NICE National Institute for Health and Care Excellence

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**Single Technology Appraisal (STA)**

**Idelalisib for relapsed or refractory chronic lymphocytic leukaemia [ID764]**

Dear Gab

The Evidence Review Group, Warwick Evidence, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 11 February 2015 by Gilead. 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**, **Thursday 19 Match**. 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 Victoria Kelly, Technical Lead (victoria.kelly@nice.org.uk). Any procedural questions should be addressed to Lori Farrar, Project Manager (lori.farrar@nice.org.uk) in the first instance.

Yours sincerely

Frances Sutcliffe
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Encl. checklist for in confidence information

**Section A: Clarification on effectiveness data**
**Literature Searches**

A1. **Priority Question.** Please clarify why the trial by Goede et al (2013) was not included as part of the evidence. This phase III trial of obinutuzumab plus chlorambucil or rituximab plus chlorambucil versus chlorambucil alone in patients with chronic lymphocytic leukaemia (CLL) does not appear to have been identified during the searching. In the absence of other evidence, the trial may provide useful data on some of the comparators which are listed in the final scope issued by NICE. Please refer to the following reference:

a. Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014 Mar 20;370(12):1101-10.

A2. **Priority Question.** In the company submission, the searches were undertaken on 13th January 2014 (RCTs in relapsed or refractory CLL patients), 12th February 2014 (non-RCTs in relapsed or refractory CLL patients) and 29th July 2014 (clinical studies in untreated CLL patients with 17p deletion or TP53 mutation). Please provide an update of all searches and screening. Please can you provide details of evidence which you may have excluded for the two comparator drugs - bendamustine and chlorambucil.

A3. **Priority Question.** It is noted that for "Adults with untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation for which chemo-immunotherapy is not suitable" the search included treated CLL patients. Please provide updates of the searches to ensure that relevant evidence post 12th February 2014 concerning untreated chronic lymphocytic leukaemia associated with 17p deletion or TP53 mutation is included.

A4. Please provide a copy of the following report: Gilead Sciences. A Phase 3, Randomized, Double-Blind, Placebo Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS 1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia. (GS-US-312-0116). 25 November 2014.

A5. Page 56. Please provide an update of abstracts from the other relevant conferences not already included in the submission. These should include:

a) American Society of Hematology (2010, 2011, 2014)

b) American Society of Clinical Oncology (for last 5 years)

c) European Hematology Association (2010, 2011, 2014)

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d) European Society of Medical Oncology (for last 5 years)

e) International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) (2011 and 2013 [biennial meeting])

f) The International Conference on Malignant Lymphoma (ICML) (2011 & 2013 [biennial meeting]) http://www.lymphcon.ch/imcl/index.php

**Clinical effectiveness data**

A6. **Priority Question.** Page 12, Table 1. Please provide further rational for selecting rituximab as the main comparator for people with relapsed or refractory CLL. Rituximab monotherapy is not recommended for this population in the UK and was not included in the final scope issued by NICE.

A7. **Priority Question.** Page 12, Table 1. Please provide further rational for excluding bendamustine (with or without rituximab) and chlorambucil (with or without rituximab) for adults with untreated CLL associated with 17p deletion or TP53 deletion, and explain the relevance to current UK standard clinical practice of rituximab as a comparator in this population?

A8. **Priority Question.** Page 67, Table 21. Please provide the number of patients who had their dose of idelalisib modified from 150 mg/day to 100 mg/day and reasons for this change in dosage.

A9. **Priority Question.** Page 67, Table 21. Please provide the mean (including standard deviation) time point, post randomisation at which the dose modification occurred?

A10. **Priority Question.** Page 84, Table 27. Please explain why there were more frequent discontinuations in the treatment arm (treatment arm 14.5 vs. placebo arm 6.4)? Please provide a table detailing reasons for discontinuation in both arms of the study (for example: progression, adverse event, patient choice).

A11. Page 12, Table 1 and Page 114. Please provide a more detailed rationale why on Page 114 it is stated that alemtuzumab is not considered an appropriate comparator for people previously untreated with a TP53 or 17p deletion. Alemtuzumab is included in the final scope issued by NICE and included in the company decision problem on page 12, table 1.

A12. Page 20. Please provide more information about how representative the patient population of Study 116 is to UK clinical practice considering that the results are based on a subsample of CLL patients with a worse prognosis (for example; older, with co-morbidities, intolerant to chemo immunotherapy, refractory or relapsed to previous treatment).

