NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)845 003 7780

Single Technology Appraisal (STA)

Aflibercept solution for injection for the treatment of macular oedema caused by central retinal vein occlusion [ID578]

Dear [redacted]

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 from Bayer on the 12 August. 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 September**. 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 Grace Jennings, Technical Lead grace.jennings@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

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

Priority question A1. In the trials, non-responders have been defined as those discontinuing prematurely and receiving less than 5 injections. Please clarify:

1. How many patients did not respond to the treatment in the two trials?
2. How non-response was defined. Table 1, on page 13 of the submission states "No improvement in visual and anatomic outcomes over the course of the first three injections". Please explain what is meant by "no improvement" Was this less than 5 letters?
3. Is it correct to assume that a stopping rule is applied at week 12 after three injections at weeks 0, 4 and 8? And if so, is it correct to assume that patients who stop receiving treatment at 12 weeks are listed under "lack of efficacy" in Figures 4 and 5, on pages 48 and 49 of the submission?

Priority question A2. Figures 6 and 7, on pages 52 and 53 of the submission, show the percentages of patients gaining 15 or more letters over time. In COPERNICUS, it appears that the plateau was reached at approximately 8 weeks, with only about a 2% increase between 8 and 12 weeks, while in GALILEO the plateau was reached after 12 weeks, with about a 10% rise between weeks 8 and 12. Please clarify:

1. Why there was a difference between the trials in the time taken to reach the plateau?
2. How many patients who gained fewer than 5 letters by week 8 later went on to gain more than 10 letters?

Priority question A3. In Table 9, on page 46 of the submission, there are references to 'LOCF, observed cases' and 'pure LOCF. Please clarify what is meant by the two terms.

Priority question A4. Please verify the figures in Tables 35 and 36 on page 104 of the submission? It is understood that table 36 was supposed to report relative risk (RR) but it appears that the figures are actually for odds ratios (ORs), as they are identical to those in table 35. If the figures have inadvertently been duplicated from table 35, please provide the correct figures.

Priority question A5. Were patients asked at the end of the trials what treatment they thought they had received?

Priority question A6. It is noted(see page 79 of the submission) that there was a slight decline in Visual Acuity in patients receiving aflibercept once they went on to PRN aflibercept, which could be 12-weekly as in COPERNICUS. Please advise what the minimum monitoring interval should be in routine care.

Priority question A7. Please clarify or correct the figures in Table 24, on page 81 of the submission. In GALILEO, these figures report that [redacted]% of patients in the aflibercept arm received no aflibercept. The mean frequency in the aflibercept arm is given as 1.3, with a maximum of [redacted] injections, which should apply only to injections between weeks 52 and 76.

Priority question A8. Tables 21 and 22 (on pages 79 and 80 of the submission) report the changes in letters differently. The ERG has converted the table into an easier format, please see below. Please confirm that the table below contains the correct figures for COPERNICUS, and please complete the table with the equivalent figures for GALILEO.

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	COPERNICUS		GALILEO	
	sham	aflib	sham	aflib
Change by 24 weeks (number of letters)				
Gain 15 or more	9	66	15	65
Gain 10-14	7	21	6	13
Gain 5-9	13	10		
Gain 0-4	9	10		
Loss 1-4	6	2	[redacted]	[redacted]
Loss 5-9	7	3		
Loss 10-14	2	0	[redacted]	[redacted]
Loss15 or more	20	2		

Please clarify why there was a large difference between the two trials in the number of patients losing 15 or more letters in the sham treatment arms. At 24 weeks, 27% of patients in COPERNICUS had lost 15 or more letters compared with [redacted]% (ERG calculation) and [redacted]% in GALILEO (table 22, page 80 of the submission)?

Priority question A9. Please check the figures in brackets in line 4, paragraph 5 on page 81 of the submission. Line 4 states “number of active injections was higher in sham group (1.7) than in aflibercept group (1.7 injections)”. Should the first 1.7 relating to the sham group be 1.3?

