Gilead Sciences Ltd

Response to Appraisal Consultation Document: Ledipasvir-sofosbuvir for treating chronic hepatitis C

23rd March 2015

Summary

Gilead Sciences Ltd. welcomes NICE's recommendation of the following LDV/SOF regimens as cost-effective treatments for chronic hepatitis C populations (including those co-infected with HIV):

- 8 weeks in GT1 treatment naïve (TN) patients without cirrhosis
- 12 weeks in GT1 and GT4 TN patients with cirrhosis
- 12 weeks in GT1 and GT4 treatment experienced (TE) patients without cirrhosis.

However, Gilead Sciences Ltd. are concerned that the NICE committee has not been given the opportunity to consider:

1. the 12 week treatment duration for TE GT1 and GT4 patients with cirrhosis
2. the benefit that IFN-free LDV/SOF-based regimens can provide in GT3 patients who are intolerant to or ineligible for interferon (IFN).

GT1 and GT4 treatment experienced patients with cirrhosis

- The decision by the NICE committee to define all TE cirrhotic patients as ineligible for the 12 week duration is not consistent with the EMA's posology recommendations for LDV/SOF.
- The EMA posology recommendations include the option to treat GT1 and GT4 TE cirrhotic patients with 12 weeks LDV/SOF, should they meet the specified criteria relating to risk of clinical disease progression and subsequent retreatment options.
- 12 weeks LDV/SOF results in an SVR12 of 90% (64/71) in TE cirrhotic patients.
- 12-weeks of LDV/SOF is cost-effective for GT1 and GT4 TE cirrhotic patients with a ICER of £5,435.

GT3 patients who are intolerant to or ineligible for interferon

- At present the only NICE-recommended treatment for GT3 patients who are intolerant to or ineligible for IFN is 24 weeks of SOF+RBV, and this is limited to patients with cirrhosis.
- The EMA considers the regimen of 24 weeks LDV/SOF+RBV as more efficacious than 24 weeks SOF+RBV, which is also supported by the data for LDV/SOF+RBV.
- 24 weeks of LDV/SOF+RBV is cost-effective for the GT3 population with cirrhosis who are intolerant to or ineligible for interferon with ICERs of £19,013 and £10,440 for the TN and TE populations, respectively.
- 12 weeks LDV/SOF+RBV also provides a highly efficacious and cost-effective treatment for non-cirrhotic GT3 patients who are TN and intolerant to or ineligible for interferon, with an ICER of £10,549. These patients currently have no treatment option until they become cirrhotic. Having become cirrhotic, the likelihood of then achieving SVR is decreased and they have a lifelong risk of hepatocellular carcinoma (HCC).

In addition, Gilead Sciences Ltd. would like to draw NICE's attention to the following points, which are discussed in detail later in this document:

- The use of the wording "Not licensed for this population" in Table 1 in the ACD should be replaced with "Not the EMA recommended regimen for this population"
- Gilead believe that combining transition probabilities from Fattovich and Cardoso in relation to the transitions from SVR to HCC and non-SVR to HCC creates an unrealistic effect, whereby the impact on the risk of HCC of having achieved SVR is reduced to virtually nil. This approach lacks face validity and is not supported by any individual data source. Gilead Sciences Ltd thus suggest that the most realistic approach is to use the TPs from Cardoso.

Key issues for consideration

GT1 and GT4 treatment experienced patients with cirrhosis

The Appraisal Committee's preliminary recommendations do not include a recommendation for the LDV/SOF 12 week regimen for adults with GT1 or GT4 HCV who are TE and have compensated cirrhosis.

ACD Section 4.21 states that:

"The Committee was aware it had been presented with ICERs from the ERG in people having the 24-week treatment only because the marketing authorisation states that 12 weeks' treatment 'may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options'. Therefore, the Committee agreed that the marketing authorisation does not recommend 12 weeks of treatment for people with treatment-experienced genotype 1 or 4 HCV with cirrhosis, and considered therefore it could not make a recommendation for 12 weeks' of treatment."

