NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Sofosbuvir for treating chronic hepatitis C

Dear [redacted]

The Evidence Review Group, Southampton Health Technology Assessments Centre, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 4th of February by Gilead Sciences. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on Wednesday 12 March 2014. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the checklist for in confidence information that is also available within the NICE Docs request.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be submitted via NICE Docs as individual documents.
If you have any further queries on the technical issues raised in this letter then please contact Grace Jennings, Technical Lead (grace.jennings@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (kate.moore@nice.org.uk) in the first instance.

Yours sincerely

Helen Knight
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Encl. checklist for in confidence information

Section A: Clarification on clinical effectiveness data

A1. **Priority Question**: Please explain the eligibility criteria or system used to define the inclusion and exclusion criteria for the phase 2 and phase 3 trials (as described in Table 8, manufacturer's submission p. 53).

A2. **Priority Question:** Please provide critical appraisal of the four included phase 2 randomised controlled trials (QUANTUM, SPARE, ATOMIC, and ELECTRON) using the same table that was used for the quality assessment of the phase 3 trials (Table 20, manufacturer's submission p. 95).

A3. **Priority Question:** Please clarify what is meant by the full analysis population (FAS) in the NEUTRINO (manufacturer's submission p. 84), POSITRON (manufacturer's submission p. 88) and VALENCE trials (manufacturer's submission p. 90).

A4. **Priority Question:** According to the Lalezari abstract (ref 47) the QUANTUM trial included a placebo arm. Please clarify why a description of the placebo arm and the results for this patient population have not been included in the manufacturer's submission (p. 127-128).

A5. **Priority Question:** Please explain why no results are presented for the placebo arm from the VALENCE trial (manufacturer's submission p. 119-121). According to the flow chart in the manufacturer's submission (p. 93) and the abstract by Zeuzem et al. (ref 40), 93% (79/85) of the placebo group discontinued the study due to termination by the sponsor (patients receiving placebo were offered treatment in an alternative protocol). Please clarify at what time in the trial this discontinuation occurred and whether it influenced the purpose of the placebo arm.

A6. **Priority Question:** In the VALENCE trial (manufacturer's submission p. 89-90) data imputation is mentioned for some outcomes but not others. Please clarify for all the reported outcomes whether data were imputed and which method(s) were employed.

A7. The flow chart for clinical effectiveness search results (Figure 3, manufacturer's submission p. 54) indicates that 30 eligible citations were included in the systematic review, and these reported on 21 studies (as shown in the table on manufacturer's submission p. 55). However, there are 35 unique citations given in the table. Please account for all of the listed citations in the table (manufacturer's submission p. 55) to ensure that the number cited in the table is in agreement with the number reported in the flow chart (Figure 3, manufacturer's submission p. 54).

A8. Please provide participant flow charts for the following phase 2 trials (LONESTAR-2, QUANTUM, ELECTRON, PHOTON-1 and P7977-0221), indicating the number of

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participants starting and completing the trial and the number of patients who were included in the statistical analyses, as per section 6.3.8 of the manufacturer's submission.

A9. Please provide critical appraisal of the four included non-randomised phase 2 trials (PROTON (cohort B), PHOTON-1, LONESTAR-2 and P7977-2025) as described in section 6.8.1 of the manufacturer's submission.

A10. In the FUSION, POSITRON and VALENCE trials please explain what is meant by a "matching placebo", that is, do the placebo elements substitute sofosbuvir alone or both sofosbuvir plus ribavirin?

A11. In the VALENCE trial please clarify how many patients were included in the statistical analysis, and please specify if the patient numbers differ by outcome (manufacturer's submission p. 89-90 and p. 93).

A12. In the manufacturer's submission, Table 10 (p. 68) indicates that the effect of treatment on health related quality of life was measured in the VALENCE trial, but the results for this outcome are not provided (manufacturer's submission p. 119-121). Please provide the results or clarify why they have not been included.

A13. In the NEUTRINO trial (manufacturer's submission p. 100), FISSION trial (manufacturer's submission p. 106), FUSION trial (manufacturer's submission p. 111), POSITRON trial (manufacturer's submission p. 118) and VALENCE trial (manufacturer's submission p. 119-121) the analyses of health related quality of life are classed as 'exploratory'. Please clarify what this means. Please explain how the quality of life outcomes were analysed statistically and the numbers of patients in these trials who were included in the statistical analyses of quality of life.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** Table 56 (manufacturer's submission p. 212-213) shows that the utility decrements owing to adverse events differed for sofosbuvir by each sub-category of genotype, treatment experience and interferon eligibility as based on the individual trials for each category. The decrements therefore ranged considerably for the different sofosbuvir arms in each trial. Please re-run the economic model using a pooled estimate of the utility decrement due to adverse events from all relevant trials and provide the results.

B2. **Priority Question:** The manufacturer's submission (p. 168) states that an economic analysis was not conducted for HCV treatment-experienced patients with genotype 1 infection. The reason given is that the SVR for these patients is extrapolated based on an FDA model (as no trial data were available). Please provide a reference for the FDA model. Please provide an estimate of cost-effectiveness based on the FDA model for genotype 1 treatment experienced patients, explaining, if necessary, the limitations of the approach.

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B3. **Priority Question:** The economic model is based on previous economic models for chronic hepatitis C developed by SHTAC. The most recent SHTAC model (Hartwell et al 2011) includes a possible transition from the SVR state to the HCC state. Please clarify why this transition was not included in the sofosbuvir economic model. If possible, please provide an amended model and results to include the transition from the cirrhotic state with SVR to the HCC state (including the transition probabilities used).

B4. **Priority Question:** Table 44 (manufacturer's submission p. 184) states that all-cause mortality is calculated as the average of male and female age-specific mortality rates (from 2011). Please clarify if a weighted average of male and female age-specific mortality was used, rather than a simple average.

B5. **Priority Question:** All-cause mortality probabilities are averaged over ten year age bands (manufacturer's submission Table 44, p. 184). Please clarify reasons for not using mortality probabilities by one year age bands.

B6. The manufacturer's submission (p. 164) shows the flow-chart for the health economic systematic review. There appear to be some errors in the flow-chart when cross referring to the numbers reported in the text of the manufacturer's submission (p. 165). For example, the final 'eligible citations' box states there were 53 eligible citations from the original review, but the numbers ('Full-text citation screening 199' - 'excluded articles after 2nd screening 163') do not correspond. Please check the numbers for this and for all other stages of the flow chart and amend them to ensure that they correspond with the text (e.g the numbers reviewed is reported at 309 in the figure but are described as 316 in the text; the 'update search' numbers at the 'titles and abstracts to review stage' and the numbers for the detailed reasons for exclusion within the 'excluded studies after 2nd screening' stage of the 'original search' appear to have miscalculations)?

B7. The manufacturer's submission states that there were 112 included studies in the systematic review of economic evaluations. Please provide a clear description of what happened to the full set of studies? In the text (manufacturer's submission p. 165), 61 of these studies are accounted for (and these are also shown in the appendices in Table 152). However, 87 studies were quality assessed in Tables 162-174, and in Tables 153-161 of the appendices there appears to be an additional 31 studies (plus numerous secondary citations within these tables) but it is unclear whether these were all identified as part of the review, because the numbers do not tally. It would be helpful if these numbers could be reconciled please.