National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ledipasvir-sofosbuvir for treating chronic hepatitis C

You are asked to check the ERG report from School of Health and Related Research (ScHARR) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Thursday 15 January 2015** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Treatment duration in genotype 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states in several places that the LDV/SOF+RBV analysis in GT3 is inconsistent with the recommended treatment duration published by the EMA. Page 5: *The company's analysis of LDV/SOF+RBV in patients with genotype 3 disease is not in line with the recommended treatment duration published by the EMA.* Page 11: *the treatment duration adopted within the modelled GT3 treatment-experienced subgroup does not adhere to recommended treatment durations listed in the EPAR.* Page 13: *the LDV/SOF treatment described for the GT3 subgroup in the company's economic model does not correspond to its licensed indication.* Page 124: *LDV/SOF+RBV treatment duration in GT3 patients is not in line with its marketing authorisation.*	All mentions of being inconsistent with the recommended 24-week duration stated within the European Public Assessment Report should be removed. Proposed text to be included: *No posology recommendation exists for GT3 non-cirrhotic treatment naïve patients. The company state that, given the clinical data available for LDV/SOF+RBV for 12 weeks in treatment naïve and treatment experienced patients, and in patients with and without cirrhosis (ELECTRON-2) where all treatment naïve patients achieved SVR12 (100%, n=26), it can be assumed that a 12 week regimen is likely to be of sufficient duration to result in cure for the majority of non-cirrhotic treatment naïve patients. This assumption was clinically validated.*	The text in the ERG report does not reflect the LDV/SOF+RBV regimens modelled for GT3 in the CS, and incorrectly describes the approach as being inconsistent with the treatment duration stated in the EPAR and SmPC. The population for which 24 weeks is recommended in the EPAR is GT3 'patients with cirrhosis and/or prior treatment failure'. The 24 week regimen is not given as a recommendation for GT3 treatment naïve patients without cirrhosis in the posology table. However, the EMA accepted the 12 week data for GT3 treatment naïve non-cirrhotic patients and included it in the SmPC (section 5.1 and 4.4; EPAR pg 55). These data provide evidence of the high efficacy rates for 12 weeks LDV/SOF+RBV in GT3 treatment naïve non-cirrhotic patients. Thus, 12 weeks is deemed an appropriate treatment duration for previously untreated GT3 patients without cirrhosis who would have subsequent retreatment options. This assumption was validated through KOL opinion.	Upon further examination of the EPAR, the ERG agrees that no posology recommendation exists for GT3 non-cirrhotic treatment naïve patients. The analyses presented by the company are in line with the assumptions about treatment durations for GT3 patients (Table 48, CS, page 143). As such, all references to LDV/SOF+RBV analysis in GT3 being inconsistent with the recommended treatment duration published by the EMA have been removed from the ERG report.

Issue 2 Treatment duration in genotype 3 (2)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states in several places that a mean treatment duration of 15 weeks is modelled for LDV/SOF+RBV in genotype 3 treatment experienced patients. Page 4: *the company's analysis of LDV/SOF+RBV in treatment-experienced patients with genotype 3 disease assumes a mean treatment duration of 15 weeks; this is inconsistent with the recommended 24-week duration stated within the European Public Assessment Report.* Page 169: *In addition, the company's analysis of LDV/SOF in treatment-experienced patients with genotype 3 disease assumes a treatment duration of 15 weeks ; this is inconsistent with the recommended 24-week duration stated within the EPAR published by the EMA.* Page 174: *The company's analysis of LDV/SOF in treatment-experienced patients with genotype 3 disease assumes a treatment duration of 15 weeks; this is inconsistent with the recommended 24-week duration stated within the EPAR published by the EMA.*	Removal of this text.	As explained in issue 1, the modelled treatment durations in GT3 are not contrary to the treatment duration recommended in the EMA. In addition, the quoted text is incorrect. The mean treatment duration of 15 weeks is modelled in treatment-naïve patients rather than treatment-experienced patients as stated in the ERG report. The mean treatment duration of 15 weeks is calculated on the basis of 75% of treatment-naïve patients (the non-cirrhotic cohort) receiving 12 weeks of treatment and the remaining 25% (the cirrhotic cohort) receiving 24 weeks.	The analyses presented by the company are in line with the assumptions about treatment durations for GT3 patients (Table 48, CS, page 143). As such, all references to modelled treatment duration of 15 weeks for LDV/SOF+RBV in genotype 3 treatment experienced patients and that LDV/SOF+RBV analysis in GT3 being inconsistent with the recommended treatment duration published by the EMA have been removed from the ERG report.

Issue 3 Genotype of patients in Phase III trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 4-5: In the following sentence, the statement in bold is not strictly true: *Clinical advisors to the ERG indicated that disease characteristics of trial populations were generally representative of current UK practice,* ***but noted that the Phase III studies of LDV/SOF include a higher proportion of patients with GT1 infection,*** *more patients of African/American origin and fewer patients of Asian origin.*	All patients in the Phase III trials (with the exception of two GT4 patients enrolled in error) were GT1 infected. Proposed amended text: *Clinical advisors to the ERG indicated that disease characteristics of trial populations were generally representative of current UK practice,* ***but noted that the Phase III studies of LDV/SOF included only patients with GT1 infection, which consisted of*** *more patients of African/American origin and fewer patients of Asian origin.*	The current statement is not correct. The ION trials were set up to examine efficacy in only GT1 patients.	Amendment made as suggested by the company

Issue 4 Lack of head-to-head trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 5: The statement, *There were no head-to-head trials comparing LDV/SOF with any of the comparators in the final NICE scope,* outlines a limitation of the clinical evidence in the submission. The statement is true but we have discussed in the submission how this is acceptable (see next column).	EMA and FDA have accepted that new treatments for chronic hepatitis C do not need an RCT design and the most appropriate comparison to make in the ION studies was with a historical control. Proposed amended text: *There were no head-to-head trials comparing LDV/SOF with any of the comparators in the final NICE scope. However, the manufacturer justified this by outlining that the EMA and FDA have accepted that new treatments for chronic hepatitis C do not need an RCT design and the*	To clearly state the rationale for the limitation.	Not a factual inaccuracy. No amendment has been made to the ERG report.

	most appropriate comparison to make in the ION studies was with a historical control.		