The decision by the NICE Committee to define all TE cirrhotic patients as ineligible for the 12 week duration is not consistent with the EMA's posology recommendations for LDV/SOF (Table 1). Below is an exact reproduction of the posology table as it appears in the SmPC. This is different in appearance to the table that was presented to the Committee during the first committee meeting (03.02.15).

Table 1: Recommended treatment duration for Harvoni and the recommended use of co-administered ribavirin for certain subgroups

Patient population*	Treatment	Duration
Patients with genotype 1 or genotype 4 CHC		
Patients without cirrhosis	Harvoni	12 weeks. - 8 weeks may be considered in previously untreated genotype 1-infected patients (see section 5.1, ION-3 study). - 24 weeks should be considered for previously treated patients with uncertain subsequent retreatment options (see section 4.4).
Patients with compensated cirrhosis	Harvoni	24 weeks. - 12 weeks may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options (see section 4.4).
Patients with decompensated cirrhosis or who are pre-/post-liver transplant	Harvoni + ribavirin	24 weeks (see sections 4.4 and 5.1)
Patients with genotype 3 CHC		
Patients with cirrhosis and/or prior treatment failure	Harvoni + ribavirin	24 weeks (see sections 4.4 and 5.1)

* Includes patients co-infected with human immunodeficiency virus (HIV).

The EMA deemed it likely that there would be a proportion of cirrhotic patients, including those that had previously been treated, who would have "*subsequent retreatment options*" and also be "*deemed at low risk of clinical disease progression*". In place of specifying individual patient groups for specific durations, the EMA elected to leave it to individual clinical judgement to determine those patients that would benefit from the 12 week regimen and those that should receive 24 weeks.

Supporting discussion of EMA recommendations

2.0.0.1. Recommendation for treatment naïve and treatment experienced patients

It should be noted that the SmPC posology recommendations for a number of products in the HCV treatment area make specific mention of TN vs TE, and recommend different treatment durations for these patient groups. In the LDV/SOF posology table, for GT1 non-cirrhotic patients, the wording for shorter treatment durations reads "*8 weeks may be considered in previously untreated genotype 1-infected patients*" clearly excluding TE patients from the 8 week duration. In contrast, for cirrhotic patients the SmPC does not specify that the 12 week regimen must only be considered for TN patients, indicating that the EMA believed the 12 week regimen should also be considered for TE patients.

2.0.0.2. Discussion of "subsequent retreatment options"

The LDV/SOF posology wording clearly highlights that the EMA does not consider that all TE patients lack retreatment options, but rather that the retreatment options available are dependent on:

- the prior treatment a patient has received
- the available data on the re-use of particular DAA classes in a retreatment regimen, following a previous exposure to a DAA of that same class

The field of HCV treatment is evolving very rapidly with new DAA drugs becoming available each year, as well as new data on already licensed drugs. The EMA therefore chose to allow individual clinical assessment of each TE patient's retreatment options at the time they are offered LDV/SOF treatment, when determining the most appropriate LDV/SOF duration. This enables clinicians to take into account the most recent data and DAA drug availability, as opposed to having to base their decision upon what was available at the date that LDV/SOF became licensed. Both clinical trial and real world data have been published confirming that retreatment with DAAs (SOF and PI regimens) is highly effective (1),(2) (3).

2.0.0.3. Discussion of "low risk of clinical disease progression"

For the compensated cirrhotic patient population the term "clinical disease progression" relates to the risk of progressing to decompensated cirrhosis or hepatocellular carcinoma (HCC).

The section of the EPAR relating to treatment duration in cirrhotics states as the justification for a 24 week regimen "*for patients with advanced liver disease, manifested, e.g., by low platelet counts or by biochemical abnormalities related to liver function, failure to achieve viral clearance may be associated with a tangible short term risk of disease progression*".

The EPAR statement highlights that the EMA considers these to be a sub-group of the overall cirrhotic population. For the majority of patients, the time taken to progress from first being classified as having compensated cirrhosis to a decompensation event, or developing HCC, is measured in years (e.g. 11 year mean time free of decompensation in compensated cirrhotic patients with a MELD score <10) (4). Thus a proportion of TE cirrhotic patients can be classified as being at low risk of clinical disease progression and should be treated with 12 weeks LDV/SOF. Again, the EMA chose to allow individual assessment of each cirrhotic patient's risk of disease progression by the treating physician when determining the appropriate treatment duration.

