NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Ledipasvir-sofosbuvir for treating chronic hepatitis C

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical practice

- **Genotype 1 and 4:** The marketing authorisation recommends 8, 12 or 24 weeks of treatment with ledipasvir–sofosbuvir according to genotype, treatment experience and other charactersitics (such as risk of clinical disease progression, or subsequent treatment options).
  - How would this relate to clinical practice; are these groups clearly defined and readily identifiable? For how long would people receive treatment?
  - The company suggests that HCV RNA less than 6 million IU/ml could be used to determine those with HCV genotype 1, non cirrhotic, treatment-naive HCV that could received 8 weeks of treatment. This does not reflect the wording of the marketing authorisation. Is this criterion appropriate?

  - The company have included a blend of patient populations (for example, cirrohotic / non-cirrohotic) who receive different treatment durations of ledipasvir-sofosbuvir in its cost-effectiveness analysis. Is it appropriate to consider these patients together?
- **Genotype 1 and 4:** Is sofosbuvir in combination with simeprevir established NHS practice in England? Is this an appropriate comparator? How long would people receive treatment for (the economic model assumes 12 weeks)?
- **Genotype 1 and 4: ‘**No treatment’ was included as a comparator. In clinical practice would those people who are not receiving treatment ever receive treatment? Would a watchful waiting approach be taken and treatment offered later?
- **Gentoype 4:** Boceprevir and telaprevir were included as comparators for people with treatment-experienced HCV, but this is outside of their marketing authorisations. Would these be used for genotype 4 in clinical practice?
- **Genotype 3:** The company excluded ‘no treatment’ (best supportive care) as a comparator for people with cirrohotic HCV genotype 3. Is this appropriate?
- **Genotype 3:** The marketing authorisation does not recommend a specific treatment regimen for treatment-naive HCV genotype 3 without cirrohosis but recommends 24-week ledipasvir-sofosbuvir with ribavirin for cirrhotic or treatment-experienced HCV gentoype 3.
  - Are people with non-cirrohotic, treatment-naive HCV genotype 3 included in the marketing authorisation?
  - If so, would people with non-cirrohotic, treatment-naïve HCV genotype 3 receive the 12-week or 24-week regimen (with ribavirin) in clinical practice?

Clinical effectiveness – general

- The Evidence Review Group (ERG) stated that the company’s searches for the comparators were not systematic. Has all relevant evidence for the comparators of this appraisal been presented?
- Relativeness effectiveness of ledipasvir-sofosbuvir with its comparators was estimated using SVR rates from single studies and naïve indirect comparisons Can these estimates be considered sufficiently robust?

- The company did not conduct a meta-analysis of the evidence for ledipasvir–sofosbuvir, but the ERG stated that this would have been possible. Would a meta-analysis have been apppropriate?
- The data for ledipasvir–sofosbuvir came from single armed trials and therefore could not be connected through a network to the comparator data. However, the comparator data could have been linked together; would a meta-analysis, or an indirect comparison, of the comparator data have been feasible and appropriate?
- Are the baseline patient and clinical characteristics of the populations in the ledipasvir–sofosbuvir and comparator studies comparable?

Clinical effectiveness – population specific

- **Genotype 3:** 24 weeks of ledipasvir–sofosbuvir plus ribavirin treatment is recommended for treatment-experienced or cirrohotic genotype 3 HCV. The data to support genotype 3 was from a small phase II trial (n=76) of 12 weeks of treatment and based on SVR4 rates. Is this sufficiently robust for decision making?
- **Genotype 4:** The summary of product characteristics recommends that genotypes 1 and 4 are treated similarly. Is the evidence for HCV genotype 1 generalisable to HCV genotype 4?
- **Genotype 1 and 4:** The marketing authorisation includes people with decompensated cirrhosis or pre/post transplant. SVR4 rates from an open label, non-RCT (n=306) of genotype 1 and 4 were presented to support treatment effect in this population. No cost-effectiveness analyses were presented. Can recommendations be made for this population?
- **HIV co-infection:** The marketing authorisation of ledipasvir–sofosbuvir includes people co-infected with HIV. The company submitted data from a phase II non-RCT of people with HCV genotype 1 co-infected with HIV (n=50), but did not explore the cost-effectiveness in this population. Can recommendations be made that include people co-infected with HIV for each HCV genotype being appraised?

Cost effectiveness - general

- The company assumed all people with non-cirrohotic, treatment-naïve HCV genotype 3 would receive ledipasvir-sofosbuvir plus ribavirin for 12 weeks. Is this population included in the marketing authorisation? Is this regimen appropriate?
- The company's base case cost-effectiveness analysis does not stratify the results by cirrhotic status. However, the ERG presented the results of their exploratory analyses separately for people with and without cirrhosis. Should cirrhotic status be considered in the cost effectiveness analysis?
- In the model, people who did not have cirrhosis and achieved SVR were cured indefinitely. People who had cirrhosis and achieved SVR had an ongoing risk of developing decompensated cirrhosis and hepatocellular carcinoma, but this risk was lower than those who did not achieve SVR. Therefore re-infection of HCV was not captured in the model. The ERG explored the potential impact from including re-infection by applying shorter time-horizons. Is it appropriate to assume SVR12 represents a cure?
- The consequences of onward transmission of HCV was not captured in the model. Is this appropriate? How may incorporating this impact the results?
- In the model, people cannot die or their disease cannot progress while on treatment with ledipasvir–sofosbuvir or the comparators. The different treatments have different treatment durations and therefore this grace period differed, favouring those with a longer treatment duration. Is this assumption appropriate?
- People enter the model with a mean age of 40 [treatment-naive] or 45 [treatment-experienced] years. The mean age of people on the ION studies was between 51 and 57 years. What should the starting age of the model be?

Cost effectiveness – inputs

- Transition probabilities for the non-cirrhotic state to the compensated cirrhosis state were estimated using probabilities for transitions between mild, moderate and cirrhotic stages of disease, and it was not clear to the ERG how this was done. Can these be considered robust?
- Transition probabilities from compensated or decompensated cirrhosis to hepatocellular carcinoma were considerably higher (0.0631) than those used by

the same company for the sofosbuvir appraisal (0.014; ID654). How robust are these?

- The company used Vera-Llonch et al. (2013) to reflect the utility gain associated with achieving SVR based on the US EQ-5D tariff. The ERG preferred the utility gain associated with achieving SVR taken from Wright et al. (2006) which used the UK EQ-5D tariff. Which is more appropriate?
- The company applied on-treatment decrements to reflect changes in health-related quality-of-life resulting from adverse reactions (which were also assumed to apply to the entire duration of treatment). The ERG noted that there is no explicit link between the on-treatment decrements and the rates of adverse reactions for each of the different treatments. Is this approach appropriate? Is the assumed on-treatment decrement of zero for ledipasvir-sofosbuvir reflective of the health-related quality-of-life data collected in the ION studies?

Innovation and equality

- All current treatment options for HCV genotype 1 and 4 involve injecting interferon on a weekly basis. Ledipasvir-sofosbuvir with or without ribavirin is an all oral treatment option. Is ledipasvir-sofosbuvir with or without ribavirin innovative? Are all substantial health-related benefits included in the QALY calculation?
- Minority ethnic groups and people with HIV co-infection are more highly represented in the genotype 4 HCV population. Is this a potential equality consideration?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of ledipasvir-sofosbuvir within its marketing authorisation for treating chronic hepatitis C.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	Adults with chronic hepatitis C: • who have not had treatment for chronic hepatitis C before (treatment-naive) • who have had treatment for chronic hepatitis C before (treatment-experienced)		The company submission focusses solely on subgroups of people with genotype 1, genotype 3 and genotype 4. Most of the data relate to people with genotype 1 disease.	The wording of the EPAR relates to people with genotype 1, genotype 3 and genotype 4 disease (see table 2).
Intervention	Ledipasvir-sofosbuvir with or without ribavirin		As per final scope.	Issues concerning the: • use of blended comparisons for ledipasvir-sofosbuvir (cost-effectiveness analysis, blended data from different treatment durations) • treatment duration adopted within the modelled genotype 3 treatment-experienced subgroup does not adhere to recommended treatment durations listed in the marketing authorisation.

Comparators	• Peginterferon alfa with ribavirin (genotypes 1-6) • Telaprevir in combination with peginterferon alfa and ribavirin (for genotype 1 only) • Boceprevir in combination with peginterferon alfa and ribavirin (for genotype 1 only) • Sofosbuvir in combination with ribavirin, with or without peginterferon alfa (genotypes 1-6; subject to ongoing NICE appraisal ID654) • Simeprevir in combination with peginterferon alfa and ribavirin (genotype 1 or 4) (subject to ongoing NICE appraisal [ID668]) • Simeprevir in combination with sofosbuvir, with or without ribavirin (for people who have genotype 1 or 4 disease and are ineligible for or intolerant to interferon treatment) (subject to ongoing NICE appraisal [ID668]) • Best supportive care (watchful waiting) (genotypes 1-6)	As per final scope. “Best supportive care” is defined as no treatment in the company’s submission.	• Mostly in line with final scope • Telaprevir and boceprevir are included in the economic analysis of treatment-experienced patients with HCV genotype 1/4 but neither product has marketing authorisation in the UK for use in genotype 4 patients • Peginterferon is not included as a treatment option for genotype 3 patients
Outcomes	• Sustained virological response • Development of resistance to ledipasvir-sofosbuvir • Mortality • Adverse effects of treatment • Health-related quality of life	As per final scope. The development of resistance to ledipasvir-sofosbuvir does not impact upon the cost-effectiveness (that is, it has no impact on cost or QALYs).	No comments.

Other considerations	If evidence allows the following subgroups will be considered: • 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	As per final scope. The company stated that the evidence allowed the following subgroup analyses: • Genotype • People with and without cirrhosis • People who are intolerant to or ineligible for interferon treatment	See Section 5.27–28 of premeeting briefing document.	No comments.

2 The technology and the treatment pathway

2.1 Ledipasvir-sofosbuvir (Harvoni) has a marketing authorisation in the UK for the treatment of chronic hepatitis C (CHC) in adults. However, the marketing authorisation specifies treatment regimens for specific populations only, which will be the focus of this appraisal (see table 2). It is taken orally as a fixed-dose combination tablet for 8, 12 or 24 weeks, with or without ribavirin.

Table 2 Ledipasvir-sofosbuvir treatment duration with co-administered medicinal products by genotype (table 1 of ledipasvir-sofosbuvir's summary of product characteristics)

Patient population*		Treatment	Duration
Patients with genotype 1 or genotype 4 chronic hepatitis c			
Patients without cirrhosis	Previously untreated 'may' consider this duration	Ledipasvir-sofosbuvir	8 weeks
	All other	Ledipasvir-sofosbuvir	12 weeks
	Previously treated HCV with uncertain subsequent retreatment options	Ledipasvir-sofosbuvir	24 weeks
Patients with compensated cirrhosis	People with low risk of clinical disease progression and who have subsequent retreatment options	Ledipasvir-sofosbuvir	12 weeks
	All other	Ledipasvir-sofosbuvir	24 weeks
Patients with decompensated cirrhosis or who are pre-/post liver transplant		Ledipasvir-sofosbuvir plus ribavirin	24 weeks
Patients with genotype 3 chronic hepatitis c			
Patients with cirrhosis and/or prior treatment failure		Ledipasvir-sofosbuvir plus ribavirin	24 weeks
* Includes people co-infected with HIV The efficacy of ledipasvir–sofosbuvir has not been studied against HCV genotype 2, 5 and 6; therefore, ledipasvir–sofosbuvir should not be used in patients infected with these genotypes.			

