NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Aflibercept for treating diabetic macular oedema

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
Bayer Pharma	We welcome the preliminary guidance from NICE to recommend aflibercept as an option for the treatment of visual impairment caused by diabetic macular oedema (DMO) for eyes with a baseline central retinal thickness (CRT) of 400 micrometres or more. However, aflibercept is a clinically and cost effective option for all patients with visual impairment due to DMO including those with a baseline CRT of under 400 micrometres and there is an unmet need for safe and effective treatments in these patients. Our key points are as follows: • The evidence of the supremacy of aflibercept compared with ranibizumab in terms of mean change in best correct visual acuity (BCVA) from baseline has not been adequately considered by the Appraisal Committee • The ERG base case, upon which the recommendations have been based, includes several assumptions that are not supported by robust evidence or adequate justification. The amendment of these assumptions to provide a more robust base case would indicate that aflibercept is a cost effective use of NHS resources in all patients with visual impairment due to DMO assuming a threshold of £20,000-£30,000 per QALY gained.	Comment noted. No action required. Comments noted. Details of the Committee's consideration of the company's new evidence are given in FAD sections 4.11- 4.18.

Consultee	Comment	Response
Bayer Pharma	In patients with a baseline CRT of less than 400 micrometres, it has been highlighted that current standard of care has evolved and that clinicians watch and wait to treat with ranibizumab when the CRT reaches the 400 threshold defined by previous NICE guidance (TA274). Consideration of a comparison versus watch and wait indicates an improved cost effectiveness profile for aflibercept in that subgroup.	Comment noted. The Committee noted that the company had not submitted any new evidence for this subgroup in its response to consultation on the appraisal consultation document. The Committee noted that it had not been presented with evidence on the cost effectiveness of aflibercept compared with bevacizumab or with a 'watch and wait' strategy.
Bayer Pharma	**Q1 Has all of the relevant evidence been taken into account**? *Significantly greater mean change in visual acuity with aflibercept compared with ranibizumab* In their consideration of the evidence (section 4.6), the Appraisal Committee have not fully considered the results of the indirect comparison and network meta-analysis that reported a (statistically) significantly better efficacy result with aflibercept compared with ranibizimab in terms of mean change in BCVA from baseline to 52 weeks.	Comment noted. Section 4.6 of FAD has been updated to include the statistically significant result for mean change in best corrected visual acuity (BCVA).

Consultee	Comment	Response
Bayer Pharma	**Q2 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The recommendations have been based on the results of the ERG economic base case. The following aspects of the ERG base case are insufficiently robust in terms of the evidence available and there is inadequate justification for the inputs and assumptions used:	Comment noted. Please see below responses to specific issues raised.

Consultee	Comment	Response
Bayer Pharma	*Issue 1: Inconsistent use of clinical trial evidence to source resource use inputs and assumptions in year 1* The ERG indicated that the clinical trial data, as opposed to evidence of expected or current resource use, should be used as the source of resource use inputs and assumptions in the economic model. However, this approach was not applied consistently in the ERG base case. Moreover, this approach is only relevant where treatment effect and safety inputs are also taken from those clinical trials (i.e. in year 1 alone). **Administration and monitoring with laser in year 1** The number of laser administrations in the included clinical studies in year 1 was based on monthly monitoring visits. This was also the case in the included ranibizumab studies where the decision to administer an injection was based on monthly monitoring in the first year. Therefore, the number of administrations and the associated efficacy from the included clinical studies was based on frequent monitoring. In VIVID and VISTA, aflibercept was administered according to a fixed regimen and was not determined by monthly monitoring visits. **Number of ranibizumab injections in year 1** The ERG excluded a key study, DRCR.net Protocol I, when estimating the number of ranibizumab injections in the first year. Whilst we accept that it is not ideal to mix mean and median estimates, the exclusion of a key study in the network meta-analysis from the estimate adds uncertainty to the estimate of 7.43 used by the ERG in their base case (DRCR.net Protocol I reported a median of 9 injections).	Comments noted. The new evidence provided by the company to support its view that the ERG's base case was insufficiently robust in terms of the evidence available are detailed in FAD sections 3.26-3.28. The ERG's critique of the new evidence is provided in the FAD section 3.29. The Committee's considerations of the new evidence are detailed in FAD sections 4.12-4.14.

Consultee	Comment	Response
Bayer Pharma	*Issue 2: Inappropriate resource use inputs and assumptions in year 2* Efficacy data from clinical studies were not used in year 2 in the ERG base case. This was mainly due to the fact that it was not possible to conduct an indirect comparison of aflibercept versus ranibizumab in year 2 due to the confounding aspect of additional treatment administered in the clinical studies. Therefore, resource use inputs from clinical studies are less relevant from year 2 onwards.	Comments noted. The new evidence provided by the company to support its view that the ERG's base case was insufficiently robust in terms of the evidence available are detailed in the FAD, sections 3.26-3.28. The ERG's critique of the new evidence is provided in the FAD, section 3.29. The Committee's considerations of the new evidence are detailed in FAD sections 4.12-4.14.

