National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ranibizumab for treating choroidal neovascularisation associated with pathological myopia [ID555]

You are asked to check the ERG report from Aberdeen HTA to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Friday 23 August** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Page 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 1. "The manufacturer's submission from Novartis Pharmaceuticals addressed the use of ranibizumab (0.5mg) in adults presenting with choroidal neovascularisation associated with pathological myopia" The above statement is not accurate with respect to the licensed indication in that it omits the words "visual impairment due to" from the description.	"The manufacturer's submission from Novartis Pharmaceuticals addressed the use of ranibizumab (0.5mg) in adults presenting with **visual impairment due to** choroidal neovascularisation associated with pathological myopia"	The error needs to be corrected in order to be consistent with the licensed posology. It is important that any medical staff that would potentially read this document are informed correctly about the license.	The proposed amendment is accepted.

Issue 2 Page 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 1. "The proportion of patients gaining 15 letters or more from baseline to 3 months was 65.5% for ranibizumab disease activity, 61.9% for ranibizumab disease stabilisation and 27.3% for vPDT, with statistical significance for each of the ranibizumab arms compared to vPDT."	"The proportion of patients gaining **10 letters** or more from baseline to 3 months was 65.5% for ranibizumab disease activity, 61.9% for ranibizumab disease stabilisation and 27.3% for vPDT, with statistical significance for each of the ranibizumab arms compared to vPDT."	The error needs to be corrected as it relates to a key clinical parameter (visual acuity), which is central to this appraisal. It is important that the committee are clear about the effectiveness of ranibizumab and vPDT for the 3 month comparison of this dichotomous endpoint.	The proposed amendment is accepted.

The above statement is incorrect as the proportions stated refer to patients gaining 10 letters or more from baseline to 3 months NOT 15 letters as written.			

Issue 3 Page 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 1. "Improvements in BCVA were observed in both ranibizumab arms over 12 months, but no statistical comparisons could be made to vPDT beyond 3 months due to the switching of treatments in this group." This statement is not accurate as Novartis provided statistical comparisons for these time-points as requested in the clarification questions – see question A3 / table A3. Therefore, it is indeed possible to undertake these comparisons but it is not clinically relevant to undertake these comparisons due to the crossover.	Improvements in BCVA were observed in both ranibizumab arms over 12 months, but no **clinically relevant** statistical comparisons could be made to vPDT beyond 3 months due to the switching of treatments in this group	The error needs to be corrected as it is incorrect to state that statistical comparisons cannot be made especially given that Novartis specifically undertook these additional bespoke analyses for the clarification response document, question A2. It is important to clarify to the committee that any comparative analyses post month 3 are not clinically relevant since the majority (n=38) of patients in the comparator arm were administered ranibizumab for ethical reasons.	The proposed amendment is accepted.

Issue 4 Page 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 2. "Development of geographic atrophy or extension of pre-existing geographic atrophy (as it has been recognised now as a potential side effect in patients with age-related macular degeneration undergoing anti-VEGF treatment) was not assessed in the Novartis phase III trial." This statement is misleading in that it fails to mention that the majority of patients entered into the study had geographic atrophy at baseline. Moreover there were no serious adverse event (SAE) reports of worsening geographic atrophy during the study.	The following statement is more appropriate and factually accurate regarding this phase III study. The majority of patients entered into the study had geographic atrophy at baseline. While atrophy was not specifically monitored for progression via fluorescein angiography or colour fundus photography, there were no SAE reports of worsening geographic atrophy during the study. The statement on geographic atrophy, if included, should also include the most relevant findings from IVAN and CATT – this was most strongly correlated with treatment regimen: 'it [geographic atrophy] has been recognised now as a potential side effect in patients with age-related macular degeneration undergoing anti-VEGF treatment, although the incidence appears to be lower with PRN (discontinuous) treatment regimens compared to monthly',	The ERG statement, as written, implicitly implies that ranibizumab is associated with geographic atrophy within the phase III clinical study. There is no evidential basis for this conclusion based on the data sent in the clarification response. The IVAN and CATT studies both demonstrated an increased incidence of geographic atrophy during the course of the studies in patients receiving monthly treatment versus PRN (discontinuous) treatment. It is important for the ERG to recognise this evidence is generated from a different patient population (wAMD versus pathologic myopia). Likewise, that the key factor associated with geographic incidence was treatment regimen: those patients who received more treatments had a higher incidence. The mean injection rates for ranibizumab in the treatment of pathologic myopia are considerably lower than for a wAMD patient population. It is important not to mislead the	The proposed amendment is not acceptable. If investigators of the Novartis phase III trial did not specifically look at the development of geographic atrophy (and the trial was probably too short to assess this) it is unlikely they would have reported it. The manufacturer submission did not report the number of patients with geographic atrophy at baseline and at follow-up, and did not indicate which imaging technology was used to assess the presence of atrophy. In response to the ERG clarification question A10, the manufacturer stated that "[redacted] but provided the number of participants with chorioretinal atrophy and those with mottling of RPE at baseline. However, information on how many patients had

		committee and public exposed to this document since it relates to a potentially serious adverse event that has not been found within the Novartis phase III study.	geographic atrophy in each arm of their trial at baseline, at 3 months and at last follow-up (12 months) was not given. We agree with the manufacturer's justification that a key factor associated with the incidence of geographic atrophy is the treatment regimen. Current evidence indicates that those patients who receive more treatments have a higher incidence. The mean injection rates for ranibizumab in the treatment of pathologic myopia are considerably lower than that for wAMD. However, it is worth noting that patients with myopic CNV are younger than those with wAMD and therefore likely to live longer. Pathological myopia has already higher risk for atrophy development (as clearly stated in the manufacturer's submission), so the matter requires proper consideration. No revision required.

