Single Technology Appraisal (STA)

Ledipasvir-sofosbuvir for treating chronic hepatitis C [ID742]

Responses to ERG Clarification Questions

27th November 2014

Section A: Clarification on search strategies

A1. Priority question: For the quality of life searches (Section 7.4 and Appendix 12 of the company's submission), the population terms are different for the main searches and the subsequent update searches. Please explain why this approach was adopted. Please confirm whether the implications of excluding ("NOTing") out the following disease terms "Hepatitis B, HIV, and recurrent hepatitis C" were considered by the company; that is, the risk that studies were indexed with these terms but contain information relevant to this appraisal?

The search terms were updated between the original and the update to increase the sensitivity. The reason for the Boolean operator "NOT" being applied to the disease terms from the original search is that, according to the original label for sofosbuvir (SOF) (to re-confirm, this search is an update to the review submitted for the sofosbuvir submission), HIV/HCV co-infected, HBV/HCV co-infected, and recurrent HCV/liver transplant patients were initially not included. The draft indication for sofosbuvir was then extended to include HIV co-infected and recurrent/liver transplant patients. Thus, the search strategies for subsequent updates to the review were adjusted to account for this.

The use of the "NOT" Boolean operator with the disease terms could have resulted in the exclusion of important articles that were indexed with these terms but contained information relevant to the appraisal. In order to account for this, systematic reviews and economic studies identified by the search were reviewed to identify any relevant articles cited within them that may have been excluded by the Boolean operator "NOT".

A2. Please provide details of the cost-effectiveness and quality of life search filters (see sections 7.1 and 7.4, and appendices 10 and 12 of the company's submission). How were these search filters derived? Please confirm whether they are published filters? If so, please provide references for these filters.

The cost-effectiveness and quality of life search filters were derived using published HTA submissions (systematic reviews and economic evaluations) for hepatitis C commissioned by NICE. At the time of the original search there were no available HTA publications that published search strategies for telaprevir (TVR) or boceprevir (BOC). Therefore, the cost-effectiveness and quality of life search filters for this submission were based on published HTAs for pegylated and non-pegylated interferons (1;2). The published search filters were used as a base to develop the strategies employed in this review and were adapted accordingly.

Generally, any differences in terms are due to testing across searches that indicated an update was required or the term was no longer relevant, e.g. terms run in the databases that returned no hits, or the same hits as similar terms. These terms were then removed. In addition, it was deemed that some terms were not relevant for the objectives of this review (e.g, willingness to pay, time trade off, etc.); these were subsequently removed.

A3. For the cost-effectiveness and quality of life searches, please clarify why two updates were carried out?

For both cost-effectiveness and quality of life searches, the original search and Update 1 were conducted in support of the NICE technology appraisal for sofosbuvir (submitted February 2014). As the original search was conducted in September 2012 when the modelling exercise for sofosbuvir was initiated, an update had to be conducted in October 2013 (Update 1) to account for the intervening period. For this current appraisal of LDV/SOF it was felt that the most appropriate approach was to re-use the original and Update 1 searches, and conduct a further update (Update 2) to account for the intervening period between October 2013 and August 2014.

A4. Please confirm whether the conferences 'Digestive Disease week' and 'APASL' (Asian Pacific Association for the Study of the Liver) were searched? If not, please provide the justification for their exclusion.

Neither 'Digestive Disease week' nor 'APASL' conferences were searched. Digestive Disease Week was not searched as the focus was on liver-specific congresses and this conference extends to gastroenterology, hepatology, endoscopy and gastrointestinal surgery. APASL was not searched as it was deemed likely that abstracts, and the patient populations described therein, would be biased towards Asian populations. Thus, identified abstracts would be of limited relevance for this submission.

A5. The Evidence Review Group's search of ongoing clinical trials identified 35 studies with the intervention terms – please see Appendix A of clarification letter (sent as a separate document). Please confirm whether any of these studies are due to report data within the next 12 months?

Table 1: Publication plan for identified clinical trials

Appendix A Study Number	NCT Number	Title	Gilead Study Number	Acronym / Alternative ID	Actual/Estimated Publication Date
1	NCT01768286	Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin for the Treatment of HCV	GS-US-337-0109	ION-2	Published:Afdhal N. et al. NEJM 2014; 370:1483-93 First presented: Afdhal N. et al. #O109, EASL, April 2014
2	NCT02125500	Pilot Study to Assess Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-dose Combination in Treatment Experienced Subjects With Hepatitis C Virus (HCV) Genotype 1 - HIV Co-infection	CO-US-337-1321	ANRS HC31 SOFTRIH	Planned: [redacted]
3	NCT01193478	A Multiple Ascending	GS-US-		Published:

		Dose Study of GS 5885 in Previously Untreated Subjects With Genotype 1 Chronic Hepatitis C	256-0102		Lawitz, EJ. et al. J Hepatol 2012; 57: 24-31 First presented: Lawitz, E. et al. #P1219, EASL, March 2011
4	NCT01353248	GS 5885 Administered Concomitantly With GS-9451, Tegobuvir and Ribavirin (RBV) in Chronic Genotype 1 Hepatitis C Virus (HCV) Infection	GS-US-248-0120		Published: Wyles, DL et al. Hepatology 2014; 60:56-64 First presented: Sulkowski, MS. Et al. #212, AASLD November 2012
5	NCT01356160	GS-5885 Alone or in Combination With GS-9451 With Peginterferon Alfa 2a and Ribavirin in Treatment Chronic Genotype 1 Hepatitis C Virus	GS-US-256-0148		First presented: Everson, G. et al. #P783, AASLD November 2012
6	NCT01435226	GS-5885, GS-9451, Tegobuvir and Ribovirin in Treatment-Experienced Subjects With Chronic Genotype 1a Or 1b Hepatitis C Virus (HCV) Infection	GS-US-248-0131		Presented: Everson, GT. et al. #O13, EASL April 2013
7	NCT01371578	Oral Antivirals (GS-5885, Tegobuvir, and/or GS-9451) With Peginterferon Alfa 2a and Ribavirin in Treatment Experienced Subjects With Chronic Genotype 1 Hepatitis C Virus Infection	GS-US-256-0124		Presented: Everson, GT. et al. #O13, EASL April 2013
8	NCT01434498	GS-5885, GS-9451, Tegobuvir and Ribavirin (RBV) in Interferon Ineligible or Intolerant Subjects With Chronic Genotype 1a or 1b Hepatitis C Virus (HCV) Infection	GS-US-248-0132		Presented: Everson, GT. et al. #O13, EASL April 2013
9	NCT01701401	Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination (FDC) With and Without Ribavirin for the Treatment of HCV	GS-US-337-0102	ION-1 2012-003387-43	Published: Afdhal N. et al. NEJM 2014; 370:1889-98 First presented: Mangia, A. et al. #O164, EASL April

					2014
10	NCT01384383	GS-5885, GS-9451 With Peginterferon Alfa 2a (PEG) and Ribavirin in Treatment-Naïve Subjects With Chronic Genotype 1 Hep C Virus Infection and IL28B CC Genotype	GS-US-248-0121		First presented: Thompson, P. et al. #P759, AASLD November 2012
11	NCT01878799	Study of A Combination Pill With GS-7977 and GS-5885 for Hepatitis C in People With HIV	ERADICATE	130159|13-I-0159 (NIH)	Presented: Osinusi, A et al. #O14, AASLD November 2014
12	NCT01924949	An Open-Label Study of Ledipasvir/Sofosbuvir Fixed-Dose Combination in Subjects With Nosocomial Genotype 1 HCV Infection	GS-US-337-0125	Mass Gen	Presented: Chung, R et al. #1970, AASLD November 2014
13	NCT01851330	Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin for the Treatment of HCV (ION-3)	GS-US-337-0108	ION-3	Published: Kowdley, KV. et al. NEJM 2014;370:1879-88 First presented: Kowdley, KV. #O56, EASL April 2014
14	NCT01984294	Ledipasvir/Sofosbuvir Fixed-Dose Combination With Ribavirin or GS-9669 in Subjects With Chronic Genotype 1 HCV Infection	GS-US-337-0133	LONESTAR-3	Presented: Lawitz, E. et al. #P1948. AASLD November 2014
15	NCT01726517	Safety and Efficacy of LDV/SOF Fixed-Dose Combination (FDC) ± Ribavirin in HCV Genotype 1 Subjects	GS-US-337-0118	LONESTAR	Published: Lawitz, E. et al. Lancet 2014; 383: 515-23 First presented: Lawitz, E. et al. #P1844, AASLD November 2013
16	NCT01965535	Efficacy and Safety of Sofosbuvir/Ledipasvir Fixed-Dose Combination ± Ribavirin in Cirrhotic Subjects With Chronic Genotype 1 HCV Infection	GS-US-337-0121	SIRIUS 2013-002296-17	Presented: Bourliere, M. #LB-6 AASLD, November 2014
17	NCT02249182	Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination in	GS-US-337-1116	Peds-FDC	[redacted]

		Adolescents and Children With Chronic HCV-Infection			
18	NCT02226549	Ledipasvir/Sofosbuvir Fixed-Dose Combination and Vedroprevir With or Without Ribavirin in Treatment-Experienced Participants With Chronic Genotype 1 HCV Infection and Cirrhosis	GS-US-337-1512	LONESTAR-4 (TRILOGY-2)	[redacted]
19	NCT02251717	Safety and Efficacy of Ledipasvir/Sofosbuvir (LDV/SOF) Fixed Dose Combination (FDC) for 12 or 24 Weeks in Kidney Transplant Recipients With Chronic HCV Infection	GS-US-337-1406	Post renal transplant 2014-002121-35	[redacted]
20	NCT02219685	Ledipasvir/Sofosbuvir Fixed-Dose Combination on Cerebral Metabolism and Neurocognition in Treatment-Naive and Treatment-Experienced Participants With Chronic Genotype 1 HCV Infection	GS-US-337-1445	Brain Imaging Study	[redacted]
21	NCT01938430	Ledipasvir/Sofosbuvir Fixed-Dose Combination + Ribavirin in Subjects With Chronic HCV With Advanced Liver Disease or Post-Liver Transplant	GS-US-337-0123	SOLAR-1	First presented: Flamm, SL. et al. #O239 AASLD, November 2014 Reddy, KR. et al. #O8 AASLD, November 2014
22	NCT02010255	Ledipasvir/Sofosbuvir Fixed-Dose Combination Plus Ribavirin in Subjects With Chronic HCV With Advanced Liver Disease or Post-Liver Transplant	GS-US-337-0124	SOLAR-2 2013-002802-30	[redacted]
23	NCT02021656	Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination in Korean and Taiwanese Participants With Chronic Genotype 1 HCV Infection	GS-US-337-0131	Korean/ Taiwan FDC	[redacted]
24	NCT01975675	Efficacy and Safety of Sofosbuvir/Ledipasvir	GS-US-337-0113	Japan GT1	Presented: Mizokami, M. et al.

		± Ribavirin in Japanese Participants With Chronic Genotype 1 HCV Infection			#P1929, AASLD November 2014
25	NCT02081079	Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination in Treatment-Naïve and Treatment-Experienced Subjects With Chronic Genotype 4 or 5 HCV Infection	GS-US-337-1119	French GT4/GT5 2013-003978-27	[redacted]
26	NCT02120300	Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination and Sofosbuvir + Ribavirin for Subjects With Chronic Hepatitis C Virus (HCV) and Inherited Bleeding Disorders	GS-US-334-1274		[redacted]
27	NCT02073656	Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 Weeks in Subjects With Chronic Genotype 1 or 4 HCV and HIV-1 Co-infection	GS-US-337-0115	ION-4	[redacted]
28	NCT01987453	Efficacy and Safety of Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin in Subjects With Chronic Genotype 1 HCV Who Participated in a Prior Gilead-Sponsored HCV Treatment Study	GS-US-337-1118	2014-001245-24	[redacted]
29	NCT01826981	Sofosbuvir Containing Regimens for the Treatment of Chronic HCV Infection in Subjects With Chronic Genotype 1, 2, 3, or 6 HCV Infection	GS-US-337-0122	ELECTRON-2	First presented: Gane, EJ. et al. #862, APASL, March 2013
30	NCT01805882	Combination Therapy for Chronic Hepatitis C Infection		SYNERGY 130066|13-I-0066	Presented: Osinusi, A. et al. #O11, EASL April 2014 Kapoor, R. et al.#O240, AASLD November 2014
31	NCT01260350	Open-Labeled Study of PSI-7977 and RBV With and Without	P7977-0523	ELECTRON	Published: Gane E. et al. Gastroenterology

		PEG-IFN in Treatment-Naïve Patients With HCV GT2 or GT3			2014;146:736–743 First presented: Gane EJ. et al. #LB-41, CROI March 2013
32	NCT02202980	Efficacy and Safety of Oral Regimens for the Treatment of Chronic HCV Infection	GS-US-337-1468	LEPTON	[redacted]
33	NCT01457755	Gilead Sustained Virologic Response (SVR) Registry	GS-US-248-0122	2011-000945-19	[redacted]
34	NCT01457768	A Gilead Sequence Registry of Subjects Who Did Not Achieve Sustained Virologic Response	GS-US-248-0123	2011-000946-39	[redacted]
35	NCT02064049	Surveillance and Treatment of Prisoners With Hepatitis C	VHCRP1302	SToP-C	[redacted]

<u>Section B: Clarification on effectiveness data</u>

Systematic literature review

B1. <u>Priority question:</u> Table 8 (page 45 of the company's submission) specifies that sustained virologic response (SVR) had to be reported for studies to be included in the systematic review. The flow chart indicates that 6 articles were excluded on the basis of outcomes. Please confirm whether any trials were excluded for not reporting SVR, but could have reported data for other relevant outcomes (for example, adverse events)?

All 6 articles that were excluded on the basis of outcomes were conference abstracts with limited data reported. In addition, the studies reported in these excluded conference abstracts were later published as journal articles which were themselves included in the systematic review. Therefore we do not believe that any relevant data have been omitted due to this.

B2. Figure 3, page 46 of the company's submission, states that 22 citations were identified by the review whereas Table 9, pages 49 to 52 of the company's submission, lists 25 published citations as well as study reports and an unpublished manuscript. In addition, section 6.2.7 of the company's submission states that 7 trials were identified by the review, whereas Table 9 lists 14 trials of which 4 are excluded. Please clarify the trials and citations identified by the systematic review.

The systematic review identified 22 citations covering nine trials (Note that the submission incorrectly stated ten trials; apologies for this error). These nine studies were: ION-1; ION-2; ION-3; LONESTAR; ELECTRON; SYNERGY; ELECTRON-2; Wyles et al; Thompson et al (3-24).

As described in section 6.2.7, Wyles et al and Thompson et al (22-24) were excluded from further discussion because none of the arms in these two studies considered LDV and SOF in combination. This left 19 citations covering seven studies from the literature review (ION-1; ION-2; ION-3; LONESTAR; ELECTRON; SYNERGY; ELECTRON-2).

Table 9 in the submission presents 26 citations, as well as study reports and one unpublished manuscript, covering 14 studies. Of the seven additional citations (i.e. not identified in the review), six were abstracts submitted and accepted for presentation at AASLD November 2014 (denoted by 'AASLD 2014' in Table 9). The publication of conference proceedings for this conference fell outside the date cut-off for the search (2nd September 2014) and hence were not picked up by the search. One further abstract was presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2014 (denoted by 'CROI' in Table 9).

Of the 14 studies presented in Table 9, seven were identified and finally included from the search, as described above. The remaining seven were additional studies from the LDV/SOF clinical trial programme which were felt by Gilead to be of relevance to the populations covered by the appraisal, but for which data was only available from AASLD 2014 or data on file (ERADICATE; SOLAR-1; SIRIUS), or were on-going studies awaiting data reporting (GS-US-337-1119, French GT4/5 study; GS-US-337-0115, ION-4; GS-US-337-0113, Japanese Phase III; GS-US-337-0124, SOLAR-2).

B3. Some ongoing studies are included in the company's submission. For the 4 ongoing studies excluded in Table 9 (pages 49 to 52 of the company's submission), please clarify whether no data are available from these trials, or if there is another reason for their exclusion? The exclusion criterion in Table 8 (page 45 of the company's submission) states "Not patients with chronic hepatitis C in relevant genotypes". However, the flow chart (Figure 3, page 46 of the company's submission) suggests that no studies were excluded on the basis of population. Please confirm whether there were no studies excluded on the basis of genotype (GT). Please also confirm the reasons for excluding the French study (GS-US-337-1119)?

As detailed in Table 9, the following 4 studies were excluded, all on the basis that data was not available at the time of submission. No studies were excluded on the basis of genotype or population.

- GS-US-337-1119 (French GT4/5 study): study excluded as no data is available to date.
  [redacted]
- GS-US-337-0115 (ION-4 HIV co-infected Phase III): study excluded as no data is available to date. [redacted]
- GS-US-337-0113 (Japanese Phase III): study excluded as SVR data was not available at the time of NICE submission. In addition, the Japanese population enrolled in the study was considered different to the population demographics of the UK and thus of less relevance than the phase III ION trials. SVR12 data was

presented at the AASLD 2014 Liver Meeting, held in Boston, MA, U.S.A. November 7-11 2014.

- GS-US-337-0124 (SOLAR-2): study excluded as no data is available to date. [redacted].

Phase II evidence

B4. <u>Priority question:</u> Please provide a critical appraisal of the included Phase II studies of ledipasvir-sofosbuvir (LDV/SOF).

A critical appraisal of the Phase II studies included in the submission are presented in the tables below.