2.2 The aim of treatment is to cure the hepatitis C virus (HCV) infection and prevent liver disease progression (cirrhosis), hepatocellular carcinoma, and HCV transmission. Sustained virological response at 12 weeks after

the end of treatment (SVR12) is considered a good indicator of successful treatment. Most patients who achieve SVR12 after the end of treatment maintain their HCV-negative status, have reduced complications from liver disease, and live longer.

2.3 Management of hepatitis C can involve a 'watchful waiting' approach, for those with mild hepatitis C, agreed between the patient and clinician on an individual basis. Once active treatment is required, the options vary according to genotype and treatment experience (Table 3):

- All current treatment options for treating HCV genotypes 1, 3 (treatment-naïve) and 4 involve injecting interferon on a weekly basis (please note that ledipasvir-sofosbuvir with or without ribavirin is an all oral treatment option).
- NICE guidance on hepatitis C (technology appraisal guidance 75 and 106) recommends ribavirin in combination with either peginterferon alfa-2a or peginterferon alfa-2b for people with chronic hepatitis C, regardless of disease severity or genotype.
  - Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended for people who are unable to tolerate ribavirin or for whom ribavirin is contraindicated.
- NICE technology appraisal guidance 200 recommends that people who have been previously treated with peginterferon alfa and ribavirin or with peginterferon alfa monotherapy have an option to receive further courses of peginterferon alfa and ribavirin. Shortened courses of combination therapy are also recommended as an option for certain people depending on their genotype and their initial response to treatment.
- For people with genotype 1 chronic hepatitis C, who have or have not been previously treated, NICE guidance recommends telaprevir in combination with peginterferon alfa and ribavirin (NICE technology appraisal guidance 252) or boceprevir in combination with

peginterferon alfa and ribavirin (NICE technology appraisal guidance 253).

- For people with genotypes 1 and 4 chronic hepatitis C, whose disease has or has not been previously treated, NICE has recommended simeprevir in combination with peginterferon alfa and ribavirin as an option (subject to final publication [ID668]). Simeprevir also has a marketing authorisation for use in combination with sofosbuvir. However, recommendations for simeprevir in combination with sofosbuvir will be developed in separate NICE guidance.
- For people with genotypes 1–6 chronic hepatitis C, whose disease has or has not been previously treated, NICE has recommended sofosbuvir in combination with ribavirin, with or without peginterferon alfa, as an option for specific people, as detailed in Appendix B (subject to final publication [ID654]).

Table 3 Treatment regimens for the populations of interest

Population†		**Treatment naive**		**Treatment experienced**	
		LDV/SOF regimen	**Comparators**	**LDV/SOF regimen**	**Comparators**
GT 1 or 4	**No cirrhosis**	8-12 weeks	• PEG/RBV • Telaprevir* • Boceprevir* • SOF* (GT1 only) • SMV* • SOF+SMV	12-24 weeks	Same as treatment naive
	Compensated Cirrhosis	12-24 weeks		Same as treatment naive	
	Decompensated cirrhosis or pre/post transplant	24 weeks + RBV		Same as treatment naive	
GT3	**No cirrhosis**	Treatment regimen not stated in SPC. Company propose 12 weeks + RBV	• PEG/RBV	24 weeks + RBV	• PEG/RBV • SOF*
	Cirrhosis	24 weeks + RBV	• PEG/RBV • SOF* • SOF/RBV (if IFN intolerant)	Same as treatment naive	

* In combination with peginterferon and ribavirin
† Includes people co-infected with HIV

3 Comments from consultees

3.1 A professional group stated that hepatitis C is predominantly treated in secondary care. They also commented that treatment decisions and response are influenced by HCV genotype.

3.2 For people with mild liver disease, the decision to start active treatment is made with the patient and guided by the likelihood of cure, the drug's side effect profile and the availability of potentially more effective and tolerable treatments in the future (for example, simeprevir, sofosbuvir plus peginterferon alfa with and without ribavirin). The professional group highlighted several subgroups whom may gain greatest benefit from treatment:

- People with more advanced liver disease (for example, cirrhosis) are a greater risk of developing liver decompensation (liver failure) and HCC.
- People on the liver transplant waiting list who have the potential to eradicate or at least suppress HCV before surgery and therefore prevent re-infection of the new liver graft.
- People co-infected with HIV and HCV (which increases the risk of developing cirrhosis).

3.3 The patient groups stated that some people with HCV do not experience any symptoms, but others may experience chronic fatigue, mood swings and sexual dysfunction. They also commented that the psychological effect of having HCV can impair people's social life and ability to work. Many people also experience stigma because of HCV's association with drug use.

3.4 The professional group and patient groups stated that the benefits of ledipasvir-sofosbuvir compared with currently available treatment options include a higher chance of a cure, fewer side effects and a shorter duration of treatment. The patient groups commented that all current treatment options involve injecting interferon on a weekly basis which

most patients are adverse too. The professional group considered that the use of a combined single pill (ledipasvir-sofosbuvir) is likely to improve compliance. However, the professional group and patient groups were concerned that the cost (budget impact) of the drug is likely to have significant implications for how the treatment is rolled out to the 160,000 infected individuals in England.

3.5 Ledipasvir-sofosbuvir could be used in either primary or secondary care setting but the professional group anticipated it will initially be taken in secondary care because of the existing infrastructure of HCV care in the NHS. Specialist nurses are needed to educate patients on the use of subcutaneous injection (interferon), and to manage the considerable side effects of current treatment. However, the professional group considered the role of specialist nurses in the future will change and focus on monitoring and improving compliance rather than managing side effects. The professional group also commented that more patients are likely to come forward for testing, and clinicians are more likely to recommend treatment given the improved efficacy and side effect profile of ledipasvir-sofosbuvir.

3.6 The professional group and a patient group commented that there is geographical variation of HCV detection rates and the percentage of patients treated. The professional group further commented that this was attributed to the availability of consultants with an interest in HCV and the provision of specialist nurses.

4 Clinical-effectiveness evidence

The premeeting briefing only presents the results of regimens that have a marketing authorisation in the UK, and the studies included in the company's economic model (ION-1, ION-2, ION-3, ELECTRON-2 and SYNERGY). Please see section 6.5.7, pages 98–112 of the company's submission for the results of the other studies.

Overview of the clinical trials

4.1 The company conducted a systematic literature review to identify studies evaluating the clinical effectiveness of ledipasvir-sofosbuvir for treating chronic hepatitis C. It presented 10 studies of ledipasvir-sofosbuvir with and without ribavirin in adults who were either previously untreated (treatment naïve) or previously treated (treatment experienced). The company focused it clinical-effectiveness submission on 3 phase III non-randomised controlled trials in people with HCV genotype 1 (ION-1 [treatment naïve], ION-2 [treatment experienced] and ION-3 [treatment naïve]). The other 7 studies submitted by the company were phase II studies and were included as 'supportive evidence'. Of these 7 studies:

- 2 included people with HCV genotype 1 whom were either treatment naïve or treatment experienced (ELECTRON, LONESTAR)
- 1 included people with HCV genotype 1 whom were treatment experienced (SIRIUS)
- 1 included people with HCV genotype 1 and 3 whom were either treatment naïve or treatment experienced (ELECTRON-2)
- 1 included people with HCV genotype 1 and 4 whom were either treatment naïve or treatment experienced (SYNERGY)
- 1 included people with HCV genotype 1 co-infected with HIV (ERADICATE)
- 1 included people with genotype 1 and 4 with advanced liver disease or after liver transplantation (SOLAR-1).

The company stated that the ION study designs were approved by the regulators without concurrent controls because at time of study enrolment

the established treatment options (peginterferon) were administered intravenously, making blinding impossible, and were associated with much longer treatment durations compared with oral ledipasvir-sofosbuvir.

Table 4 Summary of studies included in company's submission (table 9, pages 49–52 of company's submission)

Population		Treatment naive		Treatment experienced	
		LDV/SOF regimen	**Evidence source**	**LDV/SOF regimen**	**Evidence source**
GT 1 or 4	**No cirrhosis**	8 and 12 weeks	LONESTAR (GT1) ION-3[a] (GT1)	12 weeks	ELECTRON-2[a] (GT1) ELECTRON (GT1) LONESTAR (GT1) SYNERGY[b]
		12 weeks	ERADICATE* (GT1) ELECTRON (GT1) SYNERGY[b] ION-1[a] (GT1)	12 and 24 weeks	ION-2[a] (GT1)
	Compensated cirrhosis	12 weeks	ION-3[a] (GT1)	12 weeks	LONESTAR (GT1)
		12 and 24 weeks	ION-1[a] (GT1)	12 and 24 weeks	SIRIUS (GT1) ION-2[a] (GT1) ELECTRON (GT1)
	Decompensated cirrhosis or pre/post transplant	24 weeks + RBV	SOLAR-1 (GT1) ELECTRON-2[a] (GT1; 12 week regimens only)	24 weeks + RBV	SOLAR-1 (GT1)
GT3	**No cirrhosis**	Company assumed 12 weeks + RBV	ELECTRON-2[a] (12 week regimens only)	24 weeks + RBV	ELECTRON-2[a] (12 week regimens only)
	Cirrhosis	24 weeks + RBV		24 weeks + RBV	

LDV/SOF: Ledipasvir-sofosbuvir; GT: Genotype; RBV: Ribavirin; (GT1): Only genotype 1 included in trial; *People with HIV/HCV co-infection included in trial; [a]This study informed the company's economic model. [b]This study only informed the company's economic model in a scenario analysis.

ERG comments

4.2 The Evidence Review Group (ERG) considered that it was unlikely that any studies of ledipasvir-sofosbuvir relevant to this appraisal were missed. However, the ERG noted that there were some major gaps in the reporting of the searches conducted by the company, and the company's searches for comparator and adverse events were not systematic.

4.3 The ERG stated that although the 3 phase III studies were open-label, they were generally at low risk of bias. It commented that the phase II studies had small sample sizes but provided data consistent with the phase III trials.

4.4 The ERG noted that historical controls were used in the absence of a control arm. It commented that there are limitations with using historical controls, particularly when there are changes in the definition of, or diagnostic methods used to detect, the condition under consideration. However, the ERG stated this was unlikely to be an issue for hepatitis C, and that their clinical expert advised that the use of historical controls in this context was considered to be reasonable.

Genotype 1

Treatment-naïve population

4.5 ION-1 was an international (99 centres in Europe and USA; including 7 centres in England), open-label, non-RCT of 865 adults with treatment naive HCV genotype 1. The treatment groups that supported the marketing authorisation in the UK were:

- ledipasvir–sofosbuvir once daily for 12 weeks (n=214)
- ledipasvir–sofosbuvir once daily for 24 weeks (n=217).

Randomisation was stratified by HCV genotype 1 subtype (1a or 1b) and the presence or absence of cirrhosis. The company stated that the baseline patient characteristics were generally balanced among the 4 treatment groups. Patients were assessed up to 24 weeks after treatment stopped.

4.6 ION-3 was a multicentre (59 centres in USA), open-label, non-RCT in 647 adults with treatment naive HCV genotype 1 without cirrhosis. The treatment arms that supported the marketing authorisation in the UK were:

- ledipasvir–sofosbuvir for 8 weeks (n=215)
- ledipasvir–sofosbuvir for 12 weeks (n=216).

Randomisation was stratified by HCV genotype 1 subtype (1a or 1b). The company stated that the baseline patient characteristics were generally

balanced across the treatment groups. Patients were assessed up to 24 weeks after treatment stopped.