Issue 5 Page 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 2. "The ERG was concerned at the exclusion of bevacizumab as a comparator given it is used off-label for the treatment of myopic CNV in the UK" This statement is followed with no reference or evidence presented for its substantiation.	Either a reference should be supplied to substantiate this statement or it should be withdrawn	This statement relating to the choice of comparator is not supported by any reference or evidence. This is not in keeping with the NICE evidenced based approach. Providing this reference will allow the committee to appraise the quality of evidence associated with the ERG claim.	Not a factual error. The statement is based on advice from the ERG clinical expert. Although not licensed for intraocular use, bevacizumab is used in some Ophthalmic Units in the NHS to treat patients with myopic CNV. It is worth noting that the current manufacturer's submission moved away from the NICE final scope, which included bevacizumab as relevant comparator. No revision required.

Issue 6 Page 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 3. "Adverse events that affected more than around 5% of the patients of the Novartis phase III trial for ranibizumab and the VIP trial for vPDT are included in the analysis, affecting both costs and QALYs." The criteria for selecting adverse events for the NICE economic model (see page 156 of the submission, section 7.3.1) was "events that occurred in at least five patients, and the AEs that are suspected to be related to the study drug and/or ocular injection." Please note that the criteria did not include 5% as suggested here and does not include that they are suspected as being related to the study drug and/or ocular injection.	Please amend the definition of the statement as per the submission to: …events that occurred in at least five patients, and the AEs that are suspected to be related to the study drug and/or ocular injection	The ERG report inaccurately states the selection process for including adverse events.	The proposed amendment is accepted. The statement on page 3 of the ERG report has been changed to: "Adverse events that occurred in at least five patients, and those that were suspected to be related to the study drug and/or ocular injection in the Novartis phase III trial for ranibizumab and in the VIP trial for vPDT, are included in the analysis, affecting both costs and QALYs."

Issue 7 Page 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 4. “In particular, the higher rate of non-subfoveal involvement in the Novartis phase III trial may be to the benefit of ranibizumab.” This is factually incorrect and misleading as the subfoveal sub-population in the Novartis phIII trial (disease activity arm) actually had a slightly larger treatment effect (difference in means) versus vPDT of 9.1 letters compared to 8.9 for juxtafoveal and -15 letters versus the 1 patient with an extrafoveal lesion treated with vPDT. Therefore the ERG statement is reversed in the opposite direction – i.e. to the detriment of ranibizumab.	Either the ERG report is modified to state that their speculation around non-subfoveal involvement was not founded by the evidence provided herein or the statement is withdrawn.	This speculation is factually incorrect and misleading. It is important that this is amended in order that this invalid critique of the economic submission is not put to the committee. Indeed, the evidence suggests to the contrary as presented in the description in the left column.	Please note that the point made by the ERG does not relate to any subgroup effect between subfoveal and non-subfoveal within the Novartis phase III trial, which is what the manufacturer description seems to imply. The ERG statement relates to the extrapolation applied for vPDT within the modelling for months 3 to 12. This is presented in a more detailed account on page 86 of the ERG report. The vPDT arm of the VIP trial had a lower rate of non-subfoveal than both arms of the Novartis phase III trial. There may be a different prognosis for subfoveal compared to non subfoveal over the course of months 3 to 12. If this were the case, the vPDT arm of the VIP trial might tend to have fared worse than would be expected in the vPDT arm of the Novartis phase III trial had this been continued beyond 3 months out to 12 months with no cross

			over. This is the source of the potential bias to which the ERG statement refers. We are not suggesting that there is a subgroup effect upon the net gain from ranibizumab over vPDT at 3 months. It may be open to the manufacturer to present the VIP data for BCVA changes between months 3 and 12 for the subfoveal and the non-subfoveal subgroups separately to further explore this point. No revision required.

