NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Aflibercept for diabetic macular oedema

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

1 Key issues for consideration

Decision Problem

- Should bevacizumab be included as a comparator? Bevacizumab was included as a comparator in the final scope issued by NICE. The company did not present any clinical or cost effectiveness evidence for aflibercept compared with bevacizumab because it did not consider it an appropriate comparator. The company stated that bevacizumab is used as an unlicensed treatment and was not considered in the cost effectiveness analyses for the appraisals of ranibizumab and fluocinolone acetonide for diabetic macular oedema (DMO) (NICE technology appraisal guidance 274 and NICE technology appraisal guidance 301 respectively).

- Should fluocinolone acetonide and dexamethasone be included as comparators? Fluocinolone acetonide and dexamethasone were included as comparators in the

final scope issued by NICE. Fluocinolone acetonide and dexamethasone were not included in the company's base case analyses as comparators but were provided as exploratory analyses. The company explained that there was limited evidence available for any indirect comparison. The company commented that in its opinion fluocinolone acetonide cannot be considered a direct comparator for aflibercept given it is positioned for both chronic and pseudophakic patients insufficiently responsive to other available therapies. The company also commented that dexamethasone has not yet been assessed by NICE and there are restrictions in its licence for DMO.

Clinical Effectiveness

- Are the results from the VISTA and VIVID trials generalisable to patients seen in clinical practice in England?
    - The trials were conducted in 54 sites in the United States (VISTA) and 73 sites across Japan, Europe (excluding the UK) and Australia (VIVID).
    - The ERG commented that the mean HbA1c across VISTA and VIVID was between 7.6 and 7.9. The ERG stated that the majority of patients with DMO seen in clinical practice in England have higher HbA1c levels (over 8 or 9 being common). Therefore, it is possible that in clinical practice the proposed treatment will not have the same benefits as shown by the findings of the included trials, unless the diabetes becomes well controlled.

- Is it appropriate to pool the results of both trials in the analysis?
    - The ERG noted that the company presented results for the VISTA and VIVID trials separately and directly pooled together (integrated analysis). The company also provided subgroup analyses using the integrated analysis. The ERG commented that because the VISTA and VIVID trials differed significantly in the proportion of participants who had received previous anti-vascular endothelial growth factor (VEGF) treatment and mean central retinal thickness (CRT) was significantly

different between the two trials at baseline, the integrated analysis was not appropriate.

Cost Effectiveness

- What is the most appropriate source of utility values to be included in the economic model?

    - The company used utility values from Czoski-Murray (2009) in its base case analyses so that the values were consistent with those used in the economic model for the appraisal of ranibizumab for DMO NICE technology appraisal guidance 274. In order for these values to fit the 'best seeing eye' (BSE) and 'worst seeing eye' (WSE) states seperately, the company has allowed for a proportion of the BSE utility impact for a given change in the health state to apply to the same change in the health state of the WSE.
    - In addition, the company collected EQ-5D data alongside the VIVID and VISTA trials. This specifically accounted for the change in utility values between both the BSE and WSE and was in accordance with the NICE reference case. The ERG highlighted that the most appropriate analysis presented by the company for the EQ-5D results was the generalised estimating equation (GEE) analysis and this should be used in the company's base case analyses.

- What is the most appropriate cost of blindness to be included in the economic model? The ERG commented that the data used in the company's model to inform the cost of blindness (£6,448) may not be appropriate. The ERG noted that the total cost of blindness calculation in the company submission was taken from a report which was intended for a group of patients with age-related macular degeneration who tend to be older than the age assumed in the company's economic model for DMO. The ERG suggested that £7,510 for the first year total cost of blindness and £7,429 for the subsequent annual costs should be used in the model.

- How many ranibizumab monitoring visits should be included in the model in the first year?
    - The company included 12 monitoring visits for people who had received ranibizumab during the first year of treatment in the model. People who had received aflibercept had 8 monitoring visits.
    - The summary of product characteristics (SmPC) for ranibizumab has recently been revised. The frequency of monitoring visits for treatment with ranibizumab was revised from 'monthly' to 'as needed'.
    - The ERG stated that following the change to the SmPC for ranibizumab, the number of monitoring visits for ranibizumab should be the same as the number of monitoring visits for aflibercept during the first year of treatment in the model.

- How many treatments of aflibercept and ranibizumab should be included in the model in the first year?
    - The company estimated 7.93 ranibizumab injections in the first year based on the trials included in the network meta-analysis. The ERG note that the company had used the mean number of injections reported in RESTORE and REVEAL and combined it with the median number from the DCRC.net trial, which the ERG considered inappropriate. The ERG re calculated the average injections excluding the DCRC.net trial. This resulted in a weighted average of 7.43 ranibizumab injections in the first year. The ERG considered this a better estimate for the base case analyses.
    - The company had modelled 8.00 aflibercept injections in the first year. The ERG noted that 8.5 injections were more appropriate for the base case analyses because the final injection in the first year will be at the start of month 12.

- Given the concerns raised by the company regarding the appropriateness of fluocinolone acetonide and dexamethasone as comparators and its concerns

about the robustness of the clinical effectiveness results, are the ICERs presented for these comparisons a suitable basis for decision making?

2 Remit and decision problems

2.1 The remit from the Department of Health for this appraisal was to appraise the clinical and cost effectiveness of aflibercept within its licensed indication for treating diabetic macular oedema

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Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	Adults with visual impairment due to DMO.	Adults with visual impairment due to DMO.	None.	None.
Int.	Aflibercept solution for injection.	Aflibercept solution for injection.	None.	None.
Com.	Laser photocoagulation alone. The following technologies alone or in combination with laser photocoagulation: • Ranibizumab. • Corticosteroids (including fluocinolone acetonide intravitreal implant and dexamethasone). • Bevacizumab (for people in whom ranibizumab and fluocinolone	Laser photocoagulation alone. The following technologies alone or in combination with laser photocoagulation: • Ranibizumab • Corticosteroids (including fluocinolone acetonide intravitreal implant and dexamethasone)	Dexamethasone was not included in the company's base case as a comparator. The company included dexamethasone as a scenario analysis. The company explained the reason for the exclusion was that dexamethasone had not yet been assessed by NICE and there are restrictions in its licence for DMO. The company did not include bevacizumab as a comparator in its analyses. The company stated that this is because bevacizumab is used as an unlicensed treatment. It noted that even though bevacizumab was included as a comparator	The ERG noted that the comparators listed in the company submission differed from the scope and summarised the company's rationale for this. The ERG performed a literature search to establish the evidence base for bevacizumab and found a number of studies comparing bevacizumab with laser therapy for people with DMO. The ERG noted that the dosage of intravitreal injection was 1.25 mg for the majority of the identified studies.

	acetonide intravitreal implants are unsuitable).		in previous scopes for DMO appraisals; NICE technology appraisal guidance 274 and NICE technology appraisal guidance 301 it was not used as a comparator in the cost-effectiveness analyses. The company included an exploratory comparison only for intravitreal corticosteroids because of a lack of evidence available for an indirect comparison.	
Out.	The outcome measures to be considered include: • Best corrected visual acuity (affected eye). • Best corrected visual acuity (both eyes). • Central foveal subfield thickness. • Contrast sensitivity. • Mortality. • Need for cataract surgery. • Adverse effects of	The outcome measures to be considered include: • Best corrected visual acuity (treated eye, non-treated eye and both eyes – with consideration given to whether it is the best, worst or equal seeing eye). • Mortality. • Adverse effects of treatment. • Health-related quality of life.	The company stated that some outcomes listed in the scope, such as the emphasis on cataracts, relate more closely to an appraisal of corticosteroids. Incidence of glaucoma was very low in VIVID and VISTA and lower in the 2 aflibercept treatment arms compared with laser (see section 6.9 of the company submission). VIVID and VISTA included change in CRT as a secondary outcome. Contrast sensitivity was not measured.	None

	treatment, including cataract formation and glaucoma. • Health-related quality of life, including the effects of changes in visual acuity.			

3 The technology and the treatment pathway

3.1 Aflibercept is a soluble VEGF receptor fusion protein which binds to all forms of VEGF-A, VEGF-B, and the placental growth factor. VEGF is involved in the pathogenesis of DMO with VEGF-A playing a particular role. Since 2006, anti-VEGF treatments for DMO have been investigated because of the action of VEGF in DMO and retinal neovascularisation. Aflibercept is administered by intravitreous injection for people with DMO.

3.2 Laser photocoagulation is the standard of care for people with DMO. NICE technology appraisal guidance 274 recommends ranibizumab as an option for treating visual impairment due to DMO (only if the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and the manufacturer provides ranibizumab with the discount agreed in the patient access scheme). NICE technology appraisal guidance 301 recommends fluocinolone acetonide intravitreal implant for treating chronic DMO that is insufficiently responsive to available therapies (only if the implant is to be used in an eye with an intraocular pseudophakic lens). Bevacizumab, a VEGF inhibitor, is also used outside its marketing authorisation for treating DMO.

3.3 The Company suggested that aflibercept is an alternate to ranibizumab for DMO. The company stated that it expects that fluocinolone acetonide intravitreal implant will remain an option for people with chronic, pseudophakic DMO, whose disease is unresponsive to other available therapies following the introduction of aflibercept.

Figure 1 Treatment pathway for patients with DMO.