Table 2: Critical appraisal ELECTRON-2

ELECTRON-2		
Study question	**How is the question addressed in the study?**	**Grade**
Was randomisation carried out appropriately?	Eligible patients in the GT3 treatment naïve arms were randomised in a 1:1 ratio to receive open-label treatment. Patients were allocated to the other arms in the study based upon the eligibility criteria for each arm.	Yes
Was the concealment of treatment allocation adequate?	The study was open-label.	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	For the randomised GT3 treatment naïve arms there were no meaningful differences in demographic and clinical characteristics at baseline.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The study was open-label. There is no likely impact of the study design on the objective, laboratory-determined, efficacy parameter (HCV RNA).	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There were no unexpected imbalances or drop-outs between the treatment groups presented in the submission. One patient with HCV GT3 infection (treatment naïve) discontinued due to AEs in the LDV/SOF group.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No evidence in study protocol.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The analysis set for antiviral activity was the FAS which included patients who were randomised into the study and received at least one dose of study drugs. The primary analysis set for safety analyses included patients who received at least one dose of study drug.	No

Abbreviations: AE, adverse event; FAS, Full Analysis Set; GT, genotype; HCV, hepatitis C virus; LDV, ledipasvir; N/A, not applicable; SOF, sofosbuvir.

Table 3: Critical appraisal ERADICATE

ERADICATE		
Study question	**How is the question addressed in the study?**	**Grade**
Was randomisation carried out appropriately?	The study was non-randomised.	N/A
Was the concealment of treatment allocation adequate?	The study was open-label.	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Patients were allocated to the two arms based upon whether they were receiving anti-retroviral therapy for their HIV co-infection, which is related to their stage of HIV disease. The study was not designed to undertake a comparison of outcomes between the two groups.	N/A
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The study was open-label. There is no likely impact of the study design on the objective, laboratory-determined, efficacy parameter (HCV RNA).	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There were no unexpected imbalances or drop-outs between the treatment groups. None of the randomised patients discontinued the study.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No evidence in study protocol.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary and safety analyses were based on an intention-to-treat population (all patients who received at least one dose of study medication).	Yes

Abbreviations: HCV, hepatitis C virus; N/A, not applicable; RNA, ribonucleic acid.

Table 4: Critical appraisal SOLAR-1

SOLAR-1		
Study question	**How is the question addressed in the study?**	**Grade**
Was randomisation carried out appropriately?	Patients were randomised using an IWRS.	Yes
Was the concealment of treatment allocation adequate?	The study was open-label.	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Patients were grouped by their stage of liver disease and, within each group, randomised to receive 12 or 24 weeks of therapy. Within each group there were no significant differences in demographic and clinical characteristics at baseline between the 12 and 24 week randomised arms.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The study was open-label. There is no likely impact of the study design on the objective, laboratory-determined, efficacy parameter (HCV RNA).	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There was a trend towards higher on-treatment discontinuation rates in patients receiving the 24 week duration, due to patients experiencing adverse events, undergoing liver transplantation or dying. This was not unexpected.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No evidence in study protocol.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary analysis set for efficacy analysis was the FAS which included all patients who were randomised into the study and received at least one dose of the study drug. The primary analysis set for safety analysis was the safety analysis set defined as any patient who was randomised into the study and received at least one dose of the study drug.	No

Abbreviations: FAS, Full Analysis Set; HCV, hepatitis C virus; IWRS, Interactive Web Response System; N/A, not applicable; RNA, ribonucleic acid.

Table 5: Critical appraisal ELECTRON

ELECTRON		
Study question	**How is the question addressed in the study?**	**Grade**
Was randomisation carried out appropriately?	For randomised arms a computer-generated randomisation sequence was used and allocation to treatment was done sequentially and communicated to the site by e-mail based on the randomisation sequence. Patients were allocated to the other arms in the study based upon the eligibility criteria for each arm.	Yes
Was the concealment of treatment allocation adequate?	The study was open-label.	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	For the randomised arms there were no significant differences in demographic and clinical characteristics at baseline.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The study was open-label. There is no likely impact of the study design on the objective, laboratory-determined, efficacy parameter (HCV RNA).	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There were no unexpected imbalances or drop-outs between the treatment groups presented in the submission.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No evidence in study protocol.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary and safety analyses were based on an intention-to-treat population (all patients who received at least one dose of study medication).	No

Abbreviations: HCV, hepatitis C virus; N/A, not applicable; RNA, ribonucleic acid.

Table 6: Critical appraisal LONESTAR

LONESTAR		
Study question	**How is the question addressed in the study?**	**Grade**
Was randomisation carried out appropriately?	A computer-generated randomisation sequence was used and allocation to treatment was done sequentially and communicated to the site by e-mail based on the randomisation sequence.	Yes
Was the concealment of treatment allocation adequate?	The study was open-label.	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Within each cohort there were no significant differences in demographic and clinical characteristics at baseline.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The study was open-label. There is no likely impact of the study design on the objective, laboratory-determined, efficacy parameter (HCV RNA).	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There were no unexpected imbalances or drop-outs between the treatment groups presented in the submission.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No evidence in study protocol.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary and safety analyses were based on an intention-to-treat population (all patients who received at least one dose of study medication). One patient discontinued treatment due to withdrawal of consent but had HCVRNA <LLOQ at post-treatment weeks 4 and 8. The patient was lost to follow-up after week 8 but was included in the primary efficacy analysis.	Yes

Abbreviations: HCV, hepatitis C virus; LLOQ, lower limit of quantitation; N/A, RNA, ribonucleic acid.

Table 7: Critical appraisal SIRIUS

SIRIUS		
Study question	**How is the question addressed in the study?**	**Grade**
Was randomisation carried out appropriately?	A computer-generated randomise schedule based on permutated blocks was used to randomize the patients in a 1:1 ratio, stratified by HCV genotype and response to prior HCV therapy. Kit assignments were provided to the investigator using a centralized IWRS system.	Yes
Was the concealment of treatment allocation adequate?	The study was a double-blind, placebo controlled study.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	There were no significant differences in demographic and clinical characteristics at baseline.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The study was a double-blind, placebo-controlled study.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There were no unexpected imbalances or drop-outs between the treatment groups presented in the submission.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No evidence in study protocol.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary and safety analyses were based on an intention-to-treat population (all patients who received at least one dose of active study medication). One patient randomised to the 12 weeks placebo followed by 12 weeks LDV/SOF+RBV arm received LDV/SOF in place of placebo during the first 12 weeks. They are retained in the arm for the ITT-based efficacy analysis. For the safety set analysis they were included in the 24 week LDV/SOF arm. One patient who discontinued the study due to a serious AE during the placebo phase was excluded from the efficacy analysis as per pre-specified criteria (they did not receive a single dose of LDV/SOF).	No

Abbreviations: AE, adverse event; HCV, hepatitis C virus; ITT, intention-to-treat; LDV, ledipasvir; N/A, not applicable; RBV, ribavirin; SOF, sofosbuvir.

Table 8: Critical appraisal SYNERGY

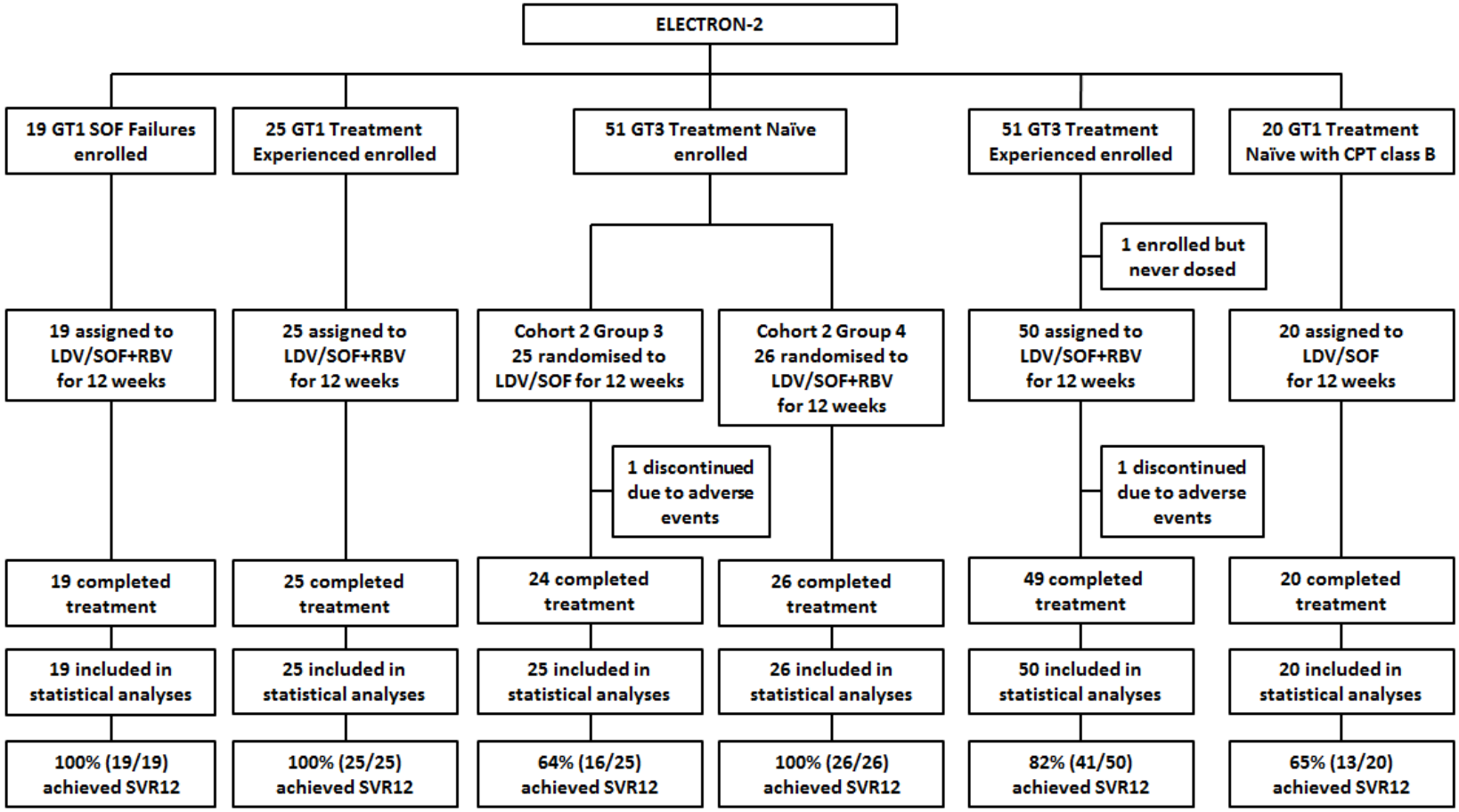
SYNERGY		
Study question	**How is the question addressed in the study?**	**Grade**
Was randomisation carried out appropriately?	Data from two groups are presented in this study but each group is of a different genotype. Randomisation was not required for the groups presented in this submission.	N/A
Was the concealment of treatment allocation adequate?	The study was open-label.	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	As the two groups presented in this submission were of different genotypes, the results were not compared with each other.	N/A
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The study was open-label. There is no likely impact of the study design on the objective, laboratory-determined, efficacy parameter (HCV RNA).	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	As the two groups presented in this submission were of different genotypes, the results were not compared with each other.	N/A
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No evidence in study protocol.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The analysis included an intention-to-treat analysis. One patient in the GT4 group was identified as non-compliant and withdrew consent at week 4 but was included in the intention-to-treat analysis. One patient had not reached the SVR12 time point at the time of first data publication and so is not included in the published efficacy analysis. They will be included in the primary endpoint analysis.	Yes

Abbreviations: HCV, hepatitis C virus; GT, genotype; RNA, ribonucleic acid; SVR, sustained virologic response.

B5. **Please provide participant flow charts for the included Phase II studies of LDV/SOF, indicating the number of participants starting and completing the trial and the number of patients who were included in the statistical analyses.**

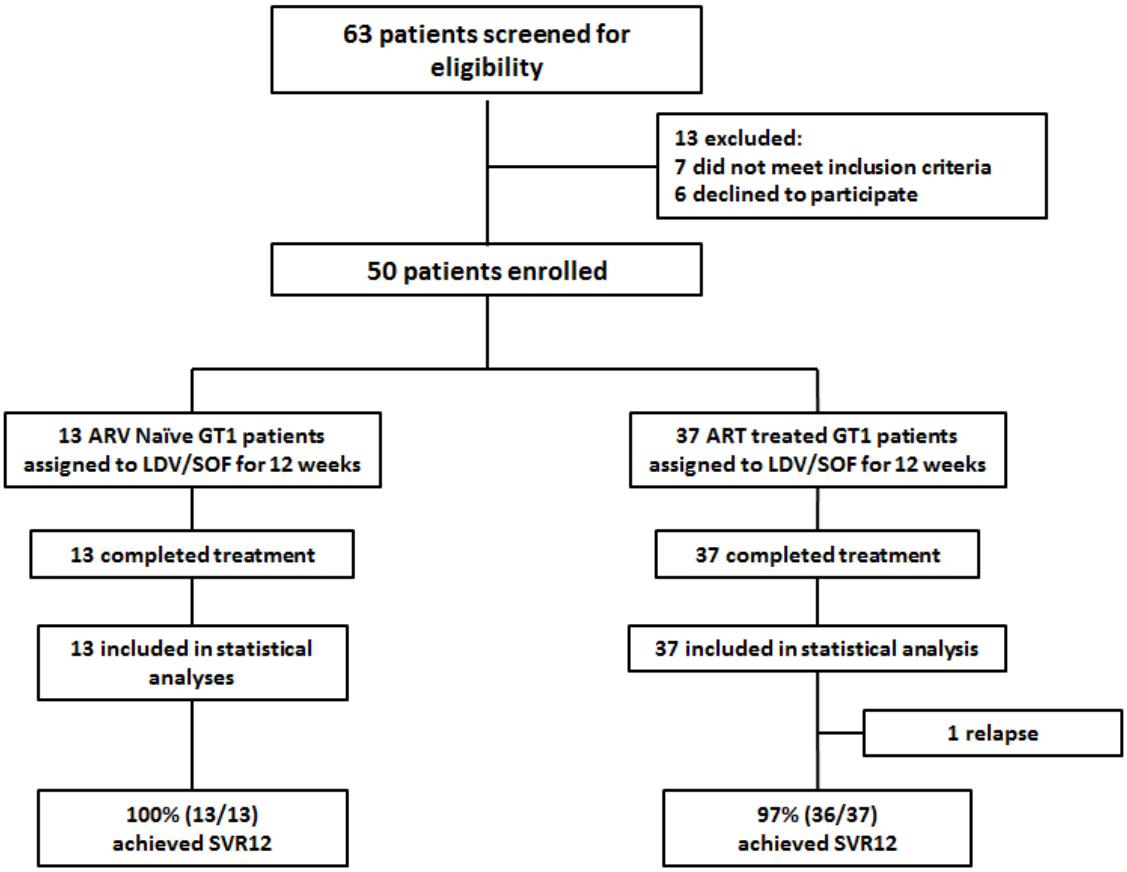
Participant flow charts for the included Phase II studies of LDV/SOF are presented below.

Figure 1: ELECTRON-2 patient disposition



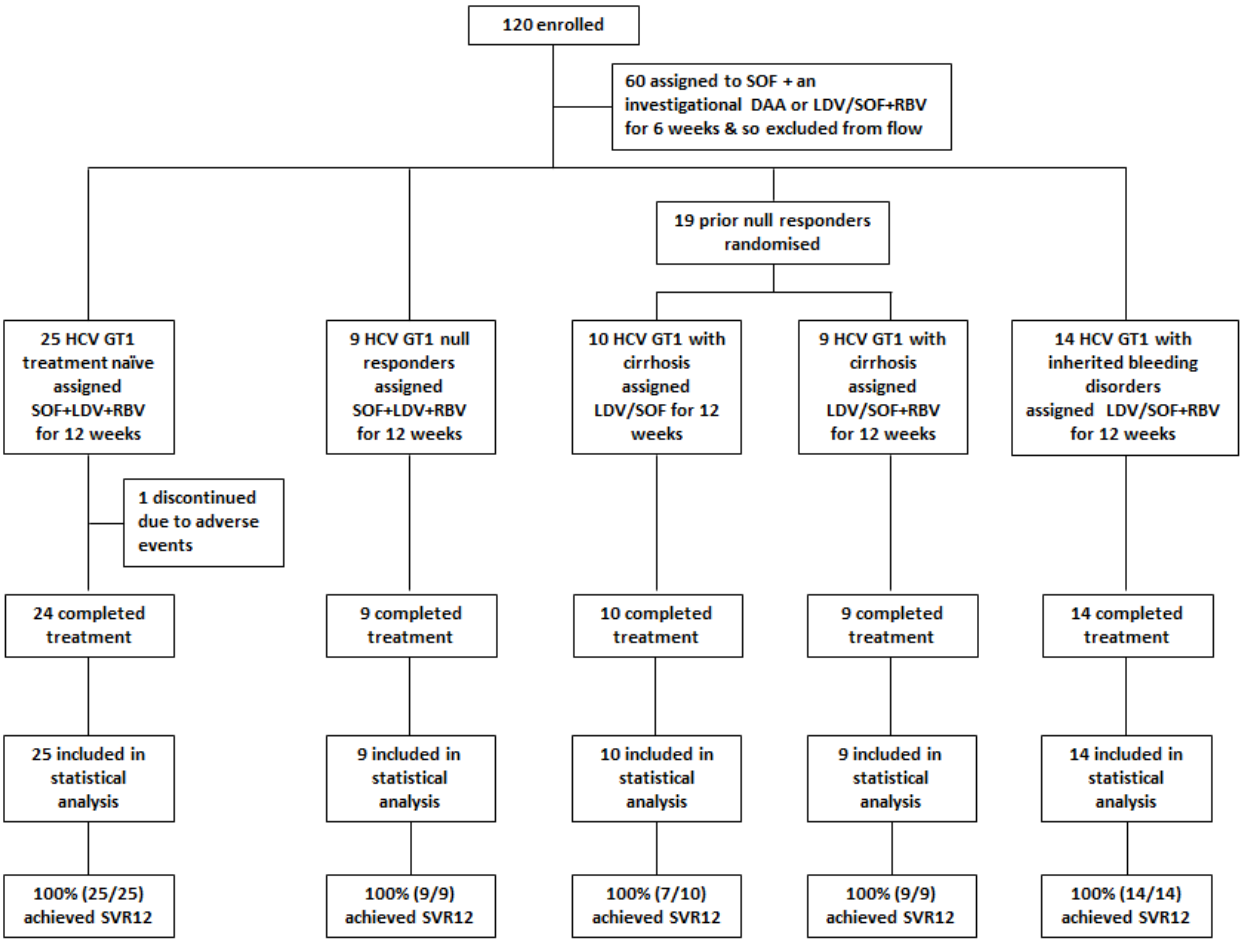
Abbreviations: CPT, Child Pugh Turcotte; HCV, hepatitis C virus; GT, genotype; LDV. ledipasvir; RBV, ribavirin, SOF, sofosbuvir; SVR sustained virologic response.
Source: Gane et al, EASL 2014 (11), Gane et al AASLD 2014 (25) and Gane et al AASLD #73.