Issue 8 **Page 4 - KEY POINT**

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 4. "The model appears to assume that ranibizumab monitoring visits can double as treatment visits but that vPDT monitoring visits cannot double as treatment visits. In the absence of other evidence, it seems more reasonable to assume that both ranibizumab and vPDT can have "1 stop" monitoring and treatment, or that neither can, and that a "2 stop" model is required." **This statement is incorrect**. The ERG (here) seems not to have recognised the change to the monitoring schedule in the SPC for ranibizumab in this specific indication. **In fact, the model assumes a very conservative position of "2 stop" for all patients on both treatments.** For both ranibizumab and vPDT the administration visit cost (injection visit costs) includes an	The Novartis economic model conservatively assumes a "2 stop" monitoring schedule for both treatments. Furthermore, the ranibizumab label would support 5.33 monitoring visits under "2-stop" rather than the 8.5 used in the model.	Monitoring is one of the key variables within the economic model. The ERG has misunderstood the SPC for this indication and has wrongly assumed that the Novartis analysis has been biased in favour of ranibizumab. In fact, Novartis has been extremely conservative as the numbers presented within the model should be 5.33 not 8.5 as used. All the ERG analyses within the report underestimate the true incremental cost differences between the treatments.	The proposed amendment is accepted. The paragraph on **page 4** has been deleted. The ERG error incorrectly added 3.5 monitoring visits to the ranibizumab side of the equation; i.e. inflated its costs by around £612 for the two stop model, with this increasing to around £700 once the 15% bilateral rate of treatment is taken into account. Section 5 of the ERG report has been revised to address the manufacturer's comment and amend this error. In particular, the following changes have been made: **Page 7** *The following values* £1,786 £8,673 £7,116 £1,178 £4,037 £1,178 £2,481 £1,342, £5,123 £3,728 £1,276 £2,570 £1,175 £254k *have been amended to* £2,474 £9,360 £7,804 £1,866 £4,725 £1,866 £3,169 £2,029

OCT scan for monitoring. In year 1, as per vPDT SPC, monitoring should be quarterly, and therefore 4 monitoring visits were accounted for in addition to the 3.4 administration visits. For ranibizumab, in addition to the 3.5 injection visits, an additional (very conservative) 8.5 monitoring visits were accounted for. If you refer to the SPC for ranibizumab in this indication, you will note the following for monitoring: "…monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year. After the first year, the frequency of monitoring should be determined by the treating physician." **Therefore, this equates to 5.33 monitoring visits required in addition to 3.5 injection visits under 2 stop conditions.** The model has very conservatively allowed for 8.5 additional monitoring visits (under 2 stop). **In summary the model is 100% "2 stop" for both treatments for**			£5,810 £4.415 £1.963 £3,257 £1,862 £391k **Page 99** *The following values in Table 51* £10,743 £1,786 £8,673 *have been amended to* £10,055 £2,474 £9,360 *The following values in Table 52* £10,743 £1,786, £7,116 *have been amended to* £10,055 £2,474, £7.804 **Page 100** All values in Tables 53 and 54 have been corrected. **Page 101** 50% and 60% *in the paragraph* "Including all the natural history studies identified by the manufacturer has quite a sizeable impact upon both the net costs and the net benefits, reducing the net health benefits to between 50% and 60% of those of the revised base case" *have been amended to* 55% and 65%. **Page 103** *The following figures* £1,786 £8,673 £7,116 £1,178

both years on treatment. The number of additional monitoring visits under 2-stop was 8.5 in the model whereas the final UK label was 5.33.			£4,037 £1,178 £2,481 £1,342 £5,123 £3,728 £1,276 £2,570 £1,175 £254k *have been amended to* £2,747 £9,360 £7,804 £1,866 £4,725 £1,866 £3,169 £2,029 £5,810 £4,415 £1,963 £3,257 £1,862 £391k

Issue 9 Page 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 5. "The manufacturer did not include bevacizumab as a comparator, despite the fact that it is used off-label for myopic CNV, but opted to include only vPDT which is not widely used in clinical practice due to its lack of long term effects." This statement is followed with no reference or evidence presented for its substantiation.	Either a reference should be supplied to substantiate this statement or it should be withdrawn	This statement relating to the choice of comparator is not supported by any reference or evidence. This is not in keeping with the NICE evidenced based approach. Providing this reference will allow the committee to appraise the quality of evidence associated with the ERG claim.	Not a factual error. The statement is based on advice from the ERG clinical expert. Although not licensed for intraocular use, bevacizumab is used in some Ophthalmic Units in the NHS to treat patients with myopic CNV. It is worth noting that the current manufacturer's submission moved away from the NICE final scope, which included bevacizumab as relevant comparator. No revision required.

Issue 10 Page 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 5. “This may result in an inflated effect of the benefit of ranibizumab.” This is factually incorrect and misleading as the subfoveal sub-population in the Novartis phIII trial (disease activity arm) actually had a slightly larger treatment effect (difference in means) versus vPDT of 9.1 letters compared to 8.9 for juxtafoveal and -15 letters versus the 1 patient with an extrafoveal lesion treated with vPDT. Therefore the ERG statement is reversed in the opposite direction – i.e. to the detriment of ranibizumab.	Either the ERG report is modified to state that their speculation around non-subfoveal involvement was not founded by the evidence provided herein or the statement is withdrawn.	This speculation is factually incorrect and misleading. It is important that this is amended in order that this invalid critique of the economic submission is not put to the committee. Indeed, the evidence suggests to the contrary as presented in the description in the left column.	Please see ERG response to Issue 7. No revision required.