4.7 The primary outcome measure of both ION-1 and ION-3 was sustained virological response weeks after stopping treatment (SVR12). A 'full analysis set' population was used to analyse the efficacy outcomes for both trials (that is, people who were randomised into the study and received at least 1 dose). The results were compared with an 'adjusted' historical control rate of 60% for SVR12 with peginterferon alfa 2a and ribavirin taken from the phase III telaprevir (ADVANCE) and boceprevir (SPRINT2) studies. On both studies, each treatment group had a SVR12 superior to the historical rate of 60% (p<0.001 for all comparisons). The results relating to the populations of interest are presented in table 5. All patients who had SVR12 also had SVR24 in both trials.

Table 5 SVR data for licensed regimens (table 47, page 133 of company's submission)

Population		Treatment naive			Treatment experienced		
		LDV/SOF regimen	**Evidence source**	**SVR12 (%)**	**LDV/SOF regimen**	**Evidence source**	**SVR12 (%)**
GT 1 or 4	**No cirrhosis**	8 weeks	ION-3[a] (GT1)	96.7 (119/123)	12 weeks	ION-2[a] (GT1)	95.4 (83/87)
		12 weeks	ION-3[a] (GT1)	96.3 (208/216)			
			ION-1[a] (GT1)	99.4 (179/180)	24 weeks		98.9 (86/87)
	Compensated Cirrhosis	12 weeks	ION-1[a] (GT1)	94.1 (32/34)	12 weeks	ION-2[a] (GT1)	86.4 (19/22)
		24 weeks		97.0 (32/33)	24 weeks	ION-2[a] (GT1) SIRIUS	100 (22/22) 97 (75/77)
	Decompensated cirrhosis or pre/ post-transplant	24 weeks + RBV	SOLAR-1 (GT1)	Decompensated cirrhosis (treatment naive and experienced)			[redacted]
				Post-transplant, no cirrhosis (treatment naive and experienced)			[redacted]
				Post-transplant, compensated cirrhosis (treatment naive and experienced)			[redacted]
				Post-transplant, decompensated cirrhosis (treatment naive and experienced)			[redacted]
GT3	**No cirrhosis**	Company assumed 12 weeks + RBV	ELECTRON-2[a] (12 weeks only)	100 (21/21)	24 weeks + RBV	ELECTRON-2[a] (12 weeks only)	SVR4: 89 (25/28)*
	Cirrhosis	24 weeks + RBV		100 (5/5)	24 weeks + RBV		SVR4: 77 (17/22)*

LDV/SOF: Ledipasvir-sofosbuvir; GT: Genotype; RBV: ribavirin; (GT1): Only genotype 1 included in trial; [a]This study informed the company's economic model.

* The company clarification response presented SVR12 data for people with treatment-experienced HCV genotype 3 (82%; 41/50), but did not present the SVR12 data by cirrhotic status.

4.8 Pre-specified subgroup analyses of ION-1 were undertaken based on patient characteristics and the randomisation strata. The company stated that high SVR12 rates were observed in people with characteristics historically associated with poor response including: cirrhosis, genotype 1a (which is considered harder to treat than 1b), non-CC IL28B allele, and specific ethic groups. For further information about the subgroup analyses undertaken by the company, see pages 72 and 79–80 of the company's submission.

4.9 Pre-specified subgroup analyses of ION-3 were undertaken based on patient characteristics and the randomisation strata. The SVR12 rates in people who received ledipasvir–sofosbuvir for 8 weeks ranged from 89–100% in all subgroups. The company commented that SVR12 in pre-specified subgroups, including those historically associated with poor response to interferon treatment, were similar to those observed in the overall population, across the treatment groups. The company also conducted a posthoc analysis that analysed relapse rates associated with baseline HCV ribonucleic acid (RNA). This analysis showed that:

- **For people with baseline HCV RNA less than 6 million IU/ml** (viral load, or the number of virus particles in the blood; a viral load less than 6 million IU/ml has been linked to better response to treatment) relapse rates were similar between the 8- (2 of 121 patients; 2%) and 12-week (2 of 128 patients; 2%) ledipasvir–sofosbuvir treatment groups.
- **For people with baseline HCV RNA 6 million IU/ml or more**, the relapse rates were different between the 8- (9 of 92 patients; 10%) and 12-week (1 of 82 patients; 1%) ledipasvir–sofosbuvir treatment groups.

The company concluded that these data supported the use of 8-week ledipasvir–sofosbuvir in treatment naïve patients with HCV genotype 1 without cirrhosis and a baseline viral load less than 6 million IU/ml. For

further information about the subgroup analyses undertaken by the company, see pages 72, 84–85 and 95 of the company's submission.

Treatment-experienced population

4.10 ION-2 was a multicentre (64 centres in USA), open-label phase III non-RCT in 440 adults with previously treated HCV genotype 1. The treatment arms that supported the marketing authorisation in the UK were:

- ledipasvir–sofosbuvir for 12 weeks (n=109)
- ledipasvir–sofosbuvir for 24 weeks (n=109)

Randomisation was stratified by HCV genotype 1 subtype (1a or 1b), the presence or absence of cirrhosis, and response to previous treatment (relapse or virologic breakthrough versus no response). The company stated that the baseline patient characteristics were generally balanced across the treatment groups, but there were differences in age between treatment groups (p=0.02). Patients were assessed up to 24 weeks after treatment stopped.

4.11 The primary outcome measure of ION-2 was SVR12. A 'full analysis set' population was used to analyse the efficacy outcomes. The results were compared with an 'adjusted' historical control rate of 25% for SVR12 in a previously treated population, based on data from the phase III telaprevir (REALIZE) and boceprevir (RESPOND-2) studies. Each treatment group had a higher SVR12 than the historical rate of 25% (p<0.001 for all comparisons). The results relating to the populations of interest are presented in table 5. All patients who had SVR12 also had a SVR24.

4.12 Pre-specified subgroup analyses were undertaken based on patient characteristics and the randomisation strata. The company stated that high SVR12 rates were observed independent of HCV genotype 1 subtype, previous treatment option and response to previous treatment. The company highlighted that in people with cirrhosis there was a difference (p=0.007) in SVR12 between the 12-week (82–86%) and 24-week (100%) regimens (of note, both of these treatment durations are

specified in the marketing authorisation). However, the company stated this observation should be considered preliminary because ION-2 was not powered for intergroup comparisons. For people previously treated with peginterferon plus ribavirin, SVR12 ranged between 93.0% and 100.0%. For people previously treated with a protease inhibitor plus peginterferon and ribavirin, the SVR12 ranged between 93.9% and 98%. For further information about the subgroup analyses undertaken by the company, please see pages 72 and 91–93 of the company's submission.

Genotype 3

4.13 ELECTRON-2 is an ongoing, multicentre (2 centres in New Zealand), open-label, non-RCT in adults with HCV genotypes 1, 3 and 6. It included the following treatment groups, relevant to this appraisal:

- People with HCV genotype 3 (with or without cirrhosis) who were treatment naïve received ledipasvir–sofosbuvir plus ribavirin for 12 weeks (n=26)
- People with previously treated HCV genotype 3 (with or without cirrhosis) received ledipasvir–sofosbuvir plus ribavirin for 12 weeks (n=50).

The primary outcome was SVR12. However, at the time of evidence submission the company only had data from an interim analysis for the treatment-experienced HCV genotype 3 population that reported SVR4. In the company's clarification response, SVR12 data was available for the treatment experienced HCV genotype 3 population (but the company did not present the SVR12 data by cirrhotic status). A 'full analysis set' population was used to analyse the efficacy outcomes. No statistical hypothesis testing was performed. The results for each population (with or without cirrhosis) are presented in table 5.

4.14 Ledipasvir–sofosbuvir with or without ribavirin for 24 weeks was not studied in ELECTRON-2. However, because of the limited clinical data available for the genotype 3 population, ledipasvir–sofosbuvir's summary

of product characteristics recommends that 24 weeks of therapy (combined with ribavirin) is advised in 'all patients with treatment-experienced HCV genotype 3' and 'those patients with treatment-naïve HCV genotype 3 with cirrhosis', to be conservative. No recommendations regarding treatment duration and use of ribavirin are presented in ledipasvir–sofosbuvir's summary of product characteristics for patients with treatment naïve genotype 3 without cirrhosis but the company has included this population in its economic model (assuming a 12-week treatment duration). For further information around the ELECTRON-2 study, please see pages 98–103 of the company's submission.

Genotype 4

4.15 The company stated that only limited data are currently available in people with HCV genotype 4 (▇), from 2 studies:

- ION-1, 2 people with HCV genotype 4 were enrolled; 1 received ledipasvir–sofosbuvir for 12 weeks and 1 received ledipasvir–sofosbuvir plus ribavirin for 24 weeks. Both patients had SVR12.
- SYNERGY, was a multicentre, open-label phase II non-RCT evaluating ledipasvir–sofosbuvir for 12 weeks in adults with HCV genotypes 1 and 4. Twenty one patients with HCV genotype 4 had ledipasvir–sofosbuvir, but the company stated data were only available for ▇ of these patients. ▇ patients had SVR12.

The company stated that HCV genotype 1 and 4 infections respond to HCV treatments similarly and therefore it was recommended in ledipasvir–sofosbuvir's summary of product characteristics that these genotypes are treated similarly.

People with advanced liver disease and after liver transplantation

4.16 SOLAR-1 is an ongoing multicentre (30 centres in USA), open-label, phase II, non-RCT in adults with HCV genotypes 1 and 4, and either advanced liver disease or liver transplantation. People were randomised to receive ledipasvir–sofosbuvir plus ribavirin for 12 weeks (n=▇;

regimen does not have a marketing authorisation in the UK) or ledipasvir–sofosbuvir plus ribavirin for 24 weeks (n=[redacted]). At time of original submission, data was only available for sustained virological response at 4 weeks (SVR4). The results are presented in table 5. For further details around SOLAR-1, please see pages 106–108 of the company's submission.

People co-infected with HIV

4.17 ERADICATE is an ongoing single centre (USA), open-label, phase II, study in adults with treatment naive HCV genotype 1 co-infected with HIV and without cirrhosis. People were allocated into 2 treatment groups of ledipasvir–sofosbuvir for 12 weeks based on whether or not they had received antiretroviral therapy for their HIV. SVR12 were reported in 49 of 50 patients (98%, 95% CI not reported). For antiretroviral naive patients, sustained virological response at 12 weeks were reported in 13 out of 13 patients (100%, 95% CI 75 to 100%). For antiretroviral experienced patients, sustained virological response at 12 weeks were reported in 36 out of 37 patients (97%, 95% CI 89 to 100%). For further details around ERADICATE, please see pages 104–106 of the company's submission.

4.18 Previous Technology Appraisals for hepatitis C have considered the HIV population in the absence of sufficient data, and made the following conclusions (please note these have not yet been published):

- **Simeprevir FAD (ID668):** "the Committee concluded that it would not need to make separate recommendations for people with HIV."
- **Sofosbuvir FAD (ID654):** "On balance, the Committee concluded that, based on the evidence presented and considered for this population, it was reasonable to include the group of people co-infected with HCV and HIV in the recommendations for the mono-infected group. However, the Committee agreed with the ERG that there were legitimate concerns about the modelling for the HIV and HCV co-infected group, and that future economic analyses should be presented separately for this population.

ERG comments

4.19 The ERG's clinical experts suggested that the disease diagnostic criteria and SVR outcomes used in the studies were representative of clinical practice in England. The ERG commented that the use of SVR12 was appropriate because there is a high concordance between SVR12 and SVR24. However, it noted SVR4 is not a suitable surrogate endpoint for cure because there is a chance of relapse between 4 and 12 weeks.