Figure 2: ERADICATE patient disposition



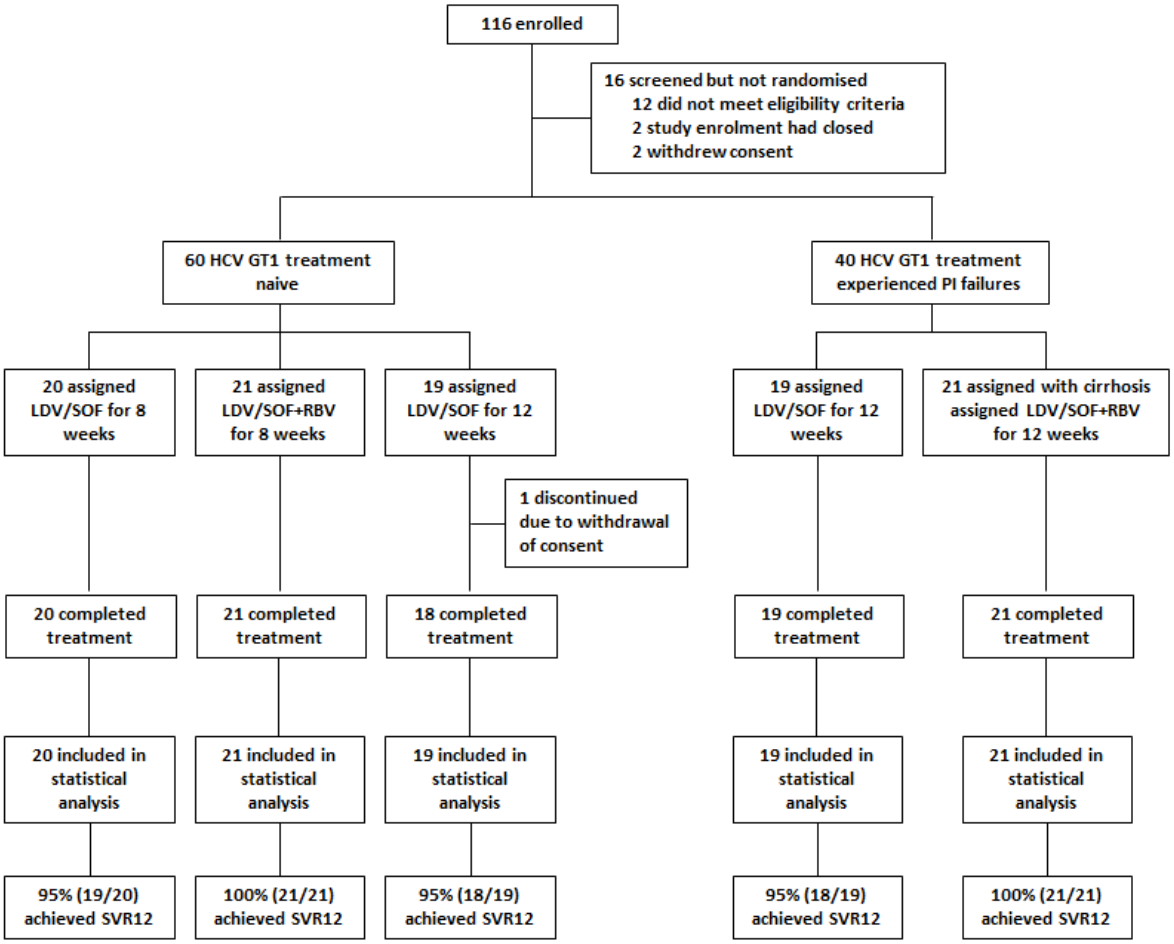
Abbreviations: ARV, antiretroviral; ART, antiretroviral therapy; GT, genotype; LDV, ledipasvir; SOF, sofosbuvir; SVR, sustained virologic response.
Source: Osinusi 2014 (submitted manuscript, not yet published) (26)

Figure 3: ELECTRON patient disposition



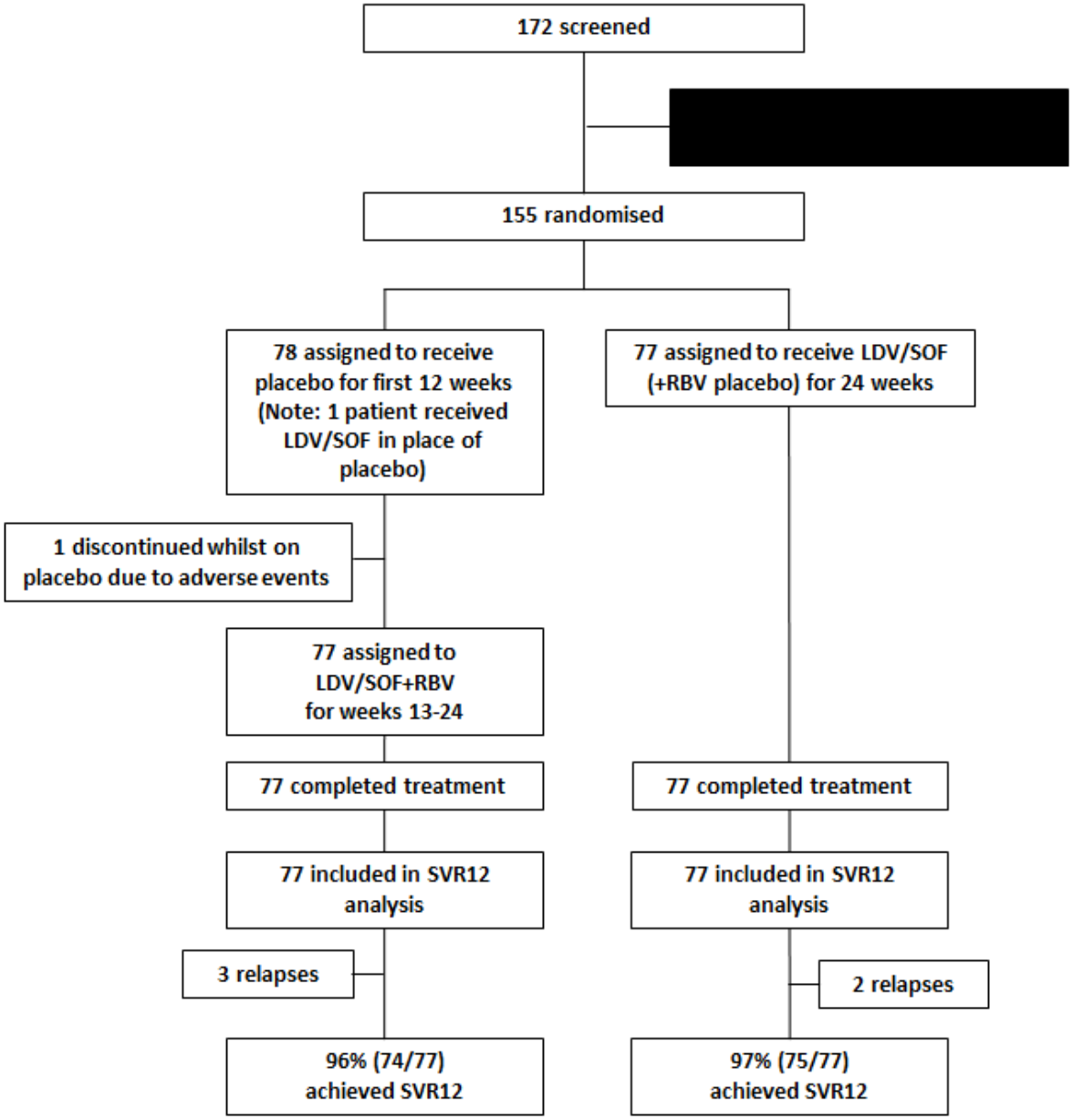
Abbreviations: HCV, hepatitis C virus; GT, genotype; LDV. ledipasvir; RBV, ribavirin, SOF, sofosbuvir; SVR, sustained virologic response.
Source: Gane et al, 2014 (13), Stedman et al, 2014 (14).

Figure 4: LONESTAR patient disposition



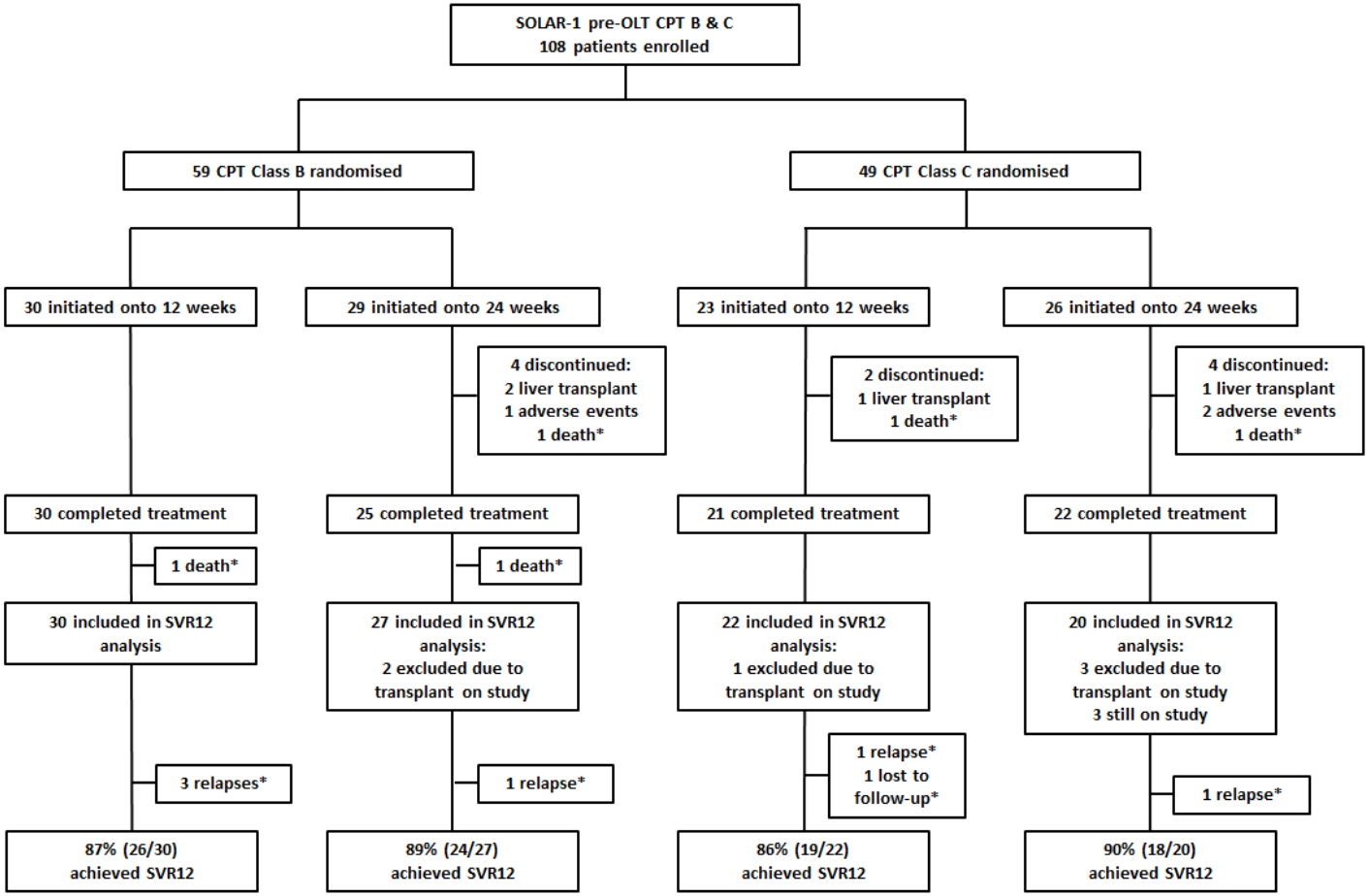
Abbreviations: GT genotype; HCV, hepatitis C virus; LDV, ledipasvir; PI, protease inhibitor; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response.
* This patient, who discontinued treatment due to withdrawal of consent, had HCV RNA <LLOQ at post treatment weeks 4 and 8 but was lost to follow-up after week 8
Source: Lawitz et al, 2013 (17).

Figure 5: SIRIUS patient disposition



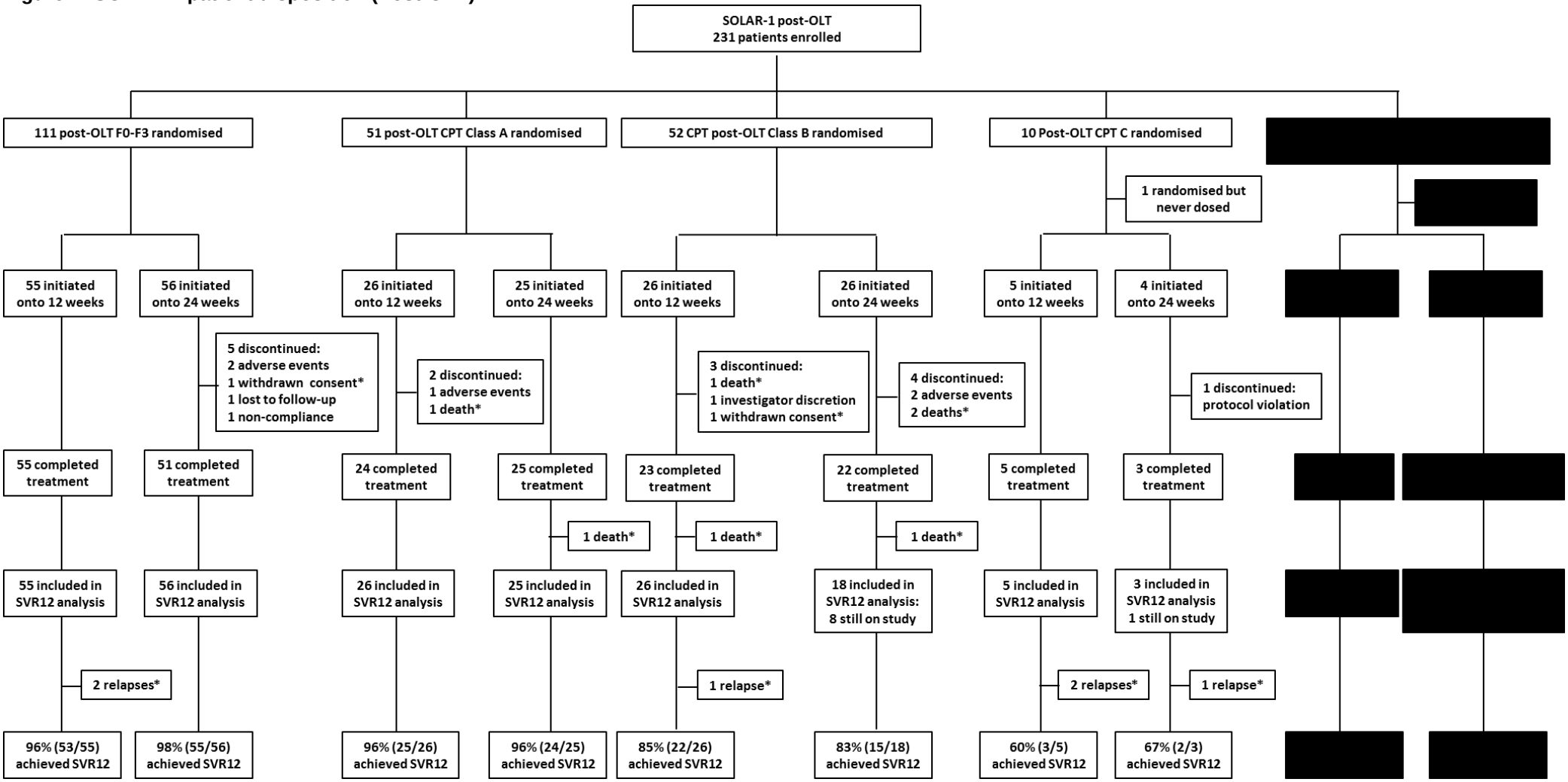
Abbreviations: LDV, ledipasvir; RBV, ribavirin SAE, serious adverse event; SOF, sofosbuvir; SVR sustained virologic response.
Source: Bourliere et al AASLD 2014 (27) with additional data from the draft CSR.

