic and cirrhotic states (two-state model) to reflect the final economic model structure adopted for this submission.
4) The Solver software was then used to obtain the final TP for the non-cirrhotic to cirrhotic transition for the two-state Markov model so that the number of patients occupying the cirrhotic stage at the end of follow up was equal between the two- and three-state models. As described above, the TPs were obtained for a follow-up period of 10, 15 and 20 years; the two-state Markov model was then rerun using the three different TPs obtained. The root mean square deviation (RMSD) for the difference between the numbers of patients in the cirrhotic state in the two- and three-state Markov model was then estimated. Finally, the probabilities for the transition between non-cirrhotic and cirrhotic selected for use in the model for each age at treatment initiation were the ones resulting in the lowest RMSD.

7.3.3 *Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.*

The model allows the TPs from non-cirrhotic to cirrhotic health states to vary by age and genotype according to published literature (225-230) (section 7.3.2). Previous economic evaluations and HTAs also indicated that TPs between advanced health states are not age-dependent (9;10;218;219). Therefore, TPs from cirrhotic to more advanced health states in the model remain constant. In addition, all-cause mortality was also considered to reflect increased probability of death with age (Appendix, section **Error! Reference source not found.**).

7.3.4 *Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?*

Not applicable

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

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

This model was based on the model submitted to NICE for the appraisal of sofosbuvir. The model structure, assumptions, and inputs for the previous sofosbuvir model were discussed and validated with two external clinical experts (a senior consultant and a nurse specialist) from England (217). Both clinical experts were selected based upon their roles within the NHS as clinical leads at a regional CHC treatment centre that treats >100 CHC patients per year.

The core assumptions that the clinical experts were asked to assess were based upon monitoring and treatment of grade 3 and 4 adverse events only where relevant literature was unavailable.

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

The medium used to collect these assumptions was through direct interview. The outputs were then validated to ensure they were consistent with current practice within advisory board discussions, incorporating an average of eight clinical experts from England and Scotland.

Since these assumptions have been consistently used in both the LDV/SOF and the sofosbuvir models, no further KOL input was sourced for this submission.

Where significant differences existed in the modelling approach for the LDV/SOF cost-effectiveness model, these were also validated by KOL opinion.

A second advisory board comprising of 11 clinical experts were consulted regarding the following modelling assumptions:

- The generalisability of GT1 data to GT4 patients

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

- The KOLs agreed that GT1 data could be generalised to GT4 for the purposes of the economic evaluation. In addition, scenario analyses have been run applying GT4-specific SVR data for LDV/SOF and comparators.

- The feasibility of modelling patients co-infected with HCV and HIV separately
  - The KOLs agreed that patients co-infected with HCV and HIV would be treated with the same regimens and respond to treatment in the same way as mono-infected HCV patients. The KOLs agreed that modelling mono-infected and co-infected patients together was a reasonable and conservative approach.
- The feasibility of modelling pre-/post-transplant treatment
  - The KOLs agreed that data did not currently exist to permit the modelling of HCV treatment in patients pre- or post-liver transplant.

In addition, 3 KOLs were consulted via direct interview regarding the split of patients who would require the different treatment durations for LDV/SOF based on the recommended durations in the SPC. Overall, the KOLs agreed with the base case assumptions as outlined in Table 48 and, based on the clinical data for LDV/SOF, thought the values chosen were conservative in relation to expected clinical practice in the UK. There were two scenarios where values were suggested as possible alternatives to explore extreme values: for TN CC where 85% had 12 week versus 15% on 24 weeks and TE CC where the proportion of patient on 12 and 24 weeks was 50% each. The model was run based on these values and the results are reported in section 7.7.9.

In addition, for TE CC patients, the clinicians who were aware of the SIRIUS data (Section 6.5.7.7) suggested they would consider the use LDV/SOF+RBV for 12 weeks in TE CC patients. While this is not a regimen currently recommended for this population within the posology table of SPC, it is included in section 7.7.9 for information.

Summary of selected values

7.3.6 ***Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.***

Data inputs were classed into two types:

- Generic clinical inputs are those common to all patient groups modelled and are provided in Table 56 to Table 57 and the appendix in section **Error! Reference source not found.** (Patient characteristics, transition probabilities, probability of death). Utility values for individual health states are covered in Section 7.4.9 (Table 72).
- Clinical inputs which differ by patient group (treatment efficacy, treatment duration, adverse event incidence) are provided in Table 58 to Table 71. Utility values by patient group are covered in Section 7.4.9 (Table 73 to Table 76).

Generic inputs

Table 56: Patient characteristics

Indication	% cirrhotic patients†	Mean age at treatment (yrs)‡	Mean weight (kg)‡
Genotype 1 and 4			
GT1 TN	21%	40	79
GT1 TE	21%	45	79

Indication	% cirrhotic patients†	Mean age at treatment (yrs)‡	Mean weight (kg)‡
Genotype 3			
GT3 TN	25%	40	79
GT3 TE	25%	45	79

Abbreviations: GT, genotype; yrs, years.
Source: † HCV UK Research Database Query (121), ‡ Hartwell et al, 2011 (10).

Table 57: Transition probabilities

From	To	TP (annual probabilities)	Source	Comments
Non-cirrhotic	Compensated cirrhosis	**GT1/4** 30 years: 0.006 40 years: 0.009 50 years: 0.016 **GT3** 30 years: 0.008 40 years: 0.013 50 years: 0.024	Calculation, described in text above	TPs were derived from TPs reported by Thompson 2008 (224) (Grishchenko et al, 2009 (211))
Non-cirrhotic, SVR	Non-cirrhotic (recurrence)	Base case: 0 Min: 0 Max: 0.01	Expert opinion	Sensitivity analysis only
	Non-cirrhotic (re-infection)	Base case: 0 Min: 0 Max: 0.01	Expert opinion	Sensitivity analysis only
Compensated cirrhosis	Decompensated cirrhosis	0.0438	Cardoso et al, 2010 (25)	Calculation as per SOF NICE
	HCC	0.0631	Cardoso et al, 2010 (25)	Calculation as per SOF NICE
Compensated cirrhosis with SVR	Compensated cirrhosis (recurrence)	Base case: 0 Min: 0 Max: 0.01	Expert opinion	Sensitivity analysis only
	Compensated cirrhosis (re-infection)	Base case: 0 Min: 0 Max: 0.01	Expert opinion	Sensitivity analysis only
	Decompensated cirrhosis	0.0064	Cardoso et al, 2010 (25)	Calculation
	HCC	0.0128	Cardoso et al, 2010 (25)	Calculation
Decompensated cirrhosis	HCC	0.0631	Cardoso et al, 2010 (25)	Calculation
	Liver transplant	0.022	Siebert et al, 2005 (231)	
	Death	0.13	Fattovich et al, 1997 (232)	Publications that used this TP: -Hartwell et al, 2011 (10) -Shepherd et al, 2007(217) -Wright et al, 2006 (218)

From	To	TP (annual probabilities)	Source	Comments
HCC	Liver transplant	Base case: 0 Min: 0 Max: 0.01	Expert opinion	Sensitivity analysis only
	Death	0.43	Fattovich et al, 1997 (232)	Publications that used this TP: -Hartwell et al, 2011 (10) -Shepherd et al, 2007 (217) -Wright et al, 2006 (218)
Liver transplant	Death, Yr1	0.21	Shepherd et al, 2007 (217)	
Post-liver transplant	Death, Yr2	0.057	Shepherd et al, 2007 (217)	

Abbreviations: GT, genotype; HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability; Yr, year.

Patient group-specific inputs

GT1 Treatment Naïve (TN)

Table 58: GT1 TN: SVR

Strategy	Initial state	SVR % (n/N)	Source
LDV/SOF (8, 12 or 24 wks)	Non-cirrhotic	97.0%	Weighted average SVR rate across the 8- and 12-week treatment regimens (79%:21% split). 8-week SVR (VL<6 million IU/ml) = 96.7% (119/123) (SPC). 12-week SVR = 97.7% ([179+208]/[180+216]). (62;68) (SVRs for 8-week arm were only considered for patients with VL< 6 million IU/ml because patients with VL>6 million IU/ml are not indicated for the short 8 wks duration)(CSRs)
	Cirrhotic	94.3%	ION-1 (CSR)(64) Weighted average SVR rate across the 12- and 24-week treatment regimens (95%:5% split). 12-week SVR = 94.1% (32/34) 24-week SVR = 97.0% (32/33)
SOF+PEG-IFN2a+ RBV (12 wks)	Non-cirrhotic	91.7% (220/240)	NEUTRINO (SPC)
	Cirrhotic	80.8% (42/52)	NEUTRINO (SPC)(1)
SMV+PEG-IFN2a+RBV (24 wks)	Non-cirrhotic	82.0% ([317+60]/[378+82])	Simeprevir SPC 2014 (Pooled data studies C208 and C216 - Table 10)
	Cirrhotic	60.4% (29/48)	Simeprevir SPC 2014 (Pooled data studies C208 and C216 - Table 10) (2)
TVR+PEG-IFN2a+RBV	Non-cirrhotic	77.3% ((237+33+140+68+38+302+65)/(290+52+177+85+59+391+88))	Telaprevir SmPC 2014 (ADVANCE (study 111), ILLUMINATE (study 108) and study C211 – Table 6, 8 and 10) (12)

Strategy	Initial state	SVR % (n/N)	Source
	Cirrhotic	53.4% ((15+24+31)/(21+49+61))	Telaprevir SmPC 2014 (ADVANCE(study 111), ILLUMINATE (study 108) and study C211 – Table 6, 8 and 10) (12)
BOC+PEG-IFN2b+RBV	Non-cirrhotic	64.1% (387/604)	Poordad et al 2012(233)
	Cirrhotic	55.0% (33/60)	Poordad et al 2012(233)
PEG-IFN2a+RBV (48 wks)	Non-cirrhotic	43.6% (376/862)	McHutchison et al, 2009 (109) (Metavir scores F0-F2) (Table 2)‡
	Cirrhotic	23.6% (26/110)	McHutchinson et al 2009(109) (Metavir score F3-F4)
NT	Non-cirrhotic	0.0%	Assumption
	Cirrhotic	0.0%	Assumption
SMV+SOF	Non-cirrhotic	92.9% (13/14)	Lawitz et al (106) – COSMOS Cohort 1 – Prior null responders and METAVIR scores F0-F2
	Cirrhotic	92.9% (13/14)	Lawitz et al (106) – COSMOS Cohort 2 – TN and prior null responders with METAVIR score F3-F4

Abbreviations: AASLD, American Association for the Study of Liver Disease; BOC, boceprevir; CSR, clinical study report; GT, genotype; IU, international units; LDV, ledipasvir; NICE, National Institute for Health and Care Excellence; NT, no treatment; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SPC, summary of product characteristics; SVR, sustained virologic response; TN, treatment-naïve; TVR, telaprevir; VL, viral load; wks, weeks.
‡This study was selected from the clinical systematic literature review as it was the most recent publication with relevant data. Roberts 2009 (234) could have been used as it provided SVRs for F0-F3 and F4 patients; however, the SVRs for F4 patients were considered unrealistically low. Mach 2010(235) and Neri 2010(236) were also considered but they only included the subtype of GT1b patients.

Table 59: GT1 TN: Treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Discontinued due to stopping/ futility rules		Source
	% pts	weeks	% patients	weeks	% pts	weeks	% pts	weeks	
LDV/SOF – non-cirrhotic	79.0% 21.0%‡,§	8.0 12.0	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	ION-1 and ION-3 (CSRs)
LDV/SOF - cirrhotic	95.0% 5.0%¶	12.0 24.0	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	ION-1 (CSR)
SOF+PEG-IFN2a+RBV	97.6%	12.0	1.7%	5.3	0.7%†	4.8	NA	NA	NEUTRINO (SPC)
SMV+PEG-IFN2a+RBV	93.3%	24.0	1.8%	12.0	4.9%†	12.0	NA	NA	Pooling QUEST1/2 + PROMISE††
TVR+PEG-IFN2a+RBV	53.7%§§§ (195/363) 20.1%¶¶¶ (73/363)	24.0 48.0	NA	NA	23.2%†	18.0	1.7%†††† 1.3%‡‡‡‡	4.0 12.0	Jacobson et al, 2011§§§§
BOC+PEG-IFN2b+RBV	44.0% (162/368)§§ 35.1% (129/368)¶¶	28.0‡‡ 48.0‡‡	NA	NA	12.0%†	24.0‡‡‡	9.0%‡‡‡ ([24+9]/[316 +52])	24.0‡‡‡	Poordad et al. 2011 (SPRINT-2)
PEG-IFN2a+RBV	60.0%	48.0	13%	24.0	27.0%†	24.0	NA	NA	McHutchinson et al 2009¶¶¶¶
NT	0.0%	0.0	0.0%	0.0	0.0%	0.0%	NA	NA	Assumption
SMV+SOF	100.0%	12.0	0.0%	0.0	0.0% †	0.0	NA	NA	COSMOS – Cohort 1 and 2 (106) –

Abbreviations: AE, adverse event; BOC, boceprevir; CSR, clinical study report; GT, genotype; IU, international units; LDV, ledipasvir; NA, not applicable; NT, no treatment; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SPC, summary of product characteristics; TN, treatment-naïve; TVR, telaprevir.
† Calculated as 100%-sum of the other categories
‡ Completed treatment 8 weeks from ION-3 and completed treatment 12 weeks from ION-1
§ 79:21 based on split between viral load < 6million IU/ml and >6 million IU/ml from LDV trials from the HCV research database (237), Table 48
¶ Assumption, see Table 48
†† Antiviral Drugs Advisory Committee Meeting – Janssen – 2013 Table 22 (238) – average number of weeks for discontinuation due to AEs and other reasons is an assumption
‡‡ Number of weeks for completed treatment from Boceprevir SmPC 2014 (page 3, table 1)
§§HCV RNA undetectable at week 8-24 (Boceprevir NICE STA (239))
¶¶ HCV RNA not undetectable at week 8-24 (calibrated with Boceprevir NICE STA (239))
‡‡‡Page 1199 and 1201 from Poordad et al 2011 (240)
§§§ eRVR positive (figure 1, T12PR group, 24 wks, from Jacobson et al, 2011 (107))
¶¶¶ eRVR negative (figure 1, T12PR group, 48 wks, from Jacobson et al, 2011 (107))
††††Up to week 4
‡‡‡‡Up to week 12
§§§§ Discontinuations up to week 4 collected from Jacobson et al, 2012(241); Average number of weeks for discontinuation other than futility reasons is an assumption (an assumption was made to obtain an average treatment duration similar to that indicated for the telaprevir treatment arm in the telaprevir STA (242))
¶¶¶¶ Numbers of weeks for discontinuation due to AEs and other reasons are assumptions

Table 60: GT1 TN: Grade 3/4 AEs

	LDV/SOF (%)	SOF+ PEG-IFN2a +RBV (%)	SMV+ PEG-IFN2a +RBV (%)	SOF+ RBV (%)	TVR+ PEGIFN2a +RBV (%)	BOC+ PEG-IFN2b +RBV (%)	PEG-IFN2a +RBV (%)	NT (%)	SMV+ SOF (%)
Nausea	[redacted]	0.0%	0.0%	0.0%	1.0% (13/1346)	0.0%	1.0%	0.0%	0.0%
Vomiting	[redacted]	0.3% (1/327)	0.0%	0.4% (1/250)	0.0%	0.0%	0.0%	0.0%	0.0%
Diarrhoea	[redacted]	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Pruritus	[redacted]	0.0%	0.1% (1/781)	0.0%	1.3% (17/1346)	0.0%	0.1%	0.0%	0.0%
Rash	[redacted]	0.3% (1/327)	0.3% (2/781)	0.0%	4.8% (65/1346)	0.0%	0.1%	0.0%	0.0%
Anaemia	[redacted]	2.1% (7/327)	1.0%	0.80% (2/250)	49.3% ((55+2+377+11)/(82+821))	0.8% (3/368)	¨24.9% ((5+85)/(21+340))	0.0%	0.0%
Thrombocyt-openia	[redacted]	0.3% (1/327)	0.0%	0.0%	2.6% ((10+1+12+0)/(82+821))	0.0%	0.6% ((0+1+1+0)/(21+340))	0.0%	0.0%
Neutropenia	[redacted]	7.0% (23/327)	10%	0.0%	10.3% ((8+2+72+11)/(82+821))	0.27% (1/368)	14.7% ((4+0+39+10)/(21+340))	0.0%	0.0%
Depression	[redacted]	0.3% (1/327)	0.0%	0.0%	0.0%	0.27% (1/368)	0.3%	0.0%	0.0%

Abbreviations: AE, adverse event; BOC, boceprevir; CSR, clinical study report; GT, genotype; LDV, ledipasvir; NT, no treatment; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TN, treatment-naïve; TVR, telaprevir.

Sources:

- LDV/SOF: ION-1(64), ION-2 (73) and ION-3(69) (CSRs)
- SOF+PEG-IFN2a+RBV: NEUTRINO(1)
- SMV+PEG-IFN2a+RBV : Pooling QUEST-1/2 + PROMISE (Antiviral Drugs Advisory Committee Meeting – Janssen, 2013(238) – Table 24 – 27
- SOF+RBV: VALENCE (243) GT3 TN 24 wks (as the required breakdown was not available from QUANTUM)
- TVR+PEGIFN2a+RBV: Anaemia/neutropenia/thrombocytopenia : Kaufman et al (2011)(244) [pooled ADVANCE and ILLUMINATE]; Rash: Cacoub (2012)(245); Other: FDA(246)
- BOC+PEGIFN2b+RBV: Poordad et al (2011) (240) - Table S2C (Supplements)
- PEGIFN2a+RBV: Anaemia/neutropenia/thrombocytopenia : Kaufman et al (2011)(244)(ADVANCE trial); Other: FDA(246)
- NT: No treatment
- SMV+SOF: COSMOS – Cohort 1 and 2 (106)

GT4 TN

This analysis is run separately to GT1 TN as the 8 week treatment duration is only recommended for GT1 TN non-cirrhotic patients and 12 weeks is recommended for all GT4 patients. All inputs are the same as in the GT1 TN analyses except those presented in following tables.

Table 61: GT4 TN: SVR

Strategy	Initial state	SVR % (n/N)	Source
LDV/SOF	Non-cirrhotic	97.7% ([179+208]/[180+216])	Assumed equal to GT1

Strategy	Initial state	SVR % (n/N)	Source
	Cirrhotic	94.3% (32/34)	Assumed equal to GT1
SOF+PEG-IFN2a+RBV (12 wks)	Non-cirrhotic	91.7% (220/240)	Assumed equal to GT1
	Cirrhotic	80.8% (42/52)	Assumed equal to GT1
SMV+PEG-IFN2a+RBV (24 wks)	Non-cirrhotic	82.0% ([317+60]/[378+82])	Assumed equal to GT1
	Cirrhotic	60.4% (29/48)	Assumed equal to GT1
PEG-IFN2a+RBV	Non-cirrhotic	43.6% (376/862)	Assumed equal to GT1
	Cirrhotic	23.6% (26/110)	Assumed equal to GT1
NT	Non-cirrhotic	0.0%	Assumption
	Cirrhotic	0.0%	Assumption
SMV+SOF	Non-cirrhotic	92.9% (13/14)	Assumed equal to GT1
	Cirrhotic	92.9% (13/14)	Assumed equal to GT1

Abbreviations: AASLD, American Association for the Study of Liver Disease; GT, genotype; LDV, ledipasvir; NICE, National Institute for Health and Care Excellence; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SPC, summary of product characteristics; SVR, sustained virologic response; TN, treatment naïve; wks, weeks.

Table 62: GT4 TN: Treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Discontinued due to stopping/ futility rules		Source
	% pts	weeks	% pts	weeks	% pts	weeks	% pts	weeks	
LDV/SOF – non-cirrhotic	100.0%	12.0	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	LDV/SOF (SPC)
LDV/SOF - cirrhotic	95.0% 5.0%‡	12.0 24.0	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	ION-1 (CSR)
SOF+PEG-IFN2a+RBV	97.6%	12.0	1.7%	5.3	0.7% †	4.8	NA	NA	NEUTRINO (SPC)
SMV+PEG-IFN2a+RBV	93.3%	24.0	1.8%	12.0	4.9% †	12.0	NA	NA	Pooling QUEST1/2 + PROMISE§
PEG-IFN2a+RBV	60.0%	48.0	13%	24.0	27.0%†	24.0	NA	NA	McHutchinson et al 2009
NT	0.0%	0.0	0.0%	0.0	0.0%	0.0%	NA	NA	Assumption
SMV+SOF	100.0%	12.0	0.0%	0.0	0.0% †	0.0	NA	NA	COSMOS – Cohort 1 and 2 (106)

Abbreviations: AE, adverse event; CSR, clinical study report; GT, genotype; LDV, ledipasvir; NA, not applicable; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SPC, summary of product characteristics; TN, treatment naïve.
† Calculated as 100%-sum of the other categories
‡Assumption see Table 48.
§Antiviral Drugs Advisory Committee Meeting – Janssen – 2013 Table 22 (238)– average number of weeks for discontinuation due to AEs and other reasons is an assumption

GT1 and GT4 Treatment experienced (TE)

Table 63: GT1 and GT4 TE: SVR

Strategy	Initial state	SVR % (n/N)	Source
LDV/SOF (12 or 24 wks)	Non-cirrhotic	95.6%	ION-2 (CSR)(73) Weighted average SVR rate across the 12- and 24-week treatment regimens (95%:5% split). 12-week SVR = 95.4% (83/87) 24-week SVR = 98.9% (86/87)
	Cirrhotic	89.8%	ION-2 (CSR) (73) Weighted average SVR rate across the 12- and 24-week treatment regimens (75%:25% split). 12-week SVR = 86.4% (19/22) 24-week SVR = 100.0% (22/22)
SOF+PEG-IFN2a+RBV (12 wks)	Non-cirrhotic	74.0% (37/50)	Pol et al 2014 (247)
	Cirrhotic	74.0% (37/50)	Pol et al 2014 (247)
SMV+PEG-IFN2a+RBV	Non-cirrhotic	76.5% (38+[14-9]+19+[7-4]+137+[61-29])/(48+[21-11]+29+[21-13]+167+[83-39])	Simeprevir SPC 2014 (Pooled data studies HPC3007 and C206 - Table 12 and Table 14)‡(2)
	Cirrhotic	66.7% ([9+4+29]/[11+13+39])	Simeprevir SPC 2014 (Pooled data studies HPC3007 and C206 - Table 12 and Table 14) ‡(2)
TVR+PEG-IFN2a+RBV	Non-cirrhotic	72.2% ((68+31+19+5+9+8)/(81+36+24+7+29+17))	Telaprevir SmPC 2014 (REALIZE – Table 13)(248)
	Cirrhotic	47.2% ((23+6+5)/(28+18+26))	Telaprevir SmPC 2014 (REALIZE – Table 13)(248)
BOC+PEG-IFN2b+RBV	Non-cirrhotic	64.4% (85/132)	Bacon BR et al 2011(50) (RESPOND-2) – Supplementary appendix – Table S2
	Cirrhotic	35.3% (6/17)	Bacon BR et al 2011(50) (RESPOND-2) – Supplementary appendix – Table S2
PEG-IFN2a+RBV (48 wks)	Non-cirrhotic	17.6% ((12+2+3+0+1+0)/(38+15+17+5+18+9))	Telaprevir SmPC 2014 (REALIZE – Table 13)(248)
	Cirrhotic	10.0% ((1+1+1)/(15+5+10))	Telaprevir SmPC 2014 (REALIZE – Table 13)(248)
No treatment	Non-cirrhotic	0.0%	Assumption
	Cirrhotic	0.0%	Assumption
SMV + SOF (12 wks)	Non-cirrhotic	92.9% (13/14)	Lawitz et al (106) – COSMOS Cohort 1 – Prior null responders and METAVIR scores F0-F2
	Cirrhotic	92.9% (13/14)	Lawitz et al (106) – COSMOS Cohort 2 – TN and prior null responders with METAVIR score F3-F4

Abbreviations: BOC, boceprevir; CSR, clinical study report; FDA, Food and Drug Administration; GT, genotype; LDV, ledipasvir; PEG-IFN, pegylated interferon; RBV, ribavirin; RGT, response-guided therapy; SMV, simeprevir; SOF, sofosbuvir; SPC, summary of product characteristics; SVR, sustained virologic response; TE, treatment-experienced; TVR, telaprevir; wks, weeks.
‡ Trials were RGT and not fixed the 48 week duration as recommended by the FDA

Table 64: GT1 and GT4 TE: Treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Discontinued due to stopping/ futility rules – during lead-in phase		Source
	% pts	weeks	% pts	weeks	% pts	weeks	% pts	weeks	
LDV/SOF – non-cirrhotic	95.0% 5.0%†	12.0 24.0	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	ION-2 (CSR)(73)
LDV/SOF - cirrhotic	75.0% 25.0%§	12.0 24.0	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	ION-2 (CSR)(73)
SOF+ PEG-IFN2a+ RBV	97.6%	12.0	1.7%	5.3	0.7%‡	4.8	NA	NA	Assumed equal to NEUTRINO(1)
SMV+ PEG-IFN2a +RBV	0% 93.3%‡	24.0 48.0	NA	NA	6.7%	12.0	0.0% 0.0%	4.0 12.0	Antiviral Drugs Advisory Committee Meeting - Janssen – 2013(238); EASL recommendations 2014(3) ¶
TVR+ PEG-IFN2a+ RBV	11.7% 72.9%	24.0 48.0	NA	NA	5.6% ‡	5.0	3.4% 6.4%	4.0 12.0	Telaprevir NICE STA 2009‡ (REALIZE - Table 30 - Table 31);(242)
BOC+ PEG-IFN2b+ RBV	45.7% 18.5%	48.0 48.0	NA	NA	32.1% ‡	36.0	3.7%	4.0	Boceprevir NICE STA 2009 (239); Boceprevir SmPC 2014
PEG-IFN2a+ RBV	37.9%	48.0	6.1%	19.5	56.0% ‡	19.5	NA	NA	Telaprevir NICE STA 2009†† (REALIZE - Table 30 - Table 31)(242);
No treatment	0.0%	0.0	0.0%	0.0	0.0% ‡	0.0	NA	NA	Assumption
SMV+SOF	100.0%	12.0	0.0%	0.0	0.0%	0.0	NA	NA	COSMOS – Cohort 1 and and 2 (106)

Abbreviations: AE, adverse event; BOC, boceprevir; CSR, clinical study report; EASL, European Association for the Study of the Liver; GT, genotype; LDV, ledipasvir; NA, not applicable; PEG-IFN, pegylated interferon; PR, pegylated interferon + ribavirin; RBV, ribavirin; RGT, response-guided therapy; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; TVR, telaprevir.

† 95:5 split based on a small SVR benefit by extending treatment duration from 12 to 24 weeks and most patients will be consider low risk and will have subsequent retreatment options (See Table 48)

‡ Calculated as 100%-sum of the other categories

§ See Table 48.

¶ According to section 7, paragraph 5, of the antiviral drugs advisory committee meeting for simeprevir (238) and the new EASL recommendations 2014(3) for SMV+PR it is recommended that GT1 TE patients receive 48 weeks of PR rather than RGT. Discontinuations to other reasons is from a pooling of QUEST1/2 and PROMISE Table 10(238); Average number of weeks for discontinuation due to other reasons is an assumption

†† Numbers of weeks for discontinuation due to AEs or other reasons calibrated to have an overall treatment duration equal to 30.2 (average between 30.0 and 30.4)

Table 65:GT1 and GT4 TE: Grade 3/4 AEs

	LDV/SOF (%)	SOF+ PEG-IFN2a +RBV (%)	SMV+ PEG-IFN2a +RBV (%)	TVR+ PEG-IFN2a +RBV (%)	BOC+ PEG-IFN2b +RBV (%)	PEG-IFN2a +RBV (%)	NT (%)	SMV+ SOF (%)
Nausea	[redacted]	0.0%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%
Vomiting	[redacted]	0.3% (1/327)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Diarrhoea	[redacted]	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Pruritus	[redacted]	0.0%	0.1%	0.0%	0.0%	0.1%	0.0%	0.0%
Rash	[redacted]	0.3% (1/327)	0.3%	4.8% (14/292)	0.0%	0.1%	0.0%	0.0%
Anaemia	[redacted]	2.1% (7/327)	1.0%	11.6% (34/292)	4.4% (9/205)	29.6% ([10+29]/ [30+102])	0.0%	0.0%
Thrombocytopenia	[redacted]	0.3% (1/327)	0.0%	12.7% ([28+9]/292)	6.3% ([10+3]/205)	3.0% ([0+1+3+0]/ [30+102])	0.0%	0.0%
Neutropenia	[redacted]	7.0% (23/327)	10.0%	2.7% ([6+2]/ 292)	4.4% ([2+7]/ 205)	14.4% ([2+1+13+3]/ [30+102])	0.0%	0.0%
Depression	[redacted]	0.3% (1/327)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Abbreviations: AE, adverse event; BOC, boceprevir; CSR, clinical study report; GT, genotype; LDV, ledipasvir; NT, no treatment; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TE, treatment-experienced; TVR, telaprevir.

Sources:

- LDV/SOF: ION-1, ION-2 and ION-3 (CSR)(73) (64;69)
- SOF+PEG-IFN2a+RBV: NEUTRINO(1)
- SMV+PEG-IFN2a+RBV: Pooling QUEST1/2 + PROMISE (Antiviral Drugs Advisory Committee Meeting - Janssen -2013 -p.72-76;83;85;111;114 - Table 24-Table 27)(238)
- TVR+PEGIFN2a+RBV: Hezode C. et al - AASLD 2012(249)
- BOC+PEGIFN2b+RBV: Hezode C. et al - AASLD 2012(249)
- PEGIFN2a+RBV: Anaemia/neutropenia/thrombocytopenia : Kaufman et al (2011)(244) (REALIZE); Other: FDA(246)
- NT: No treatment
- SMV+SOF: COSMOS – Cohort 1 and 2 (106)

GT3 TN

Table 66: GT3 TN: SVR

Strategy	Initial state	SVR % (n/N)	Source
LDV/SOF+RBV (12 or 24 wks)	Non-cirrhotic	100.0% (21/21)†	ELECTRON-2 (77)
	Cirrhotic	100.0% (5/5)†	ELECTRON-2 (77)
SOF+PEG-IFN2a+RBV (12 wks)	Non-cirrhotic	97.4% (38/39)	Average from ELECTRON(1) and PROTON(1)
	Cirrhotic	83.3%(10/12)	ELECTRON and PROTON did not include non-cirrhotic patients; therefore LONESTAR-2(1) data was used
SOF+RBV (24 wks)	Cirrhotic	92.3% (12/13)	VALENCE(250)

Strategy	Initial state	SVR % (n/N)	Source
PEG-IFN2a+RBV (24 wks)	Non-cirrhotic	71.2% (99/139)	FISSION(251)
	Cirrhotic	29.7% (11/37)	FISSION(251)
NT	Non-cirrhotic	0.0%	No treatment
	Cirrhotic	0.0%	No treatment

Abbreviations: GT, genotype; LDV, ledipasvir; NT, no treatment; PEG-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; TN, treatment-naïve; wks,: weeks.
† Only data for the 12 week LDV/SOF+RBV regimen is available

Table 67: GT3 TN: Treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% pts	weeks	% pts	weeks	% pts	weeks	
LDV/SOF+RBV - non-cirrhotic	100.0%	12.0	[redacted]	[redacted]	[redacted]	0.0	Based on GT1 TN LDV/SOF+RBV 12 weeks from ION-1(64)
LDV/SOF+RBV - cirrhotic	100.0%	24.0	[redacted]	[redacted]	[redacted]	0.0	Based on GT1 TN LDV/SOF+RBV 12 weeks from ION-1(64)
SOF+PEG-IFN2a+RBV (12 wks)	100.0%	12.0	0.0%	0.0	0.0% †	0.0	Average from ELECTRON(1)and PROTON(1)
SOF+RBV (24 wks) – cirrhotic only	98.4%	24.0	0.4%	21.5	1.2% †	21.5	VALENCE(250)‡
PEG-IFN2a+RBV (24 wks)	76.1%	24.0	10.2%	10.8	13.1%	11.9	Assumed equal to 12 weeks from FISSION(251)
NT	0.0%	0.0	0.0%	0.0	0.0%	0.0	No treatment

Abbreviations: AE, adverse event; GT, genotype; LDV, ledipasvir; NT, no treatment; PEG-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; TN, treatment-naïve; wks, weeks.
† Calculated as 100%-sum of the other categories
‡ Average number of weeks for discontinuation due to AEs and other reasons obtained from CSR, Table 4 in appendix assuming patients discontinued in the middle of each interval

Table 68: GT3 TN: Grade 3/4 AEs

	LDV/SOF+RBV (%)	SOF+PEG-IFN2a+ RBV (%)	SOF+RBV (%)	PEG-IFN2a+RBV (%)	NT (%)
Nausea	[redacted]	0.0%	0.0%	0.4% (1/243)	0.0%
Vomiting	[redacted]	0.3% (1/327)	0.4% (1/250)	0.0%	0.0%
Diarrhoea	[redacted]	0.0%	0.0%	0.0%	0.0%
Pruritus	[redacted]	0.0%	0.0%	0.0%	0.0%
Rash	[redacted]	0.3% (1/327)	0.0%	0.0%	0.0%
Anaemia	[redacted]	2.1% (7/327)	0.8% (2/250)	0.8% (2/243)	0.0%
Thrombocytopenia	[redacted]	0.3% (1/327)	0.0%	2.1% (5/243)	0.0%
Neutropenia	[redacted]	7.0% (23/327)	0.0%	3.3% (8/243)	0.0%
Depression	[redacted]	0.3% (1/327)	0.0%	0.4% (1/243)	0.0%

Abbreviations: AE, adverse event; GT, genotype; LDV, ledipasvir; NT, no treatment; PEG-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; TN, treatment-naïve.
Sources:

- LDV/SOF+RBV: Based on GT1 TN LDV/SOF +RBV 12 weeks from ION-1(64) and ION-2 (73)
- SOF+PEG-IFN2a+RBV: Assumed equal to NEUTRINO(1) (as the required breakdown was not available from LONESTAR-2)
- SOF+RBV : VALENCE(250)
- PEG-IFN2a+RBV: FISSION(251)

GT3 TE IFN-ineligible

Given the recommended 24-week LDV/SOF+RBV treatment duration for all patients in the GT3 treatment experienced population, this regimen would not be cost-effective versus the 12-week IFN-containing regimen of SOF+PEG-IFN2a+RBV due to the longer treatment duration and therefore higher treatment cost. Therefore, only the IFN ineligible population is modelled, in comparison with the IFN-free regimen of SOF+RBV or with no treatment.

Table 69: GT3 TE: SVR

Strategy	Initial state	SVR % (n/N)	Source
LDV/SOF+RBV (24 wks)	Non-cirrhotic	89.3% (25/28)	ELECTRON-2 (preliminary SVR4 data)
	Cirrhotic	77.3% (17/22)	ELECTRON-2 (preliminary SVR4 data)
SOF+RBV (24 wks)	Non-cirrhotic	87.0% (87/100)	VALENCE (250)
	Cirrhotic	60.0% (27/45)	VALENCE (250)
No treatment	Non-cirrhotic	0.0%	NT
	Cirrhotic	0.0%	NT

Abbreviations: GT, genotype; LDV, ledipasvir; NT, no treatment; PEG-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; TE, treatment-experienced; wks, weeks.

Table 70: GT3 TE: Treatment duration

Strategy	Completed treatment		Discontinued due to AEs		Discontinued due to other reasons		Source
	% pts	weeks	% pts	weeks	% pts	weeks	
LDV/SOF+RBV	100.0%	24.0	[redacted]	[redacted]	[redacted]	[redacted]	Based on GT1 TE LDV/SOF+RBV 12 weeks from ION-2 (73)
SOF+RBV	98.4%	24.0	0.4%	21.5	1.2% †	21.5	VALENCE‡ (250)
No treatment	0.0%	0.0	0.0%	0.0	0.0% †	0.0	NT

Abbreviations: AE, adverse event; GT, genotype; LDV, ledipasvir; NT, no treatment; PEG-IFN2a, pegylated-interferon; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; wks: weeks.
† Calculated as 100%-sum of the other categories
‡ Average number of weeks for discontinuation due to AEs and other reasons obtained from CSR, Table 4 in appendix assuming patients discontinued in the middle of each interval

Table 71: GT3 TE: Grade 3/4 AEs

	LDV/SOF+RBV (%)	SOF+RBV (%)	NT
Nausea	[redacted]	0.0%	0.0%
Vomiting	[redacted]	0.4% (1/250)	0.0%
Diarrhoea	[redacted]	0.0%	0.0%
Pruritus	[redacted]	0.0%	0.0%
Rash	[redacted]	0.0%	0.0%

Anaemia	[redacted]	0.8% (2/250)	0.0%
Thrombocytopenia	[redacted]	0.0%	0.0%
Neutropenia	[redacted]	0.0%	0.0%
Depression	[redacted]	0.0%	0.0%

Abbreviations: AE, adverse event; GT, genotype; NT, no treatment; PEG-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced.
Sources:

- LDV/SOF+RBV: Based on GT1 TN LDV/SOF +RBV 12 weeks from ION-1(64) and ION-2 (73)
- SOF+RBV : VALENCE(250)

7.3.7 *Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.*

The base case model was based on a lifetime horizon; that is, until patients reached 100 years of age (as utilised in previous HCV NICE HTAs and reflecting the NICE reference case). Long-term consequences (i.e. lifetime costs, life years, quality-adjusted life years, number of deaths avoided, liver transplant avoided, cirrhosis avoided, HCC cases avoided) following the success or not of the treatments (i.e. whether or not patients have reached SVR) were extrapolated by the Markov model.

SVR rates on the other hand were not extrapolated as they came directly from either the literature or clinical trials. The only assumption related to SVR was about the concordance stating equivalent SVR rates when assessed 12 or 24 weeks after the end of treatment (252). SVR12 has been established as an appropriate endpoint for regulatory approval and is now accepted by all clinical and regulatory authorities, including the EMA.

7.3.8 *Provide a list of all assumptions in the de novo economic model and a justification for each assumption.*

As already mentioned, this model is similar to the model submitted to NICE for the recent appraisal of SOF-based regimens for the treatment CHC, with updates including transition probabilities using more recent data as recommended by the ERG from Cardoso et al (25) and the addition of the transition from SVR-CC to HCC, which was not included in the original manufacturer submitted SOF model.

The LDV/SOF model assumptions are listed below. These are compared and discussed in relation to the assumptions made in previous models:

- Patients could enter the model in either the non-cirrhotic or compensated cirrhosis stages of disease. The non-cirrhotic state combined the mild and moderate or fibrosis stages (F0-F3) that have previously been modelled separately. This change reflects the design of the pivotal LDV/SOF trials and the homogeneity of the SVR rates across these patient populations.
- The previous models by Shepherd et al, 2007 (217) and Hartwell et al, 2011 (10) assumed patients who achieved SVR from either mild or moderate chronic HCV have the same risk of developing HCC as the general population. This is consistent with end of treatment biopsies from previously reported trials that did not find any evidence of disease progression following an SVR (253). Therefore a zero risk of progression for non-cirrhotic CHC with SVR to HCC was used for the base case analysis.

- In contrast to non-cirrhotic patients, patients with compensated cirrhosis that achieve SVR still have a (reduced) risk of developing HCC and decompensated cirrhosis (25).
- While patients with compensated cirrhosis that achieve SVR are followed up over a lifetime due to the persistent risk of developing decompensated cirrhosis and HCC (and therefore follow-up costs are applied during that time period), non-cirrhotic patients with SVR are only followed until the end of year two.
- The possibility of recurrence or re-infection in both non-cirrhotic and cirrhotic patients that had reached SVR was considered in sensitivity analysis.
- Shepherd et al, 2007 (217) and Hartwell et al, 2011 (10) included as sensitivity analysis the possibility for mild CHC patients to spontaneously reach SVR. This was not taken into account in this analysis since this assumption has previously been shown to have had a limited impact on these analyses.
- All patients in the decompensated cirrhosis health state are assumed to be candidates for liver transplantation.
- No patients move from the HCC health state to the liver transplant health state, however, this is tested in sensitivity analysis.
- Patients do not progress while on treatment, nor during the 12 to 24 weeks after the end of treatment.
- During treatment, patients may experience a decrement in HRQL resulting from treatment-related adverse events.
- Patients do not die during the treatment period. Background mortality is assumed to be the same as for the general population.
- Transition probabilities from non-cirrhotic to cirrhotic are based on age at treatment.
- Patients who achieve an SVR experience an improvement over their baseline HRQL.
- Data for the treatment of CHC GT1 patients with LDV/SOF is generalisable for the treatment of GT4 patients.
- Patients with HCV/HIV co-infection respond the same as those with HCV mono-infection and therefore are not modelled separately.
- SVR rates are directly comparable across different clinical trials.

These assumptions have been reviewed and confirmed as appropriate through direct interview with clinical experts from England and Scotland. In addition, they were validated to ensure they were consistent with current practice within advisory board discussions incorporating clinical experts from England and Scotland (See Section 7.3.5 for details).

7.4 *Measurement and valuation of health effects*

Patient experience

7.4.1 *Please outline the aspects of the condition that most affect patients' quality of life.*

HCV infection is associated with lower levels of HRQL relative to the general population and significantly higher levels of absenteeism, presenteeism, overall work impairment, and activity impairment (Di Bonaventura et al, 2010 (254)). Reported HRQL impairment is higher in CHC patients compared with other liver diseases as well as other chronic diseases such as type II diabetes and irritable bowel syndrome (Kallman et al, 2007(255); Mikocka-Walus et al, 2008(256)).

Treatment itself can pose an additional burden on the patient by reducing HRQL, increasing activity impairments and resulting in more resource use. Thus, significant unmet medical needs still exist for HCV patients and newer therapies with a favourable side effect profile may have both humanistic and economic benefits. Antiviral therapy is associated with psychiatric side effects and diminished quality of life; patients who developed Major Depressive Disorder as a result of treatment have more severe depressive symptoms, greater impairment on HRQL, and higher haemoglobin levels than non-depressive patients. Patients receiving interferon-based therapy often experience moderate anger while on treatment and greater anger is associated with more depression and poorer HRQL. Treatment history also impacts HRQL in HCV patients; non-responders have lower HRQL scores than untreated and relapsed patients.

Fatigue is one of the most important symptoms negatively impacting HRQL in CHC patients; this impact increases with the degree of liver fibrosis. While changes in HCV disease stage account for some changes in HRQL, this is a limited explanation; factors such as underlying comorbidities, increasing age, lower income and unattached marital status have a greater negative effect on HRQL than disease stage.

7.4.2 *Please describe how a patient's HRQL is likely to change over the course of the condition*

As illustrated by Wright et al, 2006(218), HRQL declines as HCV disease progresses to more advanced disease health states (see Table 72). Patients with non-cirrhotic disease have an average utility of 0.75 at baseline, which increases to 0.79 after treatment for patients that reached SVR. This falls to 0.55 in compensated cirrhosis. In patients with more advanced liver disease such as decompensated cirrhosis, HCC or prior to undergoing liver transplantation utility is even lower (0.45). The Wright et al, 2006(218) utility estimates are consistent with those cited by other economic evaluations, including Grishchenko et al, 2009(211); Shepherd et al, 2007 (217); Hartwell et al, 2011(10) and Grieve et al, 2006(219).

HRQL data derived from clinical trials

7.4.3 *If HRQL data were collected in the clinical trials identified in Section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.*

- ***Method of elicitation.***
- ***Method of valuation.***
- ***Point when measurements were made.***
- ***Consistency with reference case.***
- ***Appropriateness for cost-effectiveness analysis.***
- ***Results with confidence intervals.***

HRQL of patients receiving LDV/SOF±RBV therapy was collected in ION-1, ION-2 and ION-3 using the following instruments: SF-36 (Short Form 36); CLDQ-HCV (Chronic Liver Disease Questionnaire – Hepatitis C Virus); FACIT-F (Functional Assessment of Chronic Illness Therapy-Fatigue); WPAI (Work Productivity and Activity Impairment Questionnaire). Data was planned for collection at various time points during treatment and post-treatment: from baseline to 24-week post-treatment.

Patients treated with LDV/SOF experienced no on-treatment decrements in HRQL during the ION studies (Section 6.5.4, 6.5.5 and 6.5.6). Accordingly, a decrement of 0 was used to model the

effect of LDV/SOF on patients' HRQL during treatment. Although the NICE reference case recommends the use of EQ-5D in modelling, given the 'zero' score from SF-36, mapping from trial-based SF-36 data to EQ-5D was unnecessary.

Patients on LDV/SOF+RBV did experience an on-treatment decrement in quality of life, as measured using SF-36. The approach to modelling this decrement is described in section 7.4.4.

Mapping

7.4.4 ***If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.***

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique

Mapping was not applicable to LDV/SOF data, as described in 7.4.3.

For LDV/SOF+RBV, in the absence of patient level data, the on-treatment utility decrement was estimated using SOF+RBV data from the FUSION, FISSION and POSITRON trials. No on-treatment utility decrement has been observed with either SOF or LDV, therefore it was deemed appropriate to use SOF+RBV utility data as a proxy for the on-treatment utility decrement associated with RBV (and consequently LDV/SOF+RBV). Trial based HRQL data was mapped to SF-6D as described for the SOF regimens below.

For the comparator sofosbuvir (+PEG-IFN+RBV or +RBV), trial based HRQL data was mapped to SF-6D and EQ-5D as described below.

- Utility decrements using the SF-6D metric were derived from the SF-36 questionnaire, which was administered across four of the Phase III studies NEUTRINO, FISSION, FUSION and POSITRON, at each study time point to all patients. The Excel converter program for calculation of SF-6D scores from SF-36 questionnaires using a non-parametric Bayesian algorithm was provided by the University of Sheffield under the terms and conditions of non-commercial end-user license agreement.
- An additional mapping was also performed to convert SF-36 to EQ-5D using several methodological techniques published in the literature (257-259). The final mapping was based on the two-part model combining a probit and linear regression models described by Gray et al, 2004 (257).
- SF-6D values were used rather than EQ-5D values because no systematic literature review was available to select the mapping method.

