Request for Additional Information - Gilead Response – 24th September 2014

Single Technology Appraisal – Appraisal Consultation Document –Sofosbuvir for treating chronic hepatitis C

In response to a request from the Institute we are providing the following additional information for people with HCV genotype (GT) 4, 5 and 6:

- Alternative sustained virological response (SVR) rates for peginterferon alfa (PEG) and ribavirin (RBV) alone from the systematic review of published sources included in the initial Gilead submission for each genotype, together with a rationale for the preference of Manns et al. (2001) over other available studies.
- Additional economic analyses.
- HCV prevalence data by genotype (1 to 6) and ethnicity, HIV co-infection and haemophilia for the UK.

1.0 Alternative SVR rates - treatment-naïve genotype 4/5/6 patients

Systematic review – identified clinical trials

Further details on the primary trials identified within our original systematic literature review (SLR) are provided below. Seven studies[1,2,3,4,5,6,7] reporting efficacy data for patients with GT4, 5 or 6 were included from this review.

Summary results from each study are provided in Table 1. The results for PEG and RBV are in bold. All studies reported outcomes for patients with GT4.

Table 1: Results from clinical trials in genotype 4/5/6 TN patients

Publication	GT	Arms/Interventions	Primary outcome	Secondary outcomes
			SVR24	EOT
Zeuzem 2004[1]	4	Arm 1: PR24a2a (N=8)	13%	
		Arm 2: PR48a2a (N=9)	**56%**	
Rumi 2010[2]	4	**Arm 1: P(180)Ra2a (N=18)**	**44% (95%CI: 21–69%)**	
		Arm 2: P(1.5)Ra2b (N=26)	31% (95%CI: 14–51%)	
Fried 2002[3]	4	**Arm 1: PR48a2a (N=13)**	**77%**	
		Arm 2: IFNR48a2b (N=11)	36%	
		Arm 3: P48a2a (N=9)	44%	
Manns, 2001[4]	4/5/6	**Arm 1: P(1.5)R48a2b (N=16)**	**50%**	
		Arm 2: P(1.5/0.5)R48a2b (N=12)	33%	
		Arm 3: IFNRa2b (N=16)	38%	
Ferenci 2010[5]	4	**Arm 1: PR48a2a (N=12)**	**50% (95%CI: 21.1–78.9%)**	83.3% (95%CI: 51.6–97.9%)
		Arm 2: PR72a2a (N=16)	43.8% (95%CI: 19.8–80.1%)	75.% (95%CI: 47.6–92.7%)
Zeuzem 2005[6]	4/5	Arm 1: Individualized (N=9)	44%	56%
		Arm 2: PR48a2a (N=6)	**33%**	50%
Lindsay 2001[7]	4/5/6	Arm 1: P(0.5)48a2b (N=15)	20%	30%
		Arm 2: P(1.0)48a2b (N=15)	31%	46%
		Arm 3: P(1.5)48a2b (N=8)	**60%**	80%
		Arm 4; IFN48a2b (N=5)	0%	0%

P – peginterferon; R-ribavirin; IFN – Interferon, 48- 48 weeks, 72 – 72 weeks,180 - g/wk - 1.5 - g/kg per week 0.5 - g/kg per week

Rationale for the use of Manns et al.

Only two studies - Manns *et al.* 2001[4] and Lindsay *et al*. 2001[7] provided combined data on GT4/5/6 and could have been used within our economic evaluation. The Manns study was selected over that published by Lindsay on the basis of patient numbers (there were a greater number of GT4/5/6 patients in Manns (n=16) compared with Lindsay (n=8)). Due to the fact that data on responsiveness was limited, additional clinical expert opinion was sought prior to our original submission to help validate this selection.[8] Unpublished data from Imperial College London (the largest UK treatment centre for GT4 patients) presented an SVR rate of 49.5% for those patients treated with PEG/RBV as standard of care.[8] This SVR is comparable with the results from the Manns study. Upon request and with the consent of the lead clinical hepatologist, additional written correspondence has been submitted for review. (Appendix 1)

We would also like to respond to the Appraisal Committee's question as to why data from Kamal *et al*. (2011)[9] was not listed as a comparator. This publication was initially picked up at the screening phase of the systematic literature review but was excluded at the full-text article review as it only included patients from Egypt – studies that recruited solely from Egypt, Africa, Asia and the Middle East were excluded due to the documented differences in terms of response to treatment[10]. Patients enrolled within the Kamal study were also classified as non cirrhotic (median liver histology fibrosis score 1.0 (range of 0-4))

It should be noted that the upper limit comparator (Fried[3]) used within the sensitivity analyses presents an SVR above that reported in Kamal and as such could be deemed a more conservative comparator.

