NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Specification for manufacturer/sponsor submission of evidence

June 2012

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Executive summary

Decision Problem

- Aflibercept 40mg/ml solution for injection in a vial (Eylea) is licensed in the UK for the treatment of adults with neovascular wet age-related macular degeneration (AMD). Wet AMD is an increasingly common condition that, if left untreated, can lead to severe vision loss and even blindness.
- Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors, that are associated with neovascular (wet) AMD.
- Aflibercept is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections. After the first 12 months of treatment with aflibercept, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections
- Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. This provides a usable amount to deliver a single dose of 50 microlitres containing 2 mg aflibercept and is administered by intravitreal injection.
- The comparator is 0.5mg ranibizumab. Based on its summary of product characteristics (SmPC), treatment is given monthly and continued until maximum visual acuity is achieved i.e. the patient`s visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed when monitoring indicates loss of visual acuity due to wet AMD. Monthly injections should then be administered until stable visual acuity is reached again (implying a minimum of two injections).
- The list price of aflibercept is £816 plus VAT and for ranibizumab is £742.17 plus VAT (British National Formulary, 64th edition). An application for a simple discount Patient Access Scheme (PAS) for aflibercept has been made in a separate

document. Ranibizumab is also subject to a simple discount PAS but the details are confidential.

Clinical effectiveness

- The key clinical evidence for aflibercept in this submission comes from two pivotal randomised controlled trials (RCTs), the VIEW studies.
- The VIEW studies showed that aflibercept every other month (after three initial monthly doses) was non-inferior to ranibizumab every month at 52 weeks in terms of the primary endpoint of maintained vision with, per protocol, fewer injections.
- The safety profiles of the two treatments were found to be similar and outcomes were maintained over an extended 96 week period.
- An indirect treatment comparison (ITC) was conducted to compare aflibercept with ranibizumab as needed, based on monthly monitoring, as this is the regimen defined in the ranibizumab SmPC and used in practice.
- The CATT study, included in the ITC, concluded that those on monthly treatment gained more visual acuity than those on treatment as needed.
- The validity of the ITC was limited by the available evidence. Although the ITC concluded that there was no evidence of significant difference between aflibercept and an as needed (pro re nata (PRN)) regimen of ranibizumab, this conclusion should be treated with caution given the differences in baseline characteristics (Central retinal thickness (CRT) and visual acuity (VA)), number of injections and high risk of bias of the included studies.

Cost effectiveness

- A de novo economic evaluation in the form of a Markov model was submitted. A two-eye model was devised based on the defined scope and the preference expressed in previous NICE eye appraisals.
- Transition probabilities were based on the results of the ITC, despite its limitations, as the VIEW studies primarily investigated non-inferiority of aflibercept compared with monthly, rather than PRN, ranibizumab.
- Frequency of injection and monitoring for aflibercept and ranibizumab were based on the regimens specified in the UK marketing authorisations.

- Utilities were devised from EQ5D data from the VIEW 2 trial in which VA data on the fellow eye, as well as the study eye was collected.
- Aflibercept was found to be a cost effective option for the treatment of adults with neovascular wet AMD compared with ranibizumab.

Table 1 Base-case cost-effectiveness results

Item	Cost Aflibercept	Cost Ranibizumab	Increment Aflibercept vs Ranibizumab	Absolute Increment Aflibercept vs Ranibizumab	% Absolute Increment Aflibercept vs Ranibizumab
Drug costs	£18,430	£19,826	-£1,396	£1,396	39%
Physician costs	£923	£1,890	-£967	£967	27%
Monitoring tests	£2,850	£4,033	-£1,184	£1,184	33%
Cost of Blindness	£2,806	£2,866	-£60	£60	2%

Table 2 Incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	£25,009.19	10.57	7.77				
Ranibizumab	£28,615.22	10.57	7.76	£3,606	-0.001	-0.010	Dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

No subgroup analyses were submitted given the lack of evidence. Aflibercept is indicated for the treatment of adults with neovascular (wet) AMD.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Eylea 40mg/ml solution for injection in a vial. 1ml solution for injection contains 40mg aflibercept. Aflibercept solution for injection is a vascular endothelial growth factor (VEGF) inhibitor.

1.2 What is the principal mechanism of action of the technology?

Aflibercept solution for injection treats adults with neovascular (wet) age-related macular degeneration (AMD) through VEGF inhibition. It is a potent specific inhibitor of VEGF that interferes with the growth of new blood vessels that leads to retinal oedema, ischaemia and haemorrhage in diseases of ocular neovascularisation. Aflibercept is a fully human fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1. It binds to all known VEGF-A isoforms and also Placental Growth Factor (PlGF)(1-3).

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA) gave its positive opinion to aflibercept solution for injection for the treatment of adults with neovascular (wet) AMD on the 20th September 2012(4). Marketing authorisation was gained in the UK via the centralised European regulatory procedure on 22nd November 2012.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the

marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

There are no special conditions, exceptional circumstances or conditions attached to the marketing authorisation(5).