4.20 The ERG highlighted that the results of the company's subgroups analyses for factors not stratified at randomisation were potentially biased because the respective subpopulations may not be well-balanced across treatment arms.

Development of resistance to ledipasvir-sofosbuvir

4.21 No evidence was identified to suggest ledipasvir-sofosbuvir resistant variants were developed during treatment, for any genotype. For further information around development to resistance data collected in the ION studies, please see pages 81, 86 and 94 of the company's submission.

ERG comments

4.22 The ERG's clinical expert considered that the term resistance may be misleading because "resistant associated variants" at baseline do not predict response of HCV to treatment. The ERG's clinical expert explained that if treatment of HCV does 'fail', a person's HCV may still respond when given the same drugs again, for longer. The ERG were not aware of any variants that were resistant to both sofosbuvir and ledipasvir, after treatment with sofosbuvir and ledipasvir.

Health-related quality of life

4.23 Four health-related quality-of-life questionnaires were measured in ION-1, ION-2 and ION-3: Short Form 3 Health Survey (SF-36), Chronic Liver Disease Questionnaire (CLDQ-HCV), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and the Work Productivity and Activity

Impairment Questionnaire (WPAI). Mean responses to these 4 questionnaires suggested that ledipasvir–sofosbuvir alone does not generally worsen a patients' health-related quality-of-life between baseline and end of treatment but a patient's health-related quality of life reduces with addition of ribavirin. The mean responses of these 4 questionnaires generally improved from the end of treatment to 12 weeks after treatment. For further information around the health-related quality-of-life results reported for these studies, please see pages 81–82 (table 23), 101–102 (table 30) and pages 86–88 (table 26) of the company's submission.

ERG comments

4.24 The ERG stated that because the ION studies were open-label, subjective health-related quality-of-life outcomes were subject to bias.

Adverse effects of treatment

4.25 The company presented data on adverse reactions from ION-1, ION-2 and ION-3. Across all the treatment groups in these studies, at least 67% of patients had at least one adverse reaction (higher rates were generally observed in treatment groups of longer duration and those including ribavirin). The most common adverse reactions in people receiving ledipasvir-sofosbuvir (with or without ribavirin) were fatigue, headache, insomnia and nausea. However, people taking ledipasvir-sofosbuvir with ribavirin had higher rates of adverse reactions that are known to be associated with ribavirin therapy, compared with people taking ledipasvir-sofosbuvir without ribavirin (including anaemia, cough, fatigue, headache, insomnia, irritability, nausea, pruritus and rash). Most adverse reactions were mild to moderate in severity (grade 1 or 2, the range reported across all treatment groups was 90.2% to >99%). Ten of 865 people in ION-1 stopped treatment because of adverse reactions (all 10 patients had SVR12), no one in ION-2, and 3 of 647 in ION-3 (the number of these achieving SVR12 was not reported by the company). No deaths were reported in the studies. For further information around the adverse

reactions for ledipasvir-sofosbuvir with or without ribavirin, please see pages 124–131 of the company's submission.

ERG comments

4.26 No further comments.

Meta-analysis and mixed treatment comparison

4.27 The company did not conduct a meta-analysis of the available clinical studies.

4.28 The company did not conduct a mixed treatment comparison to compare the relative effectiveness of ledipasvir–sofosbuvir with the comparators listed in the scope of the appraisal. It stated that it was not possible because the evidence for ledipasvir–sofosbuvir came from studies evaluating different treatment regimens and without control groups. Therefore it could not identify a common comparator that would allow it to create a network. The company commented that while the lack of a mixed treatment comparison may be considered a limitation:

- SVR is a hard and objective endpoint consistently measured across all studies, and is not subject to bias from the patient or investigator
- the baseline characteristics of the study populations were similar except for a higher proportion of people with cirrhosis and HCV genotype 1 subtype 1a in the ledipasvir–sofosbuvir studies, both of which the company considered are associated with numerically lower SVR rates.

For further details around the lack of mixed treatment comparison, please see pages 114–123 of the company's submission.

ERG comments

4.29 The ERG commented that ION-1 (people with cirrhosis) and ION-3 would create a network of evidence, albeit without any links to the comparator treatments. The ERG considered it would have been useful for the company to:

- analyse the 6 treatment arms from these studies and estimate the joint posterior distribution of treatment effect (for example, odds ratios), because it is reasonable to assume that the effectiveness of ledipasvir-sofosbuvir depends on treatment duration
- synthesise the evidence for each comparator (for example, the company acknowledged that a meta-analysis was possible for estimating the SVR rates for boceprevir, pegylated interferon plus ribavirin, simeprevir and telaprevirin in people with HCV genotype 1).

4.30 The ERG commented that the efficacy of ledipasvir-sofosbuvir does not appear to depend on the patient characteristics prespecified in the company's subgroup analyses. However, given several patient characteristics were prespecified, it seems reasonable to assume that these may affect the efficacy of some comparators. The ERG concluded that in a given study SVR rates for comparator treatments are much more likely to vary compared with SVR rates for ledipasvir-sofosbuvir (that is, using SVR rates from a single study for comparators introduces more uncertainty than using SVR rates for ledipasvir-sofosbuvir from a single study).

4.31 The ERG's clinical experts stated that HCV genotype 1 subtype 1a, baseline viral load and IL28B CC genotype had less impact on response to treatment with ledipasvir-sofosbuvir compared with current treatment options. The ERG's clinical experts advised that there was unlikely to be any meaningful differences in baseline characteristics between the populations of the ledipasvir-sofosbuvir and comparator studies that would significantly impact on outcomes. The ERG concluded that although baseline characteristics appear similar between intervention and comparator trials, the possibility that other factors differed across trials cannot be ruled out (see section 5.14).

5 Cost-effectiveness evidence

Model structure

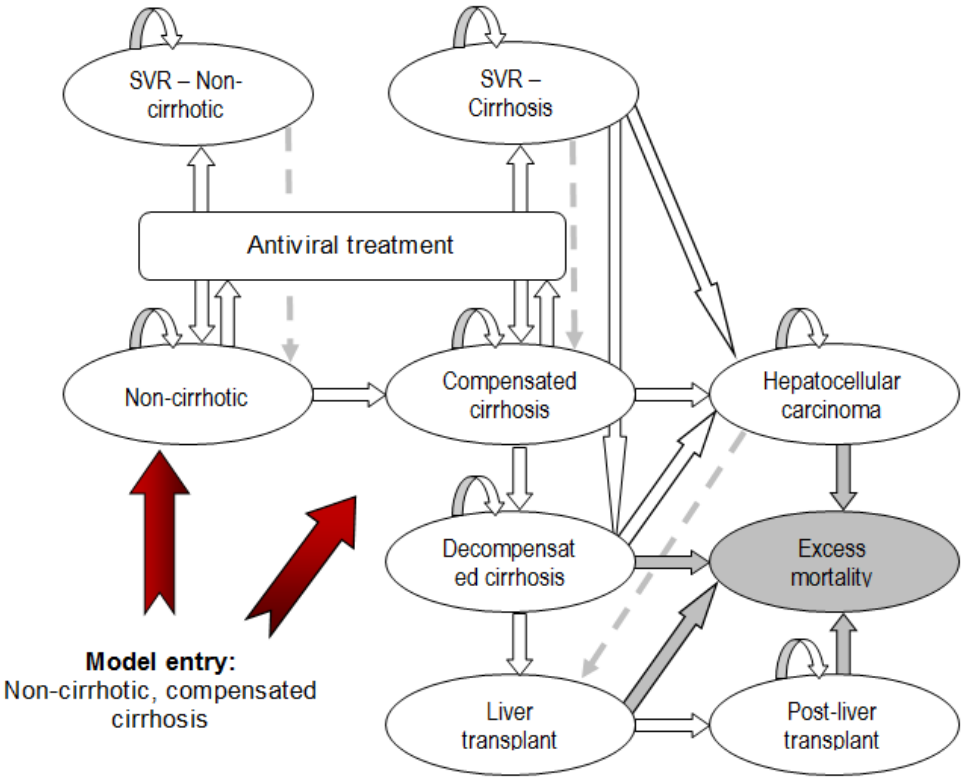
5.1 The company submitted a Markov state-transition model that reflected the natural history of chronic hepatitis C, and compared ledipasvir-sofosbuvir (with or without ribavirin) with the comparators defined in the final scope of the appraisal (see table 6). The company's economic model had 9 states, according to disease stage and treatment response (see Figure 1). The same model structure was used for all patients irrespective of HCV genotype or treatment experience. The company used a monthly cycle length for the first 18 cycles, 3-monthly until year 2 and yearly thereafter. The company conducted the economic analysis from an NHS and personal social services perspective and chose a lifetime time horizon (from age 40 [treatment-naive] or 45 [treatment-experienced] years until patients reached 100 years). Costs and health effects were discounted at an annual rate of 3.5% and a half-cycle correction was applied from year 3.

Table 6 Comparisons considered by company (table 30, page 94 of the ERG report)

Treatment option	Subgroup						
	GT1 TN	GT4 TN	GT1/4 TE	GT3 TN	GT3 TN with compensated cirrhosis	GT3 TE IFN-ineligible	GT3 TE IFN-ineligible with compensated cirrhosis
LDV/SOF	✓	✓	✓	×	×	×	×
LDV/SOF+RBV	×	×	×	✓	✓	✓	✓
PEG-IFN2a+RBV	✓	✓	✓	✓	×	×	×
SMV+ PEG-IFN2a+RBV	✓	✓	✓	×	×	×	×
TVR+PEG-IFN2a+RBV	✓	×	✓	×	×	×	×
BOC+PEG-IFN2b+RBV	✓	×	✓	×	×	×	×
SOF+ PEG-IFN2a+RBV	✓	✓	✓	×	✓	×	×
SOF+SMV	✓	✓	✓	×	×	×	×
SOF+RBV	×	×	×	×	✓	×	✓
No treatment	✓	✓	✓	✓	×	✓	×

Abbreviations: BOC, boceprevir; GT, genotype; IFN, interferon; LDV, ledipasvir; PEG-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; TN, treatment-naïve; TE, treatment-experienced.

Figure 1 Company's model schematic (Figure 12, page 155 of company's submission)



5.2 The cost-effectiveness of ledipasvir–sofosbuvir was assessed in populations defined by HCV genotype which included those with cirrhosis (but excluded HIV co-infection):

- treatment-naive HCV genotype 1
- treatment-naive HCV genotype 4
- treatment-experienced HCV genotypes 1 and 4
- treatment-naive HCV genotype 3
- treatment-experienced HCV genotype 3 unsuitable for interferon therapy.

The company did not include people with treatment-experienced HCV genotype 3 suitable for interferon therapy because it considered it was unlikely that 24-week ledipasvir–sofosbuvir would be cost-effective compared with 12-week sofosbuvir plus peginterferon alfa and ribavirin (given higher treatment costs with ledipasvir-sofosbuvir and no evidence of additional efficacy).

ERG comments

5.3 The ERG considered that the company's model structure was broadly appropriate and in line with previous economic analyses of treatments for hepatitis C.

5.4 The ERG's clinical experts noted that people with HCV genotype 3 and cirrhosis receive active treatment because of disease severity and therefore considered that the company's exclusion of 'no treatment' as a comparator for these populations was appropriate.

5.5 The ERG stated that boceprevir and telaprevir do not have a marketing authorisation in the UK for treating HCV genotype 4 and should not be considered as comparators for this population.