Issue 11 Page 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 6. "Adverse events were only included if they affected more than around 5% of the patients in the relevant arm of the Novartis trial. Consequently, retinal tears were not included." This is incorrect. As per the clarification response to question B1, there were **no adverse events of retinal tear (for the licensed and modelled posology) that were suspected as related to ocular injection or the study drug.** [redacted]	Remove the point below relating to retinal tears. "Adverse events were only included if they affected more than around 5% of the patients in the relevant arm of the Novartis trial. Consequently, retinal tears were not included. Retinal tears, if untreated, may lead to retinal detachment with the subsequent risk of visual loss. This is likely to be the case especially in eyes affected by pathological myopia in which retinal detachment rates are already higher than those in the general population."	The statement for the justification for not including retinal tears within the economic model is factually incorrect. It is important the committee are aware of the evidence presented to them within the Novartis phase III study and any implications to economic modelling. The ERG statement implies that Novartis have been biased in their approach for not including retinal tears when in fact there was no evidence to substantiate this being the case.	The proposed amendment is accepted. The bullet point on page 6 of the ERG report has been deleted. In addition, on **page 68** of the ERG report the paragraph which refers to adverse events has been changed to: "Only adverse events that occurred in at least 5 patients (i.e. 4% to 6% of the trial patients) and were suspected of being related to the study drug were included within the modelling." For clarity, the following paragraph has also been added to **page 68**: The manufacturer notes that: [redacted]

[redacted] The economic model specifically evaluates the cost effectiveness of the licensed posology in this indication (ranibizumab – Group II) and thus this AE did not meet the criteria for inclusion.			[redacted]”

Issue 12 Page 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 10. "Bevacizumab (Avastin, Genetech, USA) is an inexpensive, full-length monoclonal antibody that binds and inhibits all isoforms of anti-VEGF A. It is currently unlicensed for all eye conditions but used off-label in the NHS for the treatment of CNV associated with PM." This statement is followed with no reference or evidence presented for its substantiation.	Either a reference should be supplied to substantiate this statement or it should be withdrawn	This statement relating to the choice of comparator is not supported by any reference or evidence. This is not in keeping with the NICE evidenced based approach. Providing this reference will allow the committee to appraise the quality of evidence associated with the ERG claim.	Not a factual error. The statement is based on advice from the ERG clinical expert. Although not licensed for intraocular use, bevacizumab is used in some Ophthalmic Units in the NHS to treat patients with myopic CNV. It is worth noting that the current manufacturer's submission moved away from the NICE final scope, which included bevacizumab as relevant comparator. No revision required.

Issue 13 Page 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 11. "Ranibizumab does not currently have a UK marketing authorisation for the treatment of myopic CNV." This is factually incorrect	Marketing authorisation was granted on 4th July.	The ERG are incorrect in terms of the licensing status	The proposed amendment is accepted.

Issue 14 Page 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 11. "Rather than vPDT, clinical centres tend to use bevacizumab off-license for myopic CNV." This statement is followed with no reference or evidence presented for its substantiation.	Either a reference should be supplied to substantiate this statement or it should be withdrawn	This statement relating to the choice of comparator is not supported by any reference or evidence. This is not in keeping with the NICE evidenced based approach. Providing this reference will allow the committee to appraise the quality of evidence associated with the ERG claim.	Not a factual error. The statement is based on the advice of the ERG clinical expert. We have, however, decided to re-phrase it as follows: "Rather than vPDT, some clinical centres in the NHS opt for the use of bevacizumab off-license for the treatment of myopic CNV. This is implicitly acknowledged by the manufacturer who states in the current submission that: "*the use of unlicensed bevacizumab is not considered as established practice across the NHS*". It is worth noting that the manufacturer's submission moved away from the NICE final scope, which included bevacizumab as relevant comparator.

Issue 15 Page 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 12. "Ranibizumab at present does not have a UK marketing authorisation for visual impairment due to CNV secondary to PM." This is factually incorrect.	Marketing authorisation was granted on 4th July.	The ERG are incorrect in terms of the licensing status	The proposed amendment is accepted. The statement on page 12 of the ERG report has been changed to: "Ranibizumab was granted a UK marketing authorisation for visual impairment due to CNV secondary to PM on 4 July 2013."

Issue 16 Page 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 13. "…and marketing authorisation is expected between July and September 2013." This is factually incorrect.	Marketing authorisation was granted on 4th July.	The ERG are incorrect in terms of the licensing status	The proposed amendment is accepted. The statement on page 13 of the ERG report has been deleted. Please see also our response to Issue 15 above.

Issue 17 Page 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 13. "In their submission, the manufacturer provided an argument against bevacizumab being used as a comparator in this appraisal. They argued that, as bevacizumab has not yet been granted market authorization for use in CNV associated with PM, its unlicensed use cannot be considered as established practice across the NHS and it should not be administered when a licensed alternative is available." This statement concerning the explanation provided by Novartis as to why they do not believe that bevacizumab is a valid comparator omits key evidence supporting the argumentation	The amendment needs to incorporate the actual Novartis rationale for not including bevacizumab as a comparator rather than omit key argumentation.	The committee should be aware of all the rationale put forward by Novartis rather than a selected segment.	The ERG statement is a fair and correct summary of the manufacturer's argument against bevacizumab. No revision required.