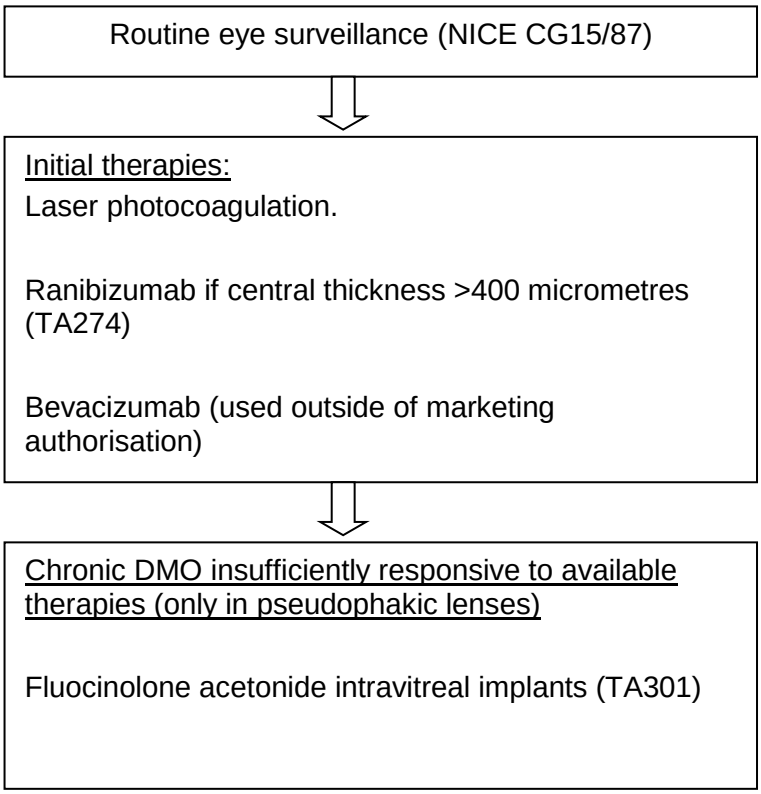


Table 2 Technology

	Aflibercept	Laser Photocoagulation	Ranibizumab	Fluocinolone acetonide intravitreal implant	Dexamethasone intravitreal implant
Marketing authorisation.	Treatment of visual impairment due to diabetic macular oedema in adults.	Laser photocoagulation is a type of surgery and therefore does not require a marketing authorisation.	Treatment of visual impairment due to diabetic macular oedema in adults.	Treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsible to available therapies.	Treatment of adult patients with visual impairment due to diabetic macular oedema who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy.
Administration method.	Intravitreal injection	Laser.	Intravitreal injection	Intravitreal implant	Intravitreal implant
Cost.	List price: £816 for a single 2 mg dose (excluding VAT). There is a confidential patient access scheme available for aflibercept (simple discount of [redacted] resulting in a price of [redacted]	£117	List price: £742.17 per vial (excl. VAT) There is a confidential patient access scheme available for ranibizumab (simple discount of [redacted] on the list price).	List price: £5500.00 per applicator (excl. VAT). There is a confidential patient access scheme available for fluocinolone acetonide intravitreal implant. ([redacted] [excluding VAT]).	List price: £870.00 per applicator (excl. VAT).

4 Comments from consultees

4.1 A patient and carer organisation explained the impact of DMO on patients. Sight loss from DMO can result in a number of life changes including forced early retirement, loss of driving licence and loss of income and dependence benefits. In addition people are more at risk of falls and accidents.

4.2 A professional organisation suggested people with DMO have limited treatment options if ranibizumab is considered an inappropriate treatment. Those people who do not have a central retinal thickness of less than 400 micrometres or do not respond to ranibizumab are offered laser treatment. Laser treatment, although effective at preventing sight loss, can lead to scaring and is less efficacious compared with anti-VEGF therapies.

4.3 The professional organisation also explained that people would benefit from the structured dose regimen of aflibercept treatment. Treatment is initiated with 1 injection per month for 5 consecutive doses, followed by 1 injection every 2 months. Because there is no requirement for monitoring between injections patients will know exactly when they will get an injection in the first year. This is different to dose regimens for other anti-VEGF treatments, which require monitoring appointments to find out if injections are needed, or not.

5 Clinical-effectiveness evidence

Overview of the clinical trials

5.1 The evidence presented in the company's submission is from the VISTA and VIVID clinical trials. VISTA (n=466) is an ongoing prospective, phase-III multi-centre, double-blind, randomised (1:1:1) active controlled superiority study carried out in 54 sites in the United States. VIVD (n=406) is an ongoing prospective, phase-III, multicentre, randomised, double-masked, active-controlled superiority study carried out in 73 sites across Japan, Europe and Australia.

5.2 Both trials compared aflibercept 2 mg given intravitreally every 4 weeks with laser photocoagulation (2Q4) and aflibercept 2 mg given intravitreally every 8 weeks (after 5 initial monthly does) with laser photocoagulation (2Q8). In both treatment arms, sham laser was given at baseline and subsequent visits (where laser re-treatment criteria were met). Laser re-treatment criteria were applicable when it was expected that the patient would benefit from a further laser treatment and at least 1 of the following conditions occurred:

- Thickening of the retina at, or within, 500 micrometres (µm) of the centre of the macula.
- Hard exudates at, or within, 500µm of the centre of the macula.
- Zone of retinal thickening, one disc area or larger.

5.3 [redacted]

5.4 The primary outcome of the trials was to demonstrate the superiority of aflibercept over laser photocoagulation on BCVA in eyes with DMO involving the centre of the macula. The Early Treatment of Diabetic Retinopathy Study (ETDRS) letter score was used at week 52 to

determine the change in BCVA. The secondary outcomes of the trials measured several end points including;

- The proportion of patients gaining ≥ 10 ETDRS letters from baseline to week 52.
- The proportion of patients gaining ≥ 15 ETDRS letters from baseline to week 52.
- The mean change in CRT from baseline to week 52, as assessed on ocular coherence tomography (OCT).
- Vision-related quality of life (assessed by National eye institute visual functioning questionnaire-25 [NEI VFQ-25])
- Quality of life (assessed by 5 dimension health questionnaire EQ-5D).
- Safety: Ocular and non-ocular adverse events and serious adverse events.

5.5 All efficacy endpoints were analysed using the Full Analysis Set (FAS). This included all randomised patients who received any study medication and had a baseline assessment and at least 1 BCVA assessment after baseline. These were analysed as randomised. The safety endpoints were analysed using the Safety set (SAF). This included all randomised patients who received any study medication (active or sham). These were analysed as treated. In the analyses of the primary and secondary endpoints, the last observation carried forward (LOCF) approach was used for missing measurements. Baseline values were not carried forward. Measurements obtained after initiation of additional treatments were censored with missing or censored values imputed using LOCF.

5.6 The company carried out a number of subgroup analyses of the primary and secondary endpoints for [redacted].

5.7 The company considered the patient characteristics at baseline to be well balanced among treatment groups in both trials. There were differences in duration of diabetes and higher BMIs in VISTA than in VIVD. Participants

in VIVID had significantly higher mean CRT than those in VISTA for the laser and aflibercept 2Q8 groups. Another difference included more eyes in VISTA receiving prior anti-VEGF treatment than eyes in VIVID (42.9% versus 8.9%, respectively). For further details of the patient characteristics at baseline, see Tables 6 and 7, pages 52-53 of the company submission.

ERG comments

5.8 The ERG noted that the company had included the 2 main trials comparing aflibercept with laser. The ERG also noted that no head-to-head trials were available for the comparison of aflibercept with ranibizumab.

5.9 The ERG commented that the main entry criterion for VIVID and VISTA was a CRT in the 1 mm central retina, as assessed by OCT (not specified in the Korobelnik et al published manuscript or in the company's submission, whether spectral domain or time domain OCT. Therefore, at entry, patients may or may not have fulfilled the standard definition of clinically significant macular oedema (CSMO). CSMO was used as re-treatment criterion for laser photocoagulation therapy. The ERG stated that it could be argued that the initial laser treatment was not given based on the presence of CSMO while the re-treatments were; the rationale for this was unclear to the ERG. The ERG noted that was not specified either whether fluorescein angiography was obtained prior to laser treatment to guide laser (as recommended by the ETDRS).

5.10 The ERG noted that participants in VIVID had a significantly higher mean CRT than those in VISTA for the laser and aflibercept 2Q8 groups. The ERG commented that this may be important, as there is evidence that clinical effectiveness of anti-VEGF treatment for DMO can vary according to baseline CRT measurements.

5.11 The ERG noted that more eyes in VISTA received prior anti-VEGF treatment than eyes in VIVID (42.9% versus 8.9%, respectively). The ERG highlighted that the company had explained that the main reason for

this difference was the relative lack of availability of anti-VEGF treatments in the countries where the VIVID trial was conducted (that is, Japan, Europe and Australia). The ERG also noted that approximately half of the patients in VISTA had also received previous laser photocoagulation treatment in the study eye. The ERG commented that it was plausible for an eye that initially failed to respond to laser therapy to respond to a subsequent anti-VEGF treatment but that it is less obvious that an eye that initially failed to respond to laser therapy may respond to the same treatment if administered again. However, eyes unlikely to respond to laser were excluded from the VISTA and VIVID trials.

5.12 The ERG commented that the mean HbA1c across VISTA and VIVID was between 7.6 and 7.9. The ERG stated that the majority of patients with DMO seen in clinical practice in England have higher HbA1c levels (over 8 or 9 being common). Therefore, it is possible that in clinical practice the proposed treatment will not have the same benefits as shown by the findings of the included trials.

Clinical trial results

5.13 The company presented the results for the VISTA and VIVID trials; separately, directly pooled together (integrated analysis) and combined in a standard meta-analysis.

5.14 The results of the primary efficacy analysis of change in BCVA at 52 weeks are presented in Table 3 and Figure 2. The results show a significant mean change in BCVA in both trials in patients receiving aflibercept compared with laser at week 52.