HRQL studies

7.4.5 ***Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.***

Details can be found in Section **Error! Reference source not found.**. The review was conducted in three stages (original, update 1 and update 2).

7.4.6 *Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.*

- ***Population in which health effects were measured.***
- ***Information on recruitment.***
- ***Interventions and comparators.***
- ***Sample size.***
- ***Response rates.***
- ***Description of health states.***
- ***Adverse events.***
- ***Appropriateness of health states given condition and treatment pathway.***
- ***Method of elicitation.***
- ***Method of valuation.***
- ***Mapping.***
- ***Uncertainty around values.***
- ***Consistency with reference case.***
- ***Appropriateness for cost-effectiveness analysis.***
- ***Results with confidence intervals.***
- ***Appropriateness of the study for cost-effectiveness analysis.***

A total of 77 (28 original review; 27 update 1; 22 update 2) studies examining different aspects of HRQL in hepatitis C patients were included in the final review. A summary of the characteristics of included publications is provided in section **Error! Reference source not found.**.

7.4.7 *Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.*

Not applicable. The utility decrement whilst on treatment with LDV/SOF was obtained from the ION clinical trials, and hence there are no values in the economic literature to compare with. The utility decrement whilst on treatment with LDV/SOF+RBV was assumed to be the same as for SOF+RBV, obtained from the pivotal SOF trials FUSION, FISSION and POSITRON clinical trials, and hence there are no additional values in the economic literature to compare with.

Adverse events

7.4.8 *Please describe how adverse events have an impact on HRQL.*

The overall impact of any AE during treatment would be captured by monitoring the QoL of a patient across the treatment course and applying this as a utility decrement to baseline utility while on treatment. The overall impact for LDV/SOF and SOF regimens was captured from clinical trial data. The utility decrements associated with other comparators are derived from published literature.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 ***Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in Sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.***

Health states

Baseline quality of life in this model is defined by the health state in which the patient enters the model. Health state utilities that are common to all the patient groups assessed in the model are presented in Table 72.

Estimates were obtained from the systematic literature reviews of cost-effectiveness and HRQL studies described in Section 7.1 and 7.4.5. The utilities chosen for the current model were those also used by UK HTAs (Hartwell et al, 2011 (10), Shepherd et al, 2007 (217)) and were predominantly based on the UK trial on mild HCV by Wright et al, 2006 (218). Patients achieving SVR are assumed to have an increase in utility of 0.04, resulting in utilities of 0.79 and 0.59 after treatment, for patients that reached SVR with non-cirrhotic disease and compensated cirrhosis respectively. Previous models have referenced a utility increment post-SVR of 0.05 (218), however the value used in this model is based on data from Vera-Llonch et al, 2013 (260), selected as the most recent data with the least uncertainty and as highlighted by NICE.

As illustrated by Wright et al, 2006 (218), HRQL declines as HCV disease progresses to more advanced disease health states (see Table 72). HCV patients with non-cirrhotic disease have an average utility of 0.75 at baseline, whereas those with compensated cirrhosis have a utility of 0.55. In patients with more advanced liver disease such as decompensated cirrhosis, HCC or prior to undergoing liver transplantation utility is even lower (0.45).

Table 72: Quality-of-life values

Health-state	Utility	Source	Comments
Baseline – non-cirrhotic	0.75	Wright et al, 2006 (218) (UK mild HCV trial)	Average of mild and moderate utilities assuming 78% mild and 22% moderate EQ-5D Publications that used this utility: -Hartwell et al, 2011 (10) -Grishchenko et al, 2009 (211) -Shepherd et al, 2007 (217)
Baseline – compensated cirrhosis	0.55	Wright et al, 2006 (218) (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al, 2011 (10) -Grishchenko et al, 2009 (211)
SVR (utility increment)	0.04	Vera-Llonch et al, 2013 (260)	Most recent data with less uncertainty than Wright et al, 2006 (218)
After treatment at non-cirrhotic stage	0.79	Calculation	Calculated as baseline – non-cirrhotic + utility increment after reaching SVR (0.75 + 0.04)
After treatment at cirrhotic stage	0.59	Calculation	Calculated as baseline – non-cirrhotic + utility increment after reaching SVR (0.55 + 0.04)

Health-state	Utility	Source	Comments
Decompensated cirrhosis	0.45	Wright et al, 2006 (218) (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al, 2011 (10) -Grishchenko et al, 2009 (211) -Shepherd et al, 2007 (217)
Hepatocellular carcinoma	0.45	Wright et al, 2006 (218) (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al, 2011 (10) -Grishchenko et al, 2009 (211) -Shepherd et al, 2007 (217)
Liver transplant	0.45	Wright et al, 2006 (218) (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al, 2011(10) -Shepherd et al, 2007 (217)
Post-liver transplant	0.67	Wright et al, 2006 (218) (UK mild HCV trial)	EQ-5D Publications that used this utility: -Hartwell et al, 2011 (10)

Abbreviations: EQ-5D, EuroQol-5 dimension; HCV, hepatitis C virus; SVR, sustained virologic response.

Treatment-related utility decrements

- LDV/SOF:
  - Zero decrement based on clinical trials (Section 7.4.3).
- LDV/SOF+RBV:
  - SF-6D values derived from mapping from SOF+RBV trials' SF-36 data (Section 7.4.4).
- SOF+PEG-IFN2a+RBV and SOF+RBV alone:
  - SF-6D values derived from mapping from trial-based SF-36 (Section 7.4.4).
- For SMV+PEG-IFN2a+RBV:
  - The utility decrement whilst on treatment was sourced from the simeprevir NICE submission (261).
- For SMV+SOF:
  - The utility decrement was assumed to be equal to that experienced by patients treated with LDV/SOF (0%).
- For PEG-IFN2a+RBV:
  - The utility decrement was obtained from the systematic review. The utility decrement chosen was that also used recent UK HTAs.
- For TVR and BOC:
  - The utility decrements were taken from NICE submissions for TVR and BOC.

Table 73: GT1 and GT4 TN: Treatment-specific quality of life

	Utility	Source
Utility decrement on LDV/SOF	0.0%	ION-1, ION-2, ION-3 (64;69;73)
Utility decrement on SOF+PEG-IFN2a+RBV	-14.5%	NEUTRINO (SF-6D) (1)
Utility decrement on SMV+PEG-IFN2a+RBV	-0.081	Absolute utility decrement from SMV NICE submission (261)
Utility decrement on TVR+PEG-IFN2a+RBV	-14.3%	Telaprevir NICE TA252 (ADVANCE)(242)
Utility decrement on BOC+PEG-IFN2b+RBV	-12.2%	Boceprevir NICE TA253(239)
Utility decrement on PEG-IFN2a+RBV	-14.7%	Shepherd et al, 2007 (217), assuming a split of 78:22% between mild and moderate from the ION trials
Utility decrement on SMV+SOF	0.0%	Assumed equal to LDV/SOF

Abbreviations: BOC, boceprevir; GT, genotype; HCV, hepatitis C virus; LDV, ledipasvir; NICE, National Institute for Health and Care Excellence; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TN, treatment-naïve; TVR, telaprevir.

Table 74:GT1 and GT4 TE: Treatment-specific quality of life

	Utility	Source
Utility decrement on LDV/SOF	0.0%	ION-1, ION-2, ION-3 (64;69;73)
Utility decrement on SOF+PEG-IFN2a+RBV	-14.5%	NEUTRINO (SF-6D)(1)
Utility decrement on SMV+PEG-IFN2a +RBV	-0.119	Absolute utility decrement from SMV NICE submission (261)
Utility decrement on TVR+PEG-IFN2a+RBV	-14.6%	Telaprevir NICE TA252(242) (REALIZE)
Utility decrement on BOC+PEG-IFN2b+RBV	-12.2%	Boceprevir NICE TA253, 2012(239)
Utility decrement on PEG-IFN2a+RBV	-14.7%	Shepherd et al, 2007 (217), assuming a split of 78:22% between mild and moderate from the ION trials
Utility decrement on SMV+SOF	0.0%	Assumed equal to LDV/SOF

Abbreviations: BOC, boceprevir; GT, genotype; LDV, ledipasvir; NICE, National Institute for Health and Care Excellence; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TE, treatment-experienced; TVR, telaprevir.

Table 75: GT3 TN: Treatment-specific quality of life

	Utility	Source
Utility decrement on LDV/SOF+RBV	-4.98%	Calculated assuming a weighted average of utility decrement of FUSION, FISSION and POSITRON
Utility decrement on SOF+PEG-IFN2a+RBV	-14.5%	NEUTRINO (SF-6D) (1)
Utility decrement on SOF+RBV	-4.98%	Calculated assuming a weighted average of utility decrement of FUSION, FISSION and POSITRON
Utility decrement on PEG-IFN2a+RBV	-14.7%	Shepherd et al, 2007 (217), assuming a split of 78:22% between mild and moderate from the ION trials

Abbreviations: GT, genotype; LDV: ledipasvir; PEG-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; TN, treatment-naïve.

Table 76: GT3 TE: Treatment-specific quality of life

	Utility	Source
Utility decrement on LDV/SOF+RBV	-4.98%	Calculated assuming a weighted average of utility decrement of FUSION, FISSION and POSITRON
Utility decrement on SOF+RBV	-4.98%	Calculated assuming a weighted average of utility decrement of FUSION, FISSION and POSITRON

Abbreviations: GT, genotype; LDV, ledipasvir; PEG-IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced.

7.4.10 *If clinical experts assessed the applicability of values available or estimated any values, please provide details. Please provide the following details[b]:*

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

See Section 7.3.5.

7.4.11 *Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?*

Liver fibrosis does not occur at the same rate in all individuals, and does not seem to progress linearly. During the non-cirrhotic (non-SVR) health state, patients may feel mild to severe tiredness, jaundice, loss of appetite, nausea and vomiting, soreness where the liver is, fever, increased moodiness and depression or joint pain. As the disease progresses, more signs and symptoms are present. This may include hypertrophic osteoarthropathy, development of ascites and hypogonadism. These complications are due to the decreased functioning of the liver. Further scarring (fibrosis) of the liver results in a progression of chronic HCV to the health state decompensated cirrhosis or can develop into hepatocellular carcinoma. As these health states can be life-threatening, a liver transplant may be an option to decrease the risk of mortality. Liver

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

transplants have risks and complications due to immunosuppressive management needed. These risk and complications contribute to a lower quality of life compared with a healthy person.

HRQL is assumed constant for as long as the patient remains in one health state and it changes when the patients moves through the different health states. The model assumes a decline in QoL when patients progress from non-cirrhotic health states to compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver transplant. However, an increase in QoL is modelled when patients achieve SVR or after liver transplant (see Table 72). The utility is assumed the same for all patients in any given health state regardless of how long they have been in that state.

7.4.12 ***Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?***

No.

7.4.13 ***If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?***

The baseline quality of life assumed in the analysis is defined by the health state in which the patient enters the model (non-cirrhotic or compensated cirrhotic).

7.4.14 ***Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.***

See Section 7.4.11.

7.4.15 ***Have the values in Sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.***

Not applicable

7.5 *Resource identification, measurement and valuation*

NHS costs

7.5.1 ***Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to Section 2.***

Costs used within the model reflect the NHS and PSS perspective, and have five components:

- Treatment costs
- Treatment-related adverse events costs
- Resource unit costs
- Treatment monitoring costs
- Health state costs

Costs are reported in detail in Section 7.5.5 to 7.5.7.

7.5.2 ***Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.***

In this economic analysis, the NHS reference costs, rather than PbR tariffs, were used for the unit costs of managing patients while on treatment. This is a conservative approach as the NHS reference costs reflect the real cost to the service while the PbR tariffs reflect how much the service is reimbursed. In addition, there is a greater level of granularity with reference costs, which

allows the implementation of a more precise and detailed micro-costing approach. This approach has been adopted to be concordant with previous NICE assessments (10;262).

Resource identification, measurement and valuation studies

7.5.3 ***Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in Section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:***

- ***country of study***
- ***date of study***
- ***applicability to UK clinical practice***
- ***cost valuations used in study***
- ***costs for use in economic analysis***
- ***technology costs.***

Published literature of relevant resource data for the UK was identified through the literature review described in Section 7.1. A summary table of the studies identified in this search is presented in Section **Error! Reference source not found.**.

7.5.4 ***If clinical experts assessed the applicability of values available or estimated any values, please provide details. Please provide the following details[c]:***

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

See Section 7.3.5.

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

Intervention and comparators' costs

7.5.5 ***Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to Sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in Section 7.2.2.***

Drug costs (LDV/SOF and comparators)

Unit costs of the drugs in the sofosbuvir and comparator regimens are presented in Table 77. Estimates for comparators were obtained from the British National Formulary (August 2014) (263).

Table 77: Treatment unit costs

Drug	Cost per pack	Unit dose	Quantity per pack	Source	Assumption
LDV/SOF	£12,993.33	400 mg	28	Gilead	
SOF	£11,660.98	400 mg	28	BNF, August 2014	
RBV	£246.65	400 mg	56	BNF, August 2014	Copegus® 400mg Tablet. Copegus® was used instead of Rebetol® as the first is less expensive and therefore is a conservative approach
PEG-IFN2a	£124.40	180 µg	1	BNF, August 2014	
SMV	£1,866.50	150 mg	7	BNF, August 2014	
TVR	£1,866.50	375 mg	42	BNF, August 2014	
BOC	£2,800	200 mg	336	BNF, August 2014	

Abbreviations: BNF, British National Formulary; BOC, boceprevir; LDV, ledipasvir; PEG-IFN2a, pegylated interferon 2a; OD, once daily; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

Monitoring costs

Monitoring costs refer to the costs of monitoring the patient while being treated with either LDV/SOF or the comparator strategy.

Unit costs used to estimate the monitoring costs are displayed in Table 78. Costs are inflated to 2012-2013 where necessary (264). Generally costs were taken from published sources including previous economic evaluations.

Total monitoring costs for each of the monitoring phases calculated for the non-cirrhotic and cirrhotic patients are presented in Table 79. It should be noted that TN patients have an additional cost of £632 for non-cirrhotic and £824 for cirrhotic for an initial new patient evaluation that is not required for a TE patient. Total monitoring costs for each indication, split by non-cirrhotic and cirrhotic are shown in Table 80.

The compilation of all costs used to calculate monitoring costs is reported in Section **Error! Reference source not found.**.

No differentiation has been made between the monitoring requirements of IFN-containing and IFN-free regimens. Patients treated with IFN may require additional support with drug administration. In

addition, patients treated with IFN would be closely monitored for the development of treatment-related adverse events. Therefore the costs of monitoring are conservative in favour of IFN-containing regimens.

Table 78: Resource use unit costs

Item	Unit cost	Cost year	Inflated £2012-2013	Comment	Source
Outpatient appointment					
Gastroenterology - Consultant Led	£140	2012-2013	£140		NHS Reference costs (265)
Gastroenterology – Non-consultant Led	£107	2012-2013	£107		NHS Reference costs (265)
Inpatient care (day case)					
Clerking in patient (one hour)	£10.18	2003-2004	£13.09		Shepherd et al, 2007 (217)
Test and investigations					
Virology					
HCV screen (RNA) = SVR test	£11.33	2003-2004	£14.57		Shepherd et al, 2007 (217)
HBV	£5.18	2003-2004	£6.66		Shepherd et al, 2007 (217)
Anti-HIV	£13.50	2012	£13.82	Personal communication	Opinion of 1 UK KOL
HIV RNA	£35.00	2012	£35.82	Personal communication	Opinion of 1 UK KOL
Chemical pathology					
Liver function tests (LFT)	£3.60	2003-2004	£4.63		Shepherd et al, 2007 (217)
Alfa-fetoprotein (AFP)	£1.31	2003-2004	£1.68		Shepherd et al, 2007 (217)
Alfa-Antitrypsin	£5.50	2003-2004	£7.07		Shepherd et al, 2007 (217)
Thyrotrophic	£3.60	2003-2004	£4.63		Shepherd et al, 2007 (217)
Free T4	£3.60	2003-2004	£4.63		Shepherd et al, 2007 (217)
Caeruloplasmin	£6.60	2003-2004	£8.49		Shepherd et al, 2007 (217)
Iron	£4.30	2003-2004	£5.53		Shepherd et al, 2007 (217)
Urea and electrolytes (U&Es)	£5.60	2003-2004	£7.20		Shepherd et al, 2007 (217)
Glucose	£2.50	2003-2004	£3.22		Shepherd et al, 2007 (217)
Pregnancy test	£0.25	2003-2004	£0.32		Shepherd et al, 2007 (217)
Thyroid function	£13.30	2003-2004	£17.10		Shepherd et al,

Item	Unit cost	Cost year	Inflated £2012-2013	Comment	Source
tests (TFT)					2007 (217)
Alanine aminotransferase (ALT)	£3.60	2003-2004	£4.63		Shepherd et al, 2007 (217)
Haematology					
Full blood count (FBC)	£2.20	2003-2004	£2.83		Shepherd et al, 2007 (217)
Ferritin	£10.00	2003-2004	£12.86		Shepherd et al, 2007 (217)
Blood clotting factors (INR)	£2.40	2003-2004	£3.09		Shepherd et al, 2007 (217)
Blood group	£2.20	2003-2004	£2.83		Shepherd et al, 2007 (217)
Immunology/chemistry					
Autoantibodies	£22.30	2003-2004	£28.68		Shepherd et al, 2007 (217)
Immunoglobulins	£2.20	2003-2004	£2.83		Shepherd et al, 2007 (217)
Cryoglobulin	£11.90	2003-2004	£15.30		Shepherd et al, 2007 (217)
Radiology					
Ultrasound scan of liver	£48.00	2003-2004	£61.73		Shepherd et al, 2007 (217)
Chest X-ray	£15.00	2003-2004	£19.29		Shepherd et al, 2007 (217)
Ultrasound guided biopsy	£173.00	2003-2004	£222.48		Shepherd et al, 2007 (217)
Ultrasound of liver	£7.20	2003-2004	£9.26		Shepherd et al, 2007 (217)
ECG	£31.00	2003-2004	£39.87		Shepherd et al, 2007 (217)
Molecular pathology					
HCV quantitative viral load	£152.27	2003-2004	£195.82		Shepherd et al, 2007 (217)
Other tests					
Pulmonary function tests	£1.00	2003-2004	£1.29		Shepherd et al, 2007 (217)
HCV genotype	£148.00	2003-2004	£190.33		Shepherd et al, 2007 (217)
Procedures					
Liver biopsy	£126.00	2003-2004	£162.04		Shepherd et al, 2007 (217)
Fibroscan	£50.00	2008-2009	£54.14	Marginal cost. Clinical input suggests that this is	Stevenson et al 2012 (page 67)

Item	Unit cost	Cost year	Inflated £2012-2013	Comment	Source
				likely to be the price charged to the NHS per scan. This is preferred to the Stamuli et al 2009 (266) estimated cost of £19.52 (range £12.44–33.94)	(267)
Fibrotest	£50.00	2008-2009	£54.14	Set similar to the cost of the Enhanced Liver Fibrosis test as both are blood tests and are likely to be competitively priced. This estimate is preferred to a value of €90–300 reported by Morra et al 2007 (268)	Stevenson et al 2012 (page 67) (267)
Endoscopy diagnosis	£110.00	2002-2003	£148.81	Average of London, Newcastle and Southampton costs	Wright et al, 2006 (218)

Abbreviations: ECG, electrocardiogram; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; KOL, key opinion leader; RNA, ribonucleic acid; SVR, sustained virologic response.

Table 79: Costs summary by monitoring phase and treatment

Item	Treatment duration	Total cost
Initial evaluation of a new patient with confirmed HCV		
Total non-cirrhotic	-	£630
Total cirrhotic	-	£822
Further investigations for treatment group		
Total non-cirrhotic	-	£471
Total cirrhotic	-	£471
Total non-cirrhotic TE	-	£471
Total cirrhotic TE	-	£471
Monitoring during active treatment (up to 12 weeks): LDV/SOF/LDV/SOF+RBV		
Total non-cirrhotic	4 weeks	£615
	8 weeks (excl. final visit)	£736
	8 weeks (incl. final visit)	£1,000
	12 weeks of treatment	£1,122
	24 weeks of treatment	£1,365
Total cirrhotic	4 weeks	£615
	8 weeks (excl. final visit)	£736

Item	Treatment duration	Total cost
	8 weeks (incl. final visit)	£1,002
	12 weeks of treatment	£1,123
	24 weeks of treatment	£1,367
Monitoring during active treatment (up to 24 weeks): SOF+PEG-IFN2a+RBV, SOF+RBV		
Total non-cirrhotic	4 weeks	£615
	8 weeks	£736
	12 weeks (excl. final visit)	£858
	12 weeks of treatment (incl. final visit)	£1,122
	24 weeks	£1,365
Total cirrhotic	4 weeks	£615
	8 weeks	£736
	12 weeks (excl. final visit)	£858
	12 weeks (incl. final visit)	£1,123
	24 weeks	£1,367
Monitoring during active treatment (up to 24 weeks): SMV+PEG-IFN2a+RBV, TVR+PEG-IFN2a+RBV, BOC+PEG-IFN2b+RBV, SMV+SOF[†]		
Total non-cirrhotic	4 weeks	£722
	8 weeks	£968
	12 weeks	£1,381
	24 weeks	£1,876
Total cirrhotic	4 weeks	£722
	8 weeks	£968
	12 weeks	£1,505
	24 weeks	£2,374
Monitoring during active treatment (from 24 to 48 weeks): SMV+PEG-IFN2a+RBV, TVR+PEG-IFN2a+RBV, BOC+PEG-IFN2b+RBV[‡]		
Total non-cirrhotic	28 weeks	£2,059
	36 weeks	£2,323
	48 weeks	£2,818
Total cirrhotic	28 weeks	£2,557
	36 weeks	£2,944
	48 weeks	£3,962
Monitoring during active treatment (up to 24 weeks): PEG-IFN2a+RBV		
Total non-cirrhotic	4 weeks	£722
	8 weeks	£968
	12 weeks	£1,320
	24 weeks	£1,755
Total cirrhotic	4 weeks	£722
	8 weeks	£968
	12 weeks	£1,444

Item	Treatment duration	Total cost
	24 weeks	£2,252
Monitoring during active treatment (from 24 to 48 weeks): PEG-IFN2a+RBV		
Total non-cirrhotic	28 weeks	£1,877
	36 weeks	£2,140
	48 weeks	£2,575
Total cirrhotic	28 weeks	£2,374
	36 weeks	£2,761
	48 weeks	£3,719

Abbreviations: HCV, hepatitis C virus; PEG-IFN, pegylated interferon; TE, treatment experienced.
† 50% of patients have 2 extra visits (assumed in week 9 and 23)
‡ 50% of patients have 2 extra visits (in week 9 and 23) and 50% of patients have 2 extra visits (assumed in week 26 and 47).

Table 80: Monitoring costs: summary by indication

Indication	Treatment	Cost, non-cirrhotic	Cost, cirrhotic
Genotypes 1 and 4			
GT1 and GT4 TN	LDV/SOF regimens	£2,127	£2,429
	SOF+PEG-IFN2a+RBV	£2,211	£2,404
	SMV+PEG-IFN2a+RBV	£2,944	£3,609
	TVR+PEG-IFN2a+RBV (GT1 only)	£3,054	£3,802
	BOC+PEG-IFN2b+RBV (GT1 only)	£3,388	£4,923
	PEG-IFN2a+RBV	£3,348	£4,426
	No treatment	£116	£356
	SMV+SOF	£2,482	£2,798
GT1 and GT4 TE	LDV/SOF regimens	£1,615	£1,617
	SOF+PEG-IFN2a+RBV	£1,581	£1,582
	SMV+PEG-IFN2a+RBV	£3,194	£4,270
	TVR+PEG-IFN2a+RBV (GT1 only)	£2,899	£3,799
	BOC+PEG-IFN2b+RBV (GT1 only)	£3,053	£3,986
	PEG-IFN2a+RBV	£2,342	£2,928
	No treatment	£116	£356
	SMV+SOF	£1,853	£1,976
Genotype 3			
GT3 TN	LDV/SOF regimens	£2,283	£2,477
	SOF+PEG-IFN2a+RBV	NA†	£2,417
	SOF+RBV	NA†	£2,654
	PEG-IFN2a+RBV	£2,716	£3,304
	No treatment	£116	£356
GT3 TE IFN-ineligible	LDV/SOF regimens	£1,836	£1,838

Indication	Treatment	Cost, non-cirrhotic	Cost, cirrhotic
	SOF+RBV	NA†	£1,832
	No treatment	£116	£356

Abbreviations: GT, genotype; PEG-IFN2a, pegylated interferon 2a; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TE, treatment experienced; TN, treatment naïve.
†To reflect NICE recommendation, SOF regimens are only considered in cirrhotic GT3 patients.

Health-state costs

7.5.6 ***Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in Section 7.2.4.***

Costs associated with each health state were obtained from the systematic review described in Section 7.1 and are reported in Table 81. The costs chosen for inclusion as model inputs were those used by the most recent HTAs and incorporating updated liver transplant costs published in 2014.

Health state costs are independent from monitoring costs described above as they are used to cost the monitoring of patients in each health state before or after, but not during, treatment. The cost associated with the non-cirrhotic health states was based on a weighted average of the cost of mild and moderate chronic hepatitis C, based on a 78/22 split between mild and moderate as reported in the ION trials. The assumption was similar to the one made for the re-estimation of the transition probabilities from non-cirrhosis to cirrhosis (See Section 7.3.2).

Apart from the costs for patients who reached SVR the health state costs chosen for inclusion in the model are from Wright et al, 2006 (218), since these were based on UK studies. The costs for the most advanced stages of the disease are from an observational study on patients recruited from three hepatology centres in London, Newcastle and Southampton; the costs for mild disease were collected from the UK mild hepatitis C RCT (218); the costs for the liver transplantation were obtained from Longworth et al, 2014 (269). Costs were reported for each phase of liver transplantation: assessment, candidacy, transplant, and post-transplant. The liver transplant cost is equal to the sum of the first three costs. For the post-liver transplant cost, Longworth et al, 2014 didn't provide the split between the first and the second year after transplantation. These costs were estimated assuming an 87:13 split between the first and the second year based on the relation between these costs in Wright et al, 2006. Costs of patients who reached SVR are from Grishchenko et al, 2009 (211) because the costs collected from the UK mild hepatitis C RCT (which were used by Shepherd et al, 2007 and Hartwell et al, 2011) (10) did not split between non-cirrhotic and cirrhotic patients. All costs have been updated to 2012/2013 costs using the Hospital and Community Health Services (HCHS) Pay and Prices Index.

Table 81: Health state costs

Health state	Annual costs	Cost year	Inflated-values cost year 2012-2013	Source
Non-cirrhotic, NT†	-	-	£363	Calculation†
Non-cirrhotic, mild, NT	£138	2002-2003	£187	Wright et al, 2006 (218)
Non-cirrhotic, moderate, NT	£730	2002-2003	£988	Wright et al, 2006 (218)

Health state	Annual costs	Cost year	Inflated-values cost year 2012-2013	Source
Non-cirrhotic, SVR†	-	-	£245	
Non-cirrhotic, SVR (mild)	£202	2006-2007	£234	Grishchenko et al, 2009 (211)
Non-cirrhotic SVR (moderate)	£247	2006-2007	£286	Grishchenko et al, 2009 (211)
Compensated cirrhosis, NT	£1,138	2002-2003	£1,540	Wright et al, 2006 (218)
Compensated cirrhosis, SVR	£437	2006-2007	£506	Grishchenko et al, 2009 (211)
Decompensated cirrhosis	£9,120	2002-2003	£12,339	Wright et al, 2006 (218)
HCC	£8,127	2002-2003	£10,994	Wright et al, 2006 (218)
Liver transplant	£83,505	2014	£83,505	Longworth et al, 2014 (269)
Post-liver transplant				
Follow-up phase (0-12 months)	£27,512	2014	£27,512	Longworth et al, 2014 (269)
Follow-up phase (12-24 months)	£4,111	2014	£4,111	Longworth et al, 2014 (269)

Abbreviations: HCC, hepatocellular carcinoma; NT, no treatment; SVR, sustained virologic response.
†Weighted average of mild and moderate health state costs; 78% of patients in the sofosbuvir trials were calculated to be mild and 22% moderate. Non-cirrhotic health state cost calculated as 78%*£187+22%*£988.

7.5.7 *Please summarise the costs for each adverse event listed in Section 6.9 (Adverse events). These should include the costs of therapies identified in Section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in Section 7.2.2.*

Treatment-related adverse event costs

Drugs used to treat each treatment-related adverse event, along with the unit costs of each drug and duration of treatment, are presented in Table 82 and Table 83. Data were obtained from the British National Formulary (263) and NHS England Reference costs (265) were used for the unit costs of a blood transfusion, which provide a level of granularity that allows the implementation of a more precise and detailed micro-costing approach. Data relating to inpatient, outpatient, hospital registrar and specialist costs related to adverse event management are provided in Table 84 to Table 86.

Table 82: Adverse event unit costs

Adverse event	Drug	Cost per pack	Unit dose	Quantity per pack	Source
Nausea	Metoclopramide	£0.96	10 mg	28	BNF, August 2014; metoclopramide tablets
Vomiting	Metoclopramide	£0.96	10 mg	28	BNF, August 2014; metoclopramide tablets

Adverse event	Drug	Cost per pack	Unit dose	Quantity per pack	Source
Diarrhoea	Loperamide	£1.07	2 mg	30	BNF, August 2014; loperamide caps
Pruritus	Piriton® (chlorphenamine)	£1.62	4 mg	28	BNF, August 2014; Piriton tablets
Anaemia (Epo)	Binocrit® (epoetin alfa)	£50.91	10,000 units	1	BNF, August 2014; Prefilled syringe
Anaemia (blood transfusion)	Blood transfusion	£1,121	NA	1	National Schedule of Reference Costs - Year 2012-13 - NHS trusts and NHS foundation trusts - Elective Inpatient HRG Data†
Rash	Hydrocortisone 1% 15g	£1.04	NA	1	BNF, August 2014; Hydrocortisone 1% cream 15g
Thrombocytopenia	Revolade® (eltrombopag)	£1,540.00	50 mg	28	BNF August 2014
Neutropenia	Neupogen® (filgrastim)	£52.70	600 µg/ml	0.5	BNF, August 2014; Singleject® 0.5-ml prefilled syringe
Depression	Citalopram	£0.96	20 mg	28	BNF, August 2014; NICE guidance CG91 Depression with a chronic physical health problem

Abbreviations: BNF, British National Formulary; HRG, healthcare resource group; NA, not applicable.
† HRG "Single Plasma Exchange, Leucophoresis or Red Cell Exchange, with length of stay 2 days or less, 19 years and over"

Table 83: Adverse event treatment dosing and duration

Adverse event	Drug	Dose	% treated	Weekly costs	Weeks of treatment	Source
Nausea	Metoclopramide	30 mg/day	100%	£0.72	4	Telaprevir manufacturer's submission to NICE (TA252)
Vomiting	Metoclopramide	30 mg/day	100%	£0.72	4	Telaprevir manufacturer's submission to NICE (TA252)
Diarrhoea	Loperamide	2 mg/day	100%	£0.25	4.3	Telaprevir manufacturer's submission to NICE (TA252)
Pruritus	Piriton® (chlorphenamine)	16 mg/day	100%	£1.62	4	Telaprevir manufacturer's submission to NICE (TA252)
Anaemia (Epo)	Binocrit® (epoetin alfa)	40,000 units/wk	1.0%	£2.04	4	Gao et al, 2012 (270)
Anaemia (blood transfusion)*	NA	1	0.7%	£7.85	NA (<2 days)	

Adverse event	Drug	Dose	% treated	Weekly costs	Weeks of treatment	Source
Rash	Hydrocortisone 1%	NA	100%	£0.29	4	Telaprevir manufacturer's submission to NICE (TA252)
Thrombocyto penia	Revolade® (eltrombopag)	50mg/day	100%	£385	4	BNF, August 2014
Neutropenia	Neupogen® (filgrastim)	395 µg/day = 5*79	100%	£486	2	BNF, August 2014 (cytotoxic neutropenia)
Depression	Citalopram	20 mg/day	100%	£0.24	4	BNF, August 2014

Abbreviations: BNF, British National Formulary; epo, erythropoietin; NA, not applicable; NICE, National Institute for Health and Care Excellence; wk, week.

Following the same assumption as in the sofosbuvir model which was based on KOL opinion, it was assumed that most adverse events would be dealt with as outpatient visits as opposed to inpatient visits.

Table 84: Other adverse event costs: Outpatient costs

Adverse event	% of patients with outpatient visits	Number of outpatient visits	Cost per outpatient visit	Total Cost	Source
Nausea	0%	0	£0.00	£0.00	KOL opinion
Vomiting	0%	0	£0.00	£0.00	KOL opinion
Diarrhoea	0%	0	£0.00	£0.00	KOL opinion
Pruritus	0%	0	£0.00	£0.00	KOL opinion
Rash	100%	4	£40.00	£160.00	KOL Opinion; PSSRU unit costs 2013 – Hospital registrar
Anaemia (Epo)	100%	6	£40.00	£240.00	KOL Opinion; PSSRU unit costs 2013 – Hospital registrar
Anaemia (blood transfusion)	NA	NA	NA	NA	Assumed to be included in the HRG cost
Thrombocytopenia	100%	6	£40.00	£240.00	KOL Opinion; PSSRU unit costs 2013 – Hospital registrar
Neutropenia	100%	6	£40.00	£240.00	KOL Opinion; PSSRU unit costs 2013 – Hospital registrar
Depression	0%	0	£0.00	£0.00	KOL opinion

Abbreviations: Epo, erythropoietin; HRG, healthcare resource group; KOL, key opinion leader; NA, not applicable; PSSRU, Personal Social Services Research Unit; wk, week.
†Each visit is assumed to take 1 hour

Table 85: Other adverse event costs: Registrar costs

Adverse event	% of patients visiting registrar	Number of registrar visits	Cost per registrar visit	Total Cost	Source

Adverse event	% of patients visiting registrar	Number of registrar visits	Cost per registrar visit	Total Cost	Source
Nausea	0%	0	£0.00	£0.00	KOL opinion
Vomiting	0%	0	£0.00	£0.00	KOL opinion
Diarrhoea	0%	0	£0.00	£0.00	KOL opinion
Pruritus	0%	0	£0.00	£0.00	KOL opinion
Rash	0%	0	£0.00	£0.00	KOL opinion
Anaemia (Epo)	0%	0	£0.00	£0.00	KOL opinion
Anaemia (blood transfusion)	0%	0	£0.00	£0.00	KOL opinion
Thrombocytopenia	0%	0	£0.00	£0.00	KOL opinion
Neutropenia	0%	0	£0.00	£0.00	KOL opinion
Depression	100%	8	£13.33	£106.67	KOL Opinion; PSSRU unit costs 2013 – Hospital registrar

Abbreviations: Epo, erythropoietin; KOL, key opinion leader; PSSRU, Personal Social Services Research Unit.
†Each visit is assumed to take 20 minutes

Table 86: Other adverse event costs: Specialist costs

Adverse event	% of patients visiting specialist	Number of specialist visits	Cost per specialist visit	Total Cost	Source
Nausea	0%	0	£0.00	£0.00	KOL opinion
Vomiting	0%	0	£0.00	£0.00	KOL opinion
Diarrhoea	0%	0	£0.00	£0.00	KOL opinion
Pruritus	0%	0	£0.00	£0.00	KOL opinion
Rash	100%	2	£215	£284.26	KOL opinion; NHS Ref costs
Anaemia (Epo)	50%	1	£215	£0.71	KOL opinion NHS Ref costs
Anaemia (blood transfusion)	50%	1	£215	£0.50	KOL opinion; NHS Ref costs
Thrombocytopenia	50%	1	£215	£71.07	KOL opinion; NHS Ref costs
Neutropenia	50%	1	£215	£71.07	KOL opinion; NHS Ref costs
Depression	0%	0	£0.00	£0.00	KOL opinion

Abbreviations: Epo, erythropoietin; KOL, key opinion leader.

Miscellaneous costs

7.5.8 ***Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.***

Not applicable.

7.6 *Sensitivity analysis*

7.6.1 *Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.*

In the deterministic sensitivity analysis (DSA), generic and patient-group specific inputs were varied. Details of the inputs varied are provided in Section **Error! Reference source not found.**. Some of the parameters were grouped and varied to perform additional multi-variable sensitivity analyses. These parameters are listed below:

- The total on-treatment cost of LDV/SOF and comparators, including drug acquisition and treatment duration, monitoring costs and adverse events
- The incidence of all adverse events, apart from anaemia treated with EPO and blood transfusion (which were varied individually). This was done separately for LDV/SOF and the comparator
- The costs of non-cirrhotic and cirrhotic disease after treatment, HCC, liver transplant and post-liver transplant
- Utility values for HCC, liver transplant and post-liver transplant
- Transition probabilities from compensated cirrhosis to HCC, from HCC, liver transplant and post-liver transplant to death and from HCC to liver transplant
- Discounting of costs and outcomes
- Background mortality

The results of the deterministic sensitivity analyses are presented in two ways:

1) Net monetary benefit

   The impact of changes in parameters on the net monetary benefit was calculated assuming a willingness-to-pay threshold of £20,000/incremental QALY. The net monetary benefit indicates whether the clinical value of an intervention (measured by assigning a value of £20,000 to each incremental QALY) exceeds its incremental cost. Similarly the net benefit can illustrate where cost savings associated with an intervention may compensate for small losses in clinical outcomes. A positive net monetary benefit indicates that the intervention may be considered cost-effective.

   Presenting the change in the net monetary benefit facilitates the interpretation of the results, especially since LDV/SOF regimens dominate in many comparisons resulting in a negative base case ICER, variations in which are more difficult to interpret.

2) Tornado diagrams

   The impact of the top ten drivers on the net monetary benefit is presented in a table and in the form of a tornado diagram for each analysis.

7.6.2 *Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in Section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.*

See appendix, Section **Error! Reference source not found.**.

7.6.3 *Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in Section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).*

A PSA was undertaken to characterise uncertainty in input parameters, propagate the uncertainty through the model and to present the implications of parameter uncertainty. Inputs are provided in the appendix, Section **Error! Reference source not found.**. For the analysis, 1,000 simulations were performed.

7.7 *Results*

Clinical outcomes from the model

7.7.1 *For the outcomes highlighted in the decision problem (see Section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.*

SVR data derived from clinical trials and presented in data input tables in section 7.3.6 (patient-group specific inputs) was not transformed in any way and the model assumed no mortality while on treatment. As such, the proportion of patients achieving SVR as predicted by the model will be the same as the SVR data inputs.

7.7.2 *Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.*

The Markov traces showing the number of patients in the cohort in each health state over time are presented in the appendix (section **Error! Reference source not found.**). For all indications the Markov trace indicates that patients receiving LDV/SOF therapy spend more time in the SVR health states compared with the other treatments. The majority of QALYs for LDV/SOF regimens are accrued in these health states.

7.7.3 *Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.*

QALYs in each cycle are accrued by multiplying the number of patients in each health state by the utility for that state and applying discounting. To calculate the ICER, QALYs are then summed across the time horizon of the analysis. Patient Markov traces, showing QALYs accrued in the cohort in each health state over time, are provided in the appendix (section **Error! Reference source not found.**) for the indications and regimens.

7.7.4 *Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:*

Model outputs by clinical outcome and total costs are presented in the tables below for each treatment regimen for each genotype. Costs, LYs and QALYs have been discounted at a rate of 3.5% and assumed a time horizon of patients reaching 100 years of age.

Across all populations significant improvements in health outcomes are noted, with reductions in long-term complications, such as DCC, HCC, LT, and mortality.

GT1 treatment naïve

Table 87: Model outputs by outcome

Treatment	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
No treatment	£18,956	13.01	18.30	2,381	1,608	2,755	151	9,931
PEG-IFN2a+RBV	£25,308	13.98	19.23	1,327	1,152	2,024	109	9,913
LDV/SOF	£38,713	15.66	20.81	73	421	915	39	9,888
SMV+PR	£38,731	15.02	20.14	427	691	1,310	66	9,897
TVR+PEG-IFN2a+RBV	£40,237	14.85	19.99	536	758	1,411	72	9,899
BOC+PEG-IFN2b+RBV	£41,299	14.66	19.93	847	851	1,570	80	9,903
SOF+PR	£45,776	15.40	20.54	198	524	1,065	49	9,891
SOF+SMV	£65,630	15.57	20.74	170	459	978	43	9,890

Abbreviations: BOC, boceprevir; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LDV, ledipasvir; LY, life year; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; wk, week.

GT4 treatment naive

Table 88: Model outputs by outcome

Treatment	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
No treatment	£18,956	13.01	18.30	2,381	1,608	2,755	151	9,931
PEG-IFN2a+RBV	£25,308	13.98	19.23	1,327	1,152	2,024	109	9,913
SMV+PR	£38,731	15.02	20.14	427	691	1,310	66	9,897
SOF+PR	£45,776	15.40	20.54	198	524	1,065	49	9,891
LDV/SOF	£46,823	15.67	20.81	54	415	905	39	9,888
SOF+SMV	£65,630	15.57	20.74	170	459	978	43	9,890

Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LDV, ledipasvir; LY, life year; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; wk, week.

GT1/GT4 treatment experienced

Table 89: Model outputs by outcome

Treatment	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
No treatment	£18,143	12.40	17.44	2,144	1,494	2,554	138	9,927
PEG-IFN2a+RBV	£24,960	12.75	17.83	1,749	1,319	2,273	122	9,920
TVR+PEG-IFN2a+RBV	£42,101	13.90	18.84	589	775	1,415	73	9,899

SMV+PR	£43,626	14.13	19.17	496	651	1,237	61	9,895
BOC+PEG-IFN2b+RBV	£45,897	13.69	18.62	752	882	1,577	83	9,903
SOF+PR	£46,756	14.21	19.16	557	640	1,234	59	9,896
LDV/SOF	£49,537	14.72	19.58	95	419	886	39	9,887
SOF+SMV	£64,720	14.71	19.60	153	423	897	39	9,888

Abbreviations: BOC, boceprevir; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LDV, ledipasvir; LY, life year; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; wk, week.

GT3 treatment naïve

Table 90: Model outputs by outcome

Treatment	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
PR	£18,937	14.01	19.07	865	1,111	1,981	106	9,910
No treatment	£21,509	12.24	17.49	3,020	1,987	3,403	187	9,945
LDV/SOF	£57,909	15.48	20.76	0	441	1,001	41	9,890

Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LDV, ledipasvir; LY, life year; PR, pegylated interferon+ribavirin; QALY, quality adjusted life year; SOF, sofosbuvir; wk, week.

Table 91: Model outputs by outcome (cirrhotic patients only)

Treatment	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt†	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
SOF+PR	£63,419	9.38	16.28	NA	2,130	4,476	202	9,963
SOF+RBV	£95,947	9.87	17.04	NA	1,927	4,207	181	9,958
LDV/SOF	£102,645	10.23	17.55	NA	1,765	4,004	164	9,955

Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LDV, ledipasvir; LY, life year; PR, pegylated interferon+ribavirin; QALY, quality adjusted life year; RBV, ribavirin; SOF, sofosbuvir; wk, week.
† All patients enter the model with compensated cirrhosis

GT3 treatment experienced IFN ineligible

Table 92: Model outputs by outcome

Treatment	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
No treatment	£20,614	11.71	16.74	2740	1847	3158	171.1	9941
LDV/SOF	£89,259	14.12	19.03	292	625	1243	58.0	9903

Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LDV, ledipasvir; LY, life year; QALY, quality adjusted life year; SOF, sofosbuvir; wk, week.

Table 93: Model outputs by outcome (cirrhotic patients only)

Treatment	Cost(£)/pt	QALYS /pt	LYs /pt	CC /10,000pt†	DCC /10,000pt	HCC /10,000pt	Liver transplant /10,000pt	Deaths /10,000pt
SOF+RBV	£101,109	8.01	14.13	NA	2,524	4,873	240	9,970
LDV/SOF	£105,761	8.76	15.24	NA	2,137	4,360	200	9,961

Abbreviations: CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LDV, ledipasvir; LY, life year; QALY, quality adjusted life year; RBV, ribavirin; SOF, sofosbuvir; wk, week.
† All patients enter the model with compensated cirrhosis

7.7.5 *Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.*

The disaggregated incremental QALYs and costs by health state and predicted resource use are shown in appendix **Error! Reference source not found.** for each population modelled.

Across all populations a higher number of QALYs are gained with the LDV/SOF regimen. This is explained by the fact that more patients are cured with LDV/SOF (that is, more patients reach the SVR health state which is associated with increased utility values), and consequently fewer patients progress to the more severe health state where HRQL is expected to decrease. This highlights the overall positive impact of LDV/SOF on a patient's quality of life.

Patients treated with LDV/SOF have lower costs associated with off-treatment health states compared with those in the comparator arms in the majority of cases. This is a consequence of better efficacy of LDV/SOF, which means that fewer patients will suffer from more advanced health states and complications. LDV/SOF is also associated with lower on-treatment costs compared with some regimens due to the shorter treatment duration and reduction in monitoring required. This is particularly evident in the GT1 TN patient population.

Base-case analysis

7.7.6 ***Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.***

A summary of the base case results for all patient populations are presented in Table 1, which provide ICERs for LDV/SOF versus each comparator. Results by population and ranked by cost are presented in Table 95 to Table 101. Cost-effectiveness frontiers are also presented (Figure 13 to Figure 19).

The results show that:

- For patients with CHC GT1 and GT4, LDV/SOF is highly cost-effective compared with all comparators in treatment naïve and treatment experienced patients.
  - In GT1 treatment naïve patients LDV/SOF dominates SOF+PEG-IFN+RBV, SMV+PEG-IFN+RBV, TVR, BOC and SMV+SOF and is highly cost-effective versus PEG-IFN+RBV and no treatment (ICERs<£8,000)
  - In GT4 treatment naïve patients LDV/SOF dominates SMV+SOF and is cost-effective versus all other active treatments and no treatment (ICERs<£13,000)
  - In GT1 and GT4 treatment experienced patients LDV/SOF dominates SMV+SOF and is cost-effective versus all other active treatments and no treatment (ICERs<£14,000)
- For treatment naïve patients with GT3 infection, ICERs <£27,000 result from comparisons with PEG-IFN, no treatment or SOF+RBV. GT3 IFN-ineligible patients without cirrhosis do not have an active treatment option at all, therefore LDV/SOF+RBV provides a much needed cost-effective option (ICER=£11,235) for these patients.
- For treatment experienced IFN ineligible patients with GT3 infection LDV/SOF is a cost-effective option versus the only active treatment available for this group of patients (£6,210 versus SOF+RBV in patients with cirrhosis). Given that patients without cirrhosis do not have an active treatment option at all, LDV/SOF appears to provide a much needed cost-effective option for these patients.

