NHS
National Institute for
Health and Clinical Excellence

NICE
Level 1A
City Tower
Piccadilly Plaza
Manchester
M1 4BT

Tel: [redacted]
Fax: [redacted]

Email: [redacted]

www.nice.org.uk

Dear [redacted]

Re: Single Technology Appraisal – Aflibercept for the treatment of wet age-related macular degeneration

The Evidence Review Group (Aberdeen Health Technology Assessment Group) and the technical team at NICE have now had an opportunity to take a look at the submission received on 8 January 2013 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, Thursday 14 February 2013**. 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 [redacted] – Technical Lead ([redacted]). Any procedural questions should be addressed to [redacted] – Project Manager [redacted] in the first instance.

Yours sincerely

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

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1: priority question
Page 45: Please clarify if the follow-up period of each of the two VIEW trials adopted the same blinding approach as outlined in Table B5. If not, please clarify what blinding approach was taken for both trials.

A2: priority question
Page 72: Please provide the patient numbers (N per column) for the 'per protocol set' in Tables B11 and B12.

A3: priority question
Page 72: For Tables B11 and B12 please provide the patient numbers (N per column) for which 52 week primary outcome data were a) observed and b) obtained through LOCF.

A4: priority question
Pages 130-131 (section 6.7.6): please clarify which Table/Figure in the Kleijnen report (reference 59) provides each of the results quoted in the text, for example:

a. Results for outcome of maintained vision do not correspond with Table 16 in reference 59.
b. Results for improved vision and change in BCVA do not correspond with Table 14 in reference 59.

A5: priority question
Please clarify to what extent the probabilities of losing letters were incorporated into the Kleijnen systematic review (reference 59). If this was not considered, please provide the rationale for this.

A6: priority question
Please provide the proportions of patients were treated in their best seeing eye at baseline in VIEW1, VIEW2 and VIEW1+VIEW2 pooled (3 separate estimates). Please also clarify whether these calculations depend upon a minimum clinically significant difference between the two eyes. If so, please define this minimum clinically significant difference between the two eyes along with the relevant reference, and please also present the proportions of patients treated in their best seeing eye at baseline in VIEW1, VIEW2 and VIEW1+VIEW2 pooled when this minimum clinically significant difference is not applied within the calculation.

A7: priority question
Please present the following effectiveness data for the treated eye for both the Aflibercept 2mg Q8 arm and the Ranibizumab arm on the basis of LOCF, for VIEW1, VIEW2 and VIEW1+VIEW2 pooled (**in 6 separate Tables**). The numbers gaining and losing letters should be relative to the original baseline values in month 0 (i.e. for the follow-up period not relative to the start of the follow-up period but to the original baseline).

Month (0=Baseline)	0	1	2	3	4	5	6	7	8	9	10	11	12
n on treatment	??	??	??	??	??	??	??	??	??	??	??	??	??
n gaining ≥30 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n gaining ≥15 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n gaining ≥0 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n losing ≥15 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n losing ≥30 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n missing data	??	??	??	??	??	??	??	??	??	??	??	??	??
n discontinued	??	??	??	??	??	??	??	??	??	??	??	??	??
Month (12=start Follow-up)	12	13	14	15	16	17	18	19	20	21	22	23	24
n on treatment	??	??	??	??	??	??	??	??	??	??	??	??	??
n gaining ≥30 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n gaining ≥15 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n gaining ≥0 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n losing ≥15 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n losing ≥30 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n missing data	??	??	??	??	??	??	??	??	??	??	??	??	??
n discontinued	??	??	??	??	??	??	??	??	??	??	??	??	??

A8: priority question

Please present the following effectiveness data for the treated eye for both the Aflibercept2mg Q8 arm and the Ranibizumab arm on the basis of the observed data, for VIEW1, VIEW2 and VIEW1+VIEW2 pooled (**in 6 separate Tables**). The numbers gaining and losing letters should be relative to the original baseline (i.e. for the follow-up period not relative to the start of the follow-up period but to the original baseline).

Month (0=Baseline)	0	1	2	3	4	5	6	7	8	9	10	11	12
n on treatment	??	??	??	??	??	??	??	??	??	??	??	??	??
n gaining ≥30 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n gaining ≥15 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n gaining ≥0 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n losing ≥15 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n losing ≥30 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n missing data	??	??	??	??	??	??	??	??	??	??	??	??	??
n discontinued	??	??	??	??	??	??	??	??	??	??	??	??	??
Month (12=start Follow-up)	12	13	14	15	16	17	18	19	20	21	22	23	24
n on treatment	??	??	??	??	??	??	??	??	??	??	??	??	??
n gaining ≥30 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n gaining ≥15 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n gaining ≥0 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n losing ≥15 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n losing ≥30 letters	??	??	??	??	??	??	??	??	??	??	??	??	??
n missing data	??	??	??	??	??	??	??	??	??	??	??	??	??
n discontinued	??	??	??	??	??	??	??	??	??	??	??	??	??