Table 3 Primary efficacy analysis of change in BCVA from baseline to week 52 (VISTA, VIVID and integrated [FAS, LOCF]) (adapted from page 72 table 14 of company submission)

Mean Change in BCVA from baseline to week 52.	**VISTA**			**VIVID**			**Integrated Analysis**		
	2Q4 (n=154)	**2Q8 (n=151)**	**Laser (n=154)**	**2Q4 (n=136)**	**2Q8 (n=135)**	**Laser (n=132)**	**2Q4 (n=290)**	**2Q8 (n=286)**	**Laser (n=286)**
Baseline Mean (SD)	58.9 (10.77)	59.4 (10.89)	59.7 (10.95)	60.8 10.74)	58.8 (11.23)	60.8 (10.61)	59.8 (10.78)	59.1 (11.03)	60.2 (10.79)
Mean Change (SD)	12.5 (9.54)	10.7 (8.21)	0.2 (12.53)	10.5 (9.55)	10.7 (9.32)	0.9 (1.00)	11.5 (9.58)	10.7 (8.74)	0.7 (11.69)
Mean Treatment difference (97.5% Confidence Interval)[1]	12.19 (9.35,15.04)	10.45 (7.73,13.17)		9.25 (6.49,12.02)	9.05 (6.35,11.76)		10.78 (8.79,12.77)	9.85 (7.92,11.77)	

[1]The CI for integrated study is based on treatment difference (aflibercept group vs. Laser) of the least squares mean change using an ANCOVA model with baseline measurement as covariate and the treatment and study as fixed factors.

FAS; Full analysis set. LOCF; Last observation carried forward. SD; Standard deviation.

Figure 2. [redacted]

5.15 The company provided subgroup analyses on the mean change in BCVA from baseline to week 52 using the integrated analysis. [redacted]. For further details, see the forest plots in Figure 10 and 11 (pages 75-76) of the company submission.

5.16 The results for the secondary efficacy endpoints are presented in Table 4. The analyses showed a significant improvement in all outcomes for both trials in people receiving aflibercept compared with laser. For the NEI-VFQ-25, the VISTA trial showed a significant advantage with aflibercept 2Q4 (but not with aflibercept 2Q8) on the near activities subscale compared with laser. No differences were observed for each aflibercept regimen versus laser within VIVID. No statistical differences were observed in either trial for the NEI-VFQ-25 distance activities subscale.

Table 4 Secondary efficacy endpoints from baseline to week 52 (VISTA, VIVID, integrated analyses [FAS, LOCF]) (page 81, table 19 of company submission)

Outcome		**VISTA**			**VIVID**			**Integrated**		
		2Q4 (n=154)	**2Q8 (n=151)**	**Laser (n=154)**	**2Q4 (n=136)**	**2Q8 (n=135)**	**Laser (n=132)**	**2Q4 (n=290)**	**2Q8 (n=286)**	**Laser (n=286)**
Patients gaining ≥ 10 letters	Number (%) gaining letters	100 (64.9)	88 (58.3)	30 (19.5)	74 (54.4)	72 (53.3)	34 (25.8)	174 (60.0)	160 (55.9)	64 (22.4)
	Adjusted difference vs Laser (97.5% CI)	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
	P value	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
Patients gaining ≥ 15 letters	Number (%) gaining letters	64 (41.6)	47 (31.1)	12 (7.8)	44 (32.4)	45 (33.3)	12 (9.1)	108 (37.2)	92 (32.2)	
	Adjusted difference vs Laser (97.5% confidence interval)	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
	P value	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
FAS; Full analysis set. LOCF; Last observation carried forward. SD; Standard deviation.										

5.17 The company carried out a number of subgroup analyses of the secondary endpoints including [redacted] For further details of the subgroup analyses, see tables 23-26, pages 93-98 of the company submission.

5.18 A number of additional efficacy outcomes were analysed by the company in support of the results for the primary and secondary endpoints. The company presented the results for the proportion of patients gaining ≥0 and ≥5 letters and the proportions of patients losing ≥5, ≥10, and ≥15 ETDRS letters from baseline. Table 5 shows the results of the analysis for the loss of ≥ 10 or ≥ 15 letters. For the results of the analyses for gaining ≥0 and ≥5 letters and for the proportions of patients losing ≥5, see Table 21, page 86 of the company submission.

Table 5 Additional efficacy endpoints: Results from baseline to week 52 in VISTA, VIVID and the integrated analyses of both trials (FAS; LOCF) (table 21, page 86 of company submission)

Outcome		VISTA			VIVID			Integrated		
		2Q4 (n=154)	2Q8 (n=151)	Laser (n=154)	2Q4 (n=136)	2Q8 (n=135)	Laser (n=132)	2Q4 (n=290)	2Q8 (n=286)	Laser (n=286)
Patients losing ≥ 10 letters	Number (%) gaining letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted difference vs Laser (97.5% CI)[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients losing ≥ 15 letters	Number (%) gaining letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted difference vs Laser (97.5% confidence interval)[1]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FAS; Full analysis set. LOCF; Last observation carried forward. SD; Standard deviation.

5.19 The two-year results for VIVID and VISTA were not finalised at the time of the company's submission to NICE. However, initial 2-year results of VISTA and VIVID were presented at EURETINA in September 2014 and 2-year clinical study reports of both trials were in draft format.

5.20 In VISTA [redacted] completed Week 100. In VISTA the improvement from baseline in BCVA was maintained at week 100 in patients receiving aflibercept 2Q4 and 2Q8 compared with those receiving laser therapy. After 2 years, patients receiving aflibercept 2Q8 had a mean change from baseline in BCVA of 11.5 letters compared with 12.5 letters at 52 weeks. Patients in the laser photocoagulation treatment group had a mean change from baseline in BCVA of 0.9 letters (0.2 letters at 52 weeks). In VIVID [redacted] of patients randomised completed week 100. Improvement in BCVA was seen by day 3 in all treatment groups. Further improvement continued through to week 52 for the 2Q4 and 2Q8 groups and was maintained through to week 92. Patients in the 2Q4 group had a larger improvement in VA compared with the 2Q8 group at week 100. The laser group showed improvement through to week 12, and then gradually declined through to week 100.

5.21 In both trials, for the gain of [redacted] and ≥ 2-step improvement in ETDRS DRSS endpoints, the sustained favourable differences to laser at Week 100 were statistically significant for both aflibercept dose groups.

5.22 [redacted].

5.23 Health related quality of life was also collected as part of the trials. Exploratory EQ-5D data were collected at baseline, week 24 and week 52 in both trials. Utility values were estimated using the UK valuation tariff by Dolan et al. A regression analysis was performed to estimate the

relationship between BCVA (in both eyes) and quality of life. Patients completed the EQ-5D questionnaires and quality of life estimates were based on a general population tariff. The mean change total score from baseline to 52 weeks in VIVID, the European arm of the study, was [redacted] and [redacted] in the laser, 2Q4 and 2Q8 groups respectively. Some data were collected for VISTA but not analysed as part of the clinical analyses.

5.24 The company undertook a meta-analysis of the results from the VISTA and VIVID trials for a number of outcomes using both fixed and random effects models. The meta-analysis comparisons were made exclusively between aflibercept 2Q8 regimen and laser. The company justified this choice by the fact that aflibercept 2Q8 is the licensed aflibercept dose in the UK and that approved by the European Medicines Agency. The results from the meta-analysis indicated that there was a greater gain in mean BCVA from baseline to 12 months with aflibercept, when compared with laser. The results also indicated that a higher proportion of patients treated with aflibercept achieved a gain of ≥ 10 letters or ≥15 letters, from baseline to 12 months, when compared with laser photocoagulation, and that a lower proportion of patients treated with aflibercept lost ≥15 letters or ≥10 letters, from baseline to 12 months, when compared with laser treatment. All the results were statistically significant. For further details, see Tables 32-34, pages 112-115 of the company submission.

5.25 The company commented that overall, the safety data indicated that aflibercept, compared with laser therapy, is well tolerated, both locally and systemically, and has a favourable safety profile out to at least 2 years in the DMO patient population. The safety profile was also consistent with that observed in the age-related macular degeneration and central retinal vein occlusion trial populations.

ERG comments

5.26 The ERG noted that the company presented results for the VISTA and VIVID trials separately and directly pooled together (integrated analysis).

The ERG explained that because the VISTA and VIVID trials differed significantly in the proportion of participants who received previous anti VEGF treatment and the mean CRT was significantly different between the 2 trials, the integrated analysis was not appropriate. The ERG noted that the integrated analyses of secondary endpoints were defined as exploratory - [redacted] in the company submission.

5.27 The ERG noted a discrepancy within the company submission on deaths reported in the VIVID trial. In VIVID, it was reported that there were 4 deaths recorded in participants in the aflibercept 2Q8 group, none in the aflibercept 2Q4 group or laser group (Page 65, Figure 6 of company submission). The ERG stated that this does not match the VIVID data (meta-analysis of aflibercept 2Q8 versus laser) presented in Figure 56 on page 164 of the company submission. Figure 56 (company submission) shows that 5 deaths were observed in the aflibercept 2Q8 group and zero in the laser group rather than five and one, respectively, as for Figure 6 of the company submission. The ERG assessed this further by considering the data presented in the Korobelnik et al publication where 2 deaths were reported in the laser treatment arm (1 in each trial), 2 in the aflibercept 2Q4 treatment arm (unclear how many in each trial) and 4 in the aflibercept 2Q8 treatment arm. As Korobelnik et al did not present data separately by treatment group, the ERG were not in the position to confirm which source was correct.

