Aflibercept solution for injection for the treatment of wet age-related macular degeneration

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Rider on responsibility for report

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Ewen Cummins reviewed the cost-effectiveness evidence, carried out further sensitivity analyses, and drafted Section 5. Rhona Johnston contributed to the checking and rebuilding the economic model. Kieran Rothnie and Miriam Brazzelli reviewed the methods of the clinical effectiveness evidence synthesis. Noemi Lois and Jennifer Burr provided clinical advice and contributed to the background and the critique of the manufacturer's decision problem sections. Shona Fielding critiqued the statistical methods used, checked all the numerical results, tables, and figures of the clinical effectiveness part of the submission, and conducted further statistical analyses. Fiona Stewart critiqued the methods used for identifying relevant studies in the literature. Miriam Brazzelli supervised the work throughout the project. All authors assisted in preparing the final manuscript and commenting on early drafts.

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LIST OF ABBREVIATIONS

AE	Adverse event
AFB	Aflibercept
AIC	Academic in confidence
AMD	Age-related macular degeneration
BCVA	Best corrected visual acuity
BNF	British National Formulary
BSC	Best supportive case
BSE	Best seeing eye
CIC	Commercial in confidence
CNV	Choroidal neovascularisation
CRT	Central retinal thickness
EQ-5D	Euroqol 5 dimensions
ERG	Evidence review group
ETRDS	Early treatment diabetic retinopathy study
FAS	Full analysis set
FDA	Food and drug administration
HES	Hospital episode statistics
HRQoL	Health related quality of life
ICER	Incremental cost effectiveness ratio
IOP	Intraocular pressure
IPCV	Idiopathic polypoidal choroidal vasculopathy
ITC	Indirect treatment comparison
LOCF	Last observation carried forward
NEI VFQ-25	National eye institute visual functioning questionnaire - 25
NICE	National Institute for health and Clinical Excellence
NMA	Network meta-analysis
OCT	Optical coherence tomography
OR	Odds ratio
PDT	Photodynamic therapy
PPS	Per protocol set
PRN	Pro re nata
PSA	Patient access scheme
PSS	Personal social services
PSSRU	Personal social service research unit
QALY	Quality adjusted life year

RAP	Retinal angiomatous proliferation
RBZ	Ranibizumab
RCT	Randomised controlled trial
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SAF	Safety analysis set
SG	Standard gamble
STA	Single technology appraisal
TEAE	Treatment emergent adverse events
TPM	Transition probability matrix
TTO	Time trade off
TZD	Thiazolidinedione
VA	Visual acuity
VEGF	Vascular endothelial growth factor
WSE	Worse seeing eye

1 SUMMARY

1.1 Scope of the submission

The manufacturer's submission from Bayer addressed the use of aflibercept (2mg every 8 weeks) in adults suffering from wet age-related macular degeneration.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The clinical effectiveness evidence submitted by the manufacturer consists of two phase-three RCTs of aflibercept versus ranibizumab and 10 additional RCTs involving either ranibizumab or aflibercept, which were used to inform the network meta-analysis.

The evidence on clinical effectiveness of 2 mg aflibercept initiated with three monthly doses and then given every 8 weeks (2mg Q8) compared to 0.5mg ranibizumab given every 4 weeks (0.5mg Q4), came from two international RCTs (VIEW 1 and VIEW 2). Both trials were sponsored by Regeneron Pharmaceuticals, New York and Bayer Healthcare, Germany. The primary outcome in the two trials was maintaining vision at 12 months (from baseline) and this was defined as losing less than 15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS). Other relevant outcomes included change in choroidal neovascularisation (CNV); change in central retinal thickness, fluid on optical coherence tomography, health-related quality of life, incidence of adverse events, and mortality rates.

Efficacy of aflibercept with fixed dose ranibizumab

In the pooled analysis, those taking aflibercept 2mg Q8 95.3% (510/535) maintained vision (loss of less than 15 letters on ETDRS) at week 52 compared to 94.4% (508/538) on ranibizumab 0.5mg Q4 (difference of -0.9%, 95% CI ; -3.5, 1.7%). The difference was similar at 96 weeks (-0.8%, 95% CI; -3.8, 2.3). For change in ETDRS from baseline to week 52, ranibizumab 0.5mg Q4 had mean change 8.74 (SD not reported) compared to aflibercept 2mg Q8 mean = 8.4 (SD not reported). The difference between treatments was found to be -0.32 letters (95% CI; -1.87, 1.23), which was not statistically significant. No difference was found between treatments for proportion of patients gaining at least 15 letters, change in quality of life (measured by the Naitonal Eye Institute Visual Functioning Questionnaire - 25), choroidal neovascularisation or central retinal thickness.

Safety

The incidence and type of adverse events (AEs) for ocular, non-ocular and injection related AEs were similar between treatment groups. The most common adverse reactions in

aflibercept patients were conjunctival haemorrhage (28%), eye pain (8.9%), vitreous detachment (7.7%), increased intraocular pressure (7.2%) and cataract (6.6%). Proportions of patients receiving ranibizumab experiencing these AEs were similar. The incidence of non-ocular serious AEs was similar in the two patient groups. Adverse event related death occurred in 15/595 (2.5%) of ranibizumab patients compared to 18/610 (3.0%) aflibercept (2mg Q8) patients. None were thought to be drug related and causes of death were consistent with the aged study population.

Efficacy of aflibercept with ranibizumab pro ne nata (PRN)

The manufacturer presented an indirect comparison of aflibercept 2mg Q8 with a PRN dosing of 0.5mg ranibizumab, the 'treat to target' dosing regimen which is used in clinical practice. The manufacturer presented results of the simple Bucher approach, frequentist network analysis and Bayesian network analysis for three outcomes: maintaining vision (loss of < 15 letters), mean change in best corrected visual acuity (BCVA), and improved vision. For the comparison of aflibercept 2mg Q8 relative to ranibizumab 0.5mg PRN, the odds ratio (OR) from the Bayesian analyses for maintained vision was 1.51 (0.42 to 5.94) and for improved vision OR = 1.28 (0.45 to 3.68). For the outcome of mean change in BCVA, the mean difference was -2.87 (-10.02 to 4.30) and with the exclusion of a trial at high risk of bias (DETAIL), mean difference = 1.15 (-3.92 to 6.09). The point estimates favoured aflibercept but with no statistically significant differences between treatments.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

There was a concern over the use of last observation carried forwards (LOCF) within VIEW 1 and VIEW 2 as it assumes stable disease which may not be appropriate for wet AMD. The ERG undertook sensitivity analyses using observed data. These data obtained through LOCF also informed the indirect comparison of the primary outcome (i.e. maintained vision at week 52), therefore the ERG repeated the analysis using the observed data as an alternative. The ERG noted that one arm of one of the trials (DETAIL) had been omitted from the network for the outcome of mean change in BCVA. The ERG undertook an additional analysis with this treatment arm included.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer models the cost effectiveness of aflibercept with ranibizumab variable dosing (PRN). The health states of the model are defined in terms of 15 ETDRS letters, with no visual impairment in the treated eye being defined as having a BCVA of more than 80 letters and blindness in the treated eye being defined as having a BCVA of no more than 35 letters.

While the aflibercept trials had a ranibizumab control arm, during the first year of the trials this was at a fixed dose. As a consequence, the manufacturer relies upon an indirect comparison to estimate the relative risks of gaining letters and maintaining vision at 12 months and at 24 months.

These relative risks are combined with the proportions gaining and maintaining vision in the aflibercept arm of the VIEW 2 trial in year 1 and year 2 to provide the parallel proportions gaining and maintaining vision in the ranibizumab arm. These are then applied to a common baseline distribution to estimate the patient distributions in the aflibercept arm and the ranibizumab arm for the first two years of the model.

For years 3 to 5 of the model, unless they are blind, patients typically remain on treatment. Those on treatment are assumed to have stable vision. A monthly discontinuation rate common to both arms is applied within the model. All patients also cease therapy at the end of year 5. The vision of those not on therapy gradually declines, in line with best supportive care (BSC).

The model has the facility to allow a monthly incidence of 2nd eye involvement from the start of year 3 onwards. This is not further described, as the ERG views the modelling approach adopted for 2nd eye involvement as untenable.

Quality of life data are drawn from the pooled EQ-5D data of the VIEW 2 trial, valued using the UK social tariff. This is then related to binocular vision states.

A 25 year time horizon is adopted, with the perspective and discounting being in line with NICE methods.

For the ex Patient Access Scheme (PAS) base case, including the modelling of 2nd eye development, the manufacturer estimates that aflibercept results in an additional 0.010 QALYs while also saving £3,606, so dominating ranibizumab.

The treatment of the aflibercept PAS is complicated by ranibizumab also having a PAS which has not been communicated to the manufacturer of aflibercept for this assessment. The [redacted] PAS for aflibercept reduces the vial price from £816 to [redacted]. This further increases the savings from aflibercept to [redacted] when compared to the ranibizumab list price. [redacted] Within the manufacturer submission, the only real uncertainty about the cost effectiveness of aflibercept compared to ranibizumab arises when applying the lower confidence limits of the relative risk estimates.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The model assumes that the untreated eye has no wet AMD and no visual impairment. This is unrealistic and not borne out by the trial data which suggest 77% of fellow eyes had visual impairment at baseline, and 19% had wet AMD at baseline as well.

For a variety of reasons, the ERG views the modelling of 2nd eye involvement as untenable. This is unfortunate, as the submission is one of the few that explicitly consider the impact of binocular vision upon quality of life. For this reason, the ERG views the model submitted as a reasonable one eye model. But the quality of life effects within the one eye model will depend upon whether the eye being treated is the better seeing eye (BSE) or the worse seeing eye (WSE). Around a quarter of patients in the trials had their BSE treated. If the BSE is treated this will increase the QALY gain from the more effective treatment, compared to when only the WSE is treated. This needs to be read alongside whether the ERG interpretation of the 24 month relative risks or the manufacturer interpretation of the 24 month relative risks is correct; i.e. which treatment is more effective.

The ERG is of the opinion that the relative risks of gaining letters and maintaining vision at 12 months and at 24 months relate to the periods from baseline. The manufacturer treats the 24 month relative risks as applying between 12 months and 24 months. Since the central estimates for the relative risks at 24 months suggest ranibizumab is superior to aflibercept this results in the ERG approach of estimating patient gains from ranibizumab, while the manufacturer approach estimates patient gains from aflibercept.

The ERG is unclear from what data the proportions gaining letters and maintaining vision have been drawn. Manufacturer supplied 'full analysis set' LOCF data do not appear to be in

line with those of the model, and suggest that a smaller proportion of patients benefit from treatment than that modelling, though note that this affects both arms proportionately.

It appears that the manufacturer may have underestimated the number of aflibercept doses during the first year, and that 8 rather than 7 would have been more reasonable. Other resource use estimates may also have tended to favour aflibercept, such as the cost per administration and the cost per optical coherence tomography examination.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

Strengths

The manufacturer identified all the relevant studies comparing aflibercept to ranibizumab.

With the proviso around the interpretation of the 24 month relative risks, the one eye model is a reasonable model structure.

Another strength of the evidence submitted is the presentation of quality of life values related to binocular vision states. This could have facilitated a richer consideration of the impact of treatment upon vision, if the approach adopted for 2nd eye modelling would have been correct.

Weaknesses and areas of uncertainty

The modelling was poorly documented within the manufacturer submission. Consequently, the ERG has rebuilt the one eye model structure as a cross check. The results of this assessment match those of the manufacturer model when 2nd eye involvement is set to zero.

An important weakness in the current submission is the modelling of 2nd eye involvement, which the ERG regards as untenable.

Within the one eye model structure, there may be a concern around the assumption that the likelihoods of improving vision and maintaining vision under treatment are the same across the health states of the model.

Regardless of the interpretation to be placed upon the 24 month relative risks, there is uncertainty around the relative risks of gaining and maintaining vision relative to ranibizumab. None of the estimates are statistically significantly different from unity.

The ERG is unclear from what data the manufacturer has drawn the proportions gaining and maintaining vision, these seeming to show little correspondence with the FAS LOCF data set supplied at clarification.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Effectiveness

The ERG repeated the indirect comparison for maintained vision using the observed data at week 52 from the full analysis set and obtained an OR = 1.74 (0.47, 6.94). This was slightly different to the manufacturer presented OR = 1.51 (0.42, 5.94) but gave the same overall conclusion of no difference between treatment groups.

Including the ranibizumab 0.3mg fixed arm from DETAIL into the network for mean change in BCVA (baseline to 12 months) provided the result of mean difference = -3.81 (-10.61, 2.95), which was similar to the manufacturer present mean difference = -2.87 (-10.02, 4.30).

Cost-effectiveness

As already mentioned, the ERG views the modelling of 2nd eye involvement as untenable but that the model structure is acceptable as a one eye model. In the light of this, the model can be viewed as a worse seeing eye (WSE) model or as a better seeing eye (BSE) model, the two differing by the quality of life values that are applied to the model health states. For the WSE modelling the ERG has retained the manufacturer quality of life estimates. For the BSE modelling, as an illustrative example the ERG has applied quality of life values drawn from Brown.[1]

Adopting the manufacturer interpretation of the 24 month relative risk data results in aflibercept being estimated to save £1,441 compared to ranibizumab. An additional 0.007 QALYs accrue in the WSE modelling and an additional 0.045 QALYs in the BSE modelling. As a consequence, aflibercept is estimated to dominate ranibizumab.

The lower confidence interval limits of the relative risks result in gains from ranibizumab of 0.016 QALYs for the WSE modelling and 0.092 QALYs for the BSE modelling, resulting in cost effectiveness estimates for ranibizumab of £116,478 per QALY and £19,707 per QALY respectively.

With the aflibercept PAS, [redacted]

[redacted]

Adopting the ERG interpretation of the 24 month relative risk data results in ranibizumab still being more costly than aflibercept, by £1,639, but yielding an additional 0.004 QALYs for the WSE modelling, resulting in a cost effectiveness estimate of £399,140 per QALY. For the BSE modelling the gain increases to 0.027 QALYs so reducing the cost effectiveness estimate to £61,653 per QALY.

The lower confidence interval limits of the relative risks result in gains from ranibizumab of 0.021 QALYs for the WSE modelling and 0.134 QALYs for the BSE modelling, resulting in cost effectiveness estimates for ranibizumab of £99,148 per QALY and £15,139 per QALY respectively.

With the aflibercept PAS, [redacted]

1.8 Key points

- The clinical efficacy of 2mg aflibercept in terms of prevention of visual loss and its safety profile are comparable with that of 0.5mg ranibizumab.
- Aflibercept appears to be more cost-effective than ranibizumab.
- There is considerable uncertainty about the validity of the 2nd eye modelling within the manufacturer's submission
- Bevacizumab has not been included as a comparator in this appraisal.

2 BACKGROUND

Age-related macular degeneration (AMD) is the major cause of vision loss and blindness in adults in industrialized countries.[3] There are two main types of AMD, wet (neovascular) and dry (non-neovascular) AMD. Neovascular (wet) AMD is characterised by pathological choroidal neovascularisation (CNV), which is the growth of abnormal new blood vessels under the retinal pigment epithelium (RPE) of the retina, over it into the subretinal space or in both locations. Leakage of fluid, blood and lipids from the CNV leads to disruption and dysfunction of the retina and eventually lost of photoreceptors and RPE with subsequent irreversible central vision loss. Two other phenotypes of neovascular AMD have been recognised namely retinal angiomatous proliferation[4] (RAP) and idiopathic polypoidal choroidal vasculopathy[5] (IPCV). These three forms of neovascular AMD (CNV, RAP and IPCV) seem to have a different natural history, prognosis and response to treatment. Vascular endothelial growth factor (VEGF) has been implicated in new blood vessel formation, increased vascular permeability and inflammation in neovascular AMD.[6,7]

With the exception of IPCV, in which peripheral visual loss can occur as a result of the disease, people with neovascular AMD retain peripheral vision but lose the ability to see detail, often leaving them unable to read, see faces, watch television, drive or carry out many other everyday tasks. Neovascular AMD often develops rapidly, leading to reduced central vision often in a short period of time. Severe visual loss is associated with chronic morbidity, increased depression, diminished quality of life due to high levels of emotional distress and increased risk of falls and increased mortality.[8,9] There are approximately 26,000 new cases of wet AMD in the UK each year.[10]

Current standard therapy for wet AMD is ranibizumab (Lucentis, Genetech/Novartis), which is routinely used in clinical practice in the UK. Other treatments include pagaptanib (Macugen, Pfizer), bevacizumab (Avastin, Roche - off licence), and photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis).

NICE currently recommend ranibizumab for the treatment of wet AMD in people who comply with a set of pre-specified criteria (TA155),[10] including a best corrected visual acuity between 6/12 and 6/96 and PDT for people who have a confirmed diagnosis of *classic with no occult* subfoveal choroidal neovascularisation and a best-corrected visual acuity of 6/60 or better (TA68).[11] There is no current recommendation from NICE with regard to the use of PDT in *occult* CNV associated with wet age-related macular degeneration. NICE does not

recommend pagaptanib for wet AMD.[10] Bevacizumab is an anti-VEGF agent currently licensed for the treatment of certain types of metastatic cancer and does not have marketing authorization for the treatment of eye diseases. Two recent randomised clinical trials, CATT and IVAN,[12,13] the latter funded by the Health Technology Assessment programme, have demonstrated the non-inferiority efficacy of bevacizumab compared with ranibizumab with no major safety concerns. However, as bevacizumab is not licensed for the treatment of patients with exudative AMD, it is not currently used in the NHS except off-licence in those patients who do not meet the NICE eligibility criteria for ranibizumab.

Aflibercept solution for eye injection (Eylea, Bayer) is a VEGF-A inhibitor. It can also attach to other proteins such as placental growth factor (PlGF). VEGF-A and PlGF are involved in stimulating the abnormal growth of blood vessels in patients with AMD. By blocking these factors, aflibercept reduces the growth of the blood vessels and controls the leakage and the swelling.

Aflibercept gained marketing authorization in the UK in November 2012. This appraisal concerns Aflibercept and its relevant comparators.

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's description of AMD in terms of prevalence, symptoms and complications is accurate.

The manufacturer does not address in their submission, RAP and IPCV. These phenotypes, although less common than CNV, account for a substantial proportion of patients with AMD. Current estimates indicate that IPCV accounts for around 10% of the Caucasian AMD population,[14-17] with higher proportions in pigmented races, such as Asians, Blacks and Hispanics.[18-20] The prevalence of RAP among patients with AMD is less certain, however conservative estimates suggest this is around 15% of the Caucasian AMD population.[21]

To consider the differences among AMD phenotypes is important as the natural course, prognosis and response to anti-VEGF treatment seems to be different among these AMD phenotypes.[22] Although anti-VEGF therapy seems to work well in patients with CNV and RAP, it is not as effective for patients with IPCV, who may require further treatment modalities.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer points out that the current standard of care for wet AMD in the UK is ranibizumab, and that treatment is associated with monthly monitoring of visual acuity and anatomical outcomes measured by optical coherence tomography (OCT).