Hepatic and/or renal impairment: No specific studies in patients with hepatic and/or renal impairment were conducted with aflibercept. Available data do not suggest a need for a dose adjustment with aflibercept in these patients.

Elderly population: No special considerations are needed.

Paediatric population: Safety and efficacy have not been established in children and adolescents. There is no relevant use of aflibercept in the paediatric population in the indication wet AMD.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Aflibercept solution for injection is indicated for adults for the treatment of neovascular (wet) AMD.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

The pivotal phase III studies for aflibercept solution for injection for the treatment of adults with neovascular (wet) AMD were the VIEW 1 and 2 studies. These studies are now completed(6;7). In these two double-masked, controlled randomised clinical trials (RCTs), where administration of 2mg aflibercept (3 loading doses then fixed 8-weekly injections over 52 weeks) provided comparable (statistically non-inferior) efficacy, in terms of prevention of moderate vision loss, to ranibizumab injections (every 4 weeks over 52 weeks). Both interventions were then given as needed during an extension phase to 96 weeks, but ‘capped’ such that all patients received at least one injection every 12 weeks. Stabilisation or improvement in visual function was maintained over the 96-week study period. Aflibercept was well tolerated, with a similar safety profile to ranibizumab(6;7).

Ongoing studies of aflibercept solution for injection for (wet) AMD include the 'TURF' study and a study in the Chinese population. The phase 4 study TURF study includes 50 patients with recalcitrant exudative AMD with a history of retinal or subretinal fluid after multiple intravitreal injections (ranibizumab 0.5mg, then ranibizumab 2.0mg, who are incomplete responders) who are treated with aflibercept 2.0mg. The study is expected to complete in February 2013(8;9). These studies are ongoing. Therefore, data will not be included in this submission.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Aflibercept solution for injection was launched in the UK for the treatment of neovascular (wet) AMD in December 2012.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

As discussed above, the marketing authorisation process for the UK was centralised through the EMA. Eylea has marketing approval from the Food and Drug Administration (FDA) in the USA(10) and from the Australian Therapeutic Goods Administration (TGA)(11) for the treatment of adults with neovascular (wet) AMD.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

An SMC submission for aflibercept for adults for the treatment of neovascular (wet) AMD was made in October 2012 with guidance to be issued in April 2013(12).

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A1 Unit costs of technology being appraised

Pharmaceutical formulation	Eylea 40 mg/ml solution for injection in a vial(5). 1 ml solution for injection contains 40 mg aflibercept. Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. This provides a usable amount to deliver a single dose of 50 microlitres containing 2 mg aflibercept.
Acquisition cost (excluding VAT)	£816 list price. A confidential simple discount patient access scheme has been submitted.
Method of administration	Aflibercept solution for injection (Eylea) is for intravitreal injection only
Doses	The recommended dose for aflibercept is 2 mg aflibercept, equivalent to 50 microlitres.
Dosing frequency	According to the Summary of Product Characteristics (SmPC)(5) for aflibercept treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections. After the first 12 months of treatment with aflibercept, the treatment interval may be extended based on visual and anatomic outcomes. In this case, the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections.
Average length of a course of treatment	The SmPC for aflibercept does not have specific criteria for stopping treatment(5). As a guide on expected use, the Royal College of Ophthalmologist guidelines for ranibizumab indicate permanent discontinuation when reduction of best corrected visual acuity (BCVA) is less than 15 letters on two consecutive visits or reduction of 30 letters or more from baseline(13).
Average cost of a course of treatment	The average cost of a course of treatment will depend on the dosing frequency and length of the course of

	treatment as described above. The price per vial = the price per dose. The average cost per patient will be discussed further in the economic evaluation.
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	Not applicable

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

According to the SmPC(5), there will not be any additional tests or investigations needed for selection for aflibercept solution for injection compared with current NHS treatment. Both aflibercept solution for injection and ranibizumab are indicated for/in adults for the treatment of neovascular (wet) AMD.

Both aflibercept solution for injection and ranibizumab require administration via intravitreal injection only. As per current practice, immediately following the intravitreal injection, patients receiving aflibercept should be monitored for elevation in intraocular pressure (IOP)(5). Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

The need for monitoring with aflibercept solution for injection is not over and above that currently required for the treatment of neovascular (wet) AMD in the NHS. In fact, the SmPC for aflibercept(5) requires less frequent monitoring than that required with ranibizumab treatment for wet AMD. The SmPC for ranibizumab specifies that

patients should be monitoring monthly for visual acuity following monthly treatment which has been continued until maximum visual acuity is achieved(14). In the first 12 months with aflibercept, there is no requirement for monitoring between injections every two months (following three initial consecutive doses). After the first 12 months of treatment with aflibercept solution for injection, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections(5).