A9: priority question

Please present the following effectiveness data for the treated eye for both the Aflibercept2mg Q8 arm and the Ranibizumab arm on the basis of LOCF for VIEW1, VIEW2 and VIEW1+VIEW2 pooled (**in 6 separate Tables**).

Month (0=Baseline)	0	1	2	3	4	5	6	7	8	9	10	11	12
NVI	??	??	??	??	??	??	??	??	??	??	??	??	??
Mild VI	??	??	??	??	??	??	??	??	??	??	??	??	??
Moderate VI	??	??	??	??	??	??	??	??	??	??	??	??	??
Severe VI	??	??	??	??	??	??	??	??	??	??	??	??	??
Blind	??	??	??	??	??	??	??	??	??	??	??	??	??
Month (12=start Follow-Up)	12	13	14	15	16	17	18	19	20	21	22	23	24
NVI	??	??	??	??	??	??	??	??	??	??	??	??	??
Mild VI	??	??	??	??	??	??	??	??	??	??	??	??	??
Moderate VI	??	??	??	??	??	??	??	??	??	??	??	??	??
Severe VI	??	??	??	??	??	??	??	??	??	??	??	??	??
Blind	??	??	??	??	??	??	??	??	??	??	??	??	??

A10: priority question
Please present the following effectiveness data for the treated eye for both the Aflibercept2mg Q8 arm and the Ranibizumab arm on the basis of the observed data for VIEW1, VIEW2 and VIEW1+VIEW2 pooled (**in 6 separate Tables**).

Month (0=Baseline)	0	1	2	3	4	5	6	7	8	9	10	11	12
NVI	??	??	??	??	??	??	??	??	??	??	??	??	??
Mild VI	??	??	??	??	??	??	??	??	??	??	??	??	??
Moderate VI	??	??	??	??	??	??	??	??	??	??	??	??	??
Severe VI	??	??	??	??	??	??	??	??	??	??	??	??	??
Blind	??	??	??	??	??	??	??	??	??	??	??	??	??
Month (12=start Follow-Up)	12	13	14	15	16	17	18	19	20	21	22	23	24
NVI	??	??	??	??	??	??	??	??	??	??	??	??	??
Mild VI	??	??	??	??	??	??	??	??	??	??	??	??	??
Moderate VI	??	??	??	??	??	??	??	??	??	??	??	??	??
Severe VI	??	??	??	??	??	??	??	??	??	??	??	??	??
Blind	??	??	??	??	??	??	??	??	??	??	??	??	??

A11: priority question
Page 190: Please clarify whether the relative risk of 0.99 for the maintenance of vision for months 12 to 24 given in Table B39 is derived from the 1.01 24 month indirect analysis of Table 15 of the Kleijnen systematic review coupled with the 1.02 12 month indirect analysis of Table 10 of the Kleijnen systematic review: i.e. 0.99*1.02=1.01? If not, please clarify how the relative risk of 0.99 for the maintenance of vision for months 12 to 24 given in Table B39 was derived.

A12: priority question
Page 190: Please clarify whether the relative risk of 0.88 for the improvement of vision for months 12 to 24 given in Table B39 is derived from the 1.05 24 month indirect analysis of Table 15 of the Kleijnen systematic review coupled with the 1.19 12 month indirect analysis of Table 10 of the Kleijnen systematic review: i.e. 0.88*1.19=1.05? If not, please clarify how the relative risk of 0.88 for the improvement of vision for months 12 to 24 given in Table B39 was derived.

A13: priority question
Please present the following relative risks for aflibercept versus ranibizumab on the basis of LOCF for VIEW1, VIEW2 and VIEW1+VIEW2 pooled (**in 3 separate Tables**).

	Gain30+	Gain15+	Gain15-30	Gain0+	Stay±15	Lose15-30	Lose15+	Lose30+
Months 0-12	??	??	??	??	??	??	??	??
Months 0-24	??	??	??	??	??	??	??	??
Months 12-24	??	??	??	??	??	??	??	??

A14
Page 49: It states that in VIEW 1 and VIEW 2 RCTs eligible patients were those that had “subfoveal CNV” but the definition of subfoveal CNV was “presence of subfoveal neovascularisation, including juxtafoveal lesions that affect the fovea”. Please clarify whether there may not have been “CNV” under the fovea but only that part of the lesion was under the fovea for some patients [for instance, Pigment Epithelial Detachment (PED)]. Please also clarify whether the number of “juxtafoveal ” lesions was equally distributed among treatment groups?