2.0.0.4. SVR outcomes in treatment experienced patients with cirrhosis treated with LDV/SOF in clinical trials

In the ION-2 TE phase III study, patients that had previously not achieved SVR with pegylated interferon + ribavirin (PR) or a protease inhibitor (PI) + PR were treated with LDV/SOF±RBV for 12 or 24 weeks. In the 12 week LDV/SOF arm, 86% (19/22) of cirrhotic patients achieved SVR12. The SVR12 in the sub-group of cirrhotic patients receiving 12 week therapy that had previously been treated with a PI based regimen remained at 86% (12/14).

Data is now published describing the first 513 patients with compensated cirrhosis in the LDV/SOF phase 2/3 clinical trial programme (5). A total of 71 TE cirrhotic GT1 patients received LDV/SOF for 12 weeks. Of these, 90% (64/71) achieved SVR12, indicating that the 12 week regimen provides the opportunity of a cure for the vast majority of TE cirrhotic patients.

GT1 or GT4 treatment experienced patients with cirrhosis: Supporting cost-effectiveness analyses

Gilead Sciences Ltd. request that the NICE committee follow the EMA's LDV/SOF duration recommendation wording as per the SmPC posology table, when assessing the cost effectiveness of the different LDV/SOF durations in GT1 and GT4 TE patients with cirrhosis.

The ERG did not provide CE analyses of the 12 week ledipasvir-sofosbuvir regimen for GT1 and GT4 TE patients with cirrhosis. To aid the Committee's assessment of this regimen, Table 3 provides cost-effectiveness results for LDV/SOF versus all relevant comparators in patients with GT1 or GT4 HCV who have compensated cirrhosis and have failed prior treatment. Based on the full incremental analysis, LDV/SOF is highly cost-effective with an ICER for LDV/SOF versus no treatment of £5,435.

In conclusion, LDV/SOF for 12 weeks is cost-effective for GT1 or GT4 TE patients with compensated cirrhosis versus and should be recommended as a treatment option.

Table 2: Cost-effectiveness results, GT1 or GT4 treatment experienced patients with compensated cirrhosis

Technologies	Cardoso			Technologies	Fattovich		
	QALYs	Costs	ICER		QALYs	Costs	ICER
SOF+SMV	9.49	£79,754	£57,900	SOF+SMV	9.67	£81,284	£104,828
LDV/SOF	9.19	£62,364	£5,435	LDV/SOF	9.51	£64,496	£6,432
SOF+PR	8.59	£63,193	Dominated	SOF+PR	9.19	£66,473	Dominated
SMV+PR	8.31	£62,046	ED	SMV+PR	9.03	£65,804	Dominated
TVR+PR	7.46	£63,325	Dominated	TVR+PR	8.59	£68,855	Dominated
BOC+PR	6.95	£68,413	Dominated	BOC+PR	8.33	£74,964	Dominated
PR	5.74	£47,441	ED	PR	7.68	£56,386	ED
No treatment	5.19	£40,651	-	No treatment	7.38	£50,797	

Abbreviations: BOC, boceprevir; ED, extendedly dominated; GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.GT3 patients who intolerant to or ineligible for interferon

Unmet need in GT3 HCV for patients who are intolerant or ineligible to interferon

Patients infected with GT3 HCV who are intolerant to or ineligible for interferon represent a significant unmet need. During the appraisal of sofosbuvir, the proportion of patients who are IFN intolerant or ineligible was discussed in depth and it was agreed that this is a small proportion of the overall population.

The only currently NICE-approved treatment option for this population is SOF+RBV for 24 weeks; however, this treatment regimen is only recommended for patients with compensated cirrhosis (NICE TA330). Therefore, GT3 infected patients who are clinically intolerant to or ineligible for interferon must wait until they are cirrhotic before they can be treated, a position that is not equitable. A diagnosis of cirrhosis is associated with an increased lifelong risk of HCC, even if the patient is subsequently cured of their HCV. Offering a cost-effective treatment to patients prior to them becoming cirrhotic is thus of significant benefit to patients, and a benefit that is not likely to be captured within current QoL measures.