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

As with current practice for the treatment of wet AMD, aflibercept intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including topical broad spectrum microbicide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface), have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended(5).

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Wet AMD is characterised by pathological choroidal neovascularisation (CNV), which is the growth of abnormal new blood vessels forming a membrane between the retinal pigment epithelial and the photoreceptor cells. Leakage from the CNV leads to disruption and dysfunction of the retina and eventual permanent central vision loss. The protein, VEGF, is implicated in new blood vessel formation (angiogenesis), vascular permeability and inflammation responsible for CNV in wet AMD(15;16).

People with wet AMD retain some 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. Wet AMD may develop rapidly, causing severe changes to the central vision in a short period of time. Severe vision 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(17-19).

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Aflibercept (Eylea) 40mg/ml solution for injection in a vial is indicated for adults for the treatment of neovascular (wet) AMD. There are no other licensed indications for aflibercept solution for injection in the UK.

AMD mainly affects people over the age of 50, can cause severe vision loss and is the leading cause of blindness in older people in the western world. It is estimated to be responsible for two thirds of registrations of visual impairment or blindness in the UK(20). Wet (exudative or neovascular) AMD affects 10-15% of people with AMD. There are 26,000 new cases of wet AMD each year in the UK(21). The ageing population means these figures are growing(17;18;22;23).

There are two distinct products, aflibercept solution for intravitreal injection (Eylea) and ziv-aflibercept injection for intravenous infusion (Zaltrap) specifically formulated and developed for two distinct uses. Eylea solution for injection is indicated for the treatment of patients with neovascular (wet) AMD. Regeneron has developed Zaltrap for use in oncology. Zaltrap was developed for oncology indications through a separate collaboration between Regeneron and Sanofi-Aventis. As Bayer is not involved in the development of Zaltrap, and is not able to comment on the differences between Eylea and Zaltrap.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

There is evidence of a link between visual impairment and mortality. For example, it is known that visual impairment can be linked to falls in older people(24). Thiagarajan et al 2005 (25) reported the rate ratio for all-cause mortality for people with binocular visual acuity (VA) <6/18 (20/60 Snellen equivalent) versus people with ≥ 6/6 VA is 1.17 (1.07 – 1.27 95% CI) after adjusting for confounders. Excess mortality for blind patients (both eyes) using the hazard ratio (1.28; 95%CI 1.07-1.53) was also reported by Christ et al 2008(26). The paper estimated the effects of vision loss on mortality using a structural equation modelling approach. However, the link between wet AMD specifically and mortality is less clear, particularly given the potential comorbidities that people of this age group (the average age of patients with neovascular (wet) AMD is over 70 years of age) are likely to have and other confounding factors(25). Please see economic section 7.3 for details.

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

There is currently no published NICE clinical guideline for the management of wet AMD. The following guidance is available for wet AMD:

- National Institute for Health and Clinical Excellence (NICE) (adopted in Scotland). Macular degeneration (age-related) – ranibizumab and pegaptanib (TA155)(August 2008, updated May 2012)

- National Institute for Health and Clinical Excellence (NICE). Macular degeneration (age-related) – photodynamic therapy (PDT) (TA68)(September 2003)
- National Institute for Health and Clinical Excellence (NICE). IPG415 Epiretinal brachytherapy for wet age-related macular degeneration. (December 2011)

In TA155, ranibizumab is recommended for the treatment of wet AMD in certain people who qualify according to the specified criteria, based on the original selection criteria for the regulatory clinical trials(20). In TA68, PDT is recommended for patients with classic with no occult subfoveal choroidal neovascularisation and a best-corrected visual acuity (BCVA) of 6/60 or better(27). Epiretinal brachytherapy is not recommended except in the context of research(28).

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Aflibercept solution for injection would be an additional and alternative option to current standard of care, ranibizumab, for adults in the treatment of neovascular (wet) AMD. With a less burdensome monitoring regimen(5) than current practice(14), aflibercept would allow a more efficient use of resources in the current treatment pathway.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

The main issue for the treatment of wet AMD in the UK is the burden of treatment and monitoring in terms of resources required and capacity available(29). With an ageing population, the burden on the NHS is increasing with new patients presenting and existing patients continuing on treatment. Current standard of care requires monthly monitoring of VA(14), and usually, anatomical outcomes using optical coherence tomography (OCT)(30). There is still an unmet need for effective treatments without the burden of monthly monitoring visits

2.7 Please identify the main comparator(s) and justify their selection.

Ranibizumab is the standard of care for the treatment of wet AMD in the NHS in England and Wales, in line with NICE guidance (TA155, reissued in May 2012)(20) and guidance from the Royal College of Ophthalmologists(30).