2.0 Additional economic analyses

In order to address the Institute's request for additional economic analyses and to meet any outstanding issues of uncertainty related to the base case ICER for GT4-6 we have modelled scenarios incorporating a revised base case and alternative outcomes. This includes economic sensitivity analyses presenting alternative ICERs based on both the highest and the lowest SVR rates derived from the original SLR literature.[3,6]

It has not been possible to model genotype 4, 5 and 6 separately due to the fact that the data are not available - comparator trial outcomes are only reported for either GT4 alone, GT4,5 or GT4-6 combined. The Gilead NEUTRINO trial presented results across each genotype separately which support similar response rates across each genotype as follows, suggesting the generalisability of GT4 outcomes to those for GT5 and GT6:

- GT4/5/6: 97% (34/35 patients)
    - GT4: non cirrhotic patients 100% (26/26); cirrhotic patients 50% (1/2)
    - GT5: non cirrhotic patients 100% (1/1)
    - GT6: non cirrhotic patient 100% (6/6)

The full list of revisions for economic analyses are as follows:

1) Revised base case model which incorporates:
    a. Transition probabilities (TPs) from compensated cirrhosis with and without SVR to hepatocellular carcinoma (HCC) from Cardoso *et al*. (2010)[11], that is, 0.0128 and 0.0631, respectively.

b. Utility increment after reaching sustained virological response (SVR) of 0.041 from Vera-Llonch *et al.* (2013)[12].

c. Probability of death re-estimated assuming the distribution between male and female from Wright et al. (2006) (61% male and 39% female)[13].

d. SVR rates from Manns *et al.* (2001)[4], that is, 50% (8/16) for non-cirrhotic and 39% (8/16*0.44/57) for cirrhotic patients.

2) Sensitivity analysis with:

a. SVR rates from Zeuzem *et al*. (2005)[6]. SVR rates were reported at 33% (2/6). No split between non-cirrhotic and cirrhotic patients was provided in this publication and therefore the same SVR rate was assumed between the two patient populations representing the most conservative approach.

b. SVR rates from Fried *et al.* (2002)[3]. SVR rates were reported at 77% (10/13). No split between non-cirrhotic and cirrhotic patients was provided and therefore the same SVR rate was assumed between the two patient populations representing the most conservative approach.

c. SVR rates for PR from Fried et al. (2002)[3] (see previous bullet point) and SVR rates for sofosbuvir assumed equal between non-cirrhotic and cirrhotic patients (to provide an equivalent comparator) based on the overall SVR rates for GT4/5/6 patients from NEUTRINO, that is, 97% (34/35).

d. TP from compensated cirrhosis (CC) without SVR to hepatocellular carcinoma (HCC) from Fattovich et al. (1997)[14], that is, 0.014, and TP from CC with SVR to HCC from Cardoso et al. (2010)[11], that is, 0.0128

ICERs for each of the previous analyses are presented below (Error! Reference source not found. **and** Error! Reference source not found.**).**

The revised base case model result using Manns *et al.* (2001) in table 2 demonstrates a slight increase from the original base case ICER. (£26,797 to £27,505.)

When the minimum SVR rate[6] is applied, the ICER drops below £20,000, whilst the maximum SVR[3] derives a significantly higher ICER of £244,387. It should be noted that the ICER derived from Fried *et al*. (2002)[3] is driven in part by the assumption that SVR rates are the same for both the non cirrhotic and cirrhotic populations (since no split was provided). By comparison, the NEUTRINO trial results did provide a split across GT4-6, demonstrating 100% (33/33) SVR for non cirrhotics and 50% (1/2) SVR for the cirrhotic population. Therefore this ICER is using an assumption that PEG + RBV is more effective than sofosbuvir + PEG + RBV in the cirrhotic population.