Issue 5 Re-infection

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states in several places that re-infection is omitted from the economic analysis. Page 4: (*ii) the exclusion of relevant health effects relating to disease transmission and re-infection from the model* Page 5: *The ERG notes that some important health effects are missing from the health economic analysis, including the possibility of re-infection in individuals with hepatitis C and potential herd immunity effects across groups of individuals.* Page 124: *3. Omission of relevant health effects on individuals with HCV - possibility of re-infection* Page 128: *(3) Omission of health effects on individuals with HCV - possibility of re-infection* *The company's model is intended to reflect the expected costs and consequences of treatment*	Wherever it is stated that re-infection has been omitted from the model it should be clarified, i.e. stated in brackets, that re-infection was considered in deterministic sensitivity analyses. Proposed amended text: Page 4: (*ii) the exclusion of relevant health effects relating to disease transmission and re-infection from the model (re-infection was considered in deterministic sensitivity analyses)* Page 5: *The ERG notes that some important health effects are missing from the health economic analysis, including the possibility of re-infection* ***(considered in deterministic sensitivity analysis)*** *in individuals with hepatitis C and potential herd immunity effects across groups of individuals.* Page 124: *3. Omission of relevant health effects on individuals with HCV - possibility of re-infection* ***(considered in deterministic sensitivity analysis)*** Page 128: *(3) Omission of health effects on individuals with HCV - possibility of re-infection (****considered in deterministic sensitivity***	It is currently misleading to suggest that no consideration was given to the possibility of re-infection in the economic analysis. The ERG did note that this was run as a sensitivity analysis and stated that *Clinical expert advice received by the ERG suggests that the value used for these probabilities (0.01 in scenario analysis) is reasonable.* During the SOF appraisal, the advice was that a scenarios analysis with 1% was sufficient. Re-infection is not a major driver in the majority of scenarios and the probability of re-infection is found to be the 10th largest driver of the net benefit in only two analyses: GT1 TN versus no treatment, and GT3 TN CC versus SOF+RBV (tables 108 and 122 of the CS, respectively). The net benefit remains positive when re-infection is considered in non-cirrhotic patients in the comparison with no treatment in	The ERG agrees that re-infection, to some degree, was captured in the company's sensitivity analysis. It does not however feature as part of the base case model and its implementation in the sensitivity analysis is not explained. It is also important to note: (1) The re-infection rate used in the SA was very low. (2) There is no consideration of further treatment for re-infection. This is potentially a very important unknown that has not been considered within the company's analysis. No amendment has been made to the ERG report.

following infection with HCV. The model does not include the possibility of re-infection with HCV for non-cirrhotic patients; rather, patients who achieve SVR12 following antiviral treatment are assumed to be cured indefinitely, without re-treatment. Page 169: *(ii) the exclusion of relevant health effects relating to disease transmission and re-infection from the model* Page 173: • *The exclusion of relevant health effects relating to disease transmission and re-infection from the model*	***analysis)*** *The company's model is intended to reflect the expected costs and consequences of treatment following infection with HCV. The model does not include the possibility of re-infection with HCV for non-cirrhotic patients* ***(considered in deterministic sensitivity analysis)****; rather, patients who achieve SVR12 following antiviral treatment are assumed to be cured indefinitely, without re-treatment.* Page 169: *(ii) the exclusion of relevant health effects relating to disease transmission and re-infection from the model* ***(re-infection is considered in deterministic sensitivity analysis)*** Page 173: • *The exclusion of relevant health effects relating to disease transmission and re-infection from the* ***model (re-infection is considered in deterministic sensitivity analysis)***	GT1 TN patients (£27,924 versus a base case value of £33,221). In the comparison with SOF+RBV in GT3 patients with compensated cirrhosis, the base case net benefit of £348 falls to -£896 when re-infection is considered.	

Issue 6 8-week LDV/SOF analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Results of an 8-week LDV/SOF analysis are incorrectly attributed to the GT1/4 population. Page 7: *Assuming an alternative treatment duration of 8 weeks LDV/SOF in the genotype 1/4 treatment-naïve non-cirrhotic subgroup, the ICER for LDV/SOF*	Proposed amended text: *Assuming an alternative treatment duration of 8 weeks LDV/SOF in the* ***genotype 1*** *treatment-naïve non-cirrhotic subgroup, the ICER for LDV/SOF versus PEG-IFN2a+RBV (the next most effective non-dominated option) is reduced to £8,894 per QALY gained.*	The 8 week LDV/SOF treatment duration is not licensed in GT4.	Amendment made as suggested by the company

versus PEG-IFN2a+RBV (the next most effective non-dominated option) is reduced to £8,894 per QALY gained.			

Issue 7 NICE preliminary recommendations for sofosbuvir

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report includes an inaccurate description of the preliminary NICE recommendations for sofosbuvir regimens. Page 9: *The CS states that SOF+PEG-IFN+RBV has preliminary recommendations for use in HCV GT1 patients, HCV GT3 patients with cirrhosis and HCV GT3 treatment-experienced patients without cirrhosis.*	Proposed amended text: *The CS states that SOF+PEG-IFN+RBV has preliminary recommendations for use in HCV GT1 patients, HCV GT3* ***treatment-naïve*** *patients with cirrhosis and HCV GT3 treatment-experienced patients* ***with or*** *without cirrhosis.*	The current text does not reflect the preliminary recommendations detailed on page 30 of the CS. *1.2 Sofosbuvir, in combination with PEG-IFN alfa and RBV, is recommended as an option for treating genotype 3 chronic hepatitis C in adults with cirrhosis.* *1.3 Sofosbuvir, in combination with PEG-IFN alfa and RBV, is recommended as an option for treating genotype 3 chronic hepatitis C in adults without cirrhosis, only if they had treatment for hepatitis C before.*	Comment noted. However, this text was paraphrased directly from the company's submission (section 2.5, page 28, CS). For the sake of accuracy, this amendment has been made within the ERG report.