Although this description of the provision of anti-VEGF agents and associated monitoring is accurate, it is also important to consider recourse to other modalities in patients refractory to anti-VEGF treatment. In particular, it is worth noting that patients with IPCV usually do not respond as well to anti-VEGF treatment, and many go on to receive photodynamic therapy (PDT). This has not been addressed in the current submission.

3 DEFINITION OF THE DECISION PROBLEM

3.1 Population

The manufacturer's submission states that aflibercept is indicated for adults with wet AMD. This population is in line with the scope for this STA and the licensed indication for aflibercept (there is no indication of aflibercept use in the paediatric population).

3.2 Intervention

The submitted technology, aflibercept, is a potent vascular endothelial growth factor (VEGF) inhibitor. Aflibercept is formulated as a solution for intravitreal injection, and is initially administered as three once monthly 2mg loading doses, followed by one dose every two months. After 12 months, the interval between doses may be extended depending on response. Aflibercept must only be administered by a doctor experienced in the administration of intravitreal injections. Immediately following the intravitreal injection, patients receiving aflibercept need to be monitored for possible elevation in intraocular pressure. Appropriate monitoring may require an assessment of the perfusion of the optic nerve head or tonometry.

Anti-VEGF therapy is the current standard of care for wet AMD. Aflibercept has been shown to have a higher affinity for VEGF than other anti-VEGF agents, and also to bind to the related placental growth factor (PlGF). Because its mode of action, the time between aflibercept injections could be increased without compromising its effectiveness, requiring, thus, fewer number of injections and less frequent monitoring visits per year.

3.3 Comparators

The NICE scope for this STA states that ranibizumab, bevacizumab and PDT should all be considered as relevant comparators for aflibercept. The manufacturer's submission differs from the scope in that only ranibizumab was considered as a comparator (see Table 1).

In their submission, the manufacturer provided an argument against bevacizumab being used as a comparator in this appraisal. They argued that, as bevacizumab has not yet granted market authorization for use in wet AMD, it should not be administered for this clinical condition since a licensed alternative (ranibizumab) is available. They also point out that previous NICE appraisal on ranibizumab for the treatment of wet AMD[10] was conducted without any comparison with bevacizumab. Furthermore, they raised concerns over the safety of the use of bevacizumab for wet AMD due to the fact that the drug has not been

manufactured or approved for intraocular administration. In particular, concerns relate to the greater systematic absorption of bevacizumab and the fact that it needs to be decanted into smaller quantities for intraocular injection, which may increase the risk of infection.

The proportion of adverse events has been reported to be higher in bevacizumab-treated patients compared with ranibizumab-treated patients in the recent CATT trial,[12] which, however, is not big enough to detect reliable clinical differences in adverse outcomes. The uncertainty about frequency of adverse events following bevacizumab intravitreal administration should be, therefore, further investigated and, more importantly, should be balanced against a potential comparable effect with ranibizumab and the huge difference in cost per single dose. We are, therefore, of the opinion that bevacizumab should have been included as a relevant comparator.

The manufacturer did not provide their rationale for not considering PDT as a relevant comparator. Patients with IPCV may not respond to anti-VEGF therapy and in these PDT may be successful and it is often recommended. We therefore believe that PDT should have been considered as a comparator for this STA.

Table 1 summarises the differences between the manufacturer's decision problem and the NICE final scope.

Table 1 Differences between the final scope issued by NICE and the decision problem addressed in the manufacturer's submission

	Final scope issued by NICE	Decision problem addressed in the submission
Population	• Adults with wet age-related macular degeneration	• Adults with **neovascular (wet) age-related macular degeneration**
Intervention	• Aflibercept solution for injection	• Aflibercept solution for injection
Comparator(s)	• Ranibizumab • Bevacizumab • Photodynamic therapy	• **Ranibizumab**
Outcomes	• Visual acuity (the affected eye) • Visual acuity (the whole person) • Adverse effects of treatment • Health-related quality of life.	• Visual acuity (the affected eye) • Visual acuity (the whole person) • Adverse effects of treatment • Health-related quality of life.
Economic analysis	• Incremental cost per quality-adjusted life year. • Lifetime horizon • Costs will be considered from an NHS and Personal Social Services perspective	• Incremental cost per quality-adjusted life year. • **(25 year) lifetime horizon** • Costs will be considered from an NHS and Personal Social Services perspective

3.4 Outcomes

The outcomes considered by the manufacturer included gain or loss of visual acuity; best corrected visual acuity, number of injections; change in CNV; change in central foveal thickness; fluid on optical coherence tomography; quality of life measures; adverse events; morbidity and mortality rates. The ERG considers these outcomes suitable for the purpose of the appraisal and in line with the NICE scope.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

Description of manufacturer's search strategies and critique

The manufacturer states that searches were undertaken in December 2011 and updated in June 2012. MEDLINE, MEDLINE-in-Process, MEDLINE Daily Update, EMBASE and the Cochrane Central Register of Controlled Trials were searched. Additionally, relevant conference proceedings from 2008 – 2012 were searched and clinical trial registers were consulted to identify ongoing studies. Full details of the search strategies are included in Appendix 2 of the submission and are reproducible.

The sources used for the identification of studies were appropriate and the search strategies were comprehensive, incorporating search filters where necessary. Controlled vocabularies and free text searching were used effectively and included a wide range of synonyms. The facets of the search (wet age-related macular degeneration; aflibercept, ranibizumab, bevacizumab; randomised controlled trials), and the synonyms within each facet, were combined correctly with Boolean operators. Overall, the search strategies were highly sensitive and fit for purpose.

Inclusion criteria

The inclusion criteria used in the systematic review of clinical effectiveness are tabulated in Table 2.

Table 2 Inclusion criteria for the systematic review of clinical effectiveness

Criteria	
Study design	Randomised controlled trials
Population	• Patients with wet AMD (neovascular or exudative AMD) • Patients with retinal angiomatous proliferation (RAP) • Patients with sub-macular haemorrhage secondary to AMD
Interventions	• Aflibercept • Ranibizumab

Criteria	

Outcomes	• Number of injections
	• Best corrected visual acuity (BCVA)
	• Gain or loss of visual acuity:
	  ○ Loss of <15 letters in ETDRS score
	  ○ Loss of >30 letters in ETDRS score
	  ○ Loss of >15 letters in ETDRS score
	  ○ Gain of >15 letters in ETDRS score
	  ○ 20/40 vision or better (Snellen chart)
	  ○ 20/200 vision or worse (Snellen chart)
	  ○ 6/12 vision or better (Snellen chart)
	  ○ 6/60 vision or better (Snellen chart)
	  ○ Gain >0 letters
	  ○ Gain >10 letters
	  ○ Gain >30 letters
	  ○ Other visual acuity outcomes
	• Change in choroidal neovascularisation (CNV) or classic:
	  ○ Optic disk area
	  ○ Area of lesion
	  ○ Size of leakage
	  ○ Greatest linear dimension
	• Fluid on OCT
	• Presence of dry leakage
	• Eyes with a dry lesion
	• Change in total lesion size
	• Change in central foveal thickness
	• Quality of life outcomes:
	  ○ NEI VFQ-25
	  ○ EQ-5D
	  ○ Other scales
	• Treatment discontinuation
	• SAEs, morbidity and mortality

Language	Any

Characteristics of the included studies

The manufacturer's search identified two relevant phase-three RCTs of aflibercept versus ranibizumab and 34 additional RCTs involving either ranibizumab or aflibercept, which were used to inform the network meta-analysis. After reasonable exclusions, 10 of the identified 34 RCTs were included in the network at 12 months and five in the 24-month network.

The two aflibercept trials (VIEW 1 and VIEW 2) were both sponsored by the manufacturer and compared aflibercept head to head with ranibizumab. The RCTs randomised patients 1:1:1:1 to 0.5mg ranibizumab intravitreally every 4 weeks (RBZ 0.5mg Q4); or 0.5mg aflibercept intravitreally every 4 weeks (AFB 0.5mg Q4); or 2mg aflibercept every 4 weeks (AFB 2mg Q4); or 2mg aflibercept every 8 weeks after three initially monthly loading doses (AFB 2mg Q8).

Regardless of assigned treatment, all patients were examined on the day of treatment and assessed every 4 weeks thereafter. Each 4-week visit included best corrected visual acuity (BCVA) assessment and anterior/posterior segment examination (with intraocular pressure determination) *before* injection (active or sham) as well as a posterior segment examination with intraocular pressure determination 30 to 60 minutes *after* injection. Fundus photography and fluorescein angiography were performed at screening and weeks 24, 52, 72 and 96.
In VIEW 1, OCT was performed at screening, at the treatment initiation visit, and at weeks 4, 12, 24, 36, and 52 (and was optional at the investigators' discretion at other study visits). In VIEW 2, OCT was performed at every study visit (every 4 weeks). The entire study duration (primary phase and extension phase) was 96 weeks for both trials.

In each trial, only one eye was to be designated as the study eye. For patients who met eligibility criteria in both eyes, the eye with the worse visual acuity was selected as the study eye. If both eyes had equal visual acuity, the eye with the clearest lens and ocular media and least amount of subfoveal scar or geographic atrophy was selected.

The baseline characteristics of VIEW 1 and VIEW 2 are summarized in Table 3.

Table 3 Baseline characteristics of VIEW 1 and VIEW 2

	VIEW 1		VIEW 2	
	Aflibercept 2mg Q8	**Ranibizumab 0.5mg Q4**	**Aflibercept 2mg Q8**	**Ranibizumab 0.5mg Q4**
N in full analysis set	301	304	306	291
Baseline sociodemographic characteristics				
Age				
Mean	77.9	78.2	73.8	73.0
Sex (%)				
Male	40.9	43.4	42.8	41.9
Female	59.1	56.6	57.2	58.1
Race (%)				
White	95.3	97.4	70.9	73.2
Black	0.3	0.3	0.7	0.3
Asian	1.3	0.0	22.5	20.6
American Indian	0.3	0.7	0.0	0.0
Native Hawaiian	0.3	0.3	0.0	0.0
Not reported	2.0	1.3	5.9	5.8
Baseline clinical characteristics				
Weight (kg)				
Mean	74.4	75.9	69.6	69.8

Height (cm)				
Mean	165.0	166.4	162.8	162.5
BMI				
Mean	27.2	27.30	26.18	26.34
BCVA (ETDRS score)				
Mean	55.7	54.0	51.6	53.8
Central retinal thickness (µm)				
Mean	324.4	315.3	342.6	325.9
Total lesion size (mm^2)				
Mean	6.89	6.99	8.22	8.01
Area of CNV (mm^2)				
Mean	300	298	305	291
Lesion type (%)				
Occult	39.2	37.8	35.9	39.9
Minimally classic	36.5	33.2	34.6	35.7
Predominantly classic	23.6	27.0	28.8	24.1
NEI VFQ-25				
	69.6	71.8	71.3	72.9
EQ 5D score				
	Not performed	Not performed	0.81	0.80

Quality assessment

The manufacturer assessed the quality of all included studies: the two aflibercept RCTs and the 10 RCTs involving either ranibizumab or aflibercept, which informed the network meta-analysis. The methods used for quality assessment were considered adequate by the ERG.

The methodological quality of the VIEW 1 and VIEW 2 was good. Methods used to achieve randomisation were adequate and sequence allocation was concealed using a central interactive voice response system. Randomisation appears to have been successful, and there was not any imbalance between groups in terms of sociodemographic factors at baseline. All patients were masked (blind) to treatment status, and masking was maintained in the aflibercept 2mg Q8 arm by giving sham injections on alternate months. The only study personnel unmasked to treatment status were those involved in the preparation and injection of the study drug. All personnel involved with outcome measurement and assessment were masked. The ERG considers the masking strategies of the VIEW trials appropriate. Although the manufacturer conducted per protocol analysis, we do not consider that this is likely to increase the risk of bias as, for non-inferiority trials, use of the full analysis set is generally not considered to be conservative.[23]

The quality of the other trials included in the indirect analysis was mixed. The report from the Kleijnen Systematic Reviews group, which accompanied the manufacturer's submission, highlighted particular concern with the CATT, DETAIL and MOON trials. The ERG shares this concern over the potential risk of bias of these trials.

The ERG performed a quality assessment of the manufacturer's systematic review using the York Centre for Reviews and Dissemination (CRD) criteria (Table 4). The quality of the systematic review was good, and the ERG has no major concerns in any of the quality areas.

Table 4 Quality assessment of the manufacturer's review

CRD quality item	Score
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	**Yes**
2. Is there evidence of a substantial effort to search for all of the relevant research?	**Yes**
3. Is the validity of included studies adequately assessed?	**Yes**
4. Are sufficient details of the individual studies presented?	**Yes**
5. Are the primary studies summarised appropriately?	**Yes**

4.2 Summary of submitted evidence

Introduction and overview

The manufacturer presented the results of VIEW 1 and VIEW 2 randomised trials for the comparison of aflibercept versus ranibizumab in the treatment of adults with wet AMD. VIEW 1 and VIEW 2 were international, multicentre RCTs with the aim of assessing non-inferiority of aflibercept (AFB 2mg Q8) compared to ranibizumab (RBZ 0.5mg Q4). The studies were near identical in design so that data could be pooled. VIEW 1 recruited 1217 participants from 154 study sites in United States and Canada. VIEW 2 recruited 1240 participants from 172 study sites in 26 countries within eight regions: India, Asia Pacific, South America, Central Europe, Eastern Europe, Hungary, North Western Europe/Israel/Australia, South Western Europe (see Table 5).

Only one eye per patient was included in the study and if the fellow eye required treatment for AMD at study entry or during the study, it was treated with any approved treatment (that would not interfere with the study drug). The studies had two phases including the primary phase (randomisation to week 48) where treatment was 'per protocol'. This was followed by a follow-up phase involving modified dosing (as needed) through week 92 and additional evaluation visits. Sham injections were used to maintain masking in the AFB 2mg Q8 treatment arm during the primary phase of treatment since all other arms required monthly injections. Sham injections were not required in the extension phase.

The primary efficacy endpoint was the proportion of patients who maintain vision at week 52, defined as losing fewer than 15 letters in the ETDRS letter score compared to baseline. Secondary endpoints were changes from baseline to week 52 for: BCVA, proportion of patients gaining at least 15 letters, total NEI VFQ-25 score and choroidal neovascularisation (CNV) area. NEI VFQ-25 total score is between 0 (worst) and 100 (best), with a change of 4-6 points corresponding to a 15 letter gain in BCVA and is considered clinically meaningful.

The manufacturer defined a number of datasets and these are provided here for reference:

- **The full analysis set (FAS)** - all randomised patients who received any study drug and had a baseline and at least one post-baseline assessment.
- **The per protocol set (PPS)** - all patients in the FAS who received at least 9 injections of study drug or sham and attended at least 9 scheduled visits during the first 52 weeks, except for those who were excluded because of major protocol violations.
- **The safety analysis (SAF)** set included all patients who received any study drug.

The manufacturer commented that the PPS was used for primary analysis. A patient who withdrew from the study before week 36 due to treatment failure was considered a non-responder by the manufacturer. Otherwise, they implemented last observation carried forward (LOCF) approach to impute missing data for all efficacy variables. Baseline values were not carried forwards. Patients withdrawing prior to week 36 were not included in the primary efficacy analysis (not in PPS), but were included in the secondary efficacy analysis (FAS).

Table 5 Summary of VIEW 1 and VIEW 2 characteristics (source: Table B4, manufacturer submission)

Study Name (Number)	Number of patients	Treatments (number of patients)	Countries	Patient type	Primary endpoints
VIEW 1 (VGFT-OD-0605 311523)	Total patients randomised = 1217 Aflibercept 2mg Q4 n=304 0.5mg Q4 n=304 2mg Q8 n=303 Ranibizumab 0.5mg Q4 n=306	Primary phase Aflibercept 0.5mg given intravitreally every 4 weeks (0.5mg Q4 intravitreal injection - IVT) 2mg given intravitreally every 4 weeks (2mg Q4 IVT) 2mg given intravitreally every 8 weeks (after 3 initial 4-weekly doses) (2mg Q8 IVT) vs. Ranibizumab 0.5mg given intravitreally every 4 weeks (0.5mg Q4 IVT) Extension phase Injections of same drug/dose level as originally assigned but at intervals determined by specific criteria (which could be as frequently as 4-weekly but no less frequently than every 12 weeks)	154 study sites from United States and Canada.	Active primary subfoveal choroidal neovascularisation (CNV) lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by fluorescein angiography (FA) in the study eye	Proportion of patients who maintained vision at Week 52 [Maintaining vision defined as '**loss of <15 letters** in the Early Treatment Diabetic Retinopathy Study Group (ETDRS) letter score compared to Baseline']
VIEW 2 (311523)	Total patients randomised = 1240 Aflibercept 2mg Q4 n=313 0.5mg Q4 n=311 2mg Q8 n=313 Ranibizumab 0.5mgQ4 n=303		172 study sites from 26 countries Each country was assigned to 1 of 8 regions as follows: India: India Asia Pacific: Japan, South Korea, Singapore South America: Argentina, Brazil, Colombia, Mexico Central Europe: Austria, Germany, Switzerland Eastern Europe: Czech Republic, Latvia, Poland, Slovakia Hungary: Hungary North Western Europe / Israel / Australia: Australia, Belgium, Israel, Sweden, The Netherlands and United Kingdom South Western Europe: France, Italy, Portugal, , Spain		

Aflibercept 2mg Q8 versus ranibizumab 0.5mg Q4

The decision problem under consideration in this report relates to AFB 2mg Q8 versus RBZ 0.5mg Q4 and results presented here will be limited to these two arms of the trials. Further detail on the remaining treatment groups can be found in the manufacturer submission. The manufacturer presented results separately for VIEW 1 and VIEW 2 and then pooled together.

Maintained vision

For the primary outcome of maintained vision at week 52, non-inferiority to ranibizumab was demonstrated for aflibercept as the upper limit of the confidence intervals for difference in proportions were below the pre-specified boundary of 10% and the point estimates favoured aflibercept (Table 6). The aflibercept regimen also met the pre-specified 5% margin of clinical equivalence compared to ranibizumab at week 52. The primary analysis defined by the manufacturer was undertaken on the 'per protocol set' (PPS) using last observation carried forward (LOCF).