There are no other relevant comparators for the first-line treatment of wet AMD. PDT is recommended by NICE in TA68(27), for a subgroup of patients with classic with no occult subfoveal choroidal neovascularisation and a best-corrected visual acuity (BCVA) of 6/60 or better. However, this guidance was issued in 2003. Current practice has since changed for the treatment of this subgroup of patients and this guidance is currently due for review in 2014, after two deferrals, alongside TA155. However, in 2007, an earlier review decision indicated that "following consultation, the majority of comments received have led to the agreement that the Institute should proceed with a review of the existing guidance on the use of PDT for AMD. We anticipate the review will be planned into the appraisal work programme to coincide with publication of the results of the on-going trial (verteporfin photodynamic therapy cohort study – UK)". The study was set up in light of the NICE guidance in 2003 to study PDT. This was published in 2011(31) and confirms PDT is no longer used as monotherapy and that newer treatments have now superseded PDT for the treatment of wet AMD.

For the reasons set out in more detail below, we consider that bevacizumab cannot be considered an appropriate comparator in the appraisal of aflibercept solution for injection for the first-line treatment of neovascular (wet) AMD because its use for treating wet AMD does not represent routine or best practice within the NHS. In addition, the high level of uncertainty associated with the appraisal and implementation of guidance for an unlicensed comparator renders any conclusions on clinical and cost effectiveness versus bevacizumab invalid.

Routine and best practice for the treatment of neovascular (wet) AMD

Ranibizumab is currently considered routine and best practice in the NHS (including existing NICE guidance) for the first-line treatment of wet AMD. Ranibizumab is recommended by the Royal College of Ophthalmologists for the management of wet AMD(30) and is recommended by NICE (TA155), re-issued in May 2012(20), for the

treatment of wet AMD in people with baseline visual acuity between 6/12 and 6/96 who meet criteria that ensure the presence of wet AMD.

This definition of the appropriate comparator is in accordance with the updated NICE guide to the methods of technology appraisal (June 2008)(32) which defines relevant comparator technologies with specific consideration given to routine and best practice in the NHS (including existing NICE guidance), including technologies that do not have a marketing authorisation for the indication defined in the scope but that are used routinely for the indication in the NHS.

SmPC for bevacizumab

The SmPC for a technology indicates how a technology should be used. In other words, it specifies best practice for that technology. Section 4.4 of the SmPC (special warnings and precautions for use) for bevacizumab(33) was updated in August 2012. The update specified that 'Avastin is not formulated for intravitreal use'. In addition, it stated the safety issues associated with intravitreal use:

"Individual cases and clusters of serious ocular adverse events have been reported following unapproved intravitreal use of Avastin compounded from vials approved for intravenous administration in cancer patients. These events included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these events have resulted in various degrees of visual loss, including permanent blindness."

Royal College of Ophthalmologist Guidelines

In May 2011(34), the Royal College outlined certain safety concerns that had been raised by the "CATT" trials that were underway in the USA. It stated:

"The College is fully aware of the current NHS funding issues but remains committed to maintaining professional standards and patient safety. It would be inappropriate for the College to compromise on safety and urges caution in the interpretation of the CATT Study. Until the safety concerns [with bevacizumab] are properly addressed,

ranibizumab remains the recommended treatment for wet AMD. The College however continues to support use of bevacizumab as part of research."

On 14 December 2011(35), the Royal College issued a statement and report on the use of anti-VEGF agents and wet AMD. Although the College statement says that it "supports" the use of bevacizumab, this is only in the event that no licensed or NICE approved alternative medication exists or if it would better serve the patient's needs. Given that there is no evidence that reformulated bevacizumab is more effective than ranibizumab for the treatment of AMD - as confirmed by the College in its report - such circumstances would be extremely limited. The statement says:

"In the treatment of AMD, where a licensed drug exists and is NICE approved, Primary Care Trusts are legally obliged to fund NHS treatment with this drug if an ophthalmologist prescribes it. Ranibizumab is the only anti-VEGF drug licensed for the treatment of neovascular AMD and is NICE approved. The College believes that the use of ranibizumab for AMD should be the default position until the NHSE commissions a NICE/MHRA assessment of bevacizumab and until a national policy is formulated… The College believes that ophthalmologists should have the discretion to use bevacizumab rather than ranibizumab for the treatment of AMD if it is in the patient's best interest to do so and so long as the ophthalmologist sources the bevacizumab from a reputable pharmacy and the patient gives informed consent. This may occur, for example, when the patient has failed to respond to ranibizumab and the ophthalmologist wishes to try treatment with an alternative anti-VEGF agent, or when the ophthalmologist feels that a patient would be best served by treatment outside the tight criteria specified by NICE such as earlier treatment of their AMD. Another example would be when a patient is not eligible for NHS treatment and cannot afford treatment with ranibizumab or when the choice is between no treatment or treatment with bevacizumab."

Importantly, the statement adds that a less intensive treatment using bevacizumab compared with ranibizumab "is not appropriate". Therefore, bevacizumab is not an appropriate comparator in this appraisal.