Consultee	Comment	Response
Bayer Pharma	**Number of injection visits assumed for aflibercept in the revised ERG base case in year 2** The ERG estimated 5.45 injections in the 2nd year for aflibercept. This is not in line with the Summary of Product Characteristics (SmPC) for aflibercept, the presented data from VIVID/VISTA, clinical opinion, and is an overestimate of the number of injections in year 2. • The SmPC posology for aflibercept differs to the treatment protocol in VISTA and VIVID beyond week 52. The trial protocols specified a bi-monthly treatment regimen in year 2. The SmPC describes a treat-and-extend dosing regimen, so that bi-monthly treatment intervals may be extended after the first year. This would lead to potentially fewer aflibercept injections in expected UK clinical practice than those reported in the clinical trials. • "After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and anatomic outcomes." • Moreover, the economic model does not include comparative efficacy data from the VIVID, VISTA or RESTORE trials in year 2 as an indirect comparison could not be conducted. Therefore, assumptions of equivalent efficacy for aflibercept and ranibizumab have been made in year 2. This means that the number of injections stated in clinical trials is not directly relevant to the other inputs assumed in the model in year 2. Given an assumption of equivalent efficacy, an assumption of equivalent injections would be more aligned, particularly given the significantly better results with aflibercept cited in our response to Q1.	Comment noted. Section 3.19 and 3.27 explains the ERG's rationale for using 5.45 injections in year 2. Section 3.31-33 includes the results of a sensitivity analysis which explored the impact on the ICER when the number of aflibercept injections in year 2 is reduced to 4.0. Details of the Committee's consideration and conclusions on the appropriate number of injections are given in section 4.12.

Consultee	Comment	Response
Bayer Pharma	• The figure used by the ERG is also not in line with the average mean number of active injections reported at week 100 from VIVID and VISTA (13.5 and 13.6 injections respectively) as presented in our submission (p194). Given the mean number of active injections at week 52 was 8.55, this leads to a difference of nearer 5 injections administered in year 2. • The ERG also state that their estimate is likely to be an underestimate of number of aflibercept injections in year 2 as reporting from VISTA and VIVID was at week 100, not week 104. However, the ERG omits to mention that RESTORE also reported up to month 23. • It is also inappropriate to compare the VISTA, VIVID, and RESTORE studies in year 2 as there is insufficient information on the RESTORE population to compare the studies. The reason for the non-enrolment of 63 patients in RESTORE in year 2 was 'not well documented' (Lang, et al. 2013).	

Consultee	Comment	Response
	Number of laser visits in year 2 It was assumed in the model that 1 laser administration visit occurred in year 2 and patients stayed in the same health state that they were in at week 52. It should be noted that this was conservative given the comparative efficacy data in year 1 from VISTA and VIVID shows the superiority of aflibercept versus laser. Moreover, as presented in our submission (p61), 35-41% participants receiving laser in VIVID/VISTA received additional rescue treatment, including aflibercept, through to week 100 and these data (p100 of the submission) were excluded from the primary analysis that showed a mean change in BCVA of 0.7 to 0.9 letters to week 100 in VIVID and VISTA respectively.	Comment noted. No change to FAD.

Consultee	Comment	Response
Bayer Pharma	*Issue 3: Inappropriate estimate of the unit cost of laser administration visits* In previous appraisals, the administration cost of an injection has been costed at the same price as a laser visit. We heard anecdotally from several consultant ophthalmologists that a laser visit is actually charged at a higher cost in clinical practice than an injection visit. Unfortunately, NHS reference costs do not distinguish a laser administration cost. • In turn, the ERG has included a lower cost for laser in their base case. This is based on feedback from one individual clinician who is based in Northern Ireland and may not fully represent all of England and Wales or clinical practice in general. • The costs used in the concurrent appraisal of dexamethasone intravitreal implant for DMO were £116.68 for both laser and injection administration visits (monitoring was costed at £80.04, with £18.06 for an optical coherence tomography (OCT)). • In addition, to note, the injection administration cost used in the submitted model (£196) included the cost of monitoring. This cost was based on that used by the ERG in NICE appraisal TA305 aflibercept for macular oedema secondary to central retinal vein occlusion (CRVO). An administration visit is assumed to include the cost of a monitoring visit and therefore the cost of an OCT is added to the baseline unit cost for administration. Therefore, to include the assumption that 50% of treatments are administered using a two-stop system (separate administration and monitoring) would double count the cost of monitoring visits.	Comments noted. The new evidence provided by the company to support its view that the ERG's base case was insufficiently robust in terms of the evidence available are detailed in FAD sections 3.26-3.28. The ERG's critique of the new evidence is provided in FAD section 3.29. The Committee's considerations of the new evidence regarding the cost of laser administration and the number of laser visits are detailed in FAD sections 4.13