A13. Page 66, Table 21. Please clarify how many patients in each centre took part in Study 116? Please list these by country (US, France, UK, Italy and Germany).

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**Section B: Clarification on cost-effectiveness data**

B1. **Priority Question.** Please provide all base case results, scenario analyses, probabilistic sensitivity analyses and subgroup analyses using the list price of idelalisib. Please remove all text which references a discounted list price.

B2. **Priority Question.** Please provide further rationale for why best supportive care was assumed to have the same clinical efficacy as rituximab monotherapy. Please clarify how the costs for best supportive care were calculated.

B3. **Priority Question.** Please provide further rationale for not including a cost-effectiveness analysis for the previously untreated TP53 or 17p deletion CLL group.

B4. **Priority Question.** Please provide further details of the parameters that were determined through clinical validation (e.g. resource use, page 196 table 82). Specific information might include; how many clinicians, and of what specialities were involved, were they asked open ended questions, or asked to comment on the plausibility of numbers they were given, were their views elicited through a formal process (e.g. a Delphi panel) or more informally, were they asked to provide only point estimates, or measures of their uncertainty as well? The reference for this is to a clinical validation meeting, and says the data is on file. Would it be possible to have access to these data?

B5. **Priority Question.** Pages 156 and 211. Please provide further rationale for assuming ofatumumab has identical clinical effectiveness to rituximab, and for assuming equal efficacy for rituximab and best supportive care.

B6. **Priority Question**. Section 5.3 (from page 156 onwards). Please provide a rational for assuming a common shape parameter for assessing overall survival and progression free survival for treatments other than those in Study 116. Digitised Kaplan–Meier curves were used to validate the fits, so standard model fitting could have been done on these digitised curves, in particular for FCR where it is stated that the assumed common distribution did not fit well to the data. Please provide the digitised Kaplan–Meier curves.

B7. **Priority Question.** Section 5.3 (from page 156 onwards). Please explain why the treatment benefit of idelalisib with rituximab has been assumed to continue both beyond the length of the trial and after treatment discontinuation. With many other cancer drugs, rates return to those of the placebo arm after treatment discontinuation. An alternative approach would be to fit models to the length of the trial data, but then to use the same parameters for each treatment when extrapolating forward from this point. Please provide a justification, (statistical or biological), for not considering this approach here?

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B8. Pages 79-80, Table 25. Please provide in a table (use a similar format to table 25 page 79), the observed baseline characteristics of patients in the UK and German sample combined in Study 116 trial for the 17p deletion or TP53 mutation subgroup.

B9. Page 84, Table 27 & Pages 86-88, Figures 8-10. Please provide a table (using a similar format to table 27) the breakdown of progression free and overall survival (for the UK sample of patients for both groups (untreated and treated) in Study 116. In addition, please provide the 3 Kaplan-Meir curves (as in Figures 8-10 for PFS, OS [ITT] and OS [RPSFT]) for the UK sample for the two populations in study 116.

B10. Page 185, Table 76. Please clarify why there are higher utility values in patients who have discontinued treatment compared to those taking rituximab alone (0.8 vs 0.75)? These data are from different sources (Dretzke et al. 2010 paper [Reference 88 in the submission] vs Study 116) so are not obviously directly comparable. The difference appears to be more than the expected impact of adverse events that was calculated.

B11. Page 200, Tables 86-87. Please provide further information on how the costs associated with diarrhoea and colitis have been estimated? Please clarify why the costs associated with the possibility of hospitalisation/more extreme adverse outcomes in relation to diarrhoea and colitis are not included and also clarify whether it is assumed that patients will require only a single outpatient visit, and if so please include the data on which this assumption is based?

**Section C: Textual clarifications and additional points**

C1. **Priority Question.** Please ensure all commercial in confidence and academic in confidence information is both highlighted and underlined. Throughout the document there is confidential information which has been highlighted but not underlined.

C2. **Priority Question.** Appendix 2, Pages 2-9. Please remove appendix 2 from the submission and submit it as part of a patient access scheme submission template. The patient access scheme submission template should also include the impact of the anticipated discounted price on clinical and cost-effectiveness analyses.

C3. Page 88, Figure 10. Please clarify if the figure on this page is commercial in confidence.