General Medical Council (GMC) guidance

The Royal College of Ophthalmologist guidelines refer to GMC guidelines on the use of unlicensed medicines. GMC guidance from 2008(36) on the use of unlicensed medicines indicates that bevacizumab is not an appropriate comparator clinically as there are now licensed alternatives for wet AMD:

"18. You can prescribe unlicensed medicines but, if you decide to do so, you must: a. Be satisfied that an alternative, licensed medicine would not meet the patient's needs, b. Be satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy, c. Take responsibility for prescribing the unlicensed medicine and for overseeing the patient's care, including monitoring and any follow up treatment (see also paragraphs 25-27 on prescribing for hospital outpatients), d. Record the medicine prescribed and, where you are not following common practice, the reasons for choosing this medicine in the patient's notes."

Thus, doctors must be satisfied that it would better serve the patient's needs than an appropriately licensed alternative and be satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy. Doctors (and their NHS employers) must also accept liability for the decision. To this end, some NHS authorities only allow off-label/unlicensed use following approval from a local prescribing committee. Therefore, the unlicensed use of bevacizumab cannot be said to be ethically appropriate, routine or best practice for treating first-line wet AMD and bevacizumab is not an appropriate comparator in this appraisal.

Endophthalmitis cases

In March 2012, Moorfields Pharmaceuticals, a so-called "specials" manufacturer of reformulated bevacizumab, was forced to recall a number of batches of reformulated bevacizumab "following a number of reports of suspected sterile endophthalmitis"(37).

A letter was subsequently sent to investigators and patients taking part in the IVAN study to inform them of the safety issues associated with the use of unlicensed bevacizumab for wet AMD(38).

Regulatory view

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) has issued a Drug Safety Alert that made specific reference to concerns over intravitreal use of bevacizumab(39):

"[U]se of bevacizumab (Avastin, licensed for treatment of various solid cancers) has been associated with reports of severe eye inflammation and sterile endophthalmitis. The production methods, formulation, and doses for bevacizumab were developed for use in oncology. Its use in the ophthalmology setting has not been authorised."

Avastin is not, and cannot be, used for intra-ocular use. Roche Products Limited markets Avastin to treat metastatic colorectal and breast cancer. It has a marketing authorisation from the European Commission for that use. Roche has not applied for a new authorisation (or a variation of its existing authorisation) for Avastin to permit its use for wet AMD. Before bevacizumab can be used for intravitreal administration, it must be reformulated. The original product - Avastin - must be diluted and split into vials or syringes of a suitable volume for intravitreal injection. This process changes the concentration, dosage and method of administration and, as NICE has confirmed, creates an unlicensed product.

The MHRA expressed the same view in August 2011(39). It stated that:

"The preparation of bevacizumab for intravitreal use involves manipulation of the authorized medicine to produce multiple aliquots [i.e. a portion of the solution], usually in plastic syringes (so-called compounding). Therefore, it is important to note that this process also results in the creation of an unlicensed medicine."

Since bevacizumab is not used in the eye, bevacizumab is not a correct comparator in this appraisal.

Bevacizumab as a comparator in previous NICE appraisals for eye conditions

Bayer is also very aware that the most recent appraisal for ranibizumab and pegaptanib for treating wet AMD re-issued in May 2012 (TA155)(21) took place without any comparison against bevacizumab. Bayer therefore has a clear procedural and legal expectation that NICE will adopt the same approach in this

appraisal. We are not aware of any objective reasons that would justify a different approach.

In the recent rapid review of the appraisal of ranibizumab for diabetic macular oedema (DMO) (TA237)(40), bevacizumab was excluded by the Committee in its consideration (section 4.24):

"…The Committee noted that the use of bevacizumab as an intravitreal injection in people with diabetic macular oedema is considered in the information from the regulatory authorities to prescribers as 'unlicensed'. Also, the Committee heard conflicting evidence about the extent to which bevacizumab is currently used to treat diabetic macular oedema in England and Wales. It concluded that bevacizumab is not in routine use throughout the NHS, but it is adopted by some clinicians and funded by some NHS trusts. The Committee was mindful that some consultees and commentators supported a comparison with bevacizumab and others opposed it. The Committee considered whether a cost-effectiveness analysis of ranibizumab compared with bevacizumab was possible. The Committee recognised that a formal comparison of the 2 drugs would need evidence not only of all aspects of clinical effectiveness and safety, but also of the costs associated with preparing and administering bevacizumab, including the dose and number of injections required. The Committee agreed that such evidence was not readily available for people with diabetic macular oedema. The Committee agreed that, taking into account all these uncertainties, it could not consider a comparison of ranibizumab with bevacizumab. The Committee also concluded that further research directly comparing the clinical and cost effectiveness of ranibizumab and bevacizumab in people with diabetic macular oedema would reduce some of these uncertainties."