Model inputs

5.6 The company used patient characteristics from the HCV UK research database to inform the mean age, the proportion with cirrhosis, and weight of the population entering the model. The company chose transition probabilities for disease progression from 2 publications used in recent NICE technology appraisals of treatments for HCV (Hartwell et al. [2011] and Shepherd et al. [2007]), and Grishchenko et al. (2009; a large sample of people with HCV who attended only non-tertiary centres in the UK). Transitions probabilities from the non-cirrhotic to cirrhotic health state varied according to age and genotype according to published literature. Age- and gender-specific general population mortality rates were also applied to each health state in the company's model.

5.7 Treatment-effect data for ledipasvir-sofosbuvir were based on SVR12 from the relevant ION studies and ELECTRON-2 (except for the genotype 3 treatment-experienced population for which only SVR4 data were available), see table 7. Treatment-effect data for the comparators were taken from publications or the summary of product characteristics. In the absence of a mixed treatment comparison (see section 4.28), the estimates of the relative effectiveness of ledipasvir–sofosbuvir with the

comparators were based on naïve indirect comparisons. In its base case analysis the company used the ledipasvir–sofosbuvir data from the genotype 1 population for the analysis of the genotype 4 population because:

- the data available for ledipasvir–sofosbuvir in genotype 4 HCV was limited ([redacted])
- ledipasvir–sofosbuvir's summary product of characteristics states that genotype 1 and 4 infections are generally treated in the same way.

The company commented that cost-effectiveness analysis for the treatment-experienced population considered genotypes 1 and 4 HCV together. However, for the treatment-naïve population, 8-weeks of ledipasvir–sofosbuvir is only recommended for treatment-naïve genotype 1 without cirrhosis (genotype 4 patients are treated with 12-weeks of ledipasvir–sofosbuvir only) and therefore separate analyses were conducted for genotypes 1 and 4 HCV in this population. The company explored genotype 4 specific data in a scenario analysis. If more than 1 treatment duration was recommended for a given genotype in ledipasvir-sofosbuvir's summary of product characteristics (based on certain patient or clinical characteristics), the company used a weighted-average of the efficacy and treatment duration data in the cost-effectiveness analysis (rather than presenting the results for each regimen of ledipasvir-sofosbuvir separately). For further information around the clinical inputs used in the company's economic model, please see pages 161–177 of the company's submission.

Table 7 Summary of genotype specific SVR rates (%) used in economic model (table 33, page 101 of ERG report)

Treatment	SVR(%) non-cirrhotic patients	SVR(%) for cirrhotic patients	Source
HCV genotype 1, treatment-naive			
LDV/SOF	97.0%	94.3%	ION-1 and *post hoc* analysis of ION-3
SOF+PEG-IFN2a+ RBV	91.7%	80.8%	NEUTRINO
SMV+PEG-IFN2a+RBV	82.0%	60.4%	Pooled data from studies QUEST and QUEST 2, taken from Simeprevir SPC 2014
TVR+PEG-IFN2a+RBV	77.3%	53.4%	ADVANCE, ILLUMINATE and Grishchenko *et al*, 2009
BOC+PEG-IFN2b+RBV	64.1%	55.0%	SPRINT-2
PEG-IFN2a+RBV	43.6%	23.6%	IDEAL
SMV+SOF	92.9%	92.9%	COSMOS
HCV genotype 4, treatment-naive			
LDV/SOF	97.7%	94.3%	ION-1 and *post hoc* analysis of ION-3
SOF+PEG-IFN2a+ RBV	91.7%	80.8%	NEUTRINO
SMV+PEG-IFN2a+RBV	82.0%	60.4%	Pooled data from studies QUEST and QUEST 2, taken from Simeprevir SPC 2014
PEG-IFN2a+RBV	43.6%	23.6%	IDEAL
SMV+SOF	92.9%	92.9%	COSMOS
HCV genotype 1 and genotype 4, treatment-experienced			
LDV/SOF	95.6%	89.8%	ION-2
SOF+PEG-IFN2a+ RBV	74.0%	74.0%	Pol *et al*, 2014
SMV+PEG-IFN2a+RBV	76.5%	66.7%	Pooled data from studies PROMISE and ASPIRE, taken from Simeprevir SPC 2014
TVR+PEG-IFN2a+RBV	72.2%	47.2%	REALIZE, taken from Telaprevir SmPC 2014
BOC+PEG-IFN2b+RBV	64.4%	35.3%	Bacon BR *et al*, 2011
PEG-IFN2a+RBV	17.6%	10.0%	REALIZE, taken from Telaprevir SmPC, 2014
SMV+SOF	92.9%	92.9%	COSMOS
HCV genotype 3, treatment-naive			
LDV/SOF	100.0%	100.0%	ELECTRON-2
SOF+PEG-IFN2a+ RBV	97.4%	83.3%	ELECTRON and PROTON
SOF+RBV (24 wks)	92.3%	-	VALENCE
PEG-IFN2a+RBV (24 wks)	71.2%	29.7%	FISSION
HCV genotype 3, treatment-experienced			
LDV/SOF	89.3%	77.3%	ELECTRON-2
SOF+RBV (24 wks)	87.0%	60.0%	VALENCE

Abbreviations: BOC, boceprevir; GT, genotype; IFN, interferon; LDV, ledipasvir; PEG-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; TN, treatment-naïve; TE, treatment-experienced; wks, weeks.

5.8 Resource use and costs in the company's economic model included those related to treatment (drug and administration), monitoring during treatment, adverse reactions and for each health-state (that is, monitoring of patients after treatment has stopped). Drug costs were based on the list prices in the British National Formulary (August 2014). Monitoring costs were based on NHS Reference Costs, published literature or company's clinical expert opinion (if a published source was unavailable). An additional cost for an 'initial patient evaluation' was included for treatment-naïve patients but the monitoring requirements for patients treated with interferon-containing regimens or interferon-free regimens did not differ. Treatment durations were also used to estimate drug and monitoring costs, and the proportion of patients on a given treatment duration were based on the company's clinical expert opinion. Costs for each of the health states in the company's economic model were taken from the published literature (Grishchenko et al. [2009], Longworth et al. [2014], Wright et al. [2006]) and inflated to 2012-13 prices. Adverse reaction costs were taken from the British National Formulary and NHS reference costs. The company assumed that the cost of each adverse reaction also depended on whether the reaction is actively treated in outpatient setting, by a hospital registrar or specialist. For further information around the costs and healthcare resources included in the company's economic model, please see pages 186–199 of the company's submission.

Table 8 Health state costs (table 81, page 195 of company's submission)

Health state	Cost per annum	Source
Non-cirrhotic, NT†	£363	Calculation†
Non-cirrhotic, mild, NT	£187	Wright et al. (2006)
Non-cirrhotic, moderate, NT	£988	Wright et al. (2006)
Non-cirrhotic, SVR†	£245	
Non-cirrhotic, SVR (mild)	£234	Grishchenko et al. (2009)
Non-cirrhotic SVR (moderate)	£286	Grishchenko et al. (2009)
Compensated cirrhosis, NT	£1,540	Wright et al. (2006)
Compensated cirrhosis, SVR	£506	Grishchenko et al. (2009)
Decompensated cirrhosis	£12,339	Wright et al. (2006)

Health state	Cost per annum	Source
HCC	£10,994	Wright et al. (2006)
Liver transplant	£83,505	Longworth et al. (2014)
Post-liver transplant		
Follow-up phase (0-12 months)	£27,512	Longworth et al. (2014)
Follow-up phase (12-24 months)	£4,111	Longworth et al. (2014)

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.

5.9 To estimate the health-related quality of life, the company used EQ-5D utility values from Wright et al. (2006) that were based on a UK trial of mild chronic hepatitis C (see table 9). For patients who had SVR, the company's economic model included a utility benefit of 0.04 taken from Vera-Llonch et al. (2013). The company's economic model also captured the health-related quality of life of patients while 'on-treatment' (independent of non-cirrhotic or cirrhotic disease). The company assumed that the health-related quality of life of patients treated with ledipasvir-sofosbuvir without ribavirin did not change while 'on-treatment' (as supported by data from health-related quality of life instruments collected in ION studies, see section 4.23), but reduced in patients treated with regimens that included ribavirin or interferon therapy. The company stated that these 'on-treatment' decrements were assumed to include any impact on health-related quality of life from treatment-related adverse reactions. For further information about the health-related related quality of life values used in the company's economic model, please see pages 179–186 of the company's submission.

Table 9 Summary of utility values (table 36, page 108 of the ERG report)

Health state	Utility value	Source
SVR (utility increment)	0.04	Vera-Llonch *et al* (US EQ-5D tariff)
After treatment at non-cirrhotic stage	0.79	Calculation (baseline utility+SVR increment)
After treatment at cirrhotic stage	0.59	Calculation (baseline utility+SVR increment)
Baseline – non-cirrhotic	0.75	Wright *et al* (UK mild HCV trial, UK EQ-5D tariff)
Baseline – compensated cirrhosis	0.55	
Decompensated cirrhosis	0.45	
Hepatocellular carcinoma	0.45	
Liver transplant	0.45	
Post-liver transplant	0.67	

ERG comments

5.10 The ERG commented that it was unclear whether the baseline proportion of patients with cirrhosis used in the company's model is representative of the HCV population in England.

5.11 The ERG commented that the details relating to how transition probabilities from the non-cirrhotic to compensated cirrhosis health states had been estimated were insufficient for the ERG to critique the robustness of the approach. The ERG highlighted that the transition probabilities from compensated or decompensated cirrhosis to hepatocellular carcinoma were considerably higher for this appraisal (0.0631) than those used by the same company in its economic model for the sofosbuvir appraisal (0.014; ID654).

5.12 The ERG commented that the company's assumption that patients cannot die or experience disease progression until 12–24 weeks after completing treatment lack credibility. However, the ERG acknowledged that the size of bias was likely to be small and would favour treatment options given over longer treatment durations.

5.13 The ERG highlighted that the use of SVR4 data for the HCV genotype 3 population is likely to overestimate the effectiveness of ledipasvir-sofosbuvir (see section 4.19).

5.14 The ERG noted that the selection criteria for comparator SVR rates in the company's economic model was not clear, and that the company's submission did not provide any indication of the range of SVR estimates possible for the comparators. The ERG stated that because the SVR rates for comparators were estimated from single studies, rather than a meta-analysis of all relevant studies, it was not clear whether they were conservative or optimistic rates. The ERG commented that the use of naïve indirect comparisons breaks randomisation and fails to fully reflect uncertainty around the SVR rates. The ERG concluded that the cost-effectiveness results may be biased by the selection of individual studies and confounded by the impact of other factors such as differences in study design, patient characteristics and trial protocols.

5.15 The ERG stated that the results should be interpreted with caution when using the company's weighted-average approach (that is, the company included more than 1 treatment duration of ledipasvir-sofosbuvir within its base case analysis of some populations listed in section 5.2 [for example, treatment-naïve HCV genotype 1], and therefore the efficacy and cost inputs used in the model were dependent on the assumed proportion of patients receiving each treatment duration). The ERG also noted that the company's submission did not explicitly state the treatment durations estimated from the company's weighted-average approach (see table 10). The ERG concluded that using cost-effectiveness results dependent on the company's weighted-average approach may result in the recommendation of some options which represent an efficient use of NHS resources and other options which represent an inefficient use of NHS resources. Particularly when taking into account that there are clear clinical reasons why specified treatment durations of ledipasvir-sofosbuvir should be considered for specific subgroups of patients.