Indirect comparison and mixed treatment comparison (network meta-analysis)

5.28 As there are no head-to-head trials comparing aflibercept with; ranibizumab, fluocinolone acetonide and dexamethasone, the company carried out a systematic review and identified 11 trials for possible inclusion in an indirect and a mixed treatment comparison (see Table 6).

5.29 The company carried out Bucher indirect comparisons of aflibercept 2Q8 with ranibizumab and aflibercept 2Q8 with dexamethasone. The company used pooled estimates from the meta-analyses that it undertook for

aflibercept 2Q8 with laser (VIVID and VISTA trials), ranibizumab with laser (RESTORE and REVEAL trials) and dexamethasone with laser (PLACID trial). The company used the Bucher indirect comparison method to synthesise, where possible, efficacy and safety data for aflibercept compared with ranibizumab and with dexamethasone. A comparison of aflibercept with fluocinolone acetonide was not possible because of a lack of a common comparator to allow an indirect analysis.

5.30 The indirect comparisons showed a significant effect in favour of anti-VEGF treatments (aflibercept and ranibizumab) compared with laser for the BCVA mean change from baseline. The indirect comparison of aflibercept with ranibizumab was significantly in favour of aflibercept with a mean difference of 4.82 (95% CI 2.52 to 7.11). The exclusion of the REVEAL trial, which was based primarily on an Asian population, reduced the size of the effect estimate but did not alter the conclusion. With regard to the secondary outcomes, the gain of ≥10 and ≥15 letters for both aflibercept and ranibizumab showed a significant improvement over laser. The indirect comparison found that aflibercept and ranibizumab were not different from each other. No differences were found between aflibercept and laser, between ranibizumab and laser and between aflibercept and ranibizumab for the safety outcomes. In the indirect comparison of aflibercept with dexamethasone, a significant advantage was observed with aflibercept for the gain of ≥10 letters, but no differences in safety outcomes were evident, despite a trend towards fewer adverse events with aflibercept treatment. For further details of the indirect comparisons between aflibercept and ranibizumab, see Tables 45 and 46, pages 179-180 of the company submission and for the indirect comparison of aflibercept with dexamethasone, see Table 47, page 181 of the company submission.

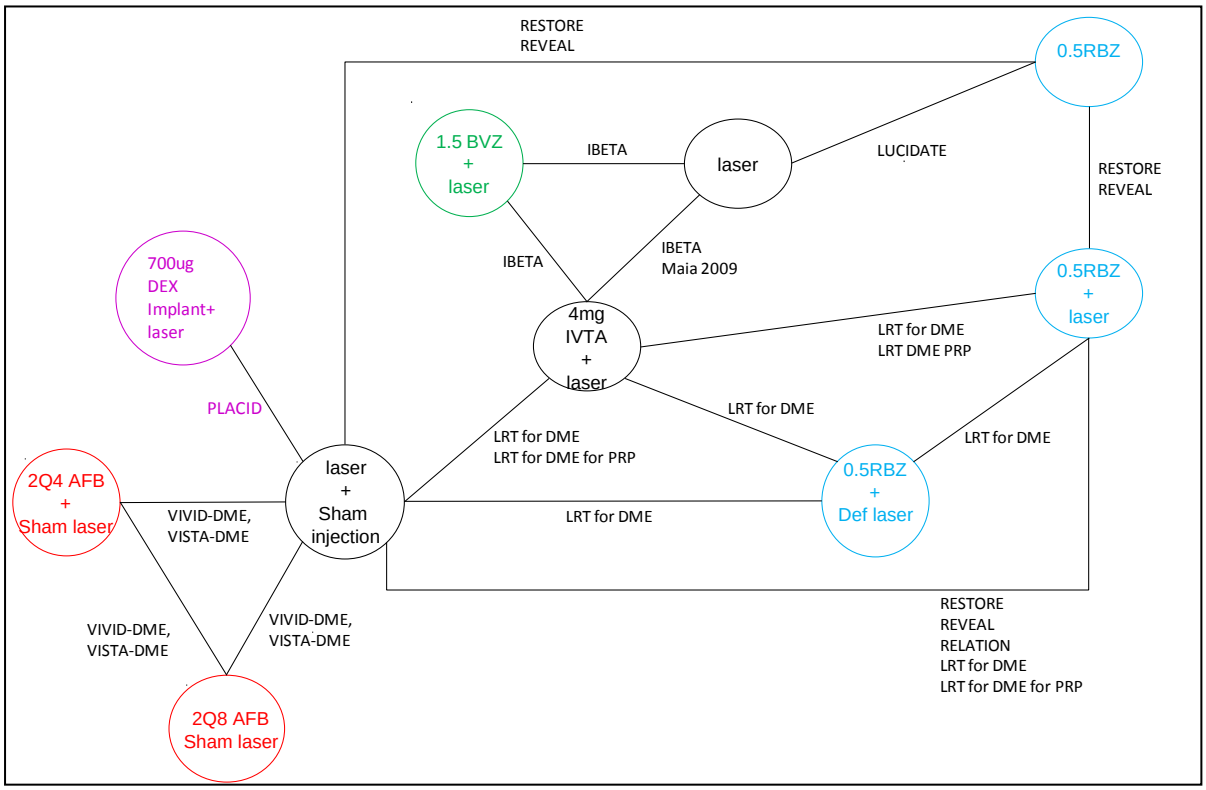
Table 6: Summary of the trials used to conduct the indirect comparison (Table 40 Page 147 of company submission)

Study	Intervention	Comparator(s)
VISTA	Aflibercept	Laser photocoagulation (laser)

VIVID	Aflibercept	Laser photocoagulation
IBETA	Laser photocoagulation	Bevacizumab (1.5 mg) + laser Triamcinolone (4 mg) + laser
RELATION	Ranibizumab + prompt laser	Laser photocoagulation + sham injections
RESTORE	Ranibizumab + laser	Laser + sham injections Ranibizumab + sham laser
REVEAL	Ranibizumab + laser	Laser + sham injections Ranibizumab + sham laser
LRT for DME	Ranibizumab + prompt laser Ranibizumab + deferred laser	Laser + sham injections Triamcinolone + laser
LRT for DME for PRP	Laser + sham injections	Ranibizumab + laser Triamcinolone + laser
LUCIDATE	Ranibizumab	Laser
Maia 2009	Triamcinolone + laser	Laser
PLACID	Dexamethasone + laser	Laser + sham injections

5.31 A summary of the network meta-analysis is presented in Figure 3. The comparison between aflibercept and fluocinolone acetonide was not possible because the fluocinolone acetonide trial (FAME which compared fluocinolone acetonide with sham fluocinolone acetonide) did not have a common comparator for a network to be formed.

Figure 3: The feasible network at 12 months (figure 18, page 149 of company submission)



5.32 Results of the network meta-analysis showed a significant improvement in visual acuity outcomes ('BCVA mean change from baseline' and 'loss ≥10 ETDRS letters') for aflibercept (2Q8 arm) compared with ranibizumab. There was no significant difference between aflibercept and ranibizumab in alternative visual acuity ('gain ≥15 ETDRS letters', 'loss ≥15 ETDRS letters', and 'gain ≥10 ETDRS letters' or safety outcomes). Results are provided in Table 7.

Table 7 Network Meta-Analysis results for aflibercept 2Q8 compared with ranibizumab for 12 month secondary outcomes (page 63, table 17 ERG report)

	Aflibercept 2Q8 compared with ranibizumab 0.5 PRN.		
Outcome	Type of analysis	Risk ratio	95% CrI
Gain of >=10 ETDRS letters	Fixed	1.32	(0.98, 1.78)
	Random	1.19	(0.90, 1.57)
Loss of >=10 ETDRS letters	Fixed	[redacted]	[redacted]
	Random	[redacted]	[redacted]
Gain of >=15 ETDRS letters	Fixed	1.78	(0.96, 3.29)
	Random	1.42	(0.93, 2.24)
Loss of >=15 ETDRS letters	Fixed	0.13	(0.004, 1.35)
	Random	0.14	(0.007, 1.52)
Treatment discontinuation	Fixed	1.12	(0.55, 2.30)
	Random	1.09	(0.39, 3.29)
All serious AE	Fixed	0.76	(0.47, 1.26)
	Random	0.82	(0.47, 1.42)
All serious ocular AE	Fixed	0.28	(0.06, 1.24)
	Random	0.30	(0.05, 2.49)
All AE	Fixed	0.79	(0.55, 1.10)
	Random	0.88	(0.64, 1.15)
All Ocular AE	Fixed	0.75	(0.54, 1.05)
	Random	0.85	(0.58, 1.25)
All serious non-ocular AE	Fixed	0.60	(0.32, 1.14)
	Random	0.67	(0.29, 1.66)
All non-ocular AE	Fixed	1.09	(0.87, 1.40)
	Random	1.03	(0.80, 1.56)
Eye pain	Fixed	0.98	(0.38, 2.70)
	Random	0.96	(0.23, 3.91)
Hypertension	Fixed	0.95	(0.44, 2.07)
	Random	0.95	(0.37, 2.55)
Cataract	Fixed	3.93	(0.77, 32.74)
	Random	3.83	(0.52, 43.72)
All-cause mortality	Fixed	2.90	(0.20, 50.4)
	random	2.76	(0.13, 79.02)
BCVA; best corrected visual acuity, PRN; pro re nata, AE; adverse events, CrI; credibility interval			

ERG comments

5.33 The ERG stated that the company had identified all the relevant trials for the indirect comparison of aflibercept with ranibizumab at 12 months. Overall risk of bias was rated as low in 4 trials (VISTA, VIVID, RESTORE, PLACID) and unclear in the remaining trials (IBETA, REVEAL, RELATION, LRT for DME, LRT for DME for PRP, LUCIDATE, Mia 2009). The ERG noted that the IBETA and REVEAL trials were not reported in full but in abstract form only and the details of the RELATION trial were available on the clinicaltrials.gov website. It commented that these reports generally contained insufficient information to fully assess risk of bias. The majority of trials did not provide sufficient information to assess the risk of bias in the random sequence generation (IBETA, REVEAL, RELATION, LRT for DME, LRT for DME for PRP, LUCIDATE, Maia 2009) or allocation concealment domains (VISTA, VIVID, IBETA, RESTORE, REVEAL, RELATION, LRT for DME, LRT for DME for PRP, Maia 2009, PLACID). Participants in the LUCIDATE and Maia 2009 trials were not blinded.