Priority question A10. Please comment on the number of injections expected in routine care, compared with the number in the protocol-driven trials. It is noted that on page 131 of the submission, states that the draft SmPC may allow less frequent injections than in the trials. For example, might aflibercept be given at weeks 0, 4, 8, and then at 8 weekly intervals as required, as in age-related macular degeneration (AMD)? That would result in 5 injections in the first 24 weeks rather than the 6 injections reported in Table 4, on page 34 of the submission.

Non-priority question A11. Please comment on why some patients who were randomised to the sham treatment arms of the trials discontinued because of adverse events (see figures 4 and 5, on pages 48 and 49 of the submission) but none of the patients randomised to the aflibercept arms of the trials did so? Please comment on the relationship between adverse events and lack of efficacy. Adverse events do not include lack of efficacy – there is a separate entry for that. Also, there are no cases of lack of efficacy at all in the aflibercept arms.

Non-priority question A12. Please comment on the differences between the COPERNICUS and GALILEO trials in relation to change in Best Corrected Visual Acuity in the sham arms. In COPERNICUS, there was very little difference in BCVA in the sham perfused and sham non-perfused groups (see Figure 11, page 66 of the submission). However in GALILEO (see Figure 12, page 66 of the submission), there was a large difference in BCVA change between perfused and non-perfused in the sham arm.

Non-priority question A13. Please advise if any patients were excluded from GALILEO and/or COPERNICUS because of more severe ischaemia.

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Non-priority question A14. The section on Subgroup analyses for Central Retinal Thickness, on page 68 of the submission, reports changes in each trial, but gives no actual data for subgroups by baseline CRT. Please advise if any subgroup analysis by bands of baseline CRT was carried out and if so, please provide details. Did improvements in VA vary according to baseline CRT, for both the aflibercept and sham treatment arms?

Non-priority question A15. In COPERNICUS, after 24 weeks almost all (57 of the 60 who reached week 24) patients who had been randomised to receive a sham treatment crossed over to receive aflibercept. They received a mean of 6.4 injections of aflibercept by week 100. Table 21on page 79 of the submission shows that by week 52, 30% of those patients who had crossed over to receive PRN aflibercept group gained 15 or more letters, and 47% gained 10 or more. These figures compare with the 58% and 76% in the aflibercept group between weeks 0 and 24. Please provide a comment as to why those crossing over to aflibercept from the in sham group did less well once they received aflibercept..

Non-priority question A16. Please provide clarification on how the figure of 6 injections was derived. Would monthly treatment given at weeks 0, 4, 8, 12, 16, 20 and 24 not represent 7 treatments? Or is the 24 week injection not counted at this stage? If so, then there would be 4 not 5 with a switch to 8-weekly after the first three.

Section B: Clarification on cost-effectiveness data

Quality of Life

Priority question B1. Please outline what variables the EQ-5D data was adjusted for and how this adjustment was derived and applied. The EQ-5D data and analysis on page 78 of the submission does not contain actual values for EQ5D. Please also provide the adjusted mean EQ-5D values by treatment arm and adjusted difference at weeks 24, 52 and 76 of GALILEO, together with the significances of the adjusted differences?

Priority question B2. Please provide the mean EQ-5D values from the European population of the GALILEO study evaluated using the UK social tariff, the sample standard deviations of these and the numbers of observations these apply to, pooled between the study arms across the health states of the model. Please supply this separately for baseline, week 24, week 52, week 76 and early termination as in the table below (one table for each time point):

		Fellow eye				
		HS1	HS2	HS3	HS4	HS5
Study eye	HS1	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?
	HS2	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?
	HS3	μ=? s.d.=?	μ=? s.d.=?	μ=? s.d.=?	μ=? s.d.=?	μ=? s.d.=?

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		n=?	n=?	n=?	n=?	n=?
	HS4	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?
	HS5	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?

Priority question B3. Please tabulate the LogMAR midpoints for each health state that were used for the calculation of the Czoski-Murray utilities.