Consultee	Comment	Response
Bayer Pharma	*Issue 4: Inappropriate estimate of fellow eye involvement using VIVID and VISTA data* It is not stated in the ERG report that the rate of fellow eye involvement was amended in the ERG base case. However, it appears that this was the case. The rate of fellow-eye involvement recommended by the ERG at baseline is inaccurate. • Several epidemiology publications for DMO in the UK highlight that the number of people with clinically significant DMO is much lower than those with any form of DMO.	Comment noted. The new evidence provided by the company to support its view that the ERG's base case was insufficiently robust in terms of the evidence available is detailed in FAD sections 3.27-3.28. The Committee's considerations of the new evidence regarding the fellow eye involvement are detailed in FAD section 4.15.
Bayer Pharma	*Issue 6: Availability of shift tables from VIVID and VISTA* The ERG criticised the use in our submitted model of monthly transition probabilities based on the published data for VISTA and VIVID and stated that it would be more appropriate to use patient level data from VIVID and VISTA. This data was available in the submitted model versus laser. Individual patient data for ranibizumab is not available so the model versus ranibizumab was based upon the network meta-analysis data. However, the ERG decided not to use this data for the laser comparison and did not ask for clarification on using this data. Using this data improves the ERG base case versus laser.	Comment noted. The new evidence provided by the company to support its view that the ERG's base case was insufficiently robust in terms of the evidence available are detailed in FAD sections 3.27-3.28. The Committee's considerations for the use of patient-level data are detailed in FAD section 4.17.

Consultee	Comment	Response
Bayer Pharma	*Other minor considerations* As stated in our response to the draft scope, the rates of glaucoma for aflibercept based on VIVID/VISTA were very low and it was not a particularly relevant outcome to include in the base case for aflibercept. However, there was a minor error in the glaucoma rates used in the submitted model. Removing the incorrect glaucoma rates from the economic model results in a small reduction in the total stated costs of aflibercept in our submitted base case by approximately £220.	Comment noted. No action required.

Consultee	Comment	Response
Bayer Pharma	**Incorporating watch and wait as the appropriate comparator for patients with CRT at baseline of <400 micrometres** It was highlighted to the Appraisal Committee that laser is not the most appropriate comparator for the subgroup of DMO patients with a baseline CRT of less than 400 micrometres at baseline. Although not included in the scope for this appraisal, watch and wait was subsequently cited as the appropriate comparator. The ICER versus watch and wait would be considerably improved compared to that proposed by the ERG versus laser. Therefore, at this stage, we cannot incorporate watch and wait into the current model without additional analysis. However, we have assessed the potential evidence available and made estimates of how this would improve the cost effectiveness profile of aflibercept in the <400 micrometres subgroup. Whereas, for observation, the main cost would be regular monitoring, the cost for watch and wait would be monitoring and then adding on the cost of treatment when people qualify for treatment at a later time. One might imagine that the cost of treatment and administration is similar whether it is delivered immediately or delayed. There is no evidence at this point to suggest that treatment continues indefinitely or that survival times would affect the duration of treatment. Assuming that monitoring takes place before and after treatment, cost of monitoring may be higher for those treated later rather than later as monitoring would be frequent enough to ensure immediate treatment when the NICE criteria are met.	Comment noted. The Committee noted that the company had not submitted any new evidence for this subgroup in its response to consultation on the appraisal consultation document. The Committee noted that it had not been presented with evidence on the cost effectiveness of aflibercept compared with bevacizumab or with a 'watch and wait' strategy. The Committee concluded that, based on its consideration of all the evidence (including no evidence of its cost effectiveness against other treatment strategies), aflibercept is not a cost-effective use of NHS resources compared with laser treatment for people with a CRT of less than 400 micrometres and is therefore not recommended. See FAD section 4.19.

Consultee	Comment	Response
	Due to the recent introduction NICE guidance into UK clinical practice for DMO, there is a paucity of long term data to indicate the impact of delaying treatment on the efficacy and safety of treatments, in addition to the costs. Anecdotal evidence suggests that treating earlier is the most appropriate treatment strategy. Patients will have longer to benefit following treatment in the long term	
Bayer Pharma	**Q3.** ***Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?*** **Technology** Section 2.3 – Description of posology The ACD cites only part of the posology from the Summary of Product Characteristics (SmPC). The posology should be cited in full as follows to avoid misleading prescribing information: • The recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitres. • Eylea treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections. • After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and anatomic outcomes. The schedule for monitoring should be determined by the treating physician. • If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Eylea should be discontinued.	Comment noted. FAD section 2.3 has been updated.

Consultee	Comment	Response
Bayer Pharma	**Clinical Effectiveness** Section 3.4 – Description of subgroup data provided by the manufacturer A subgroup analysis of the primary outcome was also provided (see page 335 of the original submission). Moreover, here and throughout the submission, the subgroup has been defined as greater than 400 micrometres. This should be 400 micrometres and greater.	Comment noted. All FAD references to the sub group now read: “400 micrometres or more”.
Bayer Pharma	Section 3.9 – Description of network meta-analysis by the manufacturer The description of the network meta-analysis does not mention the inclusion of the DRCR.net Protocol I study. Moreover, the ACD does not mention the limitations described in the submission with regard to the comparisons with corticosteroids. An indirect comparison with the pivotal MEAD study for dexamethasone was not possible as there was no common comparator.	Comment noted. FAD section 3.9 provides an overview of the company’s network meta-analysis only. It has now been updated to clarify the limitations of the comparisons with corticosteroids.

