NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Ranibizumab for the treatment of choroidal neovascularisation associated with pathological myopia [ID555]

Dear [redacted]

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 10 June 2013 by Novartis Pharmaceuticals. 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,** Wednesday 17 July 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 Bernice Dillon, Technical Lead (bernice.dillon@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] [redacted]
[redacted] [redacted] – [redacted]
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Literature searching

1. Page 48 section 6.1: The submission states that all literature searches were conducted in November 2012. However, in Appendix 10.2.2 all search dates are reported as March/April 2012. Please explain this discrepancy.

2. Page 51, Figure 7: Please clarify and provide references for the RCTs that were excluded because they did not include a ranibizumab arm.

Section A: Clarification on effectiveness data

A1. Please provide the breakdown of the number of participants by geographical location of centre (i.e. country) for each arm of the Novartis Phase III trial.

A2. **PRIORITY.** Table 3, page 19 /Table 20, page 82: Please present the data for the vPDT/ranibizumab arm for 0-6 months and 0-12 months.

A3. **PRIORITY.** Please provide the equivalent of Table 20, page 82 (including vPDT/ranibizumab results at 0-6 and 0-12 months) for the observed data, which did not include LOCF. Please indicate clearly the N involved in each efficacy result.

A4. Table 23, page 91: Please provide an explanation as to why the 'Driving' score for the two ranibizumab groups are so different.

A5. **PRIORITY.** Table 30, page 100 (VIP trial): Please provide the mean change in BCVA (with standard deviation) in each treatment group at 3, 6, 12 and 24 months. In addition please provide the n(%) of patients gaining ≥ 10 letters, ≥ 20 and ≥ 30 letters at each assessment (3, 6, 12 and 24 months). Please provide the equivalent data for a loss of at least 10, 20, and 30 letters.

A6. **PRIORITY.** Please provide the data for the Novartis phase III trial for the number (%) of patients who had 2, 3, 4 and 6 lines of loss (patients losing 10, 15, 20 and 30 ETDRS letters respectively) as well as 4 and 6 lines gain (patients gaining 20 and 30 ETDRS letters) for each of the follow up assessments (3, 6 and 12 months) for each of the three treatment groups.

A7. The primary outcome of the Novartis phase III trial (mean average change in BCVA from baseline) is measured at 3 months. Please explain the rationale for why a 3 month assessment is considered clinically relevant, rather than a longer time period.

A8. **PRIORITY.** Please provide the number (%) of patients in each treatment group at each assessment (baseline, 3, 6 and 12 months) that showed CRT thickness < 250 microns.

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A9. **PRIORITY.** Page 133 - Table 41: Please provide the safety data for the vPDT/ranibizumab arm of the trial for baseline to 6 months and for baseline to 12 months.

A10. **PRIORITY.** Ranibizumab is known to accelerate retinal pigment epithelium atrophy. Atrophy is a major issue in myopia. The manufacturer submission, however, does not include atrophy in the adverse events section. Would you please provide the rationale for this omission and clarify whether atrophy was measured in the Novartis phase III trial?

A11. **PRIORITY.** Please provide, in tabular format, the data that have been used to generate the graphs for the network analyses reported on pages 308-310 of the submission.

Section B: Clarification on cost-effectiveness data

B1. Retinal tears are not considered in the economic model as they happened in less than 5% of patients. However, a retinal tear may cause a retinal detachment which if untreated may lead to permanent visual loss. In the Novartis phase III trial, 1%-2% of patients had retinal tears. Please explain why this was not taken into consideration in the economic model.

B2. Page 183: the submission states that ranibizumab and vPDT both incur administration costs each time the patient receives treatment. The administration costs for ranibizumab was assumed to consist of the cost of the OCT and the injection visit whereas that for vPDT was assumed to consist of OCT plus an ophthalmologist consultation visit. Please explain why an ophthalmologist consultation visit was considered for vPDT but not for ranibizumab.

B3. **PRIORITY.** Please provide the baseline distribution of patient numbers for the subgroup of those who were treated in their WSE at baseline. Please provide absolute patient numbers rather than percentages (see suggested layout below)

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		BSE BCVA (untreated eye)							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25
WSE BCVA	86-100	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?
	76-85	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?
	66-75	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?
	56-65	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?
	46-55	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?
	36-45	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?
	26-35	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?
	<25	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?

B4. **PRIORITY.** Please provide the baseline distribution of patient numbers for the subgroup of those who were treated in their BSE at baseline. Please provide absolute patient numbers rather than percentages (see suggested layout below).

		BSE BCVA (treated eye)							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25
WSE BCVA	86-100	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?
	76-85	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?
	66-75	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?
	56-65	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?
	46-55	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?
	36-45	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?
	26-35	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?
	<25	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?

B5. **PRIORITY.** Please provide the baseline distribution of patient numbers for the subgroup for whom the treated eye and the untreated eye had the same BCVA at baseline. Please provide absolute patient numbers rather than percentages (see suggested layout below).

	Treated eye BCVA and untreated eye BCVA							
	86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25
Number	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?

B6. **PRIORITY.** Please provide the patient numbers underlying the cells C63:U105 of the *All Patients* worksheet, and for each of these the number that were inferred from adjacent time points, the number that were LOCF and the number that were observed.

B7. **PRIORITY.** Please provide the patient numbers for the corollary of the cells C85:K94 of the *All Patients* worksheet for the vPDT arm of the VIP trial.

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B8. Please provide the patient numbers that would underlie the corollary of cells C85:U105 of the *All Patients* worksheet for the control arm of the VIP trial.