Table 10 Weighted treatment durations (weeks) for each population included in company's model (table 41, page 113 ERG report)

Regimen	Treatment-naïve		Treatment-experienced	Source
	Non-cirrhotic	Cirrhotic	Non-cirrhotic & cirrhotic	
Genotype 1/4				
LDV/SOF	8.84	12.6	13.10	ION-1 and *post hoc* analysis of ION-3
SOF+PEG-IFN2a+ RBV	11.84	11.84	11.84	NEUTRINO
SMV+PEG-IFN2a+RBV	23.20	23.20	45.60	Pooled data from studies QUEST and QUEST 2, taken from Simeprevir SPC 2014
TVR+PEG-IFN2a+RBV	26.94	26.94	38.99	ADVANCE, ILLUMINATE and Grishchenko *et al*, 2009
BOC+PEG-IFN2b+RBV	34.17	42.98	42.52	SPRINT-2
PEG-IFN2a+RBV	38.40	38.40	30.30	IDEAL
SMV+SOF	12.00	12.00	12.00	COSMOS
Genotype 3				
LDV/SOF+RBV	15.00		24.00	ELECTRON-2
SOF+PEG-IFN2a+RBV	12.00		11.08	ELECTRON and PROTON
SOF+RBV	23.96		23.96	VALENCE
PEG-IFN2a+RBV	21.00		39.16	FISSION

5.16 The ERG highlighted that for people with treatment-naïve HCV genotype 1 the company used a 79% to 21% spilt between the 8-week and 12-week ledipasvir-sofosbuvir regimens because data from the HCV Research UK database showed 79% of this population had a pre-treatment viral load less than 6 million IU/ml (based on the company's posthoc subgroup analysis, the company stated this group is likely to receive a 8-week regimen; see section 4.9). However, the ERG considered that this criterion is not consistent with the recommendations for this treatment indication in ledipasvir-sofosbuvir's marketing authorisation (see table 2) and is based on a posthoc analysis of the ION-3 study.

5.17 The ERG considered that the company did not sufficiently explain how choices were made in the selection of costs and utility values used in its economic model, or did the company specify the source used for resource use estimates.

5.18 The ERG commented that the publication (Vera-Llonch et al. [2013]) used by the company to reflect the utility gain associated with achieving SVR was derived using the US EQ-5D tariff (0.04). It suggested that the utility gain associated with achieving SVR taken from Wright et al. (2006) which reflect the preferences of the general public in England (that is, using UK EQ-5D tariff, 0.05) would be more appropriate. The ERG stated that the 'on-treatment' decrements used by the company were applied to the entire cycle in the 'on-treatment' health state rather than the duration of treatment but the ERG noted that the impact of this bias was likely to be small.

5.19 The ERG highlighted that health effects on individuals with HCV (that is, potential for re-infection) and health effects between individuals (that is, onward transmission) are excluded from the company's model. The ERG explained that:

- Excluding re-infection is likely to overestimate the health benefits of more effective treatments while underestimating their costs (because patient may subsequently need re-treatment)
- Excluding onward transmission may underestimate the health benefits of more effective treatments.

The ERG acknowledged that models used to inform previous NICE technology appraisals in HCV did not include such health effects and exploring this issue would require the development of a different model structure. However, it concluded it was concerned that the company's results were potentially unreliable because the impact on the cost-effectiveness results from these exclusions was unclear.

Company's base case results

5.20 Please see table 11 for a summary of the company's base case cost-effectiveness results for ledipasvir-sofosbuvir compared with the comparators for all patient populations (based on deterministic analyses).

The company's cost-effectiveness results by population and ranked by cost are presented in tables 12–16.

Table 11 Summary of base-case cost-effectiveness results (ICER for LDV/SOF±RBV against each comparator £/QALY; table 94, page 206 of company's submission)

Indication (treatment durations are weighted averages, see table 10 for more information)	Ledipasvir-sofosbuvir regimen	Comparator							
		SOF+ PEG-IFN2a +RBV	SMV+ PEG-IFN2a +RBV	PEG-IFN2a +RBV	TVR+ PEG-IFN2a +RBV	BOC+ PEG-IFN2a +RBV	SOF+RBV	No treatment	SMV+SOF
Genotype 1 treatment naïve	LDV/SOF	LDV/SOF dominates	LDV/SOF dominates	£7,985	LDV/SOF dominates	LDV/SOF dominates	-	£7,458	LDV/SOF dominates
Genotype 4 treatment naïve	LDV/SOF	£3,869	£12,399	£12,715	-	-	-	£10,468	LDV/SOF dominates
Genotypes 1 and 4 treatment experienced†	LDV/SOF	£5,497	£9,984	£12,491	£9,144	£3,551	-	£13,527	LDV/SOF dominates
Genotype 3 treatment naïve	LDV/SOF+RBV	£46,691‡	-	£26,491	-	-	£19,013‡	£11,235	-
Genotype 3 treatment experienced IFN ineligible	LDV/SOF+RBV	-	-	-	-	-	£6,210‡	£28,048	-

† 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 these 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.

Table 12 Incremental cost effectiveness results for treatment-naïve HCV genotype 1 (table 95, page 207 of company's submission)

Technologies	Total			Incremental (versus no treatment)			ICER (£/QALY) versus no treatment	ICER (£/QALY) 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
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.

Table 13 Incremental cost effectiveness results for treatment-naïve HCV genotype 4 (table 96, page 208 of company's submission)

Technologies	Total			Incremental (versus no treatment)			ICER (£/QALY) versus no treatment	ICER (£/QALY) 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
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

Table 14 Incremental cost effectiveness results for treatment-experienced HCV genotypes 1 and 4 (table 97, page 209 of company's submission)

Technologies	Total			Incremental (versus no treatment)			ICER (£/QALY) versus no treatment	ICER (£/QALY) 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	£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

Table 15 Incremental cost effectiveness results for treatment-naïve HCV genotype 3 (tables 98–99, pages 210–11 of company's submission)

Technologies	Total			Incremental (versus no treatment)			ICER (£/QALY) versus no treatment	ICER (£/QALY) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Treatment naïve HCV genotype 3 (with and without compensated cirrhosis)								
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
Treatment naïve HCV genotype 3 (with compensated cirrhosis)								
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

Table 16 Incremental cost effectiveness results for treatment-experienced HCV genotype 3 unsuitable for interferon therapy (tables 100–101, page 212 of company's submission)

Technologies	Total			Incremental (versus no treatment)			ICER (£/QALY) versus no treatment	ICER (£/QALY) incremental
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Treatment-experienced HCV genotype 3 unsuitable for interferon therapy (with and without compensated cirrhosis)								
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
Treatment-experienced HCV genotype 3 unsuitable for interferon therapy (with compensated cirrohosis)								
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: 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.

5.21 For most comparisons, ledipasvir-sofosbuvir resulted in lower costs 'off-treatment' because it was associated with better efficacy (higher probability of cure therefore fewer patients move to more severe expensive health-states). For some comparisons (particularly in treatment-naïve HCV genotype 1), ledipasvir-sofosbuvir was also associated with lower 'on-treatment' costs because of shorter treatment durations and less intensive monitoring. Across all populations, a higher number of QALYs were gained with the ledipasvir-sofosbuvir regimen compared with the comparators. This is because ledipasvir-sofosbuvir is associated with a higher probability of cure and therefore more patients enter the SVR health state (associated with improved health-related quality of life) and fewer patients progress to the more severe health states (associated with poorer health-related quality of life). For the company's disaggregated cost-effectiveness results, please see Appendix 10.19 of the company's submission.

Company's sensitivity analyses

5.22 The company presented results of a univariate sensitivity analysis for ledipasvir-sofosbuvir compared with each of the comparators for each of the relevant patient populations. The univariate sensitivity analyses showed that the company's ICERs for ledipasvir-sofosbuvir were most sensitive to changes to: the on-treatment costs for non-cirrhotic patients; the discount rates used for costs and outcomes; SVR rates of ledipasvir-sofosbuvir and the comparators, and; the transition probability from non-cirrhotic to compensated cirrhosis. For more detailed results of the company's univariate sensitivity analyses, please see pages 214–243 of the company's submission.

5.23 The company conducted several scenario analyses.

- **Use of genotype 4 specific clinical data**: For people with treatment-naïve HCV genotype 4, the company's ICER comparing ledipasvir-sofosbuvir with no treatment decreased from £10,468 to £9,925 per QALY gained, but when using a fully incremental analysis the

company's ICER for ledipasvir-sofosbuvir increased from £12,715 (compared with pegylated interferon plus ribavirin) to £17,390 per QALY gained (compared with simeprevir plus pegylated interferon and ribavirin). For people with treatment-experienced HCV genotype 4, the company's ICER comparing ledipasvir-sofosbuvir with no treatment decreased from £13,527 to £12,313 per QALY gained, and when using a fully incremental analysis the company's ICER for ledipasvir-sofosbuvir decreased from £13,527 (compared with no treatment) to £12,313 per QALY gained (compared with no treatment).

- **Varying the treatment durations of ledipasvir-sofosbuvir for patients with HCV genotype 1 and 4 (see table 17)**

Table 17 Company's scenario analysis results (pages 250–51 of company's submission)

Population	Base-case (%)		Base-case ICER versus no treatment	Scenario (%)		Scenario ICER vs no treatment	Scenario incremental ICER
	12-week	24-week		12-week	24-week		
GT 1 TN	95%[a]	5%[a]	£7,458	85%[a]	15%[a]	↑ £7,756	↑ £8,453 (compared with PR)
GT 4 TN	95%[a]	5%[a]	£10,468	85%[a]	15%[a]	↑£10,760	↑ £13,580 (compared with SMV+PR)
GT 1/4 TE	75%[b]	25%[b]	£13,527	50%[b]	50%[b]	↑ £14,146	↑ £14,146 (compared with NT)

Key: [a] proportion of cirrhotic GT 1/4 TN receiving 12-week or 24-week regimen; [b] proportion of cirrhotic GT 1/4 TE receiving 12-week or 24-week regimen; ↑ indicates scenario ICER is higher than company's base case ICER; GT, genotype; NT, no treatment; PR, pegylated interferon plus ribavirin; SMV, simeprevir; TN, treatment-naïve; TE, treatment-experienced.

For further information about the methods and results of the company's scenario analyses, please see pages 247–251 of the company's submission.

5.24 The company also presented results from probabilistic analyses for each population. The company presented the probability of ledipasvir-sofosbuvir being cost-effective compared with all comparator technologies at £20,000 and £30,000 per QALY gained (table 18).

Table 18 Company's probabilistic sensitivity analyses results (section 7.7.8 of company's submission)

Indication	Probability of being less than £20,000 per QALY gained	Probability of being less than £30,000 per QALY gained
Treatment-naïve HCV genotype 1	100%	100%
Treatment-naïve HCV genotype 4	88%	100%
Treatment-experienced HCV genotypes 1 and 4	88%	100%
Treatment-naïve HCV genotype 3	2.5%	68%
Treatment-naïve HCV genotype 3 with compensated cirrhosis	2.1%	8%
Treatment-experienced HCV genotype 3 unsuitable for interferon therapy	1.4%	59.8%
Treatment-experienced HCV genotype 3 unsuitable for interferon therapy with compensated cirrhosis	78%	83%

ERG comments

5.25 The ERG highlighted that company's base case analysis uses point estimates of parameters (that is, a deterministic approach) rather than the expectation of the mean (that is, a probabilistic approach). However, the ERG considered that the results from the deterministic analyses and probabilistic analyses were similar from the company's economic model. For a summary of the company's probabilistic ICERs, please see table 46, page 127 of the ERG report.