Issue 18 Page 30

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 30. Table 7 vPDT column – values presented for 0-6 months and 0-12 months (for both mean average and change in BCVA) This value is factually inaccurate, as written, because the column labelling is not correct. These values (i.e. for 0-6 and 0-12) are for **vPDT+ranibizumab**. A note must be included on this table as it is otherwise misleading.	A footnote added to the table for these values to state that they are for the comparison of vPDT+ranibizumab rather than vPDT alone.	Table 7 is factually incorrect and misleading as currently written since the phase III trial allowed crossover from the vPDT arm after month 3 for ethical reasons. A footnote must be added in order to make it absolutely clear what the data for 0-6 and 0-12 in the vPDT arm refer to.	Not a factual error. The text on page 30 of the ERG report clearly states that beyond 3 months people in the vPDT group received ranibizumab. Revision not necessary.

Issue 19 Page 32

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 32. “(Table X1).” It is not clear where Table X1 is – It is most likely an error and needs to be rectified.	Label the table accurately.	The point that the ERG is making requires the reader to refer to a mislabelled table.	The typographical error has been amended. The Table on page 32 of the ERG report has been correctly labelled as Table 8.

Issue 20 Page 33

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 33. “In the ranibizumab activity group, the mean (SD) change from baseline to 3 months in CRT (µm) was -77.6 (9.75), while in the stabilisation group it was -61.0 (6.68)” The use of SD is incorrect. It should state SE.	Change the wording to: “In the ranibizumab activity group, the mean **(SE)** change from baseline to 3 months in CRT (µm) was -77.6 (9.75), while in the stabilisation group it was -61.0 (6.68)”	The ERG report if factually incorrect. It maintains technical accuracy of the Novartis phase III clinical data.	The proposed amendment is accepted.

Issue 21 Page 33

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 33. "The vPDT had greater reductions than it had at 3 months, but still lower than the two ranibizumab groups." Factually incorrect as it should state: The vPDT/ranibizumab group – it is ambiguous as to whether it refers to vPDT on its own or actually ranibizumab+vPDT.	Change the wording to: "The **vPDT+ranibizumab arm** had greater reductions than it had at 3 months, but still lower than the two ranibizumab groups."	The ERG report is factually incorrect as it omits the correct wording for the trial arm after the crossover occurs. It is important for the committee to be absolutely clear that the comparison discussed here is referring to the post crossover group.	Not a factual error. The paragraph on page 33 of the ERG reports reads: "Following clarification, the ERG was provided with the 0-6 months and 0-12 months data for the vPDT/ranibizumab group (Table 9). The vPDT had greater reductions than it had at 3 months, but still lower than the two ranibizumab groups."

Issue 22 Page 33

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 33. “There was no indication by the manufacturer of statistical significance” This is factually incorrect as an asterisk system was employed when a statistical comparison was significant. The was labelled in the footnote.	Remove comment	Factually incorrect as Table 22 within the clarification response clearly indicates whether a comparison was statistically significant using an asterisk system.	The proposed amendment is accepted. The sentence on page 33 has been removed.

Issue 23 Page 33

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 33. “Mean (SD) changes from baseline in CFT were -74.3 (105.58) for ranibizumab disease activity” Factually incorrect as this should state **105.08** (see page 89 of submission).	Amend number to 105.08.	The SD figure is incorrect. It should be correct in order to consistent with the submission	The typographical error on page 33 has been amended.

Issue 24 Page 53

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 53. "The manufacturer has chosen three months as the primary endpoint for clinical effectiveness within the Novartis phase III trial versus vPDT. Other studies in this clinical area have typically used 12 months and the ERG clinical opinion is that 12 months should be regarded as the bare minimum. The ERG is concerned at the choice of 3 months as the primary endpoint because this is unlikely to reflect the longer term efficacy of the treatment and will not provide accurate information on the number of treatments required to control the disease." This is not factually accurate as the Novartis phase III study provides a 12 month estimate for the **efficacy of ranibizumab and the number of injections required to control the disease.**	Amend the statement by removing the latter portion that relates to the number of treatments required to control disease. "The ERG is concerned at the choice of 3 months as the primary endpoint because this is unlikely to reflect the longer term efficacy of the treatment"	The ERG statement is factually incorrect as it suggests that the phase III study is not able to provide any accurate information pertaining to ranibizumab injection frequency after 3 months. This is not the case as injection frequency has been reported for up to 12 months. Injection frequency is an important parameter in the economic model. It is important that the committee are aware that ranibizumab data for efficacy and injection frequency are available up to 12 months. All interventional studies require approval from the relevant Competent Authority and Ethics boards. At the time of developing this study, it was well known from the VIP study that vPDT treatment resulted in a mean deterioration in visual acuity by month 12. At the same time, the efficacy of ranibizumab in wAMD had been	Not a factual error. Only 3 months data were available for the comparison between ranibizumab and vPDT. Therefore, the ERG's concern regarding the choice of 3 months as primary endpoint is justified.

		clearly proven. It was therefore ethically unacceptable to expose patients to vPDT for 12 months without the opportunity to switch to ranibizumab. The ERG clinical opinion appears to ignore the clear Ethical considerations which must be adhered to in these circumstances.	

