NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Ledipasvir-sofosbuvir for treating chronic hepatitis C [ID742]

Dear [redacted]

The Evidence Review Group, School of Health and Related Research, University of Sheffield, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 21st October 2014 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 **Thursday 27th November 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 attached checklist for in confidence information.

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 emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Martyn Burke, Technical Lead (martyn.burke@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
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on search strategies

A1. **Priority question:** For the quality of life searches (Section 7.4 and Appendix 12 of the company's submission), the population terms are different for the main searches and the subsequent update searches. Please explain why this approach was adopted. Please confirm whether the implications of excluding ("NOTing") out the following disease terms "Hepatitis B, HIV, and recurrent hepatitis C" were considered by the company; that is, the risk that studies were indexed with these terms but contain information relevant to this appraisal?

A2. Please provide details of the cost-effectiveness and quality of life search filters (see sections 7.1 and 7.4, and appendices 10 and 12 of the company's submission). How were these search filters derived? Please confirm whether they are published filters? If so, please provide references for these filters.

A3. For the cost-effectiveness and quality of life searches, please clarify why two updates were carried out?

A4. Please confirm whether the conferences 'Digestive Disease week' and 'APASL' (Asian Pacific Association for the Study of the Liver) were searched? If not, please provide the justification for their exclusion.

A5. The Evidence Review Group's search of ongoing clinical trials identified 35 studies with the intervention terms – please see Appendix A of clarification letter (sent as a separate document). Please confirm whether any of these studies are due to report data within the next 12 months?

Section B: Clarification on effectiveness data

Systematic literature review

B1. **Priority question:** Table 8 (page 45 of the company's submission) specifies that sustained virologic response (SVR) had to be reported for studies to be included in the systematic review. The flow chart indicates that 6 articles were excluded on the basis of outcomes. Please confirm whether any trials were excluded for not reporting SVR, but could have reported data for other relevant outcomes (for example, adverse events)?

B2. Figure 3, page 46 of the company's submission, states that 22 citations were identified by the review whereas Table 9, pages 49 to 52 of the company's submission, lists 25 published citations as well as study reports and an unpublished manuscript. In addition, section 6.2.7 of the company's submission states that 7 trials were identified by the review, whereas Table 9 lists 14 trials of which 4 are excluded. Please clarify the trials and citations identified by the systematic review.

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B3. Some ongoing studies are included in the company's submission. For the 4 ongoing studies excluded in Table 9 (pages 49 to 52 of the company's submission), please clarify whether no data are available from these trials, or if there is another reason for their exclusion? The exclusion criterion in Table 8 (page 45 of the company's submission) states "Not patients with chronic hepatitis C in relevant genotypes". However, the flow chart (Figure 3, page 46 of the company's submission) suggests that no studies were excluded on the basis of population. Please confirm whether there were no studies excluded on the basis of genotype (GT). Please also confirm the reasons for excluding the French study (GS-US-337-1119)?

Phase II evidence

B4. **Priority question:** Please provide a critical appraisal of the included Phase II studies of ledipasvir-sofosbuvir (LDV/SOF).

B5. Please provide participant flow charts for the included Phase II studies of LDV/SOF, indicating the number of participants starting and completing the trial and the number of patients who were included in the statistical analyses.

Comparator evidence

B6. **Priority question:** How were trials for comparators identified and selected for inclusion? (Please see section 6.7 of the company's submission).

B7. **Priority question:** Please clarify whether the company conducted a systematic review to search for trials of comparators? If there was a systematic review, please provide details. How was it decided which trials to include? For trials that were included, how was it decided which trial arms to include? Was study inclusion based on an assessment of quality?

B8. **Priority question:** Please provide a critical appraisal of trials used for comparator data in section 6.7 (Table 38 of the company's submission). Also, please justify the studies chosen for the efficacy of comparator treatments, see section 7.3.6 (Tables 58, 63, 66 and 69 of the company's submission). Please clarify why a meta-analysis of all relevant studies has not been conducted for each of the comparators.

Indirect and mixed treatment comparisons

B9. Does the company consider that it is possible to compare interventions and comparator treatments separately using two disconnected network meta-analyses? Please explain whether it is possible to estimate absolute response rate using different reference treatments within separate networks? Also, please clarify whether the inclusion of trial treatment arms with unlicensed drugs (for example, SYNERGY) would have enabled a mixed treatment comparison?

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Section C: Clarification on cost-effectiveness data

Published cost-effectiveness evaluations

C1. The systematic review of economic evaluations included a large number of studies – Section 7.1.2 of the company's submission states that a cost-effectiveness evaluation of a fixed dose combination (FDC) of LDV/SOF was identified (McGinnis et al. 2014, reference 122). Please clarify what the economic conclusions of this study were and why they are not reported in the company's submission?

Functionality of company's economic model

C2. **Priority Question**: The company's economic model has a number of default settings which work automatically (for example, when moving between worksheets). This makes it difficult for the Evidence Review Group to verify whether the results correspond to the inputs specified. Please provide a version of the economic model in which these automated settings are disabled.

C3. Please clarify why 59 worksheets are needed for an 11 state Markov model?

