Appraisal Consultation Document – Sofosbuvir for treating chronic hepatitis C

Gilead response to further analysis required by the Appraisal Committee regarding the HCV/HIV co-infected population – July 2014

1. Whether analysis G1 is for non cirrhotic patients only or for a combined population?

The analysis from study 1910[1] is based upon a non cirrhotic (F0-F3) cohort of patients who are all HCV/HIV co-infected. No cirrhotic patients were enrolled in this study. SVR rates within the non cirrhotic cohort for HCV mono-infected patients versus HCV/HIV co-infected patients were 90% reinforcing the fact that similar response rates are seen in patients treated with SOF + PR in GT1 patients regardless of HCV/HIV co-infection status.

2. ICERs/QALY for non-cirrhotic and cirrhotic HCV/HIV co-infected patients

Tables 1-3 list the ICERs from all sofosbuvir trial data available for HCV/HIV co-infection aligned to the final licensed regimens for GT1 and GT3 from the summary of product characteristics (SmPC). That is 12 weeks SOF + PR [1910] or 24 weeks SOF + RBV for the TE population [Photon 1][2].

Of note, whilst we have included ICERs for the 24wk SOF + RBV regimen vs PR in GT3 TE as requested by the Committee, we are not requesting guidance for, nor do we anticipate (as with the mono-infected population) any patients who are able to tolerate PR would be given the option of the 24 week interferon-free sofosbuvir regimen in preference to the more effective and shorter 12 week interferon-containing option. We believe that HCV/HIV co-infected patients should be treated the same as HCV mono-infected patients for the reasons outlined within our submission and also our response to the ACD

Table 1 – ICERs/QALY for HCV/HIV co-infected: combined cohort

Indication	Treatment strategies	ICERS (£/QALY) Scenario analysis model
GT1 TN	SOF+PR (12 wks) vs. PR (data for SOF from trial 1910)	NA
	SOF+RBV (24 wks) vs. NT	27,059
GT3 TE	SOF+RBV (24 wks) vs. PR (SVR for PR from Lagging et al[1] (2013) and Shoeb et al[2] (2011))	17,167
	SOF+RBV (24 wks) vs. NT	10,376

ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; NT: No treatment; PR: PEGIFN2a + RBV; QALY: Quality-adjusted life years; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; wks: Weeks

Table 2 – ICERs/QALY for HCV/HIV co-infected: non-cirrhotic cohort

Indication	Treatment strategies	ICERS (£/QALY) Scenario analysis model
GT1 TN	SOF+PR (12 wks) vs. PR (data for SOF from trial 1910)	15,866
	SOF+RBV (24 wks) vs. NT	30,499
GT3 TE	SOF+RBV (24 wks) vs. PR (SVR for PR from Lagging et al[1] (2013) and Shoeb et al[2] (2011))	14,454
	SOF+RBV (24 wks) vs. NT	8,968

ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; NT: No treatment; PR: PEGIFN2a + RBV; QALY: Quality-adjusted life years; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; wks: Weeks

Table 3 – ICERs/QALY for HCV/HIV co-infected: cirrhotic cohort

Indication	Treatment strategies	ICERS (£/QALY) Scenario analysis model
GT1 TN	SOF+PR (12 wks) vs. PR (data for SOF from trial 1910)	NA
	SOF+RBV (24 wks) vs. NT	17,660
GT3 TE	SOF+RBV (24 wks) vs. PR (SVR for PR from Lagging et al[1] (2013) and Shoeb et al[2] (2011)))	37,891
	SOF+RBV (24 wks) vs. NT	19,400

ICER: Incremental cost-effectiveness ratio; IE: Interferon eligible; GT: Genotype; NT: No treatment; PR: PEGIFN2a + RBV; QALY: Quality-adjusted life years; SOF: Sofosbuvir; TE: Treatment-experienced; TN: Treatment-naïve; wks: Weeks

3. Why the Lagging study was considered appropriate?

Firstly we would like to clarify and apologise for any confusion caused as the initial reference we provided within the additional economic analysis request was not clear. SVRs have been obtained from Lagging et al., 2013[3] using the distribution between relapsers and non-responders from Shoeb et al.,2011[4] as with the HCV mono-infected analysis.

This was considered appropriate for the HCV/HIV co-infected population in GT3 TE for the following reasons outlined below:

- Lagging et al (2013) and Shoeb et al (2011) was used in place of Labarga et al (2012)[5] because the PERICO trial only looked at HCV/HIV co-infected TN patients. This is considered to be a big limitation since a significant difference has been observed in the SVR rates between TN and TE in mono-infected patients and would thus be expected in the co-infected population. No publications have been identified that assess P/R re-treatment of HCV/HIV infected patients with GT3.

- The Lagging et al (2013) publication was selected as all the enrolled patients were treated with P/R the first time round as well as second, as opposed to having an inferior IFN/R or IFN-monotherapy as their first course of treatment (as was the case in the Poynard et al[6] (2009). and Krawitt et al (2005)[7] studies). P/R therapy was approved by NICE in 2004 and thus it is expected that the vast majority of GT 3 treatment experienced patients currently awaiting re-treatment in England would have previously received a prior P/R regimen, as opposed to I/R or monotherapy I regimen.