We have carried out additional sensitivity analysis to explore the impact of adopting a similarly conservative assumption to NEUTRINO as with Fried,[3] through applying the overall trial SVR of 97% (34/35) from NEUTRINO equally across the non cirrhotic and cirrhotic populations. In this

scenario the ICER was still significantly above the generally accepted willingness to pay threshold (£47,394).

Table 2- ICERs/QALY revised base case

ICER (£/QALY) (Revised base case)	ICER (£/QALY) (Revised base case + SVR Zeuzem)	ICER (£/QALY) (Revised base case + SVR Fried)	ICER (£/QALY) (Revised base case + SVR Fried + SVR NEUTRINO)
27,505	19,148	244,387	47,394

SVR Zeuzem et al. (2005): 33% for both non-cirrhotic and compensated cirrhosis patients on PR
SVR Fried et al. (2002): 77% for both non-cirrhotic and compensated cirrhosis patients on PR
SVR NEUTRINO: 97% for both non-cirrhotic and compensated cirrhosis patients on sofosbuvir

Table 3- ICERs/QALY using TP from CC to HCC from Fattovich et al. (1997)

ICER (£/QALY) (Revised base case + TP Fattovich)	ICER (£/QALY) (Revised base case + TP Fattovich + SVR Zeuzem)	ICER (£/QALY) (Revised base case + TP Fattovich + SVR Fried)	ICER (£/QALY) (Revised base case + SVR Fried + SVR NEUTRINO)
31,713	22,096	151,837	59,095

TP Fattovich: 0.014 from CC without SVR to HCC
SVR Zeuzem et al. (2005): 33% for both non-cirrhotic and compensated cirrhosis patients on PR
SVR Fried et al. (2002): 77% for both non-cirrhotic and compensated cirrhosis patients on PR
SVR NEUTRINO: 97% for both non-cirrhotic and compensated cirrhosis patients on sofosbuvir

3.0 HCV Prevalence

HCV prevalence data by genotype (1 to 6) and ethnicity, HIV co-infection and haemophilia is provided below.

Genotype

The distribution of genotype and ethnicity are taken from the Public Health England report *'Hepatitis C genotypes reported to the sentinel surveillance of blood-borne virus testing: A commissioned surveillance report'*[15]. The sentinel surveillance system collects information on all testing undertaken for hepatitis as well as HIV and HTLV within a network of 24 laboratories across the UK.

Between 2008 to 2012, 123,974 anti-HCV positive individuals underwent hepatitis C testing in one of 24 one of 24 sentinel laboratories in England. Among those individuals with an active HCV infection 43.1% infection 43.1% (n=37,355) had a HCV genotype (GT) recorded. Details of the distribution of genotype are genotype are provided in

Table 2 . The most commonly seen HCV genotypes were GT1 (45.4%) and 3 (44.5%), a further 3.6% had GT 4 infections. Few GT 5 (0.1%) and GT 6 (0.2%) were identified.

Table 2 : Distribution of HCV genotype 2008 to 2012[15]

Genotype	GT1	GT2	GT3	GT4	GT5	GT6	Duel
N	16,954	2,244	16,610	1,348	47	64	22
%	45.4%	6%	44.5%	3.6%	0.1%	0.2%	0.1%

Ethnicity

Ethnicity was hierarchically coded into a summary ethnicity field using self-reported ethnicity where available. Due to the small numbers of individuals tested identified as belonging to certain ethnic groups (e.g. mixed White and Black Caribbean) individuals were grouped into four broad ethnic groups – 'Asian or Asian British', 'black or black British', 'mixed and/or other ethnic groups', 'white or white British', or as being of an unknown ethnic group.

Overall, 89.1% of individuals (n=33,289) were categorised as belonging to a broad ethnic group

- 84.9% (n=28,248) were of white or white British origin (WWB)
- 12.7% (n=4,242) were of Asian or Asian British origin (AAB)
- 1.7% (=579) were of other or mixed ethnic origin (O/M)
- 0.7% (220) were of black or black British origin (BBB)

The available data does not distinguish between individuals who are recent migrants to the UK and those individuals who were born in Britain.