Rationale for treating GT3 patients who are intolerant to or ineligible for interferon with LDV/SOF+RBV

The data supporting the use of LDV/SOF+RBV in patients infected with HCV GT3 is based upon the phase II ELECTRON-2 study. All 26 TN GT3 patients (including 5 with cirrhosis) achieved SVR12 with 12 weeks LDV/SOF+RBV (6). In 50 TE patients, an overall SVR12 of 82% was observed with 12 weeks LDV/SOF+RBV; 89% (25/28) in non-cirrhotic patients and 73% (16/22) in cirrhotic patients (7).

In the SmPC the EMA states "*A conservative 24 weeks of therapy is advised in all treatment-experienced genotype 3 patients and those treatment-naïve genotype 3 patients with cirrhosis*" (SmPC page 4, section 4.4). This recommendation is based upon the fact that the EMA considers that for these patient populations "[LDV] *activity is anticipated that would be clinically relevant in patients for whom the present standard interferon-free regimen (SOF+RBV for 24 weeks) would be expected to yield inoptimal SVR rates based on available evidence*" (LDV/SOF EPAR page 60).

As set out in the SOF NICE technology appraisal guidance 330, for GT3 patients, 24 weeks SOF+RBV is "*only recommended for people with cirrhosis who are intolerant to or ineligible for interferon*". This recommendation includes both TN and TE cirrhotic GT3 patients. Given the EMA conclusion of the benefit of inclusion of LDV in the treatment of GT3 patients (versus SOF+RBV in interferon ineligible patients) the cost-effective regimen of LDV/SOF+RBV for 24 weeks should be recommended as a treatment option for GT3 interferon intolerant or ineligible patients with cirrhosis.

For TN GT3 non-cirrhotic patients, the 12 week LDV/SOF+RBV regimen provides a cost-effective treatment option for those that are intolerant to or ineligible for interferon. As detailed in the ACD (page 55), "*The NICE committee agreed with Gilead Sciences Ltd. that 12 weeks of ledipasvir–sofosbuvir plus ribavirin was included in the marketing authorisation for treatment-naive, genotype 3 HCV without cirrhosis.*"

GT3 patients who are intolerant to or ineligible for interferon: Supporting cost-effectiveness analyses

2.0.4.1. GT3 IFN intolerant or ineligible patients with cirrhosis

LDV/SOF+RBV offers higher cure rates in this patient population with an SVR rate of 100% versus 92.3% for SOF+RBV in TN patients, and 73% for LDV/SOF+RBV versus 60% for SOF+RBV in TE patients.

LDV/SOF+RBV for 24 weeks represents a cost-effective treatment option for IFN intolerant or ineligible patients who have compensated cirrhosis in GT3, with an ICER of £19,013 for TN patients and £10,440 for TE patients.

Table 3: Cost-effectiveness results, treatment naïve GT3 IFN intolerant or ineligible patients with compensated cirrhosis

Technologies	Cardoso			Technologies	Fattovich		
	QALYs	Costs	ICER		QALYs	Costs	ICER
LDV/SOF+RBV 24 weeks	10.23	£102,645	£19,013	LDV/SOF+RBV 24 weeks	10.26	£103,591	£33,130
SOF+RBV	9.87	£95,947	-	SOF+RBV	10.08	£97,657	-

Abbreviations: GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; LDV, ledipasvir; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir.

Table 4: Cost-effectiveness results, treatment experienced GT3 IFN intolerant or ineligible patients with compensated cirrhosis

Technologies	Cardoso			Technologies	Fattovich		
	QALYs	Costs	ICER		QALYs	Costs	ICER
LDV/SOF+RBV 24 weeks	8.55	£106,735	£10,440	LDV/SOF+RBV 24 weeks	9.17	£110,133	£16,549
SOF+RBV	8.01	£101,109	-	SOF+RBV	8.89	£105,608	-

Abbreviations: GT, genotype; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir.