Issue 25 Page 63

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 63. Table 23. "The base case modelling comparing bevacizumab with vPDT uses data from the phase III trial and the VIP trial" This statement in the table is incorrect as it was meant to state ranibizumab.	Amend thus: "The base case modelling comparing ranibizumab with vPDT uses data from the phase III trial and the VIP trial"	Factually incorrect statement about the base case comparator. The wrong VEGF treatment was selected. Needs to be amended as it describes the NICE reference case checklist.	The proposed amendment is accepted. The statement in Table 23, page 63 of the ERG has been amended as suggested.

Issue 26 Page 65

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 65. It is principally a one eye model, though some additional costs are included for bilateral disease at baseline It is factually incorrect as it omits "...and applied over the 24 months treatment period" As written, it could be wrongly interpreted that the model only accounts for bilateral costs at baseline and that they are not accounted for during the remaining cycles to 24 months.	Amend wording to: "It is principally a one eye model, though some additional costs are included for bilateral disease at baseline and applied over the 24 months treatment period"	Bilateral costs are important as they double the costs of treatment for those specific patients (15%) in the population. The ERG statement is misleading as it implies that only these costs applied at baseline and not for the full 24 months treatment period.	While not a factual error the ERG accepts the proposed amendment. The statement on page 65 of the ERG report has been amended as suggested.

Issue 27 Page 65

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 65. "Adverse events, which occurred in more than 5% of the patients in the Novartis phase III trial for ranibizumab and in the VIP trial for vPDT, are included in the analysis and they affect both costs and QALYs." The criteria for selecting adverse events for the NICE economic model (see page 156 of the submission, section 7.3.1) was "events that occurred in at least five patients, and the AEs that are suspected to be related to the study drug and/or ocular injection." Please note that the criteria did not include 5% as suggested here and does not include that they are suspected as being related to the study drug and/or ocular injection.	Please amend the definition of the statement as per the submission to: …events that occurred in at least five patients, and the AEs that are suspected to be related to the study drug and/or ocular injection	The ERG report inaccurately states the selection process for including adverse events.	The proposed amendment is accepted. The statement on **page 66** of the ERG report (not page 65 as stated by the manufacturer) has been changed to: "Adverse events that occurred in at least five patients, and those that were suspected to be related to the study drug and/or ocular injection in the Novartis phase III trial for ranibizumab and in the VIP trial for vPDT, are included in the analysis and they affect both costs and QALYs."

Issue 28 <u>Page 73 - KEY POINT</u>

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 73. "Table 30, which reproduces Table 60 on page 184 of the submission, assumes that the monthly monitoring visits during the first year within the ranibizumab arm could double as treatment visits. However, treatment visits for vPDT are assumed to be in addition to the quarterly monitoring visits of the VIP trial." This statement is factually incorrect as described in detail within issue 8. The ERG have misinterpreted the monitoring frequency required with ranibizumab.	Please amend as per issue 8.	As per issue 8.	The proposed amendment is accepted. The statement has been removed from page 73 of the ERG report.

Issue 29 Page 84

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 84. “Applying the 1st alternative interpretation of the results of Christ et al as above increases the gain from ranibizumab from the 0.432 QALYs of the base case to 0.400 QALYs” This should state “decreases”	Amend to: “Applying the 1st alternative interpretation of the results of Christ et al as above **decreases** the gain from ranibizumab from the 0.432 QALYs of the base case to 0.400 QALYs”	The ERG report is incorrect as moving from 0.432 QALYs to 0.400 QALYs is a decrease not increase.	The proposed amendment is accepted. The statement on page 84 has been amended as suggested.

Issue 30 Page 87

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 87. "Given the worse prognosis for patients with subfoveal CNV, the analysis may be biased in favour of ranibizumab. It is impossible for the ERG to quantify the degree of such a bias. A possible approach, given the manufacturer's access to patient level data from both trials, would be the use of data from the subfoveal subgroup only." This is factually incorrect and misleading as the subfoveal sub-population in the Novartis phIII trial (disease activity arm) actually had a slightly larger treatment effect (difference in means) versus vPDT of 9.1 letters compared to 8.9 for juxtafoveal and -15 letters versus the 1 patient with an extrafoveal lesion treated with vPDT. Therefore the ERG statement is reversed in the opposite direction – i.e. to the detriment of ranibizumab.	Either the ERG report is modified to state that their speculation around non-subfoveal involvement was not founded by the evidence provided herein or the statement is withdrawn.	This speculation is factually incorrect and misleading. It is important that this is amended in order that this invalid critique of the economic submission is not put to the committee. Indeed, the evidence suggests to the contrary as presented in the description in the left column.	Please see the ERG response to Issue 7. No revision required.