5.34 The company provided a network meta-analysis for both fixed and random effects. Although the company provided the WINBUGS codes for the model and the source data, they did not provide information on the initial values used, or the process of running the model. The ERG independently extracted source data from the references and matched them with those provided by the company. In the case of continuous outcomes, mean change from baseline in BCVA, the ERG agreed with the result presented by the company and considered the results to be consistent. For binary secondary outcomes, the results for aflibercept compared with ranibizumab replicated by the ERG were in the same direction (non-significant) and same magnitude of effect even though some discrepancies in numerical values were observed. The code for the random effects binary outcome matched exactly that used by the company while the code for the fixed effects did not. The ERG commented that this inconsistency could explain some of the observed differences. The ERG also commented that discrepancies could have

been caused by differences in burn in between the two models or numbers of iteration updates with or without thinning. Within the fixed effects model, the company estimated risk ratios as a function of the odds ratios.

5.35 The ERG noted that the mortality data presented in the submission for the fixed and random effect risk ratios did not match those calculated by the ERG. The ERG speculated that this was a consequence of the choice of the initial values used and because mortality is a rare event. It commented that it was likely that the specification of different initial values would result in different estimates. The ERG stated that between-study heterogeneity could explain the observed discrepancies. Despite the numerical differences, the risk ratios estimated by both the company and the ERG were consistent with the data.

6 Cost-effectiveness evidence

Model structure

6.1 The company provided a bilateral vision, state transition Markov model in which each eye was in one of eight possible health states. This resulted in a total of 64 possible vision states plus the additional absorbing health state of death. The health states for each eye were based on the ETDRS letter ranges (see Table 8). The two worst health states, HS7 and HS8, represented blindness.

Table 8 Individual eye health states (Table 22, page 75 ERG report)

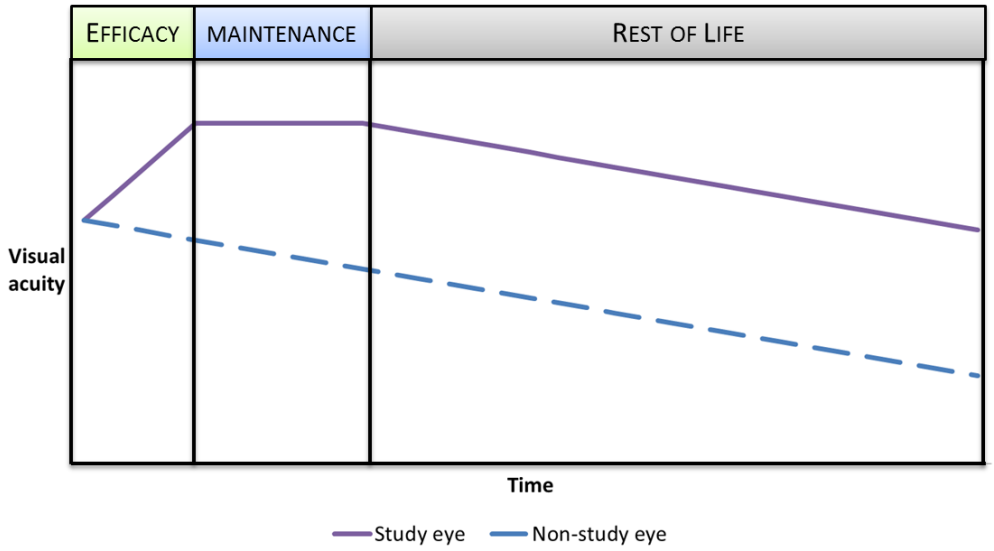
	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8
Letters	86+	76-85	66-75	56-65	46-55	36-45	26-35	0-25

6.2 Hypothetical patients entered the model having at least 1 treated for DMO. 46.5% of patients were assumed to have bilateral DMO at baseline. An additional 10% developed fellow eye DMO involvement at the start of years 2, 3, 4 and 5. It was assumed that 50% of the fellow eyes with DMO at baseline will be treated at baseline, and that 50% of incident fellow eye

DMO will be treated at incidence. The other 50% of fellow eyes with DMO were assumed not to be treated.

6.3 The model consisted of 3 distinct and separate phases; initial, maintenance and rest of life (Figure 4). Any eye that was affected by DMO and was not on treatment lost vision at a monthly rate in line with natural progression. For eyes that were treated, the efficacy phase which lasted for 1 year, was the only phase in which patient vision may improve. During this phase, gaining or losing 10 letters represented a move of 1 health state and the gaining or losing of 15 letters represented a move of 2 health states. For eyes that were treated, the efficacy phase was followed by a maintenance phase of 4 years. During the maintenance phase, all living patients who remained on treatment maintained vision. However, patients may discontinue treatment or die. If patients were off treatment during the maintenance phase, they may remain in the same health state, lose at least 10 letters of vision (one health state) or die. Blind patients were not treated during this phase. It was assumed that patients received no treatment during the rest of life phase where a long-term decline of vision occurred. Patients may remain in the same health state, lose at least 10 letters of vision (1 health state) or die.

Figure 4: Visual acuity over time: three phases of the model (non-study eye = fellow eye) (figure 67, page 242 of company submission)



6.4 The company adopted a life-time horizon for its model. It applied 4-weekly cycle lengths with no half-cycle corrections. All costs and outcomes were discounted by 3.5%. The company's base case analyses compared aflibercept with laser treatment and with ranibizumab. The company also presented scenario analyses comparing aflibercept with dexamethasone and fluocinolone acetonide.

ERG comments

6.5 The ERG identified a number of issues with the modelling approach used by the company. These are discussed in further detail in section 6.28 of this document.

Model details

Baseline Characteristics

6.6 The baseline age of patients in the model was 63 years and the proportion of female patients was 42.1%. These values were based on the population enrolled in VIVID and VISTA. The proportion of fellow eye involvement at baseline (46.5%) was drawn from expert opinion rather than the VIVID/VISTA trial data. The company noted that an estimate of 35% was used in NICE technology appraisal guidance 274. The starting vision health state distributions for the study eye and the fellow eye were estimated from the integrated VIVID/VISTA trial analyses. For further details of the starting vision health state distributions for the study eye and the fellow eye, see Table 68, page 250 of the company submission.

Clinical Effectiveness

6.7 Laser efficacy in the model was based on the probabilities of gaining or losing 10 or 15 letters from the VIVID and VISTA trials. Aflibercept and ranibizumab efficacy in the model were based on the probabilities of gaining or losing 10 or 15 letters which were estimated by applying the relative risks calculated as part of the network meta-analysis (see section 5 of this document) to the equivalent probabilities for laser. Dexamethasone efficacy was based on the probability of gaining

10 letters, which was estimated by applying the relative risks from the indirect comparison of aflibercept with dexamethasone using the PLACID study (see section 5.29 of this document). For the comparison with fluocinolone acetonide, rates of improvement were taken directly from the FAME trial (which compared fluocinolone acetonide with sham fluocinolone acetonide), while rates of worsening were assumed to be the same as those of laser. This results in the monthly transition probabilities during the first year of the model shown in Table 9.

Table 9 Monthly transition probabilities applied within the model during year 1 (table 25, page 78 of ERG report)

Treatment	Number of health state transitions			
	+2HS	+1HS	-1HS	-2HS
Laser	0.67%	1.70%	1.28%	0.78%
Aflibercept	2.08%	3.51%	[redacted]	0.02%
Ranibizumab	1.48%	2.95%	0.47%	0.15%
Dexamethasone	0.67%	2.00%	1.28%	0.78%
Fluocinolone	1.62%	1.31%	1.28%	0.78%
HS: Health state				

6.8 Patients can have their eye treated for up to 4 years of maintenance after the first year of treatment. Those eyes remaining on treatment were assumed to have stable vision. Those coming off treatment were assumed to have a steady decline in their vision, with 1.15% of eyes off treatment being assumed to decline by 10 letters and so to transfer to the next worst health state. This rate was based upon the three month 3.5% rate used in NICE technology appraisal guidance 274. Non-DMO eyes were subject to a monthly 0.17% probability of deteriorating by 1 health state.

6.9 Monthly treatment discontinuation rates were estimated using data from VIVID and VISTA and the network meta-analysis. The relative risks from the network meta-analysis were used to estimate discontinuation for aflibercept and ranibizumab to ensure randomisation was not broken. For

further details of the rates used in the model, see table 69, page 250 of the company submission.