Table 6 Results of analysis for maintained vision presented in manufacturer submission

	Ranibizumab 0.5mg Q4		**Aflibercept 2mg Q8**		
	n/N	**%**	**n/N**	**%**	**Difference (95% CI)**
Week 52 (PPS including LOCF)					
VIEW 1	254/269	94.4	252/265	95.1	-0.7 (-4.5, 3.1)
VIEW 2	254/269	94.4	258/270	95.6	-1.13 (-4.81, 2.55)
Pooled	508/538	94.4	510/535	95.3	-0.9 (-3.5, 1.7)
Week 96 (FAS including LOCF)					
VIEW 1	273/304	89.8	275/301	91.4	-1.6 (-6.2, 3.1)
VIEW 2	272/391	93.5	286/306	93.5	0.0 (-4.0, 4.0)
Pooled	545/595	91.6	561/607	92.4	-0.8 (-3.8, 2.3)

The manufacturer commented that for all evaluable subgroups (age, gender, race, baseline visual acuity, lesion type - occult, minimally classic, predominantly classic, lesion size) in each study and combined, analyses were consistent with the overall populations. No data were provided by the manufacturer and therefore the ERG is unable to comment further.

Change in ETDRS from baseline

No difference in change from baseline in ETDRS letter score was found between treatment groups (Table 7). The manufacturer commented that regardless of whether the analysis was

by LOCF, assessing completers, through multiple imputation or using observed data, the AFB 2mg Q8 achieved a mean visual acuity score within 0.3 letters of RBZ 0.5mg Q4 in the integrated analysis with a confidence interval less than two letters.

Table 7 Results of analysis for change from baseline in ETDRS letter score (FAS)

	Ranibizumab 0.5mg Q4		**Aflibercept 2mg Q8**			
	N	**Mean (SD)**	**N**	**Mean (SD)**	**Difference (95% CI)**	**p-value**
Week 52 (FAS)						
VIEW 1	304	8.1 (15.3)	301	7.9 (15)	0.26 (-1.97, 2.49)	0.818
VIEW 2	291	9.4 (13.5)	306	8.9 (14.4)	-0.90 (-3.06, 1.26)	0.413
Pooled	595	8.74 (NR)	607	8.4 (NR)	-0.32 (-1.87, 1.23)	NR
Week 96 (FAS)						
VIEW 1	304	[redacted]	301	[redacted]	[redacted]	NR
VIEW 2	291	[redacted]	306	[redacted]	[redacted]	NR
Pooled	595	[redacted]	607	[redacted]	[redacted]	NR

NR = not reported

[redacted]

Gain of at least 15 letters in ETDRS letter score

Proportion of patients gaining at least 15 letters in the ETDRS letter score at week 52 was slightly higher in the ranibizumab group for both VIEW 1 and VIEW 2, but neither estimate was significantly different to aflibercept 2mg Q8. Therefore in the pooled analysis there was very little difference between the two treatment groups. [redacted]

Table 8 Proportion of patients gaining ≥ 15 letters of vision in ETDRS letter score from baseline (FAS)

	Ranibizumab 0.5mg Q4		Aflibercept 2mg Q8		
	n/N	**%**	**n/N**	**%**	**Difference (95% CI)**
Week 52					
VIEW 1	94/304	30.9	92/301	30.6	-0.36 (-7.74,7.03)
VIEW 2	99/291	34.0	96/306	31.4	-2.65 (-10.2, 4.88)
Pooled	193/595	32.4	NR/607	30.97	-1.5 (-6.8,3.8)
Week 96					
VIEW 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIEW 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	188/595	31.6	[redacted]	[redacted]	[redacted]

Change in NEI VFQ-25 total score from baseline

In both VIEW 1 and VIEW 2, vision related quality of life improved in parallel to vision improvement during the primary phase [redacted]. The changes from baseline were very similar across treatment groups (Table 9).

Table 9 Change from baseline in NEI VFQ-25 total score (FAS)

	Ranibizumab 0.5mg Q4		Aflibercept 2mg Q8			
	N	**Mean (SD)**	**N**	**Mean (SD)**	**Difference (95% CI)**	**p-value**
Week 52						
VIEW 1	300	4.9 (14.0)	292	5.1 (14.7)	-0.60 (-2.61, 1.42)	0.5579
VIEW 2	287	6.3 (14.8)	299	4.9 (14.7)	-1.95 (-4.07, 0.17)	0.072
Pooled	587	5.6 (NR)	591	5.0 (NR)	-1.26 (2.72, 0.2)[1]	NR
Week 96						
VIEW 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIEW 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NR = not reported;
[1] as reported in Table B18, manufacturer submission: the ERG assumes it should read (-2.72, 0.2).

Change in choroidal neovascularisation (CNV) area from baseline

In both studies, each treatment group showed a decrease in CNV area from baseline and it was comparable across the groups. The decrease was significantly smaller for aflibercept 2mg Q8 within VIEW 1 (p = 0.017), but the pooled analysis found no difference between treatments. (Table 10)

Table 10 Change from baseline in CNV area (FAS)

	Ranibizumab 0.5mg Q4		**Aflibercept 2mg Q8**			
	N	**Mean (SD)**	**N**	**Mean (SD)**	**Difference (95% CI)**	**p-value**
Week 52						
VIEW 1	288	-4.2 (5.6)	286	-3.4 (6.0)	0.86 (0.15, 1.58)	0.017
VIEW 2	278	-4.16 (5.90)	289	-5.16 (5.87)	-0.73 (-1.53, 0.068)	0.073
Pooled	566	-4.21 (NR)	575	-4.28 (NR)	0.08 (-0.46, 0.61)	NR
Week 96						
VIEW 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIEW 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NR = not reported

Additional endpoints

Vision gain and loss

The manufacturer presented a number of additional endpoints relating to vision gain and vision loss from baseline as measured by the ETDRS score (Table 11). In both studies, vision gain and loss were similar in the two treatment groups.

Table 11 Proportion of patients with different extents of vision gain or loss at week 96 (FAS)

	RBZ 0.5mg Q4			AFB 2mg Q8		
	VIEW 1 N=304	**VIEW 2 N=291**	**Pooled N=595**	**VIEW 1 N=301**	**VIEW 2 N=306**	**Pooled N=607**
Gaining ≥ 0 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gaining ≥ 5 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gaining ≥ 10 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gaining ≥ 15 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gaining ≥ 30 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Losing any letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Losing ≥ 5 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Losing ≥ 10 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Losing ≥ 15 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Losing ≥ 30 letters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Change from baseline in central retinal thickness (*CRT)*

In both studies mean CRT decreased markedly in all treatment groups during the primary phase (>35-40%). [redacted] There were no meaningful differences between treatment groups.

Proportion of patients without intraretinal cystic oedema and/or subretinal fliuid (dry retina) on OCT

The manufacturer undertook a post hoc analysis to determine the percentage of patients who had fluid free retinas, defined on OCT, by the absences of both cystic intraretinal oedema and subretinal fluid. The results are presented in Table 12.

Table 12 Proportion of patients with fluid free retina at week 52 (observed and FAS)

	Ranibizumab 0.5mg Q4	**Aflibercept 2mg Q8**
VIEW 1, % (n)	63.6% (171/269)	63.4% (168/265)
VIEW 2, % (n)	60.4% (162/268)	71.9% (197/274)
Pooled, % (n)	62.0% (333/537)	67.7% (365/539)

Source: Table B21, manufacturer submission

Injection frequency

Table 13 summarises the injection information for the two treatment group of interest. Overall in VIEW 1 and VIEW 2 pooled together, the number of injections in the extension phase was lower in the AFB 2mg Q8 group (mean = 4.2, SD = 1.7) than in RBZ 0.5mg Q4 (mean = 4.7, SD = 2.2). For those treated with ranibizumab, 26.5% of patients required ≥6 injections in the extension phase compared to 15.9% of those treated with aflibercept (2mg Q8 group).

Table 13 Injection frequency data (SAF) (Source Table B23, manufacturer)

	Ranibizumab (0.5mg Q4)			**Aflibercept (2mg Q8)**		
	VIEW 1 N=304	**VIEW 2 N=291**	**Pooled N=595**	**VIEW 1 N=303**	**VIEW 2 N=307**	**Pooled N=610**
Mean total number of injections over entire study period (SD)	16.1 (3.8)	16.8 (3.7)	16.5 (3.7)	11.3 (2.9)	11.1 (2.8)	11.2 (2.9)
Mean time between injections during week 52 to week 96/100 (days)(SD)	69.4 (19.8)	66.4 (20.8)	67.9 (20.3)	70.8 (18.9)	75.5 (23.8)	73.2 (21.6)
Patients completing study medication (week 52 to week 96/100)			N=513			N=511
Mean number of injections Week 52 to Week 96/100			4.7 (2.2)			4.2 (1.7)

The manufacturer summarised that overall, in the extension phase patients treated with AFB 2mg Q8 compared to RBZ 0.5mg Q4, showed a numerical trend towards: a longer time to the first injection after fixed dose regimen, more prolonged treatment intervals, and fewer injections administered.

Adverse events

Data on adverse events (AEs) were collected at every study visit (i.e. every 4 weeks) within VIEW 1 and VIEW 2 according to standard ICH definitions. Treatment emergent adverse

events (TEAEs) refer to AEs which occurred or worsened after the first administration of the study drug. For safety analyses there were 595 patients on RBZ 0.5mg Q4 (VIEW 1: n = 304, VIEW 2: n = 291) compared to 613 on AFB 2mg Q8 (VIEW 1: n = 304, VIEW 2: n = 309). No clinically meaningful differences were found between aflibercept and ranibizumab, with incidences of reported events similar among treatment groups (Table 14).

Table 14 Summary of safety data (source table B30, manufacturer submission)

	Ranibizumab 0.5mg Q4			Aflibercept 2mg Q8		
	VIEW 1	**VIEW 2**	**Pooled**	**VIEW 1**	**VIEW 2**	**Pooled**
	[redacted]	[redacted]	**N=595**	[redacted]	[redacted]	**N=610**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any TEAE	[redacted]	[redacted]	567 (95.3)	[redacted]	[redacted]	591 (96.9)
Non-ocular (systemic)	[redacted]	[redacted]	494 (83.0)	[redacted]	[redacted]	519 (85.1)
Ocular (study eye)	[redacted]	[redacted]	486 (81.7)	[redacted]	[redacted]	483 (79.2)
Any study drug-related AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular (study eye)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any injection-related AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AE causing treatment discontinuation	[redacted]	[redacted]	21 (3.5)	[redacted]	[redacted]	30 (4.9)
Any AE-related death	[redacted]	[redacted]	15 (2.5)	[redacted]	[redacted]	18 (3.0)
Any SAE	[redacted]	[redacted]	170 (28.6)	[redacted]	[redacted]	177 (29.0)
Non-ocular (systemic)	[redacted]	[redacted]	146 (24.5)	[redacted]	[redacted]	154 (25.2)
Ocular (study eye)	[redacted]	[redacted]	26 (4.4)	[redacted]	[redacted]	24 (3.9)
Any study drug-related SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any injection-related SAE (study eye)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 15 describes the ocular TEAEs to occur throughout the study period (baseline to week 96) for both VIEW 1 and VIEW 2 pooled together. Data were not presented separately by the manufacturer. There were no obvious differences in the ocular TEAEs between study groups. Injection related TEAEs in the study eye were reported more frequently in VIEW 1 than VIEW 2. There were no differences observed between treatments in frequencies of pattern of reported injection-related TEAEs and the events mainly included mild, uncomplicated and transient conditions.

Table 15 Ocular TEAEs in the study eye occurring in ≥ 5.0% of patients at preferred term level during whole study (baseline to week 96) for pooled analysis (VIEW 1 and VIEW 2)

MedDRA preferred term	**Ranibizumab 0.5mg Q4 (N=595) n (%)**	**Aflibercept 2mg Q8 (N=610) n (%)**
Any ocular TEAE (study eye)	[redacted]	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]
Retinal haemorrhage	[redacted]	[redacted]
Visual acuity reduced	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]
Macular degeneration	[redacted]	[redacted]
Vitreous detachment	[redacted]	[redacted]
Cataract	[redacted]	[redacted]
Vitreous floaters	[redacted]	[redacted]
Increased intraocular pressure	[redacted]	[redacted]
Retinal oedema	[redacted]	[redacted]
Retinal degeneration	[redacted]	[redacted]
Maculopathy	[redacted]	[redacted]
Ocular hyperaemia	[redacted]	[redacted]

Source: Table 31 in manufacturer submission

Non-ocular AEs reported over the entire study period covered a range of medical conditions (Table 16) and are presented for the two trials combined. Data were not presented separately. Many events were associated with respiratory infections.

Table 16 Integrated analysis of non-ocular TEAEs occurring in ≥ 2.5% of patients during study period (baseline to week 96)

	RBZ 0.5mg Q4 (N=595)	AFB 2mg Q8 (N=610)
	n (%)	n (%)
Any non-ocular TEAE	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Cystitis	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Blood glucose increased	[redacted]	[redacted]
Protein urine present	[redacted]	[redacted]
Urine protein / creatinine ratio increased	[redacted]	[redacted]
Blood urine present	[redacted]	[redacted]
Blood pressure increased	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Atrioventricular block first degree	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Bundle branch block left	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Gastrooesophageal reflux disease	[redacted]	[redacted]

Vomiting	[redacted]	[redacted]
Injury, poisoning & procedural complications	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Contusion	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Vascular Disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Respiratory, Thoracic & Mediastinal disorders	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Chronic obstructive pulmonary disease	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Metabolism & Nutrition disorders	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]
Hypercholesterolaemia	[redacted]	[redacted]
General disorders & administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Skin & subcutaneous disorders	[redacted]	[redacted]
Neoplasms, benign, malignant, & unspecified (incl.	[redacted]	[redacted]
Cysts / polyps)	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]
Renal & urinary disorders	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Depression	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Blood & Lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]
Seasonal allergy	[redacted]	[redacted]
Ear & labyrinth disorders	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]
Reproductive system & Breast disorders	[redacted]	[redacted]

4.3 Critique of submitted evidence

VIEW 1 and VIEW 2: Aflibercept versus ranibizumab

The manufacturer identified VIEW 1 and VIEW 2 as their only sources of direct evidence for aflibercept 2mg every 8 weeks (AFB 2mg Q8) versus ranibizumab 0.5mg every four weeks (RBZ 0.5mg Q4). The design and conduct of these two trials seemed sensible and the ERG has no concern over this. There were no obvious sources of bias for the two trials. Given the design was identical (except for location) the ERG agrees with the manufacturer's decision to pool the data for integrated analysis.

The primary outcome (maintained vision at week 52) was analysed using a non-inferiority approach. In general the choice of the non-inferiority margin[24] must be made on both clinical and statistical grounds. No single rule can be applied to all clinical situations. In other studies, for example CATT, the non-inferiority margin has been measured against the outcome of change in ETDRS letters rather than the proportion of patients meeting a particular target (loss of less than 15 letters). The non-inferiority margin for the primary outcome within VIEW 1 and VIEW 2 was chosen as a difference of 10% in the proportion of patients losing less than 15 letters. Based on feedback from regulatory agencies the analysis of data pooled from both studies was discussed in an exploratory fashion using non-inferiority of 7% and 5%, with the latter to determine clinical equivalence. The manufacturer did not provide information on whether the original margin of 10% came from the VIEW 1 and VIEW 2 trial. After looking at Appendix 3 of the VIEW 1 and VIEW 2 trial publication[25] the ERG established that the 10% margin was chosen to preserve the ranibizumab effect for loss of less than 15 letters shown in the MARINA study[26] (comparing fixed dose RBZ 0.5mg monthly, RBZ 0.3mg monthly and sham injection monthly). The analysis was undertaken as intention to treat and the Kleijnen systematic review group considered this study to be at low risk of bias. Therefore basing the non-inferiority margin on the results of MARINA, alongside discussions with the regulatory authorities (FDA, EMA) seems appropriate to the ERG. However, the ERG clinical experts indicated that a non-inferiority margin based on the mean change in BCVA would have been more appropriate.

The CATT study used a non-inferiority margin of five letters for the mean change in BCVA between ranibizumab and bevacizumab. Using the same margin and applying it to the comparison of aflibercept and ranibizumab in the pooled VIEW 1 and VIEW 2 data with regard to mean change in BCVA, non-inferiority was established. The estimate of difference between treatments in VIEW 1 was 3.15 (0.92, 5.37) and VIEW 2 (mean diff = -1.95 (-4.10, 0.20). In the case of VIEW 2 the confidence interval is within the range (-5, 5) we are looking

for and for VIEW 1 the upper limit is only just out with this range. Therefore despite the initial slight concern over choice of non-inferiority margin, the ERG felt it was appropriate.

ERG concern over use of LOCF

The ERG have some concern about using LOCF within the analysis of the primary outcome (maintained vision at week 52) for VIEW 1 and VIEW 2. The use of LOCF has been widely criticised and is not recommended[27-29] for a primary analysis. It has the potential to introduce bias as it can artificially stabilise disease, which is inappropriate for a progressive disease like AMD. During the clarification process the ERG requested the observed results at week 52 in addition to those originally presented by the manufacturer (Table 17). There were no obvious differences between the four analyses (PPS or FAS and observed or LOCF). Therefore despite the concern over the use of LOCF within VIEW 1 and VIEW 2, the ERG are happy that this has not substantially affected the findings as the results following sensitivity analysis were similar to that presented by the manufacturer. LOCF was also used for week 96 outcomes, but the manufacturer did not provide the observed data for 96 weeks and therefore the ERG was unable to comment further as to the impact LOCF may have had on outcomes assessed at longer term.

Table 17 Results of analysis for maintained vision – following clarification

	Ranibizumab 0.5mg Q4		Aflibercept 2mg Q8		
	n/N	**%**	**n/N**	**%**	**% Difference (95% CI)**
Week 52 (PPS including LOCF – presented in MS)					
VIEW 1	254/269	94.4	252/265	95.1	-0.7 (-4.5, 3.1)
VIEW 2	254/269	94.4	258/270	95.6	-1.13 (-4.81, 2.55)
Pooled	508/538	94.4	510/535	95.3	-0.9 (-3.5, 1.7)
Week 52 (PPS Observed data – following clarification)					
VIEW 1	243/256	94.9	237/246	96.3	-1.4 (-5.0, 2.2)
VIEW 2	246/261	94.3	253/264	95.8	-1.6 (-5.3, 2.1)
Pooled	489/517	94.6	490/510	96.1	Not provided
Week 52 (FAS including LOCF – following clarification)					
VIEW 1	285/304	93.8	284/301	94.4	-0.6 (-4.4, 3.2)
VIEW 2	276/291	94.9	292/306	95.4	-0.58 (-4.03, 2.88)
Pooled	561/595	94.2	576/607	94.9	Not provided
Week 52 (FAS Observed data – following clarification)					
VIEW 1	259/273	94.9	256/266	96.2	-1.4 (-4.9, 2.1)
VIEW 2	257/272	94.5	265/278	95.3	-0.84 (-4.52,2.84)
Pooled	516/545	94.7	521/544	95.8	Not provided

4.4 Critique of indirect comparison

Outcome definition

All data relating to the primary outcome of maintained vision at 52 weeks in this section is defined by loss of ≤15 letters, but the manufacturer regularly comment in the text 'loss of less than 15 letters' which is not the same as 'equal or less than to 15 letters'. The **ERG have concern over the inconsistency in this outcome definition** but have assumed that this is probably a wording issue and not a difference in outcome definition between trials or indeed a change in the VIEW 1 and VIEW 2 reported analysis and that used for the indirect comparison.