Figure 6: SOLAR-1 patient disposition (Pre-OLT CPT B and C)



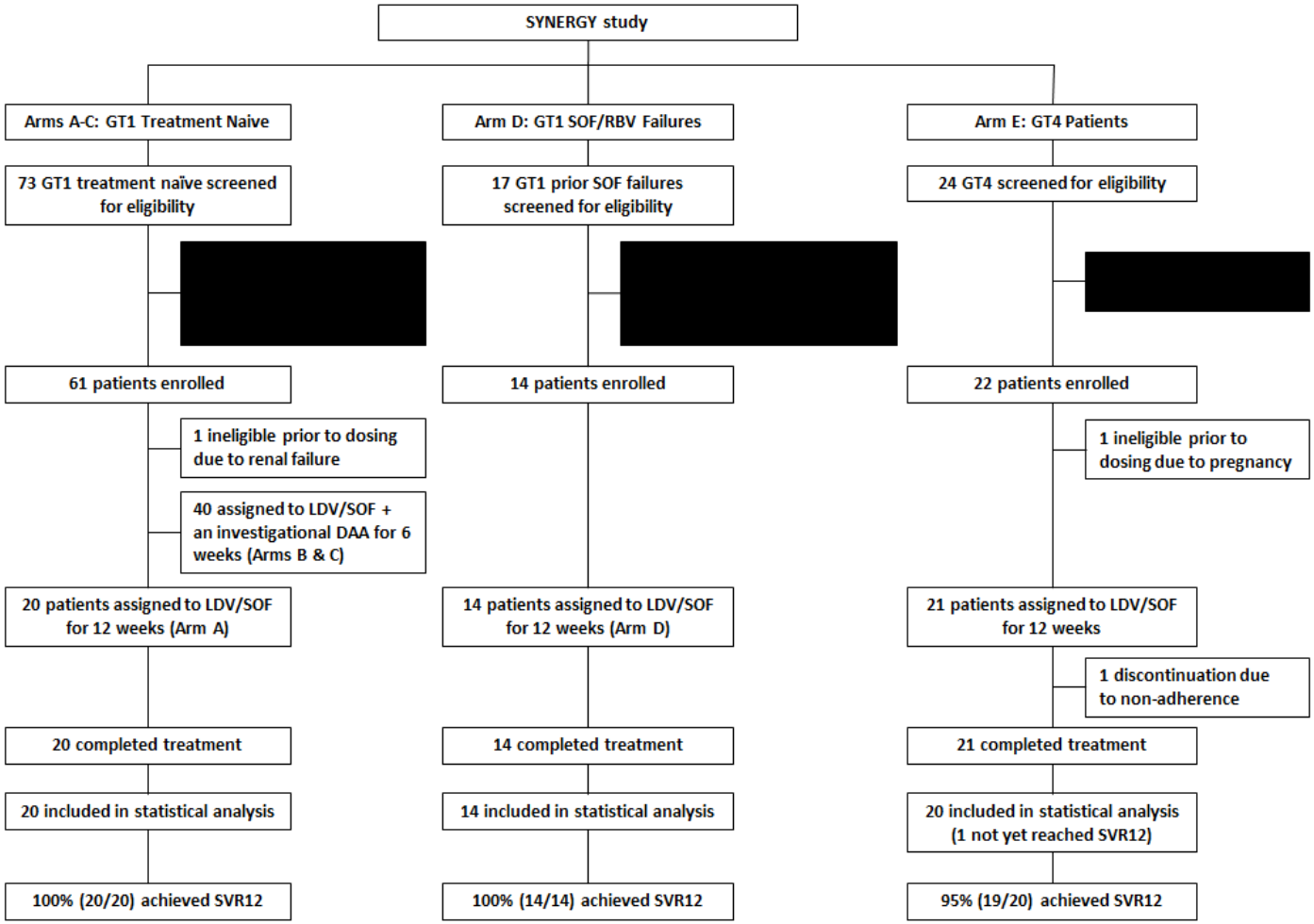
Abbreviations: CPT, Child Pugh Turcotte; OLT, orthotopic liver transplant; SVR, sustained virologic response.
*Patients recorded as SVR12 failures.
Source: Flamm et al AASLD 2014 (28).

Figure 7: SOLAR-1 patient disposition (Post-OLT)



Abbreviations: CPT, Child Pugh Turcotte; OLT; orthotopic liver transplant; SVR, sustained virologic response.
*Patients recorded as SVR12 failures.
Source: Reddy et al AASLD 2014 (29) and Gilead data on file.

Figure 8: SYNERGY patient disposition



Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; GT, genotype; LDV, ledipasvir; SOF, sofosbuvir; SVR, sustained virologic response; TVR, telaprevir.
Source: Osinusi et al, 2014 (30), Kohli et al, 2014 (31) and Kapoor et al (32) Note: this reference had not been published at the time of the SR or submission to NICE.

Comparator evidence

B6. **<u>Priority question:</u> How were trials for comparators identified and selected for inclusion? (Please see section 6.7 of the company's submission).**

The model for LDV/SOF was adapted based on the model developed for the NICE appraisal of sofosbuvir. The sofosbuvir model initially did not include GT1 treatment experienced patients as there were no data on SOF regimens in this population, although sofosbuvir did receive a licence for this population. During the appraisal of sofosbuvir, NICE requested the GT1 treatment experienced analysis was undertaken after the publication of the first ACD. Due to the short notice, there was no time to perform a systematic review hence targeted searches were undertaken. During the selection of comparator data, preference was given to high quality RCT data and where the SVR estimates were conservatively high to ensure bias was in favour of the comparator. As the NICE committee accepted the use of these data during the sofosbuvir appraisal, consideration was not given to using a different methodology.

The comparator data for GT1 and GT3 treatment naïve patients for PEG+RBV, BOC, TVR, and SOF was obtained for the systematic review from the SOF submission appraisal (detailed in response to B7 and originally presented in the Gilead submission to NICE for SOF). A further update between 2013 up to the date of the LDV/SOF submission was not conducted. However, the data were supplemented by way of targeted searches, including the use of product SPCs to identify any additional studies of interest and additional comparators including SMV-based regimens. The most appropriate data source was selected including the use of data reported in the relevant SPCs.

GT1 treatment experienced data for SOF regimens and PEG+RBV is based on the data used in the SOF submission. The SVRs for PEG-IFN-2a in GT3 treatment-experienced have been obtained from Lagging et al., 2013 using the distribution between relapsers and non-responders from Shoeb et al.,2011 (pg 293 of SOF appendices).

B7. **<u>Priority question:</u> Please clarify whether the company conducted a systematic review to search for trials of comparators? If there was a systematic review, please provide details. How was it decided which trials to include? For trials that were included, how was it decided which trial arms to include? Was study inclusion based on an assessment of quality?**

A systematic review of the literature was conducted to identify studies for comparators as part of the submission to NICE for SOF. The extract below is reported in Section 10.4, Appendix 4 of the Gilead submission to NICE for SOF:

Two searches were performed to inform the MTC analysis. The first covered 2002 to September 2012. The update covered 2012 to September 2013.

Original review (2002-2012): Relevant clinical literature was identified by way of systematic searches of PubMed, EMBASE (Ovid) and the Cochrane Library, conducted on 4th September 2012.

After the initial database search, a hand search of recent conference abstracts on new treatments of interest (i.e. SOF, simeprevir, ABT-450, asunaprevir) was also carried out. In addition, a supplemental search of references to identify recently published (i.e. from 2010 onwards) systematic reviews and meta-analyses was conducted to ensure no publications were overlooked.

Review update (2012-2013): for the update searches of the same databases were performed on 23rd September 2013. Hand-searching and supplemental searching of other reviews was also performed.

Search strategies and results retrieved

Detailed search strategies, including search terms, results retrieved and dates of the searches can be found in Appendix B, page 96 of the Appendix document submitted to NICE for the SOF technology appraisal (original and update).

Appropriate search terms were defined based on the disease area, population (adult GT1, 2/3, 4/5/6 treatment-naïve and GT2/3 treatment-experienced HCV patients), interventions of interest (e.g. PEG-IFN, RBV, telaprevir [TEL] and boceprevir [BOC]) and relevant publication types (e.g. RCTs). Search terms for treatments of interest were defined broadly to obtain the maximum number of relevant articles. PubMed and EMBASE searches were conducted using a combination of Medical Subject Headings (MeSH) terms and single keywords associated to the disease area.

Eligibility criteria for systematic review

Following the searches the titles and abstracts of retrieved articles were screened based on pre-defined inclusion and exclusion criteria. These criteria were defined based on the PICOS methodology and are described in Table 9 for the original search. Due to the breadth of the clinical literature on IFN-based treatments and the movement away from these therapies to more efficacious PEG IFN-based therapies, the search was limited to studies published in the last 10 years. This covers the time period when the first published literature on clinical trials evaluating PEG IFNs was made available.

Criteria applied for the update search were the same as for the original (except for date limits).

Table 9: Eligibility criteria for the clinical systematic review

Category	Inclusion criteria	Exclusion criteria
Language	• Studies in English, French, German, Spanish, Italian	• All other languages
Date limits	• Published between 2002 and 2012	• Anything prior to 2002

Disease and population (participants)	• Infection with HCV, genotypes 1-6
	• Adults (> 18 years)
	• TN patients
	• TE patients
		• Studies in children
		• Studies on following disease and population:
		  ○ Not focussed on adult (> 18 years)
		  ○ Studies on smaller populations (<10)

Category	Inclusion criteria	Exclusion criteria
		○ Acute HCV ○ Recurrent HCV ○ HCV/HBV co-infected ○ Renal dysfunction ○ Depression ○ Mixed hepatitis population – HCV not reported separately ○ Studies focussing on homeless populations and intravenous drug users
Study design	• RCT (Phase 2, 3 and 4) • Treatment with comparator (placebo as comparator also considered) • Conference abstracts • Systematic reviews (from 2010) • Meta-analyses (from 2010)	• Studies in animals or in vitro studies • Non-RCT • Pooled analyses of multiple RCT (original RCTs included) • Pilot study • Case study • Pharmacokinetic study • Pharmacodynamic study • Genetic study • Economic study • Guidelines • Letter or editorial • Reviews • Methodology of published or on-going trial • Educational program
Interventions and comparators	• Sofosbuvir • Telaprevir • Boceprevir • PEG IFN2a • PEG IFN2b • Ribavirin • Simeprevir • ABT-450 • ABT-333 • Asunaprevir • Daclatasvir • BMS-824393 • BMS-986094	• Studies on antiviral therapies other than those in inclusion criteria • Studies with no comparator group • Original IFN therapies‡ not compared to PEG: ○ IFN alfa ○ IFN alfa-2a ○ IFN alpha-2b ○ IFN alfacon-1
Outcomes	• SVR12 and SVR24 • RVR • EVR • EOTR • Adverse events	• Studies not on the following of antiviral therapies in HCV†: ○ Efficacy ○ Safety

EOTR, end of treatment response; EVR, early viral response; HBV, hepatitis B; HCV, hepatitis C; HIV, human immunodeficiency virus; IFN, interferon; PEG IFN2a, pegylated interferon alfa 2a; PEG IFN2b, pegylated interferon alfa 2b; RCT, randomised controlled trial; RVR, rapid viral response; SVR, sustained viral response.

†Studies not reporting SVR (i.e. only reporting other outcomes of interest) stratified by genotype were not included in the final review for data extraction; ‡Studies comparing PEG IFN to IFN were included in the review.

Study selection for systematic review

Original search: 2,313 articles were retrieved from the database search (Figure 9). After removal of duplicates and the addition of 11 publications identified in other searches (e.g., economic, HRoL), 1,731 unique titles and abstracts were screened based on eligibility

criteria Each reference was reviewed by two independent reviewers. In the instance of discrepancies between the two decisions, arbitration was carried out by an independent third-party. A total of 290 articles were deemed relevant for full-text review. Full text review was performed as for the title/abstract screen.

The main reasons for exclusion were: not about chronic hepatitis C; other antiviral therapy than included; not a RCT; pooled analysis of other studies[1]; Not about efficacy and/or safety and/or QoL of antiviral therapy; Did not report SVR by genotype; Mixed hepatitis C population; Study population <10; Reviews; Abstract where full-text article of clinical trial already obtained.

After abstract and full-text screening, 55 articles were included for data extraction. The included list was validated by cross checking against 29 previous meta-analyses and systematic literature reviews on treatments for chronic HCV. Additional references were included based on this cross-check as well as supplemental screening of conference abstracts. As a result, the total number of articles data extracted was 73 (literature review: 55; conference abstracts: 13; cross-check: 5).

Search update: A total of 538 articles were retrieved from the database search (Figure 10) and titles and abstracts were screened based on eligibility criteria described above. After removal of duplicates, 468 unique titles and abstracts were screened. A total of 123 articles were deemed relevant for full-text review. After abstract and full-text screening, 104 were excluded, leaving 19 articles for inclusion. After cross-checking and screening of conference abstracts, the total number of publications data extracted was 52 (literature review: 21; conference abstracts: 21; cross referencing/other searches: 10).

[1] In this instance the screening sheets were reviewed to ensure the acquisition and review of the original clinical trials included in the pooled analysis

Figure 9: Results from clinical systematic review (original)

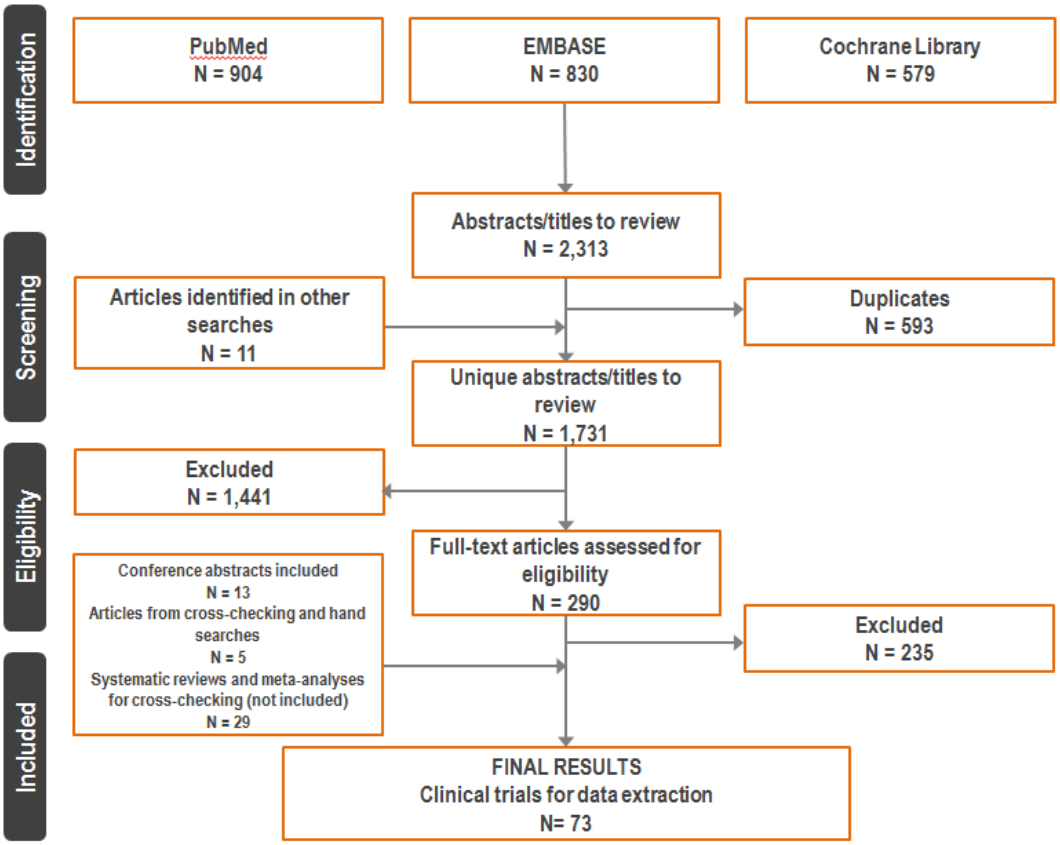
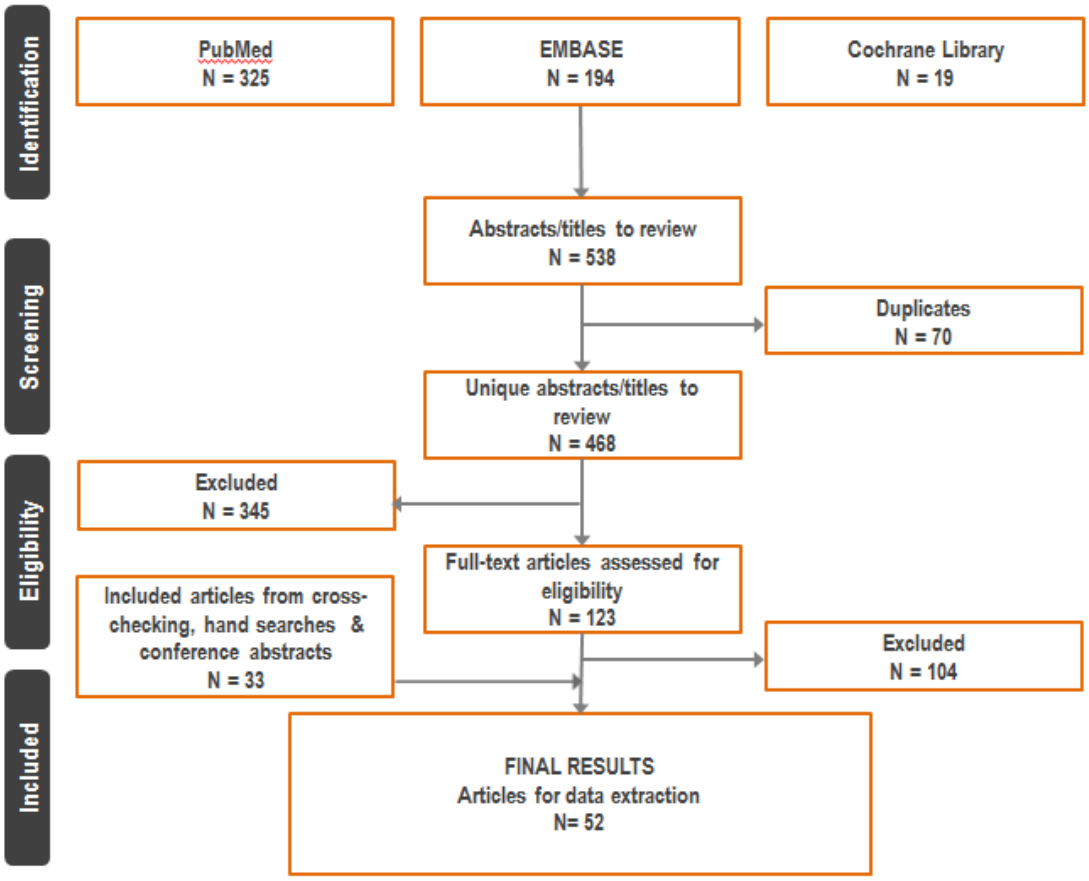


Figure 10- Results from clinical systematic review (update)



Trial arms were included if they the intervention of interest for a licensed treatment duration. The full list of studies and the reason for their exclusion is detailed in Appendix C, page 102 of the Appendix document submitted to NICE for the SOF technology appraisal. Study inclusion was based on an assessment of quality detailed in Appendix D, page 110 of the Appendix document submitted to NICE for the SOF technology appraisal.