Consultee	Comment	Response
Bayer Pharma	Section 3.13 – Description of the SmPC This section of the ACD provides an inaccurate description of the SmPCs for aflibercept and ranibizumab. We would recommend that this section be reworded in line with the wording of the SmPCs. The marketing authorisation for aflibercept specifies the fixed regimen of injections in the first year (8 injections). The SmPC does not mention injection visits doubling as monitoring visits. In addition, the revised SmPC for ranibizumab does not 'reduce the number of monitoring visits needed'. The previous reference to monthly monitoring of visual acuity has been replaced with alternative wording. The SmPC for aflibercept specifically states that no additional monitoring is required in year 1. This is not the case for ranibizumab. Aflibercept is associated with a pro-active fixed regimen in the first year whereas ranibizumab is associated with a reactive regimen based on monitoring. In addition, the ERG's revised economic model uses number of injections from the clinical trials. The number of injections for ranibizumab in year 1 in the RESTORE, REVEAL, and DRCR.net studies was based on frequent monitoring. Therefore, it is appropriate, if using numbers of injections from the studies, to take account of this frequent monitoring in the trials. This was not the case in VISTA and VIVID where the fixed regimen in year 1 and 2 was protocol driven regardless of monitoring.	Comment noted. FAD section 3.13 has been updated to clarify where the monitoring assumptions in the model were derived.

Consultee	Comment	Response
Bayer Pharma	Section 3.20 – Description of the ERG base case It is inappropriate to use the phrase 'corrected errors identified during its critique of the model' as there remains uncertainty with the inputs and assumptions used by the ERG in their base case. Even the ERG in their report acknowledge that, in terms of the dosing rates in the second year, "It is possible that this is more a reflection of the differences between the trials than any difference that will apply in the real world" (p136). It would be more appropriate to use 'The ERG built an exploratory base-case analysis using their preferred inputs and assumptions identified during the critique of the model…' The ERG base case assumes 8.55 injections of aflibercept in the first year. This is higher than the anticipated number of aflibercept injections in clinical practice in the UK in year 1.	Comments noted. FAD section 3.19 has been updated to amend the wording introducing the ERG model changes.
	• Our submission stated that the number of aflibercept injections specified in the summary of product characteristics (SmPC) is 8 injections in the first year. The SmPC refers to 5 consecutive monthly monitoring visits followed by one injection every other month. There are 12 months in a calendar year. Therefore, this amounts to 8 injections in total according to the fixed regimen in the marketing authorisation..	Comment noted. See FAD section 3.29 for the ERG's rationale and FAD section 4.12 for the Committee's consideration of the number of aflibercept injections.

Consultee	Comment	Response
Bayer Pharma	• The treatment protocol in VISTA and VIVID studies varied slightly in comparison with the licensed posology as the clinical trial protocols specified 4-weekly and 8-weekly injections rather than monthly or bi-monthly.	Comment noted. See FAD section 3.29 for the ERG's rationale and FAD section 4.12 for the Committee's consideration of the number of aflibercept injections.
	• The ERG argued that the number of injections should be based on the clinical trial data. However, the ERG excluded information from a ranibizumab study to inform the estimated number of ranibizumab injections. The ERG excluded the median estimate of 9 injections from the DRCR.net Protocol I study on the basis that information was not available on the mean. The lowest estimate for the number of ranibizumab injections based on clinical studies has been used by the ERG.	Comment noted. See FAD section 3.29 for the ERG's rationale and FAD section 4.12 for the Committee's consideration of the number of aflibercept injections.
	• The SmPC incorporates a stopping rule if visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment. This would reduce the average number of injections in clinical practice, in addition to those discontinuing for other reasons, as already incorporated into the economic model	Comment noted. No action required

Consultee	Comment	Response
Bayer Pharma	**Section 3.25, 4.5, 4.13 - Baseline CRT subgroup data** In B7, C6, C7, and C9 of the response to clarification, we provided extensive additional subgroup data, including risk ratios, to that provided in the original submission. These were provided both for the pooled VIVID and VISTA studies and for each study separately. We also provided a cost effectiveness analysis versus ranibizimab in the subgroup for 400 micrometres and over (page 337 of original submission). It is inappropriate to use the following wording: 'there was no significant improvement over laser in visual acuity outcomes'. Results indicate that improvements achieved with aflibercept over laser in vision and other outcomes were robust and similar regardless of baseline CRT. The ERG raised the question of whether the VISTA study should be included in the base case and whether it was appropriate to pool data from VISTA and VIVID. The pivotal VISTA study is a relevant clinical study to the assessment of aflibercept as the marketing authorisation for aflibercept is the treatment of adults with visual impairment due to diabetic macular oedema (DMO) is not limited to a particular subgroup of patients or a particular line of therapy. .	Commented noted. FAD section 3.16 states that a cost-effectiveness analysis for the comparison of aflibercept with ranibizumab for the subgroup of patients with CRT of 400 micrometers or more had been undertaken by the company. Comment noted. Section 4.5 of the Committee considerations section has now been updated to include the significant result for mean change in BCVA. Comment noted. No action required

Consultee	Comment	Response
Bayer Pharma	Moreover, participants in the VISTA study would not differ particularly to those seen in clinical practice in the UK which would include those who have received a variety of prior treatments, treatment naïve patients, and patients with different levels of central retinal thickness. Ignoring the VISTA study would exclude a considerable piece of evidence from the appraisal. Extensive data was provided both pooled and separately by individual study. As discussed in the ACD, about a quarter of the patients in the VISTA and VIVID study had a CRT of less than 400 micrometres at baseline. This was a post hoc sub-group analysis and, hence, the study was not designed specifically to assess this subgroup.	Comment noted. No action required.