Resource use

Priority question B4. Please provide the number of doses and number of patients remaining on trial within the aflibercept arm, separately for GALILEO and COPERNICUS by 4 weekly cycles for weeks 0-52 as in the table below. If possible, please provide the data separately for the COPERNICUS subset of patients who did not cross over at week 24 and were treated with aflibercept throughout during weeks 0-52.

From start of week to end of week	0 4	5 8	9 12	13 16	17 20	21 24	25 28	29 32	33 36	37 40	41 44	45 48	49 52
GALILEO													
doses	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?
patients on trial	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?
COPERNICUS													
doses	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?
patients on trial	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?	n=? ?

Priority question B5. Please provide the summary data by year for the responses to the resource use questionnaire “What is the average number of monitoring visits per year for a typical CRVO patient”.

Model implementation

Priority question B6. The meaning of the following statement on page 156 of the submission is unclear: “applying both the RR of improving and the RR of worsening could have led to overestimating the treatment effect” is unclear. Please explain what you mean by this statement.

Priority question B7. The SE_Transitions worksheet cells A8:G54 contain the patient numbers at the 4 weekly time points to 24 weeks. These sum to 201, 209, 203, 205, 206, 203. Please explain this variation, in particular the initial 4 week matrix having the lowest number of patients?

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Priority question B8. For the SE_Transitions worksheet cells A8:G54, with the exception of the week 12-16 matrix, the number of patients entering the various health states rarely corresponds with the relevant number given in that state in column A. For instance, between week 0 and week 4, the sum of C5:C9 suggests 31 patients are modelled as moving into the best health state. But this is given as 34 patients in cell A13, which corresponds with the sum of C13:G13. The sum of the absolute discrepancies from this source can be greater than the differences between the total sums of patients within the relevant matrices; e.g. week 0-4 totals 201 while week 4-8 totals 209, but the sum of the absolute discrepancies between the transitions in weeks 0-4 and the patient number totals at the start of weeks 4-8 is 10. Please provide an explanation for these discrepancies?

Priority question B9. Please explain how drop-outs and patients lost to follow up have been handled within the SE_Transitions worksheet cells A8:G54. Is it correct to assume that by definition, LOCF values are on the principal diagonal of each block of patient transitions? Please provide the numbers of patients within each row that have LOCF.

Start of week	0		5		9		13		17		21	
End of week	4		8		12		16		20		24	
HS start of week	N	LOCF	N	LOCF	N	LOCF	N	LOCF	N	LOCF	N	LOCF
1	0	n=?	34	n=?	48	n=?	56	n=?	72	n=?	69	n=?
2	47	n=?	91	n=?	87	n=?	81	n=?	72	n=?	73	n=?
3	81	n=?	54	n=?	42	n=?	45	n=?	40	n=?	39	n=?
4	40	n=?	17	n=?	15	n=?	10	n=?	12	n=?	14	n=?
5	33	n=?	13	n=?	11	n=?	13	n=?	10	n=?	8	n=?

Priority question B10. The 6 month rate of raised intraocular pressure (IOP) is adjusted to be a monthly rate of incidence. Costs are applied to this monthly rate.

1. The cost of hospital care for raised IOP is divided by 6. Please explain why this adjustment to the cost of hospital care is required given that it is applied to a monthly rate of incidence?
2. Similarly, the cost of medication for raised IOP is divided by 13. Please explain why this adjustment to the cost of medication is required given that it is applied to a monthly rate of incidence?
3. Are the medication costs in the Data_Inputs worksheet cells AD221:AD233 annual medication costs per incident event?

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Priority question B11. Please provide the data source for the days of treatment in the Data_Inputs worksheet cells AB221:AB233?

Priority question B12. Please explain why, for the scenario analysis that includes adverse events (AEs) it appears that the 43% rate of IOP treatment of the physician survey as per table 86 (page 205 of the submission) is applied within the modelling, but the 68% removal rate for cataracts of the physician survey is not applied within the modelling?