Bevacizumab has previously been included as a comparator in NICE scopes for the appraisal of dexamethasone (TA229)(41) and ranibizumab for macular oedema secondary to retinal vein occlusion (RVO)(42). However, these are different indications for which there was previously an absence of licensed alternative therapeutic options. In the case of wet AMD, ranibizumab has been licensed in the UK since 2007 and recommended by NICE in TA155 since 2008. Therefore, bevacizumab is not the appropriate comparator in this appraisal.

NICE workshop on bevacizumab for eye conditions

A NICE workshop in July 2010 and published in December 2010(43) on the potential appraisal of bevacizumab for eye conditions (where clinical experts, industry and academia were represented) indicated that bevacizumab is used second-line for wet AMD: *"Ophthalmologists at the workshop gave the reasons why bevacizumab might be considered as a treatment option. Although not licensed as a treatment for eye conditions, it is administered in some hospitals in the UK as an intravitreal injection to treat eye conditions where there are no other licensed treatments, or in a minority of wet AMD cases where improvements in vision have not been achieved with ranibizumab. It is also given to patients whose wet AMD does not meet the criteria in TA155, to recover some vision before further deterioration occurs."*

There is no existing NICE guidance on bevacizumab for wet AMD. Despite the workshop in July 2010, published December 2010, in a recent parliamentary questions, [70741], Mr Simon Burns stated there are no immediate plans to refer this topic to NICE for appraisal, but will keep this position under review. Moreover, the manufacturer has indicated that it does not intend to apply for a license for bevacizumab in wet AMD. In the absence of NICE guidance, some local PCTs have recently issued recommendations on the use of bevacizumab for wet AMD. However, these recommendations are based primarily on difference in acquisition cost (i.e. budget impact) rather than a comprehensive cost utility analysis using NICE methods.

In the absence of any referral of bevacizumab to NICE for appraisal, the inclusion of bevacizumab as a comparator in the appraisal for aflibercept solution for injection is likely to be considered by stakeholders as a substitute for a NICE appraisal of bevacizumab. However, this contradicts the report from the NICE workshop(43) that indicates provisions for safety are necessary for any appraisal of bevacizumab: *"There is support for an appraisal of intravitreal bevacizumab for eye conditions. Stakeholders agreed that an appraisal would need to be conditional on, or incorporate the assessment of, the safety and quality of intravitreal bevacizumab by a regulatory body or through the involvement of regulatory expertise. It was suggested that options for commissioning the relevant skills and expertise for this*

purpose be explored. Arrangements for safety monitoring / pharmacovigilance will need to be explored".

NICE is required to carry out *"such functions in connection with the promotion of clinical excellence ... "* For the reasons set out above, we query whether including an unlicensed comparator in this Appraisal that is neither in routine use nor represents best practice is consistent with NICE's function to promote health and clinical excellence, particularly given the documented safety concerns around unlicensed use of bevacizumab. The costs of pharmacovigilance are discussed in the next section.

Uncertainty associated with appraising unlicensed medicines

The cost effectiveness of aflibercept solution for injection compared with bevacizumab cannot be evaluated using NICE methods for technology appraisal(32) given the variable and highly uncertain cost for intravitreal bevacizumab and the absence of routine or best practice guidelines.

The NICE methods state that the list price of a technology should be used in the base-case of any technology appraisal (section 5.5.2) and that if the acquisition price paid differs from the public list price, prices are required to be transparent, consistently available across the NHS and the period for which the specified price is available is guaranteed (see section 5.5.2).

The price paid for the intravitreal bevacizumab used in the treatment of wet AMD is not transparent, consistent across the NHS, and defined for a specific period of time, as deemed necessary by NICE methods. Intravitreal bevacizumab is currently manufactured by independent centres from the concentrate for intravenous infusion that is licensed in the UK for the treatment of metastatic colorectal cancer and listed in the BNF at a list net price of £242.66 for a 4-ml (100mg) vial(44). These centres charge variable prices. At one patient per vial, which would not require vial splitting, the cost would be £242.66 per patient. In a previous NICE appraisal (TA229 appraisal of dexamethasone for RVO), it was acknowledged that different centres have quoted different prices from £50 to £150. The IVAN study investigators were able to source bevacizumab from a specific trial manufacturing facility charging £49 per dose. However, the IVAN study required treatment for only 610 patients. These

centres may have limited capacity to supply the entire NHS and at the same cost. In future, if demand was to increase, other centres may start to manufacturer bevacizumab at different prices, depending on the balance of supply, demand and safety requirements.