Comments received from clinical experts and patient experts

None.

Comments received from commentators

Novartis	**1 Has all the relevant evidence been taken into account?** Novartis conducted a systematic review and network meta-analysis in DMO relevant to the NICE decision problem in Q1 2014. The outputs of this work were published on July 16th in PLOSone journal. The manufacturer appears not to have considered all the appropriate and relevant evidence within their network meta-analysis. Of significance and impacting the effect size of aflibercept was not including the phase II Da Vinci study despite there being an appropriate aflibercept licensed 2q8 arm that informs the relative effectiveness estimates in the network. Furthermore, Novartis were not sure why other key evidence that informed the ranibizumab node (central to the decision problem) was omitted. Table 1 below highlights the evidence that was omitted from the manufacturer's network meta-analysis. Table 1. Key evidence omitted from the manufacturer's network meta-analysis and relevant to the decision problem. **Treatment Node** — **Omitted Evidence** **Aflibercept** — Da Vinci[2] **Ranibizumab** — READ-2 [3] DRCR.net (Protocol I)[4] RESOLVE[5]	Comment noted. FAD section 4.6 has been updated. The discussion on clinical effectiveness now includes reference to this analysis.

Novartis	In addition to the ommissions as described above, the manufacturer has chosen to include the REVEAL study as part of the network to inform the relative effectiveness estimate of ranibizumab. This study evaluated ranibizumab in an exclusively Asian population and is thus not representative of the UK wider population. Moreover, it should not be included in this evidence network for reasons of heterogeneity of inclusion criteria compared to the other studies.	Comment noted. FAD section 3.22 highlights that the ERG undertook sensitivity analysis which excluded the REVEAL trial from the analysis.
	The other critical flaw in the approach adopted by the manufacturer with respect to the network meta-analysis is that of not accounting for important covariates that impact the relative effectiveness estimates. More specifically, within randomised controlled trials in the retina field, it is imperative to match the study and control arms for baseline best corrected visual acuity (BCVA). This is essential as BCVA as a measurement scale is subject to a ceiling effect – simply put the higher your baseline vision, the lower the delta from baseline would be attainable7. There are significant differences with respect to the aflibercept pivotal VIVID8 & VISTA8 studies baseline BCVA and the ranibizumab studies – specifically that the VIVID (58.8 letters) & VISTA (59.4 letters) studies have a lower baseline BCVA compared to the pivotal ranibizumab RESTORE13 (64.8 letters) study and therefore would be more likely to have a larger mean change from baseline BCVA.	Comments noted. No change required.

Novartis	Novartis explained this critical issue in detail at the NICE scoping meeting for this appraisal and the chair agreed that this should be accounted for within the network meta-analysis. Indeed, adjustment for important disease modifiers is specifically part of the NICE reference case15 (Section 5.2.7). The effect of this discrepancy in baseline vision was empirically adjusted for via covariate adjustment within the Novartis published network meta-analysis1.	Comment noted. No change required.
	Of particular importance to the manufacturer's economic model was the important dichotomous outcome - the proportion of patients obtaining a gain of ≥ 10 letters. This dichotomous outcome was of specific significance threefold; firstly the manufacturer's model adopted a Markov structure with 10 letter states (page 243, Table 66 of manufacturer's submission); secondly the differences between aflibercept and ranibizumab were small and therefore most patients would be affected by transitioning to the adjacent Markov state rather than gaining multiple states; thirdly that very few patients lost vision and thus the proportion of patient losing ≥ 10 letters is of minor relevance. The results of the Novartis network meta-analysis, when adjusting for baseline vision for this pivotal outcome, demonstrate that ranibizumab is in fact numerically favoured, which is in fact in the opposite direction of the evidence presented within the ACD. This would therefore impact the ICER such that aflibercept would in fact be dominated (less effective and costing more).	Comment noted. No change required.

Novartis

Table 2. Pair-wise odds ratios (95% credible intervals) from the random treatment effects model with baseline BVCA included as a covariate.

	Laser	Ranibizumab 0.5 mg PRN	Aflibercept 2.0 mg bi-monthly
Laser	–		
Ranibizumab 0.5 mg PRN	5.50 (2.73–13.16)*	–	**1.59 (0.61–5.37)**
Aflibercept 2.0 mg bi-monthly	3.45 (1.62–6.84)*	0.63 (0.19–1.63)	–
Ranibizumab + laser	4.05 (2.16–8.65)*	0.74 (0.35–1.46)	1.18 (0.45–3.66)
Sham	0.85 (0.19–4.56)	0.15 (0.04–0.60)*	0.25 (0.05–1.65)

*p<0.05

Pair-wise odds ratios indicate the relative treatment effect for the treatments compared in the network meta-analysis. A statistically significant odds ratio greater than 1 indicates that the treatment in the corresponding row is superior to the treatment in the corresponding column.