Table 94: Summary of base-case cost-effectiveness results (ICER for LDV/SOF±RBV against each comparator: £/QALY)

Indication	LDV/SOF regimen	Comparator							
		SOF+ PEG-IFN2a +RBV	SMV+ PEG-IFN2a +RBV	PEG-IFN2a +RBV	TVR+ PEG-IFN2a +RBV	BOC+ PEG-IFN2a +RBV	SOF+RBV	NT	SMV+SOF
GT1 treatment naïve	LDV/SOF	LDV/SOF dominates	LDV/SOF dominates	£7,985	LDV/SOF dominates	LDV/SOF dominates	-	£7,458	LDV/SOF dominates
GT4 treatment naïve	LDV/SOF	£3,869	£12,399	£12,715	-	-	-	£10,468	LDV/SOF dominates
GT1/GT4 treatment experienced†	LDV/SOF	£5,497	£9,984	£12,491	£9,144	£3,551	-	£13,527	LDV/SOF dominates
GT3 treatment naïve‡	LDV/SOF+RBV	£46,691‡	-	£26,491	-	-	£19,013‡	£11,235	-
GT3 treatment experienced IFN ineligible‡	LDV/SOF+RBV	-	-	-	-	-	£6,210‡	£28,048	-

Abbreviations: BOC, boceprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; NT, no treatment; PEG-IFN, pegylated interferon; QALY; quality adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
† TVR+PEG-IFN2a+RBV and BOC+PEG-IFN2a+RBV are relevant for GT1 CHC only as they are not licensed for the treatment of GT4 CHC.
‡ In GT3 patients some comparisons have been restricted to cirrhotic patients only in line with preliminary NICE recommendations for particular comparators. All other scenarios include a mixed cohort of non-cirrhotic and cirrhotic patients.

GT1 treatment naïve

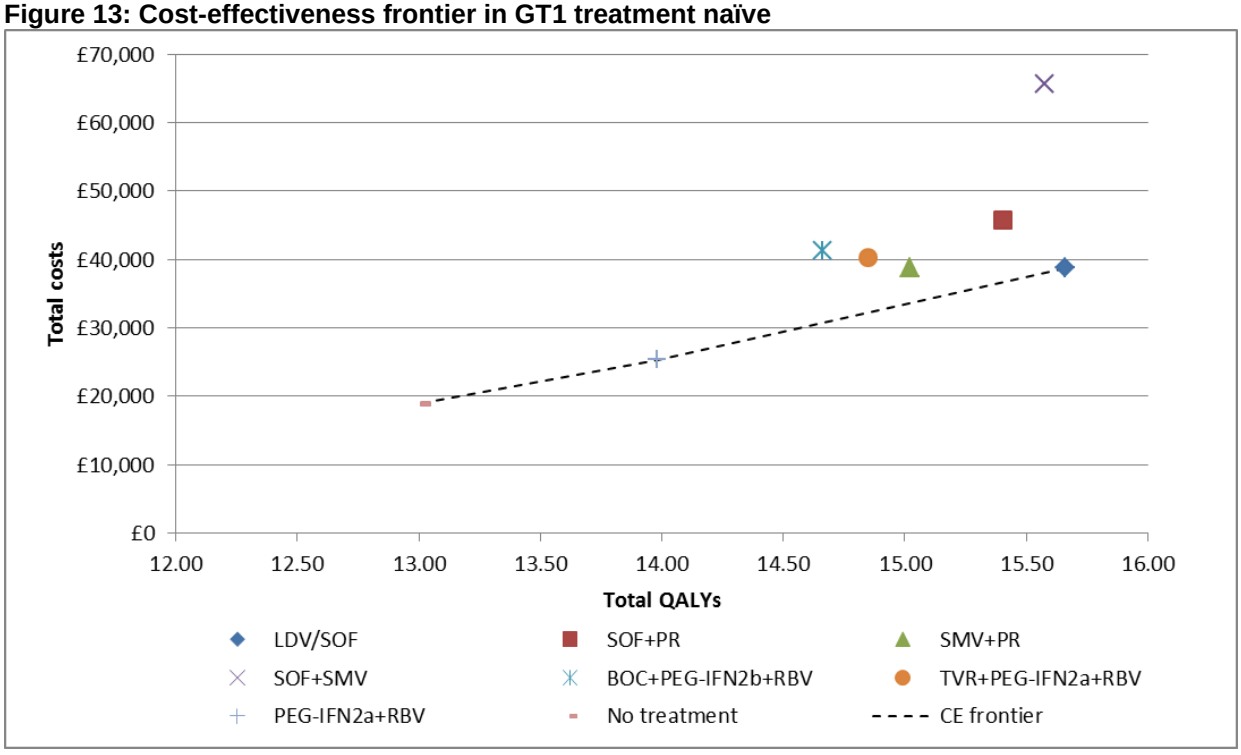
For GT1 TN patients, SMV+PEG-IFN+RBV, TVR+PEG-IFN+RBV, BOC+PEG-IFN+RBV, SOF+PEG-IFN+RBV and SMV+SOF are dominated by LDV/SOF (Table 95, Figure 13). The CE frontier consists of no treatment, PEG-IFN+RBV and LDV/SOF. ICERs for treatments on the frontier are presented in Table 95.

Table 95: Cost-effectiveness results, GT1 treatment naïve

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline (QALYs)	incremental
No treatment	£18,956	18.30	13.01					
PEG-IFN2a+RBV	£25,308	19.23	13.98	£6,352	0.94	0.97	£6,548	£6,548
LDV/SOF	£38,713	20.81	15.66	£19,757	2.51	2.65	£7,458	£7,985
SMV+PR	£38,731	20.14	15.02	£19,774	1.84	2.01	£9,840	Dominated
TVR+PEG-IFN2a+RBV	£40,237	19.99	14.85	£21,281	1.70	1.84	£11,571	Dominated
BOC+PEG-IFN2b+RBV	£41,299	19.93	14.66	£22,342	1.63	1.65	£13,537	Dominated
SOF+PR	£45,776	20.54	15.40	£26,819	2.24	2.39	£11,215	Dominated
SOF+SMV	£65,630	20.74	15.57	£46,674	2.44	2.56	£18,204	Dominated

Abbreviations: BOC, boceprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

Figure 13: Cost-effectiveness frontier in GT1 treatment naïve



Abbreviations: CE, cost-effectiveness; BOC, boceprevir; GT, genotype; LDV, ledipasvir; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

GT4 treatment naïve

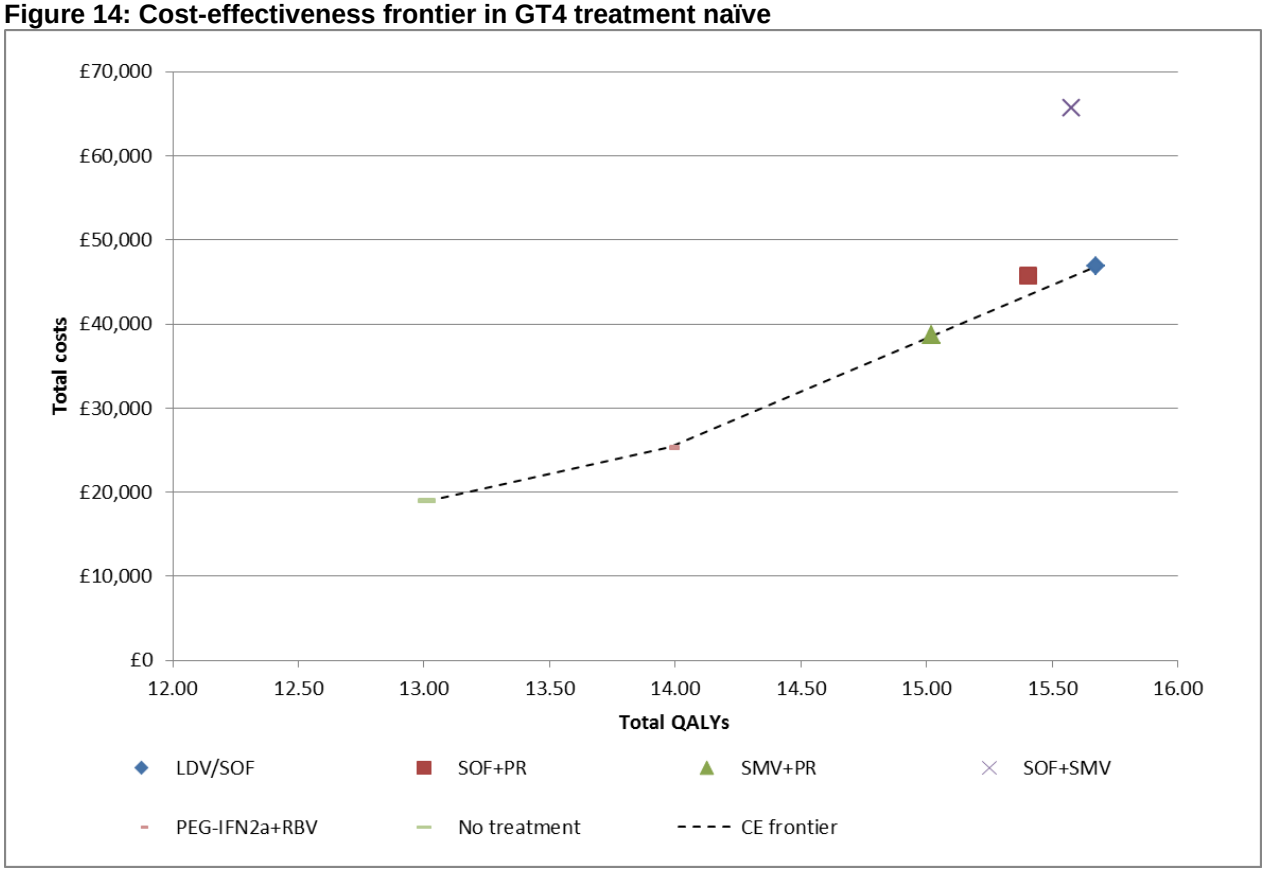
The CE frontier (Figure 14) consists of no treatment, PEG-IFN+RBV and LDV/SOF; ICERs for treatments on the frontier are provided in Table 96. SMV+SOF is dominated by LDV/SOF and SOF+PEG-IFN2a+RBV and SMV+PEG-IFN2a+RBV are dominated by the principle of extended dominance.

Table 96: Cost-effectiveness results, GT4 treatment naive

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline (QALYs)	incremental
No treatment	£18,956	18.30	13.01					
PEG-IFN2a+RBV	£25,308	19.23	13.98	£6,352	0.94	0.97	£6,548	£6,548
SMV+PR	£38,731	20.14	15.02	£19,774	1.84	2.01	£9,840	Extended dominance
SOF+PR	£45,776	20.54	15.40	£26,819	2.24	2.39	£11,215	Extended dominance
LDV/SOF	£46,823	20.81	15.67	£27,867	2.52	2.66	£10,468	£12,715
SOF+SMV	£65,630	20.74	15.57	£46,674	2.44	2.56	£18,204	Dominated

Abbreviations: GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

Figure 14: Cost-effectiveness frontier in GT4 treatment naïve



Abbreviations: CE, cost-effectiveness; BOC, boceprevir; GT, genotype; LDV, ledipasvir; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

GT1/GT4 treatment experienced

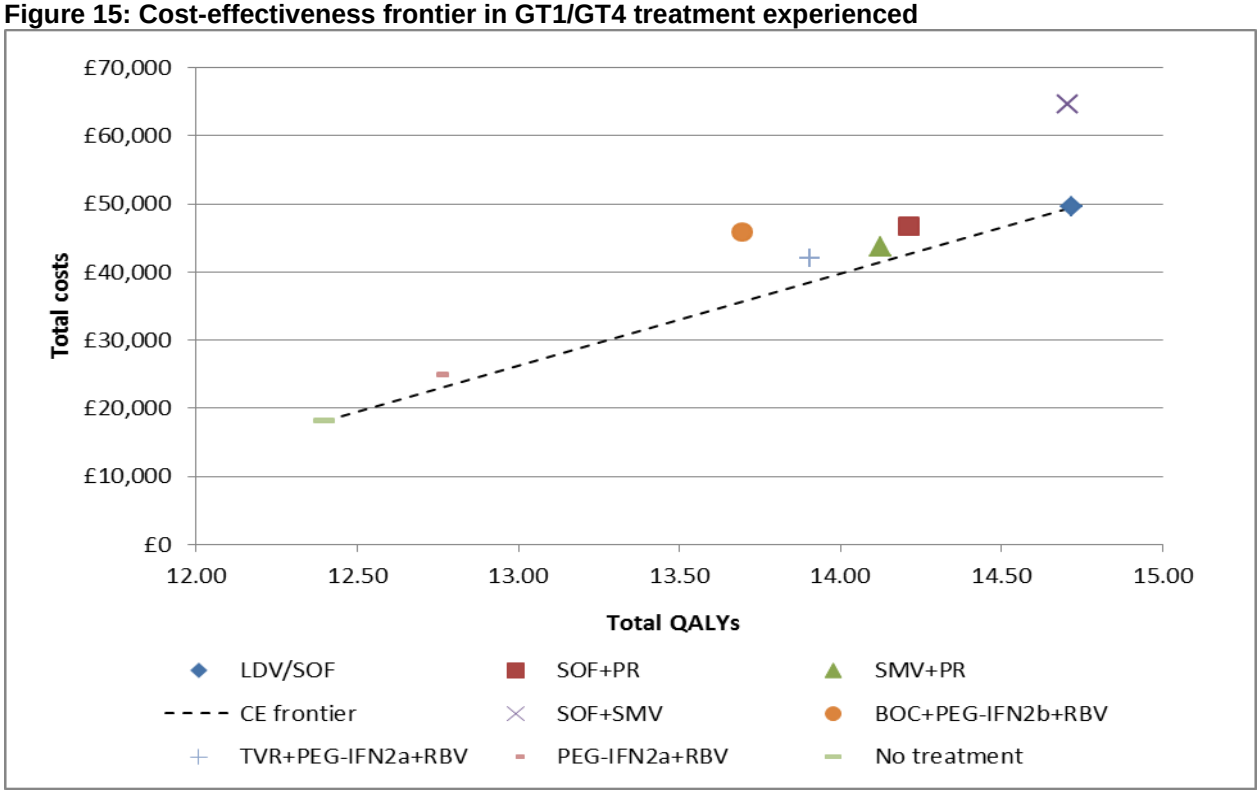
The CE frontier consists of no treatment and LDV/SOF (Figure 15); the ICER for this comparison is provided in Table 97. BOC+PEG-IFN2a+RBV and SMV+SOF were dominated by LDV/SOF and all other comparators were dominated by the principle of extended dominance.

Table 97: Cost-effectiveness results, GT1/GT4 treatment experienced†

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline (QALYs)	incremental
No treatment	£18,143	17.44	12.40					
PEG-IFN2a+RBV	£24,960	17.83	12.75	£6,817	0.39	0.35	£19,292	Extended dominance
TVR+PEG-IFN2a+RBV	£42,101	18.84	13.90	£23,959	1.40	1.51	£15,890	Extended dominance
SMV+PR	£43,626	19.17	14.13	£25,483	1.73	1.73	£14,740	Extended dominance
BOC+PEG-IFN2b+RBV	£45,897	18.62	13.69	£27,754	1.18	1.30	£21,419	Dominated
SOF+PR	£46,756	19.16	14.21	£28,613	1.72	1.81	£15,765	Extended dominance
LDV/SOF	£49,537	19.58	14.72	£31,395	2.13	2.32	£13,527	£13,527
SOF+SMV	£64,720	19.60	14.71	£46,577	2.16	2.31	£20,166	Dominated

Abbreviations: BOC, boceprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
† TVR+PEG-IFN2a+RBV and BOC+PEG-IFN2a+RBV are relevant for GT1 CHC only as they are not licensed for the treatment of GT4 CHC.

Figure 15: Cost-effectiveness frontier in GT1/GT4 treatment experienced



Abbreviations: BOC, boceprevir; GT, genotype; LDV, ledipasvir; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

GT3 treatment naïve

For GT3 treatment naïve patients the CE frontier (Figure 16) consists of PEG-IFN2a+RBV and LDV/SOF+RBV; the ICER for this comparison is provided in Table 98. No treatment was dominated by PEG-IFN2a+RBV.

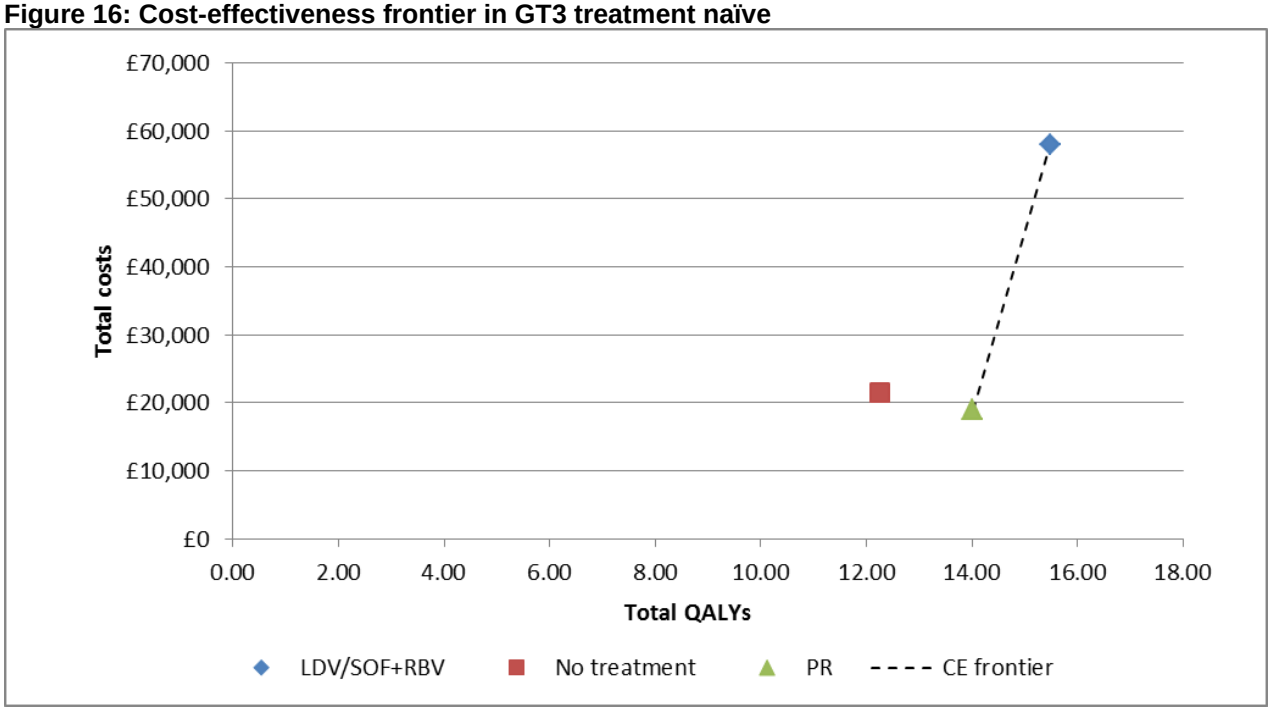
In the analysis restricted to GT3 treatment naïve cirrhotic patents only, the CE frontier consists of SOF+PEG-IFN+RBV and LDV/SOF+RBV (Figure 17); the ICER for this comparison is provided in Table 99. SOF+RBV was dominated by the principle of extended dominance.

Table 98: Cost-effectiveness results, GT3 treatment naive

Technologies	Total			Incremental			ICER (£) versus baseline (QALYs)	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
PR	£18,937	19.07	14.01					
No treatment	£21,509	17.49	12.24	£2,573	-1.58	-1.77	-£1,455	Dominated
LDV/SOF+RBV	£57,909	20.76	15.48	£38,973	1.69	1.47	£26,491	£26,491

Abbreviations: GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir.

Figure 16: Cost-effectiveness frontier in GT3 treatment naïve



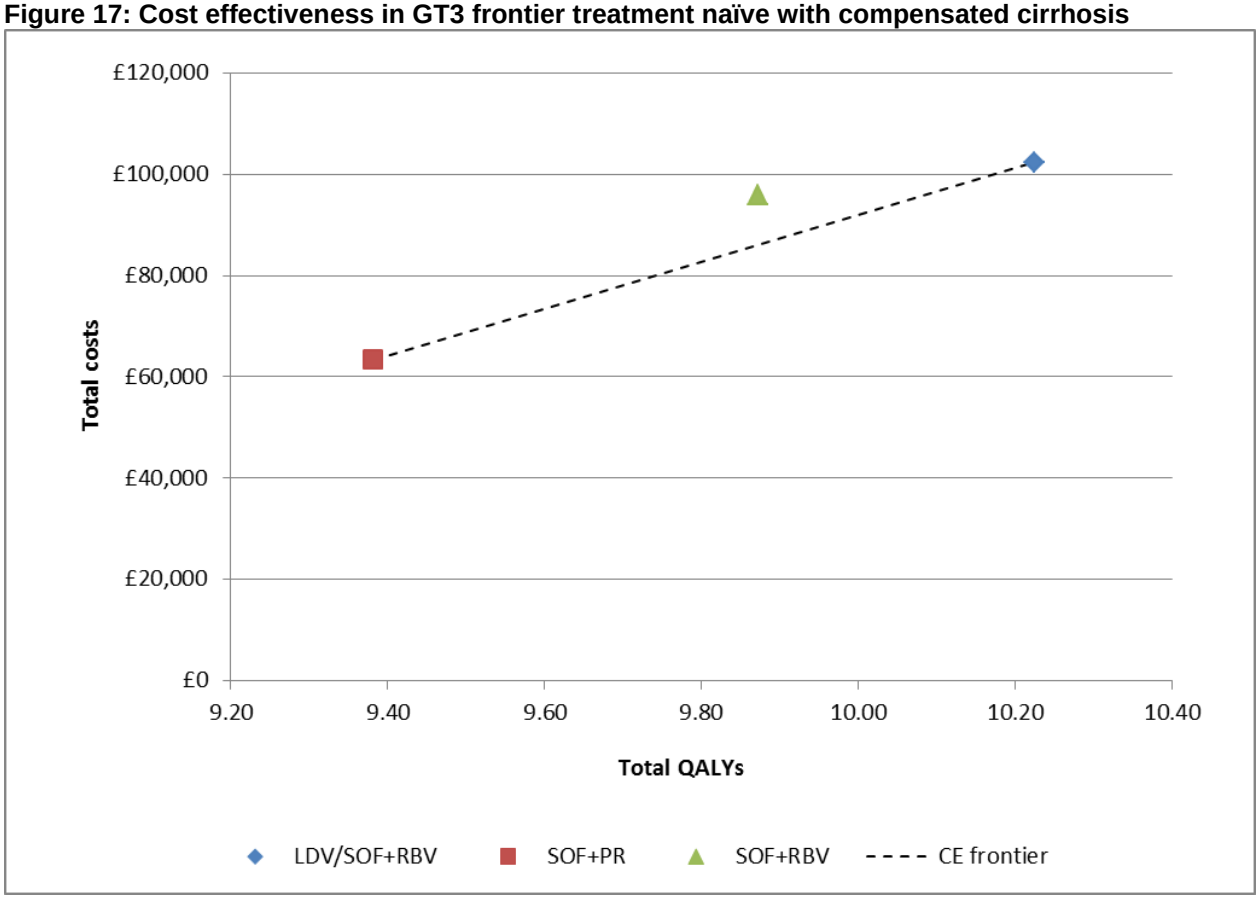
Abbreviations: CE, cost-effectiveness; GT, genotype; LDV, ledipasvir; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; SOF, sofosbuvir.

Table 99: Cost-effectiveness results, GT3 treatment naïve with compensated cirrhosis

Technologies	Total			Incremental			ICER (£) versus baseline (QALYs)	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
SOF+PR	£63,419	16.28	9.38					
SOF+RBV	£95,947	17.04	9.87	£32,529	0.76	0.49	£66,187	Extended dominance
LDV/SOF+RBV	£102,645	17.55	10.23	£39,226	1.27	0.84	£46,491	£46,491

Abbreviations: GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained;; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir.

Figure 17: Cost effectiveness in GT3 frontier treatment naïve with compensated cirrhosis



Abbreviations: CE, cost-effectiveness; GT, genotype; LDV, ledipasvir; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; SOF, sofosbuvir.

GT3 treatment experienced IFN ineligible

For GT3 treatment experienced IFN ineligible patients the CE frontier (Figure 18) consists of no treatment and LDV/SOF+RBV; the ICER for this comparison is provided in Table 100.

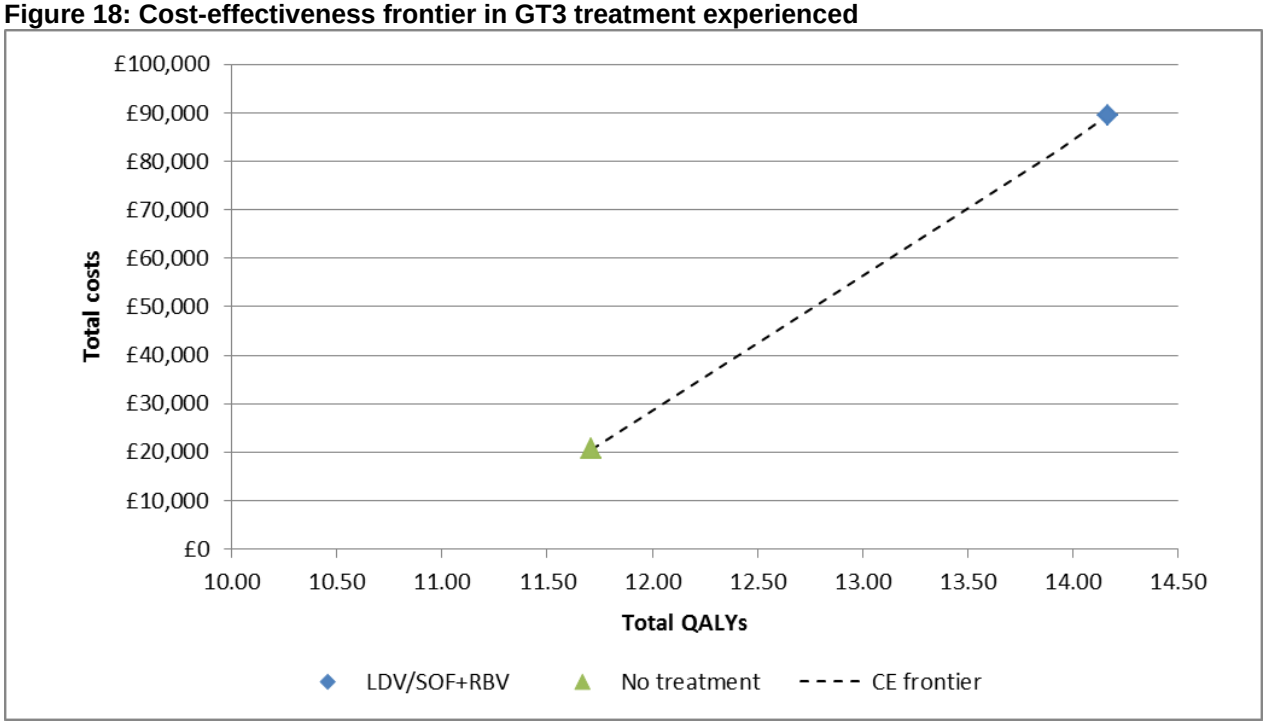
In the analysis restricted to GT3 treatment experienced cirrhotic patents only, the CE frontier consists of SOF+RBV and LDV/SOF+RBV (Figure 19); the ICER for this comparison is provided in Table 101.

Table 100: Cost-effectiveness results, GT3 treatment experienced IFN ineligible

Technologies	Total			Incremental			ICER (£) versus baseline (QALYs)	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
No treatment	£20,614	16.74	11.71					
LDV/SOF+RBV	£89,522	19.10	14.17	£68,907	2.36	2.46	£28,048	£28,048

Abbreviations: GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, Ledipasvir; LYG, life years gained; QALY, quality-adjusted life year; SOF, sofosbuvir.

Figure 18: Cost-effectiveness frontier in GT3 treatment experienced



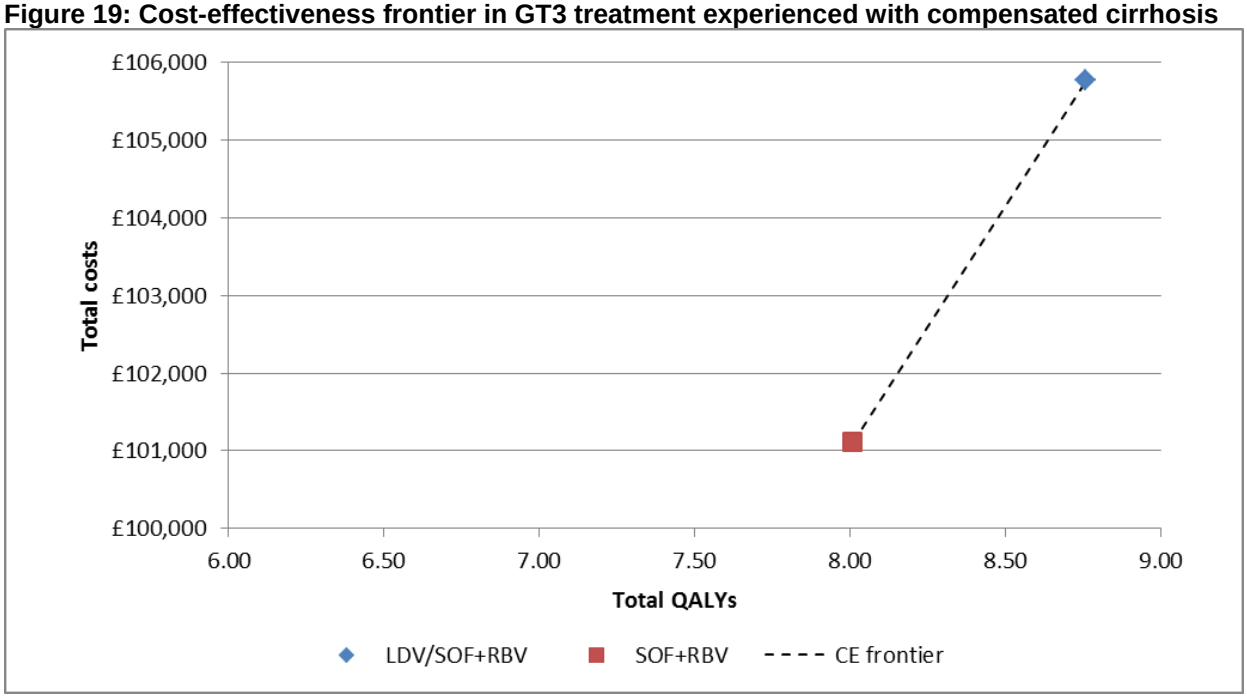
Abbreviations: CE, cost-effectiveness; GT, genotype; LDV, Ledipasvir; QALY, quality-adjusted life year; SOF, sofosbuvir.

Table 101: Cost-effectiveness results, GT3 treatment experienced IFN ineligible with compensated cirrhosis

Technologies	Total			Incremental			ICER (£) versus baseline (QALYs)	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
SOF+RBV	£101,109	14.13	8.01					
LDV/SOF+RBV	£105,761	15.24	8.76	£4,652	1.11	0.75	£6,210	£6,210

Abbreviations: GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, Ledipasvir; LYG, life years gained; QALY, quality-adjusted life year; SOF, sofosbuvir.

Figure 19: Cost-effectiveness frontier in GT3 treatment experienced with compensated cirrhosis



Abbreviations: CE, cost-effectiveness; GT, genotype; LDV, Ledipasvir; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir.

Overall weighted ICER

An overall ICER was calculated on the basis of weighted total costs and QALYs representing the relative number of patients in each subgroup with data inputs in line with the budget impact calculations (Section 8). Data on the genotype split of patients is sourced from the Hepatitis C in the UK 2014 report (21). Data from the UK HCV research database is used for the proportion of patients who are cirrhotic and non-cirrhotic (121). The treatment history of patients is based on assumptions. Market share of current treatment options are based on KOL opinion and assumptions. Across treatment naïve and treatment experienced patients in GT1, GT4 and GT3, LDV/SOF±RBV is associated with weighted average incremental costs of £15,564 per patient and weighted average incremental QALYs of 1.29 per patient, making LDV/SOF regimens cost-effective versus current treatments with an ICER of £12,107.

Table 102: Weighted costs and QALYs for LDV/SOF versus current treatment options

	LDV/SOF±RBV	Current treatments	
	Total	Total	Δ†
Total costs	£53,885	£38,321	£15,564
Total QALYs	15.29	14.00	1.29
ICER (£/QALY)			£12,107

Abbreviations: ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; QALY, quality adjusted life year; RBV, ribavirin; SOF, sofosbuvir.
† Incremental cost or benefit for LDV/SOF vs comparator.

7.7.7 *Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.*

GT1 TN

LDV/SOF vs SOF+PEG-IFN2a+RBV

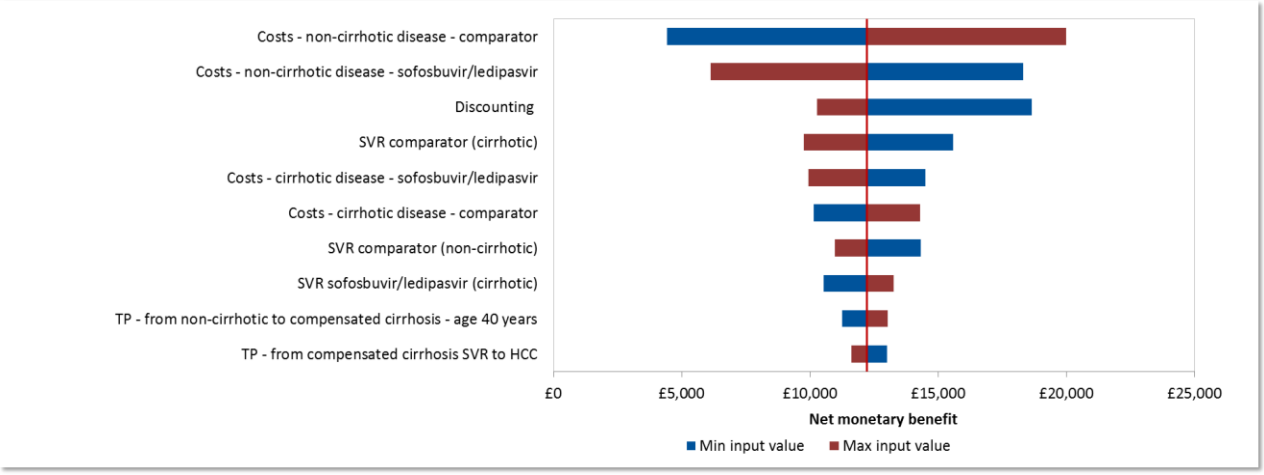
In this comparison, the net benefit was most sensitive to variation in treatment costs for non-cirrhotic patients, discount rates (varied between 0 and 6%) and the SVR rate for SOF+PEG-IFN2a+RBV in cirrhotic patients. However, the net benefit always remained above £0 (the equivalent of an ICER below £20,000). The lowest net benefit value recorded was £4,435 where the SOF+PEG-IFN2a+RBV on-treatment cost in non-cirrhotic patients (drug acquisition, AE and monitoring costs) was reduced to £29,538 from a base case value of £39,383; a reduction of 25%.

Table 103: GT1 TN: LDV/SOF vs SOF+PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Costs - non-cirrhotic disease - comparator	£39,383	£29,538	£49,229	£4,435	£19,992	£15,556
Costs - non-cirrhotic disease – LDV/SOF	£30,842	£23,132	£38,553	£18,305	£6,122	£12,183
Discounting	3.5%	0.0%	6.0%	£18,648	£10,266	£8,382
SVR comparator (cirrhotic)	80.8%	67.5%	90.4%	£15,579	£9,771	£5,808
Costs - cirrhotic disease – LDV/SOF	£43,358	£32,519	£54,198	£14,490	£9,937	£4,553
Costs - cirrhotic disease - comparator	£39,577	£29,683	£49,472	£10,136	£14,291	£4,156
SVR comparator (non-cirrhotic)	91.7%	86.9%	94.5%	£14,309	£10,968	£3,341
SVR LDV/SOF (cirrhotic)	94.3%	87.6%	98.4%	£10,528	£13,275	£2,746
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.009	0.002	0.016	£11,268	£13,027	£1,760
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£12,996	£11,604	£1,392

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

Figure 20: Tornado diagram (GT1 TN: LDV/SOF vs SOF+PEG-IFN2a+RBV)



LDV/SOF vs SMV+PEG-IFN2a+RBV

In this comparison, the net benefit was most sensitive to discount rates (varied between 0 and 6%), variation in treatment costs for non-cirrhotic patients, and the SVR rate for SMV+PEG-IFN2a+RBV in cirrhotic patients. However, the net benefit always remained above £0 (equivalent of an ICER below £20,000). The lowest net benefit value recorded was £6,715 where the LDV/SOF on-treatment cost (drug acquisition, AE and monitoring costs) in non-cirrhotic patients was increased to £38,553 from a base case value of £30,842; an increase of 25%.

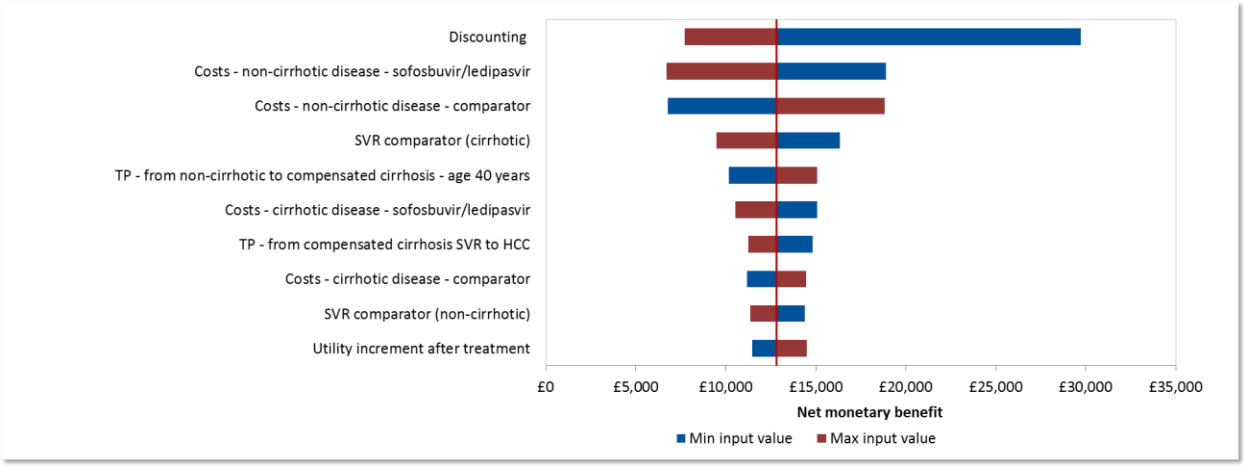
Table 104: GT1 TN: LDV/SOF vs SMV+ PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£29,732	£7,723	£22,009
Costs - non-cirrhotic disease – LDV/SOF	£30,842	£23,132	£38,553	£18,897	£6,715	£12,183
Costs - non-cirrhotic disease - comparator	£30,507	£22,881	£38,134	£6,781	£18,831	£12,050
SVR comparator (cirrhotic)	60.4%	46.4%	73.6%	£16,328	£9,490	£6,838
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.009	0.002	0.016	£10,173	£15,073	£4,900
Costs - cirrhotic disease – LDV/SOF	£43,358	£32,519	£54,198	£15,082	£10,530	£4,553
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£14,816	£11,242	£3,574
Costs - cirrhotic disease - comparator	£31,172	£23,379	£38,965	£11,169	£14,442	£3,273
SVR comparator (non-cirrhotic)	82.0%	78.3%	85.3%	£14,385	£11,341	£3,044

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Utility increment after treatment	0.04	0.02	0.06	£11,481	£14,485	£3,003

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

Figure 21: Tornado diagram (GT1 TN: LDV/SOF vs SMV+ PEG-IFN2a+RBV)



LDV/SOF vs PEG-IFN2a+RBV

In this comparison, the net benefit was most sensitive to discount rates (varied between 0 and 6%), the TP from non-cirrhotic to compensated cirrhosis and variation in LDV/SOF treatment costs for non-cirrhotic patients. However, the net benefit always remained above £0 (the equivalent of an ICER below £20,000). The lowest net benefit value recorded was £5,989 where the discount rate was increased to 6% from a base case value of 3.5%.

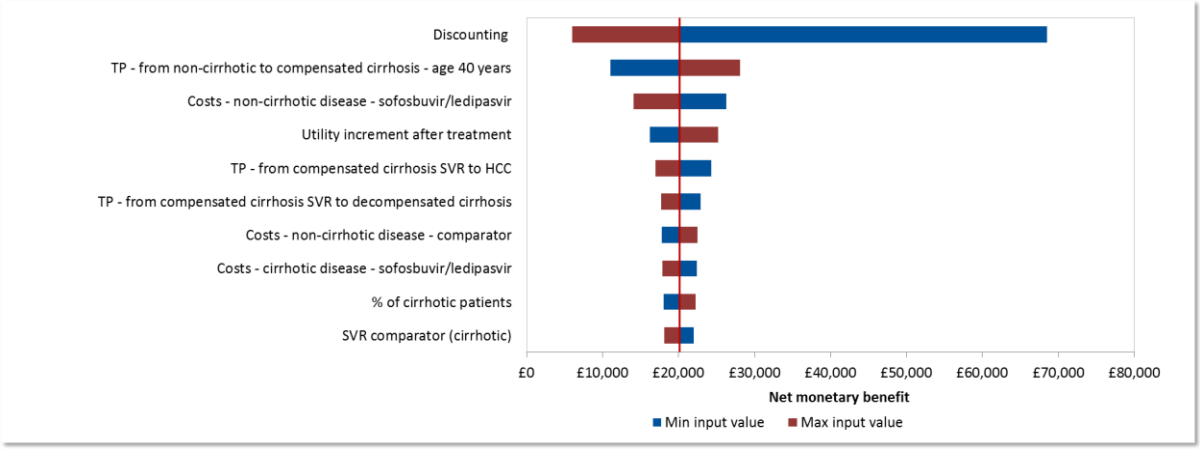
Table 105: GT1 TN: LDV/SOF vs PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£68,494	£5,989	£62,505
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.009	0.002	0.016	£10,994	£28,082	£17,088
Costs - non-cirrhotic disease – LDV/SOF	£30,842	£23,132	£38,553	£26,263	£14,080	£12,183
Utility increment after treatment	0.04	0.02	0.06	£16,185	£25,224	£9,039
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£24,310	£16,950	£7,361

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
TP - from compensated cirrhosis SVR to decompensated cirrhosis	0.006	0.000	0.013	£22,929	£17,750	£5,179
Costs - non-cirrhotic disease - comparator	£11,886	£8,915	£14,858	£17,824	£22,519	£4,695
Costs - cirrhotic disease – LDV/SOF	£43,358	£32,519	£54,198	£22,448	£17,895	£4,553
% of cirrhotic patients	21%	16%	26%	£18,058	£22,285	£4,227
SVR comparator (cirrhotic)	23.6%	16.2%	32.0%	£22,008	£18,111	£3,897

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

Figure 22: Tornado diagram (GT1 TN: LDV/SOF vs PEG-IFN2a+RBV)



LDV/SOF vs TVR+PEG-IFN2a+RBV

In this comparison, the net benefit was most sensitive to discount rates (varied between 0 and 6%), variation in treatment costs for non-cirrhotic patients and the TP from non-cirrhotic to compensated cirrhosis. However, the net benefit always remained above £0 (the equivalent of an ICER below £20,000). The lowest net benefit value recorded was £11,346 where the discount rate was increased to 6% from a base case value of 3.5%.