Meta-analysis

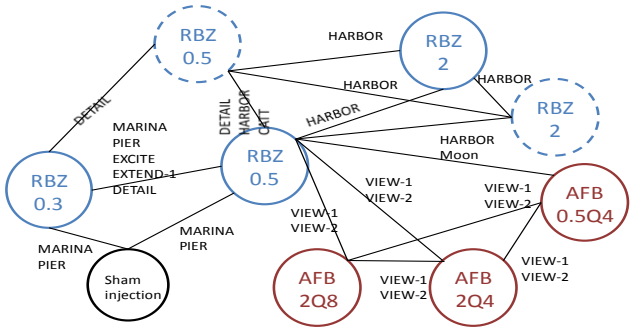
No meta-analysis of the VIEW 1 and VIEW 2 trials was presented by the manufacturer in their submission. They stated that this was because the two trials were similarly designed so that their data could be pooled directly. The meta-analysis of VIEW 1 and VIEW 2 was, however, presented within the Kleijnen systematic review (see section 5.7.1-5.7.3).

Indirect comparison – summary of results

The treatment regimen for ranibizumab used in VIEW 1 and VIEW 2 was fixed dose but the manufacturer states that in clinical practice a 'treat to target' approach is used. This involves monthly treatment until the patient's VA is stable for three consecutive months, with re-treatment in a similar way upon loss of VA (with minimum of two injections). Therefore the manufacturer commissioned a systematic review by Kleijnen Systematic Reviews group (included in the reference pack of the current submission) to identify studies which included this alternative and then undertook an indirect comparison of the data to compare fixed dose aflibercept (AFB 2mg Q8) compared with ranibizumab 0.5mg in a 'reactive dosing' or 'treat as needed' regimen. This type of dosing is referred to as 'pro re nata' (PRN). The MS describes the methods and results of the indirect treatment comparison briefly in the submission referring to the report from the Kleijnen Systematic Reviews group for more information.

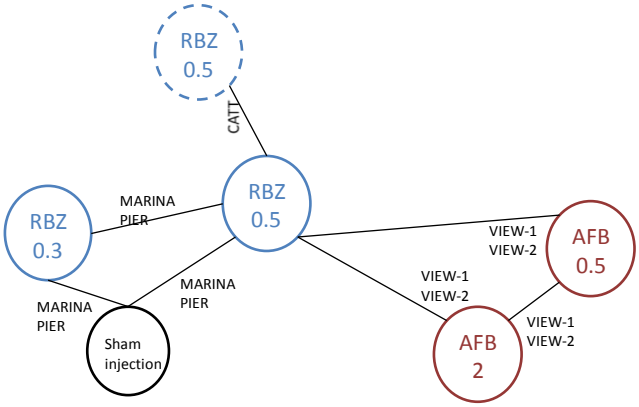
The Kleijnen Systematic Reviews group produced three networks for consideration: at six, 12, and 24 months. However, as no trials reported aflibercept results at 6 months, this network is not discussed further. Figures 1 and 2 display the networks for 12 months and 24 months respectively. Fixed dosing is represented by solid lines with dashed dosing representing PRN dosing. The networks presented cover all outcomes, with a simpler structure occurring for each individual outcome (see Figures 24-26 in MS).

Figure 1 Network comparisons of 2mg fixed Q8 aflibercept compared to PRN ranibizumab regimens at 12 months (source Figure B10, MS)



Numbers indicate drug dose in mg. Dashed line = PRN, solid line = fixed dosing regimen.

Figure 2 Network comparisons of 2mg fixed Q8 aflibercept compared to PRN ranibizumab regimens at 24 months (source Figure B11, MS)



The Kleijnen Systematic Reviews group undertook three types of indirect comparison: simple Bucher analysis, frequentist network analysis (using STATA) and Bayesian network analysis (using WinBUGS) and the results are now summarised.

Outcomes at 12 months

Table 18 summarises the network analysis results (both frequentist and Bayesian) for the 12 month outcomes. There was some uncertainty surrounding the DETAIL trial (discussed in section 4.4.4) so the results for BCVA mean change are repeated without this trial. Results were similar between the two network analysis approaches and each found no difference in 12 month outcomes between fixed AFB 2mg Q8 and RBZ 0.5mg PRN.

Table 18 12m Network analysis: Fixed AFB 2mg Q8 versus RBZ 0.5mg PRN

	No. Trials	Frequentist Method: Mean (95% CI)	Bayesian Method: Median (95% CrI)
Maintained vision	4 (VIEW 1, VIEW 2, CATT, HARBOR)	OR = 1.44 (0.68 to 3.09)	OR = 1.51 (0.42 to 5.94) RR= 1.01 (0.98 to 1.12)
BCVA mean change from baseline	10 (VIEW 1, VIEW 2, CATT, HARBOR, DETAIL, MARINA, PIER, EXCITE, EXTEND, MOON)	MD = 0.83 (-1.57 to 3.23) MD = 1.35 (-1.08 to 3.77)*	MD = -2.87 (-10.02 to 4.30) MD = 1.15 (-3.92 to 6.09)*
Improved Vision	4 (VIEW 1, VIEW 2, CATT, HARBOR)	OR = 1.29 (0.91 to 1.83)	OR = 1.28 (0.45 to 3.68) RR = 1.15 (0.71 to 2.40)

* Excluding DETAIL

The **ERG had concern** that one of the arms (RBZ 0.3mg) contained within DETAIL was not included in the network for the analysis for BCVA mean change from baseline, despite being included in Table B, Appendix 12, Kleijnen systematic review. The omission is addressed by the ERG in section 4.5.1.

In addition to Table 18 above, the Kleijnen Systematic Reviews group provided simple forest plots showing the results of the three approached to the indirect comparison for the four outcomes (Figure 29, Kleijnen systematic review). For maintained vision and improved vision, all three approaches found similar results, with the point estimate in favour of aflibercept although the differences between treatments were not significant. In the case of mean change in BCVA, the Bayesian approach differed in the direction of the point estimate, but once DETAIL was removed, the results were in line with the simple Bucher analysis and the frequentist network analysis and favoured aflibercept (without statistical significance).

Outcomes at 24 months

The Kleijnen Systematic Reviews group did not produce a network analysis of 24 month outcomes because of the treatment switching involved in VIEW 1 and VIEW 2 and CATT. The analyses presented were that using the simpler Bucher method. The ERG felt that this was appropriate.

Table 19 shows the comparison at 24 months using the switch data (VIEW 1 and VIEW 2; AFB fixed/PRN versus RBZ fixed/ PRN and CATT; RBZ fixed/ PRN versus RBZ PRN) and found no difference between treatments for any of the three outcomes. Table 20 summarises the indirect comparison using VIEW 1 and VIEW 2 switch data (AFB fixed/ PRN versus RBZ fixed/ PRN) and CATT data which were fixed or PRN (RBZ fixed versus RBZ PRN). As with the previous analyses there were no differences between treatments, but the point estimates favoured aflibercept. The analysis in Table 20 is likely to be less appropriate than Table 19 as it combines dissimilar trials. Due to the switching of treatments, the ERG believes the results should be interpreted carefully.

Table 19 24m indirect analysis (using Bucher): Fixed AFB 2mg Q8 fixed/PRN versus RBZ 0.5mg PRN (via RBZ fixed/PRN)

	No. Trials	Effect Size (95% CI)
Maintained vision	3	OR = 0.91 (0.36 to 2.34)
	(VIEW 1, VIEW 2, CATT)	RR = 0.99 (0.93 to 1.07)
BCVA mean change from baseline	3	MD = 0.31 (-4.33 to 3.71)
	(VIEW 1, VIEW 2, CATT)	
Improved Vision	3	OR = 0.84 (0.61 to 1.28)
	(VIEW 1, VIEW 2, CATT)	RR = 0.88 (0.50 to 1.42)

Table 20 24m indirect analysis (using Bucher): Fixed AFB 2mg Q8 fixed/PRN versus RBZ 0.5mg PRN (via RBZ fixed)

	No. Trials	Effect Size (95% CI)
Maintained vision	3	OR = 1.20 (0.48 to 3.01)
	(VIEW 1, VIEW 2, CATT)	RR = 1.01 (0.95 to 1.08)
BCVA mean change from baseline	3	MD = 1.69 (-2.30 to 5.68)
	(VIEW 1, VIEW 2, CATT)	
Improved Vision	3	OR = 1.07 (0.65 to 1.78)
	(VIEW 1, VIEW 2, CATT)	RR = 1.05 (0.75 to 1.48)

Indirect Comparison - critique

The manufacturer presented the data to be used in the indirect comparison in tables B26-B28 of the manufacturer's submission. The ERG observed that some of the data in Tables B26 and B28 were incorrect. This is likely an oversight and related to the spacing within the table. The

Kelijnen report was checked by the ERG and the data utilised were correctly presented there in Appendix 12 and within the WinBUGS program code (Appendices 2-4).

The **ERG were concerned** that the network meta-analysis involving the primary outcome (maintained vision at week 52) included data obtained through LOCF. After clarification the manufacturer provided outcome data for the per protocol set (PPS) and the full analysis set (FAS) for both observed and that under LOCF. The ERG considered it appropriate to run the Bayesian network meta-analysis (as a sensitivity to that presented by the manufacturer) using the observed data and that provided by the PPS in addition to the FAS. This is described in section 4.5 below.

The manufacturer raised concern over the validity of the indirect comparison as heterogeneity was present. **The ERG echoes this concern**. Several of the studies had dissimilar baseline characteristics. The Kleijnen Systematic Reviews group assessed the studies for risk of bias and found CATT, DETAIL and MOON to be high risk. It was unclear for HARBOR, EXCITE and EXTEND-1, with VIEW 1 and VIEW 2, MARINA and PIER found to be low risk. The manufacturer commented that sensitivity analyses were performed with regard to heterogeneity but the results were unchanged. It was not clear to the ERG what these sensitivity analyses were. The Kleijnen Systematic Reviews group noted that overall for the indirect analyses the studies were dissimilar for risk of bias, baseline visual acuity (CATT), central retinal thickness (CATT), retreatment criteria and number of injections received. Therefore the results of the network analyses should be treated with caution.

One of the main issues with regard to heterogeneity was with the DETAIL trial. The manufacturer reported that the patients of DETAIL appear to have responded differently to the treatment compared to other patient study groups. DETAIL carried a high risk of bias, and further investigation by Kleijnen/manufacturer found it to be open label and not clearly reported. A sensitivity analysis was undertaken for the 12 month outcome of BCVA mean change from baseline, by excluding the DETAIL trial (Table 18). This had no major impact on results with no obvious differences between the treatments.

In the network analyses, up to ten trials were used, depending on the outcome. The studies were found to be dissimilar for risk of bias, CNV, baseline visual acuity (CATT), central retinal thickness (CATT), percentage of males (EXTEND), previous therapies, retreatment criteria and number of injections received.

In summary, the manufacturer is aware the results of the indirect comparisons should be treated with caution given the potential problems with some of the trials (described above).

4.5 Additional work carried out by ERG

Bayesian network analysis for maintained vision

The ERG had concern over the use of LOCF within VIEW 1 and VIEW 2. Following clarification the manufacturer provided the observed data for the outcome of maintained vision for both the full analysis set (FAS) and per protocol set (PPS) within VIEW 1 and VIEW 2. The data used for CATT and HARBOR remains unchanged in this additional analysis. The ERG ran the Bayesian network meta-analysis for these different dataset situations and obtained the results in Table 21. Compared to the manufacturer submitted analysis there were no obvious differences using these different datasets. Therefore the ERG are satisfied that the use of LOCF did not affect the results and that those presented by the manufacturer are appropriate.

Table 21 Results of Bayesian network analysis for Maintained vision (performed by ERG)

	AFB 2mg Q8 versus RBZ 0.5mg PRN	
Maintained Vision	**OR (95% CI)**	**RR (95% CI)**
VIEW 1 and VIEW 2 FAS (using LOCF)*	1.51 (0.42, 5.94)	1.01 (0.98, 1.12)
VIEW 1 and VIEW 2 FAS (observed data)	1.74 (0.47, 6.94)	1.02 (0.99, 1.11)
VIEW 1 and VIEW 2 PPS (using LOCF)	1.62 (0.44, 6.48)	1.01 (0.98, 1.12)
VIEW 1 and VIEW 2 PPS (observed data)	1.89 (0.48, 8.39)	1.02 (0.99, 1.13)

*reported by manufacturer

Including 3rd treatment arm of DETAIL for BCVA mean change from baseline

The RBZ fixed 0.3mg arm for DETAIL was not included in the Bayesian network analysis for 12 months BCVA change from baseline (Table 166, Kleijnen systematic review) and the **ERG had concern** over the validity of the results, because of this omission. The ERG repeated the analysis including this treatment arm in the network and obtained the following result mean difference = -3.81 (-10.61, 2.95). This provides a similar conclusion to that

obtained by the manufacturer (mean difference = -2.87; -10.02, 4.30) albeit small differences in the point estimate and confidence interval limits.

4.6 Conclusions of the clinical effectiveness section

In summary, using data from VIEW 1 and VIEW 2:

- AFB 2mg Q8 was found to be non-inferior to fixed dose RBZ 0.5mg Q4 with regard to the primary outcome of maintained vision (loss of less than 15 letters from baseline to 12 months).
- No significant difference was found between treatment groups for mean change in BCVA, proportion of patients gaining at least 15 letters, change in NEI VFQ-25, CNV area or CRT.
- Incidence and type of adverse events (AEs) for ocular, non-ocular, and injection related AEs, were similar between treatment groups. In particular, there were no obvious differences in the ocular TEAEs between aflibercept and ranibzumab groups.

The indirect comparison of AFB 2mg Q8 with a PRN regimen of RBZ 0.5mg at 12 months found the following:

- No significant difference in odds of maintained vision
- No significant difference in mean change in BCVA
- No significant difference in odds of improved vision

The above summary conclusions should be weighed against the following concern of both the manufacturer and ERG with regard to the evidence synthesis:

- The validity of the network meta analysis is questionable due to the heterogeneity between the studies in terms of risk of bias, baseline visual acuity (CATT), central retinal thickness (CATT), percentage of males (EXTEND), previous therapies, retreatment criteria and number of injections received.

5 COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

The manufacturer economic evaluation of aflibercept for the treatment of wet AMD is based on a de novo economic model (Markov model) as none of the cost-effectiveness studies identified by the systematic literature review addressed the decision problem. The *de novo* economic model developed by the manufacturer is a two-eye model based on the appraisal scope.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

Comparison of economic submission with NICE reference case

Table 22 NICE reference case checklist

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice. The scope specified: • Ranibizumab • Bevacizumab • PDT	The submission only considers ranibizumab. This models variable frequency dosing with ranibizumab as drawn from the indirect comparison, rather than the monthly dosing during year 1 followed by variable dosing during year 2 as occurred within the two aflibercept RCTs: VIEW 1 and VIEW 2.
Patient group	As per NICE scope. "*Adults with wet age-related macular degeneration*"	Yes.
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	25 years, which given the mean age at baseline of 74 years as drawn from VIEW 2 is sufficient.

Synthesis of evidence on outcomes	Systematic review	Yes. An indirect comparison has been undertaken to yield the relative risks in year 1 and year 2 of gaining more than 15 letters and of maintaining vision. These are then applied to the proportions gaining more than 30 letters, gaining more than 15 letters and maintaining vision of the aflibercept arm of the VIEW 2 trial.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes. EQ-5D.
Benefit valuation	Time-trade off or standard gamble	Time trade off, using the standard UK social tariff for EQ-5D.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes.
Sensitivity analysis		A range of univariate sensitivity analyses are presented.

Model structure

The model structure is best thought of as a one eye model, with the facility for the development of 2nd eye involvement and the application of some costs and benefits to any 2nd eye involvement. Because of this, the one eye model will be described in detail followed by a description of the modelling of 2nd eye involvement. The ERG has major concerns about the modelling of 2nd eye involvement.

Visual acuity is banded into 5 health states, with these mostly being 15 letters wide, with the additional health state of death.

Table 23 Visual acuity bands within the model

BCVA	Descriptor	ETDR letters
No visual impairment	NVI	> 80
Mild visual impairment	Mild VI	66 – 80
Moderate visual impairment	Mod VI	51 – 65
Severe visual impairment	Sev VI	36 – 50
Blind	Blind	<36

Patients begin the model with wet AMD in their 1st eye, and it is assumed that there is no wet AMD and no visual impairment (NVI) in their 2nd eye. Since it is assumed that there is no wet AMD and NVI in their 2nd eye during year 1 and year 2 of the model, the bilateral vision health states for year 1 and year 2 of the model are of the form NVI – NVI, Mild VI – NVI, Mod VI – NVI, Sev VI – NVI and Blind – NVI. For ease of reference, when there is no 2nd eye involvement the descriptors can be shortened to the visual acuity descriptor for the 1st eye.

The baseline distribution between the visual acuity bands for the 1st eye is taken from the screening visit of the aflibercept arm of the VIEW 2 trial.

To model the aflibercept arm for year 1, the proportions of patients:

- Gaining more than 30 letters
- Gaining 15 to 30 letters
- Remaining within 15 letters
- Losing 15 to 30 letters; and,
- Losing more than 30 letters

Between baseline and year 1 are applied to the baseline patient distribution, with the assumption that these proportions apply equally to each health state. To model the aflibercept arm for year 2, the proportions of patients gaining and losing letters between year 1 and year 2 is applied to the estimated patient distribution at year 1. As these are LOCF distributions a proportion of patients are modelled as discontinuing and moving onto BSC and a proportion of patients are modelled as dying.

The modelling of ranibizumab PRN. in year 1 and year 2 follows the same logic, only with the year 1 proportions gaining letters for aflibercept being conditioned by the relative risk of gaining letters to provide estimates for ranibizumab, and the proportion remaining stable being similarly conditioned by the relative risk of maintaining letters. These relative risks are

drawn from the Kleijnen systematic review 12 month analyses. The year 1 to year 2 proportions gaining letters and maintaining letters for aflibercept are also conditioned by relative risks, these relative risks are drawn from the Kleijnen systematic review 24 month analyses.

The proportions discontinuing and dying in the ranibizumab arm are the same in both arms. Mortality was apparently drawn from Scottish life tables, though this element of the modelling has not been cross checked by the ERG.

For years 3 to 5 patients are assumed to remain on treatment and have stable visual acuity. But patients on treatment may exit the one eye on treatment model to BSC due to discontinuations. From the start of the third year patients may also develop 2nd eye involvement. From year 6 all patients are assumed to cease treatment and move onto BSC. BSC is associated with a steady loss of visual acuity over time.

Patients who are blind in their 1st eye are assumed to receive treatment in year 1 and year 2, but not thereafter.