A15
Page 49 and pages 50-52: It states that eligible patients were those with “CNV”. Please clarify whether other phenotypes of neovascular AMD [retinal angiomatous prolifearion (RAP) and idiopathic polypoidal choroidal vasculopathy (IPCV)] were not included in the VIEW 1 VIEW 2 RCTs? If they were included, please provide the proportion of individuals with different phenotypes in each of the treatment groups in VIEW 1 and VIEW 2.

A16
Pages 51-52: In VIEW 1 most patients were white and non Hispanic (96.6%). In VIEW2, most patients were white (72.8%) but 20% were Asian. Please clarify if there are any separate data with regards to the Asian group?

A17
Page 73: Please clarify what comparisons 4 to 15 for superiority testing using secondary endpoints were.

A18
Page 87: Please clarify whether Figure 6 is for the per-protocol set (PPS) or full analysis set (FAS).

A19
Page 89: Please present separate figures for the mean change in visual acuity at the end of 96 weeks (Figure B7) for VIEW1 and for VIEW2. Please also clarify if Figure B7 is for the PPS or FAS.

A20
Page 114: It states that “VIEW 1 and VIEW 2 were of nearly identical design”. Please clarify what were the differences in study design between these two trials? (‘nearly identical’ does not mean ‘identical’).

A21
Page 122: It states that the IVAN trial was not included in the network meta-analysis because the outcomes were combined for the as needed (PRN) and fixed dosing

regimens. Please clarify whether data from the monthly regime and those from the PRN are available separately.

A22
Page 125: Some trials included only “occult” CNV, such as MARINA. Please clarify why the ranibizumab arm of the ANCHOR trial (which included predominantly classic CNV) was not considered in the network meta-analysis?

A23
Pages 129-130: Please clarify what the purpose of the normal adjustment in the analysis of continuous outcomes was and why it was required.

A24
Please present the baseline distributions of the BCVA of the treated eye across the model health states for VIEW1, VIEW2 and VIEW1+VIEW2 pooled (**in 3 separate tables**). Please also present for each health state the proportion of untreated eyes that had wet AMD at baseline.

Baseline	N treated eyes	% untreated eyes with wet AMD
NVI	??	??
Mild VI	??	??
Moderate VI	??	??
Severe VI	??	??
Blind	??	??

A25
Please clarify if any indirect treatment comparison (ITC) of the year 1 discontinuation rate, the year 2 discontinuation rate and the 2 year discontinuation rate was undertaken in the Kleijnen systematic review. If not, please clarify the reasons for this not being part of the systematic review given its possible centrality to the cost effectiveness results.

A26
Page 190: Please clarify whether the relative risks reported in Table B39 suggest that there is a greater probability of gaining letters in year 1 from aflibercept, but a greater probability of gaining letters in year 2 from Ranibizumab. Please also clarify whether this has implications for extrapolation of effect (with the year 2 figure being potentially more relevant for extrapolation).

A27
Please present the following relative risks on the basis of observed data for VIEW1, VIEW2 and VIEW1+VIEW2 pooled (**in 3 separate Tables**).

	Gain30+	Gain15+	Gain15-30	Gain0+	Stay±15	Lose15-30	Lose15+	Lose30+
Months 0-12	??	??	??	??	??	??	??	??
Months 0-24	??	??	??	??	??	??	??	??
Months 12-24	??	??	??	??	??	??	??	??

Appendix 15, Reference Pack – Kleijnen Systematic review

A28: priority question
Page 58 - Please confirm which forest plot corresponds to which outcome and comparison (there are no titles for these plots).

A29: priority question
Figure 16, 24m direct analysis – Please clarify why the numerical results are labelled as ‘odds ratio’ in the analysis but the plots refer to ‘risk ratios’.

A30
Appendix 2-4: Please provide the STATA code used for the frequentist network meta-analysis.

A31
Please provide the Excel file used to undertake the Bucher analysis.

Section B: Clarification on cost-effectiveness data

Quality of life data

B1: priority question
Page 200: Please clarify whether the quality of life values reported in Table B42 are derived using the UK population norms for the EQ-5D. If not, please present the equivalent quality of life values for the same health states based on the UK social tariff weights for the EQ-5D.

B2: priority question
Page 200: The model structure is defined in terms of the combined BCVA of both eyes. The utilities listed in Table B42 appear to adopt counting fingers rather than the blind categorisation of the model. Please complete the following table of health state classifications for single eyes adopted within the model and within the utility study, and clarify any differences between the model and the VIEW2 EQ-5D utility analysis.