5.26 The ERG considered that the results of the company's probabilistic analyses were limited because of:

- key uncertain parameters (for example, SVR rates) being pre-sampled outside of the model rather than sampling from a distribution
- the use of inappropriate distributions for some parameters.

Subgroup analyses

5.27 The company presented ICERs for the non-cirrhotic and compensated cirrhosis subgroups (table 19). The company commented that the cost-effectiveness may vary in the presence of cirrohosis because of

differences in efficacy and treatment duration of ledipasvir-sofosbuvir or comparator regimens.

Table 19 Summary of base-case cost-effectiveness results (ICER for ledipasvir-sofosbuvir with or without ribavirin compared with each comparator; table 132, pages 255–56 of company's submission)

Indication	Base case	Non-cirrhotic	Cirrhotic
Genotype 1 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
Genotype 4 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
Genotype 1/4 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
No treatment	£13,527	£17,205	£7,415
Genotype 3 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

Indication	Base case	Non-cirrhotic	Cirrhotic
Genotype 3 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.
* SW quadrant: ledipasvir-sofosbuvir results in cost savings but fewer QALYs. † 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.

5.28 The company did not present ICERs for the following subgroups included in the final scope of the appraisal.

- **Co-infection with HIV:** The company did not model the co-infected HIV population separately because the efficacy and safety of ledipasvir-sofosbuvir regimens for treating patients co-infected with HIV and HCV is similar to that observed in mono-infected HCV patients, and as such is treated in the same way. The company stated this approach was validated by its clinical experts and was conservative because HCV co-infected with HIV is more likely to progress to more severe health states (quicker) if left untreated.
- **People who have received treatment pre- and post-liver transplantation:** The company did not model this subgroup because of a lack of clinical data.
- **Response to previous treatment**: The company did not consider this subgroup to be relevant because response to interferon-free regimens (such as ledipasvir-sofosbuvir) is not impacted by previous response to interferon-containing regimens.

ERG exploratory analyses

5.29 The ERG presented ICERs for several exploratory analyses, using deterministic analyses because of the computation time and complexity associated with running probabilistic analyses. The ERG undertook the following additional analyses:

- Scenario 1: Development of an ERG-preferred base case exploring each recommended treatment duration for ledipasvir-sofosbuvir separately (that is, removing the company's weighted-average approach; see sections 5.7 and 5.15)
- Scenario 2: Exploration of the alternative recommended treatment durations for ledipasvir-sofosbuvir for specific subgroups of patients (as stipulated in the marketing authorisation of ledipasvir-sofosbuvir; see table 2)
- Scenario 3: Use of alternative transition probabilities based on the sofosbuvir STA model (ID654; see section 5.11)
- Scenario 4: Use of UK valued utility increment derived by Wright et al. [2006] (see section 5.18)
- Scenario 5: Use of shorter time horizons (5-years and 10-years) to test the assumptions around exclusion of health effects from re-infection (see section 5.19)
- Scenario 6: Threshold analysis for SVR rates of the comparators.

Exploratory analyses 3–6 use the ERG-preferred base case analysis as a starting point, that is, they all also include scenario 1. The ERG also presented the results of ERG's exploratory analyses separately for people with and without cirrhosis because the marketing authorisation of ledipasvir-sofosbuvir makes recommendations specific to cirrhotic status.

Table 20 Results of the ERG's preferred basecase (scenario 1, table 52, page 143–44 of ERG report)

(i) Genotype 1 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	17.20	£42,160.45	0.39	£8,843.83	**£22,676**
SMV+SOF	17.09	£61,415.79	-	-	dominated*
SOF+PEG-IFN2a+RBV	17.04	£41,081.62	-	-	ext dom**
SMV+PEG-IFN2a+RBV	16.81	£33,316.62	0.85	£14,111.22	£16,601
TVR+PEG-IFN2a+RBV	16.69	£34,631.46	-	-	dominated*
BOC+PEG-IFN2b+RBV	16.41	£35,002.22	-	-	dominated*
PEG-IFN2a+RBV	15.96	£19,205.40	0.89	£6175.99	£6,939
No treatment	15.07	£13,029.41	-	-	-

(ii) Genotype 1 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	10.08	£101,051.95	0.2	£19,567.23	**£97,836**
SMV+SOF	9.88	£81,484.72	0.63	£18,051.21	£28,653
SOF+PEG-IFN2a+RBV	9.25	£63,433.51	2.71	£15,167.91	£5,597
SMV+PEG-IFN2a+RBV	8.28	£59,097.68	-	-	ext dom**
BOC+PEG-IFN2b+RBV	8.09	£64,985.45	-	-	dominated*
TVR+PEG-IFN2a+RBV	7.95	£61,326.36	-	-	ext dom**
PEG-IFN2a+RBV	6.54	£48,265.60	1.29	£7,012.58	£5,436
No treatment	5.25	£41,253.02	-	-	-
(iii) Genotype 4 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	17.20	£42,160.45	0.39	£8,843.83	**£22,676**
SMV+SOF	17.09	£61,415.79	-	-	dominated*
SOF+PEG-IFN2a+RBV	17.04	£41,081.62	-	-	ext dom**
SMV+PEG-IFN2a+RBV	16.81	£33,316.62	0.85	£14,111.22	£16,601
PEG-IFN2a+RBV	15.96	£19,205.40	0.89	£6,175.99	£6,939
No treatment	15.07	£13,029.41	-	-	-
(iv) Genotype 4 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	10.08	£101,051.95	0.2	£19,567.23	**£97,836**
SMV+SOF	9.88	£81,484.72	0.63	£18,051.21	£28,653
SOF+PEG-IFN2a+RBV	9.25	£63,433.51	2.71	£15,167.91	£5,597
SMV+PEG-IFN2a+RBV	8.28	£59,097.68	-	-	ext dom**
PEG-IFN2a+RBV	6.54	£48,265.60	1.29	£7,012.58	£5,436
No treatment	5.25	£41,253.02	-	-	-
(v) Genotype 1/4 treatment-experienced non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 12 weeks	16.11	£41,978.77	1.80	£29,819.05	**£16,566**
SMV+SOF	16.09	£60,723.61	-	-	dominated*
SOF+PEG-IFN2a+RBV	15.71	£42,386.90	-	-	dominated*
SMV+PEG-IFN2a+RBV	15.67	£38,729.70	-	-	ext dom**
TVR+PEG-IFN2a+RBV	15.62	£36,459.92	-	-	ext dom**
BOC+PEG-IFN2b+RBV	15.48	£39,911.38	-	-	dominated*
PEG-IFN2a+RBV	14.61	£18,984.11	-	-	ext dom**
No treatment	14.31	£12,159.72	-	-	-
(vi) Genotype 1/4 treatment-experienced cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF 24 weeks	9.70	£99,222.17	0.21	£19,467.86	**£92,704**
SMV+SOF	9.49	£79,754.31	0.90	£16,560.88	£18,401

SOF+PEG-IFN2a+RBV	8.59	£63,193.43	3.4	£22,542.63	£6,630
SMV+PEG-IFN2a+RBV	8.31	£62,045.65	-	-	ext dom**
TVR+PEG-IFN2a+RBV	7.46	£63,324.53	-	-	dominated*
BOC+PEG-IFN2b+RBV	6.95	£68,413.45	-	-	dominated*
PEG-IFN2a+RBV	5.74	£47,441.22	-	-	ext dom**
No treatment	5.19	£40,650.80	-	-	-
(vii) Genotype 3 treatment-naïve non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	17.24	£83,330.76	0.81	£71,970.90	**£88,853**
PEG-IFN2a+RBV	16.43	£11,359.86	-	-	-
No treatment	14.57	£14,928.01	-	-	dominated*
(viii) Genotype 3 treatment-naïve cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	10.23	£102,644.92	0.85	£39,226.39	**£46,149**
SOF+RBV	9.87	£95,947.03	-	-	ext dom**
SOF+PEG-IFN2a+RBV	9.38	£63,418.53	4.13	£22,165.51	£2,363
No treatment	5.25	£41,253.02	-	-	-
(ix) Genotype 3 treatment-experienced IFN-ineligible non-cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	15.97	£84,108.64	0.06	£7,899.24	**£131,654**
SOF+RBV	15.91	£76,209.40	2.03	£62,273.69	£30,677
No treatment	13.88	£13,935.71	-	-	-
(x) Genotype 3 treatment-experienced IFN-ineligible cirrhotic					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
LDV/SOF+RBV 24 weeks	8.76	£105,760.87	3.57	£65,110.07	**£18,238**
SOF+RBV	8.01	£101,108.73	-	-	ext dom**
No treatment	5.19	£40,650.80	-	-	-

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.

* Dominated = a technology that is dominated provides fewer QALYs at greater cost than comparator; ** Ext dom = a technology that is extendedly dominated means a combination of two of its comparators can provide equal health at a reduced cost.

Table 21 Incremental cost-effectiveness ratios of the ERG's exploratory analyses scenarios 1–5 (tables 52–57, page 143–167 of ERG report)

Option	**ERG Base case (1)**	**Alternative durations (2)**	**Alternative transition probabilities (3)**	**UK HRQoL (4)**	**5 year time horizon (5)**	**10 year time horizon (5)**
(i) Genotype 1 treatment-naïve non-cirrhotic						
LDV/SOF 12 weeks	**£22,676**	**(8 wks) £8,894**	**£25,526**	**£21,570**	**£180,286**	**£92,879**
SMV+SOF	dominated*	dominated	dominated	dominated	dominated	dominated
SOF+PEG-IFN2a+RBV	ext dom**	dominated	ext dom	ext dom	ext dom	ext dom
SMV+PEG-IFN2a+RBV	£16,601	dominated	£18,300	£15,173	ext dom	£83,137