Of note, the ERG reviewing the sofosbuvir submission concluded that this systematic review was fit for purpose and was unlikely to have missed relevant studies (pg 18 of the ERG report) (33).

B8. <u>Priority question:</u> Please provide a critical appraisal of trials used for comparator data in section 6.7 (Table 38 of the company's submission). Also, please justify the studies chosen for the efficacy of comparator treatments, see section 7.3.6 (Tables 58, 63, 66 and 69 of the company's submission). Please clarify why a meta-analysis of all relevant studies has not been conducted for each of the comparators.

A critical appraisal of the trials used for comparator data is provided in tables Table 10 to Table 12. A network meta-analysis was deemed not feasible due to the trial design meaning that a network could not be formed. The approach taken to estimate the comparator data for

this submission was thus in line with the approach taken within the sofosbuvir submission for NICE. As a network meta-analysis was not possible, the most appropriate data source was selected following a systematic review or includes the use of data reported in the relevant SPCs or the best available published data.

Table 10: Critical appraisal of simeprevir and boceprevir trials

	Simeprevir					Boceprevir	
Study name	**C208 - QUEST 1**	**C216 - QUEST 2**	**PROMISE**	**ASPIRE**	**COSMOS**	**Poordad et al SPRINT-2**	**Bacon et al 2011 RESPOND-2**
Was randomisation carried out appropriately?	Yes	Yes	Yes	Not clear	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Not clear	N/A	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Not clear	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Not clear	No	Yes	Yes
Were there any unexpected imbalances in drop- outs between groups?	No	No	No	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Sources: All critical appraisals are taken from manufacturer submissions to NICE, where available. ASPIRE and COSMOS were based on the SPC and Lawitz et al 2014, (34;35)

Table 11: Critical appraisal of telaprevir and peginterferon+ribavirin trials

	Telaprevir				Peginterferon+ribavirin		
Study name	**ADVANCE**	**REALIZE**	**ILLUMINATE**	**C211**	**IDEAL**	**REALIZE**	**P7977-1231 (FISSION)**
Was randomisation carried out appropriately?	Yes	Not clear	Not clear	Not clear	Yes	Not clear	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	N/A	N/A	Yes	Yes	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Not clear	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Not clear	Yes	No	No	Yes	Yes	N/A
Were there any unexpected imbalances in drop- outs between groups?	Yes	Yes	No	Not clear	No	Yes	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes	Yes	No	No	Unclear	Yes	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes	Unclear	Yes	Yes

Sources: All critical appraisals are taken from manufacturer submissions to NICE, where available. ILLUMINATE and C211 were based on the product SPC (36). IDEAL was based on McHutchison et al 2009 (37)

Table 12: Critical appraisal of sofosbuvir trials

	Sofosbuvir				
Trial No. (acronym)	**GS-US-334-0110 (NEUTRINO)**	**P7977-1231 (FISSION)**	**GS-US-334-0133 (VALENCE)**	**P7077-0422 (PROTON)**	**GS-US-334-0151 (LONESTAR-2)**
Was randomisation carried out appropriately?	N/A	Yes	Yes	N/A	N/A
Was the concealment of treatment allocation adequate?	N/A	N/A	Yes	N/A	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	N/A	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A	N/A	Yes	N/A	N/A
Were there any unexpected imbalances in drop- outs between groups?	N/A	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes	Yes

Sources: All critical appraisals are taken from manufacturer submissions to NICE, where available.

Indirect and mixed treatment comparisons

B9. Does the company consider that it is possible to compare interventions and comparator treatments separately using two disconnected network meta-analyses? Please explain whether it is possible to estimate absolute response rate using different reference treatments within separate networks? Also, please clarify whether the inclusion of trial treatment arms with unlicensed drugs (for example, SYNERGY) would have enabled a mixed treatment comparison?

No, it would not be possible to compare interventions and comparator treatments using two disconnected network meta-analyses. The reason for this is that LDV/SOF, SOF+PEG-IFN, SOF+RBV, SMV+SOF all cannot be connected to a network because they predominately have only been studied in uncontrolled trials.

It is possible that in GT1 CHC, PEG-IFN+RBV, BOC, TVR and SMV could be compared via a network meta-analysis. Using a single reference treatment, the absolute response rate (i.e. SVR) could be estimated for the remaining comparators. For the remaining regimens, the data would be included following the same approach as in the current analyses (i.e. naïve trial data). However, the trade-off in uncertainty of including data using two different approaches compared to using one consistent approach across all comparators is not clear. Hence, the approach utilised follows the precedent of the approach used in the sofosbuvir cost-effectiveness model.

Please refer to Appendix 4 of the sofosbuvir submission for the full detail as to why SOF+PEG-IFN and SOF+RBV could not be compared to the comparators via a network meta-analysis.

We are not aware of any trials with published data, including trials with unlicensed medicines, which would enable a mixed treatment comparison. Many of the SOF and LDV/SOF trials include multiple arms investigating different regimens, however they are not RCTs and therefore do not connect to a network.

It is expected that the approach taken will in fact favour the comparator regimens. This is due to uncertainty between the patients and trial designs from the trials which include either a PI regimen or PEG-IFN+RBV compared to the more recent trials with SOF-based regimens. These reasons include that there is a lack of data for patients with severe disease in the older trials, the LDV/SOF studies comprise a large number of IFN-intolerant patients, and a high proportion of treatment experienced patients who are have previously failed therapy on a PI. All of these patient groups are seen as harder to treat and therefore the naïve trial estimates for LDV/SOF are conservative in comparison to the older regimens.

Section C: Clarification on cost-effectiveness data

Published cost-effectiveness evaluations

C1. The systematic review of economic evaluations included a large number of studies – Section 7.1.2 of the company's submission states that a cost-effectiveness evaluation of a fixed dose combination (FDC) of LDV/SOF was identified (McGinnis et al. 2014, reference 122). Please clarify what the economic conclusions of this study were and why they are not reported in the company's submission?

The final results of the base-case analysis for the study by McGinnis et al. 2014 were presented in Table 156: Summary list of cost-effectiveness evaluations in Section 9.10.6.

The study authors concluded that the interferon-free combination therapy LDV/SOF+RBV is the most cost-effective treatment option, with an ICER of $61,291 when compared to no treatment and that the study results have important economic and policy implications for the treatment of chronic hepatitis C.

Functionality of company's economic model

C2. Priority Question: The company's economic model has a number of default settings which work automatically (for example, when moving between worksheets). This makes it difficult for the Evidence Review Group to verify whether the results correspond to the inputs specified. Please provide a version of the economic model in which these automated settings are disabled.

The economic model has a number of default sheets to allow the user to restore the default values by pressing the default buttons on each input sheet. When moving between worksheets input values are not updated. Therefore, the results displayed relate to the values that are shown on the different input sheets at the time the analysis was last run.

A worksheet change event is run when selecting the 'Results BC' sheet. This setting has been included to ensure that the 'Genotype 1 treatment-naïve (non-cirrhotic and cirrhotic patients)' population is not automatically selected since separate analyses need to be run for non-cirrhotic and cirrhotic cohorts and then combined.

Based on the explanation above we have not provided a new version of the model in which the automated settings are disabled as verification is possible with the current version, If validation is still not possible following the above explanation, we will provide an updated version.

C3. Please clarify why 59 worksheets are needed for an 11 state Markov model?

The number of worksheets in the economic model is not linked to the number of states of the Markov model. The 59 worksheets used by the economic model are described as follows:

- Presentation of the model (*Cover*, *Intro*, *Model overview*)
- Settings of the genotype and comparators for each indication (*Selection*)
- Input sheets (*Patients characteristics*, *treatment efficacy*, *treatment duration*, *treatment safety*, *treatment costs*, *monitoring costs*, *detailed monitoring costs*, *unit costs*, *health state costs*, *health state costs (inputs), indirect costs*, *inflation*, *utilities*, *TPs*, *Discounting*)
- Markov model sheets (*transition matrices*, *model patients*, *model utility*, *model costs*)
- Results sheets (*results BC*, *CE Frontier*)
- DSA sheets (*DSA inputs*, *DSA results*)
- PSA sheets (*PSA inputs*, *PSA CE plane*, *PSA CEAC*, *PSA multiple CEAC*)
- Default inputs (one sheet per input sheet)
- Calculation sheets (different sheets are used in the model to compute intermediate calculations or to execute VBA macros). These sheets are hidden.

The number of input sheets is quite high because it was decided to include each input category on a different sheet, due to the large number of populations and comparators.

C4. Please clarify why the =FLOOR() function is applied to the discounting of utilities and costs in the company's economic model?

Using the FLOOR() function allows for consistency in discounting throughout the model time horizon, given the differences in cycle durations. The use of discounting is only applied from year 2 onwards. From year 3 onwards annual cycles are employed and the FLOOR() function has no effect since it rounds values down to a specified number of significant figures (1 in the case of the model). Therefore, the effect of the FLOOR() function is seen only in year 2 where monthly cycles are applied for the first six months followed by two three-monthly cycles. Using the FLOOR() function ensured that the costs accrued throughout year 2 are discounted in a consistent manner compared with costs accrued in years 3 onwards, wherein annual cycles are used.

Clinical parameters

C5. **<u>Priority Question:</u> Table 58 (page 167 of company's submission) states that the efficacy for the GT1 treatment-naïve population for LDV/SOF 8 weeks has been estimated using data from patients with baseline HCV RNA of <6 million IU/mL. This is a *post hoc* analysis of the ION-3 study (see section 6.5.5, page 89 of the company's submission). Please justify why the patients with VL>6 million IU/ml are not indicated for the short 8 weeks duration).**

As described on page 95 and in Table 27 of the submission, a *post-hoc* analysis (38) was undertaken to investigate factors that might be predictive of relapse following 8 weeks treatment with LDV/SOF. With 8 weeks LDV/SOF, a relapse rate of 2% was observed for patients with a baseline HCV RNA of <6 million IU/mL. The corresponding SVR was 97% (119/123), compared with 96% (126/131) with 12 weeks LDV/SOF for those with baseline HCV RNA of <6 million IU/mL. For patients with baseline HCV RNA ≥6 million IU/mL, a

relapse rate of 10% was observed with 8 weeks LDV/SOF and 1% with 12 weeks LDV/SOF (Table 27). These data support the use of 8 weeks of treatment for non-cirrhotic treatment naïve GT1 patients with a baseline viral load of <6 million IU/mL, and 12 weeks LDV/SOF for those with a baseline viral load of >6 million IU/mL.

Of note, the 8 week duration is indicated in patients with VL>6 million IU/mL. However, given the higher relapse rate observed in patients with VL>6 million IU/mL, Gilead chose to submit a conservative assumption that clinicians in the UK might choose to treat these patients for 12 weeks as opposed to 8 weeks. This assumption was validated by a UK clinician.

If 100% of GT1 TN patients received 8 weeks treatment, the ICER versus PEG-IFN2a+RBV reduces from a base case value of £7,985 to a lower value of £6,720. LDV/SOF continues to dominate all other active comparators (SMV+PR, TVR+PR, BOC+PR, SOF+PR, SOF+SMV) and is associated with an ICER of £6,657 versus no treatment.

C6. <u>Priority question:</u> Please clarify why the structure of treatment duration within the company's Markov model is curtailed at 8 weeks? For example, please refer to cells AR15:16 (and many others) within the "Model patients" worksheet of the company's economic model.

The treatment duration within the Markov model is not curtailed at 8 weeks; treatment costs are calculated based on the specified treatment duration which is not limited therefore the model can consider 8, 12 or 24 weeks. [redacted]. As such the IF statements in cells AR15:16 of the 'Model patients' sheet (as well as others) serve to differentiate between these two envisaged treatment durations. This is related to question C18, wherein it is asked why the treatment costs for LDV/SOF are divided by 2 or 3 depending on the treatment duration. Please see the response to C18 for further information.

C7. **Priority question:** In the "Model patients" worksheet, cell AR21 of the company's economic model, please explain what the bold highlighted part of this formula is intended to adjust for? =IF(TreatmentWeeksSOF>8,AR20,**(AR20-(AT21-AT20)**))

The bold highlighted part of the formula described above returns the number of non-cirrhotic patients who didn't reach SVR 24 weeks after 8 weeks of treatment i.e. patients who achieved SVR (A20) in the previous cycle are removed from the next cycle calculation (A21-A20)

C8. **<u>Priority question:</u> Please comment on the validity of using a blended comparison of efficacy and treatment duration for the LDV/SOF option in each analysis.**

Using a blended comparison allows for the consideration of a representative CHC population receiving treatment, of which some sub-populations may not receive the same duration of LDV/SOF treatment.

Modelling the treatment durations separately and subsequently calculating weighted average results for the overall population returns the same results as running a combined analysis (wherein the efficacy and costs inputs are weighted to reflect the proportion receiving each treatment regimen). Running combined analyses reflects the cost-effectiveness of treating a CHC cohort according to the population characteristics, aligns with how the cost-effectiveness of CHC medicines has been assessed in previous appraisals (by subgroup not duration), and reduces the number of results presented in the submission.

C9. Please explain whether the risk of other-cause mortality was adjusted to remove the risk of death because of hepatitis C and its consequences (for example, hepatocellular carcinoma)?

No, other-cause mortality was not adjusted in the analysis to remove the risk of death due to advanced liver disease resulting from CHC. This has not typically been considered in previous economic evaluations of CHC treatment. The effect of such an adjustment is expected to be minor given the very small proportion of patients in the general population developing advanced liver disease due to CHC.

Mortality rates for each age were varied ±25% in the deterministic sensitivity analyses. Results for the top ten drivers of the net benefit were presented in Section 7.7.7 of the submission (Tables 103-124), accompanied by tornado diagrams. Reducing the mortality rates by an extreme value of 25% represents a greater reduction than would be observed if adjustments were made to remove the risk of death associated with advanced liver disease.

The mortality rates fell within the top ten drivers in a small number of analyses. In these analyses, the mortality rates were either the 8th, 9th or 10th model driver:

- GT1 TN: LDV/SOF vs no treatment
- GT4 TN: LDV/SOF vs no treatment
- GT1/4 TE: LDV/SOF vs PEG-IFN2a+RBV
- GT1/4 TE: LDV/SOF vs no treatment
- GT3 TN: LDV/SOF+RBV vs no treatment
- GT3 TE: LDV/SOF+RBV vs no treatment

Where the base case analysis indicates that the LDV/SOF regimen is cost-effective, the net benefit remains positive when the mortality rates are varied ±25%. Thus LDV/SOF remains cost-effective.

The resulting change in the net benefit is presented for each analysis in the tables below.

Table 13: Deterministic sensitivity analysis of mortality rates: GT1 TN LDV/SOF vs no treatment

	Value			Net benefit		
	Base-case	**Minimum**	**Maximum**	**Minimum**	**Maximum**	**Difference**
Mortality rates	Multiple age-specific values	All varied -25%	All varied +25%	£36,362	£30,647	£5,715

Table 14: Deterministic sensitivity analysis of mortality rates: GT4 TN LDV/SOF vs no treatment

	Value			Net benefit		
	Base-case	**Minimum**	**Maximum**	**Minimum**	**Maximum**	**Difference**
Mortality rates	Multiple age-specific values	All varied -25%	All varied +25%	£28,537	£22,786	£5,751

Table 15: Deterministic sensitivity analysis of mortality rates: GT1/4 TE LDV/SOF vs PEG-IFN2a+RBV

	Value			Net benefit		
	Base-case	**Minimum**	**Maximum**	**Minimum**	**Maximum**	**Difference**
Mortality rates	Multiple age-specific values	All varied -25%	All varied +25%	£17,541	£12,519	£5,023

Table 16: Deterministic sensitivity analysis of mortality rates: GT1/4 TE LDV/SOF vs no treatment

	Value			Net benefit		
	Base-case	**Minimum**	**Maximum**	**Minimum**	**Maximum**	**Difference**
Mortality rates	Multiple age-specific values	All varied -25%	All varied +25%	£18,328	£12,340	£5,988

Table 17: Deterministic sensitivity analysis of mortality rates: GT3 TN: LDV/SOF+RBV vs No treatment

	Value			Net benefit		
	Base-case	**Minimum**	**Maximum**	**Minimum**	**Maximum**	**Difference**
Mortality rates	Multiple age-specific values	All varied -25%	All varied +25%	£32,298	£25,199	£7,099

Table 18: Deterministic sensitivity analysis of mortality rates: GT3 TE: LDV/SOF+RBV vs No treatment

	Value			Net benefit		
	Base-case	**Minimum**	**Maximum**	**Minimum**	**Maximum**	**Difference**
Mortality rates	Multiple age-specific values	All varied -25%	All varied +25%	-£16,148	-£22,711	£6,563

For completeness, an additional analysis was considered where the annual mortality rates inputs were varied by -10%. Results for this analysis are presented in Table 19.