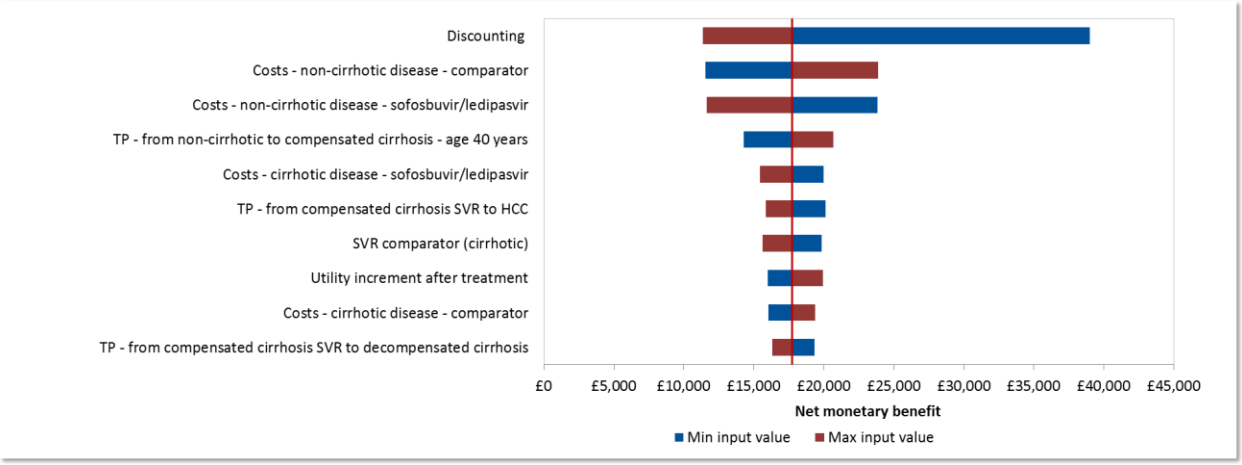
Table 106: GT1 TN: LDV/SOF vs TVR+PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£39,018	£11,346	£27,672
Costs - non-cirrhotic disease - comparator	£31,264	£23,448	£39,079	£11,544	£23,893	£12,349
Costs - non-cirrhotic disease – LDV/SOF	£30,842	£23,132	£38,553	£23,809	£11,627	£12,183

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.009	0.002	0.016	£14,290	£20,671	£6,381
Costs - cirrhotic disease – LDV/SOF	£43,358	£32,519	£54,198	£19,994	£15,442	£4,553
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£20,142	£15,833	£4,309
SVR comparator (cirrhotic)	53.4%	44.9%	61.9%	£19,855	£15,607	£4,248
Utility increment after treatment	0.04	0.02	0.06	£15,977	£19,926	£3,949
Costs - cirrhotic disease - comparator	£32,012	£24,009	£40,014	£16,038	£19,399	£3,361
TP - from compensated cirrhosis SVR to decompensated cirrhosis	0.006	0.000	0.013	£19,332	£16,302	£3,030

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

Figure 23: Tornado diagram (GT1 TN: LDV/SOF vs TVR+PEG-IFN2a+RBV)



LDV/SOF vs BOC+PEG-IFN2a+RBV

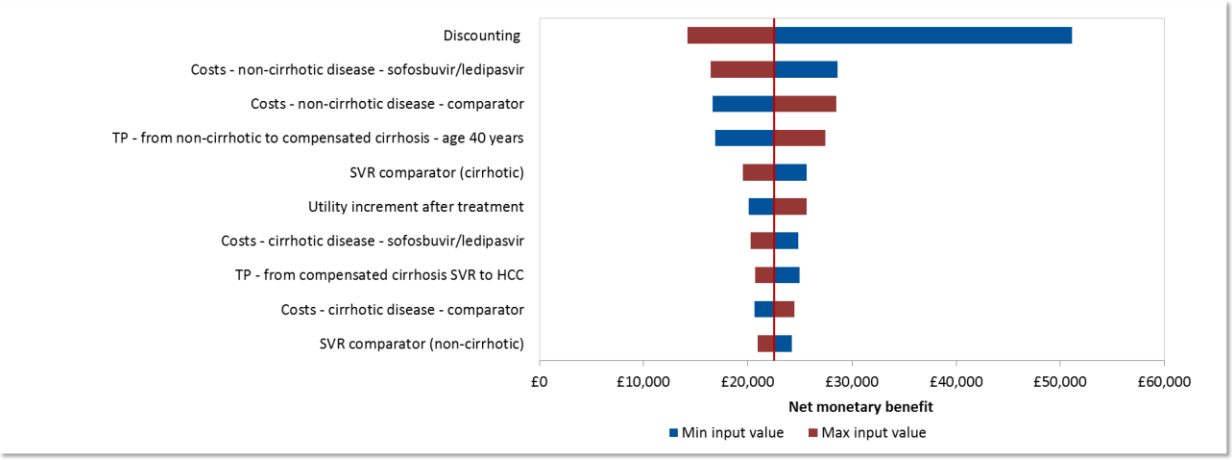
In this comparison, the net benefit was most sensitive to discount rates (varied between 0 and 6%), variation in treatment costs for non-cirrhotic patients and the TP from non-cirrhotic to compensated cirrhosis. However, the net benefit always remained above £0 (the equivalent of an ICER below £20,000). The lowest net benefit value recorded was £14,209 where the discount rate was increased to 6% from a base case value of 3.5%.

Table 107: GT1 TN: LDV/SOF vs BOC+PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£51,141	£14,209	£36,931
Costs - non-cirrhotic disease – LDV/SOF	£30,842	£23,132	£38,553	£28,645	£16,462	£12,183
Costs - non-cirrhotic disease - comparator	£30,113	£22,585	£37,641	£16,606	£28,501	£11,895
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.009	0.002	0.016	£16,870	£27,451	£10,581
SVR comparator (cirrhotic)	55.0%	42.4%	67.3%	£25,658	£19,527	£6,131
Utility increment after treatment	0.04	0.02	0.06	£20,089	£25,678	£5,589
Costs - cirrhotic disease – LDV/SOF	£43,358	£32,519	£54,198	£24,830	£20,277	£4,553
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£24,945	£20,696	£4,249
Costs - cirrhotic disease - comparator	£36,315	£27,236	£45,393	£20,647	£24,460	£3,813
SVR comparator (non-cirrhotic)	64.1%	60.2%	67.9%	£24,210	£20,936	£3,274

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

Figure 24: Tornado diagram (GT1 TN: LDV/SOF vs BOC+PEG-IFN2a+RBV)



LDV/SOF vs no treatment

In this comparison, the net benefit was most sensitive discount rates (varied between 0 and 6%), the TP from non-cirrhotic to compensated cirrhosis and the utility increment with achieving a SVR[d]. However, the net benefit always remained above £0 (the equivalent of an ICER below £20,000). The lowest net benefit value recorded was £9,524 where the discount rate was increased to 6% from a base case value of 3.5%.

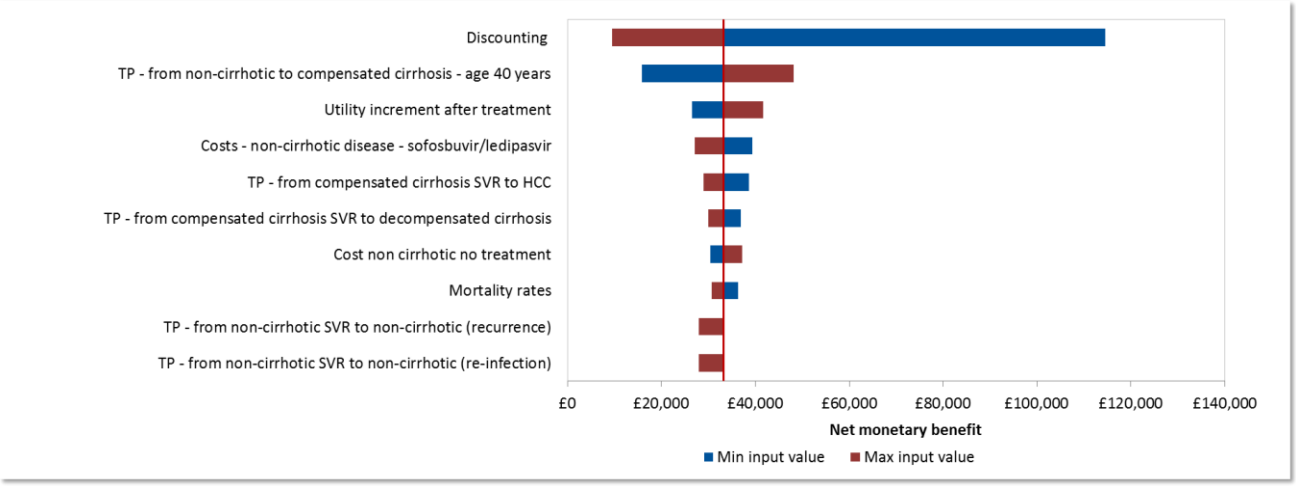
Table 108: GT1 TN: LDV/SOF vs no treatment

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£114,586	£9,524	£105,062
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.009	0.002	0.016	£15,877	£48,148	£32,271
Utility increment after treatment	0.04	0.02	0.06	£26,506	£41,733	£15,227
Costs - non-cirrhotic disease – LDV/SOF	£30,842	£23,132	£38,553	£39,312	£27,130	£12,183
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£38,687	£28,963	£9,724
TP - from compensated cirrhosis SVR to decompensated cirrhosis	0.006	0.000	0.013	£36,865	£30,020	£6,845
Cost non cirrhotic no treatment	£363	£164	£640	£30,383	£37,171	£6,788
Mortality rates	Multiple age-specific values	All varied -25%	All varied +25%	£36,362	£30,647	£5,715
TP - from non-cirrhotic SVR to non-cirrhotic (recurrence)	0.000	0.000	0.010	£33,221	£27,924	£5,298
TP - from non-cirrhotic SVR to non-cirrhotic (re-infection)	0.000	0.000	0.010	£33,221	£27,924	£5,298

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

[d] Labelled as 'utility increment after treatment'

Figure 25: Tornado diagram (GT1 TN: LDV/SOF vs no treatment)



GT4 TN

LDV/SOF vs SOF+PEG-IFN2a+RBV

In this comparison, the net benefit was most sensitive to variation in treatment costs for non-cirrhotic patients, discount rates (varied between 0 and 6%) and the SVR rate for SOF+PEG-IFN2a+RBV in cirrhotic patients. The majority of inputs retain a positive net benefit when varied between their maximum and minimum values, however the net benefit fell below £0 (equivalent to an ICER >£20K) in two scenarios:

- Net benefit of -£3,769 recorded when the treatment cost (drug acquisition, AE and monitoring costs) of LDV/SOF in non-cirrhotic patients was increased by 25% to £51,504. It should be noted that +25% is considered and unrealistically high value as drug acquisition cost (a significant component of treatment cost) is unlikely to vary to this extent (BNF list price).
- Net benefit of -£3,410 recorded when the treatment cost (drug acquisition, AE and monitoring costs) of SOF+PEG-IFN2a+RBV in non-cirrhotic patients was decreased by 25% to £29,538. Again it should be noted that -25% is considered an unrealistically high value as drug acquisition cost (a significant component of treatment cost) is unlikely to vary to this extent (BNF list price).

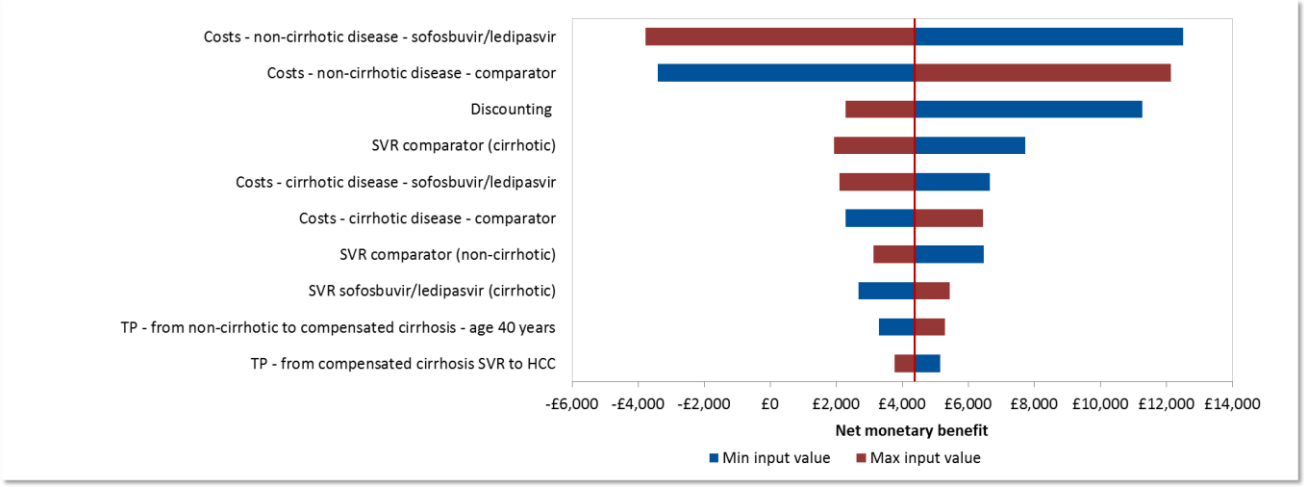
Table 109: GT4 TN: LDV/SOF vs SOF+PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Costs - non-cirrhotic disease – LDV/SOF	£41,203	£30,902	£51,504	£12,506	-£3,769	£16,275
Costs - non-cirrhotic disease - comparator	£39,383	£29,538	£49,229	-£3,410	£12,147	£15,556
Discounting	3.5%	0.0%	6.0%	£11,272	£2,291	£8,981
SVR comparator (cirrhotic)	80.8%	67.5%	90.4%	£7,734	£1,926	£5,808
Costs - cirrhotic disease – LDV/SOF	£43,358	£32,519	£54,198	£6,645	£2,092	£4,553

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Costs - cirrhotic disease - comparator	£39,577	£29,683	£49,472	£2,291	£6,446	£4,156
SVR comparator (non-cirrhotic)	91.7%	86.9%	94.5%	£6,464	£3,123	£3,341
SVR LDV/SOF (cirrhotic)	94.3%	87.6%	98.4%	£2,683	£5,430	£2,746
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.009	0.002	0.016	£3,284	£5,302	£2,017
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£5,151	£3,759	£1,392

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

Figure 26: Tornado diagram (GT4 TN: LDV/SOF vs SOF+PEG-IFN2a+RBV)



LDV/SOF vs SMV+PEG-IFN2a+RBV

In this comparison, the net benefit was most sensitive to discount rates (varied between 0 and 6%), treatment costs for non-cirrhotic patients and the SVR rate for SMV+PEG-IFN2a+RBV in cirrhotic patients. The majority of inputs retain a positive net benefit when varied between their maximum and minimum values, however the net benefit fell below £0 (equivalent to an ICER >£20K) in three scenarios:

- Net benefit of -£252 recorded when the discount rate is increased to 6%. Sensitivity to the discount rate means that a proportion of the benefit (QALY gains and cost savings) with LDV/SOF is observed in the long term.
- Net benefit of -£3,177 recorded when the treatment cost (drug acquisition, AE and monitoring costs) of LDV/SOF in non-cirrhotic patients was increased by 25% to £51,504. It should be noted that +25% is considered an unrealistically high value as drug acquisition cost (a significant component of treatment cost) is unlikely to vary to this extent (BNF list price).

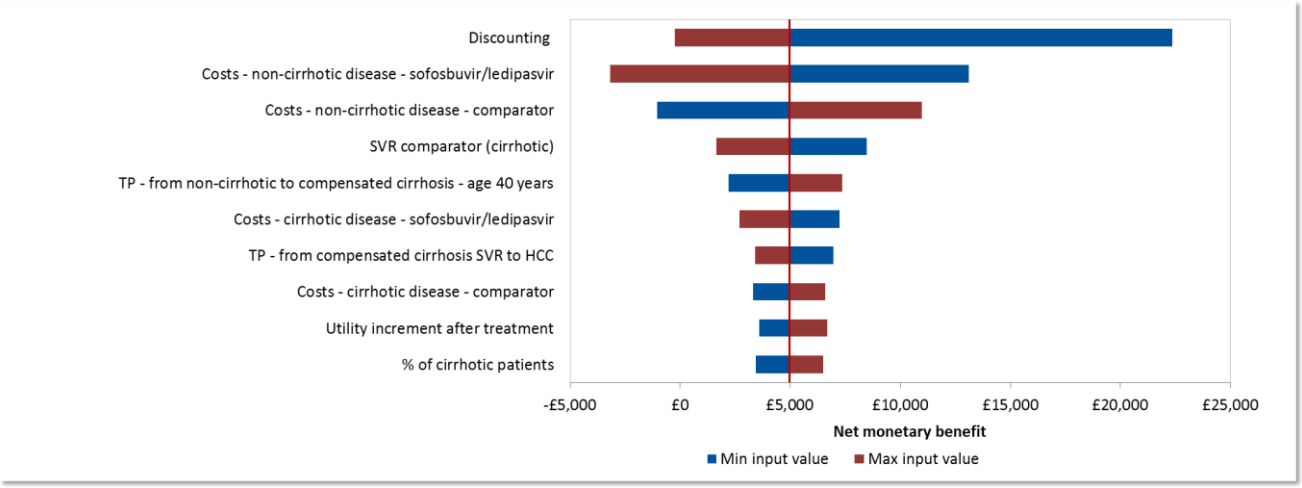
- Net benefit of -£1,064 recorded when the treatment cost (drug acquisition, AE and monitoring costs) of SMV+PEG-IFN2a+RBV in non-cirrhotic patients was decreased by 25% to £22,881. Again it should be noted that -25% is considered an unrealistically high value as drug acquisition cost (a significant component of treatment cost) is unlikely to vary to this extent (BNF list price).

Table 110: GT4 TN: LDV/SOF vs SMV+PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£22,356	-£252	£22,609
Costs - non-cirrhotic disease – LDV/SOF	£41,203	£30,902	£51,504	£13,098	-£3,177	£16,275
Costs - non-cirrhotic disease - comparator	£30,507	£22,881	£38,134	-£1,064	£10,986	£12,050
SVR comparator (cirrhotic)	60.4%	46.4%	73.6%	£8,483	£1,645	£6,838
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.009	0.002	0.016	£2,190	£7,347	£5,158
Costs - cirrhotic disease – LDV/SOF	£43,358	£32,519	£54,198	£7,237	£2,685	£4,553
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£6,971	£3,397	£3,574
Costs - cirrhotic disease - comparator	£31,172	£23,379	£38,965	£3,324	£6,597	£3,273
Utility increment after treatment	0.04	0.02	0.06	£3,591	£6,696	£3,105
% of cirrhotic patients	21%	16%	26%	£3,421	£6,501	£3,080

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

Figure 27: Tornado diagram (GT4 TN: LDV/SOF vs SMV+PEG-IFN2a+RBV)



LDV/SOF vs PEG-IFN2a+RBV

In this comparison, the net benefit was most sensitive to discount rates (varied between 0 and 6%), the TP from non-cirrhotic to compensated cirrhosis and variation in LDV/SOF treatment costs for non-cirrhotic patients. The majority of inputs retain a positive net benefit when varied between their maximum and minimum values, however the net benefit fell below £0 (equivalent to an ICER >£20K) in one scenario:

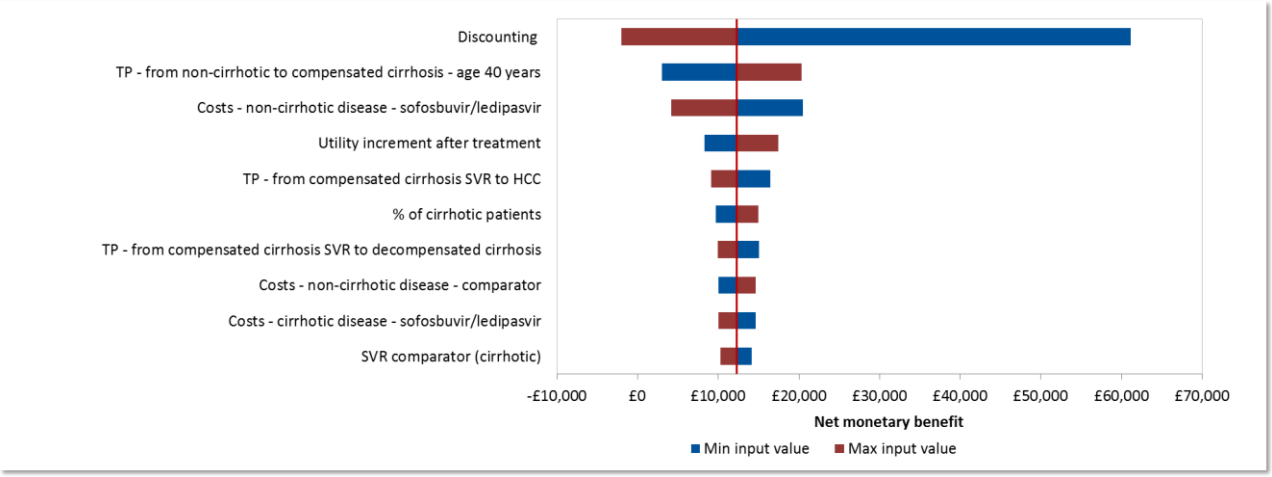
- Net benefit of -£1,986 recorded when the discount rate is increased to 6%. Sensitivity to the discount rate means that a proportion of the benefit (QALY gains and cost savings) with LDV/SOF is observed in the long term.

Table 111: GT4 TN: LDV/SOF vs PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£61,118	-£1,986	£63,104
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.009	0.002	0.016	£3,010	£20,356	£17,346
Costs - non-cirrhotic disease – LDV/SOF	£41,203	£30,902	£51,504	£20,464	£4,189	£16,275
Utility increment after treatment	0.04	0.02	0.06	£8,296	£17,436	£9,140
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£16,465	£9,105	£7,361
% of cirrhotic patients	21%	16%	26%	£9,692	£14,961	£5,269
TP - from compensated cirrhosis SVR to decompensated cirrhosis	0.006	0.000	0.013	£15,084	£9,905	£5,179
Costs - non-cirrhotic disease - comparator	£11,886	£8,915	£14,858	£9,979	£14,674	£4,695
Costs - cirrhotic disease – LDV/SOF	£43,358	£32,519	£54,198	£14,603	£10,050	£4,553
SVR comparator (cirrhotic)	53.4%	44.9%	61.9%	£14,163	£10,266	£3,897

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

Figure 28: Tornado diagram (GT4 TN: LDV/SOF vs PEG-IFN2a+RBV)



LDV/SOF vs no treatment

In this comparison, the net benefit was most sensitive to discount rates (varied between 0 and 6%), the TP from non-cirrhotic to compensated cirrhosis and variation in LDV/SOF treatment costs for non-cirrhotic patients. However, the net benefit always remained above £0 (the equivalent of an ICER below £20,000). The lowest net benefit value recorded was £1,549 where the discount rate was increased to 6% from a base case value of 3.5%.

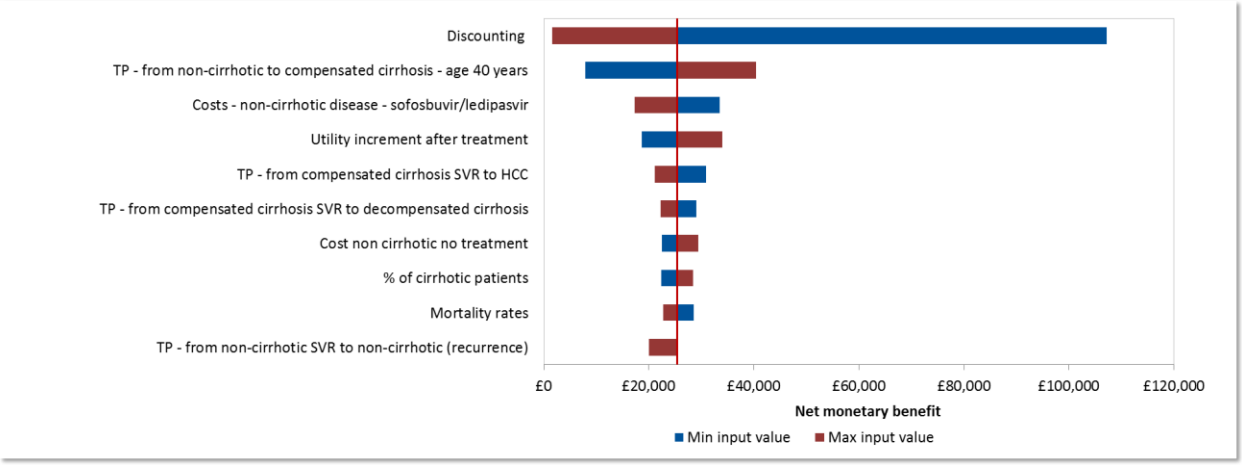
Table 112: GT4 TN: LDV/SOF vs no treatment

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£107,211	£1,549	£105,662
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.009	0.002	0.016	£7,894	£40,422	£32,529
Costs - non-cirrhotic disease – LDV/SOF	£41,203	£30,902	£51,504	£33,514	£17,239	£16,275
Utility increment after treatment	0.04	0.02	0.06	£18,616	£33,945	£15,329
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£30,842	£21,118	£9,724
TP - from compensated cirrhosis SVR to decompensated cirrhosis	0.006	0.000	0.013	£29,020	£22,175	£6,845
Cost non cirrhotic no treatment	£363	£164	£640	£22,515	£29,358	£6,842
% of cirrhotic patients	21%	16%	26%	£22,355	£28,397	£6,043

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Mortality rates	Multiple age-specific values	All varied -25%	All varied +25%	£28,537	£22,786	£5,751
TP - from non-cirrhotic SVR to non-cirrhotic (recurrence)	0.000	0.000	0.010	£25,376	£20,036	£5,340

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

Figure 29: Tornado diagram (GT4 TN: LDV/SOF vs no treatment)



GT1/4 TE

LDV/SOF vs SOF+PEG-IFN2a+RBV

In this comparison, the net benefit was most sensitive to variation in treatment costs for non-cirrhotic patients, discount rates (varied between 0 and 6%) and the SVR rate for SOF+PEG-IFN2a+RBV in non-cirrhotic patients. The majority of inputs retain a positive net benefit when varied between their maximum and minimum values, however the net benefit fell below £0 (equivalent to an ICER >£20K) in two scenarios:

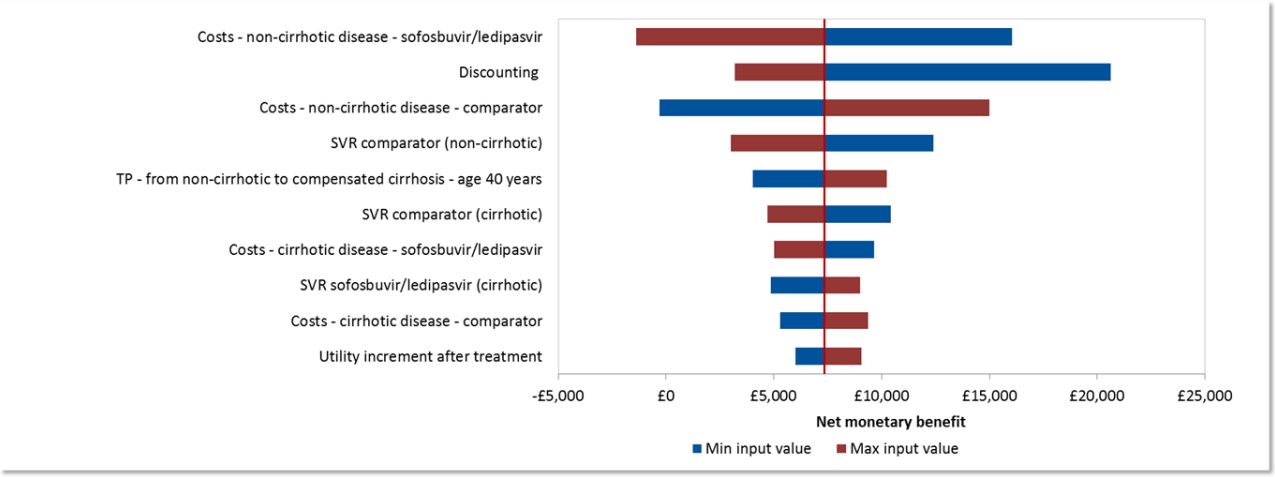
- Net benefit of -£1,387 recorded when the treatment cost (drug acquisition, AE and monitoring costs) of LDV/SOF in non-cirrhotic patients was increased by 25% to £55,227. It should be noted that +25% is considered an unrealistically high value as drug acquisition cost (a significant component of treatment cost) is unlikely to vary to this extent (BNF list price).
- Net benefit of -£315 recorded when the treatment cost (drug acquisition, AE and monitoring costs) of SOF+PEG-IFN2a+RBV in non-cirrhotic patients was decreased by 25% to £29,065. Again it should be noted that -25% is considered an unrealistically high value as drug acquisition cost (a significant component of treatment cost) is unlikely to vary to this extent (BNF list price).

Table 113: GT1/4 TE: LDV/SOF vs SOF+PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Costs - non-cirrhotic disease – LDV/SOF	£44,182	£33,136	£55,227	£16,065	-£1,387	£17,452
Discounting	3.5%	0.0%	6.0%	£20,632	£3,187	£17,445
Costs - non-cirrhotic disease - comparator	£38,754	£29,065	£48,442	-£315	£14,992	£15,308
SVR comparator (non-cirrhotic)	74%	61%	85%	£12,396	£2,995	£9,401
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.009	0.002	0.016	£4,017	£10,234	£6,218
SVR comparator (cirrhotic)	74%	61%	85%	£10,418	£4,694	£5,724
Costs - cirrhotic disease – LDV/SOF	£44,183	£33,137	£55,229	£9,658	£5,019	£4,639
SVR LDV/SOF (cirrhotic)	90%	79%	97%	£4,853	£9,015	£4,162
Costs - cirrhotic disease - comparator	£38,755	£29,066	£48,444	£5,304	£9,373	£4,069
Utility increment after treatment	0.04	0.02	0.06	£5,987	£9,051	£3,064

Abbreviations: SVR, sustained virologic response; TP, transition probability.

Figure 30: Tornado diagram (GT1/4 TE: LDV/SOF vs SOF+PEG-IFN2a+RBV)



LDV/SOF vs SMV+PEG-IFN2a+RBV

In this comparison, the net benefit was most sensitive to variation in treatment costs for non-cirrhotic patients, discount rates (varied between 0 and 6%) and the SVR rate for SMV+PEG-

IFN2a+RBV in cirrhotic patients. The majority of inputs retain a positive net benefit when varied between their maximum and minimum values, however the net benefit fell below £0 (equivalent to an ICER >£20K) in two scenarios:

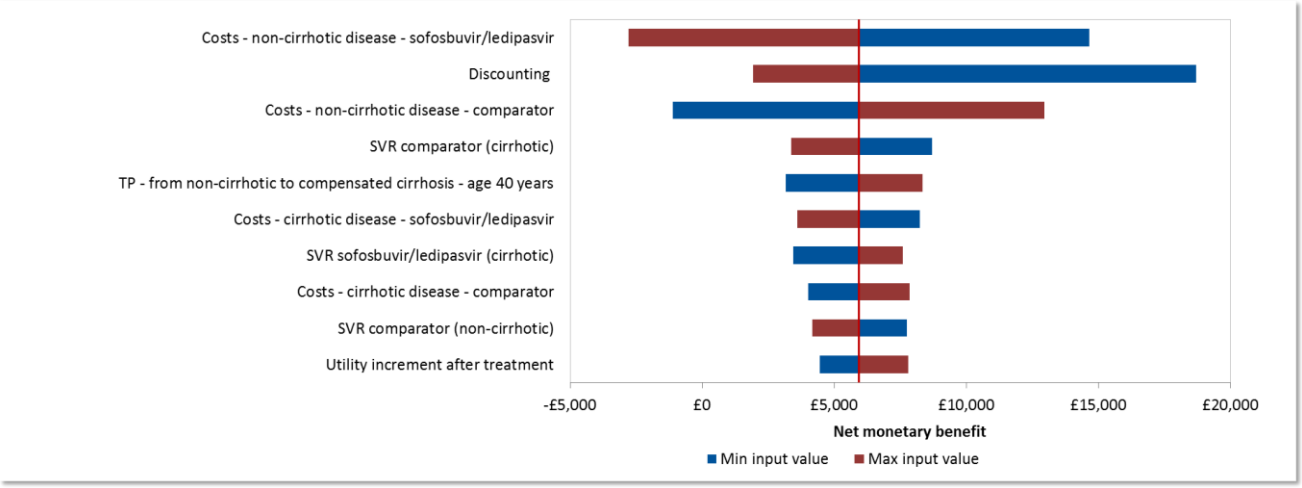
- Net benefit of -£2,796 recorded when the treatment cost (drug acquisition, AE and monitoring costs) of LDV/SOF in non-cirrhotic patients was increased by 25% to £55,227. It should be noted that +25% is considered an unrealistically high value as drug acquisition cost (a significant component of treatment cost) is unlikely to vary to this extent (BNF list price).
- Net benefit of -£1,104 recorded when the treatment cost (drug acquisition, AE and monitoring costs) of SMV+PEG-IFN2a+RBV in non-cirrhotic patients was decreased by 25% to £26,712. Again it should be noted that -25% is considered an unrealistically high value as drug acquisition cost (a significant component of treatment cost) is unlikely to vary to this extent (BNF list price).

Table 114: GT1/4 TE: LDV/SOF vs SMV+PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Costs - non-cirrhotic disease – LDV/SOF	£44,182	£33,136	£55,227	£14,656	-£2,796	£17,452
Discounting	3.5%	0.0%	6.0%	£18,711	£1,915	£16,797
Costs - non-cirrhotic disease - comparator	£ 35,616	£26,712	£44,521	-£1,104	£12,964	£14,069
SVR comparator (cirrhotic)	67%	55%	78%	£8,696	£3,378	£5,317
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.010	0.000	0.020	£3,170	£8,342	£5,173
Costs - cirrhotic disease – LDV/SOF	£44,183	£33,137	£55,229	£8,250	£3,611	£4,639
SVR LDV/SOF (cirrhotic)	90%	79%	97%	£3,444	£7,606	£4,162
Costs - cirrhotic disease - comparator	£36,693	£27,519	£45,866	£4,004	£7,857	£3,853
SVR comparator (non-cirrhotic)	76%	72%	81%	£7,745	£4,169	£3,575
Utility increment after treatment	0.04	0.02	0.06	£4,445	£7,813	£3,368

Abbreviations: SVR, sustained virologic response; TP, transition probability.

Figure 31: Tornado diagram (GT1/4 TE: LDV/SOF vs SMV+PEG-IFN2a+RBV)



LDV/SOF vs PEG-IFN2a+RBV

In this comparison, the net benefit was most sensitive to discount rates (varied between 0 and 6%), the TP from non-cirrhotic to compensated cirrhosis and variation in LDV/SOF treatment costs for non-cirrhotic patients. The majority of inputs retain a positive net benefit when varied between their maximum and minimum values, however the net benefit fell below £0 (equivalent to an ICER >£20K) in one scenario:

- Net benefit of -£1,562 recorded when the discount rate is increased to 6%. Sensitivity to the discount rate means that a proportion of the benefit (QALY gains and cost savings) with LDV/SOF is observed in the long term.

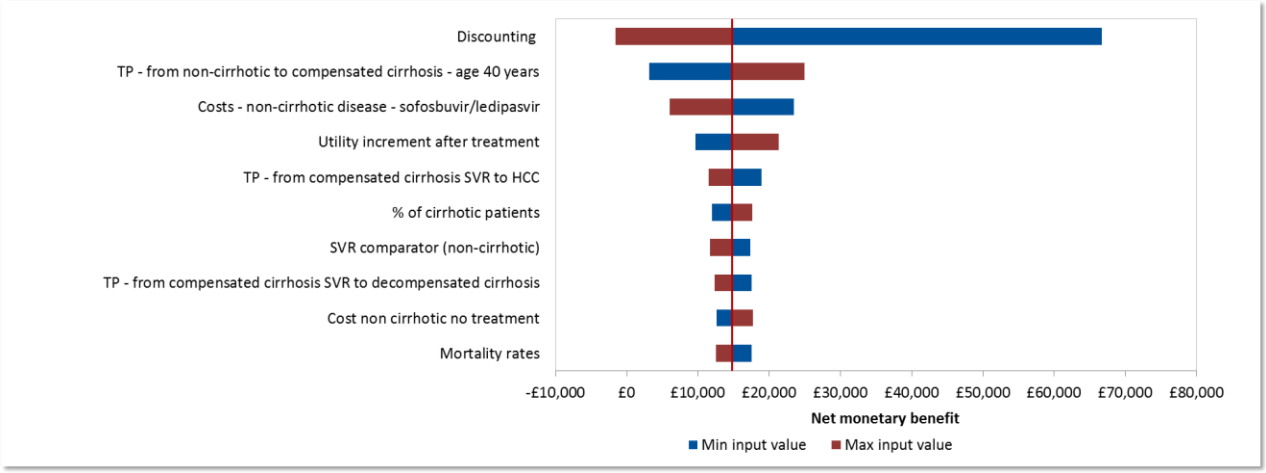
Table 115: GT1/4 TE: LDV/SOF vs PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£66,695	-£1,562	£68,257
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.009	0.002	0.016	£3,130	£24,936	£21,806
Costs - non-cirrhotic disease – LDV/SOF	£44,182	£33,136	£55,227	£23,500	£6,049	£17,452
Utility increment after treatment	0.04	0.02	0.06	£9,618	£21,310	£11,692
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£18,912	£11,499	£7,413
% of cirrhotic patients	21%	16%	26%	£11,929	£17,620	£5,691
SVR comparator (non-cirrhotic)	18%	11%	26%	£17,359	£11,729	£5,630

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
TP - from compensated cirrhosis SVR to decompensated cirrhosis	0.006	0.000	0.013	£17,556	£12,305	£5,250
Cost non cirrhotic no treatment	£363	£164	£640	£12,652	£17,728	£5,077
Mortality rates	Multiple age-specific values	All varied -25%	All varied +25%	£17,541	£12,519	£5,023

Abbreviations: SVR, sustained virologic response; TP, transition probability.

Figure 32: Tornado diagram (GT1/4 TE: LDV/SOF vs PEG-IFN2a+RBV)



LDV/SOF vs TVR+PEG-IFN2a+RBV

In this comparison, the net benefit was most sensitive to discount rates (varied between 0 and 6%), the variation in treatment costs for non-cirrhotic patients and the TP from non-cirrhotic to compensated cirrhosis. However, the net benefit always remained above £0 (the equivalent of an ICER below £20,000). The lowest net benefit value recorded was £102 where the LDV/SOF on-treatment cost (drug acquisition, AE and monitoring costs) in non-cirrhotic patients was increased to £55,227 from a base case value of £44,159; an increase of 25%.

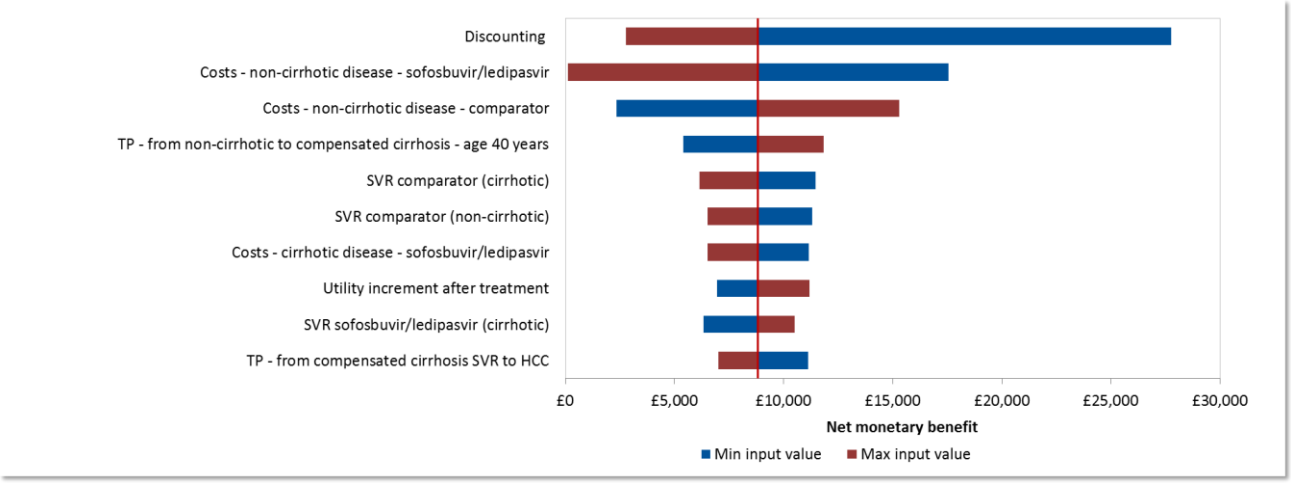
Table 116: GT1/4 TE: LDV/SOF vs TVR+PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£27,755	£2,775	£24,980
Costs - non-cirrhotic disease – LDV/SOF	£44,182	£33,136	£55,227	£17,553	£102	£17,452
Costs - non-cirrhotic disease - comparator	£32,817	£24,613	£41,021	£2,346	£15,309	£12,963

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.010	0.000	0.020	£5,390	£11,829	£6,439
SVR comparator (cirrhotic)	47%	36%	59%	£11,470	£6,151	£5,319
SVR comparator (non-cirrhotic)	72%	66%	78%	£11,301	£6,519	£4,781
Costs - cirrhotic disease – LDV/SOF	£44,161	£33,121	£55,201	£11,147	£6,508	£4,639
Utility increment after treatment	0.04	0.02	0.06	£6,954	£11,201	£4,247
SVR LDV/SOF (cirrhotic)	90%	79%	97%	£6,342	£10,504	£4,162
TP - from compensated cirrhosis SVR to HCC	0.010	0.000	0.020	£11,111	£7,023	£4,087

Abbreviations: SVR, sustained virologic response; TP, transition probability.

Figure 33: Tornado diagram (GT1/4 TE: LDV/SOF vs TVR+PEG-IFN2a+RBV)



LDV/SOF vs BOC+PEG-IFN2a+RBV

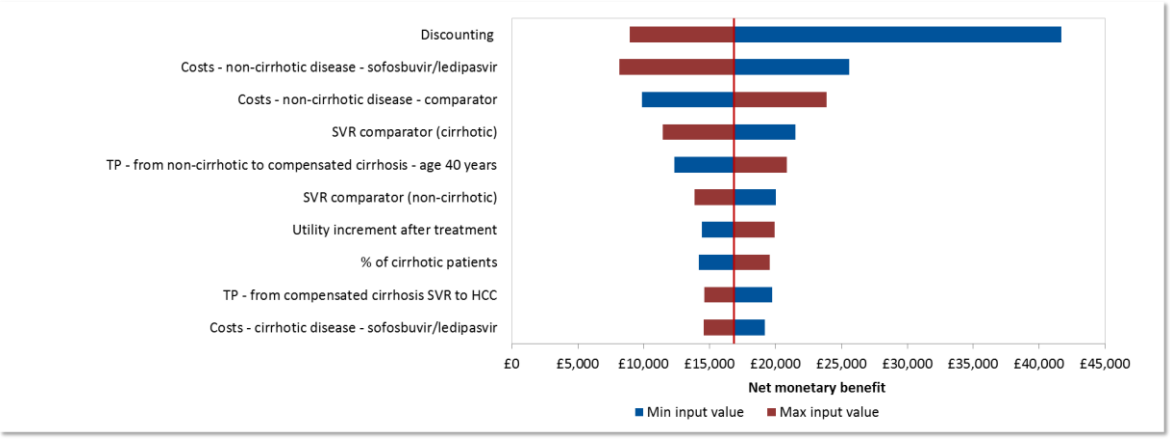
In this comparison, the net benefit was most sensitive to discount rates (varied between 0 and 6%) and the variation in treatment costs for non-cirrhotic patients. However, the net benefit always remained above £0 (the equivalent of an ICER below £20,000). The lowest net benefit value recorded was £8,138 where the LDV/SOF on-treatment cost (drug acquisition, AE and monitoring costs) in non-cirrhotic patients was increased to £55,227 from a base case value of £44,182; an increase of 25%.

Table 117: GT1/4 TE: LDV/SOF vs BOC+PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£41,702	£8,931	£32,771
Costs - non-cirrhotic disease – LDV/SOF	£44,182	£33,136	£55,227	£25,589	£8,138	£17,452
Costs - non-cirrhotic disease - comparator	£35,431	£26,574	£44,289	£9,866	£23,861	£13,995
SVR comparator (cirrhotic)	35%	15%	59%	£21,527	£11,441	£10,086
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.009	0.002	0.016	£12,306	£20,844	£8,537
SVR comparator (non-cirrhotic)	64%	56%	72%	£20,020	£13,864	£6,155
Utility increment after treatment	0.04	0.02	0.06	£14,435	£19,942	£5,508
% of cirrhotic patients	21%	16%	26%	£14,185	£19,542	£5,356
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£19,751	£14,580	£5,171
Costs - cirrhotic disease – LDV/SOF	£44,183	£33,137	£55,229	£19,183	£14,544	£4,639

Abbreviations: SVR, sustained virologic response; TP, transition probability.

Figure 34: Tornado diagram (GT1/4 TE: LDV/SOF vs BOC+PEG-IFN2a+RBV)



LDV/SOF vs no treatment

In this comparison, the net benefit was most sensitive to discount rates (varied between 0 and 6%), the TP from non-cirrhotic to compensated cirrhosis and variation in LDV/SOF treatment costs for non-cirrhotic patients. The majority of inputs retain a positive net benefit when varied between their

maximum and minimum values, however the net benefit fell below £0 (equivalent to an ICER >£20K) in one scenario:

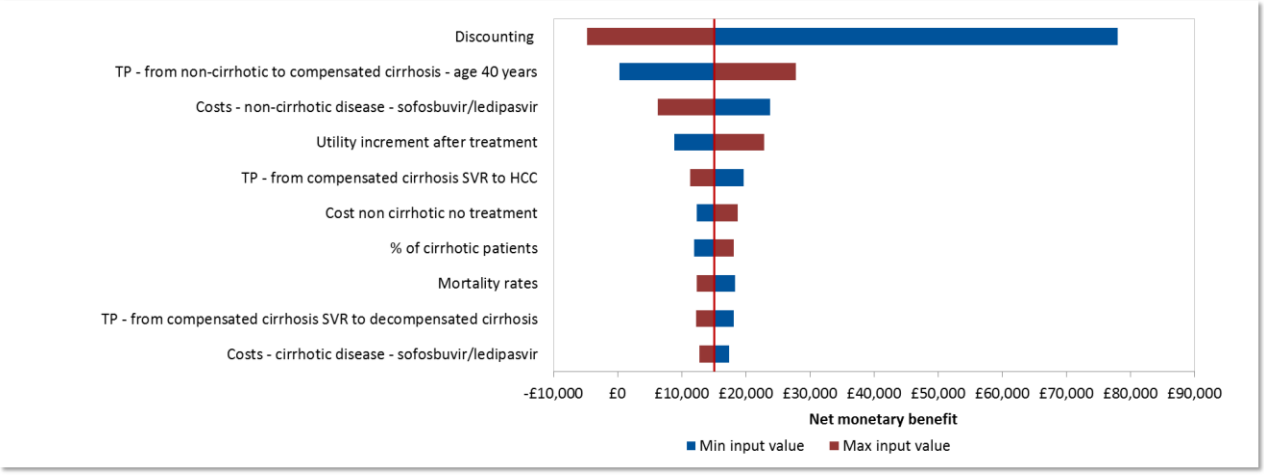
- Net benefit of -£4,777 recorded when the discount rate is increased to 6%. Sensitivity to the discount rate means that a proportion of the benefit (QALY gains and cost savings) with LDV/SOF is observed in the long term.