6.10 The following adverse events were considered in the model; cataracts, endophthalmitis, retinal detachment, vitreous haemorrhage and ocular hypertension. Adverse events were modelled to occur only in patients who were on treatment. For laser, monthly adverse events rates from VIVID and VISTA were used. For aflibercept and ranibizumab, monthly adverse event rates were estimated by applying relative risks from the network meta-analysis to the relative risks for laser. Dexamethasone and fluocinolone acetonide, monthly adverse event rates were taken directly from the trial publications. In these comparisons, observed aflibercept rates were used. The company stated that these were crude comparisons as randomisation was broken. For further details of the monthly rates of adverse events on treatment, see Table 26, page 79 of the ERG report.

6.11 Background mortality rates per patient age were taken from the England and Wales 2010-2012 national life tables. To reflect the additional risk of mortality associated with a diabetic cohort, a relative risk (compared with a non-diabetic general population) of 1.95 was applied to the background mortality rates. The mortality rates associated with diabetes were taken from the Framingham Heart Study. A relative risk of mortality associated with poor vision (1.23) was also applied to individuals who were blind (HS7 or HS8) in one or both eyes. The company stated that this was similar to the estimates used in NICE technology appraisal guidance 274.

Health related quality of life

6.12 The health states in the company's economic model were defined by vision in both eyes and therefore health state utilities (and hence QALYs) account for which was the BSE and WSE. This approach required a total of 36 utility values to account for every possible combination of BSE and WSE..

6.13 The company used 4 sources of health-related quality of life data in its cost-effectiveness analyses. For its base case analyses, the company used utility values from Czoski-Murray et al (2009). The company stated that they had used these values because they had been accepted by the appraisal committee during the appraisal of other technologies for DMO (NICE technology appraisal guidance 274). The company also used utility values from the trial EQ-5D data, Brown (1999) and Brown (2000) as scenario analyses (Table 10). The submission provided details of an ordinary least squares (OLS) analysis of the pooled VIVID and VISTA EQ-5D data. This regresses quality of life upon the logarithms of the BCVA of the BSE and of the WSE.

Table 10 BCVA quality of life: values from the literature (Table 29, page 81 of ERG report)

	Czoski Murray	**Brown 1999**	**Brown 2000**	**Trial EQ-5D[1]**
HS1	0.856	0.839	0.890	[redacted]
HS2	0.764	0.839	0.890	[redacted]
HS3	0.690	0.783	0.810	[redacted]
HS4	0.617	0.783	0.690	[redacted]
HS5	0.543	0.732	0.558	[redacted]
HS6	0.469	0.681	0.545	[redacted]
HS7	0.396	0.630	0.520	[redacted]
HS8	0.263	0.579	0.460	[redacted]

[1] For comparison, the corresponding values estimated from the VIVID/VISTA EQ-5D ordinary least squares regression are presented.

6.14 The utility values from Czoski-Murray, Brown (1999) and Brown (2000) apply to the bilateral BCVA only. In order for these values to fit the BSE and WSE states seperately, the company allowed a proportion of the BSE utility impact for a given change in the health state to apply to the same change in the health state of the WSE. This adjustment factor was given as 30% and was applied according to the formula 1/[1+(1/30%)], which resulted in a proportional effect of 23%. Table 11 shows the calculated WSE utilities. The transitional matrix used in the analysis for both WSE

and BSE are presented in tables 28-32, pages 81 and 82 of the ERG report.

Table 11 BCVA quality of life: WSE values (adapted from tables 28 and 30-32, pages 81 & 82 of ERG report)

	Czoski Murray	Brown 1999	Brown 2000	Trial EQ-5D[1]
HS1	0.8559	0.8390	0.8900	[redacted]
HS2	0.8346	0.8390	0.8900	[redacted]
HS3	0.8177	0.8261	0.8715	[redacted]
HS4	0.8007	0.8261	0.8438	[redacted]
HS5	0.7837	0.8143	0.8134	[redacted]
HS6	0.7667	0.8025	0.8104	[redacted]
HS7	0.7497	0.7908	0.8046	[redacted]
HS8	0.7192	0.7790	0.7908	[redacted]

[1] For comparison, the corresponding values estimated from the VIVID/VISTA EQ-5D ordinary least squares regression are presented.

6.15 The model assumed a constant utility in each health state meaning utility changes were only in relation to BCVA and not the duration spent in the health state. The following disutilities were applied for adverse events; cataract (0.140), endophthalmitis (0.000), retinal detachment (0.130), glaucoma (0.000), vitreous haemorrhage (0.020) and raised intraocular pressure (0.000).

Costs

6.16 The unit costs of treatment with aflibercept, ranibizumab and laser are shown in Table 12. In the company's cost effective analyses the unit cost of treatment with aflibercept was modelled using the PAS price of [redacted].

6.17 Table 13 and Table 14 show the number of treatment and monitoring visits modelled over 5 years for aflibercept and the comparators.

6.18 Adverse event costs were taken from NHS reference costs and included the cost of cataract extraction, treatment of retinal detachment and

vitreous haemorrhage. In addition, an average annual cost of blindness of £6,448 was obtained from the literature, and updated for inflation. This cost was applied to both eyes falling in HS7 or HS8. The estimated costs and probabilities associated with blindness are presented in Table 15.

Table 12 Unit costs of treatment (table 88, page 285 of company submission)

Treatment	Cost (per patient)	Source
Laser treatment	£117.00	NHS reference costs 2012-2013 (82)
Aflibercept	£816.00	British National Formulary 66
Aflibercept PAS	[redacted]	Bayer (PAS price used in analysis)
Ranibizumab	£742.17	British National Formulary 66

Table 13 Number of treatments per year (table 85, page 283 of company submission)

Number of treatments	Y 1	Y 2	Y 3	Y 4	Y 5	Beyond (annual)	Source (Yr 1 only)	Source (Yr's 2-5)
Laser	2.4	1	0.8	0.4	0.3	0	VIVID/VISTA	Physician survey
Aflibercept	8	4	2.3	1.2	1	0	SmPC	Assume same as ranibizumab
Ranibizumab	7.93	4	2.3	1.2	1	0	NMA	Physician survey
Yr; year, SmPC; summary of product characteristics, NMA; network meta analysis								

Table 14 Number of hospital visits for treatment and monitoring per year (table 86, page 284 of company submission)

No. of visits	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Source (Yr 1 only)	Source (Yr 2-5)
Laser	4	4	2.6	2.2	1.9	Professional guidelines	Physician survey
Aflibercept	8	6.3	4	4	2	SmPC	Assumption same as ranibizumab
Ranibizumab	12	6.3	4	4	2	SmPC up to Sept 2014	Physician survey
Yr; year, SmPC; summary of product characteristics							

Table 15 Estimated costs and probabilities of outcomes associated with blindness (table 84, page 281 of company submission)

Outcome	Estimated cost	Estimated 1-year probability of outcome in patients with CNV and 20/200 visual acuity
Blind registration[1]	£59.70 + £37.71	94.5%
Low vision aids	£136.33	33%
Low vision rehabilitation	£205.30	11%
Housing and council tax benefit	£2714.40	45%
Social security	£1924	63%
Tax allowance	£319	5%
Depression	£391.97	38.6%
Hip replacement	3669	5%
Community care	£2848.63	6%
Residential care	£15904.41 (~30%)[2]	30%
CNV; Choroidal neovascularisation [1]First year of blindness only; [2] ~30% of residents pay for themselves. Estimated from Meade and Hyde		

Company's base-case results and sensitivity analysis

6.19 The results of the base-case analyses (Table 16) show that aflibercept (PAS price) dominates both ranibizumab and laser.

Table 16: Company base-case results (table 107, page 314 of company submission)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
Aflibercept	[redacted]	11.398	7.690				
Laser	[redacted]	11.339	7.300	-2,438	0.059	0.3899	Dominant
Ranibizumab	[redacted]	11.384	7.598	-8,911	0.014	0.092	Dominant
Inc; Incremental. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Sensitivity analyses

6.20 The company conducted a range of determinist and probabilistic sensitivity analyses. Deterministic sensitivity analyses were performed by means of one-way and multivariate sensitivity analyses. Overall, there were 116 sensitivity analyses conducted for the base-case analyses.

6.21 The key model drivers identified for the comparison of aflibercept with ranibizumab were; the time horizon, the relative efficacy for both aflibercept and ranibizumab, the cohort starting age and the number of ranibizumab injections at year 1. When aflibercept was compared with laser, the key model drivers were; a shorter time horizon of 5 and 10 years, the starting age of the cohort and the rate at which a DMO eye visual acuity declined. For further details of the results of the sensitivity analyses, see Figures 70 & 71, page 316 of the company submission.

6.22 The probabilistic sensitivity analysis (PSA) was run with 1,000 simulations. The results of the PSA are shown in Table 17.

Table 17 Probability of being cost effective (table 109, page 317 of company submission)

	Probability of being cost-effective		
Willingness to pay	£0	£20,000	£30,000
Aflibercept vs. ranibizumab	0.996	0.996	0.996
Aflibercept vs. laser	0.580	0.971	0.993

6.23 The company explored the effect of a discount on the list price of ranibizumab (Table 18). The results showed that the ICER for aflibercept remained under £30,000 per QALY gained up to a ranibizumab price discount of 80%.