Table 19: Summary of base-case cost-effectiveness results (ICER for LDV/SOF±RBV against each comparator: £/QALY)

Indication	LDV/SOF regimen	Comparator							
		SOF+ PEG-IFN2a +RBV	SMV+ PEG-IFN2a +RBV	PEG-IFN2a +RBV	TVR+ PEG-IFN2a +RBV	BOC+ PEG-IFN2a +RBV	SOF+RBV	NT	SMV+SOF
GT1 treatment naïve	LDV/SOF	LDV/SOF dominates	LDV/SOF dominates	£7,798	LDV/SOF dominates	LDV/SOF dominates	-	£7,269	LDV/SOF dominates
GT4 treatment naïve	LDV/SOF	£3,784	£12,158	£12,438	-	-	-	£10,219	LDV/SOF dominates
GT1/GT4 treatment experienced†	LDV/SOF	£5,313	£9,724	£12,150	£8,910	£3,433	-	£13,157	LDV/SOF dominates
GT3 treatment naïve‡	LDV/SOF+RBV	£45,878‡	-	£26,001	-	-	£18,749‡	£10,970	-
GT3 treatment experienced IFN ineligible‡	LDV/SOF+RBV	-	-	-	-	-	£6,108‡	£27,317	-

Abbreviations: BOC, boceprevir; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; NT, no treatment; PEG-IFN, pegylated interferon; QALY; quality adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
† TVR+PEG-IFN2a+RBV and BOC+PEG-IFN2a+RBV are relevant for GT1 CHC only as they are not licensed for the treatment of GT4 CHC.
‡ In GT3 patients some comparisons have been restricted to cirrhotic patients only in line with preliminary NICE recommendations for particular comparators. All other scenarios include a mixed cohort of non-cirrhotic and cirrhotic patients.

C10. Please explain why the economic model requires three different cycle durations?

The economic model requires three different cycle durations due to the different treatment durations used in the model. The treatment durations in the model are approximately equal (due to incorporation of discontinuations) to 8, 12, 24 and 48 weeks. To accommodate these different treatment durations and to capture SVR 12 and 24 weeks after the end of treatment, 1-month (4 weeks) cycles for the first 18th cycles were used and 3-month (12 weeks) cycles were used for the next two cycles. After year 2, annual cycles were used.

Transition probabilities

C11. <u>Priority question:</u> Are the transition probabilities contained in the "Transition Matrices" worksheet identical for all populations and comparators? If so, please provide the justification.

Transition probabilities for the non-cirrhotic to compensated cirrhosis transition differed according to genotype, based upon published evidence (Table 20). No data has been published to support differences in the other transition probabilities based upon population or comparator; as a result they are the same for all patient populations and comparators (Table 21).

Table 20: Transition probabilities by genotype

From	To	TP (annual probabilities)	Source	Comments
Non-cirrhotic	Compensated cirrhosis	**GT1/4** 30 years: 0.006 40 years: 0.009 50 years: 0.016 **GT3** 30 years: 0.008 40 years: 0.013 50 years: 0.024	Calculation, described in text above	TPs were derived from TPs reported by Thompson 2008 (39) (Grishchenko et al, 2009 (40))

Abbreviations: GT, genotype; TP, transition probability.

Table 21: Generic transition probabilities

From	To	TP (annual probabilities)	Source	Comments
Non-cirrhotic, SVR	Non-cirrhotic (recurrence)	Base case: 0 Min: 0 Max: 0.01	Expert opinion	Sensitivity analysis only
	Non-cirrhotic (re-infection)	Base case: 0 Min: 0 Max: 0.01	Expert opinion	Sensitivity analysis only

From	To	TP (annual probabilities)	Source	Comments
Compensated cirrhosis	Decompensated cirrhosis	0.0438	Cardoso et al, 2010 (41)	Calculation as per SOF NICE
	HCC	0.0631	Cardoso et al, 2010 (41)	Calculation as per SOF NICE
Compensated cirrhosis with SVR	Compensated cirrhosis (recurrence)	Base case: 0 Min: 0 Max: 0.01	Expert opinion	Sensitivity analysis only
	Compensated cirrhosis (re-infection)	Base case: 0 Min: 0 Max: 0.01	Expert opinion	Sensitivity analysis only
	Decompensated cirrhosis	0.0064	Cardoso et al, 2010 (41)	Calculation
	HCC	0.0128	Cardoso et al, 2010 (41)	Calculation
Decompensated cirrhosis	HCC	0.0631	Cardoso et al, 2010 (41)	Calculation
	Liver transplant	0.022	Siebert et al, 2005 (42)	
	Death	0.13	Fattovich et al, 1997 (43)	Publications that used this TP: -Hartwell et al, 2011 (2) -Shepherd et al, 2007(1) -Wright et al, 2006 (44)
HCC	Liver transplant	Base case: 0 Min: 0 Max: 0.01	Expert opinion	Sensitivity analysis only
	Death	0.43	Fattovich et al, 1997 (43)	Publications that used this TP: -Hartwell et al, 2011 (2) -Shepherd et al, 2007 (1) -Wright et al, 2006 (44)
Liver transplant	Death, Yr1	0.21	Shepherd et al, 2007 (1)	
Post-liver transplant	Death, Yr2	0.057	Shepherd et al, 2007 (1)	

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

C12. Please provide some evidence to demonstrate the validity of the transition probability estimation for the non-cirrhotic to cirrhotic states, referred to in Section 7.3.2, pages 162 to 163 of the company's submission. For example, please provide the file (which uses Solver) containing the calculations that estimate the transition probabilities.

The calculations for estimating the transitions probabilities are provided in the Excel file attached.

Assumptions

C13. <u>Priority Question:</u> The company's economic model assumes that there are no deaths until 6 months after stopping treatment, either because of the hepatitis C virus (HCV) or background mortality. Please clarify why the economic model assumes that patients cannot die until 9 months after entry?

The economic model assumes that patients can die only after SVR measurement. The reason is that SVR rates are based on the intention to treat population. Therefore if we considered that patients died before SVR measurement we would be applying the SVR rates only to those patients who were alive or did not progress and this would be incorrect.

In addition, this approach has been used and accepted in previous appraisal of medicines for the treatment of CHC submitted to NICE.

C14. <u>Priority Question:</u> Section 7.3.8 states that "Patients do not progress while on treatment, nor during the 12 to 24 weeks after the end of treatment" (see page 178 of the company's submission). Please clarify why patients are assumed not to develop adverse consequences of hepatitis C (for example, cirrhosis, cancer) until after 9 months?

The economic model assumes that patients only progress to more advanced stages or death after SVR measurement. Similar to the reason stated in C13, the reason is that SVR rates are based on the intention to treat population. Therefore if we considered that patients progressed before SVR measurement we would be applying the SVR rates only to those patients who were alive or did not progress and this would be incorrect.

In addition, this approach has been used and accepted in previous appraisal of medicines for the treatment of CHC submitted to NICE.

C15. The company's economic model assumes that the utility decrement for LDV/SOF is zero (see page 183 of the company's submission). Please provide justification for this. Please also explain why this is considered by the company as 'commercial in confidence'.

No utility decrement was observed in any patients treated with LDV/SOF. In fact, due to the rapid reduction in viral load, of which patients were unaware, patients were found to experience an improvement in quality of life whilst treated with LDV/SOF. Preference-based SF-6D data presented at AASLD show that patients receiving RBV-free LDV/SOF regimens showed significant improvement in their SF-6D scores during treatment (+3.5% in the 8 weeks arm, +4.8% in 12 weeks, +4.1% in 24 weeks; all p<0.001). Preference-based data quantifying the value of the utility increase on treatment were not available at the time of submission. In light of this, a conservative approach was taken in assuming no difference in quality of life whilst treated with LDV/SOF.

This assumption was marked as commercial in confidence as the utility data from the trials had not been published at the time of submission. This data was presented at AASLD November 2014 (45).

Unit costs and healthcare resources

C16. <u>Priority question:</u> Please clarify what the cost per 28 days for LDV/SOF is intended within the economic model. Please explain why the cost per cycle increases when the treatment duration is less than 8 weeks (for example, see worksheet "Model costs" cells J13:15 in the company's economic model).

The following clarification was received from NICE with regards to this question.

"The query is regarding the cost of LDV/SOF per 28-day cycle, which appears to be linked to the treatment duration (i.e. cost per cycle changes with different treatment durations). In the excel model, sheet 'Model costs', cell I13 (='Model patients'!J13*IF(TreatmentWeeksSOF>8, 'Transition Matrices'!$AG$19/3, 'Transition Matrices'!$AG$19/2)). It is divided by two or three, where in fact the cost per cycle should be independent of duration."

It is agreed that the cost per cycle should be independent of treatment duration, with the number of cycles over which the cost is incurred reflecting the treatment duration. As explained in the response to C18, the calculations reflect the fact that when the model was developed [redacted]. Please see the response to C18 for further information on how the cost of 24 week LDV/SOF treatment is incorporated.

C17. <u>Priority question:</u> Please clarify how drug wastage is included in the economic model. For example, if the cohort needs an average of 12.6 weeks of treatment, are four packs costed? Please also comment on the expected wording of the marketing authorisation with respect to treatment duration for the overall eligible population and specific subgroups.

In the base case analysis, no treatment discontinuation is assumed for LDV/SOF as less than 1% of patients discontinued in the ION trials. In addition LDV/SOF regimens are not response-guided, that is, shorter treatment durations are not considered for patients who rapidly clear the virus from their bloodstream. As such, no drug wastage is assumed. An individual patient would receive 8, 12, or 24 weeks of treatment i.e. 2, 3, or 4 packs of

LDV/SOF. Therefore, although the weighted average treatment duration for the cohort is 12.6 weeks, this is calculated on the basis of patients receiving 8, 12, or 24 weeks of treatment.

In the case of the LDV/SOF+RBV analyses, it is noted that the average daily dose for the cohort would be 1,200mg of RBV (3 x 400mg tablets) per day. Tablets are sold in packs of 56, therefore 9 packs would be required for a 24-week LDV/SOF+RBV regimen and 5 for a 12-week LDV/SOF+RBV regimen. The base case analysis did not consider the wastage associated with the 12-week regimen (i.e. 28 tablets or half a pack).

Treatment discontinuation was considered in the case of all model comparators with the exception of SOF+PEG-IFN2a+RBV in GT3 TN non-cirrhotic patients (data from ELECTRON and PROTON), and SMV+SOF in GT1/4 (data from COSMOS). Treatment costs for all comparators were based on the average treatment duration, taking discontinuations into account, and did not adjust for drug wastage, therefore biasing the results against the LDV/SOF regimen. If drug wastage was included, the drug costs would be rounded up to the nearest pack thereby increasing the drug costs associated with the comparators.

For completeness, the analysis was re-run considering the effect of wastage for RBV when taken in combination with LDV/SOF in GT3 and for all relevant comparators. The results of these analyses are presented in Table 22.

Table 48 of the original submission presents the summary of the patient sub-populations receiving each treatment duration and the rationale including validation by UK KOLs. Overall, this means that 46.4% of the GT1 and GT4 population would receive 8 weeks treatment, 51% would receive 12 weeks treatment, and 2.7% would receive 24 weeks treatment. Of the GT3 population, 52.5% would receive 12 weeks and 47.5% would receive 24 weeks treatment.

Table 22: Summary of base-case cost-effectiveness results (ICER for LDV/SOF±RBV against each comparator: £/QALY)

Indication	LDV/SOF regimen	Comparator							
		SOF+ PEG-IFN2a +RBV	SMV+ PEG-IFN2a +RBV	PEG-IFN2a +RBV	TVR+ PEG-IFN2a +RBV	BOC+ PEG-IFN2a +RBV	SOF+RBV	NT	SMV+SOF
GT1 treatment naïve	LDV/SOF	LDV/SOF dominates	LDV/SOF dominates	£7,897	LDV/SOF dominates	LDV/SOF dominates	-	£7,458	LDV/SOF dominates
GT4 treatment naïve	LDV/SOF	£1,592	£12,285	£12,628	-	-	-	£10,468	LDV/SOF dominates
GT1/GT4 treatment experienced†	LDV/SOF	£4,278	£9,610	£12,411	£7,502	£2,646	-	£13,527	LDV/SOF dominates
GT3 treatment naïve‡	LDV/SOF+RBV	£46,345‡	-	£26,092	-	-	£18,677‡	£11,264	-
GT3 treatment experienced IFN ineligible‡	LDV/SOF+RBV	-	-	-	-	-	£6,052‡	£28,048	-

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

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

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

C18. <u>Priority question:</u> In the "Model Costs" worksheet column J of the company's economic model, please clarify why the cost is divided by 3 or 2 depending on treatment duration?

These calculations reflect the fact that when the model was developed [redacted] However, the model can consider an extended treatment duration of 24 weeks. The calculations referenced split the cost appropriately across 2 cycles for an 8 week regimen or 3 cycles for a 12 week regimen. For any treatment duration longer than 8 weeks (i.e. 12 or 24 weeks or a weighted average treatment duration) the costs are split across three cycles. In the most extreme scenario wherein a 24 week treatment duration is considered for the entire cohort the cost for 24 weeks of LDV/SOF would be split across three cycles with patients progressing through model cycles following the measurement of SVR at 12 weeks post-transplant. The impact of this is that with the model structure, patients may be progressing through the model three cycles too soon but this is anticipated to have a negligible effect on results across a lifetime time horizon. Treatment costs, as previously stated, are correctly calculated, and since no discounting is applied in the first year the application of costs across three cycles rather than six (in the case of modelling a 24 week LDV/SOF treatment) has no material impact on the results.

C19. The data presented in Table 78 includes the unit costs per resource use item (see page 189 of the company's submission). Please confirm that this is true. If so, please provide the resource use assumed to estimate the monitoring costs for each of the treatments.

Please see appendix 15 of the submission (Tables 184 to 197) for the detail of resource use assumed to be associated with each monitoring visit.

Results

C20. <u>Priority question:</u> The company's economic model runs for the cirrhotic and non-cirrhotic populations separately, and then weight the results according to the proportion of patients with/without cirrhosis. Given that the economic model structure includes both cirrhotic and non-cirrhotic states, please explain why this approach was used? Please clarify why the economic model does not allow for a mix of cirrhotic and non-cirrhotic to flow through the states simultaneously?

The economic model runs the non-cirrhotic and cirrhotic populations separately only for genotype 1 treatment-naïve patients. The reason is that at the beginning of the model development [redacted] As explained in response to C8, the results are not expected to vary significantly whether the model allowed

for a mix to flow through the states simultaneously or whether they were modelled separately and weighted at the end.

C21. <u>Priority Question:</u> In section 7.7.6 of the company's submission, please clarify whether the base case results have been derived from the probabilistic sensitivity analyses or whether they are based on point estimates of parameters (that is, deterministic analyses).

The base case results presented in section 7.7.6 are based on the deterministic analyses. These deterministic results are presented alongside the probabilistic results in tables below, both of which support the conclusions made in the original submission. Please note, a minor calculation error was discovered in the probabilistic sensitivity analysis, wherein the base case SVR rate for SMV+SOF regimens in GT1 and GT4 had not been updated to reflect the COSMOS data. Corrected multiple CEACs are presented below and only include very minor differences compared to the previous analyses.

Table 23: GT1 treatment naïve

Technologies	Deterministic results		Probabilistic results	
	Costs (£)	QALYs	Costs (£)	QALYs
No treatment	£18,956	13.01	£18,840	13.01
PEG-IFN2a+RBV	£25,308	13.98	£25,185	13.98
LDV/SOF	£38,713	15.66	£38,656	15.69
SMV+PR	£38,731	15.02	£38,586	15.04
TVR+PEG-IFN2a+RBV	£40,237	14.85	£39,890	14.87
BOC+PEG-IFN2b+RBV	£41,299	14.66	£41,248	14.68
SOF+PR	£45,776	15.40	£45,610	15.43
SOF+SMV	£65,630	15.57	£65,466	15.60

Abbreviations: BOC, boceprevir; GT, genotype; LDV, ledipasvir; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

Figure 11: Multiple CEACs GT1 treatment naïve

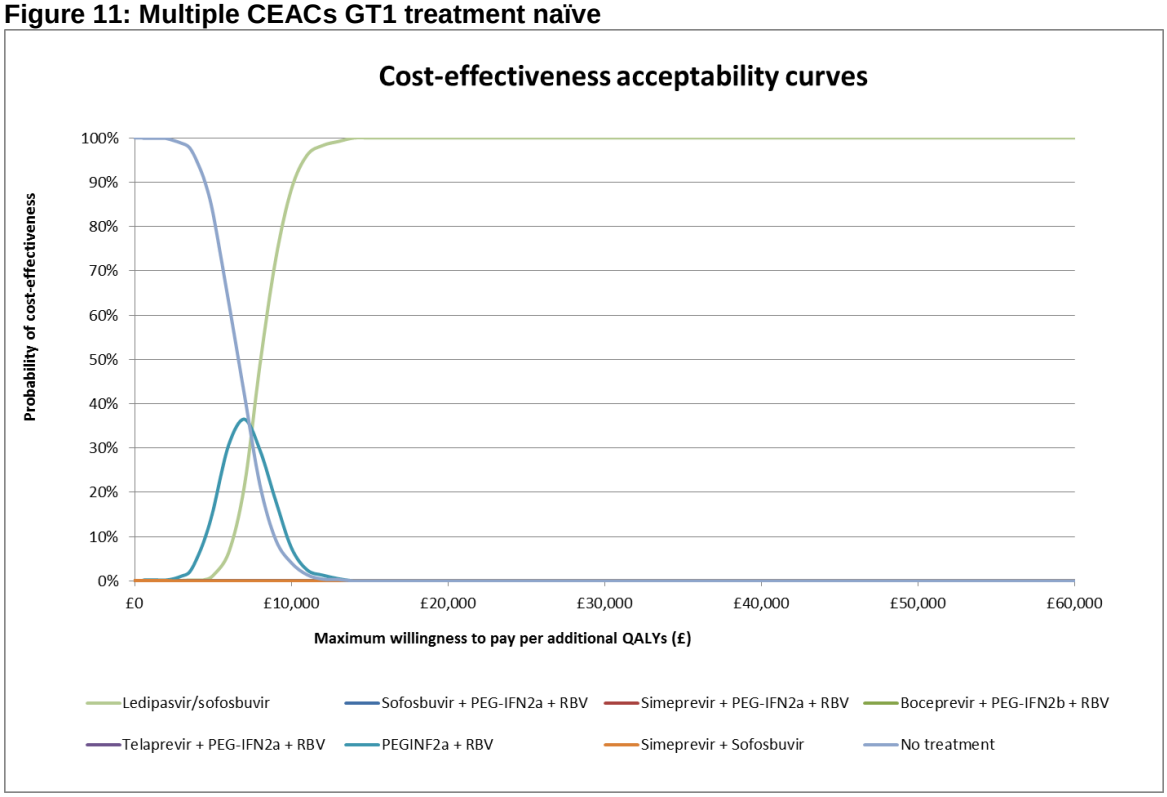


Table 24: GT4 treatment naïve

Technologies	Deterministic results		Probabilistic results	
	Costs (£)	QALYs	Costs (£)	QALYs
No treatment	£18,956	13.01	£19,131	13.01
PEG-IFN2a+RBV	£25,308	13.98	£25,290	14.00
SMV+PR	£38,731	15.02	£38,731	15.03
SOF+PR	£45,776	15.40	£45,849	15.41
LDV/SOF	£46,823	15.67	£46,774	15.69
SOF+SMV	£65,630	15.57	£65,741	15.57

