NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Aflibercept for treating diabetic macular oedema [ID717]

Dear Company,

The Evidence Review Group, Aberdeen HTA Group, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 7th October 2014 by Bayer. 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 **12th 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 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
Associate Director – Appraisals
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Encl. checklist for in confidence information

Section A: Literature searching

A1. **Priority question: Page 36. Figure 1** (of the company submission). The PRISMA diagram shows that 203 records (80 studies) have been identified in the literature and included in the submission for the assessment of the clinical effectiveness and safety of aflibercept. However, the majority of these records are not accounted for:

- 5 publications for the assessment of aflibercept compared with laser photocoagulation are listed on page 38 but 3 are abstracts and not used as data sources.
- Supplementary data provided from 2 study protocols, 4 clinical study reports, 2 abstract presentations and one assessment report are referred to in page 42.
- 9 studies are considered for the indirect and mixed treatment comparison (page 118).

Please provide a list of the remaining records, detailing their contribution to the assessment or the reasons for their exclusion. For example why was the following study not considered: Roger 2013 (RESPOND – ranibizumab vs laser photocoagulation vs combination)?

A2. **Page 270. Section 7.4.5** (of the company submission). There appears to be a spelling mistake in the text for bevacizumab. Please clarify that it was spelt correctly in the searches.

A3. **Page 272 and 343** (of the company submission). The inclusion and exclusion criteria for the search states that '18 year olds' are both included and excluded. Please clarify if they were included in the search.

Section B: Clarification on effectiveness data

B1. Please clarify why, apart from fluocinolone and dexamethasone, other corticosteroids were not considered as suitable comparators.

B2. **Page 52** (of the company submission)**.** The laser photocoagulation group in the VIVID trial has a higher baseline mean central retinal thickness (CRT) value than the 2 aflibercept groups (540 µm versus 501.9 µm and 518.4 µm respectively). Please clarify if these differences are statistically significant.

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B3. **Page 52. Table 6** (of the company submission)**.** Please explain why the number of patients who received prior laser photocoagulation in the VIVD trial is not presented.

B4. **Page 53 and 90. Tables 7 and 22** (of the company submission). Please provide the median thickness of the retinas for patients with central retinal thickness (CTR) < 400µm and that of patients with CTR ≥ 400µm for the 3 intervention groups in order to ensure a correct interpretation of the subgroup analysis. *(Laser photocoagulation is considered less effective in thicker retinas, where anti-vascular endothelial growth factors (VEGF) work best).*

B5. **Priority question: Page 91** (of the company submission)**.** Please provide the corollary of figure 13 for the other subgroups in table 22. Please also provide similar figures for tables 23, 24, 25 and 26.

B6. **Page 90-97** (of the company submission)**.** Please provide the corollary of tables 22, 23, 24, 25 and 26 for the **VIVID** trial, also including the corollary of figure 13 for all subgroups. Please provide the corollary of tables 22, 23, 24, 25 and 26 for the **VISTA** trial, also including the corollary of figure 13 for all subgroups.

B7. **Priority question: Page 169** (of the company submission)**.** Please provide the corollary of table 43 for VISTA, VIVID and the 2 trials pooled separately for:

- the subgroup of patients with CRT thickness ≥ 400µm;
- the subgroup of patients with CRT thickness < 400µm.

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B8. Please provide patient dosing information separately for VISTA and for VIVID for baseline to week 52, including any rescue treatments. Please present in the table below.

	VISTA		VIVID	
	AFB 2Q8	Laser Photocoagulation	AFB 2Q8	Laser Photocoagulation
Patient numbers (n)	???	???	???	???
Aflibercept doses total (n)	???	???	???	???
Sham injections total (n)	???	???	???	???
Laser photocoagulation administrations total (n)	???	???	???	???
Sham laser administrations total (n)	???	???	???	???

B9. Please provide patient dosing information separately for VISTA and for VIVID for end of week 52 to week 100, including any rescue treatments. Please present in the table below.