Table 18: ICERs for aflibercept (PAS price) compared with ranibizumab (using various discounts on the list price of ranibizumab). (Table 108, page 314 of company submission)

Ranibizumab PAS %	Discounted ranibizumab price (£)	Incremental Costs (£)	Incremental QALYs	ICER (£)
0%	742.2	-8,911	0.0919	Dominant
5%	705.1	-8,181	0.0919	Dominant
10%	668.0	-7,452	0.0919	Dominant
15%	630.8	-6,723	0.0919	Dominant
20%	593.7	-5,993	0.0919	Dominant
25%	556.6	-5,264	0.0919	Dominant
30%	519.5	-4,534	0.0919	Dominant
35%	482.4	-3,805	0.0919	Dominant
40%	445.3	-3,075	0.0919	Dominant
45%	408.2	-2,346	0.0919	Dominant
50%	371.1	-1,617	0.0919	Dominant
55%	334.0	-887	0.0919	Dominant
60%	296.9	-158	0.0919	Dominant
65%	259.8	572	0.0919	6,223
70%	222.7	1,301	0.0919	14,163
75%	185.5	2,030	0.0919	22,103
80%	148.4	2,760	0.0919	30,043
85%	111.3	3,489	0.0919	37,983
90%	74.2	4,219	0.0919	45,923
95%	37.1	4,948	0.0919	53,863
100%	0.0	5,678	0.0919	61,803
PAS; patient access scheme, ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years				

Company's scenario analyses

6.24 The company carried out a number of scenario analyses. These are detailed below:

- Comparing aflibercept with laser based on observed efficacy data from the VIVID and VISTA trials
- Replacing the utility values from Czoski-Murray (2009) with values from VIVID and VISTA EQ-5D data, Brown (1999) and Brown (2000).

- Applying the same efficacy and safety values to aflibercept and ranibizumab and assuming the same number of injections..
- Applying a relative risk of 2.45 to the whole population considered in the model independently on the level of visual acuity.

6.25 The results from these scenario analyses showed that aflibercept continued to dominate both laser and ranibizumab. For further details of the scenario analyses see pages 320- 325 of the company submission.

6.26 The company also undertook scenario analyses for a subgroup of patients with CRT of 400 µm or more. The company modelled the probabilities of gaining and losing letters in the laser arm specific to the CRT ≥ 400µm subgroup of the VIVID and VISTA trial data. The results of these analyses showed that aflibercept (CRT≥ 400µm subgroup) dominated both laser and ranibizumab. For further details, see pages 93-94 of the ERG report.

6.27 The company undertook exploratory subgroup analyses comparing aflibercept with dexamethasone and with fluocinolone acetonide. The company considered these scenario analyses to be exploratory because of the limitations of any evidence to inform an indirect comparison of efficacy and safety in the appropriate population. The results of these analyses are provided in tables 19 & 20.

Table 19 Exploratory scenario analysis: aflibercept compared with dexamethasone (table 118, page 328 of company submission)

Scenario	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
aflibercept	[redacted]	7.552			
Dexamethasone	[redacted]	7.232	-9,888	0.320	Dominant
Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio					

Table 20 Exploratory scenario analysis: aflibercept compared with fluocinolone acetonide (table 121, page 331 of company submission)

Scenario	Total cost	Total QALY	Inc. cost	Inc. QALY	ICER
aflibercept	[redacted]	7.552			
Fluocinolone	[redacted]	7.295	-12,414	0.271	Dominant
Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio					

6.28 The company undertook exploratory analyses comparing aflibercept with fluocinolone acetonide in a subgroup of patients with pseudophakic lenses. In this comparison, probabilities of gaining 10 and 15 letters were obtained from the pseudophakic subgroup in VIVID and VISTA and from the FAME trial (gaining 15 or more letters for fluocinolone acetonide). The probabilities of losing 10 or 15 letters were obtained from the VIVID and VISTA overall populations. The company explained that this approach had been used because a small number of patients (aflibercept treatment arm [redacted]. laser arm n=[redacted]) lost at least 10 letters in the overall population and a subgroup number would have been too small to perform a meaningful comparison. The company presented the results of the exploratory analyses using both the list price of fluocinolone acetonide and applying various discounts (0% to 100%). In all of the exploratory analyses for the comparison of aflibercept with fluocinolone acetonide in the subgroup of patients with pseudophakic lenses, aflibercept dominated. For further details of the company's exploratory analyses, see table 126 and 127, page 341 of the company submission.

ERG's comments and exploratory analyses

6.29 The ERG did not provide comments or exploratory analyses for the comparison of aflibercept with dexamethasone or with fluocinolone acetonide.

6.30 The ERG identified aspects of the company's base-case model that involved errors in data analysis, parameter values and methodology. These are list below;

Data inputs

Number of treatments

6.31 The company estimated 7.93 ranibizumab injections in the first year based on the trials included in the network meta-analysis, however the ERG noted that the mean number of injections reported in RESTORE and REVEAL have been combined with the median number from the DCRC.net trial. The ERG commented that it may not be appropriate to combine the values in this way. The ERG re-calculated the average injections excluding the DCRC.net trial. This resulted in a weighted average of 7.43 ranibizumab injections in the first year. The ERG considered this to be a better estimate for the base case analyses.

6.32 The company had modelled 8.00 aflibercept injections in the first year. However, the ERG commented that 8.5 injections were more appropriate for the base case analyses because the final injection in the first year will be at the start of month 12.

Number of monitoring visits

6.33 The ERG highlighted the recently revised SmPC for ranibizumab. The ERG stated that the update to the SmPC removes the need for additional hospital monitoring visits in the first year of treatment. The ERG suggested that because of this change, the number of hospital visits for ranibizumab in the model should reduce from 12 to 8. This would bring the number of monitoring visits for ranibizumab down to the same number as aflibercept in the base case analysis.

Cost of blindness

6.34 The ERG commented that the data used in the company's model to inform the cost of blindness (£6,448) might not be appropriate. In NICE Technology appraisal 298: Ranibizumab for treating choroidal neovascularisation associated with pathological myopia, a report from the Kings fund by McCrone et al was identified which the ERG felt, provided a better estimate for the cost of blindness than that used in Meads et al

which was used in the company's base case analyses. This results in an increased cost of blindness in the first year of £7,510 and a subsequent annual cost of £7,429.

6.35 The ERG also noted that the costing of Meads et al was intended for an patient group with age-related macular degeneration which is older than the baseline age assumed in the model. The majority of the estimated costs in Mead et al related to residential care. The ERG stated that a sensitivity analysis that reduces the proportion requiring residential care would be useful. In the current calculation, 30% of people required residential care, reducing this by a third to 20% reduced the annual costs of blindness to £5,620. However, the ERG noted that the starting age in the model was 63 years and average survival was approximately 15 years, which may tend to increase the likelihood of blindness requiring residential care as the model progresses.

Utility values

6.36 The ERG raised concerns regarding the utility values obtained from Czoski-Murray (2009) which were used in the company base case analyses. The ERG noted that these values apply only to the BCVA. As a result, utility impact for a change in the BCVA of the BSE applies the same change in BCVA of the WSE. The ERG did not understand why the company used the equation (1/(1+(1/x30%)) which was presented in the submission. When the equation was applied to estimate the WSE values, it resulted in a proportional difference of 23% not 30% (which was stated in the submission).

6.37 The ERG considered the use of the EQ-5D data collected alongside the VISTA and VIVID trials to be more appropriate because it accounts for changes in the BSE and WSE while also taking into account age and BMI as covariates. In response to a question raised during clarification (question C5) the company confirmed that the OLS, the random effect and the GEE analyses each use a data set of 2,321 observations. The ERG commented that given the pooled VIVD and VISTA number of patients of

865 across the 3 treatment arms, this suggested approximately 3 observations per patient, which would correspond with baseline, 24 weeks and 52 weeks. The ERG further commented that if this was the case and approximately 3 observations per patient were being treated as independent observations within the OLS analysis, this analysis was not valid. In these circumstances, the GEE analysis should be preferred. (for further details see pages 118-121 of the ERG report).

Modelling approach

6.38 The ERG identified some general methodological problems with the approach adopted by the company to modelling. The ERG stated these could account for the poor correspondence between the modelled health state distributions and those observed in VIVID and VISTA. The ERG identified the following potential issues:

- The proportions transferring between health states in the laser treatment arm were assumed to be constant and not related to the eye's BCVA.
- The monthly proportions transferring between health states in the laser treatment arm assumed a constant proportional change each month. The clinical evidence suggested that the changes occurred mainly during the first month with a tailing off after that to 6 months, and broad stability for the 6 months thereafter.
- The relative risks applied to the 12-month period. The approach adopted assumed that these were constant through time.
- The cost of blindness in the model was undiscounted and applied as monthly amounts, which over estimates the total costs for blindness.

ERG's exploratory analyses

6.39 The ERG undertook exploratory base case analyses using the changes identified during its critique of the model. The amendments included;

- Revising the number of aflibercept injections to 8.50, 5.45 and 3.00 in years 1, 2 and 3.

- Revising the number of ranibizumab injections to 7.43, 4.00 and 3.00 in years 1, 2 and 3.
- Assumed that eyes in HS7 and HS8 (blindness) were not treated during the maintenance phase, as in the company base case analyses.
- Revised the annual costs of blindness to £7,429.
- Revised the costs of blindness to be monthly.
- Revised the costs of blindness to be discounted.

The results of the ERG's exploratory base case analyses are provided in Table 21 (aflibercept compared with laser) and Tables 22-23 (aflibercept compared with ranibizumab).

6.40 The ERG also undertook additional exploratory sensitivity analyses (Table 24 and Table 25). The parameters explored included:

- Applying the ERG's calculated relative risks based on the 4 main trials by; excluding VISTA from the analysis, excluding REVEAL from the analysis and excluding both VISTA and REVEAL from the analysis.
- Exploring the use of the VIVID and VISTA EQ-5D values using the OLS, random effects and GEE models.
- Exploring the ERG's derived health-related quality of life values from Brown (1999) and Brown (2000) which were similar to the utility values for Czoski-Murray and result in bilateral health-related quality of life values.
- Exploring the impact of reducing the proportion of those blind that required residential care from 30% to 20%. This caused the annual average cost of blindness to reduce from £7,429 to £5,640.