Priority question B13. Within the markov worksheets, the disutilities from adverse events of columns GX:HA are added to the quality of life values for each health state within the calculations of columns BK:CI. Cell BK6 is divided by 13 to give the total number of QALYs. Is the implicit assumption within this that the duration of the quality of life (QoL) impact of an incident adverse event is 4 weeks?

Priority question B14. Please clarify the location of the ongoing costs of blindness within the model? The Markov_Aflibercept worksheet column GV appears to allow for the first month of incident blindness, though the incidence may be incorrectly calculated and searching the Markov_Aflibercept worksheet for cVisionLoss2 does not result in any matches.

Non-priority question B15. Please provide the corollary of the adverse events rates of table 96 on page 220 of the submission for weeks 24 to 52.

Non-priority question B16. For the assessment of the mean change from baseline in ETDRS letters (FAS) by treatment arm, please provide patient numbers that had LOCF for both GALILEO and COPERNICUS at week 24 and week 52.

Non-priority question B17. Please provide the numbers of patients at baseline pooled between the arms but separately for GALILEO and COPERNICUS, distributed across the 25 health states of the model as in the table below (one table for each trial):

		Fellow eye				
		HS1	HS2	HS3	HS4	HS5
Study eye	HS1	n=?	n=?	n=?	n=?	n=?
	HS2	n=?	n=?	n=?	n=?	n=?
	HS3	n=?	n=?	n=?	n=?	n=?
	HS4	n=?	n=?	n=?	n=?	n=?
	HS5	n=?	n=?	n=?	n=?	n=?

Quality of life

Non-priority question B18. Please provide the mean EQ-5D values from all patients in the GALILEO study evaluated using the UK social tariff, the sample standard deviations of these and the numbers of observations these apply to, pooled between the study arms across the health states of the model. Please supply this separately for baseline, week 24, week 52, week 76 and early termination as in the table below (one table for each time point):

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		Fellow eye				
		HS1	HS2	HS3	HS4	HS5
Study eye	HS1	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?
	HS2	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?
	HS3	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?
	HS4	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?
	HS5	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?

Non-priority question B19. Please provide the rationale for the quality of life literature review not including Brown “Vision and Quality-of-Life.” Transactions of the American Ophthalmological Society. 1999. 97:473-511.

Model implementation

Non-priority question B20. Please provide the corollary of the SE_Transitions worksheet cells A8:G54 but as a single TPM for baseline to 24 weeks.

Non-priority question B21. Please provide the corollary of the SE_Transitions worksheet cells A8:G54 for just the COPERNICUS trial.

<u>Section C - Clarification on other topics:</u>

Question C1 Please check the data that is marked as AiC and lift confidentiality marking where appropriate? Some marked data are in published papers in the public domain. In other cases, the marking seems inconsistent Examples include:

1. Table 21, on page xx of the submission, the data for weeks 52 week data for aflibercept gains of more than 15 letters is marked but the sham group is not.
2. Ttable 22, ten or more letter gains by week 24 are marked for aflibercept but not for sham.
3. Table 17, the week 100 columns for COPERNICUS are marked, but the data can be worked out from the other, unmarked columns
4. p. 48, top two boxes (screened & excluded) - numbers are in Brown et al. 2013 437.e4
5. p. 53 GALILEO n/% gaining 15 or more letters at 52 weeks - is published in: Gillies, M. Intravitreal vegf trap-eye in central retinal vein occlusion: Results of the phase 3 copernicus and galileo studies. Clinical and Experimental Ophthalmology 40, 44. 2012.
6. GALILEO subgroup analysis for primary efficacy endpoint <2 mo vs >=2 mo since diagnosis - also given in Holz et al. 2013

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7. GALILEO BCVA gain at 52 weeks - is published in: Gillies, M. Intravitreal vegf trap-eye in central retinal vein occlusion: Results of the phase 3 copernicus and galileo studies. Clinical and Experimental Ophthalmology 40, 44. 2012.
8. Same for CRT at 52 weeks in GALILEO