Issue 8 Treatment duration in genotype 3 (3)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states in two places that 75% of non-cirrhotic GT3 patients will receive 12 weeks	Proposed amended text: *The ERG notes that the company's model assumes that treatment naïve non-cirrhotic*	The current text is a misinterpretation of the treatment durations assumed in genotype 3. 75% of treatment naïve patients are	Upon further examination of the EPAR, the ERG agrees that no posology recommendation exists for

LDV/SOF+RBV. Page 10: *the ERG notes that the company's model assumes that 75% of the non-cirrhotic genotype 3 patients will receive 12 weeks LDV/SOF+RBV; this is not in line with the recommended treatment durations from the EMA.* Page 125: *Firstly, the LDV/SOF+RBV treatment duration for genotype 3 patients is not in line with recommendations from the EMA. The company's model assumes that 75% of non-cirrhotic genotype 3 patients receiving LDV/SOF+RBV will receive 12 weeks of treatment.. The SmPC recommends 24-weeks of treatment for all patients with genotype 3 disease.*	*genotype 3 patients will receive 12 weeks LDV/SOF+RBV; this is assumed in the absence of a recommended treatment duration in the posology table for this patient population from the EMA.*	assumed to receive 12 weeks of LDV/SOF+RBV since this is the proportion of the cohort which are assumed to be non-cirrhotic. A duration of 12 weeks of LDV/SOF+RBV in treatment naïve non-cirrhotic GT3 patients is consistent with the high efficacy observed in the phase 2 ELECTRON-2 study for this duration and population. The EMA accepted this data and included it in the SmPC (section 5.1). The EMA specifically did not recommend a 24 week duration in this population, despite recommending 24 weeks for cirrhotic and/or treatment experienced GT3 patients.	GT3 non-cirrhotic treatment naïve patients. The analyses presented by the company are in line with the assumptions about treatment durations for GT3 patients (Table 48, CS, page 143). As such, all references to LDV/SOF+RBV analysis in GT3 being inconsistent with the recommended treatment duration published by the EMA have been removed from the ERG report.

Issue 9 Analyses versus telaprevir and boceprevir

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG report states in several places that telaprevir and boceprevir were included as comparators for genotype 4 treatment experienced patients, against the licenses for both products. Page 1: *In addition, the cost-*	Removal of the quoted text on pages 1, 11, 14, 94 and 126.	Gilead do not agree that this constitutes a deviation from the NICE scope to warrant inclusion in table 1 on page 11. All results tables for the GT1/4 TE patients include footnote text explaining that telaprevir and boceprevir are not valid comparators for GT4 patients. The ICERs presented for GT1/4	The ERG considers that grouping two subgroups with different sets of comparators, as has been done within the company's submission, is inappropriate. The ERG report does note that the footnotes to the tables mention that telaprevir and boceprevir are

effectiveness of telaprevir (TVR) and boceprevir (BOC) is evaluated in treatment-experienced patients with genotype 1/4 (GT1/4) infection, however neither product is licensed for the treatment of patients with genotype 4; this issue is highlighted in the footnotes to the results tables in the CS but is not discussed further. Page 11: *TVR and BOC are included in the economic analysis of treatment-experienced patients with GT1/4 disease yet neither product is licensed for use in GT4 patients.* Page 14: *TVR and BOC are included in the economic analysis of GT1/4 treatment-experienced patients however neither product is licensed for use in GT4 patients. This issue is highlighted in the footnotes to the results tables within the CS but is not discussed further with respect to the results for individual genotypes.* Page 94: *It should also be noted that the company's analysis of treatment-experienced patients with GT1/4 includes both BOC and TVR; neither product is*		should be interpreted as being for either a GT1 cohort or a GT4 cohort, in line with the recommendations for each comparator i.e. the ICER is the same for either a GT1 or GT4 patient. Any results tables for the GT1/4 treatment experienced population include footnote text explaining that telaprevir and boceprevir are not valid comparators for GT4 patients.	licensed only for GT1 patients. However, there is no discussion of this issue in the text or its potential impact upon the efficiency frontier within the text hence the point remains valid. No amendment has been made to the ERG report.

licensed for use in patients with GT4 disease (this is mentioned in the footnotes to the results tables within the CS but is not discussed further). Page 126: *Secondly, TVR and BOC are evaluated in the GT1/4 treatment-experienced subgroup however neither product has marketing authorisation in patients with GT4 disease. Whilst this issue is mentioned in the table footnotes on page 206 of the CS,1 both regimens are still included in the company's analysis without further discussion.*			

Issue 10 Comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14: Section 3.3. The list of comparators has the genotypes for which the comparator was included for. The genotypes for the following comparators are incorrect: • *PEG-IFN+RBV (GT1–6)* • *SOF+RBV±PEG-IFN GT1–6; subject to ongoing NICE appraisal ID654) (* • *Best supportive care (watchful*	• *PEG-IFN+RBV* ***(GT1, GT3 and GT4)*** • *TVR+PEG-IFN+RBV (GT1 only)* • *BOC+PEG-IFN+RBV (GT1 only)* • *SOF+RBV±PEG-IFN* ***(GT1, GT3 and GT4;*** *subject to ongoing NICE appraisal ID654)* • *SMV+PEG-IFN+RBV (GT1 or GT4 subject to ongoing NICE appraisal ID668)* • *SMV+SOF (for patients with GT1 or GT4 disease and are ineligible for or intolerant to IFN treatment; subject to ongoing NICE appraisal ID668)*	Currently, the report states that the mentioned comparators were used for all genotypes (GT1-6); this is not correct.	Comment noted. However, this information was taken directly from the decision problem table reported in the company's submission (section 5, page 42, CS). No amendment has been made to the ERG report.