Model		VIEW2 EQ-5D utility analysis	
Health state	ETDRS	Health state	ETDRS
NVI and no wet AMD	>80 letters	NVI and no wet AMD	??
NVI	>80 letters	NVI	??
Mild VI	66-80 letters	Mild VI	??
Moderate VI	51-65 letters	Moderate VI	??
Severe VI	36-50 letters	Severe VI	??
Blind	<36 letters	Counting fingers	??

B3: priority question
Page 200: Please clarify whether the ETDRS letters used to define health states in the model differ from the ETDRS letters for the VIEW2 EQ-5D utility analysis. If so, please present a separate table (based on Table B42) using the ETDRS health states of the model and the UK population norms.

B4
Page 200: Please clarify whether the EQ-5D results from VIEW2 as presented in Table B42 are derived from all EQ-5D data points pooled across baseline, week 52 and week 96 and pooled across the 4 arms of VIEW2. If not, please summarise which data points have been included and which have been excluded and the reasons for this.

B5
Please present the following VIEW2 EQ-5D patient numbers at baseline, week 52 and week 96 (**in 3 separate Tables**).

Untreated eye	NVI	mild VI	moderate VI	severe VI	counting fingers
Treated eye					
NVI	??	??	??	??	??
mild VI	??	??	??	??	??
moderate VI	??	??	??	??	??
severe VI	??	??	??	??	??
counting fingers	??	??	??	??	??
missing data	??	??	??	??	??
discontinued	??	??	??	??	??

B6
Page 200: Please present a separate table (based on Table B42) for the subset of patients falling into either regions 7 or region 8 of VIEW2, applying the UK population norms for the EQ-5D, along with the relevant patient numbers at baseline, week 52 and week 96.

B7
Page 221: Please clarify how the Czoski-Murray utility values presented in Table B54 were applied within the modelling framework using the health states described in Table B42 (based on the following table).

	NVI	Mild	Moderate	Severe	Blind
NVI	??				
Mild	??	??			
Moderate	??	??	??		
Severe	??	??	??	??	
Blind	??	??	??	??	??

Resource use data

B8: priority question
Please provide the following dosing information for both the Aflibercept 2mg Q8 arm and the Ranibizumab arm for VIEW2, VIEW1 and VIEW1+VIEW2 pooled (**in 6 separate Tables**).

Month	1	2	3	4	5	6	7	8	9	10	11	12
n on treatment	??	??	??	??	??	??	??	??	??	??	??	??
n doses	??	??	??	??	??	??	??	??	??	??	??	??
Month	13	14	15	16	17	18	19	20	21	22	23	24
n on treatment	??	??	??	??	??	??	??	??	??	??	??	??
n doses	??	??	??	??	??	??	??	??	??	??	??	??

B9
Page 206: The frequency of injections for Ranibizumab in year 1 and year 2 are reported as being taken from TA155 and the EMA report. Please provide the exact table or paragraph references for these two estimates.

B10
Please provide a copy of the list of questions of the physician survey on resource use, along with a tabulation of the responses (e.g. x anticipated 3 Ranibizumab injections in year 3, y anticipated 4 Ranibizumab injections in year 3 etc).

Model structure

B11: priority question
Please clarify whether the probability of maintaining vision within the Kleijnen systematic review was defined in the same way as in the model which appears to permit gains and losses of up to (but not including) 15 letters. If the two probabilities are not aligned, please also clarify how these differences will impact on the model outcomes?

B12: priority question
Please present the parameter estimate(s) along with their source(s) for the development of wet AMD in the 2nd eye for:

- year 1 of the model;
- year 2 of the model;
- years 3-5 of the model; and,
- years 5+ of the model.

B13: priority question
The ERG has identified possible serious structural errors in the modelling of second eye involvement. Two transition probability matrices (TPMs) in the economic model are presented in the 2nd eye worksheets:

- The "post treatment" TPM in cells XM70:YK94. This appears to be applicable only when both eyes have received treatment of more than two years duration and both eyes remain on treatment. This in turn appears to imply no change in the visual acuity of either eye hence no change in health state for those to whom it is applied.
- The BSC TPM in cells XM100:YK124. This appears to be applicable only when both eyes are receiving only Best supportive care (BSC).