The Southampton Assessment Group report(43) also indicated that "…*there are no dose escalating/ranging studies of intravitreal bevacizumab and the optimum dose and dose-frequency are unknown…Safety concerns have also been raised as bevacizumab was not designed, manufactured or approved for intraocular use...*" . There has been an absence of appropriate efficacy and adequately powered safety studies to establish best practice bevacizumab for wet AMD. Whereas ranibizumab has had a recent revision of its posology conducted by the EMA to ensure optimal treatment for patients, this has not been the case for bevacizumab. Given that the SmPC for ranibizumab differs from the regimen of ranibizumab in the CATT(45) or IVAN(46) study, it is not known what would be the case for bevacizumab.

Before a medicine can be authorised for use in the UK and the European Union, the medicine must have undergone extensive testing to demonstrate that the product is safe, efficacious and of suitable quality. The manufacturer of bevacizumab has not undertaken any such studies and the studies that do consider unlicensed use of bevacizumab for eye conditions have a number of limitations. For example, although some results have been published in the CATT(45) and IVAN(46) studies, these studies are generally under-powered for safety and are therefore inadequate to form a robust safety and efficacy assessment, particularly in terms of subgroups.

Challenges to implementation of NICE guidance on unlicensed medicines

There is also an on-going judicial review against four PCTs and a PCT Cluster in the south of England challenging a policy by those PCTs recommending bevacizumab for patients for first-line wet AMD. At its meeting on 25th July 2012, the board of the SHIP (Southampton, Hampshire, Isle of Wight and Portsmouth) PCT cluster decided to discontinue its bevacizumab policy for wet AMD(47).

The bevacizumab policy was approved by the board of the PCT cluster back in September 2011 and subsequently legally challenged by Novartis. Novartis gained a judicial review of the cluster's commissioning policy for unlicensed bevacizumab.

The board of SHIP acknowledged a number of reasons that made the policy difficult to implement(48). These included:

- Further evidence from the IVAN study regarding potential equivalence of Lucentis (ranibizumab) and bevacizumab would not be available for another 12-18 months
- Local consultant ophthalmologists had chosen not to prescribe bevacizumab for wet AMD regardless of the commissioning policy
- Legal challenge led to inability of PCT cluster to exert its policy with commissioned providers
- Legal proceeding potentially not concluded by time PCTs are handing over commissioning responsibility to clinical commissioning groups (CCGs) (April 2013)
- Availability of new discounts in the cost of Lucentis as a consequence of ongoing cooperation between PCT Cluster and Novartis. The described discount is the National Patient Access Scheme which Novartis now makes available to NHS providers across the country

Finally, in the absence of a specific direction from the Secretary of State for Health requesting NICE to review bevacizumab for wet AMD, we believe (without of course accepting the legality of such a direction) that including it as a comparator in this appraisal could be viewed as conducting an appraisal of bevacizumab. We are aware that a number of PCTs are waiting for NICE to conduct some form of assessment of bevacizumab to justify illegal policies recommending reformulated bevacizumab for wet AMD. Bayer is also very aware that the most recent May 2012 re-issue of the appraisal for ranibizumab for wet AMD took place without any comparison against bevacizumab and it is the company's legitimate expectation that the same standard would be applied here. Clearly, NICE has some flexibility in choosing unlicensed comparators, particularly given that for some conditions there are no licensed and/or NICE recommended comparators. However, given the procedural, regulatory and legal issues surrounding use of unlicensed bevacizumab in particular, we request that NICE does not consider it appropriate in this Appraisal.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The VIEW studies showed aflibercept to have a similar safety profile to ranibizumab. Both treatments require intravitreal injection using proper aseptic injection techniques. In addition, serious adverse reactions related to the injection procedure have occurred in less than 1 in 1,000 intravitreal injections with aflibercept solution for injection. It is not anticipated that aflibercept will require any additional therapies to manage adverse events than those already used to manage adverse events with current standard of care.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

As with current standard of care, treatment takes place in specialist ophthalmologist clinics for the treatment of wet AMD. Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including topical broad spectrum microbicide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface), have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended(5).

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available(5). Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay. Each vial should only be used for the treatment of a single eye. After injection any unused product must be discarded(5).

2.10 Does the technology require additional infrastructure to be put in place?

No. As with current practice, administration of aflibercept will be via intravitreal injection. As with current practice, monitoring will be of VA and anatomical outcomes

using OCT. However, a reduction in monitoring requirements will enable a more efficient use of the infrastructure that is currently in place.

3 Equality

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

3.1.2 Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

As stated in the scope, wet AMD is more prevalent in women and is a condition of those aged 50 years and over. There is evidence of variation in rates of intravitreal injections by age, gender, location and over time. National Hospital Episode Statistics (HES) rates of intravitreal injection after 2002 have consistently been highest in the 70 and older age group. Annual rates have increased most in women 70 years and over(49). Multiple comorbid conditions, such as hypertension, are also an issue in this increasingly older population and a majority of AMD patients in studies are prior or current smokers(50) which may consequently link AMD to socio-economic factors.

There are no other equality issues.