waiting; GT1–6)	• *Best supportive care (no treatment; **GT1, GT3 and GT4**)*		

Issue 11 GT4 arm data

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Page 19: For the SYNERGY trial, the report states:

At the time of submission, two treatment arms had available data: GT1 prior SOF failure patients, and GT1 treatment-naïve patients, both of which were assigned to LDV/SOF for 12 weeks.

There was an additional arm reported in section 6.5.7.1 of the submission which had interim data for 14 patients with GT4 infection.

The GT4 arm has also been omitted on the following pages:

Page 26: For SYNERGY, two arms provided results in the CS, from a study with several treatment groups.

Page 38, SYNERGY row of table 8:</td>
<td>Proposed amended text:

Page 19: At the time of submission, three treatment arms had available data: GT1 prior SOF failure patients, GT1 treatment-naïve patients, and GT4 patients, all were assigned to LDV/SOF for 12 weeks.

Page 26: For SYNERGY, three arms provided results in the CS, from a study with several treatment groups.

Page 38, SYNERGY row of table 8:
<table>
<tr><th>Population</th><th>Intervention(s)
Sample size / N randomised or allocated</th></tr>
<tr><td>GT1 Treatment experienced (prior SOF/RBV) from NIAID SPARE study
No cirrhosis or compensated cirrhosis

GT1 treatment-naïve, [redacted]

GT4 treatment-naïve and treatment-</td><td>LDV/SOF for 12 weeks
Other arms not included in CS that had unlicensed anti-viral agents
[redacted] and n=14 GT4 patients.</td></tr>
</table>
</td>
<td>Little data is currently available for LDV/SOF treatment in GT4 patients. It is important that this arm of the SYNERGY trial is mentioned. The arm has also been omitted on the following pages: 26, 38 (SYNERGY row of Table 8), Updated SVR12 data for the SYNERGY GT4 arm were provided in the patient disposition figures requested as part of the ERG clarification questions.</td>
<td>Page 19

Added

“Additionally, interim data were provided for the treatment arm with GT4 patients.”

Page 26

Added

Additionally, interim data were provided for the treatment arm with GT4 patients.

Page 38

Altered

Interim data available at time of submission - GT4 treatment-naïve or treatment experienced

Page 54</td>
</tr>
</table>

	experienced, including patients with advanced fibrosis.			Interim results from clarification response added

Issue 12 Age of patients in ION-2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 22: Under the heading 'Balance between groups' the report states: *Patients treated with 24-weeks LDV/SOF+RBV were younger than in other treatment arms, mean age 55 (range 28-70).*	Proposed amended text: *The mean age of patients treated with 24 weeks LDV/SOF+RBV (55 years; range 28-70) was lower than for patients treated in the other groups (12 weeks LDV/SOF: 56 years, range 24-67; 12 weeks LDV/SOF+RBV: 57 years, range 27–75; 24 weeks LDV/SOF: 56 years, range 25–68), though the age ranges were similar.*	Suggested re-wording to clarify meaning.	Page 22 Added For the other two treatment groups, mean age was 56 (see table 22).

Issue 13 Minor spelling error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 35: 'SYRIUS' is the incorrect spelling of the trial	Please amend to '**SIRIUS**.'	Spelling error	Page 35 Amended spelling

Issue 14 ION-1 GT1a SVR12 data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 48: Table 16:	Propose to replace table cells with the correct values as presented below:	ION-1 is one of the pivotal	The figures in the

<table>
<tr>
<td>SVR12 in GT1 treatment-naïve patients. The fourth row of the table contains SVR12 rates for GT1a Non-cirrhotic and compensated cirrhosis patients from ION-1. The numbers are incorrect.</td>
<td>
<table>
<tr><td colspan="2">LDV/SOF 12wks</td><td colspan="2">LDV/SOF +RBV 12wks (not licensed)</td><td colspan="2">LDV/SOF 24wks</td><td colspan="2">LDV/SOF +RBV 24wks</td></tr>
<tr><td>n/N</td><td>%
95%CI</td><td>n/N</td><td>%
95%CI</td><td>n/N</td><td>%
95%CI</td><td>n/N</td><td>%
95%CI</td></tr>
<tr><td>141/144</td><td>97.9
94.0–99.6</td><td>143/148</td><td>96.6
92.3–98.9</td><td>144/146</td><td>98.6
95.1–99.8</td><td>141/143</td><td>98.6
95.0–99.8</td></tr>
</table>
</td>
<td>trials in the submission. The SVR12 rate needs to be amended as per the CS.</td>
<td>table were taken from the NEJM publication of ION-1, as referenced, as values were not presented in the CS.

We have amended to use the final clinical study report as the reference, and marked as AIC.</td>
</tr>
</table>

Issue 15 ION-1 GT1b SVR12 data

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Page 48: Table 16: SVR12 in GT1 treatment-naïve patients. The fifth row of the table contains SVR12 rates for GT1b Non-cirrhotic and compensated cirrhosis patients from ION-1. The numbers for LDV/SOF+RBV 12 wks are incorrect</td>
<td>Propose to replace table cells with the correct values as presented below:
<table>
<tr><td colspan="2">LDV/SOF +RBV 12wks (not licensed)</td></tr>
<tr><td>n/N</td><td>%
95% CI</td></tr>
<tr><td>67/68</td><td>98.5
92.1–100.0</td></tr>
</table>
</td>
<td>ION-1 is one of the pivotal trials in the submission. The SVR12 rate needs to be amended as per the CS.</td>
<td>The figures in the table were taken from the NEJM publication of ION-1, as referenced, as values were not presented in the CS.