Table 118: GT1/4 TE: LDV/SOF vs no treatment

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£77,969	-£4,777	£82,746
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.009	0.002	0.016	£308	£27,853	£27,544
Costs - non-cirrhotic disease – LDV/SOF	£44,182	£33,136	£55,227	£23,750	£6,299	£17,452
Utility increment after treatment	0.04	0.02	0.06	£8,817	£22,893	£14,076
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£19,667	£11,349	£8,318
Cost non cirrhotic no treatment	£363	£164	£640	£12,368	£18,722	£6,355
% of cirrhotic patients	21%	16%	26%	£11,956	£18,094	£6,138
Mortality rates	Multiple age-specific values	All varied -25%	All varied +25%	£18,328	£12,340	£5,988
TP - from compensated cirrhosis SVR to decompensated cirrhosis	0.006	0.000	0.013	£18,145	£12,254	£5,892
Costs - cirrhotic disease – LDV/SOF	£44,183	£33,137	£55,229	£17,344	£12,705	£4,639

Abbreviations: SVR, sustained virologic response; TP, transition probability.

Figure 35: Tornado diagram (GT1/4 TE: LDV/SOF vs no treatment)



GT3 TN

LDV/SOF+RBV vs PEG-IFN2a+RBV

In this comparison, the net benefit was most sensitive to discount rates (varied between 0 and 6%), variation in LDV/SOF+RBV treatment costs for non-cirrhotic patients and the TP from non-cirrhotic to compensated cirrhosis. The base case net benefit is -£9,643 (ICER = £26,587) and consequentially all minimum net benefits fell below £0 (equivalent to an ICER >£20K). Scenarios with the two lowest net benefits:

- Net benefit of -£21,708 recorded when the discount rate is increased to 6%. Sensitivity to the discount rate means that a proportion of the benefit (QALY gains and cost savings) with LDV/SOF is observed in the long term.
- Net benefit of -£19,374 recorded when the treatment cost (drug acquisition, AE and monitoring costs) of LDV/SOF+RBV in non-cirrhotic patients was increased by 25% to £65,503. It should be noted that +25% is not a plausible value as drug acquisition cost (a significant component of treatment cost) is fixed (BNF list price).

Scenarios with positive net benefits:

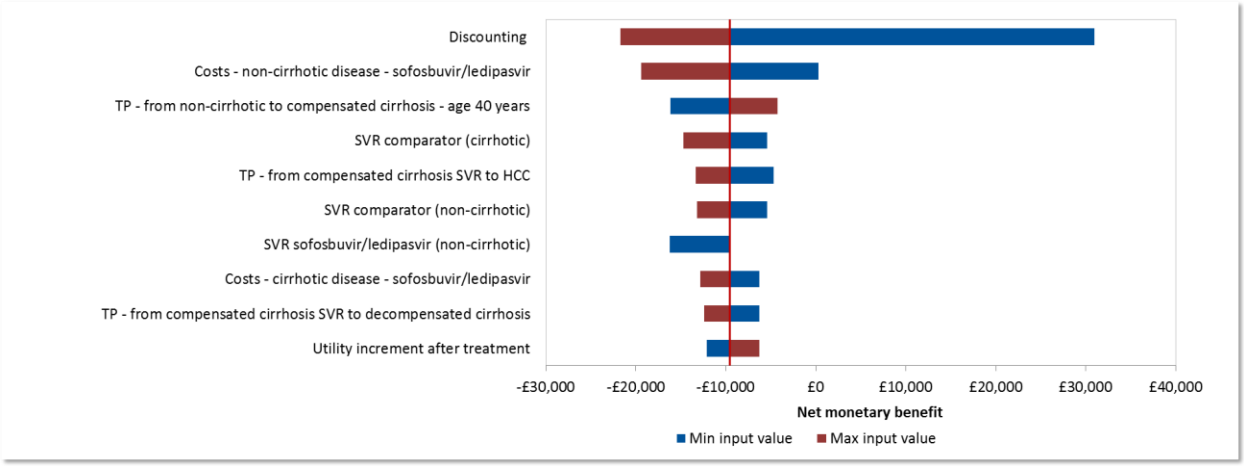
- Net benefit of £30,916 recorded when the discount rate is reduced to 0%. Sensitivity to the discount rate means that a proportion of the benefit (QALY gains and cost savings) with LDV/SOF is observed in the long term.
- Net benefit of £277 recorded when the treatment cost (drug acquisition, AE and monitoring costs) of LDV/SOF+RBV in non-cirrhotic patients was reduced by 25% to £39,302. Again it should be noted that -25% is considered an unrealistically high value as drug acquisition cost (a significant component of treatment cost) is unlikely to vary to this extent (BNF list price).

Table 119: GT3 TN: LDV/SOF+RBV vs PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£30,916	-£21,708	£52,624
Costs - non-cirrhotic disease – LDV/SOF	£52,402	£39,302	£65,503	£277	-£19,374	£19,651
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.01	0.00	0.02	-£16,128	-£4,223	£11,905
SVR comparator (cirrhotic)	30%	16%	47%	-£5,418	-£14,708	£9,290
TP - from compensated cirrhosis SVR to HCC	0.01	0.00	0.02	-£4,670	-£13,348	£8,678
SVR comparator (non-cirrhotic)	71%	63%	79%	-£5,389	-£13,236	£7,847
SVR LDV/SOF (non-cirrhotic)	100%	87%	100%	-£16,235	-£9,549	£6,686
Costs - cirrhotic disease – LDV/SOF	£52,596	£39,447	£65,745	-£6,262	-£12,836	£6,575
TP - from compensated cirrhosis SVR to decompensated cirrhosis	0.01	0.00	0.01	-£6,297	-£12,405	£6,108
Utility increment after treatment	0.04	0.02	0.06	-£12,154	-£6,246	£5,908

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

Figure 36: Tornado diagram (GT3 TN: LDV/SOF+RBV vs PEG-IFN2a+RBV)



LDV/SOF+RBV vs no treatment

In this comparison, the net benefit was most sensitive to discount rates (varied between 0 and 6%), the TP from non-cirrhotic to compensated cirrhosis and variation in LDV/SOF+RBV treatment costs for non-cirrhotic patients. The majority of inputs retain a positive net benefit when varied between their maximum and minimum values, however the net benefit fell below £0 (equivalent to an ICER >£20K) in one scenario:

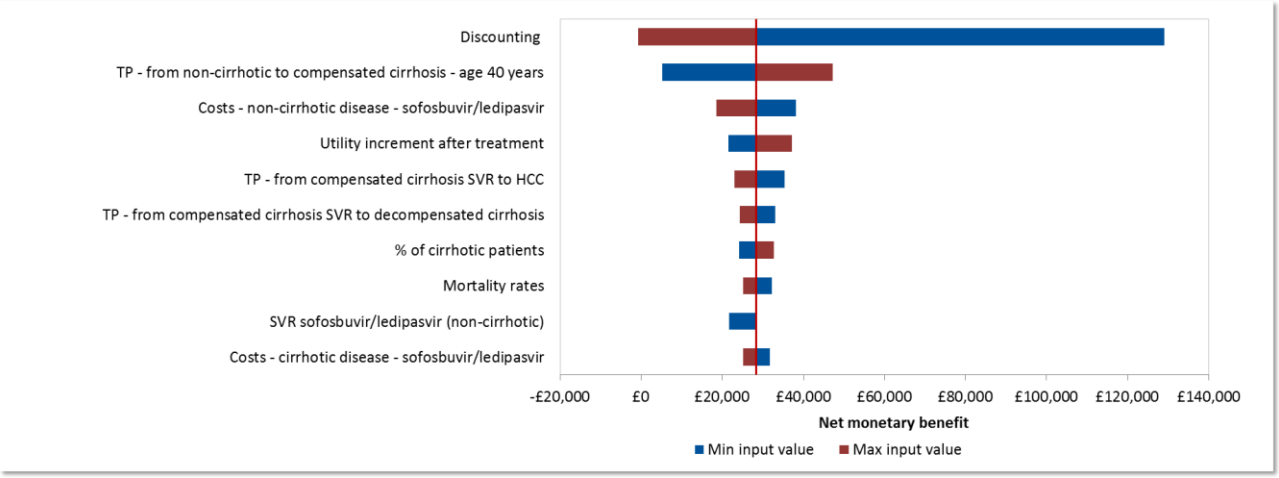
- Net benefit of -£815 recorded when the discount rate is increased to 6%. Sensitivity to the discount rate means that a proportion of the benefit (QALY gains and cost savings) with LDV/SOF is observed in the long term.

Table 120: GT3 TN: LDV/SOF+RBV vs no treatment

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£129,127	-£815	£129,942
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.01	0.00	0.02	£5,176	£47,175	£41,999
Costs - non-cirrhotic disease – LDV/SOF	£52,402	£39,302	£65,503	£38,222	£18,571	£19,651
Utility increment after treatment	0.04	0.02	0.06	£21,509	£37,125	£15,616
TP - from compensated cirrhosis SVR to HCC	0.01	0.00	0.02	£35,300	£23,019	£12,281
TP - from compensated cirrhosis SVR to decompensated cirrhosis	0.01	0.00	0.01	£32,999	£24,354	£8,645
% of cirrhotic patients	25%	19%	31%	£24,122	£32,671	£8,550
Mortality rates	Multiple age-specific values	All varied -25%	All varied +25%	£32,298	£25,199	£7,099
SVR LDV/SOF (non-cirrhotic)	100%	87%	100%	£21,710	£28,396	£6,686
Costs - cirrhotic disease – LDV/SOF	£52,596	£39,447	£65,745	£31,684	£25,109	£6,575

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

Figure 37: Tornado diagram (GT3 TN: LDV/SOF+RBV vs no treatment)



GT3 TN CC

LDV/SOF+RBV vs SOF+PEG-IFN2a+RBV

In this comparison, the net benefit was most sensitive to variation in the SVR rate for SOF+PEG-IFN2a+RBV in cirrhotic patients, the LDV/SOF+RBV treatment costs for cirrhotic patients and discount rates (varied between 0 and 6%). The base case net benefit is -£22,351 (ICER = £46,491) and consequentially all minimum net benefits fell below £0 (equivalent to an ICER >£20K). Scenarios with the two lowest net benefits:

- Net benefit of -£43,063 was recorded when the treatment cost (drug acquisition, AE and monitoring costs) of LDV/SOF+RBV in cirrhotic patients was increased by 25% to £103,558. It should be noted that +25% is not a plausible value as drug acquisition cost (a significant component of treatment cost) is fixed (BNF list price).
- Net benefit of -£38,294 was recorded when the SVR rate for SOF+PEG-IFN2a+RBV was increased to the upper bound of the estimated 95% CI[e].

Scenarios with positive net benefits:

- Net benefit of £7,373 was recorded when the SVR rate for SOF+PEG-IFN2a+RBV was reduced to the lower bound of the estimated 95% CI[e].

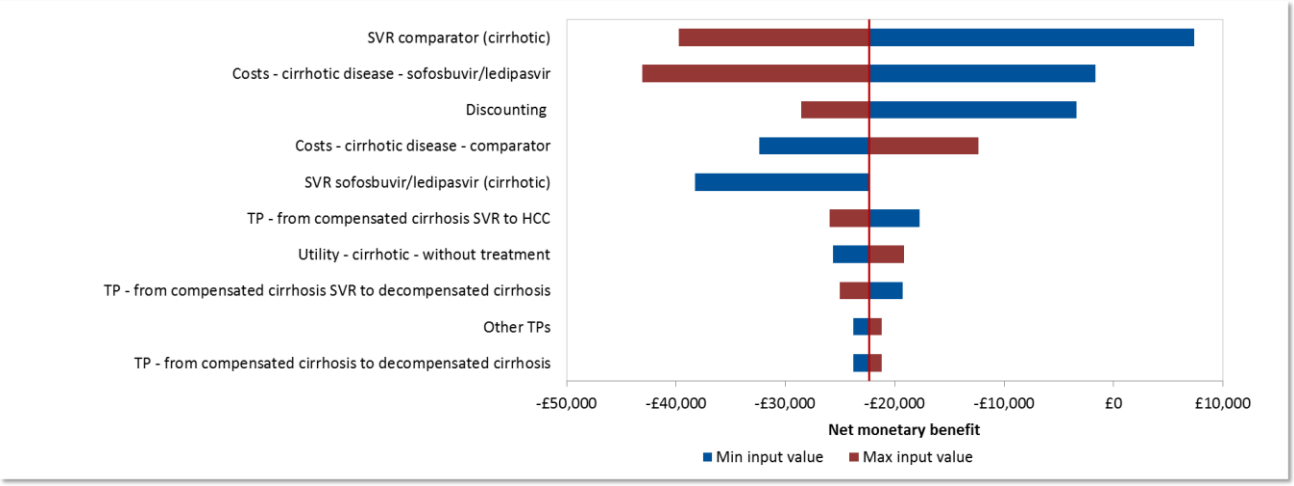
[e] ELECTRON and PROTON did not include non-cirrhotic patients; therefore LONESTAR-2 data was used; 95% CI estimated assuming a BETA distribution

Table 121: GT3 TN CC: LDV/SOF+RBV vs SOF+PEG-IFN2a+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
SVR comparator (cirrhotic)	83%	59%	98%	£7,373	-£39,723	£47,096
Costs - cirrhotic disease – LDV/SOF	£82,846	£62,135	£103,558	-£1,640	-£43,063	£41,423
Discounting	3.5%	0.0%	6.0%	-£3,367	-£28,579	£25,212
Costs - cirrhotic disease - comparator	£40,103	£30,078	£50,129	-£32,377	-£12,326	£20,052
SVR LDV/SOF (cirrhotic)	100%	87%	100%	-£38,294	-£22,351	£15,942
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	-£17,749	-£25,936	£8,187
Utility - cirrhotic - without treatment	0.55	0.44	0.65	-£25,632	-£19,140	£6,491
TP - from compensated cirrhosis SVR to decompensated cirrhosis	0.006	0.000	0.013	-£19,283	-£25,047	£5,763
Other TPs	Compensated cirrhosis to HCC: 0.06 HCC to death: 0.43 LT to death: 0.21 Post-LT to death: 0.06 HCC to LT: 0.00	0.05 0.37 0.13 0.04 0.00	0.08 0.49 0.31 0.08 0.01	-£23,795	-£21,223	£2,572
TP - from compensated cirrhosis to decompensated cirrhosis	0.04	0.03	0.06	-£23,762	-£21,217	£2,545

Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplant; SVR, sustained virologic response; TP, transition probability.

Figure 38: Tornado diagram (GT3 TN CC: LDV/SOF+RBV vs SOF+PEG-IFN2a+RBV)



LDV/SOF+RBV vs SOF+RBV

In this comparison, the net benefit was most sensitive to variation the SVR rate for SMV+PEG-IFN2a+RBV in cirrhotic patients and the treatment costs for cirrhotic patients. The base case net benefit is close to zero, £348 (ICER = £19,013) and consequentially all minimum net benefits fell below £0 (equivalent to an ICER >£20K). Scenarios with the two lowest net benefits:

- Net benefit of -£20,364 recorded when the treatment cost (drug acquisition, AE and monitoring costs) of LDV/SOF+RBV in cirrhotic patients was increased by 25% to £103,558. It should be noted that +25% is not a plausible value as drug acquisition cost (a significant component of treatment cost) is fixed (BNF list price).
- Net benefit of -£18,333 recorded when the treatment cost (drug acquisition, AE and monitoring costs) of SOF+RBV in cirrhotic patients was decreased by 25% to £56,041. Again, it should be noted that +25% is not a plausible value as drug acquisition cost (a significant component of treatment cost) is fixed (BNF list price).

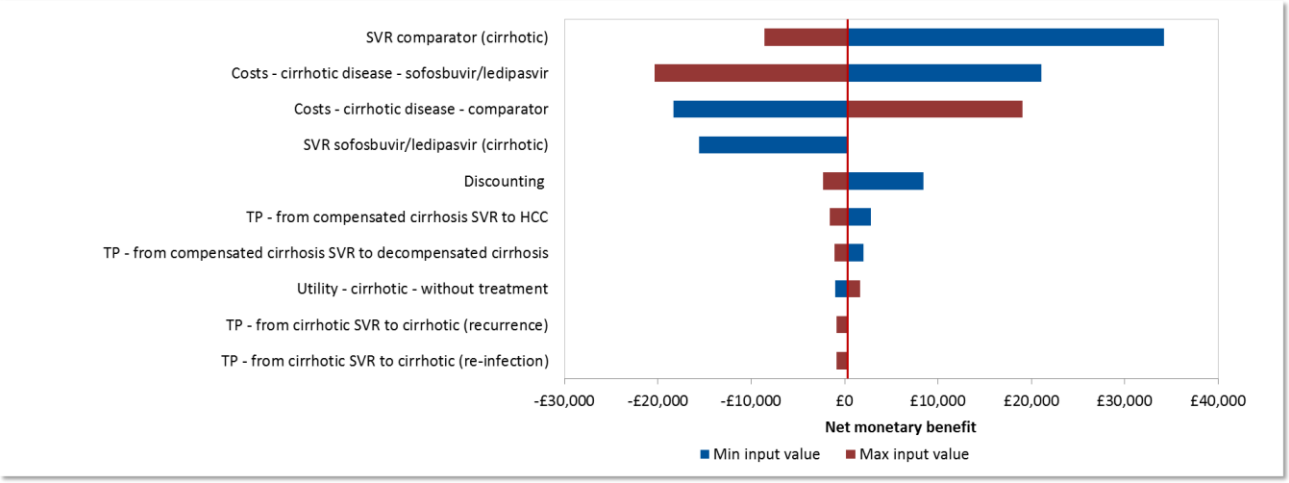
Table 122: GT3 TN CC: LDV/SOF+RBV vs SOF+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
SVR comparator (cirrhotic)	92%	64%	100%	£34,171	-£8,604	£42,775
Costs - cirrhotic disease – LDV/SOF	£82,846	£62,135	£103,558	£21,059	-£20,364	£41,423
Costs - cirrhotic disease - comparator	£74,722	£56,041	£93,402	-£18,333	£19,028	£37,361
SVR LDV/SOF (cirrhotic)	100%	87%	100%	-£15,594	£348	£15,942
Discounting	3.5%	0.0%	6.0%	£8,454	-£2,294	£10,749
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£2,819	-£1,561	£4,380

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
TP - from compensated cirrhosis SVR to decompensated cirrhosis	0.006	0.000	0.013	£1,984	-£1,081	£3,064
Utility - cirrhotic - without treatment	0.55	0.44	0.65	-£982	£1,649	£2,631
TP - from cirrhotic SVR to cirrhotic (recurrence)	0.000	0.000	0.010	£348	-£896	£1,243
TP - from cirrhotic SVR to cirrhotic (re-infection)	0.000	0.000	0.010	£348	-£896	£1,243

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

Figure 39: Tornado diagram (GT3 TN CC: LDV/SOF+RBV vs SOF+RBV)



GT3 TE

LDV/SOF+RBV vs no treatment

In this comparison, the net benefit was most sensitive to variation in the discount rates (varied between 0 and 6%), the TP from non-cirrhotic to compensated cirrhosis and the LDV/SOF+RBV treatment costs for non-cirrhotic patients. The base case net benefit is -£19,772 (ICER = £28,048) and consequentially all minimum net benefits fell below £0 (equivalent to an ICER >£20K). Scenarios with the two lowest net benefits:

- Net benefit of -£41,083 recorded when the discount rate is increased to 6%. Sensitivity to the discount rate means that a proportion of the benefit (QALY gains and cost savings) with LDV/SOF is observed in the long term.
- Net benefit of -£37,699 recorded when the TP from non-cirrhotic to compensated cirrhosis was increased by 75% to 0.02275.

Scenarios with positive net benefits:

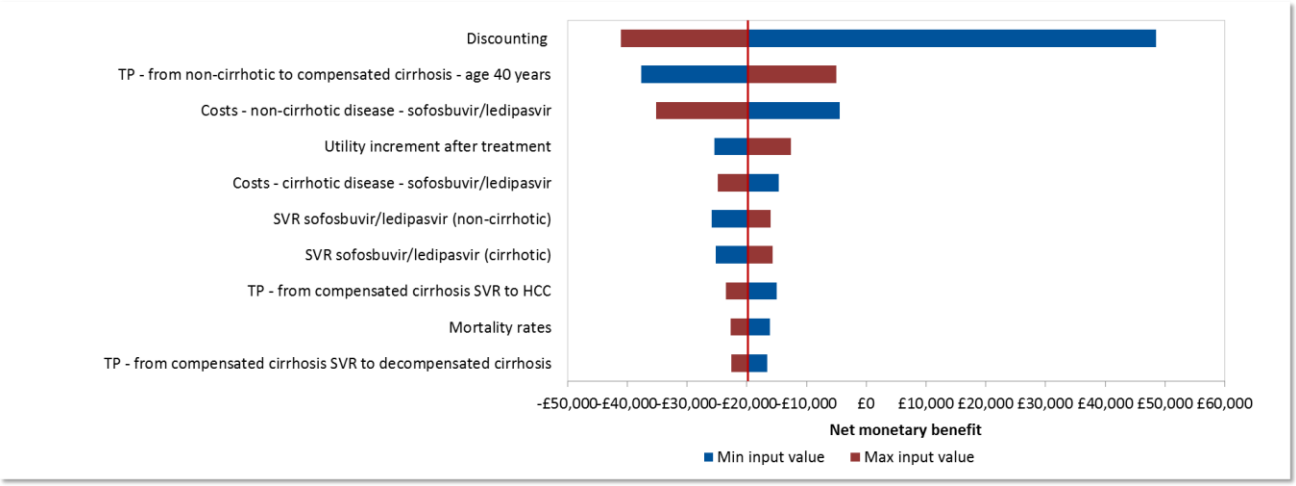
- Net benefit of £48,520 recorded when the discount rate is reduced to 0%.

Table 123: GT3 TE: LDV/SOF+RBV vs no treatment

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Discounting	3.5%	0.0%	6.0%	£48,520	-£41,083	£89,603
TP - from non-cirrhotic to compensated cirrhosis - age 40 years	0.013	0.003	0.023	-£37,699	-£5,015	£32,684
Costs - non-cirrhotic disease – LDV/SOF	£82,022	£61,517	£102,528	-£4,392	-£35,151	£30,758
Utility increment after treatment	0.04	0.02	0.06	-£25,415	-£12,618	£12,797
Costs - cirrhotic disease – LDV/SOF	£82,024	£61,518	£102,530	-£14,645	-£24,898	£10,253
SVR LDV/SOF (non-cirrhotic)	89%	76%	98%	-£25,890	-£16,003	£9,886
SVR LDV/SOF (cirrhotic)	77%	58%	92%	-£25,235	-£15,639	£9,596
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	-£15,015	-£23,538	£8,523
Mortality rates	Multiple age-specific values	All varied -25%	All varied +25%	-£16,148	-£22,711	£6,563
TP - from compensated cirrhosis SVR to decompensated cirrhosis	0.006	0.000	0.013	-£16,574	-£22,611	£6,037

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

Figure 40: Tornado diagram (GT3 TE: LDV/SOF+RBV vs no treatment)



GT3 TE CC

LDV/SOF+RBV vs SOF+RBV

In this comparison, the net benefit was most sensitive to variation the treatment costs for cirrhotic patients and the SVR rate for SOF+RBV in cirrhotic patients. The majority of inputs retain a positive net benefit when varied between their maximum and minimum values, however the net benefit fell below £0 (equivalent to an ICER >£20K) in four scenarios:

- Net benefit of -£10,176 was recorded when the treatment cost (drug acquisition, AE and monitoring costs) of LDV/SOF+RBV in cirrhotic patients was increased by 25% to £102,530. It should be noted that +25% is not a plausible value as drug acquisition cost (a significant component of treatment cost) is fixed (BNF list price).
- Net benefit of -£8,144 was recorded when the treatment cost (drug acquisition, AE and monitoring costs) of SOF+RBV in cirrhotic patients was decreased by 25% to £55,425. Again, it should be noted that +25% is not a plausible value as drug acquisition cost (a significant component of treatment cost) is fixed (BNF list price).
- Net benefit of -£11,522 was recorded when the SVR rate for LDV/SOF+RBV was reduced to the lower bound, 58%.
- Net benefit of -£5,777 was recorded when the SVR rate for SOF+RBV was increased to the upper bound, 74%.

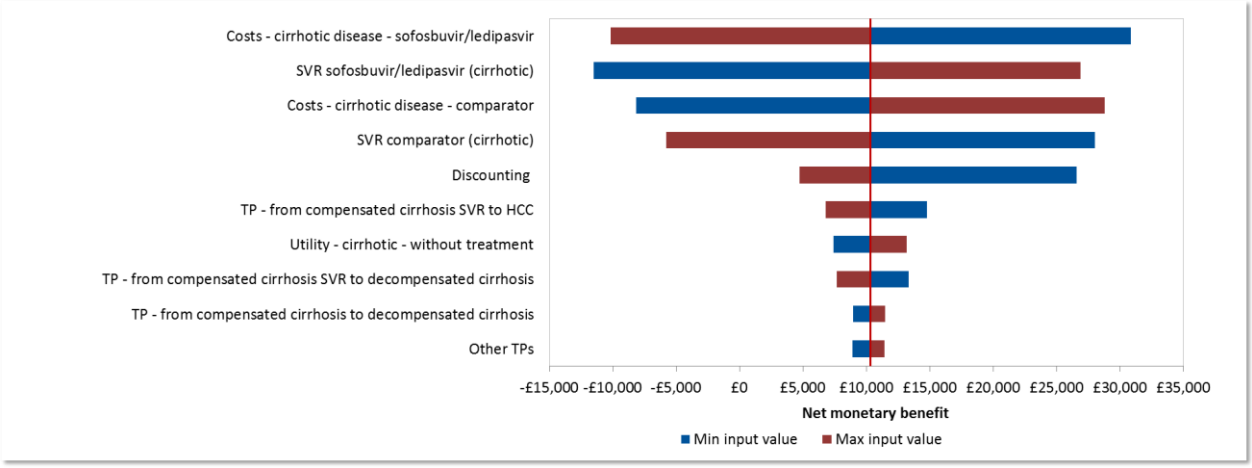
Table 124: GT3 TE CC: LDV/SOF+RBV vs SOF+RBV

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
Costs - cirrhotic disease – LDV/SOF	£82,024	£61,518	£102,530	£30,837	-£10,176	£41,012
SVR LDV/SOF (cirrhotic)	77%	58%	92%	-£11,522	£26,862	£38,384
Costs - cirrhotic disease - comparator	£73,899	£55,425	£92,374	-£8,144	£28,805	£36,950
SVR comparator (cirrhotic)	60%	44%	74%	£28,015	-£5,777	£33,792
Discounting	3.5%	0.0%	6.0%	£26,562	£4,729	£21,832
TP - from compensated cirrhosis SVR to HCC	0.013	0.003	0.022	£14,800	£6,801	£8,000
Utility - cirrhotic - without treatment	0.55	0.44	0.65	£7,432	£13,168	£5,736
TP - from compensated cirrhosis SVR to decompensated cirrhosis	0.006	0.000	0.013	£13,328	£7,674	£5,654

Parameter	Value			Net benefit		
	Base-case	Minimum	Maximum	Minimum	Maximum	Difference
TP - from compensated cirrhosis to decompensated cirrhosis	0.044	0.029	0.058	£8,931	£11,463	£2,532
Other TPs	Compensated cirrhosis to HCC: 0.06 HCC to death: 0.43 LT to death: 0.21 Post-LT to death: 0.06 HCC to LT: 0.00	0.05 0.37 0.13 0.04 0.00	0.08 0.49 0.31 0.08 0.01	£8,921	£11,453	£2,532

Abbreviations: HCC, hepatocellular carcinoma; SVR, sustained virologic response; TP, transition probability.

Figure 41: Tornado diagram (GT3 TE CC: LDV/SOF+RBV vs SOF+RBV)



7.7.8 *Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.*

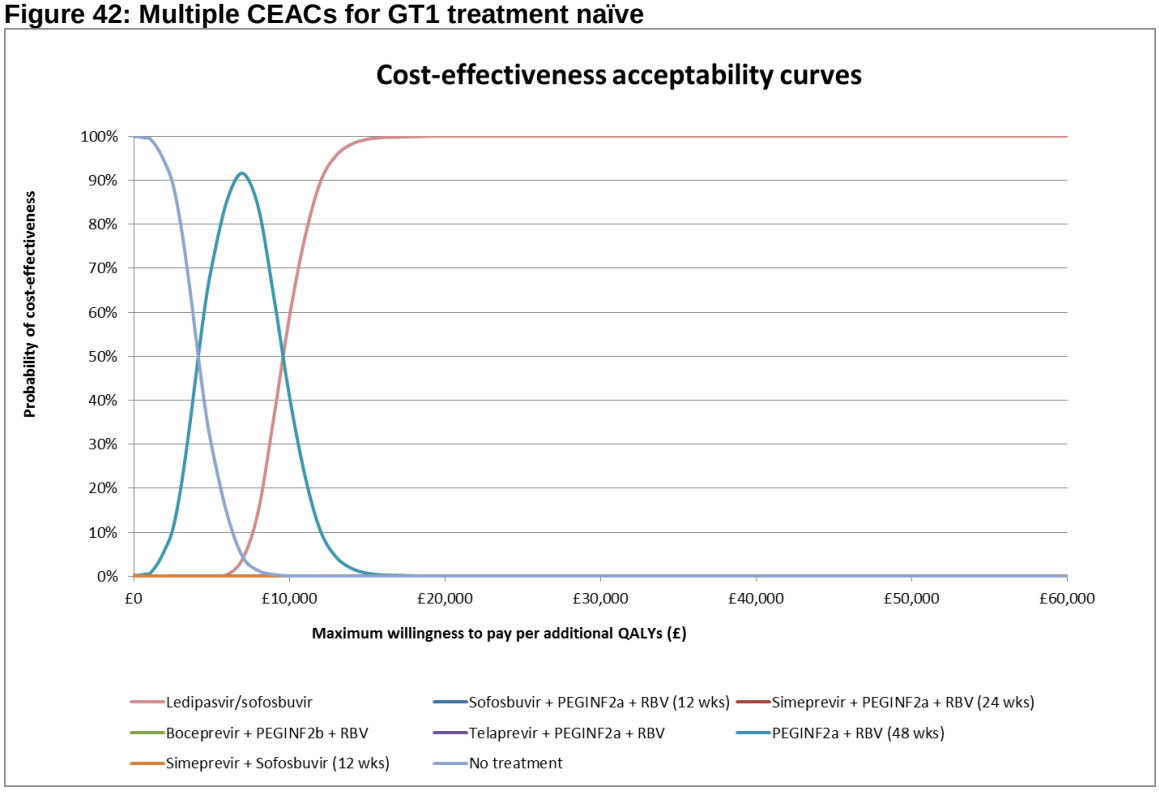
The probabilistic sensitivity analysis (PSA) was performed on each patient population defined by genotype and treatment experience. The analysis was completed for 1,000 simulations. The results are shown in the form of multiple cost effectiveness acceptability curves (CEACs). All comparators are represented on the same graph demonstrating the probability that each treatment is cost-effective at different values of the willingness to pay threshold.

The probability that LDV/SOF is considered cost effective at a willingness to pay threshold of £20,000 per QALY is also reported.

GT1 treatment naïve

The CEACs are presented in Figure 42. The CE frontier consists of no treatment, PEG-IFN2a+RBV and LDV/SOF. The probability that LDV/SOF is a cost effective option compared with all other comparators at a £20,000 per QALY threshold is 100%.

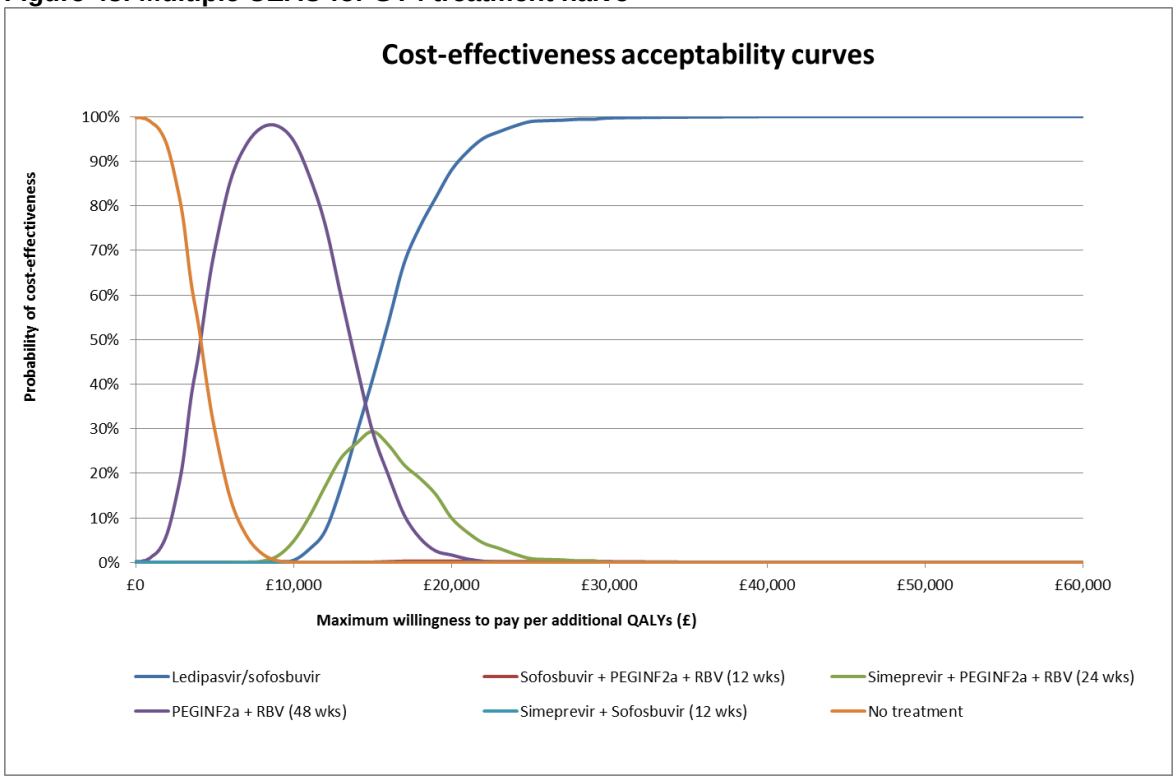
Figure 42: Multiple CEACs for GT1 treatment naïve



GT4 treatment naïve

The CEACs are presented in Figure 43. The CE frontier consists of no treatment, PEG-IFN2a+RBV and LDV/SOF. The probability that LDV/SOF is a cost effective option compared with all other comparators is 88% at a £20,000 per QALY threshold and 100% at a £30,000 per QALY threshold.

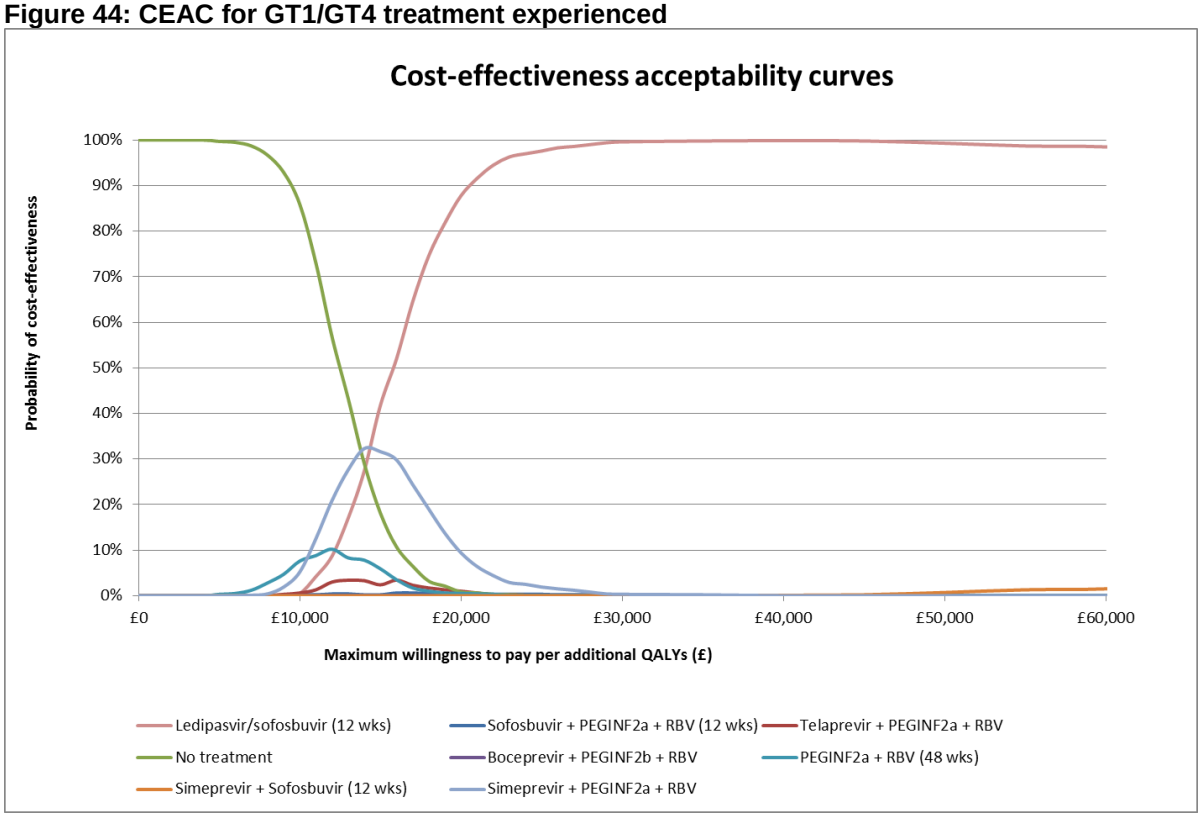
Figure 43: Multiple CEAC for GT4 treatment naïve



GT1/GT4 treatment experienced

The CEACs are presented in Figure 44. The CE frontier consists of no treatment, SMV+PEG-IFN2a+RBV and LDV/SOF. The probability that LDV/SOF is a cost effective option compared with all other comparators is 88% at a £20,000 per QALY threshold and 100% at a £30,000 per QALY threshold.

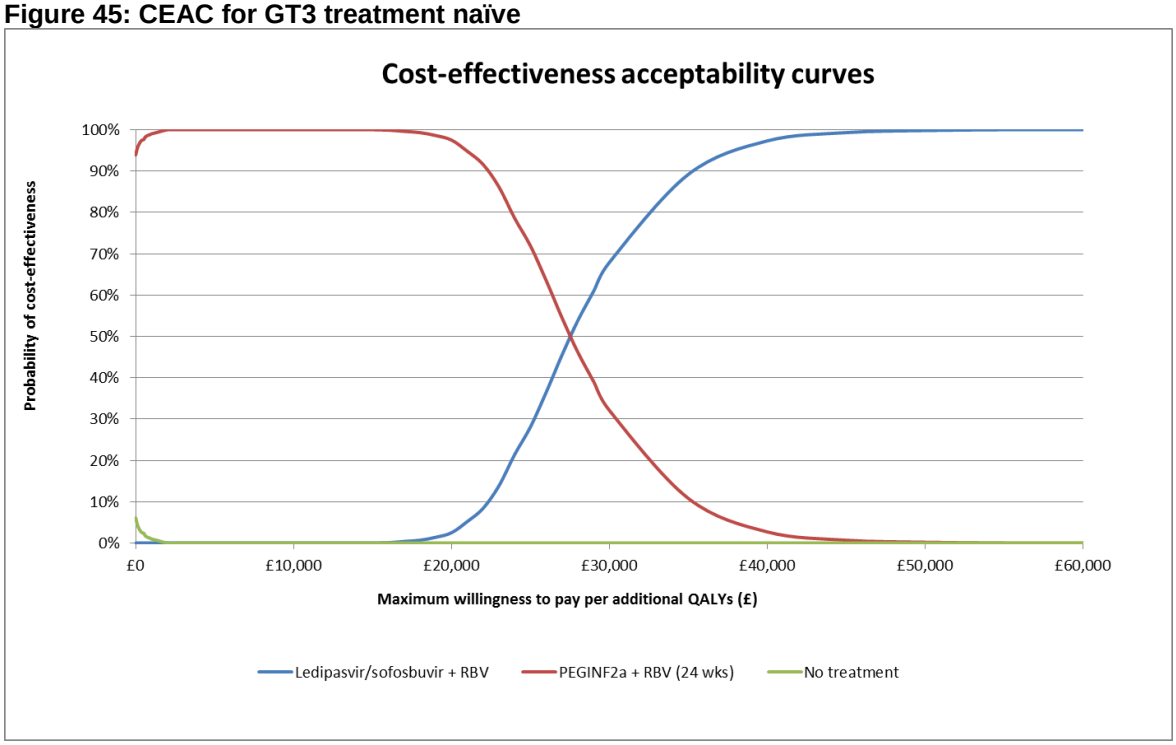
Figure 44: CEAC for GT1/GT4 treatment experienced



GT3 treatment naïve

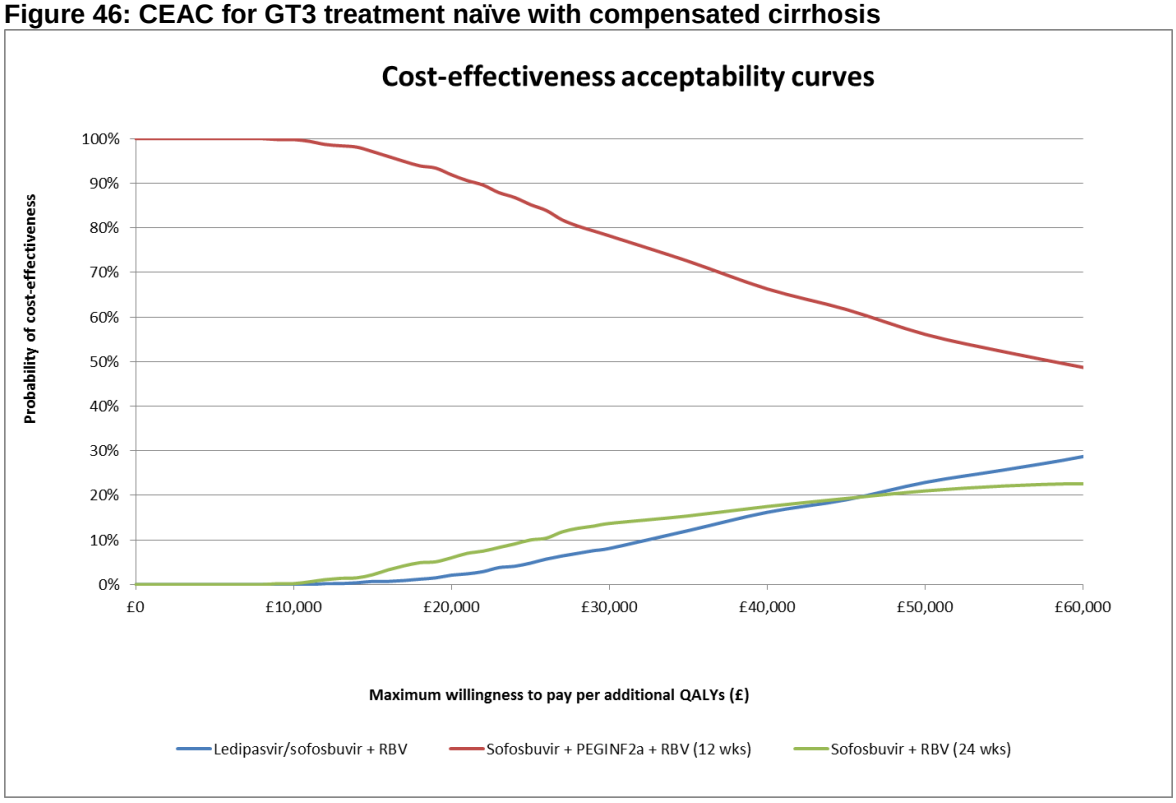
The CEACs are presented in Figure 45. The CE frontier consists of PEG-IFN2a+RBV and LDV/SOF+RBV. The probability that LDV/SOF+RBV is a cost effective option compared with all other comparators is 2.5% at a £20,000 per QALY threshold and 68% at a £30,000 per QALY threshold.

Figure 45: CEAC for GT3 treatment naïve



The CEACs for the analysis restricted to GT3 treatment naïve patients with compensated cirrhosis are presented in Figure 46. The CE frontier consists of SOF+PEG-IFN2a+RBV. The probability that LDV/SOF+RBV is a cost effective option compared with all other comparators is 2.1% at a £20,000 per QALY threshold and 8% at a £30,000 per QALY threshold (base case ICER = £46,491).

