Appraisal Consultation Document – Sofosbuvir for treating chronic hepatitis C

Gilead response to factual inaccuracies within the ERG report – July 11th

We are concerned that a number of factual inaccuracies exist within the recent ERG report prepared for the second Appraisal Committee meeting. The comments made by the ERG on the additional analysis provided are not consistent with the discussions we had with the NICE project team and the points which were agreed prior to providing the additional requested analysis.

We have highlighted all factual inaccuracies below and request confirmation that the this information will be provided to the Appraisal Committee, reviewed and taken into account in advance of the second Appraisal Committee meeting in order to ensure that all of the factual inaccuracies described below are considered in full.

Factual Inaccuracy 1

Section 2; ERG analysis 6

'The manufacturer incorporated a change to the transition from the cirrhotic health state to the HCC health state, although this change was not requested by the Committee. The manufacturer used a transition probability from Cardoso et al. (2010) of 0.0631, whilst the transition probability of 0.014 in the base case model was from Fattovich et al. (1997). The manufacturer justified changing the transition probability for consistency with Cardoso et al. (2010).'

The ERG comment is factually incorrect for the following reasons:

The NICE Appraisal Committee requested that the manufacturer include the transition from the sustained virological response (SVR) - cirrhotic health state to the hepatocellular carcinoma health state, using the transition probability estimates from Cardoso et al (2010). During discussion with the NICE project team (June 6th 2014) it was also agreed that the manufacturer should also include the TP from the non SVR – cirrhotic state for the following reasons.

1. The original base case included a TP from the non SVR – cirrhotic state of 0.014 from Fattovich et al. (1997)[1]. Importantly the publication from Fattovich et al. (1997) does not highlight a TP from the SVR – cirrhotic state.
2. The publication from Cardoso et al. (2010)[2] includes both a TP from the non SVR – cirrhotic state (0.0631) and also the SVR – cirrhotic state (0.0128). The TP's are consistent with the literature which suggests that the risk of progressing to Hepatocellular Carcinoma (HCC) is approximately 4 to 5 times lower in cirrhotic patients who achieve SVR versus those that do not.
3. It was agreed with the NICE project team on June 6th that given the publication from Fattovich et al. (1997) does not include TP's for both non SVR and SVR – cirrhotic health states that it would be more plausible to include the TPs from Cardoso et al. (2010) which incorporate both.

[1] Fattovich G, Giustina G, Degos F et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112:463-472

[2] Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol. 2010;52(5):652–657.

In summary given the above points and after agreement with the NICE project team we have followed the criteria requested by the Committee.

We also would like to highlight that the results of the revised ERG analysis (tables 1-10) include a TP of 0.0128 for SVR – cirrhotic from Cardoso et al. (2010) and a TP of 0.014 for non SVR – cirrhotic from Fattovich et al. (1997) as opposed to using the TPs from the one publication (Cardoso et al. 2010) that incorporates both. The revised ERG analysis should therefore be interpreted with caution for this reason. Including the TP from SVR - cirrhotic to HCC from Cardoso et al (2010), but keeping the TP from non SVR - cirrhotic as per Fattovich et al. (1997), essentially would be modelling a scenario where curing a patient of HCV once they have cirrhosis has almost no impact on their likelihood of developing liver cancer. As liver cancer is one of the major causes of mortality in HCV, an assumption that achieving SVR has a very limited impact on rates of liver cancer would be a fundamental shift to the view of the clinical progress of the disease, which would need to be supported by clinical data.

Factual Inaccuracy 2

Section 4, (summary)

'However the ERG is concerned that the manufacturer has not followed the criteria requested by the Committee. The manufacturer has included an additional change to the transition probability for compensated cirrhosis to HCC and has not included the alternative SVR12 estimates from Hadziyannis et al. (2004) in the revised base case.'