We have amended to use the final clinical study report as the reference, and marked as AIC</td>
</tr>
</table>

Issue 16 ION-3 GT1a SVR12 data

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Page 49: Table 16: SVR12 in GT1 treatment-naïve patients.</td>
<td>Propose to replace table cells with the correct values as presented below:</td>
<td>ION-3 is one of the pivotal trials in the submission. The SVR12 rate</td>
<td>The figures in the table (163/172) were taken from the</td>
</tr>
</table>

The SVR12 rates for GT1a Non-cirrhotic patients from ION-3 are incorrect and n/N has been entered in place of the %.	<table><tr><td colspan="2">LDV/SOF 12wks</td></tr><tr><td>n/N</td><td>% 95% CI</td></tr><tr><td>165/172</td><td>95.9 91.8–98.3</td></tr></table>	needs to be amended as per the CS.	NEJM publication of ION-3, as referenced, as values were not presented in the CS. We have amended to use the final clinical study report as the reference, and marked as AIC.

Issue 17 ELECTRON GT1 SVR12 data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 49: Table 16: SVR12 in GT1 treatment-naïve patients. The SVR12 rates for GT1 Non-cirrhotic patients from ELECTRON is not for LDV/SOF (single tablet) +RBV regimen. It is for the LDV+SOF+RBV individually.	There is no LDV/SOF+RBV 12wk arm with non-cirrhotic patients presented in the submission. Suggest removal of table row.	The reporting in the ERG report is currently incorrect.	Amended table to clarify LDV+SOF+RBV

Issue 18 GT1a treatment-naïve SVR12 data in text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 50: *For GT1a treatment-naïve patients, SVR12 rates ranged from 92.4% to 100% in the ION trials* [redacted] The SVR12 rates mentioned in the text for GT1a treatment-naïve	Proposed amended text: *For GT1a treatment-naïve patients, SVR12 rates ranged from **92.4% to 96.6%** in the ION trials (**90.5% to 100**% if further subgrouped by cirrhosis).*	The reporting in the ERG report is currently incorrect.	Added -100%

patients are incorrect.			

Issue 19 ION-3 data in text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 51:The last paragraph begins with: *In the **ION-2** trial (see CS page 91…* The data discussed in this paragraph is from the ION-3 trial. Additionally, the treatment difference and 97.5% CI stated in the last sentence of the paragraph *(treatment difference -2.3%; 97.5% confidence interval: -7.2% to 3.6%)* are incorrect. The values presented currently are for a comparison between LDV/SOF 8 wks and LDV/SOF 12 wks	Proposed amended text: *In the **ION-3** trial (see CS page 91, and EPAR) the addition of RBV (in the LDV/SOF+RBV 8 weeks arm) did not significantly enhance the observed SVR12 rates (p-values not reported) compared with either LDV/SOF 8 weeks treatment (treatment difference 0.9%; 95% confidence interval: -3.9% to 5.7%), or LDV/SOF 12 weeks treatment **(treatment difference -3.2%; 97.5% confidence interval: -8.3% to 1.8%).***	The reporting in the ERG report is currently incorrect.	Amended to In the ION-2 trial, the addition of RBV did not significantly enhance the observed SVR12 rates (*p*-values not reported) (see CS[1] page 91). Similarly for ION-3, the addition of RBV did not significantly enhance the observed SVR12 rates, for LDV/SOF+RBV 8 weeks compared with LDV/SOF 8 weeks treatment (treatment difference 0.9%; 95% confidence interval: -3.9% to 5.7%).

Issue 20 Number of deaths in SOLAR-1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 57: The number of treatment discontinuations from adverse events and deaths for SOLAR-1 are stated as: *From 231 post-liver transplant*	Proposed amended text: [redacted]	The reporting in the ERG report is currently incorrect.	Text amended to seven deaths

*patients, there were **12** deaths and five discontinuations due to AEs.* The number of deaths in this sentence is incorrect. In the post-liver transplant patients, there were seven deaths. Twelve is the number of deaths in the pre- and post-liver transplant patients combined.			

Issue 21 Number of SAEs in ION-1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 57: The report states: *In ION-1, 33 patients out of **845** patients (3.8%) experienced a serious adverse event (SAE).* The number, 845, is incorrect	Proposed amended text: *In ION-1, 33 patients out of **865** patients (3.8%) experienced a serious adverse event (SAE).*	The reporting in the ERG report is currently incorrect.	Text amended to 865

Issue 22 Number of SAEs in ION-3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 57: The report states the SAEs in the LDV/SOF groups: *SAEs in the LDV/SOF groups occurred in 9 patients out of **647** patients (1.4%), and…'* 647 is the total number of patients in ION-3, including those in the	Proposed amended text: *SAEs in the LDV/SOF groups occurred in 9 patients out of **431** patients (**2.1%**), and…*	The reporting in the ERG report is currently incorrect.	Text amended to nine patients out of 431 patients (2.1%)

LDV/SOF+RBV group. In the LDV/SOF groups, there were 431 patients.			