The distribution of HCV genotypes varies by broad ethnic group see

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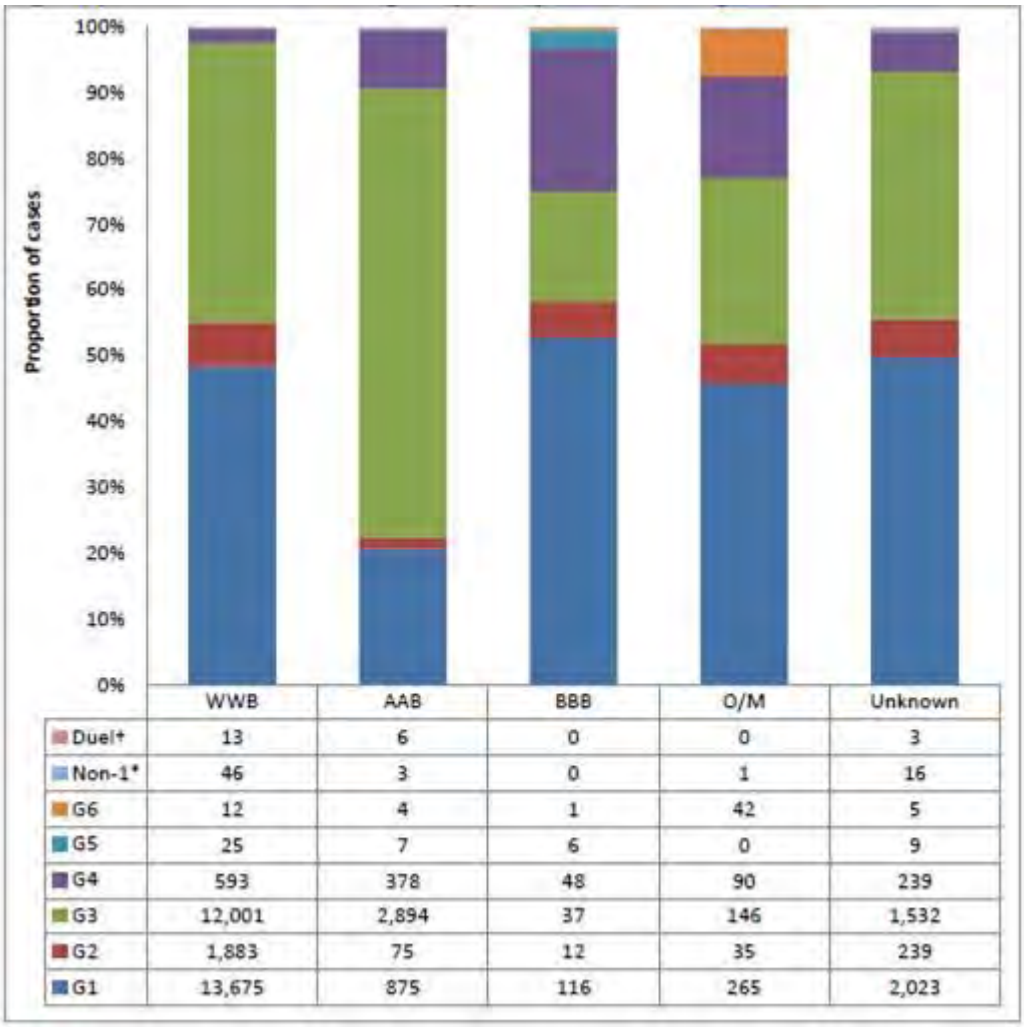
- A similar proportion of GT1 and GT3 infections was seen among WWB individuals (48.4% and 42.5% respectively), whereas GT 3 infections accounted for the majority of individuals of AAB ethnic origin, accounting for over two-thirds of all infections among this group (68.2%).
- A greater proportion of GT 4 infections were seen among BBB and O/M individuals (21.8% and 15.5% respectively) compared to 2.1% among WWB individuals and 8.9% among AAB individuals.
- Overall, the greatest number (n=25) of genotype 5 infections were seen among WWB individuals, however the greatest proportion of GT 5 infections (2.7%) were among BBB individuals.