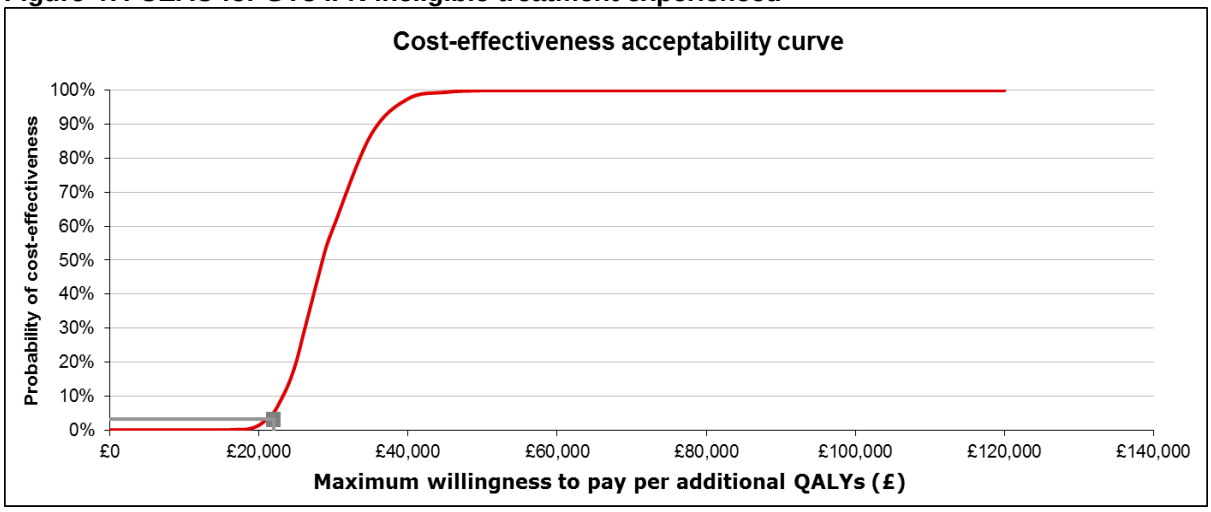
Figure 46: CEAC for GT3 treatment naïve with compensated cirrhosis



GT3 treatment experienced IFN ineligible versus no treatment

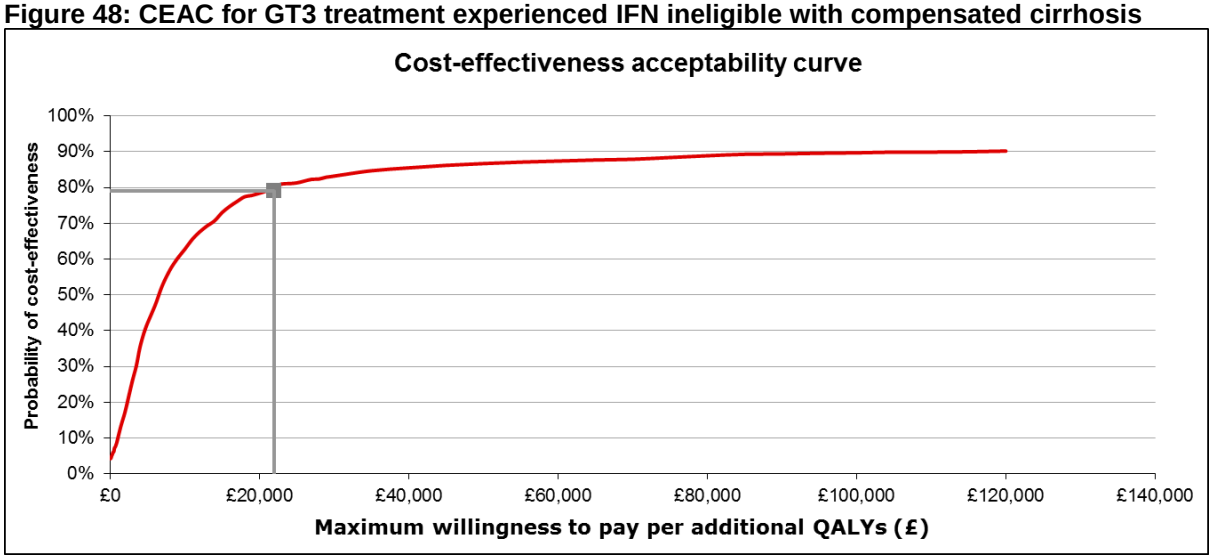
The CEAC is presented in Figure 47 for LDV/SOF+RBV versus no treatment. The probability that LDV/SOF+RBV is a cost effective option compared with all other comparators is 1.4% at a £20,000 per QALY threshold and 59.8% at a £30,00 per QALY threshold (base case ICER = £28,048).

Figure 47: CEAC for GT3 IFN ineligible treatment experienced



The CEAC for the analysis restricted to GT3 treatment experienced IFN ineligible cirrhotic patents is presented in Figure 48 for LDV/SOF+RBV versus SOF+RBV (SOF+RBV is only recommended as a treatment option for GT3 TE cirrhotic patients). The probability that LDV/SOF+RBV is a cost effective option compared with SOF+RBV is 78% at a £20,000 per QALY threshold and 83% at a £30,000 per QALY threshold (base case ICER = £6,210).

Figure 48: CEAC for GT3 treatment experienced IFN ineligible with compensated cirrhosis



7.7.9 *Please present the results of scenario analysis. Include details of structural sensitivity analysis.*

Scenario 1: Treating all GT1/4 treatment experienced cirrhotic patients with LDV/SOF+RBV for 12 weeks instead of LDV/SOF for 12 or 24 weeks

The SPC for LDV/SOF recommends a regimen of 24 weeks in patients with compensated cirrhosis, with a 12 week regimen for those at low risk of clinical progression and who have

subsequent retreatment options. Data from SIRIUS (section 6.5.7.7), which became available after the SPC was finalised, demonstrates that treatment experienced patients with GT1 infection and with compensated cirrhosis can achieve very high SVR12 rates (≥96%) with either LDV/SOF for 24 weeks or LDV/SOF+RBV for 12 weeks. In addition, KOL opinion suggested this 12 week LDV/SOF+RBV regimen might be used to treat these patients. Therefore a scenario analysis was conducted modelling LDV/SOF+RBV for 12 weeks for all treatment experienced cirrhotic patients with GT1 and GT4 rather than LDV/SOF for 12 or 24 weeks. In GT1 and GT4 treatment experienced patients without cirrhosis the LDV/SOF regimen remains unchanged.

In this scenario there is a small reduction from base case in total treatment costs (£47,428 from £49,537) and a small increase in QALYs (14.78 from 14.72). As such the frontier consists of no treatment and LDV/SOF as in the base case, with a similar ICER (ICER £12,299 vs base case £13,527). The modest reduction in ICER is not unexpected; despite the substantial reduction in treatment cost that results by changing from a 24 week LDV/SOF regimen to a 12 week regimen of LDV/SOF+RBV, this change only accounts for a relatively small proportion of the overall treatment experienced population modelled (~5%; 21% of GT1/4 treatment experienced are cirrhotic, 25% of these assumed to receive LDV/SOF 24 weeks in base case).

The analysis demonstrates that LDV/SOF+RBV for 12 weeks provides an alternative option to 12/24 weeks of LDV/SOF that is equally efficacious and cost-effective for treatment experienced GT1/4 patients with compensated cirrhosis.

Table 125: Cost-effectiveness results, GT1/GT4 treatment experienced†

Technologies	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus baseline (QALYs)	incremental
No treatment	£18,143	17.44	12.40					
PEG-IFN2a+RBV	£24,960	17.83	12.75	£6,817	0.39	0.35	£19,292	Extended dominance
TVR+PEG-IFN2a+RBV	£42,101	18.84	13.90	£23,959	1.40	1.51	£15,890	Extended dominance
SMV+PR	£43,626	19.17	14.13	£25,483	1.73	1.73	£14,740	Extended dominance
BOC+PEG-IFN2b+RBV	£45,897	18.62	13.69	£27,754	1.18	1.30	£21,419	Dominated
SOF+PR	£46,756	19.16	14.21	£28,613	1.72	1.81	£15,765	Extended dominance
LDV/SOF	£47,428	19.67	14.78	£29,285	2.23	2.38	£12,299	£12,299
SOF+SMV	£64,720	19.60	14.71	£46,577	2.16	2.31	£20,166	Dominated

Abbreviations: BOC, boceprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
† TVR+PEG-IFN2a+RBV and BOC+PEG-IFN2a+RBV are relevant for GT1 CHC only as they are not licensed for the treatment of GT4 CHC.

Scenario 2: Use of GT4 specific clinical data instead of GT1 data

For all comparisons in the base case GT1 clinical data was applied across GT1 and GT4 populations based on the assumption that GT1 and GT4 respond in a similar way, as described in

section 7.2.1. In this scenario, the limited clinical data that is available for all interventions was modelled.

GT4 treatment naïve

This scenario analysis confirms the approach taken in the base case, with LDV/SOF remaining cost-effective (all ICERs <£18,000) versus all comparators (Table 126). The CE frontier consists of no treatment, PEG-IFN+RBV, SMV+PEG-IFN+RBV and LDV/SOF. SMV+SOF is dominated and SOF+PEG-IFN2a+RBV is dominated by the principle of extended dominance.

Table 126: Cost-effectiveness results, GT4 treatment naive

Technologies	Total			Incremental			ICER (£) versus baseline (QALYs)	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
No treatment	£18,956	18.30	13.01				NA	NA
PR	£24,045	19.53	14.24	£5,089	1.23	1.23	£4,137	£4,137
SMV+PR	£37,654	20.50	15.27	£18,698	2.20	2.26	£8,273	£13,213
SOF+PR	£44,970	20.62	15.55	£26,014	2.32	2.54	£10,242	Extended dominance
LDV/SOF	£46,349	20.93	15.77	£27,393	2.63	2.76	£9,925	£17,390
SOF+SMV	£65,630	20.74	15.57	£46,674	2.44	2.56	£18,232	Dominated

Abbreviations: GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

GT4 treatment experienced

This scenario analysis confirms the approach taken in the base case, with LDV/SOF remaining cost-effective (all ICERs <£13,000) versus all comparators (Table 127). The CE frontier consists of no treatment and LDV/SOF. SMV+SOF was dominated and all other comparators were dominated by the principle of extended dominance.

Table 127: Cost-effectiveness results, GT4 treatment experienced†

Technologies	Total			Incremental			ICER (£) versus baseline (QALYs)	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
No treatment	£18,143	17.44	12.40				NA	NA
PR	£24,960	17.83	12.75	£6,817	0.39	0.35	£19,477	Extended dominance
SMV+PR	£45,762	18.88	13.75	£27,619	1.44	1.35	£20,459	Extended dominance
SOF+PR	£46,756	19.16	14.21	£28,613	1.72	1.81	£15,808	Extended dominance
LDV/SOF	£48,680	19.77	14.88	£30,537	2.33	2.48	£12,313	£12,313
SOF+SMV	£64,720	19.60	14.71	£46,577	2.16	2.31	£20,163	Dominated

Abbreviations: BOC, boceprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

† TVR+PEG-IFN2a+RBV and BOC+PEG-IFN2a+RBV are relevant for GT1 CHC only as they are not licensed for the treatment of GT4 CHC.

Scenario 3: Variation in treatment duration splits

Based on KOL input several scenarios were run in which alternative 'worst case scenarios' LDV/SOF treatment duration splits were tested.

GT1 treatment naïve

In the base case it was assumed that in treatment naïve patients with compensated cirrhosis 95% of patients would be treated with LDV/SOF for 12 weeks and 5% with LDV/SOF for 24 weeks. In this scenario the ratio was changed to test the 'worst case scenario' of 15% of patients treated with the longer duration (85%:15%).

As shown in Table 128 the overall conclusion remains unchanged versus the base case, with the CE frontier consisting of no treatment, PEG-IFN+RBV and LDV/SOF. ICERs for LDV/SOF versus comparators on the frontier are <£9,000.

Table 128: Cost-effectiveness results, GT1 treatment naïve

Technologies	Total			Incremental			ICER (£) versus baseline (QALYs)	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
No treatment	£18,956	18.30	13.01					
PEG-IFN2a+RBV	£25,308	19.23	13.98	£6,352	0.94	0.97	£6,548	£6,548
SMV+PR	£38,731	20.14	15.02	£19,774	1.84	2.01	£9,840	Extended dominance
LDV/SOF	£39,524	20.81	15.66	£20,568	2.51	2.65	£7,756	£8,453
TVR+PEG-IFN2a+RBV	£40,237	19.99	14.85	£21,281	1.70	1.84	£11,571	Dominated
BOC+PEG-IFN2b+RBV	£41,299	19.93	14.66	£22,342	1.63	1.65	£13,537	Dominated
SOF+PR	£45,776	20.54	15.40	£26,819	2.24	2.39	£11,215	Dominated
SOF+SMV	£65,630	20.74	15.57	£46,674	2.44	2.56	£18,204	Dominated

Abbreviations: BOC, boceprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

GT4 treatment naïve

Assuming the same 85:15% treatment duration for 12:24 weeks, for GT4 treatment naive compensated cirrhotic patients as used in the GT1 treatment naïve scenario, the overall conclusions remain unchanged versus the base case. The CE frontier consists of no treatment, PEG-IFN+RBV, SMV+PEG-IFN+RBV and LDV/SOF (Table 95). ICERs for LDV/SOF versus comparators on the frontier are <£14,000 (Table 129).

Table 129: Cost-effectiveness results, GT4 treatment naive

Technologies	Total			Incremental			ICER (£) versus baseline (QALYs)	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
No treatment	£18,956	18.30	13.01					
PEG-IFN2a+RBV	£25,308	19.23	13.98	£6,352	0.94	0.97	£6,548	£6,548
SMV+PR	£38,731	20.14	15.02	£19,774	1.84	2.01	£9,840	£12,914
SOF+PR	£45,776	20.54	15.40	£26,819	2.24	2.39	£11,215	Extended dominance
LDV/SOF	£47,634	20.82	15.68	£28,678	2.52	2.67	£10,760	£13,580
SOF+SMV	£65,630	20.74	15.57	£46,674	2.44	2.56	£18,204	Dominated

Abbreviations: GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

GT1/GT4 treatment experienced

In the base case it was assumed that in treatment experienced patients with compensated cirrhosis, 75% of patients would be treated with LDV/SOF for 12 weeks and 25% with LDV/SOF for 24 weeks. In this scenario the ratio was changed to test the 'worst case scenario' in which 50% of patients were treated with the longer duration (50%:50%).

In this scenario the conclusion remains unchanged from base case. The CE frontier consists of no treatment and LDV/SOF (ICER: £14,146; Table 130). BOC+PEG-IFN2a+RBV and SMV+SOF were dominated and all other comparators were dominated by the principle of extended dominance.

Table 130: Cost-effectiveness results, GT1/GT4 treatment experienced†

Technologies	Total			Incremental			ICER (£) versus baseline (QALYs)	ICER (£) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
No treatment	£18,143	17.44	12.40					
PEG-IFN2a+RBV	£24,960	17.83	12.75	£6,817	0.39	0.35	£19,292	Extended dominance
TVR+PEG-IFN2a+RBV	£42,101	18.84	13.90	£23,959	1.40	1.51	£15,890	Extended dominance
SMV+PR	£43,626	19.17	14.13	£25,483	1.73	1.73	£14,740	Extended dominance
BOC+PEG-IFN2b+RBV	£45,897	18.62	13.69	£27,754	1.18	1.30	£21,419	Dominated
SOF+PR	£46,756	19.16	14.21	£28,613	1.72	1.81	£15,765	Extended dominance
LDV/SOF	£51,443	19.63	14.75	£33,300	2.19	2.35	£14,146	£14,146
SOF+SMV	£64,720	19.60	14.71	£46,577	2.16	2.31	£20,166	Dominated

Abbreviations: BOC, boceprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

† TVR+PEG-IFN2a+RBV and BOC+PEG-IFN2a+RBV are relevant for GT1 CHC only as they are not licensed for the treatment of GT4 CHC.

7.7.10 *What were the main findings of each of the sensitivity analyses?*

Deterministic sensitivity analyses

GT1 TN

The one-way DSA shows the cost-effectiveness of LDV/SOF was robust across all comparators to changes to all parameter values; such that LDV/SOF remained cost-effective in all analyses (net benefit >£0, ICER <£20,000). The net benefit was most sensitive to on-treatment costs for non-cirrhotic patients (both LDV/SOF and the comparator), the discount rate and the transition probability from non-cirrhotic to compensated cirrhosis.

GT4 TN and GT1/4 TE

The one-way DSA shows the cost-effectiveness of LDV/SOF was sensitive, for some comparators, to changes in on-treatment costs for non-cirrhotic patients (both LDV/SOF and the comparator) and increasing the discount rate to 6%. When extreme values were used, which biased against LDV/SOF, the net benefit fell below £0 (equivalent to an ICER >£20K), see Table 131.

- The likelihood of LDV/SOF on-treatment costs increasing to +25% of the base case value is very low as the main constituent of on-treatment cost is drug costs. Similarly comparator costs decreasing to −25% of base case is unlikely.
- Discounting both costs and benefits at a rate of 6% indicates that a proportion of the benefit (QALY gains and cost savings) with LDV/SOF is observed in the long term. The NICE Reference Case (271) stipulates a base case discount rate of 3.5% with a sensitivity analysis of 1.5% therefore discounting at 6% is outside of the range considered useful in decision making.

The net benefit was also sensitive to comparator SVR rates in cirrhotic patients and the transition probability from non-cirrhotic to compensated cirrhosis. However, LDV/SOF remained cost-effectiveness (net benefit >£0, ICER <£20,000).

Table 131: GT4 TN and GT1/4 TE DSA results with a net benefit<£0 (ICER >£20,000)

Comparator	Net benefit <£0		
	On-treatment LDV/SOF cost +25%	On-treatment comparator cost -25%	Discount rate 6%
GT4 TN			
SOF+PEG-IFN2a+RBV	Yes	Yes	
SMV+PEG-IFN2a+RBV	Yes	Yes	Yes
PEG-IFN2a+RBV			Yes
No treatment			
GT1/4 TE			
SOF+PEG-IFN2a+RBV	Yes	Yes	
SMV+PEG-IFN2a+RBV	Yes	Yes	
PEG-IFN2a+RBV			Yes
TVR+PEG-IFN1a+RBV			
BOC+PEG-IFN1a+RBV			

No treatment			Yes

GT3 TN

The one-way DSA shows that overall the economic results are sensitive to the discount rates for both costs and outcomes, changes in on-treatment costs for non-cirrhotic patients (LDV/SOF only) and transition probability from non-cirrhotic to compensated cirrhosis.

GT3 TN CC

The one-way DSA shows that overall the economic results are sensitive to the changes in the SVR rates (LDV/SOF and comparator), changes in on-treatment costs for cirrhotic patients (LDV/SOF and the comparator) and the discount rate.

GT3 TE

The one-way DSA shows that overall the comparison of LDV/SOF+RBV vs no treatment is sensitive to the changes in the discount rate, transition probability from non-cirrhotic to compensated cirrhosis and changes in on-treatment costs for non-cirrhotic patients (LDV/SOF).

GT3 TE CC

The one-way DSA for LDV/SOF+RBV vs SOF+RBV, shows the cost-effectiveness of LDV/SOF was sensitive to changes in on-treatment costs for cirrhotic patients (both LDV/SOF+RBV and the comparator) and the SVR rates (LDV/SOF+RBV and the comparator). When extreme values were used which biased against LDV/SOF, the net benefit fell below £0 (equivalent to an ICER >£20K).

- The likelihood of LDV/SOF on-treatment costs increasing to +25% of base case is very low as the main constituent of on-treatment cost is drug costs which is known to be fixed (BNF list price). Similarly, comparator costs decreasing to -25% of base case is unlikely.

Probabilistic sensitivity analyses

- For patients with CHC GT1 and GT4, LDV/SOF is cost-effective compared with all comparators in treatment naïve and treatment experienced patients.
  - The probability that LDV/SOF is the most cost effective option at a threshold of £20,000 per QALY is 100% for GT1 treatment naïve patients.
  - The probability that LDV/SOF is the most cost effective option at a threshold of £30,000 per QALY is 100% for GT4 treatment naïve and GT1/GT4 treatment experienced patients.
- For GT3 treatment naïve patients, the probability that LDV/SOF+RBV is the most cost effective option at a threshold of £30,000 per QALY is 68% versus no treatment and PEG-IFN+RBV. When compared for SOF+PEG-IFN+RBV (cirrhotic patients only), LDV/SOF+RBV has a low probability of being cost-effective.
- For treatment experienced IFN ineligible patients with GT3 infection, the probability that LDV/SOF+RBV is the most cost effective option at a threshold of £20,000 per QALY versus SOF+RBV (only active treatment option) is 78%.

7.7.11 *What are the key drivers of the cost-effectiveness results?*

Key drivers, based on DSA have been presented and discussed for each population versus each comparator in section 7.7.7, and summarised in section 7.7.10.

7.8 *Validation*

7.8.1 *Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.*

The model underwent internal and external validation.

In the internal validation three distinct quality assessments were made to the model. The first was conducted by a senior modeller and a senior statistician with previous experience in HCV. The second check was made by a second modeller not familiar with the project. Finally, a third validation was undertaken by an independent modeller with a focus on reviewing the validity of the model via a series of logical and consistency checks. A number of hypothetical scenarios were tested and the results produced by the model compared with the expected outcomes.

Scenarios tested included, but were not limited to, the following:

- Testing equal SVR rates, treatment durations and on-treatment QoL decrements and checking that clinical results matched in both arms in the model
- Setting all health state utility values to 1 and checking that the number of QALYs matched the number of life years
- Modelling a 100% SVR rate in a non-cirrhotic cohort and checking that no patients progressed to advanced liver disease health states
- Removal of the excess mortality associated with advanced liver disease and checking that there were no differences in the number of deaths between both arms of the model
- Removal of background mortality and excess mortality associated with advanced liver disease and checking that 10,000 patients were alive in both arms of the model at the end of the time horizon

KOL input was sought to validate major assumptions in the LDV/SOF model as described in section 7.3.5.

7.9 *Subgroup analysis*

7.9.1 *Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to Section 6.3.7.*

Base case analyses were conducted on mixed populations of non-cirrhotic and compensated cirrhosis patients. In this sub-group analysis ICERs are presented for the non-cirrhotic and compensated cirrhosis sub-groups. All clinical, HRQL and cost input data was the same as for the base case analyses.

Cost-effectiveness may vary by the presence of cirrhosis due to differences in efficacy of LDV/SOF or the comparator regimen and/or treatment duration.

7.9.2 *Please clearly define the characteristics of patients in the subgroup.*

See section 7.9.1.

7.9.3 *Please describe how the statistical analysis was undertaken.*

N/A

7.9.4 *What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in Section 7.7.6 (Base-case analysis).*

ICRs generated for cirrhotic and non-cirrhotic sub groups are provided in Table 132, along with the base case ICERS generated in mixed cirrhotic/non-cirrhotic cohorts.

LDV/SOF remains cost-effective in all GT1 and GT4 populations. In GT1/4 treatment experienced cirrhotic patients LDV/SOF falls in the south-west quadrant versus SMV+SOF (ICER: £58,284), whereas in the base case LDV/SOF was dominant for this comparison. The ICER in the cirrhotic population is driven by a small reduction in QALYs (lower SVR rate) and combined with a cost-saving for LDV/SOF versus SMV+SOF. It should be noted that the data from SMV+SOF comes from a small Phase II trial compared to LDV/SOF data which is based on phase III trial data.

In GT3 patients two ICERs are pushed above £30,000 compared with the base case: versus PEG-IFN+RBV in treatment naïve non-cirrhotics (£39,149) and versus no treatment in treatment experienced non-cirrhotics (£33,631). In GT3 cirrhotic patients, LDV/SOF is cost-effective compared to the nearly all the comparators in both treatment naïve and treatment experienced IFN-ineligible populations, the exception being SOF+PEG-IFN+RBV.

Table 132: Summary of base-case cost-effectiveness results (ICER for LDV/SOF±RBV against each comparator: £/QALY)

Indication	Base case	Non-cirrhotic	Cirrhotic
GT1 treatment naïve			
SOF+PR	LDV/SOF dominates	LDV/SOF dominates	£1,349
SMV+PR	LDV/SOF dominates	LDV/SOF dominates	£3,156
SMV+SOF	LDV/SOF dominates	LDV/SOF dominates	LDV/SOF dominates
BOC+PEG-IFN2b+RBV	LDV/SOF dominates	LDV/SOF dominates	LDV/SOF dominates
TVR+PEG-IFN2a+RBV	LDV/SOF dominates	LDV/SOF dominates	£1,522
PEG-IFN2a+RBV	£7,985	£10,397	£4,731
No treatment	£7,458	£8,965	£4,920
GT4 treatment naïve			
SOF+PR	£3,869	£6,790	£1,349
SMV+PR	£12,399	£23,136	£3,156
SMV+SOF	LDV/SOF dominates	LDV/SOF dominates	LDV/SOF dominates
PEG-IFN2a+RBV	£12,715	£18,555	£4,731
No treatment	£10,468	£13,734	£4,920
GT1/4 treatment experienced			
SOF+PR	£5,497	£3,011	£11,001
SMV+PR	£9,984	£10,494	£9,102
SMV+SOF	LDV/SOF dominates	LDV/SOF dominates	SW quadrant
BOC+PEG-IFN2b+RBV†	£3,551	£5,748	£1,265
TVR+PEG-IFN2a+RBV†	£9,144	£13,741	£4,303
PEG-IFN2a+RBV	£12,491	£16,125	£6,666

Indication	Base case	Non-cirrhotic	Cirrhotic
No treatment	£13,527	£17,205	£7,415
GT3 treatment naïve (LDV/SOF+RBV)			
SOF+PR	£46,491	NA	£46,491
SOF+RBV	£19,013	NA	£19,013
PR	£26,491	£39,149	£17,622
No treatment	£11,235	£10,549	£12,335
GT3 treatment experienced (LDV/SOF+RBV)			
SOF+RBV	£6,210	NA	£6,210
No treatment	£28,048	£33,631	£18,252

Abbreviations: BOC, boceprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; NT, no treatment; PEG-IFN, pegylated interferon; QALY; quality adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
† TVR+PEG-IFN2a+RBV and BOC+PEG-IFN2a+RBV are relevant for GT1 CHC only as they are not licensed for the treatment of GT4 CHC.

7.9.5 *Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in Section 5.*

The scope suggested that the following subgroups should be considered if evidence allows:

- Genotype
- Co-infection with HIV
- People with and without cirrhosis
- People who have received treatment pre- and post-liver transplantation
- Response to previous treatment (non-response, partial response, relapsed)
- People who are intolerant to or ineligible for interferon treatment

The base case results were split by genotype with results presented for GT1 and GT4 combined and GT3. An additional scenario analysis was presented for GT4 patients separately using GT4 specific data where available, in section 7.7.9. In addition, subgroup analyses are presented for people with and without cirrhosis in section 7.9.

As LDV/SOF is IFN-free, subgroup analyses by IFN ineligibility are not required as the only difference for this patient population is the choice of comparators. IFN-free comparators that provide treatment options for this patient population have been included in the base case analyses (including SOF+RBV, SMV+SOF, and no treatment).

The remaining subgroups were not modelled for the following reasons:

HCV/HIV co-infection

As per the licensed indication, the efficacy and safety of LDV/SOF based regimens in the treatment of HCV/HIV co-infected populations is similar to that observed in HCV mono-infected populations and as such they should be treated the same (see section 6.5.7.3). Therefore the co-infected population is not modelled separately in the base case. This is a similar approach to that taken in previous NICE submissions including sofosbuvir and simeprevir, and has been validated with KOLs (section 7.3.5). This approach is considered conservative as HCV/HIV co-infected patients are likely to transition faster to the more advanced CHC disease states if left untreated, and

therefore would be more cost-effective compared to the mono-infected population for a given treatment.

Patients who are pre-/post-liver transplant

The treatment of patients who are pre-/post-liver transplant are not modelled separately in this submission due to a lack of data. Although the natural history of patients experiencing HCV recurrence is well documented, there is currently a lack of clinical data on the outcomes, costs and quality of life of patients who either achieve post-transplant virologic response following pre-transplant treatment or who achieve SVR following treatment post-transplant, reflecting the fact that these patients have not historically been treated. In addition, the transition probabilities are not known for patients post-transplant with graft re-infection of HCV. This approach was discussed at an Advisory Board with 11 clinicians in the UK, all of whom were in agreement that at this time the data would not support the development of a cost-effectiveness model for this population (section 7.3.5). For the purposes of this submission we assume these patients are modelled based on their genotype and presence of cirrhosis.

Response to previous treatment

A subgroup analyses was not undertaken investigating the cost-effectiveness of LDV/SOF and the comparators due to a lack of relevance. Historically this type of analyses has been included as it was relevant to understand how well patients responded to previous IFN-based treatment. With the newer IFN-free SOF-based treatment regimens, response is not impacted by previous response to IFN treatment; hence this analysis is not included.

7.10 *Interpretation of economic evidence*

7.10.1 *Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?*

There are no published economic models exploring the cost-effectiveness of any LDV/SOF-based regimen in CHC GT1, GT3 or GT4.

7.10.2 *Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in Section 5?*

The results of this economic evaluation are relevant to all groups of patients, defined in Section 5, as the clinical data included in the model reflects that from the Phase II and III clinical trials in these patients.

For patients who are IFN ineligible, only GT3 patients with cirrhosis currently have a treatment option that is NICE approved (based on preliminary guidance for SOF). For all other IFN ineligible patients the current option is best supportive care (no treatment).

7.10.3 *What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?*

Strengths of the evaluation

The modelling approach was deemed the most adequate to reflect the natural history of HCV. By choosing a Markov model the costs, QALYs and clinical effectiveness can be extrapolated beyond the duration of the trials to assess the long-term impact of this new regimen.

The model structure is similar to that used in previously developed cost-effectiveness analyses and NICE HCV HTAs, including that for SOF (9;10). As with the model used for the sofosbuvir HTA, to reflect UK clinical practice and the design of the LDV/SOF (and sofosbuvir) trials, the mild and moderate health states were combined into a single non-cirrhotic health state to reflect patient's disease severity at baseline.

The model structure reflects comments made by the Evidence Review Group for the sofosbuvir NICE submission, which include the following:

- An incorporation of possible transitions between compensated cirrhosis with SVR and advanced liver disease health states (HCC or decompensated cirrhosis) in line with the most recent Southampton Health Technology Assessment Centre (SHTAC) model (Hartwell et al, 2011 (10)).
- Annual background mortality rates that are weighted to reflect the HCV population gender split.
- Utility increment after treatment from the 2013 ADVANCE study publication by Vera-Llonch (260).

The analysis incorporated all important health effects, that is, SVRs, AEs and HRQL. The model was populated with clinical data from the Phase II and III clinical trials on LDV/SOF supporting the licensed indication, providing a direct comparison between the currently available treatments in the NHS for each patient group and the licensed dose of LDV/SOF. The data for the clinical effectiveness of the comparator treatments was obtained from the Phase III clinical trials, when available, and from a systematic literature review. A systematic literature review was also conducted to obtain information on utilities, transition probabilities, health state costs and resource use while monitoring during treatment. Where possible, the inputs selected for the model were those considered the most appropriate by NICE in previous cost-effectiveness analyses.

During the consultation on the sofosbuvir NICE submission there was discussion around the most appropriate data source for the SVR for PEG-IFN+RBV in GT1 TN. As with the sofosbuvir submission, McHutchison et al. (2009) was included in these analyses as it was deemed the most appropriate source by clinical experts, being the largest (1035 vs. 271 patients in Hadziyannis et al) and most recent publication and also commonly cited as being the most representative of current treatment practice and outcomes. It should also be noted that compared with the Hadziyannis study the patients in the McHutchison study were older (48 years vs. 43 years), heavier (82.8kg. vs. 77.3kg) and with a higher proportion of patients with black ethnicity (19% vs. 3%), thus being more representative of the population seen within the ION trials for GT1, making a more suitable comparator for the LDV/SOF data.

Also during the sofosbuvir appraisal, discussion was held regarding the use of Fattovich et al vs Cardoso et al for the transition from compensated cirrhosis (CC) to Hepatocellular carcinoma (HCC) and SVR-cirrhosis to HCC. Importantly the publication from Fattovich et al does not report a transition probability (TP) from SVR-cirrhosis to HCC. In addition to being a more recent publication (2010 vs 1997), Cardoso et al includes both a TP from CC to HCC (0.0631) and from SVR-CC to HCC (0.0128). The TPs are consistent with the literature and KOL opinion, which suggests that the risk of progressing to HCC is approximately 4 to 5 times lower in cirrhotic patients who achieve SVR versus those that do not. Thus the use of Cardoso et al achieves face validity. The same transition is used for decompensated cirrhosis to HCC as for CC to HCC, in line with previous models.

The costs for liver transplant and post-liver transplant were updated using a more recent study by the authors (Longworth et al.) who published the costs used in previous NICE submissions.

The distribution of patients according to cirrhosis state is based on a broad UK registry which captures HCV patients recruited from >45 liver centres across the country, increasing the reliability and applicability of the results to the England and Wales HCV population awaiting treatment. Similarly, management of adverse events is also reflective of UK practice as validated by external experts.

Extensive deterministic and probabilistic sensitivity analyses were conducted by varying several input parameters. In general, the results were robust to variations in these parameters and the ICERs for the cost-effective patient groups did not often exceed £20,000/QALY or £30,000/QALY.

The model was thoroughly validated by three internal modellers and a statistician and externally validated by clinical experts in the area of HCV.

Weaknesses of the evaluation

Similar to the situation with the sofosbuvir NICE submission, no network meta-analysis (NMA) was possible for LDV/SOF. As described in section 6, the Phase III trial programme evaluated LDV/SOF regimens with and without RBV for different treatment durations without classical active control arms. In order to link LDV/SOF via a network to the currently recommended regimens for the treatment of CHC patients, a common comparator would be required. As described in section 6.10.2, there were no appropriate comparators for the LDV/SOF trials and therefore they were uncontrolled (historical control) studies. Therefore, the approach taken to source efficacy data for comparators was one of naïve comparison, taking data from individual studies across all patient groups modelled in the economic evaluation (see section 6.7 for summary of studies).

While the lack of a network meta-analysis may be considered a limitation, SVR is a hard and objective end point consistently measured across all trials, and is not subject to bias from the patient or investigator. In addition, patients in the LDV/SOF trials are considered more difficult to treatment, meaning the naïve comparisons are likely to be conservative in favour of the comparators. It should be noted that this overall approach is in line with the approach taken for SOF and accepted by HTA bodies as being an appropriate methodology given the available data.

The recommended LDV/SOF+RBV treatment duration for GT3 patients is 24 weeks for those with cirrhosis and/or with prior treatment failure. The clinical data for CHC GT3 are currently limited to LDV/SOF+RBV for 12 weeks (ELECTRON-2). These data show that all treatment naïve patients treated with LDV/SOF+RBV achieved SVR12, including those with cirrhosis. The extended 24 week duration in the licence is a reflection of the regulators' decision to maximize the chance of a cure for patients with LDV/SOF who are considered more difficult to cure. Data in treatment experienced patients are currently limited to SVR4 with rates of 89.3% (25/28) in patients without cirrhosis and 77.3% (17/22) in patients with compensated cirrhosis. No study data is available for a 24 week regimen in GT3. In the economic analyses, a 12 week LDV/SOF+RBV regimen was considered in GT3 TN patients without cirrhosis, although this is only provided within Section 5.1 of the SPC (and not given as a recommended duration in the posology table). A 24 week regimen was modelled in all treatment experienced patients, and in treatment naïve patients with compensated cirrhosis, in line with the SPC recommendation for these populations. The ELECTRON-2 trial is ongoing and SVR12 data in treatment experienced GT3 patients treated for 12 weeks is expected in Q4 2014. In the modelling, the SVR4 data from ELECTRON-2 was used for the analyses in treatment experienced patients with SVR12 data used in treatment naïve patients. The SVR rates associated with a 24 week LDV/SOF+RBV regimen (modelled in GT3 TN patients with compensated cirrhosis and in treatment experienced patients) may actually be higher than the SVR4 data with 12 week treatment duration as included in the economic model.

In the absence of patient-level data from the ION trials, the treatment-related utility decrement for patients treated with LDV/SOF+RBV was estimated using SOF+RBV patient data from FUSION, FISSION and POSITRON as a proxy. No treatment-related utility decrement has been observed with either LDV or SOF.

The clinical data for CHC GT4 are currently limited (data available for [redacted] patients [redacted] achieved SVR12) and trials are on-going (SYNERGY and a French study [GS-US-337-1119]). However, GT4 and GT1 infections are recognised to respond in a similar way, as shown previously for GT1 and GT4 patients treated with other HCV therapies) and it is recommended in the SPC that GT1 and GT4 infections are generally treated equivalently with LDV/SOF (see SPC). GT1 data was used as proxy for GT4 data in the base case analysis to reflect the larger data base in this indication. However, a scenario analysis was run wherein GT4-specific SVR rates were used for both LDV/SOF and relevant comparators. LDV/SOF remains cost-effective versus all comparators.

The calculation of treatment costs is based on the average treatment duration. Nevertheless, the results of the sensitivity analyses around the cost of non-cirrhotic and cirrhotic disease while on treatment were included in the analysis. The total cost of treatment of non-cirrhotic and cirrhotic disease were varied by 25% in the deterministic sensitivity analysis as an encompassing approach to capture elements such as changes in treatment duration, wastage, monitoring and adverse events.

The economic analyses do not consider the reduced HCV transmission due to improved treatment success associated with LDV/SOF relative to current treatment options. The potential benefit of LDV/SOF in alleviating the public health burden of HCV in England and Wales is therefore underestimated.

7.10.4 *What further analyses could be undertaken to enhance the robustness/completeness of the results?*

The impact of reducing the onwards transmission of HCV has not been incorporated in this economic evaluation. This evaluation therefore underestimates the QALY gain and wider societal benefit that will be observed following the introduction of LDV/SOF. Allowing for this in the model, fewer transmissions would occur as a result of higher cure rates, and therefore patients would experience high QALYs and costs to the NHS will be reduced.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 ***How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.***

GT1 & 4

Table 133: Estimation of GT1 and 4 patients eligible for treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population, n	179,246	179,246	179,246	179,246	179,246
Patient with chronic HCV treated each year, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible patients treated each year in sub-set, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HCV, Hepatitis C Virus.

GT3

Table 134: Estimation of GT3 patients eligible for treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalent population, n	179,246	179,246	179,246	179,246	179,246
Patient with chronic HCV treated each year, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible patients treated each year in sub-set, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HCV, Hepatitis C Virus.

Assumptions:

- Adult population in England and Wales: 44,811,567 (272)
- Prevalence of chronic HCV infection in England: 0.4% (21)
  - Assume that this value represents the true value in Wales
- Proportion of patients with chronic HCV who are treated per year in England: 3.1% (23)
  - Assume that this value represents the true value in Wales
- Genotype split (21)
  - GT1: 45%
  - GT3: 45%
  - GT4: 3.47% (assumes that the ratio of GT2, GT4, GT5 and GT6 is the same in England & Wales [not reported] as it is in Northern Ireland [reported])
- Proportion of patients who were treatment naïve
  - GT1: 80% (assumption)

- GT4: 80% (it is conservatively assumed that GT4 %TN = GT1 %TN, however it is understood that GT4 %TN > GT1 %TN as GT4 patients had fewer treatment options and therefore are less likely to have received treatment)
- GT3: 70% (assumption)

- Proportion of patients who have compensated cirrhosis (121)
  - GT1: 21%
  - GT4: 21% (assumption that GT4 TN %CC = GT1 TN %CC)
  - GT3: 25%

8.2 *What assumption(s) were made about current treatment options and uptake of technologies?*

The anticipated update of LDV/SOF regimens across a 5-year time horizon is indicated in Table 135.

Table 135: Estimation of uptake of LDV/SOF regimens

	Year 1	Year 2	Year 3	Year 4	Year 5
GT1 & GT4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GT3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GT, Genotype.

Current treatment options considered in the budget impact analysis are described in Table 136 and are consistent with comparators used in the cost-utility analysis.

Table 136: LDV/SOF comparator for each HCV genotype

	GT1	GT4	GT3 TN	GT3 TE
SOF+PEG-IFN2a+RBV	✔	✔	✔ (cirrhosis only)	-
SMV+PEG-IFN2a+RBV	✔	✔	-	-
BOC+PEG-IFN2b+RBV	✔	-	-	-
TVR+PEG-IFN2a+RBV	✔	-	-	-
PEG-IFN2a+RBV	✔	✔	✔	-
No treatment	✔	✔	✔	✔
SMV+SOF	✔	✔	-	-
SOF+RBV	-	-	✔ (cirrhosis only)	✔ (cirrhosis only)

Abbreviations: BOC, boceprevir; GT, Genotype; IFN, interferon; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TE, treatment experienced; TN, treatment naïve; TVR, telaprevir.

8.3 *What assumption(s) were made about market share (when relevant)?*

The level of displacement of each LDV/SOF comparator is assumed to be constant over time. The displacement for each comparator within each genotype / patient group is described in Table 137.

Table 137: LDV/SOF comparator displacement

	GT1	GT4	GT3 TN NC	GT3 TN CC	GT3 TE NC	GT3 TE CC
SOF+PEG-IFN2a+RBV	[redacted]	[redacted]	-	[redacted]	-	-
SMV+PEG-IFN2a+RBV	[redacted]	[redacted]	-	-	-	-
BOC+PEG-IFN2b+RBV	[redacted]	-	-	-	-	-
TVR+PEG-IFN2a+RBV	[redacted]	-	-	-	-	-
PEG-IFN2a+RBV	[redacted]	[redacted]	[redacted]	[redacted]	-	-
No treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SMV+SOF	[redacted]	[redacted]	-	-	-	-
SOF+RBV	-	-		[redacted]	-	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BOC, boceprevir; GT, Genotype; IFN, interferon; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TE, treatment experienced; TN, treatment naïve; TVR, telaprevir.

8.4 *In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).*

There are no other significant costs associated with LDV/SOF regimens displacing existing HCV treatments.

8.5 *What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?*

Treatment costs used in budget impact calculations are consistent with treatment costs used in the cost-utility analysis; references are provided in Table 77.

Key assumptions:

- Discontinuation rate is assumed to be 0% (data from the ION studies have shown LDV/SOF to have a discontinuation rates <1% due to AEs. Assuming 0% discontinuation is conservative as it represents the largest budget impact)
- Treatment durations for LDV/SOF regimens are as presented in Table 48.
- All drug costs were taken from BNF September 2014 (273)
- All doses were consistent with those used in the cost-effectiveness analysis and are presented in Table 54. Treatment durations were also consistent with the cost-effectiveness analysis presented in Section 7.3.6.
    - The ribavirin doses in comparator regimens in GT1 and GT4 are conditional on body weight. In these cases a body weight of 79 Kg was used (10)

8.6 *Were there any estimates of resource savings? If so, what were they?*

There are several sources of cost savings which could be realised with the introduction of LDV/SOF regimens.

Less monitoring should be required with LDV/SOF regimens compared with currently available regimens and hence lead to resource savings. Firstly, there is no requirement for response guided therapy as there is with PEG-IFN or first generation PI-based therapies, removing the need for regular on-treatment viral load monitoring and clinic visits. Secondly, adverse event monitoring and management of AEs should also be reduced; PEG-IFN, PIs and RBV all have monitoring requirements for specific AEs, whereas the only AEs identified for LDV/SOF that were more common than placebo were fatigue and headache. During 2013, data was collected from a single UK centre to measure the patient management costs of triple therapy with established PIs (TVR and BOC) which estimated that management costs could be up to 6 times higher than that reported in HTA submissions (274). This suggests that the cost of managing patients with PIs in clinical practice is significantly higher than the figures being used within this submission suggesting a conservative approach.

Since LDV/SOF is generally associated with higher SVR rates for all GT1, GT3 & GT4 comparators, the costs associated with the management of patients who do not achieve a SVR are also projected to decrease.

Finally, for patients who are IFN ineligible, only GT3 patients with cirrhosis currently have a treatment option that is NICE approved (based on preliminary guidance for SOF and SMV). For all other IFN ineligible patients the current option is best supportive care (no treatment). The introduction of LDV/SOF regimens should decrease the costs of managing patients who are currently on the waiting list.

8.7 *What is the estimated annual budget impact for the NHS in England and Wales?*

GT1 and GT4

The net total budget impact for GT1 and GT4 patients is described in Table 138. LDV/SOF is anticipated to have a small positive negative impact in England and Wales for patients with GT1 and GT4 (cost saving). Key drivers for this negative budget impact are:

- The high proportion of patients eligible for an 8 week course of LDV/SOF (79% of GT1 TN NC patients corresponding to 46.4% of the total GT1 and GT4 populations); which contributes towards a mean LDV/SOF price of £34,001 across the GT1 and GT4 populations.
- High proportion of displaced SOF+PEG-IFN2a+RBV regimen which costs £37,072.
- Displaced SMV+SOF regimen which costs £57,381.
- Different ‘net total budget impact’ over time due to anticipated variations in market share described in Table 135.

Table 138: Budget impact for GT1 and GT4

	Year 1	Year 2	Year 3	Year 4	Year 5
Medicine acquisition cost per patient per annum	£34,001	£34,001	£34,001	£34,001	£34,001
Displaced medicines cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net additional medicines savings/costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated in each year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NET TOTAL BUDGET IMPACT	**-£114,839**	**-£143,549**	**-£129,194**	**-£86,130**	**-£43,065**

GT3

The net total budget impact for GT3 patients in Years 1 to 5 is described in Table 139. LDV/SOF+RBV is anticipated to have a positive budget impact in England and Wales for patients with GT3. Key drivers for this budget impact are:

- High proportion of patients expected to receive LDV/SOF+RBV who would have not been treated (72.3% of the GT3 population) which for the purposes of this budget impact is assumed to have no cost.
- Proportion of displaced PEG-IFN2a+RBV (7.0% of the entire GT3 population) which has a low cost (£3,907).
- Different 'net total budget impact' over time due to anticipated variations in market share described in Table 135.

Table 139: Budget impact for GT3

	Year 1	Year 2	Year 3	Year 4	Year 5
Medicine acquisition cost per patient per annum	£59,133	£59,133	£59,133	£59,133	£59,133
Displaced medicines cost per patient per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net additional medicines savings/costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated in each year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NET TOTAL BUDGET IMPACT	**£11,280,182**	**£22,560,363**	**£16,920,272**	**£11,280,182**	**£5,640,091**

8.8 ***Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?***

The short time horizon of the budget impact model fails to capture savings caused by avoiding more severe health states that take a longer time to occur, such as decompensated cirrhosis, HCC and liver transplants. The long term outcomes could also mean an eradication to HCV-induced hepatocellular carcinoma and HCV-related liver transplant, since both of these events stem from cirrhotic patients which have to date proven to be a very difficult to treat population.

We have also not included any of the costs associated with adverse events, monitoring and costs of managing patients on waiting lists.

In addition, the higher SVR rates induce to some extent a long-term public health benefit by preventing onwards transmission in higher risk population and therefore reduce future HCV prevalence. However, this benefit is not possible to capture in a budget impact model.

References

(1) Gilead Sciences Ltd. Sovaldi (sofosbuvir) summary of product characteristics. 2014.
Ref Type: Online Source

(2) Janssen-Cilag Ltd. Olysio, summary of product characteristics. https://www.medicines.org.uk/emc/medicine/28888/SPC/OLYSIO+150mg+hard+capsules/ . 2014.
Ref Type: Online Source

(3) EASL Recomendations on Treatment of Hepatitis C. April 2014. http://www easl eu/_newsroom/latest-news/easl-recommendations-on-treatment-of-hepatitis-c-2014 2014

(4) Miller MH, Agarwal K, Austin A, Brown A, Barclay ST, Dundas P, et al. Review article: 2014 UK consensus guidelines - hepatitis C management and direct-acting anti-viral therapy. Aliment Pharmacol Ther 2014 Jun;39(12):1363-75.