Issue 23 Data inaccuracies in conclusion of the clinical effectiveness section

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 83: First sentence: *For subgroups of GT1 treatment-naïve patients, SVR12 rates ranged from 92.4% to **100%** for GT1a patients; and from 95.5% to 100% for GT1b patients.* The SVR12 rates for GT1 are incorrect. Third paragraph: *For subgroups of GT1 treatment-experienced patients, GT1a patients, SVR12 rates ranged from 95.3% to **98.8%,** and for GT1b patients.* The SVR12 rates are incorrect.	Proposed amended text: First sentence: *For subgroups of GT1 treatment-naïve patients, SVR12 rates ranged from 92.4% to **98.6%** for GT1a patients; and from 95.5% to 100% for GT1b patients.* Third paragraph: *For subgroups of GT1 treatment-experienced patients, GT1a patients, SVR12 rates ranged from 95.3% to **98.9**%, and for GT1b patients*.	The reporting in the ERG report is currently incorrect.	Text amended

Issue 24 Comparators in GT3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 94 of the ERG report states that *It should be noted that the option of no treatment is not considered within the company's analysis of the subgroup of patients with GT3 disease with compensated cirrhosis who are treatment-naïve or within the subgroup of patients with GT3 disease with compensated cirrhosis who are treatment-experienced and IFN-ineligible.* Page 124: *No treatment not included as comparator within the company's analysis of the subgroups of patients with GT3 disease with compensated cirrhosis who are treatment-naïve or patients with GT3 disease with compensated cirrhosis who are treatment-experienced and IFN-ineligible.*	This text should be removed.	The text quoted is a misinterpretation of the analyses considered. Separate analyses were reported in full for the population with compensated cirrhosis in genotype 3 to reflect preliminary recommendations from NICE for SOF+PEG-IFN2a+RBV and SOF+RBV. In the case of all other comparators no such restrictions needed to be considered. However, cirrhotic patients were also included within the main two analyses in GT3 (TN and TE, respectively) which considered mixed cohorts consisting of both non-cirrhotic and cirrhotic patients. No treatment was considered as a comparator in both of these analyses. Separate ICERs were presented for non-cirrhotic and cirrhotic cohorts on page 262 of the CS.	The base case analyses presented in Tables 99 and 101 do not include 'no treatment'. Whilst this option may have been included in the company's subgroup analysis, it is not included in the company's base case analysis. This point has been reflected in the text of the ERG report.

Issue 25 8 week treatment option in GT1 TN non-cirrhotic patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 102: It is stated that: *This is based on the assumption that 8 weeks LDV/SOF will be used for genotype 1 treatment-naïve patients without cirrhosis who have a baseline viral load of <6million IU/mL, and 12 weeks LDV/SOF in patients with a baseline viral load ≥6million IU/mL. The company used a 79% to 21% split of 8-week and 12-week treatment regimens of LDV/SOF, stating that patient-level data from the HCV Research UK database showed that 79% of genotype 1 non-cirrhotic patients (n=408) in the UK had a pre-treatment viral load <6million IU/mL. It should be noted that the cut-off of 6 million IU/ml is based on a post hoc analysis of the ION-3 study (see CS Section 6.5.5 page 89)* ***and is not consistent with the treatment indication mentioned in the EPAR.***	Removal of the text in bold. Proposed amended text: *This is based on the assumption that 8 weeks LDV/SOF will be used for genotype 1 treatment-naïve patients without cirrhosis who have a baseline viral load of <6million IU/mL, and 12 weeks LDV/SOF in patients with a baseline viral load ≥6million IU/mL. The company used a 79% to 21% split of 8-week and 12-week treatment regimens of LDV/SOF, stating that patient-level data from the HCV Research UK database showed that 79% of genotype 1 non-cirrhotic patients (n=408) in the UK had a pre-treatment viral load <6million IU/mL. It should be noted that the cut-off of 6 million IU/ml is based on a post hoc analysis of the ION-3 study (see CS Section 6.5.5 page 89).*	This text is misleading since there is no strict definition of the patient population eligible for 8 weeks LDV/SOF treatment in the EPAR. The post-hoc analysis, which was conducted to identify patients who would be suitable to receive 8 weeks of treatment versus those potentially requiring 12 weeks, was accepted by the EMA and is presented on page 21 of the final SPC. It was included in the CS to provide a mechanism of stratifying treatment naïve non-cirrhotic patients to 8 versus 12 weeks. This is not inconsistent with the treatment indication	This is an issue of clarity rather than inaccuracy. The text has been amended to read: "***and is not mentioned within the treatment indication in the EPAR."***

Issue 26 Transition probabilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 105: *The model assumes the same probabilities for all HCV genotypes with the exception of the probability of transition from the non-cirrhotic state to the compensated cirrhosis state, which is different* ***between genotype 1 and other genotypes .***	Proposed amended text: *The model assumes the same probabilities for all HCV genotypes with the exception of the probability of transition from the non-cirrhotic state to the compensated cirrhosis state, which is* ***different between genotypes 1/4 and genotype 3****.*	The same TPs are used for GT1/4, with different values for GT3. This data can be found in table 57 of the CS.	Amendment made as suggested by the company

Issue 27 Mortality

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 107: *The risk of death for patients with decompensated cirrhosis, HCC, liver transplant, and post-liver transplantation states was modelled by applying age-specific general population mortality rates to each health state in the model, obtained from ONS.*	Proposed amended text: *Background mortality rates were applied to all health states based on age-specific general population mortality rates obtained from ONS. These were not adjusted to remove deaths associated with the consequences of HCV. Increased mortality risks were associated with advanced liver disease health states (decompensated cirrhosis, HCC, liver transplant and post-liver transplant).*	The current text is incorrect and does not reflect how mortality is modelled.	Amendment made as suggested by the company

Issue 28 Budget impact analysis patient numbers

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 114: *In their budget impact analysis, the company predicts a little over 5000 patients (2557 GT1/4 and 2500 GT3) will be eligible for treatment each year.*	Corrected text: *In their budget impact analysis, the company predicts a little over 5000 patients (**2693** GT1/4 and 2500 GT3) will be eligible for treatment each year.*	The number of GT1/4 patients estimated to be eligible for treatment each year is incorrectly quoted.	Amendment made as suggested by the company