- The greatest number and proportion of GT 6 infections was seen among O/M individuals (n=42; 7.3%).

Figure 1: Distribution of HCV genotype by broad ethnic group, 2008 to 2012[15]



	WWB	AAB	BBB	O/M	Unknown
Duel†	13	6	0	0	3
Non-1*	46	3	0	1	16
G6	12	4	1	42	5
G5	25	7	6	0	9
G4	593	378	48	90	239
G3	12,001	2,894	37	146	1,532
G2	1,883	75	12	35	239
G1	13,675	875	116	265	2,023

* HCV genotype result reported as 'genotype 2 or genotype 3'
† Individuals identified as having a duel infection

The Immunisation Department within Public Health England has provided Gilead Sciences Ltd with this HCV genotype surveillance report, which has been made available to the National Institute for Health and Care Excellence as part of a technology appraisal. A cost recovery charge has been made for this report.

Haemophilia

Genotype distribution data from the 2012 UKHCDO look-back exercise[16] shows a prevalence of 3% and 1% of genotypes 4 and 5 respectively amongst UK HCV-infected haemophiliacs. Genotypes 1, 2 and 3 make up 96% of all HCV-infected haemophiliacs

Personal communication with a leading UK haemophilia expert suggests that ethnicity data is not available for the different genotypes (data on file SOFUK1405[17]).

HIV/HCV co-infected

Information provided from the XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXX[17] recorded the genotype for XXXXXXXXXXXX The number of individuals classed by each respective genotype are shown in

Table 3.

Whilst numbers are XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX[17]

Table 3: Genotype distribution of HIV and hepatitis C co-infected individuals in UK[17]

Genotype	**Total number of infections with each genotype (%)[1]**	**By ethnicity (%)**			
		White	Black African	Black other	Other/unknown
1	XXX (XX.X)	XXX	XXX	XXX	XXX
2	XXX (XX.X)	XXX	XXX	XXX	XXX
3	XXX (XX.X)	XXX	XXX	XXX	XXX
4	XXX (XX.X)	XXX	XXX	XXX	XXX
6	XXX (XX.X)	XXX	XXX	XXX	XXX
Total	XXXX	XXXX	XXXX	XXXX	XXXX

Appendix 1

XX XXXX XX XXX XXXXXXX

Dear NICE committee member

I am writing to you in my capacity as a Consultant Hepatologist and clinical lead for viral hepatitis working at Imperial College Healthcare NHS Trust, London.

I am concerned that NICE has made no recommendation for the use of Sofosbuvir in genotype 4 (GT4) patients. While I acknowledge that G4 is not generally considered a major population in the UK, (and that numbers of GT4 patients in the NEUTRINO study on which to base a decision were small), I would ask that this population are not forgotten.

I believe that our unit has the highest prevalence of GT4 patients anywhere in the UK. Over the past 8 years we have treated 118 GT4 patients with PEG/RBV as standard of care. At least 25% of these patients had one or more co-morbidities including HIV/HCV co-infection, end-stage renal disease and post liver transplant. More than half had moderate to severe fibrosis or cirrhosis on liver biopsy (Ishak 3/6 or greater). The mean age on starting treatment was 48 years. Despite the fact that in all other groups of patients, our Unit can achieve results in excess of registration trials, in this particular GT4 cohort only 49.5% (57/118) achieved SVR (a figure in keeping with the registration study of Manns et al. (2001))

It is also worth noting that 14% (6/42) patients currently registered for the NHS England Early Access Programme at this site are GT4 – indicating the advanced disease state of many of these patients. Similarly, GT4 patients are disproportionately represented in those patients referred to our MDT with primary liver cancer.

I would urge the committee to reconsider the lack of recommendation in this group since I feel they represent a siginificant cohort in this country with a great unmet need - particularly for patients with advanced fibrosis and/or cirrhosis (for whom current options are suboptimal) and for those who are treatment experienced (for whom further treatment options currently do not exist).

Yours faithfully

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References

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