Abbreviations: GT, genotype; LDV, ledipasvir; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

Figure 12: Multiple CEACs GT4 treatment naïve

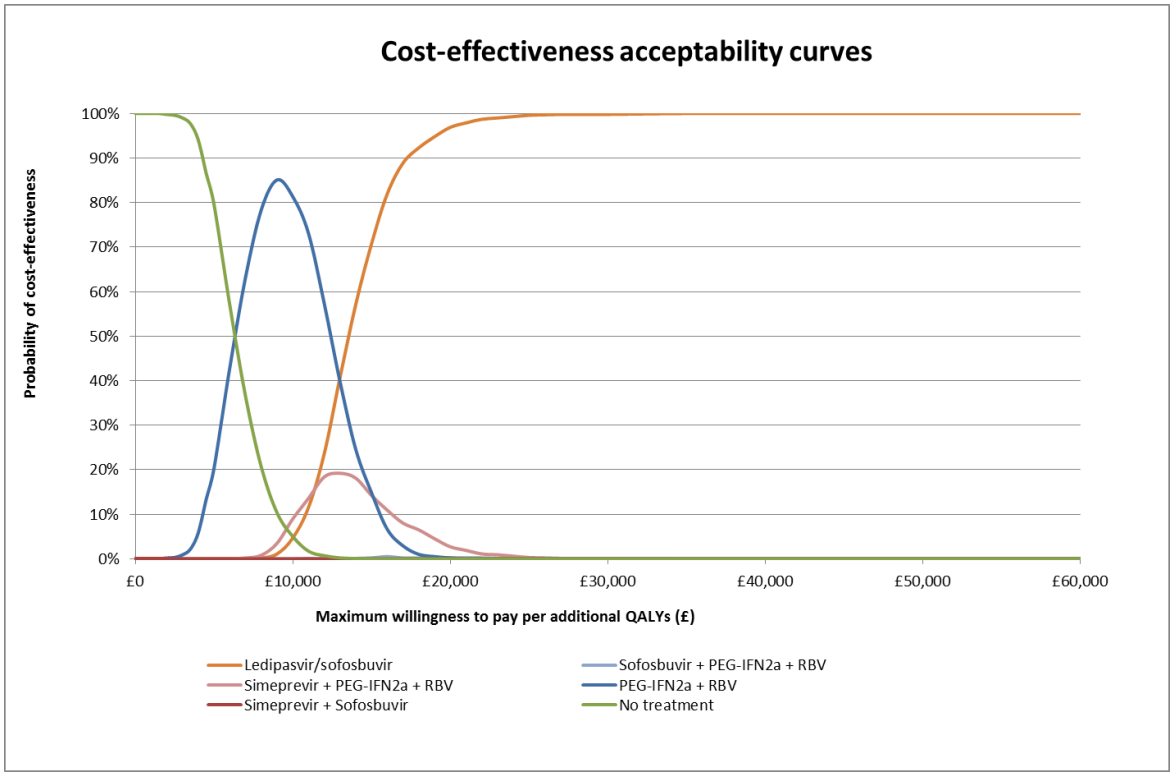


Table 25: GT1 and GT4 treatment experienced

Technologies	Deterministic results		Probabilistic results	
	Costs (£)	QALYs	Costs (£)	QALYs
No treatment	£18,143	12.40	£18,344	12.42
PEG-IFN2a+RBV	£24,960	12.75	£24,992	12.77
TVR+PEG-IFN2a+RBV	£42,101	13.90	£41,922	13.93
SMV+PR	£43,626	14.13	£43,646	14.14
BOC+PEG-IFN2b+RBV	£45,897	13.69	£45,872	13.71
SOF+PR	£46,756	14.21	£46,875	14.22
LDV/SOF	£49,537	14.72	£49,560	14.73
SOF+SMV	£64,720	14.71	£65,249	14.64

Abbreviations: BOC, boceprevir; GT, genotype; LDV, ledipasvir; PEG-IFN, pegylated interferon; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

Figure 13: Multiple CEACs GT1and GT4 treatment experienced

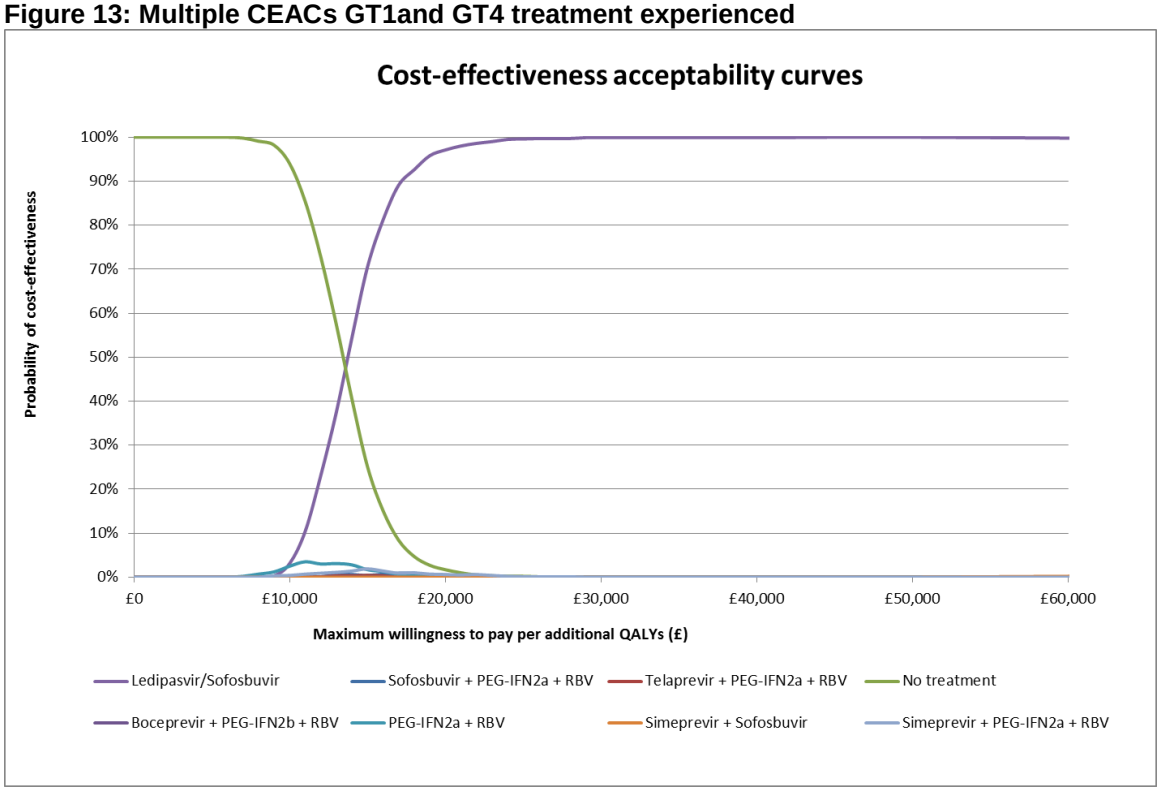


Table 26: GT3 treatment naïve

Technologies	Deterministic results		Probabilistic results	
	Costs (£)	QALYs	Costs (£)	QALYs
PR	£18,937	14.01	£18,848	14.03
No treatment	£21,509	12.24	£21,485	12.27
LDV/SOF+RBV	£57,909	15.48	£58,091	15.46

Abbreviations: GT, genotype; LDV, ledipasvir; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir.

Table 27: GT3 treatment naïve compensated cirrhosis

Technologies	Deterministic results		Probabilistic results	
	Costs (£)	QALYs	Costs (£)	QALYs
SOF+PR	£63,419	9.38	£63,210	9.51
SOF+RBV	£95,947	9.87	£95,890	9.97
LDV/SOF+RBV	£102,645	10.23	£102,811	10.25

Abbreviations: GT, genotype; LDV, ledipasvir; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir.

Table 28: GT3 treatment experienced

Technologies	Deterministic results		Probabilistic results	
	Costs (£)	QALYs	Costs (£)	QALYs
No treatment	£20,614	11.71	£20,464	11.74
LDV/SOF+RBV	£89,522	14.17	£89,506	14.17

Abbreviations: GT, genotype; LDV, ledipasvir; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir.

Table 29: GT3 treatment experienced with compensated cirrhosis

Technologies	Deterministic results		Probabilistic results	
	Costs (£)	QALYs	Costs (£)	QALYs
SOF+RBV	£101,109	8.01	£100,888	8.07
LDV/SOF+RBV	£105,761	8.76	£105,599	8.80

Abbreviations: GT, genotype; LDV, ledipasvir; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir.

C22. Section 7.2.7, page 159 of the company's submission states that: "*ICERs are only reported herein for comparisons with regimens incorporating PEG-IFN2a. This is a conservative approach in terms of costs as PEG-IFN2a is more expensive than PEG-IFN2b*". Please clarify if this (that is, PEG-IFN2a is more expensive than PEG-IFN2b) is a typographical error.

The statement 'This is a conservative approach in terms of costs as PEG-IFN2a is more expensive than PEG-IFN2b' was included in error. PEG-IFN2a, however, has approximately 80% of the market share, and is therefore the most valid pegylated interferon to include. In addition PEG-IFN2a was also used with SOF in the clinical trials. However, an additional analysis was run wherein PEG-IFN2b-containing regimens were considered. The results of these analyses are presentedTable 30. The conclusions of the analyses are unchanged versus the base case results.

Table 30: Summary of base-case cost-effectiveness results (ICER for LDV/SOF±RBV against each comparator: £/QALY)

Indication	LDV/SOF regimen	Comparator							
		SOF+ PEG-IFN2a +RBV	SMV+ PEG-IFN2a +RBV	PEG-IFN2a +RBV	TVR+ PEG-IFN2a +RBV	BOC+ PEG-IFN2a +RBV	SOF+RBV	NT	SMV+SOF
GT1 treatment naïve	LDV/SOF	LDV/SOF dominates	LDV/SOF dominates	£7,182	LDV/SOF dominates	LDV/SOF dominates	-	£7,458	LDV/SOF dominates
GT4 treatment naïve	LDV/SOF	£2,335	£11,151	£11,918	-	-	-	£10,468	LDV/SOF dominates
GT1/GT4 treatment experienced†	LDV/SOF	£4,675	£7,280	£11,950	£7,461	£3,551	-	£13,527	LDV/SOF dominates
GT3 treatment naïve‡	LDV/SOF+RBV	£45,991‡	-	£25,989	-	-	£19,013‡	£11,235	-
GT3 treatment experienced IFN ineligible‡	LDV/SOF+RBV	-	-	-	-	-	£6,210‡	£28,048	-

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

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

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

C23. For the PSA, please clarify whether common random numbers are used between the options? If so, please explain how to run the PSA using common random numbers across options in the economic model.

For the PSA, which plots the incremental costs and incremental outcomes for one comparison, one set of random numbers is generated per simulation and results are displayed for each set of inputs.

For the multiple PSA, which generates the total costs and total outcomes for all the different treatments in one indication, one set of random numbers is also generated per simulation and the same set is used to compute the results for each treatment. The random input numbers are recorded in the hidden sheet "Record_simulation".

C24. Please clarify whether it was intentional to include zero as a parameter in some probability distributions for the PSA? For example, a gamma distribution is used to represent uncertainty about parameters for 'Quality of life (utilities decrement) during year of treatment' and 'SVR quality of life increment' in the company's economic model (see "PSA inputs" worksheet). The Evidence Review Group note that gamma distribution is represented by two parameters that must take values greater than zero. The Evidence Review Group therefore consider that some probability distributions are not defined when one of the parameters is exactly zero (and distributions can also be poorly defined when parameters are close to zero).

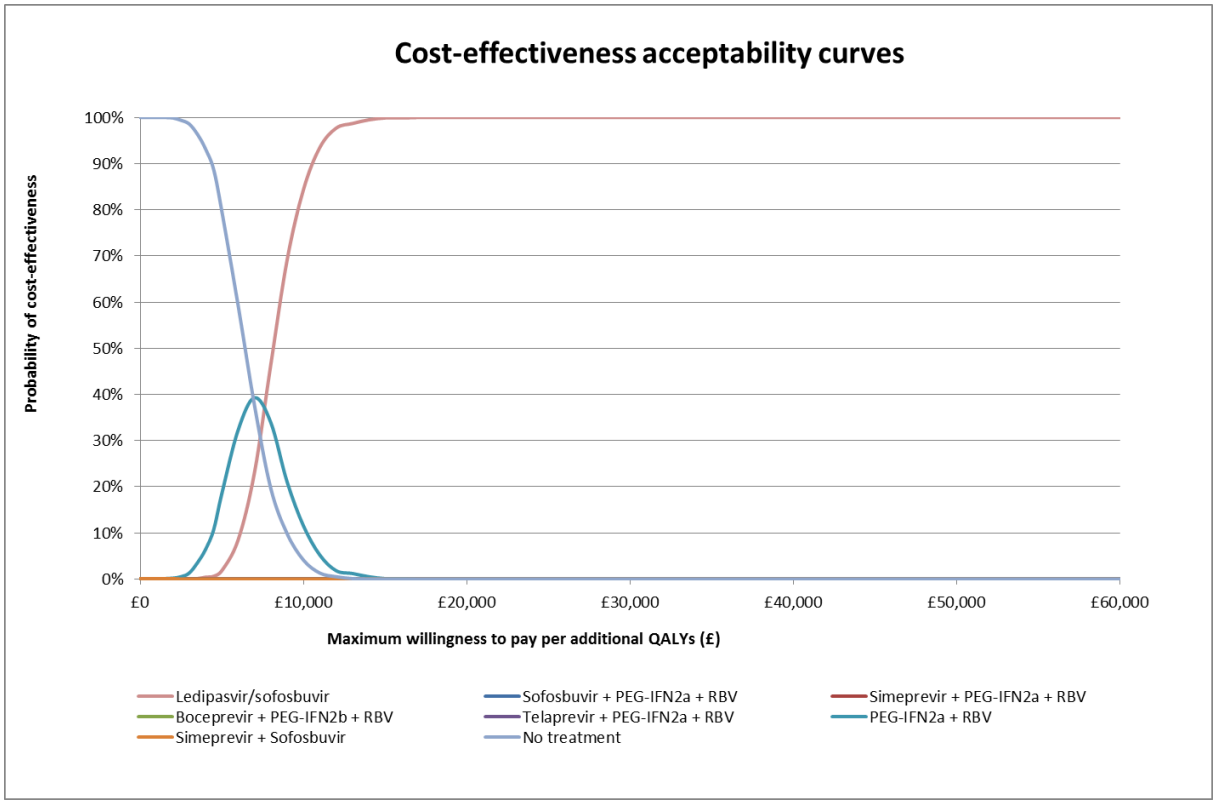
No variation is assumed around the quality of life decrement on treatment for LDV/SOF (0% base case). This is a structural assumption and is conservative given that all patients treated with RBV-free LDV/SOF regimens in the ION trials experienced an improvement in their utility (45).

The multiple probabilistic sensitivity analyses were re-run considering normal distributions for the utility decrements associated with treatment and the utility increments associated with achieving SVR. In addition, for patients treated with LDV/SOF it was conservatively assumed that they had the same distribution utility decrement as patients treated with LDV/SOF+RBV. Results were closely aligned with the original analysis.

GT1 treatment naïve

The CEACs are presented in Figure 14. The CE frontier consists of no treatment, PEG-IFN2a+RBV and LDV/SOF. The probability that LDV/SOF is a cost effective option compared with all other comparators at a £20,000 per QALY threshold is 100%.