- UK clinical practice would suggest (in line with current EASL guidance) that it is very uncommon to retreat non GT1 patients who fail to achieve an SVR with PEG-IFN + RBV in the first instance unless they have an urgent indication for therapy, and/or if there is evidence of inadequate exposure to either PEG-IFN or RBV due to dose adjustments or poor adherence during the first course of therapy. Even for the small percentage of patients who do undertake retreatment, KOL consensus is that the SVR's seen would be very low in practice. This may in part explain the limited number of publications detailing re-treatment of GT3 P/R failures in practice.

4. **What the patient characteristics in the Lagging study were (the publication does not provide detail).**

The patient characteristics are outlined below under 'Group A'

Table I. Baseline characteristics.

	Group A	Group B	Group C
		(non-RVR)	(RVR)
	48 weeks therapy	48 weeks therapy	24 weeks therapy
Characteristic	(n = 38)	(n = 21)	(n = 12)
Gender			
Male[a]	29 (76%)	15 (71%)	10 (83%)
Female[a]	9 (24%)	6 (29%)	2 (17%)
Age (years)[b]	50.2 (7.3)	52.0 (7.2)	46.6 (10.0)
BMI (kg/m^2)[b]	27.6 (5.0)	27.0 (5.4)	26.2 (3.1)
Route of transmission[a]			
Intravenous drug use	25 (66%)	9 (43%)	10 (83%)
Blood products	3 (8%)	2 (10%)	2 (17%)
Sexual	1 (3%)	5 (24%)	0
Unkown	9 (24%)	5 (24%)	0
Genotype 2[a]	7 (18%)	7 (33%)	3 (25%)
Genotype 3[a]	31 (82%)	14 (67%)	9 (75%)
Duration of infection (years)[b]	27.1 (9.7)	22.8 (12.6)	18.3 (9.1)
APRI (nAST * 100/ Platelet Count)[c]	0.99 (0.89)	1.14 (1.71)	0.70 (0.77)
GUCI (nAST * PT-INR * 100/ Platelet Count)[c]	1.07 (1.07)	1.25 (2.02)	0.76 (0.94)
Fibrosis Stage (Ishak score 0 2/ 3 4/ 5 6)[d]	2/ 3/ 3	6/ 5/ 3	1/ 3/ 1
Steatosis Grade (0/1/2/3)[d]	2/ 1/ 5/ 0	5/6/3/0	2/1/1/1
Log_{10} HCV-RNA (IU/mL)[b]	6.09 (0.71)	6.07 (0.82)	5.73 (0.86)
IL28B SNP polymorphism[d] (*rs12979860* CC/CT/TT)	17/ 17/ 1	11/ 7/ 2	6/ 4/ 2
Race (Caucasian/Asian)[d]	38/ 0	20/ 1	12/ 0
Alcohol Consumption (units/week)[c]	1.6 (2.9)	2.8 (5.0)	3.9 (5.0)

Data presented as [a]n (%), [b]Mean (SD), [c]Median (Mean), and [d]n.
Forty six patients had no prior liver biopsy available for evaluation.

[1]Labarga P, Barreiro P, da SA, Guardiola JM, Rubio R, Aguirrebengoa K, et al. Comparison of high ribavirin induction versus standard ribavirin dosing, plus peginterferon-alpha for the treatment of chronic hepatitis C in HIV-infected patients: the PERICO trial. J Infect Dis 2012 Sep 15;206(6):961-8.

[2.] Sulkowski M et al., All-Oral Therapy With Sofosbuvir Plus Ribavirin For the Treatment of HCV Genotype 1, 2, and 3 Infection in Patients Co-infected With HIV (PHOTON-1). 64th Annual Meeting of the American Association for the Study of Liver diseases, November 1-5, 2013, Washington, SA; oral abstract 212

[3] Lagging M, Rembeck K, Buhl MR et al. Retreatment with peg-interferon and ribavirin in patients with chronic hepatitis C virus genotype 2 or 3 infection with prior relapse. Scandinavian journal of gastroenterology 2013;48:839-847.

[4] Shoeb D, Rowe IA, Freshwater D et al. Response to antiviral therapy in patients with genotype 3 chronic hepatitis C: fibrosis but not race encourages relapse. *Eur J Gastroenterol Hepatol* 2011;23:747-753

[5] Labarga P, Barreiro P, da SA, Guardiola JM, Rubio R, Aguirrebengoa K, et al. Comparison of high ribavirin induction versus standard ribavirin dosing, plus peginterferon-alpha for the treatment of chronic hepatitis C in HIV-infected patients: the PERICO trial. J Infect Dis 2012 Sep 15;206(6):961-8

[6] Poynard T, Colombo M, Bruix J, Schiff E, Terg R, Flamm S, et al. Peginterferon alfa-2b and ribavirin:effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. Gastroenterology 2009;136:1618–28; e2.

[7] Krawitt EL, Ashikaga T, Gordon SR, Ashikaga T, Gordon SR, Ferrentino N, Ray MA, Lidofsky SD, New York New England Study Team: Peginterferon alpha-2b and ribavirin for treatment-refractory chronic hepatitis C. J Hepatol 2005, 43:243-9