Option	ERG Base case (1)	Alternative durations (2)	Alternative transition probabilities (3)	UK HRQoL (4)	5 year time horizon (5)	10 year time horizon (5)
TVR+PEG-IFN2a+RBV	dominated*	dominated	dominated	dominated	dominated	dominated
BOC+PEG-IFN2b+RBV	dominated*	dominated	dominated	dominated	ext dom	dominated
PEG-IFN2a+RBV	£6,939	£6,939	£7,572	£6,367	dominated	ext dom
No treatment	-	-	-	-	-	-
(ii) Genotype 1 treatment-naïve cirrhotic						
LDV/SOF 24 weeks	**£97,836**	**(12 wks) £4,518**	**£174,023**	**£93,177**	**£1,000,548**	**£393,527**
SMV+SOF	£28,653	dominated	£49,447	£28,205	£276,370	£114,810
SOF+PEG-IFN2a+RBV	£5,597	dominated	£6,597	£5,437	£101,033	£28,347
SMV+PEG-IFN2a+RBV	ext dom**	ext dom	ext dom	ext dom	ext dom	ext dom
BOC+PEG-IFN2b+RBV	dominated*	dominated	dominated	dominated	dominated	dominated
TVR+PEG-IFN2a+RBV	ext dom**	ext dom	dominated	ext dom	dominated	dominated
PEG-IFN2a+RBV	£5,436	ext dom	£6,012	£5,273	£95,602	£21,926
No treatment	-	-	-	-	-	-
(iii) Genotype 4 treatment-naïve non-cirrhotic						
LDV/SOF 12 weeks	**£22,676**	n/a	**£25,526**	**£21,570**	**£180,286**	**£92,879**
SMV+SOF	dominated*		dominated	dominated	dominated	dominated
SOF+PEG-IFN2a+RBV	ext dom**		ext dom	ext dom	ext dom	ext dom
SMV+PEG-IFN2a+RBV	£16,601		£18,300	£15,173	ext dom	£83,137
PEG-IFN2a+RBV	£6,939		£7,572	£6,637	dominated	ext dom
No treatment	-		-	-	-	-
(iv) Genotype 4 treatment-naïve cirrhotic						
LDV/SOF 24 weeks	**£97,836**	n/a	**£174,023**	**£93,177**	**£1,000,548**	**£393,527**
SMV+SOF	£28,653		£49,447	£28,205	£276,370	£114,810
SOF+PEG-IFN2a+RBV	£5,597		£6,597	£5,437	£101,033	£28,347
SMV+PEG-IFN2a+RBV	ext dom**		ext dom	ext dom	ext dom	ext dom
PEG-IFN2a+RBV	£5,436		£6,012	£5,273	£95,602	£21,926
No treatment	-		-	-	-	-
(v) Genotype 1/4 treatment-experienced non-cirrhotic						
LDV/SOF 12 weeks	**£16,566**	**(24 wks) £165,445**	**£18,614**	**£15,137**	**£177,710**	**£88,532**
SMV+SOF	dominated*	£52,366	dominated	dominated	dominated	dominated
SOF+PEG-IFN2a+RBV	dominated*	ext dom	dominated	dominated	ext dom	ext dom
SMV+PEG-IFN2a+RBV	ext dom**	£45,396	ext dom	ext dom	ext dom (TVR+PR)	ext dom (TVR+PR)
TVR+PEG-IFN2a+RBV	ext dom**	£18,550	ext dom	ext dom	Dominated (BOC+PR)	Dominated (SMV+PR)
BOC+PEG-IFN2b+RBV	dominated*	dominated	dominated	dominated	Dominated (SMV+PR)	Dominated (BOC+PR)
PEG-IFN2a+RBV	ext dom**	ext dom	ext dom	ext dom	- (NT)	Dominated (PR)
No treatment	-	-	-	-	Dominated (PR)	- (NT)
(vi) Genotype 1/4 treatment-experienced cirrhotic						
LDV/SOF 24 weeks	**£92,704**	n/a	**£173,148**	**£92,704**	**£998,514**	**£326,762**

Option	ERG Base case (1)	Alternative durations (2)	Alternative transition probabilities (3)	UK HRQoL (4)	5 year time horizon (5)	10 year time horizon (5)
SMV+SOF	£18,401		£30,856	£18,001	£186,463	£71,389
SOF+PEG-IFN2a+RBV	£6,630		£8,660	£6,422	£109,738	£29,510
SMV+PEG-IFN2a+RBV	ext dom**		ext dom	ext dom	ext dom	ext dom
TVR+PEG-IFN2a+RBV	dominated*		dominated	dominated	dominated	dominated
BOC+PEG-IFN2b+RBV	dominated*		dominated	dominated	dominated	dominated
PEG-IFN2a+RBV	ext dom**		ext dom	ext dom	ext dom	ext dom
No treatment	-		-	-	-	-
(vii) Genotype 3 treatment-naïve non-cirrhotic						
LDV/SOF+RBV 24 weeks	**£88,853**	n/a	**£102,210**	**£82,725**	**£629,814**	**£374,545**
PEG-IFN2a+RBV	-		-	-	£49,091	£12,805
No treatment	dominated*		dominated	dominated	-	-
(viii) Genotype 3 treatment-naïve cirrhotic						
LDV/SOF+RBV 24 weeks	**£46,149**	n/a	**£79,825**	**£45,088**	**£455,683**	**£188,883**
SOF+RBV	ext dom**		ext dom	ext dom	ext dom	ext dom
SOF+PEG-IFN2a+RBV	£2,363		£1,392	£2,333	£10,127	£4,921
No treatment	-		-	-	-	-
(ix) Genotype 3 treatment-experienced IFN-ineligible non-cirrhotic						
LDV/SOF+RBV 24 weeks	**£131,654**	n/a	**£131,268**	**£112,846**	**£407,936**	**£270,310**
SOF+RBV	£30,677		£35,609	£28,566	£380,838	£171,513
No treatment	-		-	-	-	-
(x) Genotype 3 treatment-experienced IFN-ineligible cirrhotic						
LDV/SOF+RBV 24 weeks	**£18,238**	n/a	**£30,495**	**£17,693**	**£237,600**	**£75,793**
SOF+RBV	ext dom**		ext dom	ext dom	ext dom	ext dom
No treatment	-		-	-	-	-

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

* Dominated = a technology that is dominated provides fewer QALYs at greater cost than comparator; ** Ext dom = a technology that is extendedly dominated means a combination of two of its comparators can provide equal health at a reduced cost.

Note: Treatments are order by decreasing QALYs (that is, first treatment listed provides the most QALYs); use of parentheses in scenario 5 for the ERG's exploratory of the genotype 1/4 treatment-experienced non-cirrhotic population indicate changes to the order of treatment options providing the most QALYs [columns 6 and 7].

5.30 For further details around the methods and results of the ERG's exploratory analyses, please see pages 139–171 of the ERG report.

Innovation

5.31 Ledipasvir-sofosbuvir is considered to be innovative because:

- it has a shorter treatment duration and higher chance of cure compared with current treatment options for genotype 1 and 4 HCV
- of the reduction in onward transmission of the HCV
- of the potential for regression of liver fibrosis (once HCV is cured)
- of its potential to improve social relationships (for example, with family members) and reduce absenteeism (for example, from work)
- it is an all-oral treatment (interferon free) with fewer side effects.

6 Equality issues

6.1 During consultation of the draft scope, one consultee highlighted that NICE should be aware that HCV adversely affects certain populations who could be considered at risk of being disadvantaged in terms of access to the healthcare system and therefore at risk of inequity of access to innovative new treatments. For example:

- Certain immigrant populations
- Prison populations
- Intravenous drug users

Attendees (including NICE) at the scoping workshop were in agreement that any guidance should ensure it does not exclude these patient groups unless there is evidence on the risk of harm due to drug interaction.

6.2 Gilead Sciences commented that in the single technology appraisal of sofosbuvir for treating chronic hepatitis C [ID654] it was highlighted during consultation of the second appraisal consultation document that minority ethnic groups and people with HIV co-infection are more highly represented in the genotype 4 HCV population. The second appraisal consultation document made optimised recommendations for the use of sofosbuvir in people with genotypes HCV 1 and 3 but did not recommend the use of sofosbuvir in people with genotype 4. The Appraisal Committee considered evidence presented by Gilead Sciences regarding the genotype distribution of HCV in people with HCV and HIV co-infection and agreed that a disproportionate number of people had genotype 4 HCV

and HIV co-infection compared with the overall population of people with HCV in England. The Appraisal Committee concluded further consideration should be given as to whether a higher ICER should be considered as part of NICE's obligation to promote equality of access of treatment.

[*Note: this data also presented in the company's submission for 'ledipasvir-sofosbuvir for treating chronic hepatitis C' appraisal, please see section 3, pages 36–37*]

7 Authors

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

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003850/WC500177996.pdf

- **Genotype 3**

Page 60 of EPAR: "While no role is foreseen for LDV in the treatment of genotype 2 infection, clinical data in genotype 3 are available from the ELECTRON-2 study. In a small sample of treatment naïve patients, some of whom had cirrhosis, 12 weeks of SOF/LDV therapy was associated with a 64% SVR rate (16/25) with the remaining patients relapsing. While not well characterized, it seems unlikely that SOF monotherapy for 12 weeks would have achieved a 64% response rate in 12 weeks of therapy for genotype 3. Furthermore, SOF/LDV+RBV for 12 weeks yielded a 100% SVR rate (26/26) including five cirrhotics all reaching SVR. As the efficacy of SOF+RBV alone when used for 12 weeks in a treatment naïve genotype 3 population was around 60% in phase III trials, these data are also indicative that LDV has clinically relevant activity within a combination regimen for the treatment of genotype 3. However, as noted above, EC50 is substantially higher in GT3 compared to GT1 (168 nM versus 0.004-0.031 nM). Further, there are no viral kinetic data to show a direct effect of LDV on genotype 3 virus and there is no clear evidence of a selection pressure of LDV in genotype 3. Therefore, it is recognized that any conclusions that LDV has activity against genotype 3 rests on cross-study comparisons of the anticipated activity of the background regimens (SOF and SOF+RBV). On this basis, activity is anticipated that would be clinically relevant in patients for whom the present standard interferon-free regimen (SOF+RBV for 24 weeks) would be expected to yield inoptimal SVR rates based on available evidence (cirrhotics and/or treatment experienced patients). LDV might be added to such a regimen in order to increase antiviral drug pressure and presumably efficacy".

Page 79 of EPAR: "While the totality of evidence indicates that LDV adds activity against genotype 3, no extrapolations from genotype 1 can be made, due to the considerably higher EC50 value in genotype 3. Furthermore, available clinical data are scarce, and the absolute efficacy of SOF/LDV+RBV for 12 weeks in a broad population is unknown. SOF+RBV for 24 weeks (the presently approved IFN-free

regimen for GT-3 infection) has not been compared to SOF/LDV + RBV for 12 weeks within the same study (the latter may in fact be inferior). The only conclusion on appropriate use that can be drawn is that the addition of LDV to a regimen of SOF+RBV most likely increases the chance for SVR in those patients where SOF+RBV alone is not an optimal treatment regimen. On this basis, the use of SOF/LDV + RBV (rather than SOF + RBV) for 24 weeks may be recommended in treatment experienced and/or cirrhotic patients with genotype 3-infection."

- **Genotype 4**

Page 55 of EPAR: "The in vitro EC50 for LDV against GT4 (GT4a 0.39 nM, GT4d 0.6 nM) is intermediate between that recorded for GT1 (0.004-0.031 nM), where the bulk of clinical efficacy data are available, and GT3 (168nM) where data indicate that LDV does retain clinically relevant, albeit reduced, activity. Furthermore, SOF is equally effective against GT1 and GT4."

Page 60 of EPAR: "The applicant has submitted data from a cohort of patients with GT4, including treatment experienced patients and a few patients with cirrhosis that have been treated with SOF/LDV for 12 weeks. While it is recognized that these data are immature, such results would be very unlikely with SOF alone, and are indicative of a substantial contribution of LDV to efficacy, which is anticipated to be high. The combination of in vitro data and available clinical outcomes are indicative that SOF/LDV for 12 weeks is an effective regimen for the treatment of GT4 infection."

Page 79 of EPAR: "In vitro data are indicative that SOF/LDV for 12 weeks should be an effective regimen against genotype 4. This is supported by SVR4 data. By extrapolation, the regimens studied in different clinical situations for genotype 1 are considered of relevance also for genotype 4. However, EC50 values are higher than in GT1. Furthermore, patients with genotype 4 infection tend on average to have lower plasma HCV-RNA than patients with genotype 1 infection. These circumstances create some uncertainty to relative efficacy of 8 versus 12 weeks of therapy in genotype 4. For this reason, a sufficient basis for an 8 week recommendation in genotype 4 is considered lacking."

- **HIV co-infected**

Page 60 of EPAR: "As anticipated based on previous data with direct acting antiviral treatment regimens, available data from the ERADICATE study are not indicative that HIV coinfection impacts response to SOF/LDV."

Appendix B: 'Sofosbuvir for treating chronic hepatitis C' FAD recommendations [ID654]

Table 1 Summary of recommendations

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

HCV – hepatitis C virus

Treatment-naive – the person has not had treatment for chronic hepatitis C

Treatment-experienced – the person's hepatitis C has not adequately responded to interferon-based treatment

Interferon unsuitable – the person is intolerant to or ineligible for interferon