	VISTA		VIVID	
	AFB 2Q8	Laser Photocoagulation	AFB 2Q8	Laser Photocoagulation
Patient numbers (n)	???	???	???	???
Aflibercept doses total (n)	???	???	???	???
Sham injections total (n)	???	???	???	???
Laser photocoagulation administrations total (n)	???	???	???	???
Sham laser administrations total (n)	???	???	???	???

B10. Please provide the following patient numbers (not percentages) split by the health states used in the economic model for:

- VISTA patients with no bilateral DMO at baseline
- VISTA patients with bilateral DMO at baseline
- VIVID patients with no bilateral DMO at baseline
- VIVID patients with bilateral DMO at baseline

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If information on bilateral DMO involvement at baseline is not available, please provide the patient numbers separately for VISTA and for VIVID in the table below.

Aflibercept 2Q8									
		NSE							
		HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8
SE	HS1	???	???	???	???	???	???	???	???
	HS2	???	???	???	???	???	???	???	???
	HS3	???	???	???	???	???	???	???	???
	HS4	???	???	???	???	???	???	???	???
	HS5	???	???	???	???	???	???	???	???
	HS6	???	???	???	???	???	???	???	???
	HS7	???	???	???	???	???	???	???	???
	HS8	???	???	???	???	???	???	???	???
Laser Photocoagulation									
		NSE							
		HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8
SE	HS1	???	???	???	???	???	???	???	???
	HS2	???	???	???	???	???	???	???	???
	HS3	???	???	???	???	???	???	???	???
	HS4	???	???	???	???	???	???	???	???
	HS5	???	???	???	???	???	???	???	???
	HS6	???	???	???	???	???	???	???	???
	HS7	???	???	???	???	???	???	???	???
	HS8	???	???	???	???	???	???	???	???

B11. **Page 152. Figure 22** (of the company submission). Please clarify whether the right hand side of the axis favours aflibercept and the left hand side favours laser photocoagulation. The axes appear incorrectly labelled.

B12. **Page 151 onwards** (of the company submission). Please clarify the reason for only including the aflibercept 2Q8 arm in the meta-analysis and network meta-analysis presentation of results.

B13. **Priority question: Page 169. Table 43** (of the company submission). Please provide the equivalent table for the effect estimates from fixed effect models for both risk ratio (RR) and odds ratio (OR).

B14. **Priority question: Page 179. Table 45** (of the company submission)**.** The fixed effect estimate for gain >=10 letters is presented as RR = 0.993 (0.65, 1.52). Please confirm whether this result is the correct way round for estimating the relative effectiveness of aflibercept with ranibizumab?

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B15. **Priority question:** Please confirm that the direction of all relative risk (RR) and odds ratio (OR) estimates presented for aflibercept compared with relevant comparators (i.e. ranibizumab, dexamethasone etc) throughout the clinical effectiveness section of the submission are correct.

B16. **Page 173** (of the company submission).Please confirm that the results immediately above 'all non-ocular adverse events' relate to all ocular adverse events.

B17. **Priority question: Page 171. Table 44** (of the company submission). Please provide the results for the random effects models for the outcome 'all-cause mortality' as they appear to be missing from the submission.

B18. **Page 60. Table 12** (of the company submission). Please provide the reasons for study discontinuation separately for the aflibercept and laser photocoagulation arms of VISTA and VIVID.

B19. **Priority question: Page 209. Table 60** (of the company submission). Please clarify if the difference between laser photocoagulation and each of the aflibercept group, and the difference between laser photocoagulation and the aggregated aflibercept result is statistically significant.

Section C: Clarification on cost-effectiveness data

C1. **Priority question: Page 274. Figure 69** (of the company submission). The PRISMA diagram states that 67 studies were included in the health-related quality of life review of which only 7 are cited in the submission. Please provide a list of the remaining studies, detailing their contribution to the assessment of health-related quality of life data.