BCVA, best-corrected visual acuity; PRN; pro re nata (as needed).

Novartis	<u>Evidence post committee meeting</u> Subsequent to the appraisal committee meeting (21st January 2015), an article from The Diabetic Retinopathy Clinical Research Network was published in the New England Journal of Medicine that compared the relative efficacy and safety of an unlicensed, pro re nata (PRN) posology of aflibercept (EU label is loading with 5 consecutive injections and then fixed bimonthly for the first year), unlicensed intravitreal bevacizumab, and an unlicensed dose/posology of ranibizumab. This study is known more commonly in the medical retina field as the Protocol T study. This evidence for the comparison versus ranibizumab is not relevant to the decision problem and appraisal committee since the comparator arm of ranibizumab was dosed at 0.3mg PRN, which is an unapproved dose of ranibizumab in the UK – the license is for 0.5mg10. Indeed 0.3mg PRN is not an approved and tested posology in any other country in the world18. Lucentis 0.3 mg is approved in the US only for monthly treatment in DME. Furthermore, the Protocol T study was only a partially blinded study and thus the results should be interpreted with due caution as with any non-double blinded source of evidence, and in alignment with the methodology checklist detailed in Appendix C of the NICE Guidelines Manual.	Comments noted. FAD section 4.5 has been up-dated to take account of the Committee's consideration of the Protocol T study.

Novartis	These critical issues notwithstanding, Protocol T demonstrates a non-clinically relevant gain of +2.1 letters with an unlicensed posology of aflibercept compared to an untested and unlicensed dose and posology of ranibizumab on the primary endpoint and therefore Novartis agrees with the already established page 19 committee conclusion on relative effectiveness and that Protocol T does not change this: “The Committee concluded that aflibercept is likely to have similar clinical effectiveness to ranibizumab, based on the results of the network meta-analysis and clinical expert opinion.” The provisional recommendation for aflibercept in DMO is specifically bound by the following conditions: The eye has a central retinal thickness of 400 micrometres or more at the start of treatment and The company provides aflibercept with the discount agreed in the patient access scheme. In terms of the above restriction on central retinal thickness of 400 micrometres, the Protocol T study provides some very limited evidence for the comparative effectiveness of aflibercept versus unlicensed intravitreal bevacizumab, and an unlicensed dose/posology of ranibizumab in those patients for whom it is not currently provisionally recommended, i.e. those with thinner retinas of < 400 micrometres (see Table S8 Appendix, page 27 of 52); 112 patients with < 400 micrometre retinas were compared – the mean change from baseline BCVA was similar with all three treatments (+10.9 letters with aflibercept, +10.1 letters with an untested and unlicensed dose of ranibizumab, and +9.5 letters with unlicensed intavitreal bevacizumab). Therefore, this would have no impact on the provisional recommendation.	

Novartis	**2 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Page 5, Section 3.3. The ACD states: "…the results showed a statistically significant improvement for all outcomes in both trials in people having aflibercept compared with laser." This statement is incongruous and false as confirmed by the next sentence that follows: "No statistically significant differences were observed in either trial for the NEI-VFQ-25 Distance Activities subscale."	Comment noted. FAD Section 3.3 has been amended to remove this sentence.
Novartis	Page 7, Section 3.9. As has been described in the preceding section of this document, the inclusion of the REVEAL trial is not appropriate in the context of the NICE decision problem. This study evaluates ranibizumab in an exclusively Asian population and is thus not representative of the UK wider population. Moreover, it should not be included in a network for reasons of heterogeneity between the other studies inclusion criteria.	Comment noted. FAD section 3.22 has been updated to include the ERG's rationale for excluding REVEAL in its sensitivity analysis.

Novartis	Page 7, Section 3.9. The ACD states: “Results of the network meta-analysis showed a statistically significant improvement in visual acuity as measured by BCVA mean change from baseline and loss of 10 or more ETDRS letters for aflibercept 2Q8 compared with ranibizumab” The results from the manufacturer’s network meta-analysis are misleading as there has been no attempt to empirically account for the significant discrepancies with respect to baseline BCVA (important disease modifier) between the aflibercept and ranibizumab studies as stipulated in the NICE reference case and agreed at the NICE scoping meeting for this appraisal. This specific issue is discussed at length in the previous section (page 2) of this document.	Comment noted. No change required.

Novartis	Page 8, Section 3.10. Novartis notes that the assumption for fellow eye involvement at baseline of 46.5% was not derived from the aflibercept trial data and not as per TA27412 but rather by expert opinion. The value used in a scenario analysis in TA274 was 35%. This is important since the model is very sensitive to this parameter as confirmed by the tornado plot (Figure 70) on page 316 of the manufacturer's submission. More specifically, if one increases the proportion of fellow eye involvement as has been done within the present submission (by 11.5%), the incremental QALYs also increase and the resultant ICER being lower. Moreover, the manufacturer has not accounted for the value of 35% even within the lowest bound of the sensitivity analysis, which ranged from 37.2% to 55.8% (Table 76, page 263, manufacturer's submission). Succinctly put, the net result will be a less favourable ICER than has been determined thus far verses all comparators. The ICER (page 22, Section 4.13) of significance in the key decision context is: "…for people with a CRT of greater than 400 micrometres was £21,958 per QALY gained" Adjusting the level of fellow eye involvement to 35% will increase the ICER further into the normal willingness-to-pay threshold of £20k per QALY.	Comment noted. FAD section 4.15 details the Committee's considerations and conclusion regarding fellow eye involvement at baseline. The Committee concluded that it was not necessary to decrease the rate of fellow eye involvement.