The TN ICER is relatively sensitive to Fattovich vs Cardoso because the Fattovich transitions assume no reduction in the risk of HCC as a result of achieving SVR. This is not supported by the data or UK clinical opinion. To provide additional insight to support decision-making, an additional analysis was conducted in which the relative risk reduction in HCC as a result of achieving an SVR estimated by Cardoso was applied to the Fattovich transition from CC to HCC (i.e. to estimate the transition from SVR CC to HCC). The ICER that resulted from this analysis was £19,575, demonstrating that the only reason LDV/SOF+RBV appears not cost-effective is because the reduction in risk of HCC as a result of HCC is removed.

2.0.4.2. GT3 IFN intolerant or ineligible patients without cirrhosis

Currently interferon intolerant or ineligible GT3 patients without cirrhosis have no treatment options. The requirement that a patient must become cirrhotic prior to becoming eligible for treatment results in a lifelong increase in the risk of hepatocellular carcinoma (HCC), regardless of their future treatment outcome.

LDV/SOF+RBV for 12 weeks is a much-needed cost-effective treatment option for non-cirrhotic GT3 patients who are TN and intolerant or ineligible for interferon, and as a result have no treatment options.

Table 5: Cost-effectiveness results, treatment naïve GT3 IFN intolerant or ineligible patients without cirrhosis

Technologies	Cardoso			Technologies	Fattovich		
	QALYs	Costs	ICER		QALYs	Costs	ICER
LDV/SOF+RBV 12 weeks	17.24	£42,997	£10,549	LDV/SOF+RBV 12 weeks	17.24	£42,997	£11,727
No treatment	14.57	£14,928	-	No treatment	14.97	£16,430	-

Abbreviations: GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; LDV, ledipasvir; LYG, life years gained; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir.

Table 6: Cost-effectiveness results, treatment experienced GT3 IFN intolerant or ineligible patients without cirrhosis

Technologies	Cardoso			Technologies	Fattovich		
	QALYs	Costs	ICER		QALYs	Costs	ICER
LDV/SOF+RBV 24 weeks	15.97	£84,109	£33,631	LDV/SOF+RBV 24 weeks	16.01	£84,234	£38,793
No treatment	13.88	£13,936	-	No treatment	14.23	£15,110	-

Abbreviations: GT, genotype; ICER, incremental cost-effectiveness ratio; IFN, interferon; LDV, ledipasvir; QALY, quality-adjusted life year; RBV, ribavirin; SOF, sofosbuvir.

LDV/SOF+RBV for 24 weeks offers a valuable treatment option for IFN intolerant or ineligible GT3 patients who are TE and are not eligible for any treatment until they become cirrhotic. While the ICER for LDV/SOF+RBV is above the threshold at which NICE would usually consider a drug cost-effective, this is a much needed treatment option for this patient population that currently has no treatment options.

Use of "Not licensed for this population" to describe the LDV/SOF+RBV regimen for GT1/GT4 populations

The use of RBV in combination with LDV/SOF for the treatment of GT1 and GT4 CHC is encompassed by the indication for LDV/SOF and is supported by all three phase III clinical trials, as detailed in Section 5.1 of the SmPC. As such, it is incorrect to state that this regimen is "unlicensed". Gilead Sciences Ltd. requests that the wording is changed from "Not licensed for this population" to "Not the EMA recommended regimen for this population"

Choice of transition probabilities for economic modelling: Cardoso vs Fattovich

NICE commented on the relative merits of using specific transition probabilities from Cardoso et al and Fattovich et al, and concluded that "the transition probabilities for compensated or decompensated cirrhosis to hepatocellular carcinoma may lie somewhere between the Cardoso et al. and Fattovich et al. estimates." Gilead Sciences maintains the view that Cardoso et al is the most appropriate source for these inputs. This is because it reflects the relative decrease in the risk of developing HCC in patients

who have compensated cirrhosis and achieve SVR versus patients who have compensated cirrhosis who are untreated or who fail to clear the virus (relative risk reduction 80%). These data have face validity as there is a significant risk reduction for HCC in a cirrhotic patient who achieves SVR, as supported by data and UK clinician opinion. If the Fattovich source is selected for the transition from compensated cirrhosis to HCC (0.014), while retaining the compensated cirrhosis with SVR to HCC TP from Cardoso et al (0.0128) then this is equivalent to a risk reduction of only 8.6%.