C2. **Priority question: Page 268** (of the company submission)**.** Given the inclusion of body mass index (BMI) in the regression equation for health-related quality of life, it appears that a number of functional forms were explored before a decision was made to use the functional form. Please outline all the functional forms that were explored, the coefficients and summary statistics of these functional forms and the rationale for choosing the form adopted.

C3. **Page 288. Section 7.6.1** (of the company submission)**.** Bullet point 5 refers to the "ERG suggested relative risk of mortality". Please clarify what this means.

C4. **Pages 321-338. Tables 111, 113, 114, 116, 118, 121, 126** (of the company submission). The tables listed in this section show the comparator technologies as

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dominant over aflibercept. Should this be the other way round? If so, please amend the table to make it clearer.

C5. It seems likely that body mass index (BMI), best corrected visual acuity (BCVA) in the best seeing eye (BSE) and BCVA of the worst seeing eye (WSE) may be positively correlated with the other complications of diabetes. These will all have an impact upon quality of life, but the analysis is restricted to BMI, BCVA BSE and BCVA WSE only. This could argue for a repeated measures analysis. Please clarify why this approach was not considered?

C6. **Priority question: Page 255**. **Table 71** (of the company submission)**.** This table appears to be the key input table for the economic modelling. No detail has been presented about how the values have been calculated within the submission. Based on cells K159:N169 of the CRT-SHIFT worksheet it appears that it is based on the proportions transitioning between baseline and week 52, with this then being adjusted along the lines of ((1+K169)^(1/12))-1.

- Please confirm that this is the method that has been used. If not, please clarify which method has been used.

- Please provide the corollary of cells B159:B167 and B327:I335 of the CRT-SHIFT worksheet for all patient populations so that the values in Table71 and cells X13:AS27 of the Tx_Input worksheet can be cross checked.

C7. **Priority question:** Please provide the corollary of cells B4:I335 of the *CRT-SHIFT* worksheet for the subgroup of patients with central retinal thickness (CRT) thickness < 400µm.

C8. **Page 255. Table 71** (of the company submission). Please provide the information in table 71 separately for the VISTA trial and the VIVID trial.

C9. **Priority question: Page 255. Table 71** (of the company submission)**.** Please provide table 71 split by central retinal thickness (CRT) ≥ 400 µm and CRT thickness < 400 µm.

C10. **Priority question:** It is not clear how to run the model to replicate the results for the subgroup with CRT thickness ≥ 400 µm of Tables 124 and 125 of the submission. Please explain how these results were generated.

C11. Within the Markov-Laser worksheet there is a drop down 'Yes/No' option located around the AL82 cell location. The corollary of this does not seem to appear in the

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other Markov worksheets. Please clarify the function of this drop down and which cells are directly affected by it.

Section D: Textual clarifications and additional points

D1. **Pages 72-96. Figures 9, 10, 13, 14, and 15** (of the company submission). The text in these figures is difficult to read because of the small size. Please provide enlarged text.

D2. **Page 77** (of the company submission)**.** The figure at the top of the page does not have a figure number or title. Please clarify what this figure relates to and add a figure number and title.

D3. **Pages 197 and 337** (of the company submission). Please correct the referencing error in the text.

D4. **Pages 310, 320 and 322** (of the company submission). The tables on these pages do not have numbers or titles. Please clarify what these tables relate to and add a table number and title?

D5. **Page 331** (of the company submission)**.** The text discussing the time horizon in the model is not clear. Please clarify if this is 1 year or 10 years.

D6. **Page 334. Figure 76** (of the company submission)**.** The bottom figure does not have a title or number. Please clarify what this figure relates to and add a figure number and title. In addition both figures are small and it is difficult to read the text contained in them. Please provide clearer versions of these figures.

D7. **Page 335. Table 122** (of the company submission)**.** There is a table and a figure which do not have a number or title. Please clarify what they relate to and add table and figure numbers and titles.

D8. **Page 431** (of the company submission). This page is left blank. Please confirm that this was intentional.