Novartis	The manufacturer underestimates the number of injections required in the first year with their technology (aflibercept) and over-inflates the number of injections requires with ranibizumab. **Underestimation**: The ACD reports that the manufacturer modelled 8 treatments with aflibercept in the first year. This assumption is misleading and incongruous with the evidence. The protocol for the VIVID/VISTA studies stipulates that this should be 9 and the actual data was 8.4 and 8.7 respectively. Novartis agrees with the ERG revision of this estimate in Section 3.2, page 14 of the ACD. **Over-inflation**: The manufacturer models ranibizumab with 7.93 injections in the 1st year together with 12 monitoring visits. Novartis concur with the comments from the ERG that the empirical methods of arriving at 7.93 are not appropriate (page 13, section 3.19). The ACD states: “The company acknowledged that the summary of product characteristics for ranibizumab had recently changed to reduce the number of monitoring visits needed in the first year.” This statement is inaccurate as the summary of product characteristics for ranibizumab has indeed been revised. However, not to reduce the number of monitoring visits needed merely in the first year but throughout treatment.. “This change was not included in the model because it was not considered by the company to be established practice in England.” The only large scale, multicenter, real-world, published evidence that Novartis are aware of that cites the monitoring frequency associated with ranibizumab based on the original monitoring label comes from Tufail et al. (2014)16. This provides data from 11,135 patients across 14 UK centres over a maximum period of 5 years. This reports a monitoring frequency in year 1 of 9.2. Novartis considers that this provides the most appropriate evidence to substantiate “established” use on this parameter and therefore the assumption of 12 is incorrect. Whilst this source of evidence is in wAMD, there is no evidence to suggest that it would differ in DMO.	Comment noted. FAD section 3.29 provides a discussion of the ERG’s rationale for its preferred number of injections in the economic model. FAD section 4.12 details the Committee’s consideration and conclusion regarding the number of injections. The Committee concluded that the economic modelling of treatment should be based on trial data, and that a sensitivity analysis that included an equalisation of the number of injections of aflibercept and ranibizumab in year 2 was an acceptable basis for its decision making.

Novartis	Page 11, Section 3.16. “The company performed a scenario analysis for a subgroup of patients with CRT of greater than 400 micrometres, using the probabilities of gaining and losing ETDRS letters for the subgroup of patients in the VIVID and VISTA trials. The results showed that aflibercept dominated both laser and ranibizumab” This analysis is invalid and misleading since the manufacturer has derived transition probabilities for aflibercept based on the > 400 micrometres data, which has a larger effect size, and compares it to transition probabilities for ranibizumab for the full population, which therefore results in an underestimation of the ranibizumab treatment effect in the > 400 micrometre population (this is because the < 400 micrometres population have a lower effect size). This is therefore not relevant to the decision problem and misleading for decision makers and adopters of this guidance.	Comment noted. FAD section 4.5 details the Committee’s consideration of the subgroup analyses for people with CRT of 400 micrometres or more.

Novartis	Page 13, Section 3.19. "The number of ranibizumab injections in the first year (7.93) may have been overestimated by the company"	
	Novartis agree with the ERG as previously described on the previous page of this document.	Comment noted. No change required.
	"…company combined the mean number of injections reported in the RESTORE and REVEAL trials with the median number from the DCRC.net trial." The abbreviation "DCRC.net" should read "DRCR.net."	Comment noted. FAD section 3.19 has now been updated with the correct trial name.
	It is inappropriate to over-inflate the ranibizumab injection frequency by using data from a study (DRCR.net Protocol I) that is not then part of the relative effectiveness estimate within the network meta-analysis. The manufacturer's network meta-analysis does not incorporate evidence from the pivotal DRCR.net study – please see Table 1, page 2 of this document.	Comment noted. No change required.
	"The number of monitoring visits for ranibizumab (12) in the first year may have been overestimated because the recently revised summary of product characteristics for ranibizumab removes the need for additional hospital monitoring visits in the first year of treatment." As previously described, this statement is inaccurate as the summary of product characteristics for ranibizumab has indeed been revised. However, not to reduce the number of monitoring visits needed merely in the first year but throughout treatment.	Comment noted. FAD section 3.29 provides a discussion of the ERG's rationale for its preferred number of injections in the economic model. FAD section 4.12 details the Committee's consideration and conclusion regarding the number of injections.