Figure 14: Multiple CEAC for GT1 treatment naïve

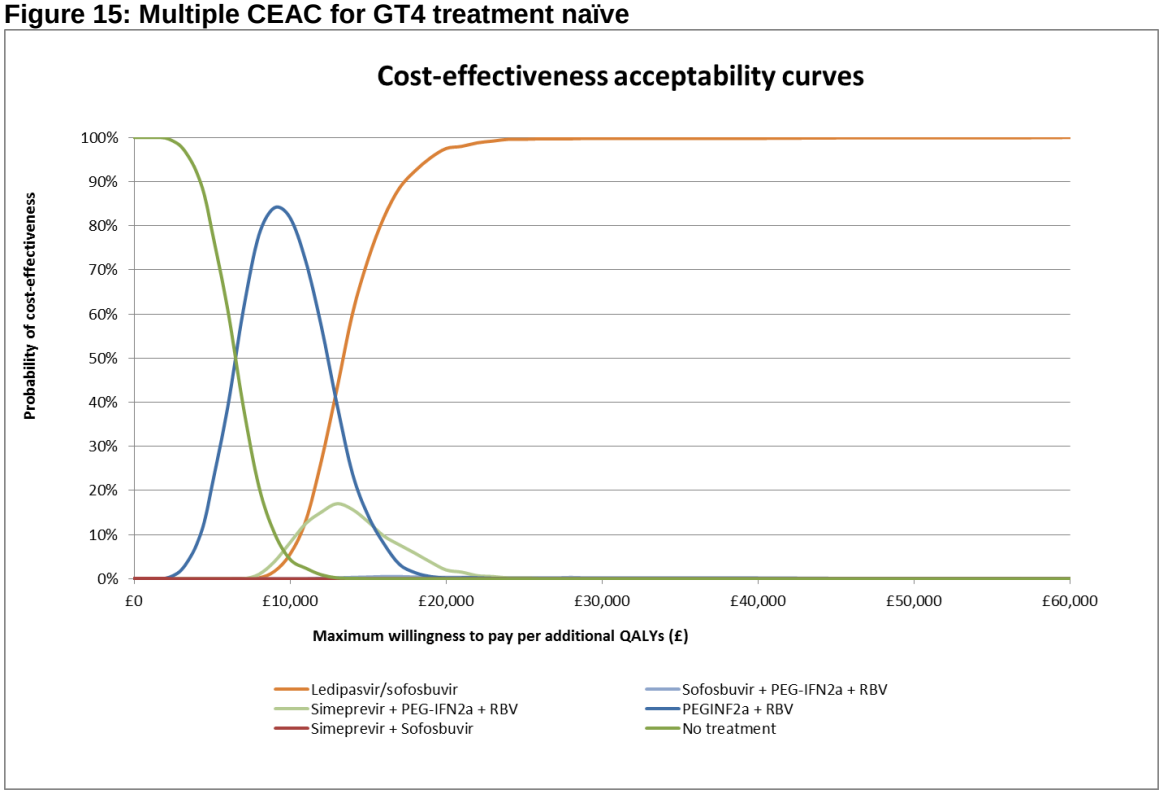


Abbreviations: GT, genotype; PEG-IFN, pegylated interferon; QALY, quality-adjusted life year; RBV, ribavirin; wks, weeks.

GT4 treatment naïve

The CEACs are presented in Figure 15. The CE frontier consists of no treatment, PEG-IFN2a+RBV and LDV/SOF. The probability that LDV/SOF is a cost effective option compared with all other comparators is 98% at a £20,000 per QALY threshold and 100% at a £30,000 per QALY threshold.

Figure 15: Multiple CEAC for GT4 treatment naïve

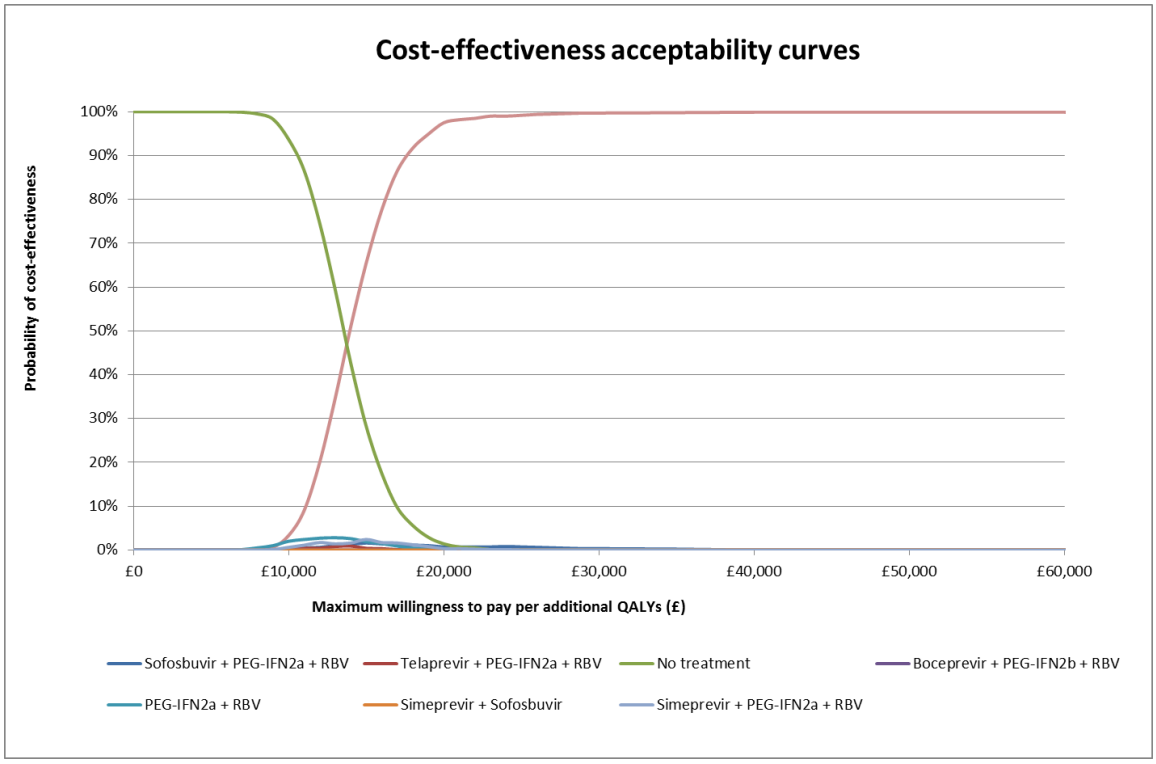


Abbreviations: GT, genotype; PEG-IFN, pegylated interferon; QALY, quality-adjusted life year; RBV, ribavirin; wks, weeks; TN, treatment naïve; wks, weeks.

GT1 and GT4 treatment experienced

The CEACs are presented in Figure 13: . The CE frontier consists of no treatment, SMV+PEG-IFN2a+RBV and LDV/SOF. The probability that LDV/SOF is a cost effective option compared with all other comparators is 98% at a £20,000 per QALY threshold and 100% at a £30,000 per QALY threshold.

Figure 13: Multiple CEAC for GT1 and GT4 treatment experienced

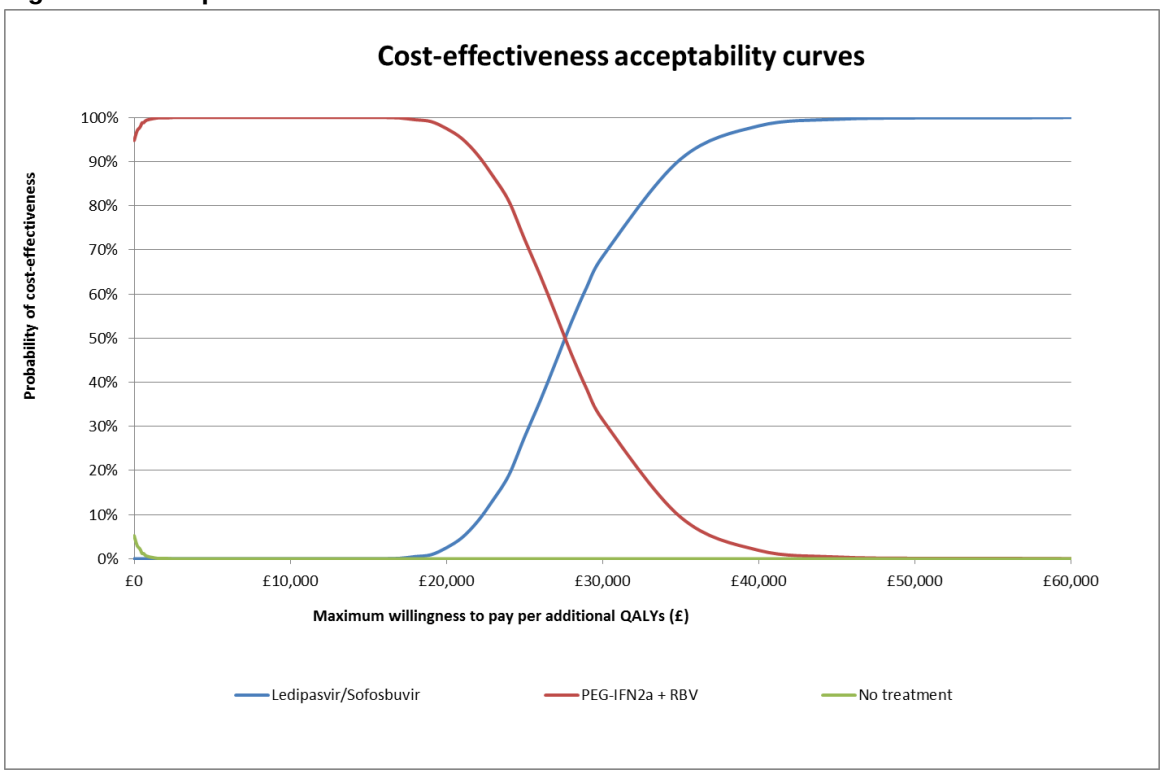


Abbreviations: GT, genotype; PEG-IFN, pegylated interferon; QALY, quality-adjusted life year; RBV, ribavirin; wks, weeks; TN, treatment naïve; wks, weeks.

GT3 treatment naïve

The CEACs are presented in Figure 16. The CE frontier consists of PEG-IFN2a+RBV and LDV/SOF+RBV. The probability that LDV/SOF+RBV is a cost effective option compared with all other comparators is 2.5% at a £20,000 per QALY threshold and 68% at a £30,000 per QALY threshold.

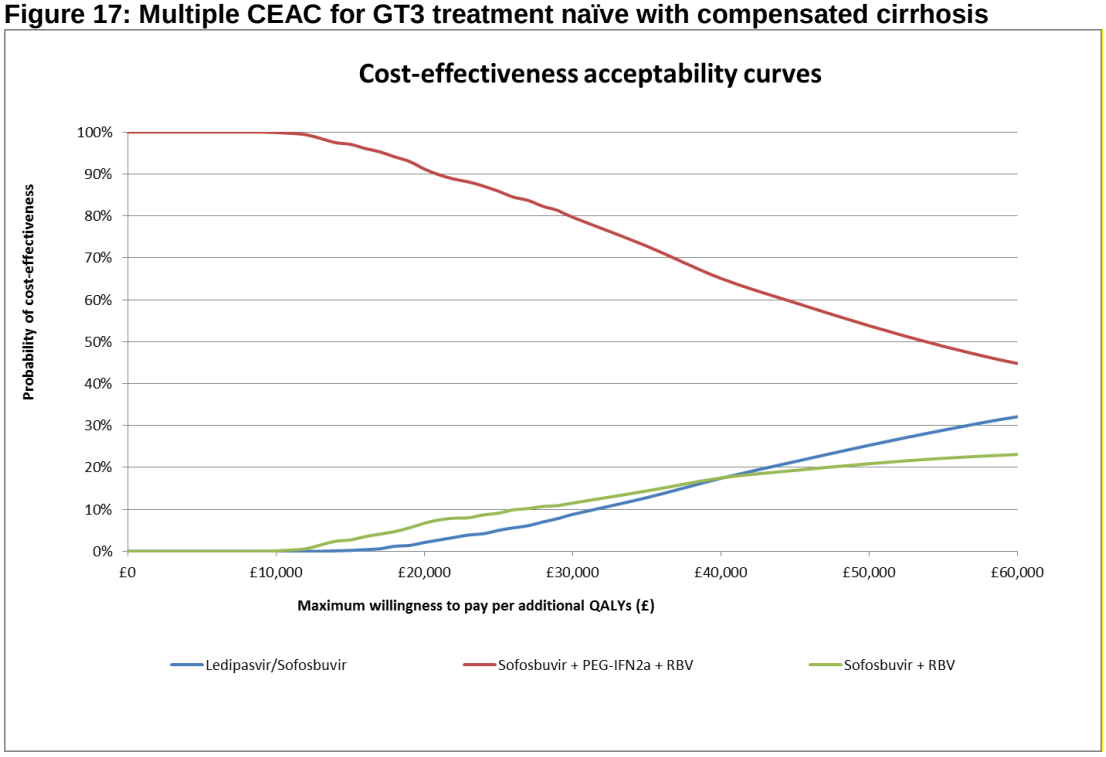
Figure 16: Multiple CEAC for GT3 treatment naïve



Abbreviations: GT, genotype; PEG-IFN, pegylated interferon; QALY, quality-adjusted life year; RBV, ribavirin; wks, weeks; wks, weeks.

The CEACs for the analysis restricted to GT3 treatment naïve patients with compensated cirrhosis are presented in Figure 16. The CE frontier consists of SOF+PEG-IFN2a+RBV. The probability that LDV/SOF+RBV is a cost effective option compared with all other comparators is 2.1% at a £20,000 per QALY threshold and 8.8% at a £30,000 per QALY threshold (base case ICER = £46,491).

Figure 17: Multiple CEAC for GT3 treatment naïve with compensated cirrhosis

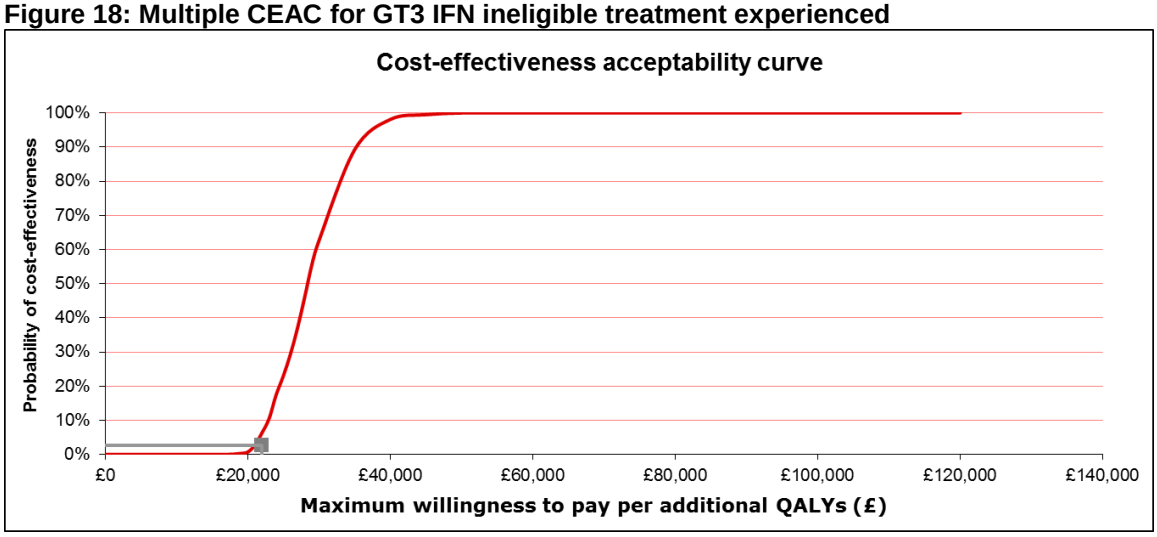


Abbreviations: GT, genotype; PEG-IFN, pegylated interferon; QALY, quality-adjusted life year; RBV, ribavirin; wks, weeks; wks, weeks.

GT3 treatment experienced IFN ineligible versus no treatment

The CEAC is presented in Figure 18 for LDV/SOF+RBV versus no treatment. The probability that LDV/SOF+RBV is a cost effective option compared with all other comparators is 0.7% at a £20,000 per QALY threshold and 62.6% at a £30,00 per QALY threshold (base case ICER = £28,048).

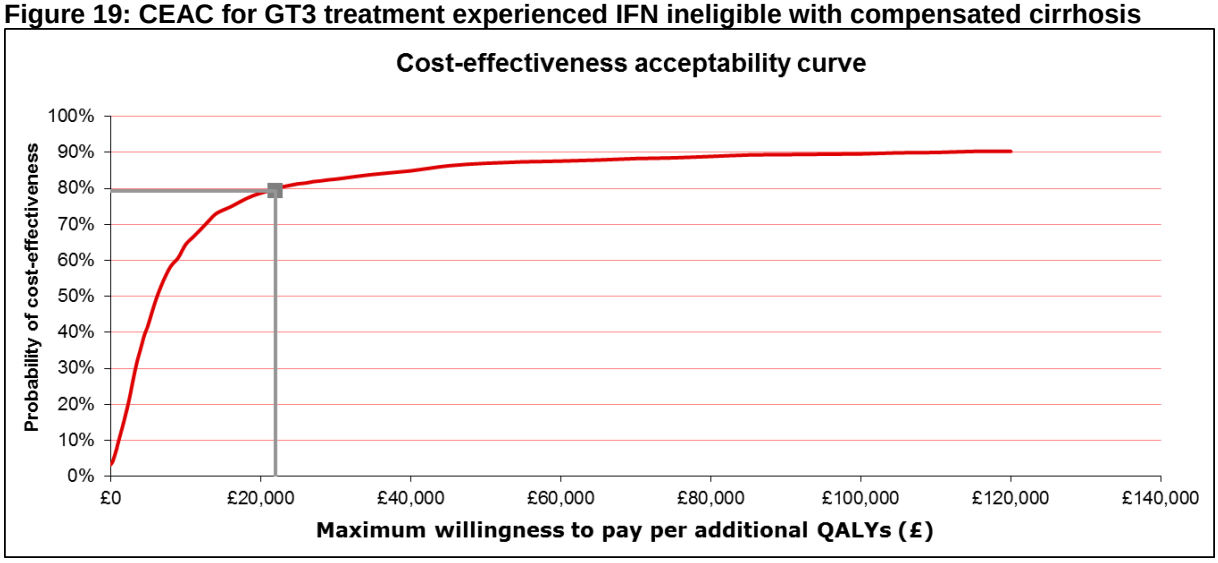
Figure 18: Multiple CEAC for GT3 IFN ineligible treatment experienced



The CEAC for the analysis restricted to GT3 treatment experienced IFN ineligible cirrhotic patents is presented in Figure 19 for LDV/SOF+RBV versus SOF+RBV (SOF+RBV is only

recommended as a treatment option for GT3 TE cirrhotic patients). The probability that LDV/SOF+RBV is a cost effective option compared with SOF+RBV is 79% at a £20,000 per QALY threshold and 83% at a £30,000 per QALY threshold (base case ICER = £6,210).

Figure 19: CEAC for GT3 treatment experienced IFN ineligible with compensated cirrhosis



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