Issue 31 <u>Page 87 - KEY POINT</u>

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 87. "Treatment and monitoring visits No justification has been offered for the apparent assumption that monitoring visits can double as treatment visits for ranibizumab but not for vPDT. It may be argued that some patients may receive one stop treatment and other patients two stop treatment, with the proportions differing between ranibizumab and vPDT. However, the base case assumption is the most extreme that can be made and is to the benefit of ranibizumab" "In the absence of any consideration of the proportions receiving one stop and two stop treatment, it seems most reasonable to assume either that monitoring visits can double as treatment visits for both arms or that monitoring visits cannot double as treatment visits for both arms." Unfortunately, as described in detail within issue 8, the ERG has	Please see issue 8.	Please see issue 8.	The proposed amendment is accepted. Both paragraphs on page 87 of the ERG report have been deleted.

misunderstood the SPC relating to monitoring of ranibizumab in this indication and do not understand how this translates into “1-stop” and “2-stop” scenarios. Please see full detail in issue 8.			

Issue 32 Page 97

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 97. The TPMs are based upon 112 patients for ranibizumab, 56 patients for vPDT for baseline to month 3 and 82 patients for vPDT for 3 months to 12 months as this latter is drawn from the vPDT arm of the VIP trial. Given the 8 health states of the model, this is in the context of being required to populate TPMs with 64 entries. While the patient numbers are typically clustered around the principal diagonal of the TPM with zero probabilities for the more extreme transitions, this still results in quite a large number of probabilities being populated by relatively few patients. Based upon the patient numbers supplied in response to the ERG clarification questions, the empty columns, the number of populated cells, the number of populated cells with only one patient, the number of unpopulated cells and the number of unpopulated cells that are "holes" in the TPMs, can be presented. **Factually incorrect as written as this represented the case only in scenario 1.** Novartis also	The ERG report should acknowledge that Novartis acknowledged this issue within the submission and consequently presented 2 other scenarios, one of which addressed the lack of sample size within the full matrix. Furthermore, that there were inherent advantages and disadvantages with all methods. Nonetheless, all three methods had only minor differences in their results.	It is a misleading statement by omitting a key scenario analysis for this very issue that was transparently reported within the submission. It is important to let the committee know that Novartis recognised this issue and reported results using another method with very similar results. This should not raise unfounded doubt about the validity of the modelling methodology.	To address the problem raised by the manufacturer, the following additional section has been added to **page 76** of the ERG report: *Scenario analyses pooling patient level data* In the light of some transitions being populated with small patient numbers, the manufacturer also presents two scenario analyses use alternative calculations for the transitions. • Scenario 2: Calculating the transitions for the top two health states based upon the patient level data, but pooling the patient level data for the other health states with the additional assumption that patients could only gain or lose between two and four lines between cycles. This scenario is undertaken to try to avoid the possible ceiling effects that the top two health

supplied results for 2 additional scenarios. The “constant across VA methodology” ameliorates the holes as discussed in the subsequent paragraph hence undertaking the work and presenting NICE with the results.			states might impose upon the analysis of scenario 3 outlined below. • Scenario 3: Pooling the patient level data with the additional assumption that patients could only gain or lose between two and four lines between cycles. The more usual approach for a pooled analysis would be for the likelihoods of gains and losses in the ranibizumab arm to have been conditioned by the relative risks of these for vPDT. These relative risks could have been drawn from the Novartis phase III trial for the first 3 months, and from the indirect comparison with the VIP trial thereafter. The scenario analyses results in an estimated 0.43 QALY gain and a £4,078 cost saving for scenario 2, and in an estimated 0.42 QALY gain and £4,032 cost saving for scenario 3: roughly the same QALY gain but somewhat larger cost savings compared to the base case. The intuition underlying

			this is not clear.”

Issue 33 Page 98

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 98. “This may question the reliability of the approach for the base case modelling and whether the patient numbers within the trials provide sufficient patient level data to be able to sensibly populate a model with 8 health states and the resulting 64 cell TPMs.” Please see exact comment above (issue 32) as it relates to the same issue.	As per issue 32.	As per issue 32.	The proposed amendment is accepted. An additional section has been added to **page 76** of the ERG report. Please see ERG response to Issue 32 above.

Issue 34 <u>Page 98 - KEY POINT</u>

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 98. "Assumed a two stop model for monitoring and dosing." Incorrect as explained in detail within issue 8.	As per issue 8.	As per issue 8.	The proposed amendment is accepted. The following bullet point and related footonote on page 98 have been deleted: "Assumed a two stop model for monitoring and dosing[1]. *Implemented within the Cost_Inputs worksheet by setting cell E30=12, E31=4, G30=4 and G31=4"*

Issue 35 Page 101

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 101. “The differing proportions of non-subfoveal involvement in the ranibizumab arm of the Novartis phase III trial and the vPDT arm of the VIP trial.” This is factually incorrect and misleading as the subfoveal sub-population in the Novartis phIII trial (disease activity arm) actually had a slightly larger treatment effect (difference in means) versus vPDT of 9.1 letters compared to 8.9 for juxtafoveal and -15 letters versus the 1 patient with an extrafoveal lesion treated with vPDT. Therefore the ERG statement is reversed in the opposite direction – i.e. to the detriment of ranibizumab.	Either the ERG report is modified to state that their speculation around non-subfoveal involvement was not founded by the evidence provided herein or the statement is withdrawn.	This speculation is factually incorrect and misleading. It is important that this is amended in order that this invalid critique of the economic submission is not put to the committee. Indeed, the evidence suggests to the contrary as presented in the description in the left column.	Please see ERG response to Issue 7. No revision required.