In addition, the data from Cardoso is more recently published (2010 vs 1997 for Fattovich) and this study was specifically designed to assess the risk of HCC in HCV infected patients with cirrhosis compared to patients with cirrhosis and who have achieved an SVR. As such, we recommend that the NICE committee assess the cost-effectiveness of LDV/SOF based on the transition probabilities from Cardoso et al.

For completeness, analyses included in this response have been provided using the two alternative values for the transition probabilities (TPs), as detailed in Table 7.

Table 7: Transition probabilities varied in the analyses

From	To	Cardoso et al 2010	Fattovich et al 1998
Compensated cirrhosis SVR	HCC	0.0128†	NA
Compensated cirrhosis	Decompensated cirrhosis	0.0438	0.039
	HCC	0.0631	0.014
Decompensated cirrhosis	HCC	0.0631	0.014

Abbreviations: HCC, hepatocellular carcinoma; TP, transition probability. †TP from Cardoso et al for this health state used for both analyses in the absence of data from Fattovich et al.

Factual inaccuracies

Location and description	Proposed amendment
Section 1.1 Table 1 Ledipasvir–sofosbuvir for treating adults with chronic hepatitis C - States that ledipasvir-sofosbuvir in combination with ribavirin is "*not licensed*" in adults with genotype 1 and genotype 4, which is inaccurate and misleading. - The use of RBV in combination with LDV/SOF for the treatment of GT1 and GT4 CHC is encompassed by the LDV/SOF indication and is supported by all three phase III clinical trials, as detailed in Section 5.1 of the SmPC. As such, it is incorrect to state that this regimen is "unlicensed".	Proposed wording for LDV/SOF in combination with RBV in adults with GT1 and GT4 HCV: "Not the EMA recommended regimen for this population" (An example table using the recommendations from the ACD is provided at the end of this document)
Section 3.20 - It is stated that 'The cost-effectiveness of ledipasvir-sofosbuvir was assessed in populations defined by HCV genotype, which included those with cirrhosis (but excluded HIV co-infection)'. - The cost-effectiveness analyses did not exclude patients with HIV co-infection, rather, it is assumed that the efficacy and safety of ledipasvir–sofosbuvir treatments for people co-infected with HIV and HCV is	Remove '(but excluded HIV co-infection)'.

similar to that seen in people with HCV mono-infection, and as such is treated in the same way. Please refer to page 25 of the ACD where more detail is provided on the approach to modelling HIV co-infection and the associated justification.	
Section 3.22 - The bulleted reasons provided for why GT4 was modelled alongside GT1 do not include reference to the fact that this approach was validated with KOLs.	Add a third bullet point explaining that KOL validation was a factor in the decision to model these genotypes together.
Section 3.23 -States that 'Treatment durations were also used to estimate drug and monitoring costs, and the proportion of people on a given treatment duration were generally based on Gilead Sciences Ltd.'s clinical expert opinion.' - It should be stated that this refers to the treatment duration of LDV/SOF specifically.	Change text to: 'Treatment durations were also used to estimate drug and monitoring costs, and the proportion of people on a given **LDV/SOF** treatment duration were based on the clinical expert opinion received by Gilead Sciences Ltd..'
Section 3.25, Table 6 Incremental cost-effectiveness results for treatment-experienced genotype 1 and 4 HCV - Footnote symbol (*) incorrectly assigned to SMV+PR	Move footnote symbol to BOC+PR
Section 3.54 ERG comments on the PSA -States that 'key uncertain parameters (for example, SVR rates) being pre-sampled outside of the model rather than sampling from a distribution' is a limitation of the PSA. - This is incorrect; all values were randomly sampled from a distribution. For all populations, except GT1 TN, data inputs are linked up to the randomly generated values on the 'PSA sheet'. The confusion may have arisen from the GT1 TN patient group specifically where the model has to run the simulations for non-cirrhotic patients and then for cirrhotic patients separately but needs to ensure that the same common values are used. For this population only, all data values for any single PSA run are randomly generated and recorded on 'Sheet5', which gives the impression that these values are fixed. However, on each PSA run the content of 'Sheet 5' is updated with the new randomly generated data.	Remove 'key uncertain parameters (for example, SVR rates) being pre-sampled outside of the model rather than sampling from a distribution'.