The ERG comment is factually incorrect for the following reasons:

Section 2, scenario 2 of the Gilead 'additional economic analyses' report incorporates the following parameter changes as requested by the Appraisal Committee and as agreed during discussion with the NICE project team on 6th June:

- Alternative SVR estimates for peginterferon alfa and ribavirin from Hadziyannis et al (2004)[3]
- Transition probabilities (TPs) from compensated cirrhosis with and without SVR to hepatocellular carcinoma (HCC) from Cardoso et al. (2010), that is, 0.0128 and 0.0631, respectively.
- Utility increment after reaching SVR of 0.041 from Vera-Llonch et al. (2013)[4]
- Probability of death re-estimated assuming the distribution between male and female from Wright et al. (2006) (61% male and 39% female)
- Average cost for generic ribavirin (RBV) based on eMIT: £42.50 for a 56-tablet pack size.

[3] Hadziyannis SJ, Sette J, Morgan TR, Balan V, Diago M, Marcellin P et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004; 140(5):346-355.
[4] Vera-Llonch M, Martin M, Aggarwal J, et al. Health-related quality of life in genotype 1 treatment-naïve chronic hepatitis C patients receiving telaprevir combination treatment in the ADVANCE study. Aliment Pharmacol Ther 2013; 38: 124–33

In the Gilead report,Table 4 presents the results of this analysis for both the combined, non cirrhotic and cirrhotic health states. Figures 10 and 11 present the results from the PSA for this analysis, whilst table 14 presents the mean probabilistic ICERs as requested.

We therefore believe that we have followed the Committee's direction in incorporating the above changes.

Factual Inaccuracy 3

Section 2, ERG comments point 3.

'The ERG notes that in the McHutchison et al. (2009) study, non-cirrhotic and cirrhosis were also grouped by METAVIR scores as F0-F2 and F3-F4 (similarly to Hadziyannis et al.) and therefore this is not an appropriate justification to not use Hadziyannis et al. data'

The ERG's interpretation of our response is factually incorrect for the following reasons:

As consistently stated within our ACD responses, the justification for choosing McHutchison et al. (2009)[5] within the base case as opposed Hadziyannis et al. (2004) was not due to the fact that both studies defined cirrhosis and non cirrhosis by METAVIR score F0-F2 and F3-F4 as opposed to sofosbuvir own data which combined F0-F3 and F4, but due to the fact that McHutchison et al. (2009) was deemed by expert clinical opinion to be the most appropriate source.

McHutchison et al. (2009) was deemed as the most appropriate source by these clinical experts since it is the largest (1035 vs. 271 patients in Hadziyannis et al) and most recent publication and is also commonly cited as being the most representative of current treatment practice and outcomes. It should also be noted that compared with the Hadziyannis study the patients in the McHutchison study were older (48 years vs. 43 years), heavier (82.8kg. vs. 77.3kg) and with a higher proportion of patients with black ethnicity (19% vs. 3%), thus being more difficult to treat as well as being more representative of the population seen within the NEUTRINO trial for GT1, making a more suitable comparator for the sofosbuvir data.

Using Hadziyannis et al. (2004) should not be considered appropriate because the baseline characteristics of this population would be deemed as easier to treat compared to the populations incorporated within both McHutchison et al. (2009) and the NEUTRINO trials. When added to the fact that both the McHutchison and Hadziyannis trials also incorporated a different definition of cirrhosis and non cirrhosis compared to the NEUTRINO trial, using Hadziyannis et al. (2004) results in a highly conservative approach from what was an already conservative position in using McHutchison et al. (2009)

[5] McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffmann R et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 2009; 360:1827-1838

In further support of this fact we have also highlighted within the ACD how the publication from Roberts et al. (2009)[6] includes results aligned to the F0-3 and F4 definition of cirrhosis as used within our model. Were we to have incorporated arguably this more appropriate publication as the comparator study, the ICER for the GT1 treatment naive population versus P/R would be lower than that seen from the base case using McHutchison et al. (2009).