As already noted, 2nd eye involvement may occur from year 3 onwards. Those who develop 2nd eye involvement while either on treatment in their 1st eye or subsequent to having completed 5 years of treatment in their 1st eye receive are treated in their 2nd eye. Those who develop 2nd eye involvement subsequent to discontinuing treatment in their 1st eye before receiving a full 5 years of treatment are not treated in their 2nd eye and both eyes remain on BSC. 2nd eye involvement is assumed to result in the 2nd eye having mild VI when 2nd eye involvement occurs.

Among those being treated in their 2nd eye, for years 3 to 5 stable visual acuity in both eyes is assumed. Patients on treatment may exit the two eye on treatment model due to discontinuations, and so receive BSC, or death. Discontinuation rates and death rates are the same for both arms.

From year 6 the steady loss of visual acuity associated with BSC is applied to both eyes. Note that despite there being newly incident cases of 2nd eye involvement from year 3 to year 25 of the model, the treatment of 2nd eye involvement is restricted to years 3 to 5 of the model. 2nd eye treatment costs can only occur during years 3 to 5 of the model.

Those developing 2nd eye involvement who do not have it treated have the steady loss of visual acuity associated with BSC applied to both eyes.

Bilateral blindness is associated with the costs of blindness and a blindness mortality multiplier.

Adverse events are not considered in the base case, though a sensitivity analysis of equal rates of adverse events between the arms is presented in a sensitivity analysis.

Utility values for the bilateral BCVA health states are drawn from EQ-5D data collected under VIEW 2.

Population

The patient population reflects the aflibercept arm of the VIEW 2 trial.

Interventions and comparators

Aflibercept 2 mg as administered within the 2mg Q8 arm of the VIEW trials is compared with variable dosing ranibizumab 0.5mg (PRN.). Since the VIEW trials administered ranibizumab 0.5mg on a fixed monthly basis during the first 52 weeks, evidence for ranibizumab 0.5mg (PRN.) is drawn from the manufacturer commissioned Kleijnen systematic review.

Perspective, time horizon and discounting

The perspective is as per the NICE methods guide: patients for benefits and the NHS and PSS for costs. The time horizon is 25 years. Costs and benefits are discounted as per the NICE methods guide at 3.5%.

Treatment effectiveness and extrapolation

Treatment effectiveness: 1st eye treated

The treatment effectiveness is based upon the relative risks estimated within the Kleijnen systematic review, where in the following a relative risk of more than 1 indicates the event is more likely with aflibercept than with ranibizumab.

Table 24 Relative risks from the Kleijnen systematic review

	12 month analyses	24 month analyses
Maintaining vision	1.02 (0.98 – 1.06)	0.99 (0.93 – 1.07)
Improving vision	1.19 (0.93 – 1.51)	0.88 (0.61 – 1.28)

The relative risk for improving vision is applied to the VIEW 2 LOCF proportion of patients improving by 30 letters and the proportion of patients improving by 15 letters in the aflibercept arm to derive the proportion of patients improving by 30 letters and the proportion of patients improving by 15 letters in the ranibizumab arm.

The relative risk for maintaining vision is applied to the total proportion of patients improving or with stable visual acuity and a change of less than ±15 letters in the aflibercept arm to derive the corresponding total proportion for the ranibizumab arm. The proportion with a change of less than ±15 letters in the ranibizumab arm is total proportion with maintained vision minus the proportion improving by either 30 letters or by 15 letters.

For the ranibizumab arm this then results in a residual that is the proportion of losing 15 letters or more. This is split into those losing 15 letters and those losing 30 letters in the same proportion to those losing 15 letters and those losing 30 letters in the aflibercept arm.

Table 25 Proportions modelled as gaining and losing letters in year 1 and year 2

	Year 1				Year 2			
	AFB		RR	RBZ	AFB		RR	RBZ
Gain 30+	[redacted]	[redacted]	1.19	[redacted]	[redacted]	[redacted]	0.88	[redacted]
Gain 15-30	[redacted]	[redacted]	1.19	[redacted]	[redacted]	[redacted]	0.88	[redacted]
Stay ± 15	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]
patients maintained	[redacted]	[redacted]	1.02	[redacted]	[redacted]	[redacted]	0.99	[redacted]
Lose 15-30	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]
Lose 30+	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]
n	305				305			

The proportions gaining and losing letters in year 1 are applied to the VIEW 2 baseline patient distribution, and similarly the proportions gaining and losing letters in year 2 are applied to the modelled year 1 distribution. The key assumption underlying this is that the probability of, say, gaining 15 letters is the same across the baseline patient distribution; i.e. a patient with mild VI has the same probability of gaining 15 letters as a patient with severe VI, or indeed as

a blind patient. Note also that for year 2 the relative risks drawn from the Kleijnen systematic review are not applied to the probabilities of gaining and maintaining vision relative to baseline but to the probabilities of gaining and maintaining vision relative to the end of year 1.

Due to the data being LOCF, the resulting distributions are the conditioned by cumulative discontinuation rates and death rates of 2.7% and 0.76% respectively for baseline to year 1 and 3.5% and 1.60% for baseline to year 2. Discontinuation rates and death rates are not differentiated by arm. This results in the following patient distributions at baseline, 52 weeks and 96 weeks.

Table 26 VIEW 2 patient distributions at baseline, 52 weeks and 96 weeks

	On treatment					Off treatment					
	NVI	Mild VI	Mod VI	Sev VI	Blind	NVI	Mild VI	Mod VI	Sev VI	Blind	Dead
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]						0.0%
AFB											
52 weeks	15.2%	25.9%	27.1%	18.2%	10.1%	0.4%	0.7%	0.8%	0.5%	0.3%	0.8%
96 weeks	16.1%	23.1%	24.8%	18.4%	12.7%	0.6%	0.8%	0.9%	0.7%	0.5%	1.6%
RBZ											
52 weeks	12.8%	23.9%	28.3%	19.6%	12.0%	0.4%	0.7%	0.8%	0.5%	0.3%	0.8%
96 weeks	14.6%	21.7%	25.1%	19.4%	14.1%	0.5%	0.8%	0.9%	0.7%	0.5%	1.6%

Interpolation for the cycles between baseline and 52 weeks and between 52 weeks and 96 weeks is based upon a simple linear interpolation, independently for each health state.

Extrapolation 1st eye treated: Visual Acuity

For years 3 to 5 of the modelling when patients are assumed to remain on treatment, stable visual acuity is assumed.

For those discontinuing therapy during year 3 to year 5 and for years 6+ when all patients remaining on treatment are assumed to discontinue and only receive BSC, visual acuity is assumed to decline. The 18.2% and 43.3% 3 year probabilities of losing 15 letters and of losing 30 letters are taken from the meta analysis of Wong et al.[30] These are translated into 0.56% and 1.56% monthly probabilities, with stable visual acuity being assumed for the residual of 97.9%.

Efficacy and extrapolation: 2nd eye involvement

It is assumed that there is no 2nd eye involvement at baseline, and that there is no development of 2nd eye involvement in year 1 or in year 2 of the model. For years 3+ a 0.65% monthly probability of developing 2nd eye involvement is drawn from Wong et al,[30] who report 26.8% over four years.

The submission states that "*Efficacy for the fellow eye while on treatment was calculated with the same methodology as for the "treated eye"* ". But based upon an examination of the electronic model structure this appears to be incorrect.

The ERG clarification question B13 asked a number of questions around the model structure for 2nd eye involvement. Some responses are non-answers, while others are partial. Resubmission of the unanswered clarification questions was requested by the ERG but declined by NICE.

But based upon an examination of the electronic model the efficacy and extrapolation of 2nd eye involvement appears to run along the following lines.

- There is no 2nd eye involvement at baseline, or during year 1 or year 2 of the model.
- From the start of year 3 to the end of the modelling horizon there is a 0.65% monthly probability of developing 2nd eye involvement.
- At incidence of 2nd eye involvement the BCVA of the 2nd eye changes from NVI to Mild VI.
- The clinical efficacy estimates for likelihood of gaining vision and maintaining vision for an eye treated with aflibercept during the first two years of treatment are not applied within the modelling of 2nd eye involvement.
- The relative risks of gaining vision and maintaining vision for an eye treated with ranibizumab during the first two years of treatment are not applied within the modelling of 2nd eye involvement.
- During years 3 to 5 of the modelling of 2nd eye involvement, stable visual acuity is assumed in both eyes. Thereafter visual acuity in both eyes is assumed to deteriorate in line with BSC; i.e. a patient developing 2nd eye involvement at the start of year 3 has three years' stable visual acuity in the 2nd eye, but a patient developing 2nd eye involvement at the start of year 5 has only one year's stable visual acuity in the 2nd eye, and those developing 2nd eye involvement in years 6+ have no years' stable visual acuity in the 2nd eye.
- Treatment costs for 2nd eye involvement are only applied during years 3 to 5 of the modelling of 2nd eye involvement; i.e. a patient developing 2nd eye involvement at the

start of year 3 has three years' treatment costs applied, but a patient developing 2nd eye involvement at the start of year 5 has only one year's treatment costs applied, and those developing 2nd eye involvement in years 6+ have no treatment costs applied.

Extrapolation: Discontinuations

The 18.7% annual probability of discontinuing therapy for years 3+ of the model is drawn from expert opinion. This translates into a 1.7% monthly probability of discontinuation.

Health related quality of life

The health related quality of life values are derived from EQ-5D data within the VIEW 2 trial using the UK social tariff. This was collected at baseline, 52 weeks and 96 weeks. Due to some non-monotonicity within the resulting values, as in bold below, the manufacturer has adjusted some values to impose monotonicity, also in bold below. The adjusted values are the average of the adjacent vertical values.

Table 27 Raw HRQoL values from VIEW 2 EQ-5D

	NVI	Mild VI	Mod VI	Sev VI	Blind
NVI	[redacted]				
Mild VI	[redacted]	[redacted]			
Mod VI	[redacted]	[redacted]	[redacted]		
Sev VI	[redacted]	[redacted]	[redacted]	[redacted]	
Blind	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 28 Adjusted HRQoL values from VIEW 2 EQ-5D

	NVI	Mild VI	Mod VI	Sev VI	Blind
NVI	[redacted]				
Mild VI	[redacted]	[redacted]			
Mod VI	[redacted]	[redacted]	[redacted]		
Sev VI	[redacted]	[redacted]	[redacted]	[redacted]	
Blind	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Resources and costs

Direct drug, administration and monitoring costs

The direct drug costs per administration are as below.

Table 29 Direct drug costs

	Ex PAS	Inc. PAS
Aflibercept	£816.00	[redacted]
Ranibizumab	£742.17	n.a.

Aflibercept is being offered with a PAS which is a straight [redacted] discount to the list price, resulting in a PAS inclusive price of [redacted] per vial. Unfortunately, the manufacturer of ranibizumab has declined to communicate its PAS during this assessment. As a consequence, the current submission performs sensitivity analyses on the list price of ranibizumab, reducing it by between 10% and 50%. These sensitivity analyses are included within the presentation of the base case cost effectiveness estimates in what follows.

Note that though the dose of aflibercept is 2mg with each vial containing 4mg, even for the situation of one patient being treated in both eyes it is assumed that each injection requires a separate vial.

The cost per administration visit is based upon a weighted average of 2010-11 HES data for the two OPCS 4 codes C79.4 and C89.3.

Table 30 OPCS codes used for administration costing

Main procedure/ intervention code	OP All	Day case
C79.1 Vitrectomy using anterior approach	5	1161
C79.2 Vitrectomy using pars plana approach	622	8077
C79.3 Injection of vitreous substitute into vitreous body	27	348
C79.4 Injection into vitreous body NEC	**34187**	**56994**
C79.5 Internal tamponade of retina using gas	6	113
C79.6 Internal tamponade of retina using liquid	1	51
C79.7 Removal of internal tamponade agent from vitreous body	1	729
C79.8 Other specified operations on vitreous body	61	124
C79.9 Unspecified operations on vitreous body		5
C89.1 Insertion of sustained release device into posterior segment of eye	115	10
C89.2 Injection of steroid into posterior segment of eye	243	655
C89.3 Injection of therapeutic substance into posterior segment of eye NEC	**14329**	**2622**
C89.8 Other specified operations on posterior segment of eye	5	1
C79.4+C89.3	**48516**	**59616**
Balance	45%	55%

NEC: Not Elsewhere Classified

The unit costs for administration and monitoring are taken from NHS reference costs.

Table 31 Unit costs for administration and monitoring

	NHS reference cost	Unit cost
Outpatient: administration	Consultant led: Follow up attendance: Non admitted: 130	£80
Day case: administration	Day case: BZ23Z: Minor vitreous retinal procedures	£402
Average administration 45% Outpatient and 55% Day case		£275
Outpatient monitoring	Consultant led: Follow up attendance: Non admitted: 130	£80
OCT	Outpatient procedures: BZ23Z: Minor vitreous retinal procedures	£117
Fluorescein angiography	Outpatient procedures: BZ23Z: Minor vitreous retinal procedures	£117

All patients are modelled as requiring one fluorescein angiography at the start of treatment.

Administration and monitoring may occur at the same visit, the one stop model, or may require dedicated visits for each, the two stop model. In the absence of other information the manufacturer has assumed an equal split between the one stop and the two stop models. Given the number of injections that are assumed, this leads to the following numbers of administration visits, monitoring visits and OCT visits over the first five years. Due to a lack of comparative data, the manufacturer has conservatively assumed that in years 3 to 5 the numbers of injections and visits in the ranibizumab arm is the same as in the aflibercept arm.

Table 32 Aflibercept injections and administration visits

	Year 1	Year 2	Year 3	Year 4	Year 5
AFB injections (A)	7	4	4	4	4
AFB monitoring (B)	7	6	7	7	7
Two stop					
AFB administration visits @£257 = (A)	7	4	4	4	4
AFB dedicated monitoring @ £80 = (B)	7	6	7	7	7
AFB dedicated OCT @ £117 = (B)	7	6	7	7	7
One Stop					
AFB administration visits @£257 = (A)	7	4	4	4	4
AFB dedicated monitoring @ £80 = (B) - (A)	0	2	3	3	3
AFB dedicated OCT @ £117 = (B)	7	6	7	7	7

Table 33 Ranibizumab injections and administration visits

	Year 1	Year 2	Year 3	Year 4	Year 5
RBZ injections (A)	8	6	4	4	4
RBZ monitoring (B)	12	12	7	7	7
Two stop					
RBZ administration visits @£250 = (A)	8	6	4	4	4
RBZ dedicated monitoring @ £80 = (B)	12	12	7	7	7
RBZ dedicated OCT @ £117 = (B)	12	12	7	7	7
One Stop					
RBZ administration visits @£250 = (A)	8	6	4	4	4
RBZ dedicated monitoring @ £80 = (B) - (A)	4	6	3	3	3
RBZ dedicated OCT @ £117 = (B)	12	12	7	7	7

The submission states that a common 50:50 split is assumed between the one stop and two stop models.[a]

This results in the following direct costs.

Table 34 Direct treatment and administration costs

	Year 1	Year 2	Year 3	Year 4	Year 5
AFB					
Drug cost excl. PAS	£5,712	£3,264	£3,264	£3,264	£3,264
Drug administration	£1,802	£1,030	£1,030	£1,030	£1,030
Monitoring visits	£0	£319	£399	£399	£399
OCT visits	£821	£704	£821	£821	£821
Total excl. PAS	£8,335	£5,316	£5,513	£5,513	£5,513
RBZ					
Drug cost excl. PAS	£5,937	£4,453	£2,969	£2,969	£2,969
Drug administration	£2,060	£1,545	£1,030	£1,030	£1,030
Monitoring visits	£638	£718	£399	£399	£399
OCT visits	£1,407	£1,407	£821	£821	£821
Total excl. PAS	£10,042	£8,123	£5,218	£5,218	£5,218

Note that in contrast to the values stated in table B51, for those modelled as being blind it is assumed that the above treatment and monitoring costs are applied in year 1 and year 2 but not thereafter[b].

Adverse event costs

Adverse events are not included in the base case. A sensitivity analysis applies equal rates of adverse events to both arms.

The costs of blindness

The annual costs of blindness are taken from Meads et al,[31] the December 2000 costs reported in Meads et al being increased by 46% to 2011 figures using the PSSRU Hospital & Community Health Services index. Both the monthly cost and the implied annual cost are reported below, as it appears there may have been some confusion between the two in the model implementation.

[a] From the electronic model it appears that in year 1 the proportion of one stop visits for aflibercept may be assumed to be 100% while the proportion for ranibizumab is assumed to be 50%. The ERG has not quite bottomed this out.

[b] The treatment costs in the 1st eye worksheets apply the patient numbers SUM(CA9:CB9) for the 1st cycle with a similar format for the subsequent 23 cycles but only CA33 for the 25th cycle and thereafter.

Table 35 Submission costs of blindness from Meades et al 2003

	% requiring	Cost (2000)	Cost (2011)	Annual	Monthly
Low vision aids	33%	£136	£199	£65	£5.45
Low vision rehabilitation	11%	£205	£300	£33	£2.74
Depression	39%	£392	£572	£220	£18.33
Hip replacement	5%	£3,669	£5,357	£267	£22.23
Total				£585	£49

The model applies a monthly cost of £585[c].

Cost effectiveness results

The base case results are as below. Note that life years are undiscounted but QALYs and costs are discounted, and that the probabilistic analysis is run over 1,000 iterations.

Table 36 Base case deterministic results: excluding PAS

	Life years	QALYs	Drug&Admin	Monitoring	Blindness	Total
AFB	11.995	7.767	£18,430	£3,773	£2,806	£25,009
RBZ	11.994	7.758	£19,826	£5,923	£2,866	£28,615
Net	-0.001	-0.010	£1,396	£2,150	£60	£3,606
ICER				Aflibercept dominates ranibizumab		

[c] The *DirMedBlind* variable in the model has the default value £584.95. It is multiplied by the patient numbers in column SN of the 2nd eye worksheets of the model. These values are summed in cells DH10 and DH11 of the 1st eye worksheets. The ERG has not identified any division by 12 within this process.