Table 21 ERG's exploratory analyses: aflibercept compared with laser (tables 37 & 73, pages 86 & 126 of ERG report)

	Company base case results			**ERG exploratory analysis**		
	Aflibercept	Laser	Incremental Cost	Aflibercept	Laser	Incremental Cost
Treatment 1st eye	[redacted]	[redacted]	£7,643	[redacted]	[redacted]	£9,327
Treatment 2nd eye	[redacted]	[redacted]	£3,271	[redacted]	[redacted]	£4,179
Adverse events 1st eye	[redacted]	[redacted]	-£71	[redacted]	[redacted]	-£5
Adverse events 2nd eye	[redacted]	[redacted]	-£22	[redacted]	[redacted]	-£5
Fl. Angio.	[redacted]	[redacted]	£0	[redacted]	[redacted]	£0
Visits	[redacted]	[redacted]	-£213	[redacted]	[redacted]	-£355
Blindness	[redacted]	[redacted]	-£13,046	[redacted]	[redacted]	-£211
Total Costs	[redacted]	[redacted]	-£2,438	[redacted]	[redacted]	£12,931
Total QALYs	7.690	7.300	0.390	7.424	7.043	0.381
ICER			**Dominant**			**£33,921**
Fl. Angio: fluorescein angiography; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio						

Table 22 ERG's exploratory analyses: aflibercept compared with ranibizumab (tables 39 & 74, pages 86 & 126 of ERG report)

	Company base case results			**ERG exploratory analysis**		
	Aflibercept	Ranibizumab	Incremental Cost	Aflibercept	Ranibizumab	Incremental Cost
Treatment 1st eye	[redacted]	[redacted]	-£4,225	[redacted]	[redacted]	-£2,797
Treatment 2nd eye	[redacted]	[redacted]	-£1,813	[redacted]	[redacted]	-£1,263
Adverse events 1st eye	[redacted]	[redacted]	£376	[redacted]	[redacted]	£307
Adverse events 2nd eye	[redacted]	[redacted]	£117	[redacted]	[redacted]	£138
Fl. Angio.	[redacted]	[redacted]	£0	[redacted]	[redacted]	£0
Visits	[redacted]	[redacted]	-£568	[redacted]	[redacted]	-£739
Blindness	[redacted]	[redacted]	-£2,798	[redacted]	[redacted]	-£35
Total Costs	[redacted]	[redacted]	-£8,911	[redacted]	[redacted]	-£4, 90
Total QALYs	7.690	7.598	0.092	7.424	7.333	0.091
ICER	**Dominant**			**Dominant**		
Fl. Angio: fluorescein angiography; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio						

Table 23 ERG's exploratory base case results for aflibercept compared with ranibizumab (applying discounts to the list price of ranibizumab) (erratum for Table 75, page 127 of ERG report)

Ranibizumab PAS	Incremental Cost	ICER
5%	-£3,663	Dominant
10%	-£2,936	Dominant
15%	-£2,209	Dominant
20%	-£1,481	Dominant
25%	-£754	Dominant
30%	-£27	Dominant
35%	£700	£7,667
40%	£1,427	£15,633
45%	£2,154	£23,598
50%	£2,881	£31,563
55%	£3,608	£39,528
60%	£4,335	£47,494
65%	£5,063	£55,459
70%	£5,790	£63,424
75%	£6,517	£71,389
80%	£7,244	£79,354
85%	£7,971	£87,320
90%	£8,698	£95,285
95%	£9,425	£103,250
100%	£10,152	£111,215
PAS; patient access scheme, ICER; incremental cost effectiveness ratio		

Table 24 ERG's exploratory sensitivity analyses comparing aflibercept with laser (with aflibercept PAS) (table 76, page 128 of ERG report.

	Inc. QALY	Inc. Cost	ICER
ERG Base case	0.381	£12,931	£33,921
RR from all trials	0.382	£12,910	£33,810
RR excluding VISTA	0.358	£13,035	£36,363
RR excluding REVEAL	0.376	£12,909	£34,356
RR excluding VISTA & REVEAL	0.358	£12,971	£36,242
EQ-5D OLS analysis	0.128	£12,931	£101,198
EQ-5D Random effects analysis	0.111	£12,931	£116,800
EQ-5D GEE analysis	0.110	£12,931	£117,222
Brown 1999 quality of life values	0.287	£12,931	£45,024
Brown 2000 quality of life values	0.432	£12,931	£29,915
46% fellow eye involvement at baseline	0.346	£11,660	£33,657
Revert to company mid letters for HS1 and HS8	0.403	£12,931	£32,121
Proportion needing residential care from 30% to 20%	0.381	£12,982	£34,056
Proportion of visits shared between SE and FE from 50% to 0%	0.277	£8,804	£31,757
Proportion of visits shared between SE and FE from 50% to 100%	0.485	£17,058	£35,158
Proportion of treatment visits that double as monitoring to from 100% to 50%	0.381	£13,768	£36,117
Proportion of visits that are shared between SE and FE to 0%	0.381	£12,770	£33,500
Revised blindness mortality multiplier to not apply to those blind in only one eye	0.358	£12,908	£36,063
4.0 aflibercept treatments in year 2	0.381	[redacted]	[redacted]
2.3 ranibizumab treatments in year 3.	0.381	[redacted]	[redacted]
Inc; incremental, QALY; quality adjusted life year, ICER; incremental cost effectiveness ratio, RR; relative risk, OLS; ordinary least squares, GEE; generalised estimating equation, FE; fellow eye, SE; study eye			

Table 25 ERG's exploratory sensitivity analyses comparing aflibercept with ranibizumab: (with aflibercept PAS and discounts applied to the list price of ranibizumab (erratum for table 78, page 132 of ERG report)

		Estimated ranibizumab Patient Access Scheme Discounts							
		25% PAS		**30% PAS**		**35% PAS**		**40% PAS**	
Change made to base case	Inc QALYs	Inc Costs	ICER	Inc Costs	ICER	Inc Costs	ICER	Inc Costs	ICER
ERG base case	0.091	-£754	Dominant	-£27	Dominant	£700	£7,667	£1,427	£15,633
RR excluding VISTA	0.073	-£650	Dominant	£77	£1,056	£804	£11,012	£1,531	£20,967
RR excluding REVEAL	0.152	£64	£422	£753	£4,973	£1,443	£9,524	£2,133	£14,075
RR excluding VISTA & REVEAL	0.072	£81	£1,129	£774	£10,728	£1,466	£20,328	£2,158	£29,928
EQ-5D OLS analysis	0.012	-£754	Dominant	-£27	Dominant	£700	£56,402	£1,427	£114,995
EQ-5D GEE analysis	0.008	-£754	Dominant	-£27	Dominant	£700	£86,915	£1,427	£177,205
Brown 1999 quality of life values	0.061	-£754	Dominant	-£27	Dominant	£700	£11,548	£1,427	£23,545
Brown 2000 quality of life values	0.106	-£754	Dominant	-£27	Dominant	£700	£6,597	£1,427	£13,449
46% fellow eye involvement at baseline	0.082	-£740	Dominant	-£82	Dominant	£575	£6,993	£1,232	£14,988
Revert to company mid letters for HS1 and HS8	0.098	-£754	Dominant	-£27	Dominant	£700	£7,110	£1,427	£14,497
Proportion needing residential care from 30% to 20%	0.091	-£746	Dominant	-£19	Dominant	£709	£7,762	£1,436	£15,727
Proportion of visits shared between SE and FE from 50% to 0%	0.064	-£715	Dominant	-£213	Dominant	£289	£4,485	£791	£12,275

Proportion of visits shared between SE and FE from 50% to 100%	0.118	-£794	Dominant	£158	£1,341	£1,111	£9,402	£2,063	£17,463
Proportion of treatment visits that double as monitoring to from 100% to 50%	0.091	-£634	Dominant	£93	£1,021	£820	£8,986	£1,547	£16,951
Proportion of visits that are shared between SE and FE to 0%	0.091	-£1,031	Dominant	-£304	Dominant	£423	£4,632	£1,150	£12,597
Revised blindness mortality multiplier to not apply to those blind in only one eye	0.087	-£759	Dominant	-£31	Dominant	£696	£8,034	£1,423	£16,431
8.1 ranibizumab treatments in yr 1	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4.0 aflibercept treatments in yr 2	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2.3 treatment visits in yr 3 (both treatments)	0.091	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8.0 monitoring visits for ranibizumab in yr 1	0.091	-£201	Dominant	£526	£5,765	£1,253	£13,730	£1,980	£21,695
Inc; incremental, QALY; quality adjusted life year, ICER; incremental cost effectiveness ratio, RR; relative risk, OLS; ordinary least squares, GEE; generalised estimating equation, FE; fellow eye, SE; study eye									

7 Innovation

7.1 Justifications for considering aflibercept to be innovative:

The company commented that aflibercept solution for injection is innovative as it has a different mode of action to the other VEGF inhibitors. It addresses a wider range of growth factors and includes Placental Growth Factor (PIGF) binding which current treatments do not. It is expected that aflibercept solution for injection will provide for reductions in both case load and budget requirements. There would be cost and capacity savings in frequency of monitoring compared with current licensed anti-VEGF treatments in an NHS which is currently under increasing pressure for its ophthalmology services.

8 Equality issues

8.1 None reported

9 Authors

Victoria Kelly
Technical Lead

Nicola Hay
Technical Adviser

With input from the Lead Team (Emily Lam, Suzanne Martin, and Paul Tappenden).

Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002392/WC500135815.pdf