The ERG has identified possible **major concerns** around the application of these TPMs, and the probabilities within them, in the modelling of bilateral wet AMD. The ERG has also not been able to identify any other TPMs applied in the modelling of bilateral wet AMD. It would be appreciated if each of the following bullet points could be addressed individually in turn:

- Please clarify whether there is no consideration of the impact of the initial two years of treatment upon the BCVA of the 2nd eye; i.e. cells GR6:GX65 of the 1st eye worksheets appear to be applied to the annual incidences of 2nd eye involvement, with ongoing annual incidences of 2nd eye involvement occurring over the time horizon of the model and receiving this treatment effect. If this is not correct, please provide some indication of the location of these calculations and the underlying model logic, along with how it applies any treatment of the

ongoing annual incidences of 2nd eye involvement over the time horizon of the model.

- Please clarify whether the "post treatment" TPM of no change in BCVA of either eye is applied for years 3-5, with the BSC TPM being applied from year 6 onwards. Please also clarify whether this does not apply any initial 2 years treatment effect for the 2nd eye, but also does not take into account the differential timing of the development of wet AMD in the 2nd eye. For example, those developing 2nd eye involvement at the start of year 3 appears to have the "post treatment" TPM applied for three years, those developing 2nd eye involvement at the start of year 5 appear to have it applied for one year, and those developing 2nd eye involvement at the start of year 6 do not have it applied at all. If this is correct, please provide the rationale behind this model structure.
- Please clarify whether the treatment costs for second eye involvement are limited to years 3-5 of the model; e.g. cells SO8:SO368 are zero with the exception of cells SO34:SO68. If this is correct, please provide the rationale for this given that 2nd eye involvement can occur over the time horizon of the model and so presumably treatment costs can be incurred over the time horizon of the model.
- The ERG has identified a possible error within the modelling of 2nd eye involvement in terms of discontinuations. Please clarify whether some patients discontinue in years 3, 4 and 5 based upon the variable *pDiscont3_VTE2q8*, with there being no discontinuations thereafter. Please also clarify whether this fails to take into account patients who develop 2nd eye involvement throughout the time horizon of the model and so may both start and discontinue treatment throughout the time horizon of the model. If this is correct, please provide the rationale behind this model structure.
- It seems possible that further issues similar to those of the previous four bullet points may arise. In light of the responses to the above four bullet points, is the manufacturer confident that "*Efficacy for the fellow eye while on treatment was calculated with the same methodology as for the "treated eye"*" [Bayer submission page 187] and that the modelling of 2nd eye involvement is tenable?

B14
Please provide the rationale as to why the model appears to rely upon the VIEW2 trial for many of its inputs rather than VIEW1 or the pooled VIEW1+VIEW2.

B15
Please clarify whether patients in the single eye cohort flow who discontinue therapy after year 2 transfer to the same health state in the next period rather than have the appropriate TPM applied to them. If this is correct, what is the rationale and impact of this assumption?

B16
Please clarify whether patients in the single eye cohort flow who exit to another health state do not have the mortality rate applied to them and that it is assumed that all deaths occur among those not changing health state. If this is correct, what is the rationale and impact of this assumption?

B17
For the mortality data in cells C294:D344 of the *Model_Parameters* worksheet please clarify the source data underlying cells C294:C344 and the arithmetic underlying them. Please also clarify if cells D294:D344 are derived from C294:C344, and if so the arithmetic underlying this. If cells D294:D344 are not derived from C294:C344,

please clarify the source data underlying cells D294:D344 and the arithmetic underlying them.

B18
It appears that Please clarify whether patients who develop 2nd eye involvement of wet AMD are all assumed to have mild visual impairment (VI) in the 2nd eye upon its development. If this is correct, what is the rationale behind this assumption?

B19
Please clarify if the mortality rates in the first two years of the modelling, 0.76% and 1.60%, are cumulative (i.e. the mortality rate in the 2nd year is around 0.83%)? Please also provide a reference or calculation for these figures (preferably an explicit table (or text) reference could be given for these, together with a presentation of any further underlying arithmetic that is required to calculate them).

B20
Please clarify if the discontinuation rates in the first two years of the modelling, 2.7% and 3.5%, are cumulative (i.e. the discontinuation rate in the 2nd year is 0.8%)?

B21
The ERG has identified a possible error in the 1st eye cohort flow worksheets for the 1st eye mild – 2nd eye no wet AMD (NVI). In general the formulae for those exiting are applied to those “beginning” plus those “entering”. For reasons that are unclear, within the 1st eye Mild - 2nd eye no-wAMD (NVI) group the formulae apply the proportions exiting only to those “beginning”:
e.g. T418=(R418-SUM(W418:Y418))*(BSC_G3lines+BSC_G6lines), though there is some variation in this between the 1st six years and thereafter and between active treatment and BSC. Please clarify whether this is the intended model structure or an error.