Table 37 Base case deterministic results: including aflibercept PAS and ranibizumab price sensitivities

	Life years	QALYs	Drug&Admin	Monitoring	Blindness	Total
AFB	11.995	7.767	[redacted]	£3,773	£2,806	[redacted]
RBZ						
0% PAS	11.994	7.758	£19,826	£5,923	£2,866	£28,615
10% PAS			£18,343			£27,132
15% PAS			£17,602			£26,391
20% PAS			£16,861			£25,650
25% PAS			£16,119			£24,908
30% PAS			£15,378			£24,167
35% PAS			£14,636			£23,425
40% PAS			£13,895			£22,684
45% PAS			£13,153			£21,942
50% PAS			£12,412			£21,201
Net						
0% PAS	-0.001	-0.010	[redacted]	£2,150	£60	[redacted]
10% PAS			[redacted]			[redacted]
15% PAS			[redacted]			[redacted]
20% PAS			[redacted]			[redacted]
25% PAS			[redacted]			[redacted]
30% PAS			[redacted]			[redacted]
35% PAS			[redacted]			[redacted]
40% PAS			[redacted]			[redacted]
45% PAS			[redacted]			[redacted]
50% PAS			[redacted]			[redacted]

Given the aflibercept PAS of [redacted]

Table38 Base case probabilistic results: excluding PAS

	Life years	QALYs	Drug&Admin	Monitoring	Blindness	Total
AFB	11.997	7.769	£18,533	£3,480	£2,794	£24,807
RBZ	11.996	7.759	£19,914	£5,634	£2,850	£28,615
Net	-0.001	-0.009	£1,380	£2,154	£56	£3,808
ICER				Aflibercept dominates ranibizumab		

For all willingness to pay values, the model estimates that there is no probability of ranibizumab being cost effective.

Table 39 Base case probabilistic results: including aflibercept PAS

	Life years	QALYs	Drug&Admin	Monitoring	Blindness	Total
AFB	10.578	7.766	[redacted]	£3,768	£2,753	[redacted]
RBZ	10.577	7.757	£19,844	£5,914	£2,808	£28,615
Net	-0.001	-0.009	[redacted]	£2,146	£55	[redacted]
ICER				Aflibercept dominates ranibizumab		

For all willingness to pay values, the model estimates that there is no probability of ranibizumab being cost effective.

Sensitivity analyses

A range of univariate sensitivity analyses were presented around resource use, coupled with two sensitivity analyses around the relative risk of improving vision in year 1 and the relative risk of maintaining vision in year 2. It appears that other univariate sensitivity analyses were conducted, as outlined in table B56 of the submission, but that only the 15 most important in terms of their impact upon the net health benefits are presented in table B71 of the submission.

While the cross-over between table B56 and table B71 of the submission is not unambiguous, the univariate sensitivity analyses of the original submission are, in order of importance:

- SA01: The price of ranibizumab being varied from the base case £742 by ±20%: £594 and £891.
- SA02: The price of aflibercept being varied from the base case £816 ±20%: £653 and £979.
- SA03: The number of aflibercept injections for years 3 to 5 being varied from the base case of 4 by ±20%: 3.2 and 4.8.

- SA04: The number of ranibizumab injections for years 3 to 5 being varied from the base case of 4 by ±20%: 3.2 and 4.8.
- SA05: The number of aflibercept physician and OCT visits for years 1 to 5 being varied from the base case 7, 6, 7, 7, 7[d] by ±20%: 5.6, 4.8, 5.6, 5.6, 5.6 and 8.4, 7.2, 8.4, 8.4, 8.4.
- SA06: The relative risk of improving vision in year 1 from the base case of 1.19: 0.93 and 1.51
- SA07: The number of ranibizumab physician and OCT visits for years 1 to 5 being varied from the base case 12, 12, 7, 7, 7 by ±20%: 9.6, 9.6, 5.6, 5.6, 5.6 and 14.4, 14.4, 8.4, 8.4, 8.4.
- SA08: The proportion of ranibizumab patients receiving therapy in a one stop clinic during year 1 from the base case of 50% by ±50%: 25% and 75%
- SA09: The proportion of ranibizumab patients receiving therapy in a one stop clinic during year 2 from the base case of 50% by ±50%: 25% and 75%
- SA10: The relative risk of improving vision in year 2 from the base case of 0.88: 0.61 and 1.28.
- SA11: The proportion of aflibercept patients receiving therapy in a one stop clinic during year 2 from the base case of 50% by ±50%: 25% and 75%
- SA12: The relative risk of maintaining vision in year 2 from the base case of 0.99: 0.93 and 1.07.
- SA13: The proportion of aflibercept patients receiving therapy in a one stop clinic during year 3 from the base case of 50% by ±50%: 25% and 75%
- SA14: The proportion of ranibizumab patients receiving therapy in a one stop clinic during year 3 from the base case of 50% by ±50%: 25% and 75%
- SA15: The proportion of aflibercept patients receiving therapy in a one stop clinic during year 4 from the base case of 50% by ±50%: 25% and 75%

It may have been more sensible to have performed the sensitivity analyses varying the proportion receiving therapy in one stop clinics across all five years of treatment, rather than varying it for individual years.

The sensitivity analysis with aflibercept PAS are of less obvious relevance, as they apply the aflibercept PAS but do not further explore the impact upon these of assuming a PAS for ranibizumab. The most important sensitivity analyses are broadly as for the no PAS

[d] This number of visits applying to both physician visits and OCT visits; i.e. a total of 68 visits over the 5 years.

sensitivity analyses, though the discontinuation rate for aflibercept and ranibizumab in year 3 to year 5 comes more to the fore.

Table 40 Base case univariate sensitivity analyses

	Low parameter value(s)			High parameter value(s)		
Sensitivity analysis	**Costs**	**QALYs**	**NMB**	**Costs**	**QALYs**	**NMB**
SA01 RBZ drug cost	-£645	0.013	£903	-£6,576	0.013	£6,834
SA02 AFB drug cost	-£6,435	0.013	£6,693	-£786	0.013	£1,044
SA03 AFB injections : Years 3-5	-£5,019	0.013	£5,277	-£2,203	0.013	£2,460
SA04 RBZ injections : Years 3-5	-£2,325	0.013	£2,583	-£4,897	0.013	£5,154
SA05 RBZ Physician/OCT visits : Years 1-5	-£2,984	0.013	£3,241	-£4,238	0.013	£4,496
SA06 RR gaining letters : Year 1	-£3,696	-0.008	£3,530	-£3,546	0.029	£4,125
SA07 AFB Physician/OCT visits : Years 1-5	-£3,906	0.013	£4,164	-£3,316	0.013	£3,574
SA08 RBZ 1 stop : Year 1	-£3,383	0.013	£3,641	-£3,839	0.013	£4,096
SA09 RBZ 1 stop : Year 2	-£3,396	0.013	£3,654	-£3,825	0.013	£4,083
SA10 RR gaining letters: Year 2	-£3,649	0.002	£3,698	-£3,583	0.020	£3,989
SA11 AFB 1 stop : Year 2	-£3,718	0.013	£3,976	-£3,504	0.013	£3,761
SA12 RR maintaining letters : Year 2	-£3,669	0.006	£3,787	-£3,543	0.021	£3,963
SA13 AFB 1 stop : Year 3	-£3,691	0.013	£3,949	-£3,531	0.013	£3,788
SA14 RBZ 1 stop : Year 3	-£3,532	0.013	£3,790	-£3,690	0.013	£3,947
SA15 AFB 1 stop : Year 4	-£3,672	0.013	£3,930	-£3,550	0.013	£3,807

The ERG has not cross checked the sensitivity analyses for the no PAS scenario, with the exception of SA06: The relative risk of improving vision in year 1 from the base case of 1.19: 0.93 and 1.51. The ERG cross check of this sensitivity analysis[e] suggests that a relative risk of 0.93 results in -0.006 net QALYs and -£3,697 net costs, while the relative risk of 1.51 results in 0.022 net QALYs and -£3,537 net costs. The relative risk of 0.93 resulting in -0.006 net QALYs and -£3,697 net costs suggests a cost effectiveness of ranibizumab of £575k per QALY compared to aflibercept.

Similarly, the ERG has not cross checked the sensitivity analyses for the with aflibercept PAS scenario and for the reasons already noted has not presented them here. But the sensitivity analysis around the proportion of ranibizumab patients receiving one stop therapy in year 1 appear peculiar as the net QALYs are affected.

[e] Setting cell B76 of the *Model_Parameters* worksheet to 0.93 and 1.51.

Model validation and face validity check

Model validation is limited to comparing the modelled distribution of visual acuity for the study eye for the aflibercept 2mg Q8 arm with the trial data at baseline, 52 weeks and 96 weeks. The manufacturer response to ERG clarification questions A9 and A10 provides the distributions of the treated eyes within the trials, though note that this reporting has switched to the Safety Analysis Set.

Table 41 SAS LOCF aflibercept 2mg Q8 distribution of patients' treated eye VA

	VIEW 1			**VIEW 2**			**Pooled**		
	baseline	week 52	week 96	baseline	week 52	week 96	baseline	week 52	week 96
No VI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild VI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mod VI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sev VI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blind	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note that table B36 of the submission summarises the VIEW 2 distribution at screening rather than at baseline.

Table 42 Modelled aflibercept 2mg Q8 distribution of patients' treated eye VA (survivors)

	screen	**baseline**	**week 52**	**week 96**
No VI	[redacted]	[redacted]	15.7%	17.0%
Mild VI	[redacted]	[redacted]	26.8%	24.3%
Mod VI	[redacted]	[redacted]	28.1%	26.1%
Sev VI	[redacted]	[redacted]	18.9%	19.3%
Blind	[redacted]	[redacted]	10.5%	13.4%

The discrepancies between the trial and the model may arise due to the model assuming an equal likelihood of, say, gaining 15 letters for each of the health states. This may not have applied within the trial, which might argue for estimating proportions gaining and losing letters that are specific to each health state. In order to preserve reasonable patient numbers, this might in turn argue for using the pooled VIEW 1 and VIEW 2 patient data rather than restricting the analysis to the VIEW 2 data.

5.3 ERG cross check and critique

Base case results

The base case deterministic results and probabilistic results of the submission cross check with those of the model and a re-run of the probabilistic modelling.

Data Inputs: Correspondence between written submission and sources cited

Clinical effectiveness inputs: aflibercept

In response to the ERG clarification questions A7 and A8, the manufacturer provided the numbers of treated eyes gaining at least 30 letters, gaining at least 15 letters, losing at least 15 letters and losing at least 30 letters over the 96 weeks of the VIEW trials. This enables the proportions of those gaining at least 30 letters, gaining at between 15 letters and 30 letters, losing at between 15 letters and 30 letters and remaining within 15 letters of their baseline value to be extracted for week 52 and week 96. The numbers reported below relate to the FAS LOCF data set for the aflibercept 2mg Q8 arms of the VIEW trials.

Table 43 FAS LOCF aflibercept 2mg Q8 patients gaining and losing letters

	VIEW 1				VIEW 2				Pooled			
	Weeks 0-52		Weeks 0-96		Weeks 0-52		Weeks 0-96		Weeks 0-52		Weeks 0-96	
Gain 30+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gain 15-30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stay ±15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lose 15-30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lose 30+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N	301		301		306		306		607		607	

In the above, the proportions gaining and losing letters at 52 weeks and at 96 weeks are broadly similar between the trials and there is no suggestion of bias arising from choosing to use VIEW 2 trial data rather than the pooled trial data.

But there is no ready read across from the proportions of the above with those applied within the model.

Table 44 Modelled aflibercept 2mg Q8 patients gaining and losing letters

	Weeks 0-52		Weeks 52-96	
Gain 30+	[redacted]	[redacted]	[redacted]	[redacted]
Gain 15-30	[redacted]	[redacted]	[redacted]	[redacted]
Stay ±15	[redacted]	[redacted]	[redacted]	[redacted]
Lose 15-30	[redacted]	[redacted]	[redacted]	[redacted]
Lose 30+	[redacted]	[redacted]	[redacted]	[redacted]
N	305		305	

The model appears to estimate a much small proportion at week 52 remaining in their original health state. More are modelled as declining, but the bigger effect is that more are modelled as improving at week 52 than the FAS LOCF data would seem to suggest. There may be an error of interpretation on the part of the ERG, but this the key data within the modelling and it would seem to require some reconciliation between these figures to be presented.

The manufacturer submission states that "*clinical trial data from the aflibercept 2mg Q8 arm of the VIEW 2 trial was incorporated into the model to define the baseline distribution … during years one and two of the simulation the distribution of patients at 52 weeks and 96 weeks from the clinical trial data was reproduced. The analysis of the trial data was based on the LOCF population*". While not explicit, the ERG assumes that the 52 week data and the 96 week data also relate to VIEW 2.

Extrapolation: Visual Acuity

The monthly proportions worsening by 15 letters and by 30 letters are derived from Wong et al (2008). The 18.2% of the submission corresponds with those losing between 3 and 6 lines at 36 months, and the 43.3% of the submission corresponds with and those losing more than 6 lines at 36 months. These values are converted within the model to monthly probabilities of 0.56% and 1.56% respectively.

Table 45 Wong et al proportions losing lines with BSC

Time point	Proportion of patients losing:			
	<3 lines	3 to 6 lines	>6 lines	Total
3 months	76.0%	14.1%	10.1%	100.2%
6 months	65.0%	15.4%	19.8%	100.2%
12 months	49.3%	27.0%	28.3%	104.6%
24 months	43.4%	25.4%	39.0%	107.8%
36 months	43.6%	18.2%	43.3%	105.1%

Note that Wong et al[30] also report 43.6% losing less than 3 lines at 36 months, with the three percentages summing to 105% for reasons that are not clear. Arbitrarily reducing all the Wong et al percentages proportionately by 105% would result in minor reductions in the monthly probabilities of losing 15 letters and losing 30 letters to 0.53% and 1.46% respectively

The 0.56% and 1.56% are then in effect used to populate a monthly TPM for BSC. This is slightly at odds with the figures within Wong et al,[30] in that the latter are the absolute percentages at a given time point. To illustrate this, the proportions of a given health state modelled as losing 0, 15, 30, 45 and 60 letters by month 36 can be derived through repeated application of the implied TPM.

Table 46 Submission method for the Wong 2008 BSC percentages at 36 months

Initial health state	36 month percentage losing the following number of letters				
	0	15	30	45	60
NVI	46%	9%	28%	5%	11%
Mild VI	46%	9%	28%	17%	..
Moderate VI	46%	9%	44%	..	..
Severe VI	46%	54%	..	..	..
Blind	100%	..	..	..	..

The above suggests that the model may tend to overstate the worsening of BCVA under BSC over 36 months for those initially in one of the better health states. However, this is complicated by Wong et al[30] providing data on the proportion losing more than six lines, or 30 letters, at 36 months which may include proportions worsening by 45 letters and by 60 letters.

For extrapolation beyond 36 months of BSC, it appears that most of those who were relatively stable up to month 12 remained so between month 12 and month 26, while those who had lost between 3 and 6 lines by month 12 continued to worsen between month 12 and month 36. Implementing this within the model would require the further complication of splitting the patient group on BSC into those being relatively stable up at month 12, and those deteriorating more quickly. There may be limited mileage in pursuing this. But the impact might be to polarise those on BSC, with a resulting higher proportion remaining with a relatively good BCVA, a higher proportion falling into blindness in one or both eyes and the middle ground falling away. This might in turn increase the importance of the discontinuation rate if this was thought to differ between the arms.

Extrapolation: 2nd eye involvement

Wong et al[30] report 12.2% developing wet AMD in the 2nd eye by 12 months, and 26.8% by 4 years. The submission applies a monthly rate of 0.65% which corresponds with 26.8% by 4 years. But again this may tend to slightly overstate the development of 2nd eye involvement given the monthly rate of 1.09% for the first 12 months, which in turn suggests a monthly rate of 0.50% between month 12 and month 48: i.e. 22% less than that applied subsequent to the first year.

Resource use: Numbers of drug administrations in year 1 and year 2

The Kleijnen systematic review presents the following mean numbers of doses, excluding sham injections, in table 13. Note that the values for the VIEW trials for year 2 have been annualised to 52 weeks based upon the 44 weeks from week 52 to week 96. The model assumptions about the number of injections are also presented for ease of reference.

Table 47 Frequency of injections reported within Kleijnen systematic review

	AFB					RBZ				
	n	**Year 1**		**Year 2**		**n**	**Year 1**		**Year 2**	
VIEW 1	303	Fixed	7.5	PRN.	4.5	306	Fixed	12.1	PRN.	4.7
VIEW 2	313	Fixed	7.7	PRN.	4.0	303	Fixed	12.7	PRN.	4.8
CATT						301	PRN.	6.9	PRN.	5.7
HARBOR						276	Fixed	11.3		
HARBOR						275	PRN.	7.7		
DETAIL						n.a.	PRN.	9.0		
DETAIL						n.a.	PRN.	12.0		
EXTEND-1						33			PRN.	3.9
Model		Fixed	7	PRN.	4		PRN.	8	PRN.	6

In the above fixed apparently corresponds to a fixed monthly injection schedule for ranibizumab, and the other fixed dosing schedules for ranibizumab reported within the Kleijnen systematic review are not presented here.

CATT PRN. dosing is reported as occurring after the initial injection, and "*retreatment was given when signs of active neovascularisation were present*". HARBOR PRN. dosing is reported as having 3 loading doses with "*retreatment given if there was evidence of disease activity by OCT or ≥ 5 letters decrease from previous visit*". DETAIL PRN. dosing is reported as having 3 loading doses with "*treatment until macular fluid was absent, or until both macular fluid and PED were absent*".

The above appears to suggest that 8 injections of aflibercept in year 1 might be the more natural modelling assumption, with 4 injections in year 2 being reasonable. Note that the aflibercept SPC suggests "one injection per month for three consecutive doses, followed by one injection every two months". The ERG interpretation of this is that dosing is not per calendar month but is four weekly. This also suggests 8 injections of aflibercept in year 1 for those remaining on treatment throughout the year[f]. Also bear in mind that the model takes into account patient discontinuations, which will tend to reduce the average number of injections to below 8 in year 1.

For ranibizumab in year 1 the picture is slightly complicated by the patient numbers in the relevant arms of the DETAIL trial not being reported. But the DETAIL trial was a relatively

[f] Dosing at the start of weeks 0, 4, 8, 16, 24, 32, 40 and 48

small trial with only 58 patients treated, these patients being randomised between four arms. From the Kleijnen systematic review it appears that the DETAIL trial had two PRN dosing arms, these differing as to whether retreatment was based upon the presence of macular fluid, or upon the presence of macular fluid and pigment epithelial detachment. But the patient numbers within the DETAIL trial were small.

Excluding the DETAIL trial would suggest a weighted average of 7.3 injections, while including it would suggest a weighted average of 7.4 injections if equal weight is given to both retreatment criteria. This appears to suggest that 7 injections of ranibizumab in year 1 might be the more natural modelling assumption.

The network meta-analysis that derived the relative risk of maintaining vision and the relative risk improving vision from baseline to year 2 relied upon the CATT trial. As a consequence, 6 injections in year 2 appears to be a reasonable assumption for the base case.

Resource use: Costs of blindness

As already noted, the manufacturer estimates an annual cost of blindness of £585.95 but in the model treats this cost as a monthly cost. However, there are a number of other elements to the costs of blindness within Meads et al[31] that are not included within the manufacturer estimate. Rather than uprating the Meads et al[31] residential care cost for inflation, the 2011 PSSRU Unit Costs of Health and Social Care figure of £497 per week can be used, and adjusted for the 30% who pay for themselves. This results in the following estimates.