Issue 36 Page 104

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 104. “In particular, the higher rate of non-subfoveal involvement in the Novartis trial may benefit ranibizumab.” This is factually incorrect and misleading as the subfoveal sub-population in the Novartis phIII trial (disease activity arm) actually had a slightly larger treatment effect (difference in means) versus vPDT of 9.1 letters compared to 8.9 for juxtafoveal and -15 letters versus the 1 patient with an extrafoveal lesion treated with vPDT. Therefore the ERG statement is reversed in the opposite direction – i.e. to the detriment of ranibizumab.	Either the ERG report is modified to state that their speculation around non-subfoveal involvement was not founded by the evidence provided herein or the statement is withdrawn.	This speculation is factually incorrect and misleading. It is important that this is amended in order that this invalid critique of the economic submission is not put to the committee. Indeed, the evidence suggests to the contrary as presented in the description in the left column.	Please see ERG response to Issue 7. No revision required.

Issue 37 Page 106

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 106. “The Novartis phase III trial, from which effectiveness data for ranibizumab are drawn, and the VIP trial, from which the majority of effectiveness data for vPDT are drawn, are not balanced in terms of the proportion of patients presenting with non-subfoveal involvement.This may result in an inflated effect of the benefit of ranibizumab.” This is factually incorrect and misleading as the subfoveal sub-population in the Novartis phIII trial (disease activity arm) actually had a slightly larger treatment effect (difference in means) versus vPDT of 9.1 letters compared to 8.9 for juxtafoveal and -15 letters versus the 1 patient with an extrafoveal lesion treated with vPDT. Therefore the ERG statement is reversed in the opposite direction – i.e. to the detriment of ranibizumab.	Either the ERG report is modified to state that their speculation around non-subfoveal involvement was not founded by the evidence provided herein or the statement is withdrawn.	This speculation is factually incorrect and misleading. It is important that this is amended in order that this invalid critique of the economic submission is not put to the committee. Indeed, the evidence suggests to the contrary as presented in the description in the left column.	Please see ERG response to Issue 7. No revision required.

Issue 38 Page 107

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 107. “Adverse events were only included if they affected more than around 5% of the patients in the relevant arm of the Novartis phase III trial. Subsequently, retinal tears were not included.” This is incorrect. As per the clarification response to question B1, there were **no adverse events of retinal tear (for the licensed and modelled posology) that were suspected as related to ocular injection or the study drug.** [redacted]	Remove the point below relating to retinal tears. “Adverse events were only included if they affected more than around 5% of the patients in the relevant arm of the Novartis trial. Consequently, retinal tears were not included. Retinal tears, if untreated, may lead to retinal detachment with the subsequent risk of visual loss. This is likely to be the case especially in eyes affected by pathological myopia in which retinal detachment rates are already higher than those in the general population.”	The statement for the justification for not including retinal tears within the economic model is factually incorrect. It is important the committee are aware of the evidence presented to them within the Novartis phase III study and any implications to economic modelling. The ERG statement implies that Novartis have been biased in their approach for not including retinal tears when in fact there was no evidence to substantiate this being the case.	The proposed amendment is accepted. This bullet point on page 107 of the ERG report has been deleted.

[redacted] The economic model specifically evaluates the cost effectiveness of the licensed posology in this indication (ranibizumab – Group II) and thus this AE did not meet the criteria for inclusion.			

Issue 39 Page 104

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 119. "Two sets of deterministic results are presented within the submission, those of the base case of section 7.7.6 and those of appendix 16." This is factually inaccurate and misleading. The results in appendix 16 are not presented in the submission. Appendix 16 refers to an early model development meeting held with UK ophthalmologists in order to validate modelling assumptions. Novartis stated clearly in the clarification response that these results were not valid and did not constitute part of the submission.	Remove reference to these results as they are not valid and do not constitute results for the NICE submission	The statement is inaccurate and misleading. The appendix was attached as a means of demonstrating any early discussions around modelling assumptions only. The ERG asked for clarification regarding these results and Novartis responded that they did not constitute results as part of the submission.	To address the problem raised by the manufacturer, the following paragraph on page 119 of the ERG report (not page 104 as stated by the manufacturer): "Two sets of deterministic results are presented within the submission, those of the base case of section 7.7.6 and those of Appendix 16. The deterministic results of Appendix 16 include pairwise comparisons with vPDT, observation and bevacizumab." **has been changed to:** "The deterministic results of Appendix 16 of the submission include pairwise comparisons with vPDT, observation, and bevacizumab. The manufacturer maintains that '*these results were attached as a mean of demonstrating any early discussions around modelling assumptions only*'."

Issue 40 Page 121

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 121. “Lacono 2012” The author of the paper is spelt incorrectly.	Iacono 2012 Please note that it is an “i” nor an “L”	Making sure that the information within the ERG report is accurate and correct	The spelling mistake on page 121 has been amended.