(5) EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. J Hepatol 2014 Feb;60(2):392-420.

(6) Roche Products Limited. Pegasys (Peginterferon alfa-2a) summary of product characteristics. 2013.
Ref Type: Online Source

(7) Merck Sharp & Dohme Ltd. ViraferonPeg (peginterferon alfa-2b) summary of product characteristics. 2013.
Ref Type: Online Source

(8) Roche Products Limited. Copegus (Ribavirin) summary of product characteristics. 2014.
Ref Type: Generic

(9) Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. Health Technol Assess 2007 Mar;11(11):1-205, iii.

(10) Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. Health Technol Assess 2011 Apr;15(17):i-210.

(11) National Institute for Health and Care Excellence. Hepatitis C (chronic) - sofosbuvir [ID654] Hepatitis C (chronic) - sofosbuvir: consultation document. http://www.nice.org.uk/guidance/gid-tag445/resources/hepatitis-c-chronic-sofosbuvir-consultation-document. http://www.nice.org.uk/guidance/gid-tag445/resources/hepatitis-c-chronic-sofosbuvir-consultation-document . 15-8-2014.
Ref Type: Online Source

(12) Janssen-Cilag Ltd. Incivo (telaprevir) summary of product characteristics. 2013.
Ref Type: Online Source

(13) Merck Sharp and Dohme Ltd. Victrelis (boceprevir) summary of product characteristics. 2013.
Ref Type: Online Source

(14) Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci 2006;3(2):47-52.

(15) Lee MH, Yang HI, Lu SN, Jen CL, You SL, Wang LY, et al. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. J Infect Dis 2012 Aug 15;206(4):469-77.

(16) Himoto T, Masaki T. Extrahepatic manifestations and autoantibodies in patients with hepatitis C virus infection. Clin Dev Immunol 2012;2012:871401.

(17) Zaltron S, Spinetti A, Biasi L, Baiguera C, Castelli F. Chronic HCV infection: epidemiological and clinical relevance. BMC Infect Dis 2012;12 Suppl 2:S2.

(18) Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. Hepatology 1998 Jan;27(1):209-12.

(19) Miller ER, McNally S, Wallace J, Schlichthorst M. The ongoing impacts of hepatitis c--a systematic narrative review of the literature. BMC Public Health 2012;12:672.

(20) Zacks S, Beavers K, Theodore D, Dougherty K, Batey B, Shumaker J, et al. Social stigmatization and hepatitis C virus infection. J Clin Gastroenterol 2006 Mar;40(3):220-4.

(21) Public Health England. Hepatitis C in the UK. 2014 report 2014.

(22) Probst A, Dang T, Bochud M, Egger M, Negro F, Bochud PY. Role of hepatitis C virus genotype 3 in liver fibrosis progression--a systematic review and meta-analysis. J Viral Hepat 2011 Nov;18(11):745-59.

(23) Harris RJ, Thomas B, Griffiths J, Costella A, Chapman R, Ramsay M, et al. Increased uptake and new therapies are needed to avert rising hepatitis C-related end stage liver disease in England: Modelling the predicted impact of treatment under different scenarios. J Hepatol 2014 Sep;61(3):530-7.

(24) Scottish Intercollegiate Guidelines Network (SIGN). Management of hepatitis C. SIGN publication no.133.Available at: http://www.sign.ac.uk . 2013.
Ref Type: Online Source

(25) Cardoso AC, Moucari R, Figueiredo-Mendes C, Ripault MP, Giuily N, Castelnau C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol 2010 May;52(5):652-7.

(26) van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. The number needed to treat to prevent mortality and cirrhosis-related complications among patients with cirrhosis and HCV genotype 1 infection. J Viral Hepat 2014 Aug;21(8):568-77.

(27) Ng V, Saab S. Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C. Clin Gastroenterol Hepatol 2011 Nov;9(11):923-30.

(28) van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012 Dec 26;308(24):2584-93.

(29) Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med 2013 Mar 5;158(5 Pt 1):329-37.

(30) Manos MM, Darbinian J, Rubin J, Ray GT, Shvachko V, Denis B, et al. The effect of hepatitis C treatment response on medical costs: a longitudinal analysis in an integrated care setting. J Manag Care Pharm 2013 Jul;19(6):438-47.

(31) Hepatitis C genotypes reported to the sentinel surveillance of blood-borne virus testing: A commissioned surveillance report. Authors: Public Health England. Report commissioned by Gilead. 2014.

(32) Neal KR, Ramsay S, Thomson BJ, Irving WL. Excess mortality rates in a cohort of patients infected with the hepatitis C virus: a prospective study. Gut 2007 Aug;56(8):1098-104.

(33) British Society for Gastroenterology. Chronic management: Management of patients with chronic liver disease. 2014.
Ref Type: Generic

(34) National Institute for Health and Care Excellence. Hepatitis C (chronic) - sofosbuvir [ID654] Hepatitis C (chronic) - sofosbuvir: consultation document. http://www.nice.org.uk/guidance/gid-tag445/resources/hepatitis-c-chronic-sofosbuvir-consultation-document. http://www.nice.org.uk/guidance/gid-tag445/resources/hepatitis-c-chronic-sofosbuvir-consultation-document . 15-8-2014.
Ref Type: Online Source

(35) National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance TA 253. Boceprevir for the treatment of genotype 1 chronic hepatitis C. Clinical Drug Investigation . 2012. 18-6-2012.
Ref Type: Online Source

(36) National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance TA252 - Telaprevir for the treatment of genotype 1 chronic hepatitis C. April. 2012.
Ref Type: Online Source

(37) National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance TA 200. Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. September. 2010.
Ref Type: Online Source

(38) National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance TA106. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. August. 2006.
Ref Type: Online Source

(39) National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance TA75. Interferon alpha (pegylated and non-peglyated) and ribavirn for the treatment of chronic hepatitis C. January. 2004.
Ref Type: Online Source

(40) NICE Public Health Guidance No PH43. Hepatitis B and C: ways to promote and offer testing to people at risk of infection. Marcg. 2013.
Ref Type: Online Source

(41) Interim Clinical Commissioning Policy Statement: Sofosbuvir + Daclatasvir/Ledipasvir +/- Ribivirin for defined patients with Hepatitis C April 2014 Reference: NHS ENGLAND A02/PS/b. 1-4-2014.
Ref Type: Online Source

(42) Shah N, Pierce T, Kowdley KV. Review of direct-acting antiviral agents for the treatment of chronic hepatitis C. Expert Opin Investig Drugs 2013 Sep;22(9):1107-21.

(43) Falck-Ytter Y, Kale H, Mullen KD, Sarbah SA, Sorescu L, McCullough AJ. Surprisingly small effect of antiviral treatment in patients with hepatitis C. Ann Intern Med 2002 Feb 19;136(4):288-92.

(44) National Institute for Health and Care Excellence. Hepatitis C (chronic) - sofosbuvir [ID654] Hepatitis C (chronic) - sofosbuvir: consultation document. http://www nice org uk/guidance/gid-tag445/resources/hepatitis-c-chronic-sofosbuvir-consultation-document 2014 August 15

(45) Wyles DL. Beyond telaprevir and boceprevir: resistance and new agents for hepatitis C virus infection. Top Antivir Med 2012 Oct;20(4):139-45.

(46) Kiser JJ, Burton JR, Anderson PL, Everson GT. Review and management of drug interactions with boceprevir and telaprevir. Hepatology 2012 May;55(5):1620-8.

(47) North CS, Hong BA, Adewuyi SA, Pollio DE, Jain MK, Devereaux R, et al. Hepatitis C treatment and SVR: the gap between clinical trials and real-world treatment aspirations. Gen Hosp Psychiatry 2013 Mar;35(2):122-8.

(48) Kanda T, Nakamoto S, Wu S, Yokosuka O. New treatments for genotype 1 chronic hepatitis C - focus on simeprevir. Ther Clin Risk Manag 2014;10:387-94.

(49) Takehara T. Simeprevir for the treatment of chronic hepatitis C genotype 1 infection. Expert Rev Anti Infect Ther 2014 Aug;12(8):909-17.

(50) Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011 Mar 31;364(13):1207-17.

(51) Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011 Jun 23;364(25):2417-28.

(52) Reddy KR, Zeuzem S, Zoulim F, Weiland O, Horban A, Stanciu C, et al. A Phase III randomised, double-blind study to evaluate the efficacy, safety and tolerability of simeprevir vs telaprevir in combination with pegylated interferon and ribavirin in chronic hepatitis C virus genotype 1 treatment-experienced patients: the ATTAIN study (Conference reports for NATAP). Presented at APASL 2014, March 12-15, Brisbane, Australia 2014 Mar 24.

(53) UK Collaborative HIV Cohort (UK CHIC). Data on file SOF1405 2014.

(54) Kennedy I. Appraising the value of innovation and other benefits. A short study for NICE. 2009.
Ref Type: Generic

(55) Department of Health. NHS Outcomes Framework 2014 to 2015. https://www gov uk/government/publications/nhs-outcomes-framework-2014-to-2015 2013

(56) Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg DJ, et al. Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. Hepatology 2012 Jan;55(1):49-57.

(57) Martin NK, Vickerman P, Hickman M. Mathematical modelling of hepatitis C treatment for injecting drug users. J Theor Biol 2011 Apr 7;274(1):58-66.

(58) Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. J Hepatol 2011 Jun;54(6):1137-44.

(59) Wyles DL, Rodriguez-Torres M, Lawitz E, Shiffman ML, Pol S, Herring RW, et al. All-oral combination of ledipasvir, vedroprevir, tegobuvir, and ribavirin in treatment-naive patients with genotype 1 HCV infection. Hepatology 2014;60(1):56-64.

(60) Thompson A, Shiffman M, Pianko S, Kanwar B, McHutchison J, Muir AJ, et al. Ledipasvir + GS-9451 + peginterferon and ribavrin (PR) for six or 12 weeks achieves a high SVR12 in treatment naive genotype 1 IL28B CC patients. Journal of Gastroenterology and Hepatology Conference: Australian Gastroenterology Week 2013;#20131007 Conference End(var.pagings):20131009.

(61) Thompson A, Han S, Shiffman ML, Rossaro L, Ghalib R, Beavers K, et al. GS-5885 + GS-9451 + peginterferon and ribavirin (PR) for six or twelve weeks achieves high SVR12 rates in treatment-naive genotype 1 IL28B CC patients. Journal of Hepatology Conference: 2013;48th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress, Amsterdam, Netherlands(var.pagings):Conference.

(62) Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014 May 15;370(20):1889-98.

(63) Gilead Sciences Inc. Interim clinical study report: GS-US-337-0102 (ION-1): A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination ± Ribavirin for 12 and 24 Weeks in Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection. Data on file 2014 Jan 8.

(64) Gilead Sciences Inc. Final clinical study report: GS-US-337-0102 (ION-1): A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination +/- Ribavirin for 12 and 24 Weeks in Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection. Data on file 2014 Jul 28.

(65) Jacobson IM, Marcellin P, Mangia A, Kwo PY, Foster G, Buti M, et al. All oral fixed-dose combination sofosbuvir/ledipasvir with or without ribavirin for 12 or 24 weeks in treatment-naive genotype 1 HCV-infected patients: The phase 3 ION-1 study. Gastroenterology Conference: Digestive Disease Week 2014;Chicago, IL United States(var.pagings):Conference-903.

(66) Mangia A, Marcellin P, Kwo P, Foster GR, Buti M, Brau N, et al. All oral fixed-dose combination sofosbuvir/ledipasvir with or without ribavirin for 12 or 24 weeks in treatment-naive genotype 1 HCV-infected patients: The phase 3 ION-1 study. Journal of Hepatology Conference: 2014;49th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress14 London United Kingdom(var.pagings):Conference-S524.

(67) Younossi Z. Ledipasvir (LDV) and sofosbuvir (SOF) combination improves patient-reported outcomes (PRO) during treatment of chronic hepatitis C (CH-C) patients: Results from the ION-1 clinical trial. Journal of Hepatology Conference: 49th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress 2014 2014.

(68) Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014 May 15;370(20):1879-88.

(69) Gilead Sciences Ltd. Final synoptic clinical study report: GS-US-337-0108 (ION-3): A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination +/- Ribavirin for 8 Weeks and Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection. Data on file 2014 Jun 9.

(70) Gilead Sciences Inc. Interim clinical study report: GS-US-337-0108 (ION-3): A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination +/- Ribavirin for 8 Weeks and Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Treatment-Naive Subjects with Chronic Genotype 1 HCV Infection. Data on file 2014 Jan 17.

(71) Kowdley KV. Sofosbuvir/ledipasvir with and without ribavirin for 8 weeks compared to sofosbuvir/ledipasvir for 12 weeks in treatment-naïve non-cirrhotic genotype-1 HCV-infected patients: The Phase 3 ION-3 study. Journal of Hepatology Conference: 49th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress 2014 2014.

(72) Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014 Apr 17;370(16):1483-93.

(73) Gilead Sciences Ltd. Final synoptic clinical study report: GS-US-337-0109 (ION-2): A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination +/- Ribavirin for 12 and 24 Weeks in Treatment-Experienced Subjects with Chronic Genotype 1 HCV Infection. Data on file 2014 Jun 9.

(74) Gilead Sciences Inc. Interim clinical study report: GS-US-337-0109 (ION-2): A Phase 3, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5885 Fixed-Dose Combination +/- Ribavirin for 12 and 24 Weeks in Treatment-Experienced Subjects with Chronic Genotype 1 HCV Infection. Data on file 2014 Jan 9.

(75) Afdhal N. All oral fixed-dose combination sofosbuvir/ledipasvir with or without ribavirin for 12 or 24 weeks in treatment-experienced genotype 1 HCV-infected patients: The Phase 3 ION-2 study. Journal of Hepatology Conference: 49th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress 2014 2014.

(76) Gane EJ, Hyland RH, An D, Pang PS, Symonds WT, McHutchinson JG, et al. Ledipasvir/Sofosbuvir Fixed-Dose Combination Is Safe and Effective in Difficult-to-Treat Populations Including GT 3 Patients, Decompensated GT 1 Patients, and GT 1 Patients With Prior Sofosbuvir Experience. Presented at The Liver Meeting 2014, London, UK 2014.

(77) Gilead Sciences Inc. Interim synoptic clinical study report: GS-US-337-0122 (ELECTRON 2): A Phase 2, Multicenter, Open-Label Study to Assess the Efficacy and Safety of Sofosbuvir Containing Regimens for the Treatment of Chronic HCV Infection. Data on file 2014 Jan 6.

(78) Gane EJ, Iacono P, An D, Svarovskaia E, Pang PS, Symonds WT, et al. High Efficacy of LDV/SOF Regimens for 12 Weeks for Patients with HCV Genotype 3 or 6 Infection. Abstract LB-11 To be presented at AASLD 2014, November 7-11, Boston, MA, USA 2014 Oct.

(79) Gane E, Hyland RH, Pang P, Symonds WT, McHutchison JG, Stedman CA. Sofosbuvir/ledipasvir fixed dose combination is safe and effective in hcv infected populations including decompensated patients and patients with prior sofosbuvir treatment experience. Gastroenterology Conference: Digestive Disease Week 2014;Chicago, IL United States(var.pagings):Conference-S905.

(80) National Institute of Allergy and Infectious Diseases. Clinical study protocol: 13-I-0159. An Open Label Trial to Assess Safety, Tolerability, and Efficacy of the Fixed Dose Combination of GS-5885 and GS-7977 in HCV Genotype 1 Subjects Coinfected with HIV. Data on file 2014.

(81) Osinusi A, Townsend K, Kohli A, Nelson A, Seamon C, Meissner E, et al. A Pilot Study to Evaluate the Safety and Efficacy of Ledipasvir/Sofosbuvir in HCV Genotype 1 Subjects Coinfected with HIV Infection. Manuscript submitted 2014.

(82) Gilead Sciences Inc. Clinical study protocol: A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant. Data on file 2013 Jun 14.

(83) Reddy RK, Everson GT, Flamm SL, Denning JM, Arterburn S, Brandt-Sarif T, et al. Ledipasvir/Sofosbuvir with Ribavirin for the Treatment of HCV in Patients with Post Transplant Recurrence: Preliminary Results of a Prospective, Multicenter Study. Abstract 8 To be presented at AASLD 2014, November 7-11, Boston, MA, USA 2014 Oct.

(84) Flamm SL, Everson GT, Charlton M, Denning JM, Arterburn S, Brandt-Sarif T, et al. Ledipasvir/Sofosbuvir with Ribavirin for the Treatment of HCV in Patients with Decompensated Cirrhosis: Preliminary Results of a Prospective, Multicenter Study. Abstract 239 To be presented at AASLD 2014, November 7-11, Boston, MA, USA 2014 Oct.

(85) Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Subramanian GM, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. Gastroenterology 2014 Mar;146(3):736-43.

(86) Stedman CA, Hyland RH, Ding X, Pang PS, Symonds WT, McHutchinson JG, et al. Once Daily Sofosbuvir/Ledipasvir Fixed-Dose Combination With Ribavirin in Patients With Inherited Bleeding Disorders and HCV Infection. Poster 734 Presented at teh Asian Pacific Association for the Study of the Liver (APASL), March 12-15, 2014, Brisbane, Australia 2014.

(87) Gilead Sciences Inc. Final synoptic clinical study report: P7977-0523 (ELECTRON): A Multi-center, Open-Labeled Exploratory Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Oral Administration of PSI-7977 400 mg and Ribavirin for 12 Weeks With and Without Pegylated Interferon in Treatment-Naive Patients with Chronic HCV Infection Genotype 2 or Genotype 3. Data on file 2014 Mar 11.

(88) Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia ES, Pang PS, et al. Once daily sofosbuvir/ledipasvir fixed dose combination with or without ribavirin: The electron trial. Hepatology Conference: 2013;64th Annual Meeting of the American Association for the Study of Liver Diseases(var.pagings).

(89) Gane EJ, Hyland RH, Ding X, An D, Svarovskaia ES, Pang PS, et al. Once daily sofosbuvir/ledipasvir fixed dose combination with or without RBV: The electron trials. Hepatology International Conference: 2014;23rd Conference of the Asian Pacific Association for the Study of the Liver, APASL14 Brisbane, QLD Australia(var.pagings):Conference.

(90) Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet 2014 Feb 8;383(9916):515-23.

(91) Lawitz E, Poordad F, Hyland RH, Ding X, Mo H, Pang PS, et al. Once daily sofosbuvir/ledipasvir fixed dose combination with or without ribavirin resulted in 97% sustained virologic response in patients with HCV genotype 1, including patients with cirrhosis: The Lonestar trial. Hepatology International Conference: 2014;23rd Conference of the Asian Pacific Association for the Study of the Liver, APASL14 Brisbane, QLD Australia(var.pagings):Conference.

(92) Lawitz E, Poordad F, Membreno FE, Hyland RH, Ding X, Hebner C, et al. Once daily sofosbuvir/ledipasvir fixed dose combination with or without ribavirin resulted in >95% sustained virlogical response in patients with HCV genotype 1, including patients with cirrhosis: the LONESTAR trial. Oral presentation at AASLD, Washington DC 2013.

(93) Bourliere M, Bronowicki J, de Ledinghen, Hézode C, Zoulim F, Mathurin P, et al. Ledipasvir/Sofosbuvir Fixed Dose Combination is Safe and Efficacious in Cirrhotic Patients Who Have Previously Failed Protease-Inhibitor Based Triple Therapy. Abstract LB-6 To be presented at AASLD 2014, November 7-11, Boston, MA, USA 2014 Oct.

(94) Kohli A, Sims Z, Marti M, Nelson A, Osinusi A, Bon D, et al. Combination Oral, Hepatitis C Antiviral Therapy for 6 or 12 weeks: Results of the SYNERGY Trial. Poster presented at CROI 2014, March 3-6, Boston, MA, USA 2014.

(95) Kapoor R, Kohli A, Sidharthan S, Sims Z, Petersen T, Osinusi A, et al. All Oral Treatment for Genotype 4 Chronic Hepatitis C Infection with Sofosbuvir and Ledipasvir: Interim Results from the NIAID SYNERGY Trial. Abstract 240 To be presented at AASLD 2014, November 7-11, Boston, MA, USA 2014.

(96) Kohli A, Sims Z, Marti M, Osinusi A, Bon D, Hermann E, et al. Combination Oral, Ribavirin Free, Antiviral Therapy to Optimize Treatment Outcomes for Hepatitis C Treatment Naïve Patients: Interim Results from the NIAID SYNERGY Trial. Poster presented at AASLD 2013 2013.

(97) Osinusi A, Marti M, Townsend K, Nelson A, Kohli A, Silk R, et al. Retreatment of relapsers to Sofosbuvir/ribavirin with Sofosbuvir/ledipasvir: Complete and rapid virologic suppression by Week 4. Journal of Hepatology Conference: 49th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress 2014 2014.

(98) Gilead Sciences I. Clinical Study Protocol. GS-US-337-0122. A Phase 2, Multicenter, Open-Label Study to Assess the Efficacy and Safety of Sofosbuvir Containing Regimens for the Treatment of Chronic HCV Infection. Data on file 2014 May 15.

(99) Gilead Sciences Ltd. Harvoni (ledipasvir/sofosbuvir). Summary of product characteristics. 2014. Ref Type: Online Source

(100) Gilead Sciences. Ledipasvir/Sofosbuvir Fixed-dose Combination Safety Update. NDA 205834. Data on file 2014 Apr 30.

(101) Osinusi A, Marti M, Kohli A, Meissner E, Townsend K, Nelson A, et al. Sofosbuvir/Ledipasvir In Retreatment Of HCV Genotype-1 Patients Who Previously Failed Sofosbuvir/Ribavirin Therapy. Oral presentation 011 Presented at EASL 2014 2014.

(102) Osinusi A, Meissner EG, Lee YJ, Bon D, Heytens L, Nelson A, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA 2013 Aug 28;310(8):804-11.

(103) Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013 May 16;368(20):1878-87.

(104) Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet 2014 Aug 2;384(9941):403-13.

(105) Manns M, Marcellin P, Poordad F, de Araujo ES, Buti M, Horsmans Y, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2014 Aug 2;384(9941):414-26.

(106) Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet 2014 Jul 26.

(107) Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011 Jun 23;364(25):2405-16.

(108) Poordad F, Lawitz E, Reddy KR, Afdhal NH, Hezode C, Zeuzem S, et al. Effects of ribavirin dose reduction vs erythropoietin for boceprevir-related anemia in patients with chronic hepatitis C virus genotype 1 infection--a randomized trial. Gastroenterology 2013 Nov;145(5):1035-44.

(109) McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009;361(6):580-93.

(110) Forns X, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. Gastroenterology 2014 Jun;146(7):1669-79.

(111) Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med 2013 Jan 3;368(1):34-44.

(112) Lawitz E, Lalezari JP, Hassanein T, Kowdley KV, Poordad FF, Sheikh AM, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. Lancet Infect Dis 2013 May;13(5):401-8.

(113) Gilead Sciences Inc. Final clinical study report: P7977-0422 (PROTON). A Multi-center, Placebo-Controlled, Dose Ranging Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics following Oral Administration of PSI-7977 in Combination with Pegylated Interferon and Ribavirin in Treatment-Naive Patients with Chronic HCV Infection Genotype 1, and an Open Label Assessment of PSI-7977 in Patients with HCV Genotypes 2 or 3. Data on file 2013.

(114) Lawitz E, Poordad F, Brainard D, et al. Sofosbuvir in Combination With PegIFN and Ribavirin for 12 Weeks Provides High SVR Rates in HCV-Infected Genotype 2 or 3 Treatment- Experienced Patients with and without Compensated Cirrhosis: Results from the LONESTAR-2 Study. Oral presentation at AASLD, Washington DC 2013.

(115) Gilead Sciences Inc. Clinical study protocol: GS-US-334-0151. A Phase 2, Open-Label study of Sofosbuvir in Combination with PEG and Ribavirin for 12 Weeks in Treatment Experienced Subjects with Chronic HCV Infection Genotype 2 or 3. Data on file 2013.

(116) Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and Ribavirin in HCV Genotypes 2 and 3. N Engl J Med 2014 May 4.

(117) Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013 May 16;368(20):1867-77.

(118) Dibonaventura MD, Yuan Y, Lescrauwaet B, L'italien G, Liu GG, Kamae I, et al. Multicountry burden of chronic hepatitis C viral infection among those aware of their diagnosis: a patient survey. PLoS One 2014;9(1):e86070.

(119) EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2011 Aug;55(2):245-64.

(120) Chen J, Florian J, Carter W, Fleischer RD, Hammerstrom TS, Jadhav PR, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology 2013 Jun;144(7):1450-5.

(121) HCV UK Research Database. 2014.
Ref Type: Unpublished Work

(122) McGinnis JJ, Hay JW. The cost-effectiveness of hepatitis C treatments in treatment naive genotype 1 patients. Value in Health Conference: ISPOR 2014 May 31;#20140604(var.pagings):Conference-A275.

(123) Coffin PO, Scott JD, Golden MR, Sullivan SD. Cost-effectiveness and population outcomes of general population screening for hepatitis C. Clin Infect Dis 2012 May;54(9):1259-71.

(124) McGarry LJ, Pawar VS, Panchmatia HR, Rubin JL, Davis GL, Younossi ZM, et al. Economic model of a birth cohort screening program for hepatitis C virus. Hepatology 2012 May;55(5):1344-55.

(125) Rein DB, Smith BD, Wittenborn JS, Lesesne SB, Wagner LD, Roblin DW, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. Ann Intern Med 2012 Feb 21;156(4):263-70.

(126) Cicchetti A, Ruggeri DM, Coretti S, Piscaglia A, Ponziani FR, Lanati E, et al. Valutazione economica di un programma di screening anti-HCV in Italia. Pharmacoeconomics-Ital-Res-Articles 2011;13(2):81-99.

(127) Liu S, Schwarzinger M, Carrat F, Goldhaber-Fiebert JD. Cost effectiveness of fibrosis assessment prior to treatment for chronic hepatitis C patients. PLoS One 2011;6(12):e26783.

(128) Liu S, Cipriano L, Holodniy M, Goldhaber-Fiebert J. Cost-effectiveness analysis of risk-factor guided and birth-cohort screening for chronic hepatitis C infection in the United States. PLOS ONE 2013;8(3):e58975.

(129) Patel D, Terrault NA, Yao FY, Bass NM, Ladabaum U. Cost-effectiveness of hepatocellular carcinoma surveillance in patients with hepatitis C virus-related cirrhosis. Clin Gastroenterol Hepatol 2005 Jan;3(1):75-84.

(130) Deuffic-Burban S, Schwarzinger M, Obach D, Mallet V, Pol S, Pageaux GP, et al. Should we await IFN-free regimens to treat HCV genotype 1 treatment-naive patients? A cost-effectiveness analysis (ANRS 95141). Journal of Hepatology 2014;61(1):7-14.

(131) Younossi ZM, Singer ME, Mir HM, Henry L, Hunt S. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. Journal of Hepatology 2014;60(3):530-7.

(132) Deuffic-Burban S, Schwarzinger M, Obach D, Mallet V, Pol S, Pageaux GP, et al. Should we await interferon-free regimens to treat HCV genotype 1 treatment-naive patients? a cost-effectiveness analysis (ANRS 12188). Journal of Hepatology Conference: 2014;49th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress14 London United Kingdom(var.pagings):Conference.

(133) Lee A, Granados D, Hulbert E, McGarry L, Fleischmann J. Cost-effectiveness of hepatitisc virus (HCV) treatment with telaprevir/pegylated interferon alpha/ribavirin triple therapy versus waiting for new regimens in France. Value in Health Conference: ISPOR 2013 Nov 2;16th Annual European Congress Dublin Ireland. Conference Start(var.pagings):131102.

(134) Saab S, Hunt DR, Stone MA, McClune A, Tong MJ. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: a decision analysis model. Liver Transpl 2010 Jun;16(6):748-59.

(135) Gerkens S, Nechelput M, Annemans L, Peraux B, Mouchart M, Beguin C, et al. A health economic model to assess the cost-effectiveness of PEG IFN alpha-2a and ribavirin in patients with mild chronic hepatitis C. J Viral Hepat 2007;14(8):523-36.

(136) Gerkens S, Nechelput M, Annemans L, Peraux B, Beguin C, Horsmans Y. A health economic model to assess the cost-effectiveness of pegylated interferon alpha-2a and ribavirin in patients with moderate chronic hepatitis C and persistently normal alanine aminotransferase levels. Acta Gastro-Enterologica Belgica 2007;70(2):April/June.

(137) Cure S, Bianic F, Cawston H, Dartois L, Zhang H. Impact of Sustained Virological Response After Antiviral Treatment in Chronic Hepatitis C Patients on Life Expectancy and Quality-adjusted Life-years. 2010.

(138) Obach D, Deuffic-Burban S, Esmat G, Anwar WA, Dewedar S, Canva V, et al. Effectiveness and cost-effectiveness of immediate versus delayed treatment of hepatitis C virus-infected patients in a country with limited resources: The case of Egypt. Clinical Infectious Diseases 2014;58(8):1064-71.

(139) Miners AH, Martin NK, Ghosh A, Hickman M, Vickerman P. Assessing the cost-effectiveness of finding cases of hepatitis C infection in UK migrant populations and the value of further research. Journal of Viral Hepatitis 2014 Sep;21(9):616-23.

(140) De Compadri P., Koleva D, Mangia A, Motterlini N, Garattini L. Cost minimisation analysis of 12 or 24 weeks of peginterferon alfa-2b + ribavirin for hepatitis C virus. Journal of Medical Economics 2008;11(1):2008.

(141) Gellad ZF, Reed SD, Muir A, McHutchinson JG, Sievert W, Sharara AI. Truncated therapy based on rapid virologic response is a cost effective treatment paradigm for chronic hepatitis C. 2011 Jul 5; *Chicago, IL United States* 2011.

(142) Garcia-Retortillo M, Cirera I, Dolors Gimenez M, Marquez C, Canete N, Carrion JA, et al. Cost-Effectiveness Analysis Of A Multidisciplinary Support Program In Hepatitis C Treatment.: WILEY-BLACKWELL COMMERCE PLACE, 350 MAIN ST, MALDEN 02148, MA USA; 2011 p. 800A-1A.

(143) Younossi Z, Singer M, Mir H. Interferon-based and interferon-free regimens for patients with chronic hepatitis c, genotype 1: Potential cost-effectiveness of biopsy-guided treatment versus treat all strategies. Gastroenterology Conference : Digestive Disease Week 2013;#2013 Orlando, FL United States:S988.

(144) Gellad ZF, Naggie S, Reed SD, Clark PJ, Thompson AJ, Schulman KA. The cost-effectiveness of a telaprevir-inclusive regimen as initial therapy for genotype 1 hepatitis C infection in individuals with the CC IL-28B polymorphism. *San Francisco, CA United States* 2011 p. 417A-8A.

(145) McEwan P, Kim R, Yuan Y. Assessing the cost utility of response-guided therapy in patients with chronic hepatitis C genotype 1 in the UK using the MONARCH model. Appl Health Econ Health Policy 2013;11(1):53-63.

(146) Papatheodoridis G, Arzoumanidou D. Cost-effectiveness analysis of different protease inhibitors-based strategies in the treatment of naive patients with genotype 1 chronic hepatitis C (G1-CHC). Hepatology Conference : 2012;63rd Annual Meeting of the American Association for the Study of Liver Diseases:1014A.

(147) Hartwell D, Jones J, Baxter L, Shepherd J. Shortened peginterferon and ribavirin treatment for chronic hepatitis C. Int J Technol Assess Health Care 2012;28(4):398-406.

(148) Deuffic-Burban S, Schwarzinger M, Mallet V, Pol S, Pageaux G, Canva-Delcambre V, et al. Immediate or delayed treatment initiation with 'previr' containing regimens in HCV-infected naive genotype 1 (G1) patients without severe fibrosis? a cost-effectiveness analysis (ANRS No12188). Journal of Hepatology Conference : 2013;48th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress13 Amsterdam Netherlands:S331.

(149) Petta S, Cabibbo G, Enea M, Macaluso FS, Plaia A, Bruno R, et al. Cost-effectiveness of sofosbuvir-based triple therapy for untreated patients with genotype 1 chronic hepatitis C. Hepatology 2014;59(5):1692-705.

(150) Cortesi PA, Ciaccio A, Rota M, De S, Okolicsanyi S, Vinci M, et al. Management of chronic hepatitis C (CHC) genotype 1 treatment-naive patients in an era of rising opportunities and costs: A cost-effectiveness analysis. Digestive and Liver Disease Conference: 2014;47th Annual Meeting of the Italian Association for the Study of the Liver, A.I.S.F.14 Rome Italy(var.pagings):Conference.

(151) Linas BP, Barter DM, Leff JA, DiLorenzo M, Schackman BR, Horsburgh CR, et al. The cost-effectiveness of improved hepatitis C virus therapies in HIV/hepatitis C virus coinfected patients. AIDS 2014;28(3):365-76.

(152) Fairley K, Bock J, Smith R, Maeng D, Pitcavage J, Inverso N, et al. Cost-effectiveness of IL-28 genotype-guided protease inhibitor therapy in Hepatitis C-infected patients. American Journal of Gastroenterology Conference: 2013 Oct 11;78th Annual Scientific Meeting of the American College of Gastroenterology San Diego, CA United States. Conference Start(var.pagings):131011.

(153) Camma C, Petta S, Enea M, Bruno R, Bronte F, Capursi V, et al. Cost-effectiveness of boceprevir or telaprevir for untreated patients with genotype 1 chronic hepatitis C. Hepatology 2012;56(3):850-60.

(154) Townsend R, McEwan P, Kim R, Yuan Y. Structural frameworks and key model parameters in cost-effectiveness analyses for current and future treatments of chronic hepatitis C. Value Health 2011 Dec;14(8):1068-77.

(155) McEwan P, Yuan Y, Townsend R, Kim RW. The impact of age dependent utility on the cost effectiveness of pegylated interferon and ribavirin versus interferon and ribavirin as therapy for genotype 1 patients with chronic hepatitis C. Value in Health Conference: 15th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2010 Atlanta, GA United States Conference Start: 20100515 Conference End: 20100519 Conference Publication: (va 2010;13(3 SUPPL.#3):May.

(156) Siebert U, Sroczynski G, Aidelsburger P, Rossol S, Wasem J, Manns MP, et al. Clinical effectiveness and cost effectiveness of tailoring chronic hepatitis C treatment with peginterferon alpha-2b plus ribavirin to HCV genotype and early viral response: a decision analysis based on German guidelines. Pharmacoeconomics 2009;27(4):341-54.

(157) Becker B, Chhatwal J, Ferrante S, Elbasha E, Krobot K. Cost-effectiveness of boceprevir-based treatment of chronic genotype 1 hepatitis C virus (HCV) infection from the perspective of the german statutory health insurance (SHI). Value in Health Conference : ISPOR 2012;15th Annual European Congress Berlin Germany:A392.

(158) Elbasha E, Chhatwal J, Ferrante S, El KA, Laires P. Cost-effectiveness analysis of boceprevir for the treatment of chronic hepatitis C virus genotype 1 infection in Portugal. Appl Health Econ Health Policy 2013;11(1):65-78.

(159) Northup PG, Al-Osaimi AM, Caldwell SH, Argo CK. Cost effectiveness of STAT-C agents in treating genotype 1 chronic hepatitis C. Hepatology Conference: 60th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2009 Boston, MA United States Conference Start: 20091030 Conference End: 20091103 Conference Publication: (var pagings)50(pp 671A):2009.

(160) Ramachandran S, Mahabaleshwarkar R, Yang Y. Cost effectiveness analysis of addition of telaprevir or boceprevir to standard therapy versus standard therapy alone for the treatment of previously untreated chronic Hepatitis-C virus genotype 1 infection. Value in Health Conference: 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2012 Washington, DC United States Conference Start: 20120602 Conference End: 20120606 Conference Publication: 2012;15(4):June.

(161) Ferrante SA, Chhatwal J, Elbasha E, Dasbach EJ, El KA, Poordad FF, et al. Cost-effectiveness of boceprevir based regimens in previously untreated adult subjects with chronic hepatitis C genotype 1. Hepatology Conference: 62nd Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2011 San Francisco, CA United States Conference Start: 20111104 Conference End: 20111108 Conference Publication: (var pagings) 2011;54(pp 795A-796A):October.

(162) Mendes D, White K, Cooper K, Bryant J. Boceprevir for the treatment of genotype 1 chronic hepatitis C. Health Technology Assessment 2011.

(163) Nikoglou E, Humphreys S, El KA, Ferrante SA, O'Regan C. The clinical efficacy and cost-effectiveness of boceprevir in combination with pegylated interferon-alfa and ribavirin for the treatment of genotype 1 chronic hepatitis C patients: A within trial analysis from the perspective of the scottish national health service (NHS). Value in Health Conference: ISPOR 14th Annual European Congress Madrid Spain Conference Start: 20111105 Conference End: 20111108 Conference Publication: (var pagings) 2011;14(7):November.

(164) Humphreys S, Elbasha E, Ferrante S, Lion M, O'Regan C. Cost-effectiveness of boceprevir in combination with pegylated interferon alfa and ribavirin for the treatment of genotype 1 chronic hepatitis c: Submission to the national institute for health and clinical excellence (NICE). Value in Health Conference : ISPOR 2012;15th Annual European Congress Berlin Germany:A329.

(165) Mernagh P, Feng J, Del C. Cost-effectiveness of boceprevir therapy in adult patients with chronic hepatitis C (HCV) genotype 1. Value in Health Conference : ISPOR 2013;18th Annual International Meeting New Orleans, LA United States:A94.

(166) Odhiambo R, Chhatwal J, Ferrante S, El K, Elbasha E. Economic evaluation of boceprevir for the treatment of patients with genotype 1 chronic hepatitis C virus infection in hungary. Value in Health Conference : ISPOR 2012;15th Annual European Congress Berlin Germany:A390.

(167) Chan K, Lai M, Groessl E, Hanchate A, Wong J, Clark J, et al. Cost Effectiveness of Direct-Acting Antiviral Therapy for Treatment-Naive Patients With Chronic HCV Genotype 1 Infection in the Veterans Health Administration. Clin Gastroenterol Hepatol 2013;11:1503-10.

(168) de Ledinghen V, Orsini M, Foucher J, Vergniol J, Chermak F, Messaoudi N, et al. Cost-effectiveness of HCV treatment in genotype 1 naive patients in 2012. Journal of Hepatology Conference: 47th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress 2012 Barcelona Spain Conference Start: 20120418 Conference End: 20120422 Conference Publication: (var pagings) 2012;56(pp S384-S385):April.

(169) Jalundhwala YJ, Manzoor BS, Patel H, Cheng WH, Patel P, Touchette DR. Cost-effectiveness of pharmacotherapies for treatment naive hepatitis C genotype 1 patients: A payer's perspective. Value in Health Conference: ISPOR 2014 May 31;#20140604(var.pagings):Conference.

(170) Ivakhnenko O, Omelyanovsky VV, Rebrova O, Khachatryan G. Comparative economic analysis of retreatment strategies for HCV genotype 1 patients in Russia. Value in Health Conference: ISPOR 2013 Nov 2;16th Annual European Congress Dublin Ireland. Conference Start(var.pagings):131102.

(171) Mernagh P, Feng J, Del C. Cost-effectiveness of boceprevir therapy in previously treated adult patients with chronic hepatitis C (HCV) genotype 1. Hepatology International Conference: 2013;23rd Conference of the Asian Pacific Association for the Study of the Liver, APASL13 Singapore Singapore(var.pagings):Conference.

(172) Ferrante S, Elbasha EH, Poynard T, Boyaval G. Boceprevir use in France: A markov model of disease progression and cost-effectiveness for chronic hepatitisc (virus g1). Value in Health Conference: ISPOR 2013 Nov 2;16th Annual European Congress Dublin Ireland. Conference Start(var.pagings):131102.

(173) Ehlers L, Ferrante S, Kristensen MH, Leutscher PDC, Chhatwal J. Cost-effectiveness of boceprevir add-on treatment of hepatitisc virus genotype 1 patients in Denmark. Value in Health Conference: ISPOR 2013 Nov 2;16th Annual European Congress Dublin Ireland. Conference Start(var.pagings):131102.

(174) Athanasakis K, Karampli E, Retsa MP, Theodoropoulou T, Kyriopoulos J. Cost effectiveness analysis of boceprevir (BOC) added to pegifn/ ribavirin (p/r) versus pegifn/ribavirin (current standard of care) for the treatment of patients with genotype 1 chronic hepatitisc in Greece. Value in Health Conference: ISPOR 2013 Nov 2;16th Annual European Congress Dublin Ireland. Conference Start(var.pagings):131102.

(175) Ferrante S, Chhatwal J, Brass C, El KA, Poordad F, Bronowicki J, et al. Boceprevir for previously untreated patients with chronic hepatitis C Genotype 1 infection: a US-based cost-effectiveness modeling study. BMC Infect Dis 2013;13(1):190.

(176) Chhatwal J, Ferrante S, Brass C, El K, Burroughs M, Bacon B, et al. Cost-effectiveness of boceprevir in patients previously treated for chronic hepatitis C genotype 1 infection in the United States. Value in Health 2013;16(6):973-86.

(177) Blazquez-Perez A, San M, Mar J. Cost-Effectiveness Analysis of Triple Therapy with Protease Inhibitors in Treatment-Naive Hepatitis C Patients. Pharmacoeconomics 2013;31(10):919-31.

(178) Fonseca M, Garran V, Araujo G. Cost effectiveness of the combination of boceprevir plus peginterferon alpha and ribavirin versus telaprevir plus peginterferon alfa and ribavirin in the retreatment of patients with chronic hepatitis c virus genotype I infection. Value in Health Conference : ISPOR 2012;15th Annual European Congress Berlin Germany:A329.

(179) Camma C, Petta S, Cabibbo G, Ruggeri M, Enea M, Bruno R, et al. Cost-effectiveness of boceprevir or telaprevir for previously treated patients with genotype 1 chronic hepatitis C. J Hepatol 2013;59(4):658-66.

(180) Cure S, Curtis S, Bianic F, Gavart S, Dearden L, Fleischmann J, et al. The cost-effectiveness of telaprevir (TVR) in combination with pegylated interferon-alfa and ribavirin (PR) for the treatment of genotype 1(G1) chronic Hepatitis C patients. Value in Health Conference : 2012;17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR12 Washington, DC United States:A242.

(181) Jones J, Hartwell D, Baxter L, Harris P. TA252 Hepatitis C (Genotype 1) - Telaprevir: Guidance. NHS; 2011.

(182) Lukac M, Bielik J, Holoman J, Tomek D, Suvadova A, Foltanova T, et al. Cost-utility analysis of telaprevir in combination with peginterferon alpha and ribavirin in previously treated patients with chronic hepatitis c. Value in Health Conference : ISPOR 2012;15th Annual European Congress Berlin Germany:A330.

(183) Stahmeyer J, Schauer S, Wirth D, Fleischmann J, Lee S, Gavart S, et al. Cost-effectiveness of triple therapy with telaprevir for the treatment of treatment-naive genotype 1 chronic hepatitis c patients in germany. Value in Health Conference : ISPOR 2012;15th Annual European Congress Berlin Germany:A396.

(184) Jacobson I, Baldini A, DeMasi R, Gavart S, Luo D, Mrus J, et al. Efficacy, safety and UK cost-effectiveness in treatment-naive patients with F2 fibrosis treated with telaprevir (TVR; T) in combination with peginterferon (P) and ribavirin (R) vs peginterferon and ribavirin alone. American Journal of Gastroenterology Conference : 2012;77th Annual Scientific Meeting of the American College of Gastroenterology Las Vegas, NV United States:S180.

(185) Bock J, Fairley K, Smith R, Maeng D, Pitcavage J, Inverso N, et al. A1-2: Cost-Effectiveness of Interleukin 28B Genotype-Guided Protease Inhibitor Therapy in Treatment-Naive Patients with Hepatitis C Virus Genotype 2 or 3. Clin Med Res 2013;11(3):142.

(186) Brogan AJ, Talbird SE, Thompson JR, Miller JD, Rubin J, Deniz B. Cost-effectiveness of telaprevir combination therapy for chronic hepatitis C. PLoS ONE 2014;9(3).

(187) Cure S, Bianic F, Gavart S, Curtis S, Lee S, Dusheiko G. Cost-effectiveness of telaprevir in combination with pegylated interferon alpha and ribavirin in previously untreated chronic hepatitis C genotype 1 patients. Journal of Medical Economics 2014;17(1):65-76.

(188) Paveliu MS, Comsa R, Mircea R. Cost-utility analysis of telaprevir in combination with peginterferon alpha and ribavirin in previously untreated patients with chronic hepatitis in a romanian setting. Value in Health Conference: ISPOR 2013 Nov 2;16th Annual European Congress Dublin Ireland. Conference Start(var.pagings):131102.

(189) Garcia M, Alcaraz A, Valanzasca P, Garay OU, McMullen M, Rey A, et al. Cost-effectiveness of telaprevir in genotype 1 chronic hepatitis-C virus infection in Venezuela. Value in Health Conference: ISPOR 2013 Sep 12;4th Latin America Conference Buenos Aires Argentina. Conference Start(var.pagings):130912.

(190) Garcia M, Alcaraz A, Valanzasca P, Garay OU, McMullen M, Rey A, et al. Cost-effectiveness of telaprevir in genotype 1 chronic hepa titis C virus (HCV) infection in Colombia. Value in Health Conference: ISPOR 2013 Sep 12;4th Latin America Conference Buenos Aires Argentina. Conference Start(var.pagings):130912.

(191) Garcia M, Alcaraz A, Valanzasca P, Garay U, McMullen M, Rey A, et al. Cost-effectiveness of telaprevir in genotype 1 chronic hepa titis C virus (HCV) infection in Chile. Value in Health Conference: ISPOR 2013 Sep 12;4th Latin America Conference Buenos Aires Argentina. Conference Start(var.pagings):130912-A693.