Table 48 The costs of blindness from Meads 2003

	% requiring	Cost (2000)	Cost (2011)	Annual	Monthly
Blindness registration	95%	£97	£137	£130	£10.83
Low-vision aids	33%	£136	£191	£63	£5.27
Low-vision rehabilitation	11%	£205	£288	£32	£2.64
Community care	6%	£2,849	£4,001	£240	£20.01
Residential care	30%		£18,091	£5,427	£452.27
Depression	39%	£392	£551	£215	£17.89
Hip replacement	5%	£3,669	£5,153	£258	£21.47
Total year 1				£6,365	£530.38
Total year 2+				£6,140	£511.64

The year 2+ figure excludes the first three elements which can be seen as one off costs. By coincidence, the monthly average £511.64 is not so very different from the £585.95 applied by the manufacturer.

Data Inputs: Correspondence between written submission and electronic model

The ERG has rebuilt the one eye deterministic modelling using the data inputs of the written submission. The results of this rebuild cross check with those of the manufacturer model, with some slight corrections to the manufacturer model treatment of those with mild VI, when the development of 2nd eye involvement is set to zero[g].

There are some minor discrepancies between table B51 of the submission and the electronic model; e.g. the model applies treatment costs to those blind in one eye during year 1 and year 2 of the model, but these seem unlikely to have a major impact upon results.

ERG commentary on model structure, assumptions and data inputs

Application of relative risks within the model

The ERG interpretation of the relative risks reported within the Kleijnen systematic review is that for the 12 month analyses these relate to the probabilities of gaining or maintaining vision between baseline and 12 months, and for the 24 month analyses these relate to the probabilities of gaining or maintaining vision between baseline and 24 months.

This is a key difference of interpretation between the ERG and the manufacturer. Table B39 of the manufacturer submission describing these relative risks as "*relative risk aflibercept vs ranibizumab Year 2 compared to Year 1*". But the ERG can find nothing in the Kleijnen systematic review that suggests the 24 month analyses relate to the probabilities of gaining or maintaining vision between 12 months and 24 months, with everything implying that these estimates relate to the probabilities of gaining or maintaining vision between baseline and 24 months.

Table 49 Relative risks within the model: aflibercept vs ranibizumab PRN.

	12 month analyses	**24 month analyses**
Maintaining vision	1.02 (0.98 – 1.06)	0.99 (0.93 – 1.07)
Improving vision	1.19 (0.93 – 1.51)	0.88 (0.61 – 1.28)

[g] And a concern that the one stop model may be applied to all in the aflibercept arm for the 1st cycle.

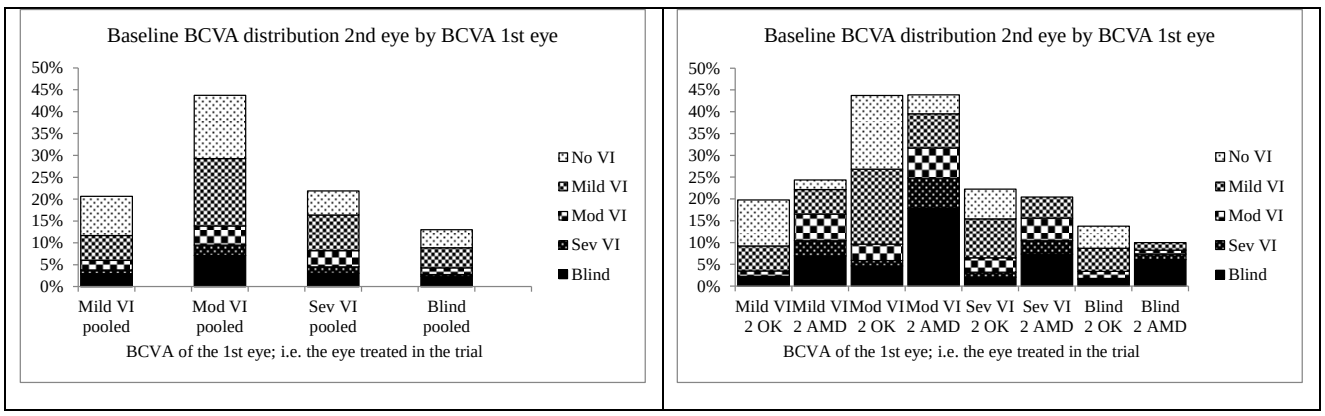
The model implementation applies the 24 month relative risks to the probabilities of gaining or maintaining vision between 12 months and 24 months. This results in aflibercept being estimated to have a superior distribution of visual acuity in the treated eye at 24 months compared to ranibizumab. But the relative risks of the above table suggest the opposite: aflibercept has a relative risk of 0.99 of maintaining vision between baseline and 24 months compared to ranibizumab and a relative risk of 0.88 of improving vision between baseline and 24 months compared to ranibizumab. This should result in the aflibercept arm being estimated to have a worse distribution of visual acuities in the treated eyes at 24 months than the ranibizumab arm.

To implement this within the model requires estimates for the proportions of aflibercept patients gaining at least 30 letters between baseline and 24 months, gaining between 15 letters and 30 letters between baseline and 24 months and maintaining vision between baseline and 24 months. As already noted in Table 44 above, the model only provides this data for the baseline to 12 months period and the 12 months to 24 months period. It is also not clear what data set this is drawn from. The ERG is constrained to the FAS LOCF data supplied in answer to ERG clarification questions A7 and A8 as summarised in Table 43 above.

2nd eye involvement at baseline

The model assumes that at baseline all 2nd eyes have no visual impairment and are also free of wet AMD. As outlined in the manufacturer response to ERG clarification question A24, at baseline of the pooled VIEW 1 and VIEW 2 patient population only a minority of 33% of the 2nd eyes has no visual impairment at baseline, and 19% had wet AMD at baseline.

Figure 3 Baseline BCVA of 2nd eye by BCVA of the 1st eye[h]



[h] Due to reasons of space, those without wet AMD in their 2nd eye at baseline have been described as "2 OK" while those with wet AMD in their 2nd eye at baseline have been described as "2 AMD". These figures also ignore the very small patient numbers with missing data.

2nd eye modelling.

The ERG clarification question B13 posed a number of questions around the modelling of 2nd eye involvement. Most significant of these[i] was:

> *As far as the ERG can ascertain, there is no consideration of the impact of the initial two years of treatment upon the BCVA of the 2nd eye; i.e. something along the lines of cells GR6:GX65 of the 1st eye worksheets being applied to the annual incidences of 2nd eye involvement, with ongoing annual incidences of 2nd eye involvement occurring over the time horizon of the model and receiving this treatment effect. Is this correct? If it is not correct, it would be much appreciated if some indication could be given of the location of these calculations and the underlying model logic, coupled with how it copes with treatment of the ongoing annual incidences of 2nd eye involvement over the time horizon of the model.*

To which the manufacturer responded:

> *The assumption/simplification incorporated into the model is that the second eye cannot develop wet AMD until after year 2.*

As this does not address the question that was asked, the ERG requested that the manufacturer be asked this question again with the ERG proposing a further simplification of the wording of the question. NICE declined to resubmit this question to the manufacturer and as a consequence the ERG has not been able to clarify whether the manufacturer agrees that no treatment effect is applied within the modelling of 2nd eye involvement.

The ERG has not rebuilt the modelling of 2nd eye involvement as it views the submitted approach to be incorrect. To the extent that the ERG has reviewed the modelling of 2nd eye involvement, the reasons for this are:

- It appears that there are no treatment effects. The likelihood of gaining vision and maintaining vision for an eye treated with aflibercept and the relative risks of these for an eye treated with ranibizumab during the first two years of treatment are not applied within the modelling of 2nd eye involvement.
- There is no consideration of the baseline prevalence of 2nd eye involvement. As already reviewed, within the VIEW trials the baseline prevalence of 2nd eye wet AMD was 19%.
- The model assumes that there is no incidence of 2nd eye involvement during years 1 and 2 of the model.

[i] The wording of this was lightly revised by NICE prior to sending to the manufacturer, but it was sufficiently close to the original as to retain the sense of it.

- There is no sensible consideration of the timing of the incidence of 2nd eye involvement.
  - The costs of the treatment of 2nd eye involvement are limited to years 3, 4 and 5 of the model; i.e. a three year maximum compared to a five year maximum for the 1st eye. Furthermore, somebody developing 2nd eye involvement at the start of year 3 incurs three years' costs of treatment for that eye, but somebody developing 2nd eye involvement at the start of year 5 incurs only one year's costs of treatment for that eye, and somebody developing 2nd eye involvement at the start of year 6 incurs no costs of treatment for that eye at all.
  - The visual stability associated with "treatment" is limited to years 3, 4 and 5 of the model. Somebody developing 2nd eye involvement at the start of year 3 experiences stability in the BCVA of their 2nd eye for three years, but somebody developing 2nd eye involvement at the start of year 5 experiences stability in the BCVA of their 2nd eye for only one year, and somebody developing 2nd eye involvement at the start of year 6 experiences no stability in the BCVA of their 2nd with this immediately deteriorating as per BSC.
  - The manufacturer further confirms that "*Those patients who develop wet AMD in their second eye after year 5 are not treated; however their HRQoL will be impacted as the utility value assigned to model health states reflects the impact of the visual acuity in both eyes*".

In the light of the above, the ERG has not fully interrogated the modelling of 2nd eye involvement. It is possible that further concerns could arise if the ERG were to rebuild the modelling of 2nd eye involvement.

Within their clarification response, the manufacturer compares two analyses: one with no 2nd eye development and one with 2nd eye development as per the submitted model. It notes that there are only limited differences in the net costs and net QALYs between the arms of these two analyses. But this does not address what a genuine model of 2nd eye development would estimate in terms of costs and benefits, taking into account: the clinical effects of treatment; a baseline prevalence of 2nd eye involvement; and, sensible consideration of the timings of the subsequent incidences of 2nd eye involvement.

Quality of life data

The EQ-5D quality of life data within the manufacturer submission are pooled across all patients and time points to derive the average utility values presented within Table 27 above. It should be noted that three has apparently been no attempt to control for possible covariates. Within the current context it might be anticipated that older patients might be more likely to

have poor vision in one or both eyes, but also to have generally poorer health. But this comment also applies more generally to other utility estimates for wet AMD within the literature.

Unfortunately, as reviewed above, the modelling of 2nd eye involvement may not be tenable. This may mean that the model may be limited to being a one eye model, with there being the usual sensitivity of results to whether it is a better seeing eye (BSE) that is being treated, or a worse seeing eye (WSE) that is being treated. Within the submitted model, setting 2nd eye involvement to zero results in a WSE model, with the additional assumption of the fellow eye having NVI. To make the one eye model a BSE model, the parallel assumption of the WSE being blind could be made and this would enable BSE utility values to be extracted, but this is less obviously reasonable and may argue for some consideration of utility values within the wider literature.

A number of papers exist within the literature, and the ERG have not undertaken a systematic review of these. But two papers considered in previous assessments may be relevant to the current assessment: Brown[1] and Brown et al,[2] and are considered briefly below.

Brown[1] employed Time Trade Off (TTO) and Standard Gamble (SG) to assess the HRQoL among 325 US patients with impaired vision of at least 20/40 in at least one eye. Note that 1/3rd had diabetes related eye disease, 1/3rd had age related macular degeneration (ARMD) and the remainder a range of other conditions.

There were 78 patients with good vision of 20/20 to 20/25 in one eye. These patients were subdivided by the BCVA in the fellow eye into 5 groups with TTO and SG being applied to them. This resulted in the following patient distribution and HRQoL estimates.

Table 50 HRQoL by BCVA in WSE among patients with good vision in BSE: Brown 1999

BCVA in WSE	n	TTO	SG
20/40-20/50	18	0.860	0.930
20/70-20/100	12	0.900	0.960
20/200-20/400	13	0.950	0.940
≤ 20/800 (CF)	28	0.880	0.920
≤ 20/1600 (HM/NLP)	7	0.810	0.950

CF: Counting fingers

HM: Detecting hand movement

NLP: No light perception

As can be seen from the above, among the patients who had good vision in their BSE eye there was no strong relationship between HRQoL and vision in the WSE. Based upon TTO the above could be taken to indicate that given good vision in one eye, the other eye has to drop to levels below 20/400 for there to be an impact upon HRQoL values.

The ERG has assumed that the BCVA values refer to the upper band of the range and draws the following values from Brown (1999).[1] The weighted averages for the range of values within Brown (1999)[1] that span the model health state can then be calculated, suggesting the following.

Table 51 TTO BSE HRQoL values: Brown 1999

Model			Brown[1]		HRQoL	
State	**ETDRS**	**Snellen**	**Snellen**	**N**	**Paper**	**Applied**
NVI	> 80	> 20/25	20/20	32	0.920	0.920
Mild VI	66 - 80	> 20/50 to 20/25	20/25	50	0.870	
			20/30	44	0.840	0.836
			20/40	54	0.800	
Mod VI	51 - 65	> 20/100 to 20/50	20/50	31	0.770	0.753
			20/70	40	0.740	
Sev VI	36 - 50	> 20/200 to 20/100	20/100	18	0.670	0.670
Blind	≤ 35	≤ 20/200	20/200	16	0.660	
			20/300	13	0.630	0.621
			20/400	9	0.540	
			20/800	12	0.520	
			20/1600	6	0.350	

Brown et al (2000)[2] employed Time Trade Off (TTO) and Standard Gamble (SG) to assess the HRQoL among 72 US patients with ARMD, with vision loss in at least one eye to 20/40.

Table 52 TTO BSE HRQoL values: Brown 2000

Model			**Brown[2]**		**HRQoL**	
State	**ETDRS**	**Snellen**	**Snellen**	**N**	**Paper**	**Applied**
NVI	> 80	> 20/25	20/20-20/25	21	0.890	0.890
Mild VI	66 - 80	> 20/50 to 20/25	20/30-20/50	23	0.810	0.810
Mod VI	51 - 65	> 20/100 to 20/50	20/60-20/100	11	0.570	0.570
Sev VI	36 - 50	> 20/200 to 20/100	n.a.	n.a.	n.a.	0.545
Blind	≤ 35	≤ 20/200	20/200-20/400	12	0.520	0.520

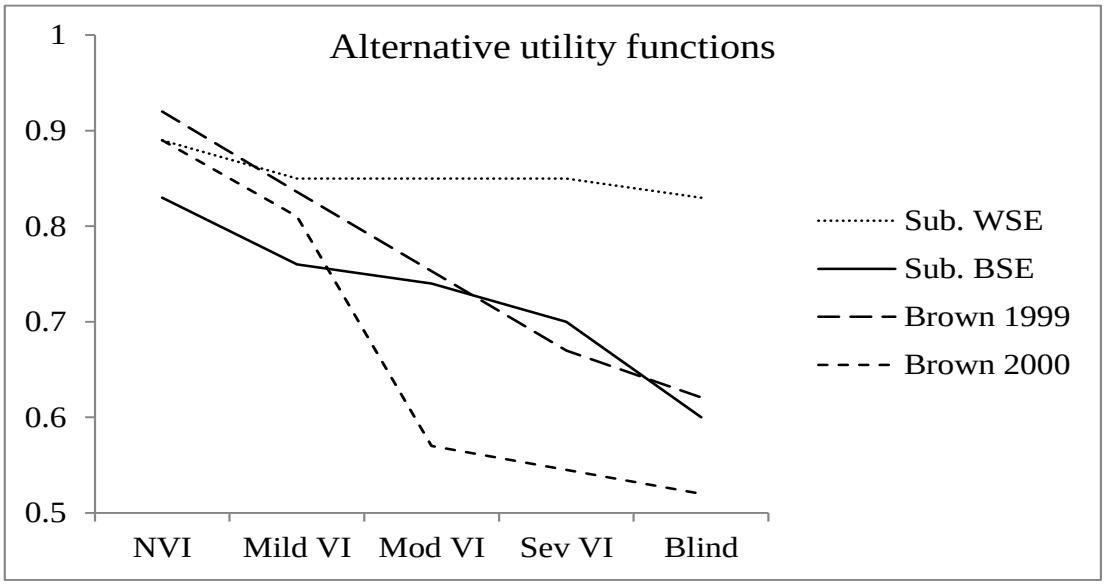
Due to the limited patient numbers and gradation, the value for severe VI has been taken to be a simple average of the two adjacent values.

This suggests a range of possible values for the modelling:

Table 53 Some possible utility estimates for the model health states

	WSE model	**BSE model**		
State	**Sub. EQ-5D**	**Sub. EQ-5D**	**Brown 1999**	**Brown 2000**
NVI	[redacted]	[redacted]	0.920	0.890
Mild VI	[redacted]	[redacted]	0.836	0.810
Mod VI	[redacted]	[redacted]	0.753	0.570
Sev VI	[redacted]	[redacted]	0.670	0.545
Blind	[redacted]	[redacted]	0.621	0.520

Figure 4 Some possible utility estimates for the model health states



For the WSE modelling, the submission values suggest that the WSE has minimal impact upon quality of life. For the BSE modelling, the submission values and Brown (1999)[1] are broadly in line, though Brown (1999)[1] suggests a slightly greater quality of life impact. Brown (2000),[2] while specific to ARMD, shows a large step and possibly relatively poor gradation due to the small patient numbers involved.

The manufacturer response to ERG clarification question A6 notes that 21% of the ranibizumab patients and 24% of the aflibercept 2mg Q8 patients were treated in their BSE in the pooled VIEW trials.

Frequency and cost of monitoring visits

The monitoring of both aflibercept and ranibizumab was 4 weekly during both the initial 52 weeks and the subsequent 44 weeks of the VIEW trials. The modelling assumes that aflibercept patients are only monitored 7 times during year 1 and 6 times during year 2, but that ranibizumab patients are monitored 12 times during year 1 and 12 times during year 2. Less frequent monitoring may reduce clinical effectiveness and the optimisation of treatment.

Table 54 HES 2010-11 and HES 2011-12 data

	OP All	Day case
2010-11 HES data		
C79.4 Injection into vitreous body NEC	34,187 (37%)	56,994 (63%)
C89.3 Injection of therapeutic substance into posterior segment of eye NEC	14,329 (85%)	2,622 (15%)
C79.4+C89.3	48,516 (45%)	59,616 (55%)
2011-12 HES data		
C79.4 Injection into vitreous body NEC	61,328 (46%)	70,648 (54%)
C89.3 Injection of therapeutic substance into posterior segment of eye NEC	17,224 (96%)	771 (4%)
C79.4+C89.3	78,552 (52%)	71,419 (48%)

For the administration cost, the 45% outpatient to 55% day-cases split was based upon the OPCS 4 codes C79.4: and C89.3: using 2010-11 HES data. 2011-12 HES data suggest a split of 52% outpatient to 48% day-cases. Coupled with the 2011-12 NHS reference costs of £79.74 per ophthalmology consultant led non-admitted follow-up and £402.08 per BZ23Z – minor vitreous retinal procedure day case this results in a slightly lower weighted average of £233.24 compared to the manufacturer estimate of £257.45.