C4. Please clarify why the =FLOOR() function is applied to the discounting of utilities and costs in the company's economic model?

Clinical parameters

C5. **Priority Question**: Table 58 (page 167 of company's submission) states that the efficacy for the GT1 treatment-naïve population for LDV/SOF 8 weeks has been estimated using data from patients with baseline HCV RNA of <6 million IU/mL. This is a *post hoc* analysis of the ION-3 study (see section 6.5.5, page 89 of the company's submission). Please justify why the patients with VL>6 million IU/ml are not indicated for the short 8 weeks duration).

C6. **Priority question:** Please clarify why the structure of treatment duration within the company's Markov model is curtailed at 8 weeks? For example, please refer to cells AR15:16 (and many others) within the "Model patients" worksheet of the company's economic model.

C7. **Priority question:** In the "Model patients" worksheet, cell AR21 of the company's economic model, please explain what the bold highlighted part of this formula is intended to adjust for? =IF(TreatmentWeeksSOF>8,AR20,**(AR20-(AT21-AT20)**))

C8. **Priority question:** Please comment on the validity of using a blended comparison of efficacy and treatment duration for the LDV/SOF option in each analysis.

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C9. Please explain whether the risk of other-cause mortality was adjusted to remove the risk of death because of hepatitis C and its consequences (for example, hepatocellular carcinoma)?

C10. Please explain why the economic model requires three different cycle durations?

Transition probabilities

C11. **Priority question:** Are the transition probabilities contained in the "Transition Matrices" worksheet identical for all populations and comparators? If so, please provide the justification.

C12. Please provide some evidence to demonstrate the validity of the transition probability estimation for the non-cirrhotic to cirrhotic states, referred to in Section 7.3.2, pages 162 to 163 of the company's submission. For example, please provide the file (which uses Solver) containing the calculations that estimate the transition probabilities.

Assumptions

C13. **Priority Question:** The company's economic model assumes that there are no deaths until 6 months after stopping treatment, either because of the hepatitis C virus (HCV) or background mortality. Please clarify why the economic model assumes that patients cannot die until 9 months after entry?

C14. **Priority Question:** Section 7.3.8 states that "Patients do not progress while on treatment, nor during the 12 to 24 weeks after the end of treatment" (see page 178 of the company's submission). Please clarify why patients are assumed not to develop adverse consequences of hepatitis C (for example, cirrhosis, cancer) until after 9 months?

C15. The company's economic model assumes that the utility decrement for LDV/SOF is zero (see page 183 of the company's submission). Please provide justification for this. Please also explain why this is considered by the company as 'commercial in confidence'.

Unit costs and healthcare resources

C16. **Priority question:** Please clarify what the cost per 28 days for LDV/SOF is intended within the economic model. Please explain why the cost per cycle increases when the treatment duration is less than 8 weeks (for example, see worksheet "Model costs" cells J13:15 in the company's economic model).

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C17. **Priority question:** Please clarify how drug wastage is included in the economic model. For example, if the cohort needs an average of 12.6 weeks of treatment, are four packs costed? Please also comment on the expected wording of the marketing authorisation with respect to treatment duration for the overall eligible population and specific subgroups.

C18. **Priority question:** In the "Model Costs" worksheet column J of the company's economic model, please clarify why the cost is divided by 3 or 2 depending on treatment duration?

C19. The data presented in Table 78 includes the unit costs per resource use item (see page 189 of the company's submission). Please confirm that this is true. If so, please provide the resource use assumed to estimate the monitoring costs for each of the treatments.

Results

C20. **Priority question:** The company's economic model runs for the cirrhotic and non-cirrhotic populations separately, and then weight the results according to the proportion of patients with/without cirrhosis. Given that the economic model structure includes both cirrhotic and non-cirrhotic states, please explain why this approach was used? Please clarify why the economic model does not allow for a mix of cirrhotic and non-cirrhotic to flow through the states simultaneously?

C21. **Priority Question:** In section 7.7.6 of the company's submission, please clarify whether the base case results have been derived from the probabilistic sensitivity analyses or whether they are based on point estimates of parameters (that is, deterministic analyses).

C22. Section 7.2.7, page 159 of the company's submission states that: "*ICERs are only reported herein for comparisons with regimens incorporating PEG-IFN2a. This is a conservative approach in terms of costs as PEG-IFN2a is more expensive than PEG-IFN2b*". Please clarify if this (that is, PEG-IFN2a is more expensive than PEG-IFN2b) is a typographical error.

Probabilistic Sensitivity Analysis (PSA)

C23. For the PSA, please clarify whether common random numbers are used between the options? If so, please explain how to run the PSA using common random numbers across options in the economic model.

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C24. Please clarify whether it was intentional to include zero as a parameter in some probability distributions for the PSA? For example, a gamma distribution is used to represent uncertainty about parameters for 'Quality of life (utilities decrement) during year of treatment' and 'SVR quality of life increment' in the company's economic model (see "PSA inputs" worksheet). The Evidence Review Group note that gamma distribution is represented by two parameters that must take values greater than zero. The Evidence Review Group therefore consider that some probability distributions are not defined when one of the parameters is exactly zero (and distributions can also be poorly defined when parameters are close to zero).