Issue 29 GT4 TN results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 115, Table 42: States that SOF+PR and SMV+PR are dominated in the GT4 TN analysis. In addition, corresponding text on page 117 states: *All options excluding LDV/SOF, PEG-IFN2a+RBV and no treatment are ruled out due to simple dominance.*	Both these treatments are extendedly dominated. Therefore, 'dominated' should be replaced with 'ext dom' for both these comparators in the ICER column of table 42. Proposed amended text for page 117: *All options excluding LDV/SOF, PEG-IFN2a+RBV and no treatment are ruled out due to **simple or extended** dominance.*	The conclusions of the incremental analysis are currently incorrect.	Amendment made as suggested by the company

Issue 30 Scenario analysis 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 122: *The ICER for SMV+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be*	Proposed amended text: *The ICER for PEG-IFN2a+RBV versus no treatment is estimated to be £4,137. The ICER*	The conclusions of the incremental analysis are currently incorrectly reported with ICERs being	Amendment made as suggested by the company

£4,137 per QALY gained. The ICER for LDV/SOF versus SMV+PEG=IFN2a+RBV is estimated to be £13,213 per QALY gained.	*for SMV+PEG-IFN2a+RBV versus PEG-IFN2a+RBV is estimated to be £13,213. The ICER for LDV/SOF versus SMV+PEG-IFN2a+RBV is estimated to be £17,390.*	attributed to incorrect comparisons.	

Issue 31 Scenario analysis 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 122: *A third scenario analysis was undertaken in which 15% of patients were assumed to receive 24 weeks LDV/SOF with the remaining 85% patients receiving 12 weeks LDV/SOF.*	Proposed amended text: *A third scenario analysis was undertaken in which the proportion of patient receiving 24 weeks of treatment was increased in each patient population, as detailed below:* *The GT1 TN analysis tested an assumption of 85% of compensated cirrhosis patients receiving 12 weeks of treatment and the remaining 15% receiving 24 weeks.* *Similarly, the GT4 TN analysis tested an assumption of 85% of compensated cirrhosis patients receiving 12 weeks of treatment and the remaining 15% receiving 24 weeks.* *The GT1/4 TE analysis tested an assumption of 50% of compensated cirrhosis patients receiving 12 weeks of treatment and the remaining 50% receiving 24 weeks.*	The current text does not include enough detail to adequately describe the scenario analysis and is misleading as a result.	Amendment made as suggested by the company

Issue 32 Use of SVR4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 131: *The use of SVR4 data would therefore likely overestimate the effectiveness of LDV/SOF+RBV. Given the small numbers of patients and use of SVR4 data, the results for GT3 treatment-experienced patients should be treated with caution.*	Proposed amended text: *SVR4 data (42/50; 84%) were submitted as part of the CS for GT3 treatment experienced patients. Such data may overestimate the the effectiveness of LDV/SOF+RBV. However, during clarification questions, SVR12 data (41/50; 82%) were provided for this population as part of the participant flow charts, confirming efficacy of LDV/SOF+RBV in GT3 treatment experienced patients.*	To accurately reflect data submitted in both the CS and clarification questions.	Not a factual inaccuracy. No amendment has been made to the ERG report.

Issue 33 Source of utility increment for SVR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 135: The ERG highlight their concern over the source for the utility increment for SVR. The value used in the CS is based on a study by Vera-Llonch et al 2013, which has been derived using a US EQ-5D tariff. The ERG state: *This estimate may not reflect the preferences of the general public in England and Wales and represents a deviation from the NICE Reference Case*.	Suggested amended text: *This estimate may not reflect the preferences of the general public in England and Wales, although this was the preferred source for the utility increment for SVR in appraisal of sofosbuvir for the treatment of CHC*	During the appraisal of sofosbuvir, the NICE Appraisal Committee, the ERG (Southampton) and the manufacturer discussed at length the preferred data source for this input. It was decided that the Vera-Llonch et al 2013 value was the preferred source for the base case. For consistency, we think that the preferences of different ERGs for particular data sources should be reported.	The issue highlighted by the ERG is that this study uses the US tariff and therefore may not reflect preferences of the general public in England and Wales. The issue is not whether the source represents the preferences of one ERG over another, it is that its use represents a deviation from the NICE Reference Case. No amendment has been made to the ERG report.

Issue 34 Accuracy of results reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
For all analyses conducted by the ERG, the ICER is calculated based on QALYs and costs for interventions which are rounded to 2 decimal points. This leads to a certain loss of accuracy in the results. This affects all ICERs in tables 46, 52, 53, 54, 55, 56 and 57 and the associated summary text.	Please include a statement on page 139, explaining that the results reported give an indication of the magnitude of the ICERs but are subject to rounding error. Proposed wording: *All ERG analyses report total costs and QALYs for LDV/SOF and each comparator to two decimal places. ICERs have been calculated using these figures, therefore there is some discrepancy between the figures reported and those generated by the model, especially in scenarios where the incremental QALY benefit is small.*	It is misleading to suggest that the ICERs currently presented represent the results from the model. Loss of accuracy can have a marked effect on the ICER calculated in some scenarios, especially where the incremental QALY benefit is small. For example, in table 57, the ICER for LDV/SOF versus SMV+PEG-IFN2a+RBV in GT1 TN non-cirrhotic patients is reported as £92,879, however, the model generates an ICER of £86,937, meaning that the ICER reported is 7% higher than the ICER generated by the model.	This is a matter of accuracy but not factual inaccuracy. We agree that there may be some loss of accuracy. However, note that it was necessary to generate all ICERs in a separate worksheet and the company model was not capable of doing this directly. The following text has been added to the report: "All ERG analyses report total costs and QALYs for LDV/SOF and each comparator to two decimal places. This may produce some rounding error in the calculation of ICERs."