Novartis	Page 14, Section 3.20. "…revising the number of ranibizumab injections to 7.43, 4.00 and 3.00 in years 1, 2 and 3" The injection frequencies for years 2 and 3 should be 3.9 and 2.9 respectively as per the evidence published from the RESTORE extension11. "…applying a discount of 3.5% to the costs of blindness" The ACD also needs to state that the ERG amended the error whereby annual costs of blindness had been applied on a monthly basis (page 13 of ACD and page 123 of ERG report).	Comment noted. FAD section 3.29 provides a discussion of the ERG's rationale for its preferred number of injections in the economic model. FAD section 4.12 details the Committee's consideration and conclusion regarding the number of injections. FAD section 4.21 details the Committee's considerations and conclusion on its preferred analysis.
Novartis	Page 14, Section 3.22. Important. "The results of the ERG's base-case analysis comparing aflibercept with ranibizumab showed that aflibercept dominated ranibizumab. This statement is misleading unless the words "ranibizumab at list price" are inserted. The ERG analysis does not demonstrate that aflibercept dominates ranibizumab at the ranibizumab patient access scheme price – the ICER is in the North East quadrant of the cost-effectiveness plane (see ERG report & addendum).	Comment noted. FAD section 3.21 has been amended.

Novartis	"The Committee discussed how innovative aflibercept is in its potential to make a significant and substantial impact on health-related benefits. It agreed that aflibercept could be considered a slight advance compared with ranibizumab because of the less frequent administration of treatment and the reduced need for monitoring." This conclusion is incorrect. There is not "less frequent administration" as determined by the number of treatments within the evidence, as concluded by the ERG, and modelled over the three year period in the revised analysis. Please see page 14, Section 3.20 in the ACD: **Table 3. Summary of Injection Frequencies as corrected for errors identified by ERG** **Year 1** / **Year 2** / **Year 3** **Ranibizumab** 7.43 / 4 / 3 **Aflibercept** 8.5 / 5.45 / 3 There are also not any advantages for less monitoring with aflibercept – the ranibizumab label does not stipulate any specific numbers that would mean that one would monitor more frequently with ranibizumab than with aflibercept – please see precise wording from Section 4.2 of the ranibizumab SmPC: "…monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography)." Novartis therefore requests that this statement is removed from the ACD as it is not substantiated by the facts and evidence that were presented, discussed, and critiqued by the Committee.	

Novartis	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Novartis agrees that the provisional recommendations are sound and a suitable basis for guidance to the NHS.	Comment noted. No change required.
Alimera	**Clinical application of aflibercept.** No option for patients with a central retinal thickness less than 400 micrometres AFLIBER is being recommended as an option for treating visual impairment caused by DMO only if: a. The eye has a central retinal thickness of 400 micrometres or more at the start of treatment; and b. The company provides AFLIBER with the discount agreed in the patient access scheme. In effect this means that patients with a central retinal thickness less than 400 micrometres will not have access to a first-line therapy. This means that these patients will be denied treatment until their disease has progressed to a stage where permanent damage to the eye has already begun.3	Comment noted. FAD section 4.3 provides details of the Committee's consideration of these comments. The Committee concluded that laser is an appropriate comparator for aflibercept for people with a CRT less than 400 micrometres.

Alimera	Watch and wait is not a therapy for DMO In effect, by ignoring this group of patients, NICE is encouraging clinicians to adopt a 'watch and wait' therapy (i.e., no active treatment received). We would like to highlight that 'watch and wait' is not a standard of care (SOC) for patients with DMO and potentially detrimental to a patient's outcome, with reports claiming that nearly half of the patients developing DMO lose two or more lines of visual acuity within 2 years	Comment noted. FAD section 4.3 provides details of the Committee's consideration of these comments. The Committee heard from the clinical experts that some clinicians may adopt a 'watch and wait' approach. FAD Section 4.19 highlights that the Committee had not been presented with evidence on the cost effectiveness of aflibercept compared with a 'watch and wait' strategy. No change required.

Alimera	There is an evidence base to support the use of AFLIBER in patients where central retinal thickness is less than 400 micrometres Furthermore, the current evidence,5 shows that intravitreous AFLIBER, bevacizumab, and ranibizumab improved vision in eyes with center-involved DMO but the relative effect depended on baseline visual acuity. When the initial visual-acuity loss was mild (visual acuity between 20/32 and 20.40 at baseline), there were no apparent differences, on average, among study groups. At worse levels of initial visual acuity (20/50 or worse at baseline), AFLIBER was more effective at improving vision (please see www.ClinicalTrials.gov; trial number, NCT01627249). However, the data for the mild visual-acuity loss shows that AFLIBER was effective with central subfield thickness decreasing from 373±108 (mean±SD) at baseline to 242±57 micrometres after one year (mean change of -129±110 micrometres).5 This clearly shows the AFLIBER was effective in a group where mean central subfield thickness was less than 400 micrometres.	Comment noted. FAD section 4.5 has been up-dated to take account of the Committee's consideration of the Protocol T study.
Alimera	There is no evidence base to support switching between anti-VEGF therapies No data was presented in the above report to suggest that switching between anti-VEGF therapies would be an effective strategy as a first-line therapy for the management of DMO. Hence, based on this trial where visual acuity was taken into account, AFLIBER would be the logical first choice in patients with a central subfield thickness less than and greater than 400 microns.	Comment noted. FAD section 4.22 details the Committee's consideration on the sequential treatment with anti-VEGFs. The Committee concluded that, in the absence of evidence, no recommendations could be made on the cost effectiveness of sequential treatments with ant-VEGFs. No change required.

Comments received from members of the public

No comments received