NEC: Not Elsewhere Classified would appear to suggest that C89.3 is the more specific coding for injection of a therapeutic substance into the posterior segment of the eye, with C79.4 covering injections into the vitreous that are Not Elsewhere Classified; i.e. excluding those covered by C89.3. This is also in line with ERG expert opinion. If applicable, based upon the 2010-11 HES data would suggest a weighted average administration cost of £129.60, but with C89.3 becoming overwhelmingly an outpatient procedure in 2011-12 this weighted average administration cost would drop to £93.55.

But all the above costings assume that the outpatient administration is costed at the £80 of the Consultant led: Follow up attendance: Non-admitted: 130 Ophthalmology. It seems more reasonable to the ERG that it should be costed at the £117 of the Outpatient procedures: BZ23Z: Minor vitreous retinal procedures. The weighted average of the 2011-12 C79.4 and C89.3 would then result in an average administration cost of £252.90, while the 2011-12 C89.3 alone would result in an average administration cost of £129.46.

Note that for the STA of ranibizumab for DMO the FAD stated that *"administration costs for ranibizumab monotherapy were estimated at £150 per visit, and heard from clinical specialists that this value underestimates the true costs of ranibizumab administration. The clinical specialists believed that the true cost would be a minimum of £200 and could be as high as £400 per visit."* But further note that Novartis provided a further bottom up costing in response to the FAD that suggested only around £143 per administration which broadly paralleled the cost of the then current BZ23Z - Vitreous Retinal Procedures Category 1: Outpatient procedures.

The model also appears to assume in addition to a monitoring visit, a separate additional monitoring visit is required for OCT. ERG expert opinion suggests that only one visit would be necessary, during which OCT and any other required monitoring would occur. It should also be noted that the manufacturer has costed OCT at the same cost as fluorescein angiography: £117.26 based upon NHS reference costs Outpatient procedures: BZ23Z – Minor Vitreous Retinal Procedures. Alternative NHS reference costs suggest themselves for this. Either BZ23Z from the Direct Access Diagnostics chapter at a cost of £40.64, or from the Outpatient Diagnostic Imaging chapter code RA23Z: Ultrasound Scan less than 20 minutes at a cost of £51.27. Since these are both less than the £79.74 ophthalmology outpatient appointment cost, there may be an argument for viewing the costs of OCT as being within the ophthalmology outpatient appointment cost. But the revised ERG base case will apply an OCT cost of £51.27.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

The ERG is of the opinion that the submitted modelling of 2nd eye involvement is untenable. In the light of this, the ERG views the submitted model as a reasonable starting point for a one eye model if the baseline prevalence and subsequent incidence of 2nd eye involvement is set to zero[j]. The resulting one eye model is further modified along the following lines:

- The number of injections in year 1 being 8 for both aflibercept and ranibizumab, followed in year 2 by 4 injections for aflibercept and 6 for ranibizumab[k].
- Administration cost £129.46[l].
- OCT cost of £51.27[m].
- 50% one stop for both aflibercept and ranibizumab in year 1[n].

[j] Cell H17 of the *Population* worksheet.
[k] Cell D23 of the *Treatment* worksheet.
[l] Cells G21 and G23 of the *Tx_Costs* worksheet.
[m] Cell G19 of the *Monitoring_Costs* worksheet.
[n] Cell D55 of the *Monitoring* worksheet.

- Quality of life values for the WSE model being as per the manufacturer submission, but quality of life values for the BSE model being drawn from Brown[1] as previously outlined in table HHH[o].

Sensitivity analyses are presented that apply[p]:

- Lower confidence limits for the relative risks: 0.98 and 0.93 for maintaining vision and 0.93 and 0.61 for improving vision from the 12 month and 24 month analyses respectively.
- Upper confidence limits for the relative risks: 1.06 and 1.07 for maintaining vision and 1.51 and 1.28 for improving vision from the 12 month and 24 month analyses respectively.

These are presented for two scenarios. The first adopts the manufacturer interpretation that the Kleijnen systematic review 24 month analyses provide relative risks relating to the 12 to 24 month period. As such, it retains the proportions of patients maintaining and gaining letters of the submitted model.

The second adopts the ERG interpretation that the Kleijnen systematic review 24 month analyses provide relative risks relating to the baseline to month 24 period. Note that this retains the baseline distribution of the manufacturer submission. The patient numbers improving and retaining vision from the pooled data are applied[q].

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[o] Cells K23, K25, K27, K29 and K31 of the *Utilities* worksheet, while retaining the option of "Utilities from VIEW 2" in the K16 dropdown menu.

[p] Cells G75, G76, G79 and G80 of the *Model_Parameters* worksheet.

[q] Implemented within the *1st_Eye_RbzPRN* worksheet by cutting and pasting the relevant proportions into cells HG17:HG21 and HK17:HK21, revising HG12=HG17+HG18, HG13=HG17+HG18+HG19, HG14=HG13-HG12, HK12=HK17+HK18, HK13=HK17+HK18+HK19, HK14=HK13-HK12 and setting HM25:HM29=HD25:HD29 and HM32:HM37=HD25:HD29

Scenario 1: WSE modelling

Table 55 Deterministic results: excluding PAS

	Life years	QALYs	Drug&Admin	Monitoring	Total	ICER
AFB	9.498	8.038	£16,626	£2,445	£19,070	
RBZ	9.498	8.032	£16,815	£3,696	£20,511	
Net	0.000	-0.007	£189	£1,252	£1,441	AFB Dom.
Relative risks' lower confidence intervals' limits						
Net	0.000	0.016	£495	£1,318	£1,813	£116,478
Relative risks' upper confidence intervals' limits						
Net	-0.001	-0.024	-£114	£1,186	£1,072	AFB Dom.

The source of the slight loss of life years for the sensitivity analysis that applies the upper confidence is difficult to understand, particularly given the zero costs of blindness. The lower confidence limits for the relative risks result in a cost effectiveness estimate for ranibizumab compared to aflibercept of £116,478 per QALY.

Table 56 Deterministic results: including aflibercept PAS and ranibizumab price sensitivities

	Life years	QALYs	Drug&Admin	Monitoring	Total	ICER
AFB	9.498	8.038	[redacted]	£2,445	[redacted]	
RBZ						
0% PAS	9.498	8.032	£16,815	£3,696	£20,511	
10% PAS			£15,383		£19,079	
15% PAS			£14,667		£18,363	
20% PAS			£13,951		£17,647	
25% PAS			£13,235		£16,932	
30% PAS			£12,520		£16,216	
35% PAS			£11,804		£15,500	
40% PAS			£11,088		£14,784	
45% PAS			£10,372		£14,068	
50% PAS			£9,656		£13,352	
Net						
0% PAS	0.000	-0.007	[redacted]	£1,252	[redacted]	[redacted]
10% PAS			[redacted]		[redacted]	[redacted]
15% PAS			[redacted]		[redacted]	[redacted]

	Life years	QALYs	Drug&Admin	Monitoring	Total	ICER
20% PAS			[redacted]		[redacted]	[redacted]
25% PAS			[redacted]		[redacted]	[redacted]
30% PAS			[redacted]		[redacted]	[redacted]
35% PAS			[redacted]		[redacted]	[redacted]
40% PAS			[redacted]		[redacted]	[redacted]
45% PAS			[redacted]		[redacted]	[redacted]
50% PAS			[redacted]		[redacted]	[redacted]

[redacted]

Scenario 1: BSE modelling

Table 57 Deterministic results: excluding PAS

	Life years	QALYs	Drug&Admin	Monitoring	Total	ICER
AFB	9.498	6.824	£16,626	£2,445	£19,070	
RBZ	9.498	6.779	£16,815	£3,696	£20,511	
Net	0.000	-0.045	£189	£1,252	£1,441	AFB Dom.
Relative risks' lower confidence intervals' limits						
Net	0.000	0.092	£495	£1,318	£1,813	£19,707
Relative risks' upper confidence intervals' limits						
Net	-0.001	-0.156	-£114	£1,186	£1,072	AFB Dom.

The lower confidence limits for the relative risks result in a cost effectiveness estimate for ranibizumab compared to aflibercept of £19,707 per QALY.

Table 58 Deterministic results: including aflibercept PAS and ranibizumab price sensitivities

	Life years	QALYs	Drug&Admin	Monitoring	Total	ICER
AFB	9.498	6.824	[redacted]	£2,445	[redacted]	
RBZ						
0% PAS	9.498	6.779	£16,815	£3,696	£20,511	
10% PAS			£15,383		£19,079	
15% PAS			£14,667		£18,363	
20% PAS			£13,951		£17,647	
25% PAS			£13,235		£16,932	
30% PAS			£12,520		£16,216	
35% PAS			£11,804		£15,500	
40% PAS			£11,088		£14,784	
45% PAS			£10,372		£14,068	
50% PAS			£9,656		£13,352	
Net						
0% PAS	0.000	-0.045	[redacted]	£1,252	[redacted]	[redacted]
10% PAS			[redacted]		[redacted]	[redacted]
15% PAS			[redacted]		[redacted]	[redacted]
20% PAS			[redacted]		[redacted]	[redacted]
25% PAS			[redacted]		[redacted]	[redacted]
30% PAS			[redacted]		[redacted]	[redacted]
35% PAS			[redacted]		[redacted]	[redacted]
40% PAS			[redacted]		[redacted]	[redacted]
45% PAS			[redacted]		[redacted]	[redacted]
50% PAS			[redacted]		[redacted]	[redacted]

[redacted]

Scenario 2: WSE modelling

Table 59 Deterministic results: excluding PAS

	Life years	QALYs	Drug&Admin	Monitoring	Total	ICER
AFB	9.498	8.014	£16,629	£2,445	£19,075	
RBZ	9.498	8.018	£16,982	£3,732	£20,714	
Net	0.000	0.004	£352	£1,287	£1,639	£399,140
Relative risks' lower confidence intervals' limits						
Net	0.001	0.021	£676	£1,357	£2,033	£99,148
Relative risks' upper confidence intervals' limits						
Net	0.000	-0.009	£49	£1,221	£1,271	AFB Dom.

Table 60 Deterministic results: including aflibercept PAS and ranibizumab price sensitivities

	Life years	QALYs	Drug&Admin	Monitoring	Total	ICER
AFB	9.498	8.014	[redacted]	£2,445	[redacted]	
RBZ						
0% PAS	9.498	8.018	£16,982		£20,714	
10% PAS			£15,536		£19,268	
15% PAS			£14,813		£18,545	
20% PAS			£14,090		£17,822	
25% PAS			£13,367		£17,099	
30% PAS			£12,644		£16,376	
35% PAS			£11,921		£15,653	
40% PAS			£11,198		£14,930	
45% PAS			£10,475		£14,207	
50% PAS			£9,752		£13,484	
Net						
0% PAS	0.000	0.004	[redacted]		[redacted]	[redacted]
10% PAS			[redacted]		[redacted]	[redacted]
15% PAS			[redacted]		[redacted]	[redacted]
20% PAS			[redacted]		[redacted]	[redacted]
25% PAS			[redacted]		[redacted]	[redacted]
30% PAS			[redacted]		[redacted]	[redacted]
35% PAS			[redacted]		[redacted]	[redacted]

40% PAS	[redacted]	[redacted]	[redacted]
45% PAS	[redacted]	[redacted]	[redacted]
50% PAS	[redacted]	[redacted]	[redacted]

[redacted]

Scenario 2: BSE modelling

Table 61 Deterministic results: excluding PAS

	Life years	QALYs	Drug&Admin	Monitoring	Total	ICER
AFB	9.498	6.692	£16,629	£2,445	£19,075	
RBZ	9.498	6.719	£16,982	£3,732	£20,714	
Net	0.000	0.027	£352	£1,287	£1,639	£61,653
Relative risks' lower confidence intervals' limits						
Net	0.001	0.134	£676	£1,357	£2,033	£15,139
Relative risks' upper confidence intervals' limits						
Net	0.000	-0.060	£49	£1,221	£1,271	AFB Dom.

Again, the source of the small additional survival when applying the lower confidence limits is unclear, but the main impact is upon the net QALYs which increase to 0.134 QALYs resulting in a cost effectiveness for ranibizumab compared to aflibercept of £15,139 per QALY.

Table 62 Deterministic results: including aflibercept PAS and ranibizumab price sensitivities

	Life years	QALYs	Drug&Admin	Monitoring	Total	ICER
AFB	9.498	6.692	[redacted]	£2,445	[redacted]	
RBZ						
0% PAS	9.498	6.719	£16,982		£20,714	
10% PAS			£15,536		£19,268	
15% PAS			£14,813		£18,545	
20% PAS			£14,090		£17,822	
25% PAS			£13,367		£17,099	
30% PAS			£12,644		£16,376	
35% PAS			£11,921		£15,653	
40% PAS			£11,198		£14,930	
45% PAS			£10,475		£14,207	
50% PAS			£9,752		£13,484	
Net						
0% PAS	0.000	0.027	[redacted]		[redacted]	[redacted]
10% PAS			[redacted]		[redacted]	[redacted]
15% PAS			[redacted]		[redacted]	[redacted]
20% PAS			[redacted]		[redacted]	[redacted]
25% PAS			[redacted]		[redacted]	[redacted]
30% PAS			[redacted]		[redacted]	[redacted]
35% PAS			[redacted]		[redacted]	[redacted]
40% PAS			[redacted]		[redacted]	[redacted]
45% PAS			[redacted]		[redacted]	[redacted]
50% PAS			[redacted]		[redacted]	[redacted]

5.5 Conclusions of the cost effectiveness section

Aflibercept appears to be a cost-effective option for the treatment of adults with wet AMD compared with ranibizumab.

There may be concerns about the choice of comparators. ERG expert opinion indicated that there may be a sub-group of patients with wet AMD in whom PDT might be a valid treatment option. There is also a concern over the exclusion of bevacizumab as a comparator for this appraisal.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG is of the opinion that the modelling of 2nd eye involvement in the current submission is incorrect. Correcting this would require extensive remodelling, to the extent that it would no longer be the manufacturer model. For this reason, the ERG considers the submitted model as a reasonable one-eye model – if the baseline prevalence and subsequent incidence of 2nd eye involvement is set to zero [r] - even though it is not clear whether the 24 month relative risk relates to the period from 12 to 24 months or to the period from baseline to 24 months.

Adopting the manufacturer interpretation of the 24 month relative risk data results in aflibercept being estimated to save £1,441 compared to ranibizumab. An additional 0.007 QALYs accrue in the WSE modelling and an additional 0.045 QALYs in the BSE modelling. As a consequence, aflibercept is estimated to dominate ranibizumab.

The lower confidence interval limits of the relative risks result in gains from ranibizumab of 0.016 QALYs for the WSE modelling and 0.092 QALYs for the BSE modelling, resulting in cost effectiveness estimates for ranibizumab of £116,478 per QALY and £19,707 per QALY respectively.

With the aflibercept PAS, [redacted]

Adopting the ERG interpretation of the 24 month relative risk data results in ranibizumab still being more costly than aflibercept, by £1,639, but yielding an additional 0.004 QALYs for the WSE modelling, resulting in a cost effectiveness estimate of £399,140 per QALY. For the BSE modelling the gain increases to 0.027 QALYs so reducing the cost effectiveness estimate to £61,653 per QALY.

[r] Cell H17 of the *Population* worksheet.

The lower confidence interval limits of the relative risks result in gains from ranibizumab of 0.021 QALYs for the WSE modelling and 0.134 QALYs for the BSE modelling, resulting in cost effectiveness estimates for ranibizumab of £99,148 per QALY and £15,139 per QALY respectively.

With the aflibercept PAS, [redacted]

7 OVERALL CONCLUSIONS

The manufacturer included in the current submission two RCTs comparing aflibercept with ranibizumab and 10 RCTs involving either ranibizumab or aflibercept,which informed the network meta-analysis. The quality of the two main aflibercept trials was good whilst that of the RCTs included in the network meta-analysis was mixed, with some trials at high risk of bias.

Clinical Effectiveness

Results from the pooled analysis suggested that 2mg aflibercept given every 8 weeks was not inferior to 0.5mg ranibizumab given every 4 weeks with respect to the primary outcome of the proportion of patients losing less than 15 letters from baseline to 12 months. No significant differences were found between treatment groups for:

- Mean change in BCVA
- Proportion of patients gaining at least 15 letters
- Change in NEI VFQ-25 (quality of life)
- Choroidal neovascularisation (CNV)
- Central retinal thinkness (CRT)
- Incidence of adverse events (ocular, non-ocular, and injection related events)

The manufacturer also presented also an indirect comparison of 2mg aflibercept (given every 8 weeks) compared to a 'treat as needed regimen' of 0.5mg ranibizumab. No differences in the odds of maintained vision, mean change in BCVA or the odds of improved vision were found. However, due to heterogeneity among included studies as well as the inclusion of studies at high risk of bias, these results should be treated with caution.

Our conclusions were that i) the clinical efficacy of aflibercept, in terms of prevention of visual loss, was comparable (non-inferior) to that of ranibizumab; ii) aflibercept had a similar safety profile with regard to ocular and non-ocular adverse events to that of ranibizumab.

Further concerns relate to the lack of assessment of both PDT (which is potentially useful in the treatment of wet AMD patients who do not respond well to anti-VEGF treatment) and bevacizumab.

Cost-effectiveness

The main differences of opinion between the ERG and the manufacturer relate to the model structure and the interpretation of the 24 month relative risks of the systematic review.

In the opinion of the ERG the model structure is adequate for modelling one eye, but not for modelling 2nd eye involvement. This is slightly qualified by the vast majority of patients having some visual impairment in their fellow eye at baseline, which is not taken into account in the utility values applied within the one eye modelling, despite the binocular vision quality of life data presented.

The ERG interprets the 24 month relative risks of the systematic review as relating to the period from baseline to 24 months. The manufacturer interprets the 24 month relative risks of the systematic review as relating to the period from 12 months to 24 months. Since the central estimates of these relative risks suggest that ranibizumab is better, the ERG approach causes ranibizumab to result in QALY gains. The manufacturer approach enables the 12 month relative risks to come to the fore, and causes aflibercept to result in QALY gains. In this context, it should be borne in mind that the relative risks are not statistically significantly different from unity.

7.1 Implications for research

Future well-designed randomised trials assessing patients with wet AMD with recent visual loss should evaluate:

i) Distance and near visual acuity in both eyes and their relation with scores achieved on generic health status as well as vision specific patient reported measures;

ii) The changes taking place over time (as patients get use to their improved sight);

iii) Patient's preference (e.g. some patients would prefer avoiding further injections should their sight remain the same or at the cost of experiencing some visual loss). This could also inform a patient-based economic model (including two eyes).

Should bevacizumab obtain market authorization for the treatment of wet AMD, it would be useful to assess 2.0mg aflibercept versus bevacizumab in head to head well-designed randomised trials, with particular attention to cost-effectiveness and adverse events.

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