Issue 35 GT3 TN cirrhotic analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG have omitted PEG-IFN2a+RBV from all new analyses presented for the GT3 TN cirrhotic cohort. This affects all ICERs in tables 52, 53, 54, 55, 56 and 57 and the associated summary text.	Rerun of analysis for the GT3 TN cirrhotic population and presentation of the results in the report.	PEG-IFN2a+RBV should be included as a comparator in these analyses.	The set of comparators included in the ERG exploratory analyses reflects those reported in the company's submission (pages 211 and 246, CS). Our intention was to explore the consequences of altering

			values within the model rather than its scope. No amendment has been made to the ERG report.

Issue 36 GT3 TE IFN-ineligible non-cirrhotic

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG have included SOF+RBV as a comparator for the GT3 TE IFN-ineligible population in error. This affects all ICERs in tables 52, 53, 54, 55, 56 and 57 and the associated summary text.	Rerun of analysis for the GT3 TE IFN-ineligible non-cirrhotic population and presentation of the results in the report.	Preliminary recommendations from NICE suggest that SOF+RBV is not recommended in non-cirrhotic patients and should not therefore be included in an analysis of a non-cirrhotic population.	This recommendation is currently preliminary. Given the information in the table, the committee is able to recalculate the ICERs excluding SOF+RBV should they wish to do so. No amendment has been made to the ERG report.

Issue 37 Interpretation of frontier (ERG analysis 5, GT1/4 TE non-cirrhotic)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 161: *Within the genotype 1/4 treatment-experienced non-cirrhotic subgroup, the model suggests that LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. PEG-IFN2a+RBV is expected to produce the fewest QALYs. All other options are expected to be ruled out due to simple or extended dominance. The ICER*	Proposed amended text: *Within the genotype 1/4 treatment-experienced non-cirrhotic subgroup, the model suggests that LDV/SOF (24 weeks) is expected to produce the greatest number of QALYs. PEG-IFN2a+RBV is expected to produce the fewest QALYs* ***at a higher cost than no treatment and is therefore dominated****. The ICER for LDV/SOF* ***versus no treatment*** *is estimated to be £177,710 per QALY gained.*	Current write-up is unclear and suggests that PEG-IFN2a+RBV is not dominated. It is not explained that the ICER presented is versus no treatment.	Amendment made as suggested by the company.

for LDV/SOF is estimated to be £177,710 per QALY gained.			

Issue 38 Incorrect base case ICER quoted

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 169: *Within the genotype 3 treatment-naïve with compensated cirrhosis subgroup, the ICER for LDV/SOF+RBV versus SOF+PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be £46,491 per QALY gained.*	Proposed amended text: *Within the genotype 3 treatment-naïve with compensated cirrhosis subgroup, the ICER for LDV/SOF+RBV versus SOF+PEG-IFN2a+RBV (the next most effective non-dominated option) is estimated to be* ***£46,691*** *per QALY gained.*	Current ICER quoted is incorrect.	The CS states this value to be £46,491/QALY in the text (six instances) but also reports it to be £46,691/QALY in two tables. The ERG has rerun this analysis and the correct ICER is actually £46,491 per QALY gained – this is the value already reported in the ERG report. No amendment has been made.

Issue 39 ERG preferred base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 140: The justification for the treatment durations and SVR rates used for the ERG preferred base case analyses is unclear.	Propose stating that the ERG preferred base case analyses represents the ERG's interpretation of the required treatment durations and have not been clinically validated, presuming that this is true. Proposed amended text: *Please note that the ERG preferred base case analyses represent the ERG's interpretation of the required treatment durations and have not*	Based on extensive discussions held with clinicians, a blended comparison was submitted in the CS, reflecting expected clinical practice of treating the vast majority of GT1 TN NC patients with 8 weeks, and the vast majority of remaining GT1, and the GT4 patient groups with 12 weeks treatment. To acknowledge the potential for some TN NC patients receiving 12 weeks	Not a factual inaccuracy. The basis of these calculations is clear from Table 50. The issues around blended comparisons and their interpretation are clearly discussed in the ERG report. No amendment has been made to the ERG report.

	been validated with clinicians.	and some patients receiving 24 weeks, we conservatively modelled a blended comparison to reflect the cost-effectiveness of LDV/SOF for a population. Should a single treatment duration approach be selected as the base case, clinician preference is for 8 weeks (GT1 TN NC) and 12 weeks (GT1 other and GT4) durations. This is consistent with the SmPC posology table and EPAR. Specifically, in the EPAR it states that “In general, treatment for more than 12 weeks or the addition of ribavirin is not needed to increase efficacy. In patients with compensated cirrhosis and/or patients with reduced viral susceptibility to LDV at baseline, the relapse rate is higher with 12 weeks than with 24 weeks of therapy. The increment with an extra 12 weeks is not well characterised, and likely depends on a number of host and viral factors.” and: “Factors to take into account when evaluating the incremental benefit of a marginal increase in SVR with prolonged therapy includes the risk of clinical disease progression in case of failure to clear virus, as well as available effective retreatment options in case of failure with	

		selection of resistant variants.”	

Issue 40 Transition probabilities from non-cirrhotic to compensated cirrhosis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 133: *It should also be noted that these transition probabilities are marginally different to those used in the model used to inform the recent appraisal of sofosbuvir.*	Proposed amended text: *It should also be noted that these transition probabilities are marginally different to those used in the model used to inform the recent appraisal of sofosbuvir;* ***this reflects the fact that the transition probabilities were re-estimated for the purposes of this submission to reflect the slight difference in the starting distribution of patients in the mild and moderate health states in the ION trials versus the sofosbuvir trials. 78% of patients were mild at baseline in the ION trials compared with 79% of patients across the sofosbuvir trials.***	It is misleading to suggest that there was no justification for this discrepancy. The methodology used to calculate this transition is described on page 169 of the CS.	Not a factual inaccuracy. No amendment has been made to the ERG report.