B9. **PRIORITY.** Please provide the baseline distribution of patient numbers with bilateral involvement at baseline. Please provide absolute patient numbers rather than percentages (see suggested layout below).

	Treated eye BCVA							
	86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25
Bilateral	n=?	n=?	n=?	n=?	n=?	n=?	n=?	n=?

B10. Please provide the baseline mean values to which the NEI VFQ-25 changes of tables 23, 24 and 25 relate to, in the same format as tables 23, 24 and 25.

B11. The *QoL* worksheet cell G10 permits the WSE utility function *VFQ25 mapping (WSE)* to be selected. Please provide details of the VFQ25 data feeding into each of the 8 utilities, its standard deviations, the number of patients this relates to and the mapping function employed (Payakatchat 2009?). Please also provide the corollary of this VFQ25 data for the 8 health states of the BSE.

B12. **PRIORITY.** The NICE methods guide is explicit about the preference for EQ-5D HRQoL data valued using the UK social tariff for the reference case, and Novartis has used EQ-5D HRQoL data valued using the UK social tariff for previous ranibizumab submissions to NICE. Please present the mean value, standard deviation of the sample and number of observations by arm at baseline, 1 month, 3 months, 6 months, 9 months and 12 months, or by the schedule of the EQ-5D measurements if this differed (see suggested layout below).

	EQ-5D data valued using UK social tariff					
	0 mth	1 mth	3 mths	6 mths	9 mths	12 mths
Ranibizumab	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?
vPDT	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?

B13. **PRIORITY.** Please also present the EQ-5D HRQoL data valued using the social tariff pooled across arms and time points in the following format. Note that this does not need to take into account whether the treated eye is or was the BSE or the WSE and relates solely to binocular vision states (see suggested layout below).

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		BSE BCVA							
		86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25
WSE BCVA	86-100	μ=? s.d.=? n=?							
	76-85	μ=? s.d.=? n=?	μ=? s.d.=? n=?						
	66-75	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?					
	56-65	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?				
	46-55	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?			
	36-45	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?		
	26-35	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	
	<25	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?	μ=? s.d.=? n=?

B14. Please provide more detail of the source and calculation of the all-cause mortality data in cells D12:D112 of the *Mortality* worksheet; e.g. gender averaging.

B15. **PRIORITY.** Please outline the number of vPDT doses in months 0-3, 3-6, 6-9, 9-12, 12-15, 15-18, 18-21 and 21-24 in the vPDT arm of the VIP trial; i.e. each quarter, coupled with the number of patients remaining in the vPDT arm of the VIP trial for these periods.

B16. **PRIORITY.** Please submit the model validation report of the external expert health economist at Oxford University referred to on page 220.

B17. **PRIORITY.** The reason for dividing (1 minus the monthly rate) by 3 in the equation *Probability = 1 – exp(ln[1 – rate] / 3)* to arrive at the quarterly probability is not understood by the ERG. At face value it also appears to result in counterintuitive values within table 51, such as the monthly rate for Yoshida being 0.8% but the quarterly rate being only 0.3%. This may be a misinterpretation of the underlying data on the part of the ERG, but it would seem more intuitive to multiply (1 minus the monthly rate) by 3. Some further explanation of this calculation, its data inputs, the intuition underlying it and its results would be much appreciated.

B18. It appears that the annual costs of recurrence may not have been divided by 4 to give quarterly amounts. Please clarify if this requires amendment.

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B19. The adverse event costs appear to be limited to the first year. Is this correct, and if so what is the justification for this? Recurrence also appears to not include adverse event costs. Is this correct, and if so what is the justification for this?

B20. The calculation of QALYs appears to mix patient numbers that have half cycle correction applied to them with patient numbers which have not had half cycle correction applied to them, and also to possibly confuse cycles. For instance, cell D12 of the *Tx_QALYs* worksheet relies upon cell D11 and cell BM11 of the *Calculations* worksheet. Cell D11 of the *Calculations* worksheet appears to have half cycle correction while cell BM11 of the *Calculations* worksheet appears not to have half cycle correction. Cell D12 of the *Tx_QALYs* worksheet also relates to the 2nd cycle of the model while cell BM11 of the *Calculations* worksheet relates to the 1st cycle of the model. Are these errors, and if they are what is the effect of them upon results?

B21. The assumed 15% rate of bilateral involvement appears to only impact the first two years of the model. Is it assumed that there is no further development of bilateral involvement subsequent to baseline?

B22. PRIORITY. Page 315: The submission provides an estimate of the cost effectiveness of ranibizumab relative to bevacizumab of £21,922 per QALY. Please tabulate the assumptions and data inputs underlying this estimate, including the transition probability matrices or the data underlying them. Please also clarify the status of this estimate.

Section C: Textual clarifications and additional points

C1. Table 20, page 82: Please indicate whether the change in BCVA from baseline compared to vPDT is statistically significant (line 2 of the table).

C2. Table 20, page 82: Please indicate whether the change in CRT from baseline compared to vPDT is statistically significant.

C3. What data has been redacted from Figure 10, page 317 of the submission, and what were the reasons for the redaction?

C4. A lot of information has been marked as confidential (AiC) in your submission. In line with NICE process for 'confidential information to be kept to an absolute minimum to ensure transparency in the appraisal process'. Please consider 'lifting' confidentiality status for the submission. Please also note that the timescale of publication for any items marked as academic in confidence (AiC), before appraisal documentation is shared outside NICE (at the ACD consultation stage) should be 'lifted'.