(192) Buti M, Gros B, Oyaguez I, Andrade RJ, Serra MA, Turnes J, et al. Cost-effectiveness analysis of telaprevir triple therapy for treatment-naive patients with chronic hepatitis C based on the combined efficacy data of the ADVANCE and OPTIMIZE studies. Hepatology Conference: 2013;64th Annual Meeting of the American Association for the Study of Liver Diseases(var.pagings):The.

(193) Morais AD, Pereira ML. Cost-effectiveness of telaprevir plus peginterferon/riba virin (TVR+PR) versus peginterferon/riba virin (PR) in treatment-naive genotype 1 chronic hepatitisc patients with f2 fibrosis in Brazil. Value in Health Conference: ISPOR 2013 Nov 2;16th Annual European Congress Dublin Ireland. Conference Start(var.pagings):131102.

(194) Kaczor MP, Wojcik R, Pawlik D, Skrzekowska-Baran I, Tronczynski K. Cost-effectiveness of telaprevir combinat ion therapy compared to peginterferon with ribav irin alone for naive and treatment experienced patients with genotype 1 chronic hepatitisc in Poland. Value in Health Conference: ISPOR 2013 Nov 2;16th Annual European Congress Dublin Ireland. Conference Start(var.pagings):131102-A360.

(195) Brogan A, Talbird S, Thompson J, Miller J, George S, Hvidsten K. Cost-effectiveness of first-line versus second-line telaprevir combination treatment in the management of chronic hepatitis c virus infection for treatment-naive patients with IL28B genotype CC. Gastroenterology Conference : Digestive Diease Week 2012;#2012 San Diego, CA United States:S173.

(196) Cure S, Bianic F, Gavart S, Curtis S, Lee S, Dusheiko G. Cost-effectiveness of Telaprevir in Combination with Pegylated Interferon Alpha and Ribavirin in Treatment-experienced Chronic Hepatitis C Genotype 1 Patients. J Med Econ 2013;doi.

(197) Said M, Dragosits A, Walter E. Cost-effectiveness-analysis of the combination-therapy telaprevir, peg-ifn+2a and ribavirin in patients with chronic hepatitis-C in austria. Value in Health Conference : ISPOR 2012;15th Annual European Congress Berlin Germany:A392.

(198) Ruggeri M. Using bayesian modelling to estimate the cost effectiveness of telaprevir and boceprevir in Italian naive patients with hepatitis C. Value in Health Conference: ISPOR 2014 May 31;#20140604(var.pagings):Conference.

(199) Hasan SS, Sears DM, Lorden AL. A real world analysis of the cost of current HCV treatment. Gastroenterology Conference: Digestive Disease Week 2014;#2014 Chicago, IL United States(var.pagings):Conference-909.

(200) Ariza JG, Hinojosa R. Economic evaluation of Direct Acting Antiviral (DAA) treatments for hepa titis C virus (HCV) infection in previously treated patients from the peruvian health care system perspective. Value in Health Conference: ISPOR 2013 Sep 12;4th Latin America Conference Buenos Aires Argentina. Conference Start(var.pagings):130912.

(201) Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. Ann Intern Med 2012 Feb 21;156(4):279-90.

(202) Norris S, Campbell S, Radalj L, Elliott L, Dunlop SL. Cost effectiveness of pegylated-interferon alpha 2b + ribarvirin for chronic hepatitis C (CHC) in patients who have previously failed treatmetn with interferon-based therapy in Australia. 2009 p. *(var pagings)*.

(203) Logge C, Vettorazzi E, Fischer L, Nashan B, Sterneck M. Cost-effectiveness analysis of antiviral treatment in liver transplant recipients with HCV infection. Transpl Int 2013;26(5):527-34.

(204) Brady B, Siebert U, Sroczynski G, Murphy G, Husereau D, Sherman M, et al. Pegylated interferon combined with ribavirin for chronic hepatitis C virus infection: an economic evaluation. Report. 2007.

(205) Siebert U, Muhlberger N, Conrads-Francenk A, Sroczynski G, Schwarzer R. Using Iqwig's efficiency frontier approh for the economic evaluation of heaptitis c treatment - a pilot and feasibility study commissioned by IQWIG. Value in Health Conference: ISPOR 12th Annual European Congress Paris France Conference Start: 20091024 Conference End: 20091027 Conference Publication: (var pagings) 2009;12(7):October.

(206) Ventayol-Bosch P, Rubio-Terres C, Garcia-Samaniego J, Planas R, Sola-Lamoglia R, Romero-Gomez M, et al. Cost-effectiveness analysis of treatment of chronic hepatitis c patients with peginterferon alfa-2a or peginterferon alfa-2b both plus ribavirin in Spain. Value in Health Conference: ISPOR 13th Annual European Congress Prague Czech Republic Conference Start: 20101106 Conference End: 20101109 Conference Publication: (var pagings) 2010;13(7):November.

(207) Yeh WS, Armstrong EP, Skrepnek GH, Malone DC. Peginterferon alfa-2a versus peginterferon alfa-2b as initial treatment of hepatitis C virus infection: a cost-utility analysis from the perspective of the Veterans Affairs Health Care System. Pharmacotherapy 2007 Jun;27(6):813-24.

(208) Barros FMR, Cheinquer H, Tsuchiya CT, Santos EAV. Cost-effectiveness analysis of treatment with peginterferon-alfa-2a versus peginterferon-alfa-2b for patients with chronic hepatitis C under the public payer perspective in Brazil. Cost Effectiveness and Resource Allocation 2013;11(1).

(209) Turnes J, Romero-Gomez M, Planas R, Sola R, Garcia-Samaniego J, Diago M, et al. Pharmacoeconomic analysis of the treatment of chronic hepatitis C with peginterferon alfa-2a or peginterferon alfa-2b plus ribavirin in Spain. Gastroenterologia y Hepatologia 2013;36(9):555-64.

(210) Ryazhenov VV, Sboyeva SG, Emchenko IV. Pharmac oeconomic analysis of different antiviral therapies in the treatment of Russian patients with chronic hepatitisc. Value in Health Conference: ISPOR 2013 Nov 2;16th Annual European Congress Dublin Ireland. Conference Start(var.pagings):131102.

(211) Grishchenko M, Grieve RD, Sweeting MJ, De AD, Thomson BJ, Ryder SD, et al. Cost-effectiveness of pegylated interferon and ribavirin for patients with chronic hepatitis C treated in routine clinical practice. Int J Technol Assess Health Care 2009 Apr;25(2):171-80.

(212) Hagan LM, Sulkowski MS, Schinazi RF. Cost analysis of sofosbuvir/ribavirin versus sofosbuvir/simeprevir for genotype 1 hepatitis C virus in interferon-ineligible/intolerant individuals. Hepatology 2014;60(1):37-45.

(213) Hagan LM, Yang Z, Ehteshami M, Schinazi RF. All-oral, interferon-free treatment for chronic hepatitis C: Cost-effectiveness analyses. Journal of Viral Hepatitis 2013;#2013(12):Date.

(214) Rein DB, Wittenborn JS, Liffmann DK, Hasche JC, Borton JM, Kramer JR, et al. Projected health and economic impact of hepatitis c on the united states veterans administration health system from 2014 to 2024. Journal of Hepatology Conference: 2014;49th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress14 London United Kingdom(var.pagings):Conference.

(215) Younossi Z, Gordon S, Saab S, Ahmed A, Park H, Sulkowski M. Health and economic outcomes of sofosbuvir therapy as predicted by a markov model in the HCV/HIV co-infected cohort. Value in Health Conference: ISPOR 2014 May 31;#20140604(var.pagings):Conference.

(216) Dusheiko GM, Roberts JA. Treatment of chronic type B and C hepatitis with interferon alfa: an economic appraisal. Hepatology 1995 Dec;22(6):1863-73.

(217) Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. Health Technology Assessment 2007;11(11):1-224.

(218) Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technol Assess 2006 Jul;10(21):1-113, iii.

(219) Grieve R, Roberts J, Wright M, Sweeting M, DeAngelis D, Rosenberg W, et al. Cost effectiveness of interferon alpha or peginterferon alpha with ribavirin for histologically mild chronic hepatitis C. Gut 2006 Sep;55(9):1332-8.

(220) National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. http://www.nice.org.uk/article/PMG9/chapter/Foreword . 2013.
Ref Type: Online Source

(221) National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance TA252 - Telaprevir for the treatment of genotype 1 chronic hepatitis C. April. 2012. 18-6-2012.
Ref Type: Online Source

(222) Southampton Health Technology Assessments Centre. Evidence review Group Report commissioned by the NIHR HTA programme on behalf of NICE: Sofosbuvir for treating chronic hepatitis C. http://www nice org uk/guidance/indevelopment/gid-tag445/documents 2014 April 7

(223) Office for National Statistics. National Life Tables, United Kingdom, 2012-2012. Available at http://www.ons.gov.uk/ons/rel/lifetables/national-life-tables/2010---2012/stb-uk-2010-2012.html (last accessed: August 2014). 2014 Mar 12.

(224) Thomson BJ, Kwong G, Ratib S, Sweeting M, Ryder SD, De AD, et al. Response rates to combination therapy for chronic HCV infection in a clinical setting and derivation of probability tables for individual patient management. J Viral Hepat 2008 Apr;15(4):271-8.

(225) Minola E, Prati D, Suter F, Maggiolo F, Caprioli F, Sonzogni A, et al. Age at infection affects the long-term outcome of transfusion-associated chronic hepatitis C. Blood 2002 Jun 15;99(12):4588-91.

(226) Murakami C, Hino K, Korenaga M, Okazaki M, Okuda M, Nukui K, et al. Factors predicting progression to cirrhosis and hepatocellular carcinoma in patients with transfusion-associated hepatitis C virus infection. J Clin Gastroenterol 1999 Mar;28(2):148-52.

(227) Pinzani M, Romanelli RG, Magli S. Progression of fibrosis in chronic liver diseases: time to tally the score. J Hepatol 2001 May;34(5):764-7.

(228) Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997 Mar 22;349(9055):825-32.

(229) Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c. J Hepatol 2001 May;34(5):730-9.

(230) Pradat P, Voirin N, Tillmann HL, Chevallier M, Trepo C. Progression to cirrhosis in hepatitis C patients: an age-dependent process. Liver Int 2007 Apr;27(3):335-9.

(231) Siebert U, Sroczynski G, Wasem J, Greiner W, Ravens-Sieberer U, Aidelsburger P, et al. Using competence network collaboration and decision-analytic modeling to assess the cost-effectiveness of interferon alpha-2b plus ribavirin as initial treatment of chronic hepatitis C in Germany. Eur J Health Econ 2005 Jun;6(2):112-23.

(232) Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997 Feb;112(2):463-72.

(233) Poordad F, Lawitz E, Reddy KR, Afdhal NH, Hezode C, Zeuzem S, et al. Effects of ribavirin dose reduction vs erythropoietin for boceprevir-related anemia in patients with chronic hepatitis C virus genotype 1 infection--a randomized trial. Gastroenterology 2013 Nov;145(5):1035-44.

(234) Roberts SK, Weltman MD, Crawford DH, McCaughan GW, Sievert W, Cheng WS, et al. Impact of high-dose peginterferon alfa-2A on virological response rates in patients with hepatitis C genotype 1: a randomized controlled trial. Hepatology 2009 Oct;50(4):1045-55.

(235) Mach TH, CieÅ›la A, Warunek W, Janas-Skulina U, Cibor D, Owczarek D, et al. Efficacy of pegylated interferon alfa-2a or alfa-2b in combination with ribavirin in the treatment of chronic hepatitis caused by hepatitis C virus genotype 1b. Pol Arch Med Wewn 2011;121(12):434-9.

(236) Neri S, Bertino G, Petralia A, Giancarlo C, Rizzotto A, Calvagno GS, et al. A multidisciplinary therapeutic approach for reducing the risk of psychiatric side effects in patients with chronic hepatitis C treated with pegylated interferon Î± and ribavirin. J Clin Gastroenterol 2010;44(9):e210-e217.

(237) HCV UK Research Database; http://www.hcvresearchuk.org/. 2014.
Ref Type: Unpublished Work

(238) Janssen pharmaceutical companies of Johnson&Johnson, FDA. FDA Antiviral Drugs Advisory Committee Meeting: Simeprevir (TMC435) Treatment of patients with chronic hepatitis C. 24-10-2013.
Ref Type: Generic

(239) National Institute for Health and Clinical Excellence. Boceprevir for the treatment of genotype 1 chronic hepatitis C - NICE technology appraisal guidance 253. 2012. 18-6-2012.
Ref Type: Online Source

(240) Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011 Mar 31;364(13):1195-206.

(241) Jacobson I, Bartels D, Gritz L, Kieffer T, de Meyer S, Tomaka F, et al. Futility Rules in Telaprevir Combination Treatment. 2012 Apr 18-2012 Apr 22; 2012.

(242) Janssen pharmaceutical companies of Johnson&Johnson. Telaprevir for the treatment of genotype 1 chronic hepatitis C: NICE Single Technology Appraisal (STA). 2011 Oct 21.

(243) Gilead Sciences. VALENCE, INTERIM SYNOPTIC CLINICAL STUDY REPORT, Foster City. 2013 Aug 10.

(244) Kauffman R, Muir A, Nelson D, Andreone P, Everson G, Dusheiko G, et al. Review Activity/Safety: Telaprevir in Combination with Peginterferon Alfa-2a and Ribavirin Increased Sustained Virologic Response in Genotype 1 Chronic HCV. 2011 Dec 4; 2011.

(245) Cacoub P, Bourliere M, Lubbe J, Dupin N, Buggisch P, Dusheiko G, et al. Dermatological side effects of hepatitis C and its treatment: patient management in the era of direct-acting antivirals. J Hepatol 2012 Feb;56(2):455-63.

(246) FDA. Telaprevir 375-mg Film-Coated Tablet for the Treatment of Genotype 1 Chronic Hepatitis C: FDA Advisory Committee Briefing Document. 2011.

(247) Pol S, Sulkowski M, Hassanein T, Gane E, Li N, Mo H, et al. Successful retreatment of HCV genotype-1 infected patients who failed prior therapy with peginterferon + ribavirin plus 1 or 2 other direct-acting antiviral agents with sofosbuvir. 49th annual meeting of the European Association for the Study of the Liver London, UK, April 9-13, 2014 2014.

(248) EMA. Incivo, summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002313/WC500115529.pdf . 2014.
Ref Type: Online Source

(249) Hezode C. Boceprevir and telaprevir for the treatment of chronic hepatitis C: safety management in clinical practice. Liver Int 2012 Feb;32 Suppl 1:32-8.

(250) Gilead Sciences. VALENCE, INTERIM SYNOPTIC CLINICAL STUDY REPORT, Foster City. 2013 Aug 10.

(251) Lawitz E, Mangia A, Wyles D. Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection: Supplementary Appendix. N Engl J Med 2013.

(252) Chen J, Florian J, Carter W, Fleischer RD, Hammerstrom TS, Jadhav PR, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology 2013 Jun;144(7):1450-5.

(253) Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002 May;122(5):1303-13.

(254) Di Bonaventura M, Yuan Y, L'Italien G, Kim WR. The impact of hepatitis C on health-related quality of life, work productivity, and healthcare utilization. *Boston, MA United States* 2010 p. 1244A-5A.

(255) Kallman J, O'Neil MM, Larive B, Boparai N, Calabrese L, Younossi ZM. Fatigue and health-related quality of life (HRQL) in chronic hepatitis C virus infection. Dig Dis Sci 2007 Oct;52(10):2531-9.

(256) Mikocka-Walus AA, Turnbull DA, Andrews JM, Moulding NT, Wilson IG, Harley HA, et al. Psychological problems in gastroenterology outpatients: A South Australian experience. Psychological co-morbidity in IBD, IBS and hepatitis C. Clin Pract Epidemiol Ment Health 2008;4:15.

(257) Gray A, Clarke P, Rivero-Arias O. Estimating the association between SF-36 responses and EQ-5D utility values by direct mapping. 2004.

(258) Richardson J, Khan M, Lezzi A, Maxwell A. Cross-national comparison of twelve quality of life instruments: MIC paper 3 - United Kingdom. Melbourne, Centre for Health Economics, Monash University; 2012.

(259) Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). Value Health 2008 Dec;11(7):1131-43.

(260) Vera-Llonch M, Martin M, Aggarwal J, Donepudi M, Bayliss M, Goss T, et al. Health-related quality of life in genotype 1 treatment-naive chronic hepatitis C patients receiving telaprevir combination treatment in the ADVANCE study. Aliment Pharmacol Ther 2013 Jul;38(2):124-33.

(261) Janssen pharmaceuticals. Simeprevir for the treatment of genotype 1 and genotype 4 chronic hepatitis C: NICE Single Technology Appraisal (STA). Available at: http://www.nice.org.uk/guidance/indevelopment/gid-tag455/documents. 2014 Sep 18.

(262) Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation
1686. Health Technology Assessment 2007;11(11):1-224.

(263) British Medical Association. British National Formulary (BNF). August 2014 .
Ref Type: Generic

(264) PSSRU PSSRU. Unit Costs of Health and Social Care 2013. Available at http://www.pssru.ac.uk/project-pages/unit-costs/2013/. Last accessed Aug 2014. 2013.

(265) Department of Health. NHS Reference costs 2012-2013. https://www gov uk/government/publications/nhs-reference-costs-2012-to-2013 2013.

(266) Stamuli E, Kruger J, Hutton J. Cost-effectiveness of ultrasound elastography in the assessment of liver fibrosis. Centre for Evidence-Based Purchasing Economic Report; 2009. Report No.: CEP08053.

(267) Stevenson M, Lloyd-Jones M, Morgan MY, Wong R. Non-invasive diagnostic assessment tools for the detection of liver fibrosis in patients with suspected alcohol-related liver disease: a systematic review and economic evaluation. Health Technol Assess 2012;16(4):1-174.

(268) Morra R, Munteanu M, Imbert-Bismut F, Messous D, Ratziu V, Poynard T. FibroMAX: towards a new universal biomarker of liver disease? Expert Rev Mol Diagn 2007 Sep;7(5):481-90.

(269) Longworth L, Singh J. Estimating the cost of liver transplantation in patients diagnosed with chronic hepatitis C and B in the UK. In press. 2014.

(270) Gao X, Stephens JM, Carter JA, Haider S, Rustgi VK. Impact of adverse events on costs and quality of life in protease inhibitor-based combination therapy for hepatitis C. Expert Rev Pharmacoecon Outcomes Res 2012 Jun;12(3):335-43.

(271) National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. National Health Service 2008Available from: URL: http://www.nice.org.uk/media/b52/a7/tamethodsguideupdatedjune2008.pdf

(272) Office for National Statistics. Population Estimates by single year of age and sex for local authorities in the UK, mid-2013. Contained within Zip file 'Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2013'. http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-322718. 2014.
Ref Type: Online Source

(273) British Medical Association. British National Formulary (BNF). September 2014 .
Ref Type: Generic

(274) Barnabas A, Trueman D, Goad C, Barron A, Agarwal K. Costs associated with adverse events in the treatment of hepatitis C virus infection with protease inhibitor triple therapy in a specialist UK centre. Poster presentation, APASL Brisbane 2014 2014.

(275) Cicchetti A, Ruggeri M, Coretti S, Piscaglia A, Ponziani FR, Lanati E, et al. Economic evaluation of an anti-HCV screening program in Italy. PharmacoEconomics - Italian Research Articles 2011;13(2):81-99.

(276) Gellad ZF, Muir AJ, McHutchison JG, Sievert W, Sharara AI, Brown KA, et al. Cost-effectiveness of truncated therapy for hepatitis C based on rapid virologic response. Value in Health 2012;15(6):876-86.

(277) Mihajlo B, Zeljko D, PJ D, Predrag S, Olgica M, Mirjana R, et al. Assessment of viral genotype impact to the cost-effectiveness and overall costs of care for PEG-interferon-2alpha + ribavirine treated chronic hepatitis C patients. Hepat Mon 2013;13(6):e6750.

(278) Jacobson I, Baldini A, DeMasi R, Gavart S, Luo D, Mrus J, et al. Efficacy, safety and UK cost-effectiveness in treatment-naive patients with F2 fibrosis treated with telaprevir (TVR; T) in combination with peginterferon (P) and ribavirin (R) vs peginterferon and ribavirin alone. American Journal of Gastroenterology Conference: 2012 Oct 19;77th Annual Scientific Meeting of the American College of Gastroenterology Las Vegas, NV United States. Conference Start(var.pagings):121019-S180.

(279) Obach D, Deuffic-Burban S, Esmat G, Anwar WA, Dewedar S, Canva V, et al. Immediate vs. delayed treatment in genotype 4-HCV infected patients in a limited resources country: A cost-effectiveness analysis in Egypt (ANRS 12215). Journal of Hepatology Conference: 2013;48th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress13 Amsterdam Netherlands(var.pagings):Conference.

(280) Cortesi PA, Ciaccio A, Rota M, De S, Vinci M, Belli LS, et al. Management of chronic hepatitis C (CHC) genotype 1 treatment-naive patients in an era of rising opportunities and costs-a cost-effectiveness analysis of treatment options. Journal of Hepatology Conference: 2014;49th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress14 London United Kingdom(var.pagings):Conference.

(281) Brady B, Siebert U, Sroczynski G, Murphy G, Husereau D, Sherman M, et al. Clinical and cost-effectiveness of interferon-based therapies for chronic hepatitis C virus infection. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH) 2007;18.

(282) Gavart S, Lee S, D'Angelo E, DeMasi R, Cure S, Bianic F. Economic Value of Telaprevir for the Treatment of PreviouslyUntreated F2 Fibrosis Chronic Hepatitis C Patients. 2012 Nov 3; 2012.

(283) El Khoury AC, Vietri J, Prajapati G. The burden of untreated hepatitis C virus infection: a US patients' perspective. Dig Dis Sci 2012;57(11):2995-3003.

(284) Di Bonaventura M, Yuan Y, L'Italien G, Lescrauwaet B. The effect of Hepatitis C treatment on health-related quality of life, work productivity, and healthcare resource use among patients in Europe. 2012 p. S434.

(285) Thal G, Nuyts G, Mcallister S, Luo D, Muir AJ, Sherman KE. Work productivity among genotype 1 hepatitis C virus (HCV) treatment-naive patients receiving telaprevir-based treatment regimens: Results from advance and illuminate studies.: *Value in Health Conference*; 2011.

(286) Hsu PC, Federico CA, Krajden M, Yoshida EM, Bremner KE, Anderson FH, et al. Health utilities and psychometric quality of life in patients with early- and late-stage hepatitis C virus infection. J Gastroenterol Hepatol 2012 Jan;27(1):149-57.

(287) Myers RP, Cooper C, Sherman M, Lalonde R, Witt-Sullivan H, Elkashab M, et al. Outcomes of chronic hepatitis C therapy in patients treated in community versus academic centres in Canada: final results of APPROACH (a prospective study of peginterferon alfa-2a and ribavirin at academic and community centres in Canada). Can J Gastroenterol 2011 Sep;25(9):503-10.

(288) Rodis JL, Kibbe P. Evaluation of medication adherence and quality of life in patients with hepatitis C virus receiving combination therapy. Gastroenterol Nurs 2010 Sep;33(5):368-73.

(289) Di Sciascio G, CalÃ² S, Nardini M. Haematological abnormalities and quality of life in patients with chronic hepatitis C who meet major depression disorder during antiviral therapy. 2010.

(290) Rothenhausler HB, Scherr M, Putz-Bankuti C, Kapper A, Stepan A, Baranyi A, et al. [The relationship between emotional distress, cognitive performance and health - related quality of life in patients with hepatitis C prior to antiviral treatment]. Fortschr Neurol Psychiatr 2009 Aug;77(8):457-63.

(291) Beste LA, Straits-Troster K, Zickmund S, Larson M, Chapko M, Dominitz JA. Specialty care and education associated with greater disease-specific knowledge but not satisfaction with care for chronic hepatitis C. Aliment Pharmacol Ther 2009 Aug;30(3):275-82.

(292) Falasca K, Mancino P, Ucciferri C, Dalessandro M, Manzoli L, Pizzigallo E, et al. Quality of life, depression, and cytokine patterns in patients with chronic hepatitis C treated with antiviral therapy. Clin Invest Med 2009;32(3):E212-E218.

(293) Bailey DE, Jr., Landerman L, Barroso J, Bixby P, Mishel MH, Muir AJ, et al. Uncertainty, symptoms, and quality of life in persons with chronic hepatitis C. Psychosomatics 2009 Mar;50(2):138-46.

(294) Minazzato L, Amodio P, Cillo U, Zanus G, Schiff S, Bombonato G, et al. Subjective satisfaction and quality of life in patients prior to listing for liver transplantation. Int J Artif Organs 2009 Jan;32(1):39-42.

(295) Hsu PC, Krajden M, Yoshida EM, Anderson FH, Tomlinson GA, Krahn MD. Does cirrhosis affect quality of life in hepatitis C virus-infected patients? Liver Int 2009;29(3):449-58.

(296) Payen JL, Pillard F, Mascarell V, Riviere D, Couzigou P, Kharlov N. Is physical activity possible and beneficial for patients with hepatitis C receiving pegylated interferon and ribavirin therapy? Gastroenterol Clin Biol 2009 Jan;33(1 Pt 1):8-14.

(297) John-Baptiste AA, Tomlinson G, Hsu PC, Krajden M, Heathcote EJ, Laporte A, et al. Sustained responders have better quality of life and productivity compared with treatment failures long after antiviral therapy for hepatitis C
2935. American Journal of Gastroenterology 2009 Oct;104(10):2439-48.

(298) Palmer M. Improvement in treatment adherence in patients with chronic hepatitis C. Practical Gastroenterology 2008;32(12).

(299) Gunasekera S, Fraser J, Alexander C. Quality of life in Hepatitis C virus infection: assessment of rural patients living in north-western New South Wales. Aust J Rural Health 2008;16(4):213-20.

(300) Kwan JW, Cronkite RC, Yiu A, Goldstein MK, Kazis L, Cheung RC. The impact of chronic hepatitis C and co-morbid illnesses on health-related quality of life. Qual Life Res 2008 Jun;17(5):715-24.

(301) Taliani G, Rucci P, Biliotti E, Cirrincione L, Aghemo A, Alberti A, et al. Therapy expectations and physical comorbidity affect quality of life in chronic hepatitis C virus infection. Journal of Viral Hepatitis 2007 Dec;14(12):875-82.

(302) Dan AA, Crone C, Wise TN, Martin LM, Ramsey L, Magee S, et al. Anger experiences among hepatitis C patients: relationship to depressive symptoms and health-related quality of life. Psychosomatics 2007;48(3):223-9.

(303) Tillmann HL, Wiese M, Braun Y, Wiegand J, Tenckhoff S, Mossner J, et al. Quality of life in patients with various liver diseases: patients with HCV show greater mental impairment, while patients with PBC have greater physical impairment. J Viral Hepat 2011 Apr;18(4):252-61.

(304) Teuber G, Schafer A, Rimpel J, Paul K, Keicher C, Scheurlen M, et al. Deterioration of health-related quality of life and fatigue in patients with chronic hepatitis C: Association with demographic factors, inflammatory activity, and degree of fibrosis. J Hepatol 2008 Dec;49(6):923-9.

(305) McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. Med Decis Making 2008 Jul;28(4):582-92.

(306) Ahluwalia V, Wade J, Thacker L, Kraft K, Sterling R, Stravitz R, et al. Differential impact of hyponatremia and hepatic encephalopathy on health-related quality of life and brain metabolite abnormalities in cirrhosis. J Hepatol 2013;59(3):467-73.

(307) Alves G, aldessar M, Pereira G, Kuehlkamp V, Hilzendeger. Quality of life of patients with hepatitis C. Rev Soc Bras Med Trop 2012;45(5):553-7.

(308) Anderson R, Baran R, Dietz B, Kallwitz E, Erickson P, Revicki D. Development and initial psychometric evaluation of the hepatitis C virus-patient-reported outcomes (HCV-PRO) instrument. Qual Life Res 2013;doi-0505.

(309) Baranyi A, Meinitzer A, Stepan A, Putz-Bankuti C, Breitenecker R, Stauber R, et al. A biopsychosocial model of interferon-alpha-induced depression in patients with chronic hepatitis C infection. Psychother Psychosom 2013;82(5):332-40.

(310) Chang C, o L, Tseng C, Hsu Y, Lin J. Dynamic changes of health-related quality of life after pegylated interferon and ribavirin treatment for chronic hepatitis c. Gastroenterology Conference : Digestive Disease Week 2013;#2013 Orlando, FL United States:S981.

(311) Da C, Gontijo E, Monteiro N, Barcelos V, Rainha A, Diniz K, et al. Factors influencing the quality of life on patients with chronic hepatitis C, evaluated with generic questionnaire SF-36. Hepatology Conference : 2012;63rd Annual Meeting of the American Association for the Study of Liver Diseases:670A.

(312) Da C, Araujo R, Da C, Lucinda L, Teixeira R, Komatsuzaki F, et al. Decreased health-related quality of life (HRQoL) in chronic hepatitis C (CHC): Association with major depressive disorder (MDD), anxiety disorders, clinical comorbidity and sociodemographic factors. Hepatology Conference : 2012;63rd Annual Meeting of the American Association for the Study of Liver Diseases:667A.

(313) Di B, Gross H, Wagner J. The effect of anemia on health status and work productivity among treated Hepatitis C patients. Value in Health Conference : 2012;17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR12 Washington, DC United States:A245.

(314) DiBonaventura MD, Yuan Y, Lescrauwaet B, L'Italien G, Liu G, Kamae I, et al. The humanistic and economic burden of Hepatitis C across the United States, Europe, and Asia. Value in Health Conference : 2012;17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR12 Washington, DC United States:A245-A246.

(315) Escheik C, Gerber L, Rover L, Arsalla Z, Otgonsuren M, Younossi Z. Validation of CLDQ-HCV as a Health Related Quality of Life (HRQL) instrument for patients with chronic hepatitis C (CH-C). American Journal of Gastroenterology Conference : 2012;77th Annual Scientific Meeting of the American College of Gastroenterology Las Vegas, NV United States.

(316) Fabregas B, de AR, Faria M, Moura A, Carmo R, Teixeira A. Health related quality of life among patients with chronic hepatitis C: a cross-sectional study of sociodemographic, psychopathological and psychiatric determinants. Braz J Infect Dis 2013;http.

(317) Gillis J, Cooper C, Rourke S, Rueda S, O'Brien K, Collins E, et al. Impact of hepatitis B and C co-infection on health-related quality of life in HIV positive individuals. Qual Life Res 2013;22(7):1525-35.

(318) Isaacs D, Jack J, Keller M, Tibble J, Haq I. Measuring the response of extra-hepatic symptoms and quality of life to antiviral treatment in patients with hepatitis c. Rheumatology (United Kingdom) Conference : British Society for Rheumatology and British Health Professionals in Rheumatology Annual Meeting 2012;#2012 Glasgow United Kingdom:57.

(319) Kemmer N, Hua L, Andersen J, Chung R, Butt A, Sherman K. Health-related quality of life in subjects with HCV/HIV coinfection: results from ACTG 5178 study. J Viral Hepat 2012;19(11):792-800.

(320) Kerr C, Lloyd A, Ali S, Gore C, Tyas D. Impact of treatment attributes of peginterferon for hepatitis C on quality of life and treatment preference. Health Outcomes Research in Medicine 2012;3(3):e153-e167.

(321) Kieran J, Mushtaq H, Bergin C, Norris S, Barry M. Demographics and health-state utilities of irish patients with hepatitis C infection; use of the 5-level EQ-5D questionnaire. Value in Health Conference : ISPOR 2012;15th Annual European Congress Berlin Germany:A528.

(322) Lane S, irbach S, Gooch K, Grinspan J, Kallwitz E, Szabo S, et al. Evaluation of patient preferences for treatment outcomes in Hepatitis C Virus (HCV). Hepatology Conference : 2012;63rd Annual Meeting of the American Association for the Study of Liver Diseases:1025A.

(323) Loria A, Escheik C, Gerber L, Price J, Younossi Z. The chronic liver disease questionnaire-Hepatitis C (CLDQ-HCV): A sensitive and valid health related quality of life instrument. Hepatology Conference : 2012;63rd Annual Meeting of the American Association for the Study of Liver Diseases:646A.

(324) Mandorfer M, Payer B, Scheiner B, Breitenecker F, Aichelburg M, Grabmeier-Pfistershammer K, et al. Health-related quality of life and severity of fatigue in HIV/HCV co-infected patients before, during, and after antiviral therapy with pegylated interferon plus ribavirin. Liver Int 2013;doi.

(325) Mousa O, Langley G, Pham L, Egwim C, Zela S, Ankoma-Sey V. Consequences of Current Hepatitis C Direct Anti-Viral Agents (Telaprevir and Boceprevir) on the Health- Related Quality of Life. Hepatology Conference : 2012;63rd Annual Meeting of the American Association for the Study of Liver Diseases:668A.

(326) Sargsyants N. Influence of predictor variables on quality of life of patients with chronic viral hepatitis C. Journal of Hepatology Conference : 2013;48th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress13 Amsterdam Netherlands:S200-S201.

(327) Scalone L, Cortesi P, Ciampichini R, Okolicsanyi S, Rota M, Ciaccio A, et al. Relationship between clinical severity and health related quality of life in chronic liver diseases. Value in Health Conference : ISPOR 2012;15th Annual European Congress Berlin Germany:A332.

(328) Scott J, Rosa K, Fu M, Cerri K, Peeters M, Beumont-Mauviel M, et al. Improved SVR with simeprevir (TMC435) associated with reduced time with patient-reported fatigue in treatment-naive, HCV-infected patients in the pillar phase IIb trial. Journal of Hepatology Conference : 2013;48th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress13 Amsterdam Netherlands:S371-S372.

(329) Sherman K, Muir A, Aggarwal J, Donepudi M, Goss T, Martin M, et al. Health-related quality-of-life among genotype 1 treatment-experienced chronic hepatitis C patients: Post-HOC analyses from the realize study. Journal of Hepatology Conference : 2013;48th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress13 Amsterdam Netherlands:S372.

(330) Vera-Llonch M, Martin M, Aggarwal J, Donepudi M, Bayliss M, Goss T, et al. Health-related quality of life in genotype 1 treatment-naive chronic hepatitis C patients receiving telaprevir combination treatment in the ADVANCE study. Aliment Pharmacol Ther 2013;38(2):124-33.

(331) Younossi ZM, Stepanova M, Mir H, Jacobson I, Gane E, Nader F, et al. Minimal impact of sofosbuvir+ribavirin on health related quality of life (HRQL) compared to pegylated interferon + ribavirin for chronic hepatitis C (CH-C): Results from fission+positron studies. Journal of Hepatology Conference : 2013;48th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress13 Amsterdam Netherlands:S577.

(332) Baranyi A, Meinitzer A, Stepan A, Matejka J, Stauber R, Kapfhammer H, et al. [Interferon alpha therapy in patients with chronic hepatitis C infection: biopsychosocial consequences]. Nervenarzt 2012;83(9):1169-77.

(333) El K, Vietri J, Prajapati G. Health-related quality of life in patients with hepatitis C virus infection in Brazil. Pan American Journal of Public Health 2014 Mar;35(3):200-6.

(334) Younossi ZM, Stepanova M, Nelson D, Lawitz E, Nader F, Hunt S. Health-related quality of life (HRQL) in chronic hepatitisc (CH-C) patients treated with sofosbuvir containing interferon-free regimens. Value in Health Conference: ISPOR 2013 Nov 2;16th Annual European Congress Dublin Ireland. Conference Start(var.pagings):131102.

(335) Baran RW, Xie W, Liu Y, Cohen DE, Gooch KL. Health-related quality of life (HRQoL), health state, function and wellbeing of chronic HCV patients treated with interferon-free, oral DAA Regimens: Patient Reported Outcome (PRO) results from the AVIATOR study. Hepatology Conference: 2013;64th Annual Meeting of the American Association for the Study of Liver Diseases(var.pagings):The-751A.

(336) Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, et al. Minimal impact of sofosbuvir and ribavirin on health related quality of life in Chronic Hepatitis C (CH-C). Journal of Hepatology 2014;60(4):741-7.

(337) Younossi ZM, Stepanova M, Lawitz E, Nelson DR, Jacobson IM, Gane EJ, et al. Health utilities in patients with chronic hepatitis C treated with sofosbuvir (SOF) containing regimens: Results from positron, fisson, fusion and neutrino studies. Hepatology Conference: 2013;64th Annual Meeting of the American Association for the Study of Liver Diseases(var.pagings):The-386A.

(338) Forlenza JB, Lopatto J, Annunziata K, Sternbach N, Tandon N. Characteristics, treatment rates, quality of life (QOL), and activity impairment among united states adults with hepatitis C-an analysis by birth cohort. Value in Health Conference: ISPOR 2014 May 31;#20140604(var.pagings):Conference.

(339) Matza LS, Sapra S, Kalsekar A, Dillon JF, Davies E, Devine MK, et al. Health state utilities associated with att ributes of treatments for hepatitis C. Value in Health Conference: ISPOR 2014 May 31;#20140604(var.pagings):Conference.

(340) Samp JC, Perry R, Piercy J, Baran RW. Utility values of hepatitis C patients in France: Results by liver disease stage and treatment outcome. Value in Health Conference: ISPOR 2014 May 31;#20140604(var.pagings):Conference.

(341) Perry R, Piercy J, Nwankwo C. Description of the patient burden observed in treated versus untreated patients with hepatitis C virus in a real world setting: Results of a cross sectional study in USA and France. Hepatology International Conference: 2014;23rd Conference of the Asian Pacific Association for the Study of the Liver, APASL14 Brisbane, QLD Australia(var.pagings):Conference.

(342) Price J, Escheik C, Azim Y, Hunt S, Fang Y, Oe B, et al. Sustained virologic response (SVR) in hepatitis C (HCV) patients does not demonstrate differences in physical performance, fatigue, sleep, and health-related quality of life (HRQL). American Journal of Gastroenterology Conference: 2013 Oct 11;78th Annual Scientific Meeting of the American College of Gastroenterology San Diego, CA United States. Conference Start(var.pagings):131011.

(343) Reimer J, Hueppe D, Sandow P, Naumann U, Goelz J, Christensen S, et al. Quality of life profiles in patients in contact with the hepatitis C virus. Suchtmedizin in Forschung und Praxis Conference: 2013 Sep 5;3rd International Symposium on Hepatitis Care in Substance Users Munich Germany. Conference Start(var.pagings):130905.

(344) Forlenza JB, Lopatto J, Annunziata K, Sternbach N, Freedman D, Tandon N. Quality of life, productivity, and activity impairment among U.S. survey respondents with hepatitis C: An evaluation of HCV and six select medical conditions. Gastroenterology Conference: Digestive Disease Week 2014;#2014 Chicago, IL United States(var.pagings):Conference-S967.

(345) Forlenza JB, Annunziata K, Tandon N. Comorbidity, Healthcare Resource Use (HRU), productivity, and Quality of Life (QOL) burden in hepatitis C (HEP C): Results from a 2012 U.S. health survey. Hepatology Conference: 2013;64th Annual Meeting of the American Association for the Study of Liver Diseases(var.pagings):The.

(346) Yuan Y, Da C, L'Italien G, Hines P, Gordon L, Mauskopf J. The relative disease burden of viral hepatitis C: A comparison with viral hepatitis B. Hepatology International Conference: 2013;23rd Conference of the Asian Pacific Association for the Study of the Liver, APASL13 Singapore Singapore(var.pagings):Conference.

(347) Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, et al. Effects of Sofosbuvir-Based Treatment, With and Without Interferon, on Outcome and Productivity of Patients With Chronic Hepatitis C. Clinical Gastroenterology and Hepatology 2014;12(8):1349-1359e13.

(348) Younossi ZM, Stepanova M, Nader F, Nelson D, Lawitz E, Jacobson IM, et al. Patient-reported outcomes (PROs) in chronic hepatitis c patients with cirrhosis treated with sofosbuvir (SOF) containing regimens. Journal of Hepatology Conference: 2014;49th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress14 London United Kingdom(var.pagings):Conference-S450.

(349) Younossi ZM, Stepanova M, Nader F, Nelson D, Lawitz E, Jacobson IM, et al. Independent predictors of patient-reported outcomes (PROs) and quality of life (QoL) in chronic hepatitis c patients receiving interferon (IFN)-free versus IFN-containing regimens with sofosbuvir (SOF). Journal of Hepatology Conference: 2014;49th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress14 London United Kingdom(var.pagings):Conference.

(350) Younossi ZM, Stepanova M, Lawitz E, Nelson DR, Cooper C, Nader F, et al. Minimal impact of sofosbuvir+ribavirin (SOF+RBV) on work productivity of patients with chronic hepatitis C (CH-C). Hepatology Conference: 2013;64th Annual Meeting of the American Association for the Study of Liver Diseases(var.pagings):The.

(351) Younossi Z, Stepanova M, Gerber L, Lawitz E, Nelson D, Nader F, et al. Successful treatment with sofosbuvir (SOF) regimen improves patient-reported outcomes (PROS) in patients with chronic Hepatitis c (CH-C). American Journal of Gastroenterology Conference: 2013 Oct 11;78th Annual Scientific Meeting of the American College of Gastroenterology San Diego, CA United States. Conference Start(var.pagings):131011.

(352) Younossi ZM, Stepanova M, Lawitz E, Nelson DR, Kaita KD, Nader F, et al. Successful treatment with sofosbuvir regimen improves fatigue scores in patients with chronic hepatitis C (CHC). Hepatology Conference: 2013;64th Annual Meeting of the American Association for the Study of Liver Diseases(var.pagings):The.

(353) Younossi Z, Stepanova M, Marcellin P, Afdhal N, Nader F, Hunt S. Ledipasvir (LDV) and sofosbuvir (SOF) combination improves patient-reported outcomes (PRO) during treatment of chronic hepatitis C (CH-C) patients: Results from the ion-1 clinical trial. Journal of Hepatology Conference: 2014;49th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress14 London United Kingdom(var.pagings):Conference-S537.

(354) Scott J, Gilles L, Peeters M, Cerri K, Beumont-Mauviel M. Simeprevir reduces time with peginterferon/ribavirininduced symptoms and quality-of-life impairments: 72-week results from three phase III studies. Journal of Hepatology Conference: 2014;49th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress14 London United Kingdom(var.pagings):Conference-S451.

(355) Scott JA, Gilles L, Fu M, Peeters M, Brohan E, Amatya R, et al. Adding simeprevir to peginterferon/ribavirin for HCV shortens time with patient-reported symptoms and impairment in quality of life: Results from the simeprevir Phase III QUEST 1, QUEST 2 and PROMISE studies. Hepatology Conference: 2013;64th Annual Meeting of the American Association for the Study of Liver Diseases(var.pagings):The.

(356) Mauss S, Petersen J, Witthoeft T, Busch HW, Christensen S, Zehnter E, et al. Sustained responders after antiviral treatment of chronic hepatitis c have a better quality of life and productivity independent of genotype, age and opioid maintenance. Gastroenterology Conference: Digestive Disease Week 2013;#2013 Orlando, FL United States(var.pagings):Conference.

(357) DiBonaventura MD, Yuan Y, Lescrauwaet B, L'Italien G, Liu GG, Kamae I, et al. Multicountry burden of chronic hepatitis C viral infection among those aware of their diagnosis: a patient survey. PLoS ONE [Electronic Resource] 2014;9(1):e86070.

(358) Simpson KN, Simpson AN, Cline SK, Gooch KL. Trends in liver-related healthcare resource utilization for HCV-infected individuals in the US: 2002-2010. Hepatology Conference: 2013;64th Annual Meeting of the American Association for the Study of Liver Diseases(var.pagings):The.

(359) Younossi ZM, Stepanova M, Zeuzem S, Dusheiko G, Esteban R, Hezode C, et al. Patient-reported outcomes assessment in chronic hepatitis C treated with sofosbuvir and ribavirin: The VALENCE study. Journal of Hepatology 2014;61(2):228-34.

(360) Younossi ZM, Stepanova M, Nader F, Jacobson IM, Gane E, Nelson D, et al. Patient-reported outcomes in chronic hepatitis C patients with cirrhosis treated with sofosbuvir-containing regimens. Hepatology 2014;59(6):2161-9.

(361) Heeren M, Sojref F, Schuppner R, Worthmann H, Pflugrad H, Tryc AB, et al. Active at night, sleepy all day - Sleep disturbances in patients with hepatitis C virus infection. Journal of Hepatology 2014;60(4):732-40.

(362) Younossi ZM, Stepanova M, Cure S, Bourhis F, Nader F, Hunt SL. Estimating health status using EQ5D for chronic hepatitis c (CH-C) patients treated with sofosbuvir (SOF) containing regimens. Journal of Hepatology Conference: 2014;49th Annual Meeting of the European Association for the Study of the Liver, International Liver Congress14 London United Kingdom(var.pagings):Conference.

(363) Vera-Llonch M, Martin M, Aggarwal J, Donepudi M, Bayliss M, Goss T, et al. Health-related quality of life in genotype 1 treatment-naive chronic hepatitis C patients receiving telaprevir combination treatment in the ADVANCE study. Aliment Pharmacol Ther 2013 Jul;38(2):124-33.

(364) Longworth L, Singh J. Estimating the cost of liver transplantation in patients diagnosed with chronic hepatitis C and B in the UK. 2014.

(365) Cardoso AC, Moucari R, Figueiredo-Mendes C, Ripault MP, Giuily N, Castelnau C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol 2010 May;52(5):652-7.

(366) EMA. Sovaldi Summary of Product Characteristics (SmPC). www.ema.europa.eu . 2014.
Ref Type: Online Source

(367) emc. Olysio, summary of product characteristics. https://www.medicines.org.uk/emc/medicine/28888/SPC/OLYSIO+150mg+hard+capsules/ . 2014.
Ref Type: Online Source

(368) Gilead Sciences. ION-2, INTERIM CLINICAL STUDY REPORT, GS-US-337-0109, Foster City. 2014.

(369) Gilead Sciences. ION-1, INTERIM CLINICAL STUDY REPORT, GS-US-337-0102, Foster City. 2014.

(370) Gilead Sciences. FISSION, INTERIM SYNOPTIC CLINICAL STUDY REPORT, P7977-1231, Foster City. 2013 Feb 25.