In summary we would like to like to clarify that McHutchison et al. (2009) was chosen over Roberts et al. (2009) because of clinical expert opinion supporting the conservative nature of this approach, and over Hadziyannis et al. (2004) because the baseline patient characteristics of this population would be deemed easier to treat than those seen in the McHutchison and NEUTRINO trials. Even noting these reservations, we provided the analysis as requested.

Factual Inaccuracy 4

Section 2

'*The manufacturer provides scenarios assuming that 100% of patients who are interferon eligible will receive 24 weeks of SOF+RBV versus PEG+RBV and a scenario assuming that either 98% or 80% of patients receive SOF+PEG+RBV for 12 weeks and 2% or 20% receive SOF+RBV. As noted above, the manufacturer has not applied the full set of assumptions requested by NICE in the ACD in their new base case. Therefore, the ERG has re-run this analysis (see section 3).'*

The ERG comment is factually incorrect for the following reasons:

The ERG has re-run the same analysis as the Gilead, but has incorporated a TP of 0.0128 for SVR – cirrhotic from Cardoso et al. (2010) and a TP of 0.014 for non SVR – cirrhotic from Fattovich et al. (1997) as opposed to using published data based on Cardoso et al. (2010) which was agreed with the NICE project team (6th June). The ERG analysis - tables 4-7 should therefore be interpreted with caution as they are not as has been agreed with the NICE project team.

Factual Inaccuracy 5

Section 2, Lagging.

'The manufacturer states that they obtained a 35% SVR rate for mono-infected cirrhotic patients based on the paper by Lagging et al (2013). However, the Lagging et al. (2013) study reports that it contained only 7 confirmed cirrhotic patients and provided an SVR for 6

[6] Roberts SK, Weltman MD, Crawford DH, McCaughan GW, Sievert W, Cheng WS et al. Impact of high-dose peginterferon alfa-2A on virological response rates in patients with hepatitis C genotype 1: a randomized controlled trial. Hepatology 2009; 50:1045-1055.

of these, which was 50%. It is not clear where the manufacturer's 35% comes from. The HCV genotypes of the cirrhotic patients (i.e. whether genotype 2 or 3) and the PEG+RBV retreatment groups they were assigned to were not specified in the Lagging et al. (2013) paper. '

This point was clarified by Gilead upon request from the ERG on July 7th as per below:

SVRs have been obtained from Lagging et al. (2013) using the distribution between relapsers and non-responders from Shoeb et al.(2011)[7] as with the HCV mono-infected analysis.

In summary we believe that we have already provided this information within both our original submission on February 4th (detailed calculation in appendix 10.14.1) and also as part of the additional clarification questions requested by the ERG.

<u>Factual inaccuracy 6</u>

Section 2.

'The manufacturer has not applied the full set of assumptions requested by NICE in the ACD in their new base case. The ERG has re-run the revised base case and sensitivity analyses in line with the changes requested by NICE (see Section 3 below).'

The ERG comment is factually incorrect for the following reasons:

We disagree with the ERG statement - all of the additional information as requested by the Appraisal Committee was provided in full, with the exception <u>on agreement from the NICE project team</u> of the incorporation of the TP's from Cardoso et al. (2010).

We therefore believe that the revised ERG analysis (tables 1-10) should be interpreted with caution as the TP's used within their analysis were taken from two different publications.

Finally, we would like to note that in agreement with the NICE project team we provided all of the economic analysis a full week in advance of the July 4th deadline to ensure that if the ERG had any further requests these could be provided by Gilead. Indeed the addition mean probabilistic ICERs was incorporated after checking with the NICE project team to ensure that all the analyses were provided as requested.

Having provided the analyses a full week in advance of the final deadline to allow the ERG additional time, we are disappointed that the ERG did not take the opportunity to come to the manufacturer for clarification regarding these areas in advance of providing a final report.

In summary, we request confirmation that the above information will be provided to the Appraisal Committee, reviewed and taken into account in advance of the second Appraisal

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[7] 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

Committee meeting to ensure that all of the factual inaccuracies described are considered in full.