Revised Table 1

Genotype*	Ledipasvir–sofosbuvir		Ledipasvir–sofosbuvir in combination with ribavirin	
	Treatment history	**Recommendation**	**Treatment history**	**Recommendation**
Adults with genotype 1 HCV	Treatment-naïve	8 weeks' treatment recommended for people without cirrhosis; 12 weeks' treatment not recommended for people without cirrhosis	All	Not the EMA recommended regimen for this population
		12 weeks' treatment recommended for people with cirrhosis; 24 weeks' treatment not recommended for people with cirrhosis		
	Treatment-experienced	12 weeks' treatment recommended for people without cirrhosis; 24 weeks' treatment not recommended for people without cirrhosis		
		24 weeks' treatment not recommended for people with cirrhosis		
Adults with genotype 3 HCV	All	Not licensed for this population	All	Not recommended
Adults with genotype 4 HCV	Treatment-naïve	12 weeks' treatment not recommended for people without cirrhosis	All	Not the EMA recommended regimen for this population
		12 weeks' treatment recommended for people with cirrhosis; 24 weeks' treatment not recommended for people with cirrhosis		
	Treatment-experienced	12 weeks' treatment recommended for people without cirrhosis; 24 weeks' treatment not recommended for people without cirrhosis		
		24 weeks' treatment not recommended for people with cirrhosis		

HCV, hepatitis C virus

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

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

Reference List

(1) Wyles D, Pockros P, Zhu Y, Yang JC, Pang PS, McHutchinson JG, et al. Retreatment of patients who failed prior sofosbuvir-based regimens with all oral fixed-dose combination ledipasvir/sofosbuvir plus ribavirin for 12 weeks. Oral presentation O235, AASLD, 7-11 November 2014, Boston, MA 2014.

(2) Esteban R, et al. Successful Retreatment With Sofosbuvir-containing Regimens for HCV Genotype 2 or 3 Infected Patients who Failed Prior Sofosbuvir Plus Ribavirin Therapy. Oral presentation O8, International Liver Congress 2014, London, UK 2014.

(3) Dieterich D, Bacon B, Flamm S, Kowdley K, Milligan S, Tsai N, et al. Evaluation of sofosbuvir and simeprevir-based regimens in the TRIO network. Oral presentation 046 Presented at AASLD 7-11 November 2014 Boston, MA 2014.

(4) Bruno S, Zuin M, Crosignani A, Rossi S, Zadra F, Roffi L, et al. Predicting mortality risk in patients with compensated HCV-induced cirrhosis: a long-term prospective study. Am J Gastroenterol 2009 May;104(5):1147-58.

(5) Bourliere M, et al. An Integrated Safety and Efficacy Analysis of >500 Patients With Compensated Cirrhosis Treated With Ledipasvir/Sofosbuvir With or Without Ribavirin. Oral presentation O82, AASLD, 7-11 November 2014, Boston, MA 2014.

(6) Gane EJ, Hyland RH, An D, Pang PS, Symonds WT, McHutchinson JG, et al. Ledipasvir/Sofosbuvir Fixed-Dose Combination Is Safe and Effective in Difficult-to-Treat Populations Including GT 3 Patients, Decompensated GT 1 Patients, and GT 1 Patients With Prior Sofosbuvir Experience. Presented at The Liver Meeting 2014, London, UK 2014.

(7) Gane EJ, Hyland RH, An D, Svarovskaia ES, Pang PS, Symonds WT, et al. High Efficacy of LDV/SOF Regimens for 12 weeks for Patients with HCV Genotype 3 or 6 Infection. Poster LB-11 Presented at AASLD, 7-11 November 2014 Boston, MA 2014.