3.1.3 How has the analysis addressed these issues?

Not applicable

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Aflibercept solution for injection is innovative as it has a different mode of action to the other VEGF inhibitors. It addresses a wider range of growth factors and includes Placental Growth Factor (PIGF) binding(1-3). With less frequent monitoring requirements compared with current treatments for wet AMD(5;14), aflibercept is also offering a step-change in the management of wet AMD.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

It is expected that aflibercept solution for injection will provide for reductions in both case load and budget requirements. There would be cost and capacity savings in frequency of monitoring compared with current licensed anti-VEGF treatments in an NHS which is currently under increasing pressure for its ophthalmology services. This impact on service capacity is unlikely to be captured by the QALY calculation.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Not applicable – see response above

5 Statement of the decision problem

Table A2. Decision problem

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	Adults with wet age-related macular degeneration	Adults with neovascular (wet) age-related macular degeneration	Not applicable
Intervention	Aflibercept solution for injection	Aflibercept solution for injection	Not applicable
Comparator(s)	Ranibizumab Bevacizumab Photodynamic therapy	Ranibizumab	Please see section 2.7 for the rationale for ranibizumab alone as the standard of care for the treatment of wet AMD in the NHS
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.	Not applicable
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	Not applicable.
Subgroups to be considered	If evidence allows, potential subgroups could be defined according to the composition of the lesion type in terms of classic and occult choroidal neovascularisation	If evidence allows, potential subgroups could be defined according to the composition of the lesion type in terms of classic and occult choroidal neovascularisation	Not applicable
Special considerations/equity or equality	None	Not applicable	Not applicable

Section B – Clinical and cost effectiveness

6 Clinical evidence

Summary of clinical effectiveness

- A systematic review of high quality evidence (RCTs) of the clinical effectiveness of aflibercept compared with ranibizumab was conducted. The two pivotal VIEW studies were the only RCT available directly comparing aflibercept to ranibizumab.
- The two VIEW studies demonstrated that 2mg aflibercept, initiated with three monthly doses and then given every 8 weeks was non-inferior to ranibizumab 0.5mg given every 4 weeks at 52 weeks in terms of the primary endpoint of maintained vision.
  - After an additional exploratory phase of 44 weeks, outcomes were maintained.
  - The studies established that aflibercept and ranibizumab have similar safety profiles
- An indirect comparison (ITC) was conducted, using the VIEW studies, to compare aflibercept to ranibizumab administered in an 'as needed' regimen based on monthly monitoring, given this regimen is that used in clinical practice and specified in the UK marketing authorisation.
- The ITC was limited by the available evidence (the CATT, HARBOUR and DETAIL studies) because the studies varied in terms of baseline characteristics (central retinal thickness (CRT), BCVA), retreatment criteria and number of injections. The three additional studies were also at high risk of bias. Data up to 24 months was available. The ITC was not able to establish any significant differences between the clinical effectiveness of aflibercept and reactive ranibizumab based on monthly monitoring.
- The CATT study, included in the ITC, concluded that those on monthly treatment gained more visual acuity than those on treatment as needed.
- The evidence available, including the VIEW study and ITC, has limitations in terms of the addressing the decision problem. For example, the evidence available for ranibizumab does not represent the retreatment regimen specified in the UK marketing authorisation. Similarly, the VIEW studies included monthly assessments for masking/analysis purposes so the benefit of less-than-monthly monitoring has not been captured in measures of quality of life (QOL).

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A systematic search of the literature was undertaken to identify RCT investigating the efficacy and safety of aflibercept for wet AMD. The search was undertaken on June 27th-28th 2012 using Medline, Medline in process, Medline daily update, EMBASE and The Cochrane Central Register of Controlled Trials (CENTRAL), various sources of relevant conference abstracts, and online clinical trial registers. Whilst the initial aim of the search was to find head-to-head RCT comparing aflibercept with current NHS standard of care, if available, the search formed part of a broader search for evidence to support any requirement for indirect comparisons or network meta-analysis (NMA) of aflibercept versus ranibizumab in various dosing regimens (fixed or treatment as needed (*pro re nata* [PRN]) in wet AMD.

Within the broader search, studies actively comparing treatment (including placebo or other active comparators) for wet AMD (and two other related retinal or macular eye conditions), with either aflibercept or ranibizumab were included.

Full details of the literature search strategy including search terms employed are provided in Section 10.2, Appendix 2. In addition, the reference lists from any retrieved studies were checked for other relevant studies and a search of the Bayer in-house databases was undertaken for unpublished literature.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent.

Two reviewers independently screened retrieved database files for relevance and any disagreements were resolved through consensus. Studies that appeared to be potentially

relevant were ordered and assessed for inclusion by one reviewer and checked by a second. The selection of studies was not limited by language or publication status. Abstracts were included, where full manuscripts were not available. A flow diagram of the numbers of records included and excluded at each stage is provided in section 6.2.2

Inclusion and exclusion criteria

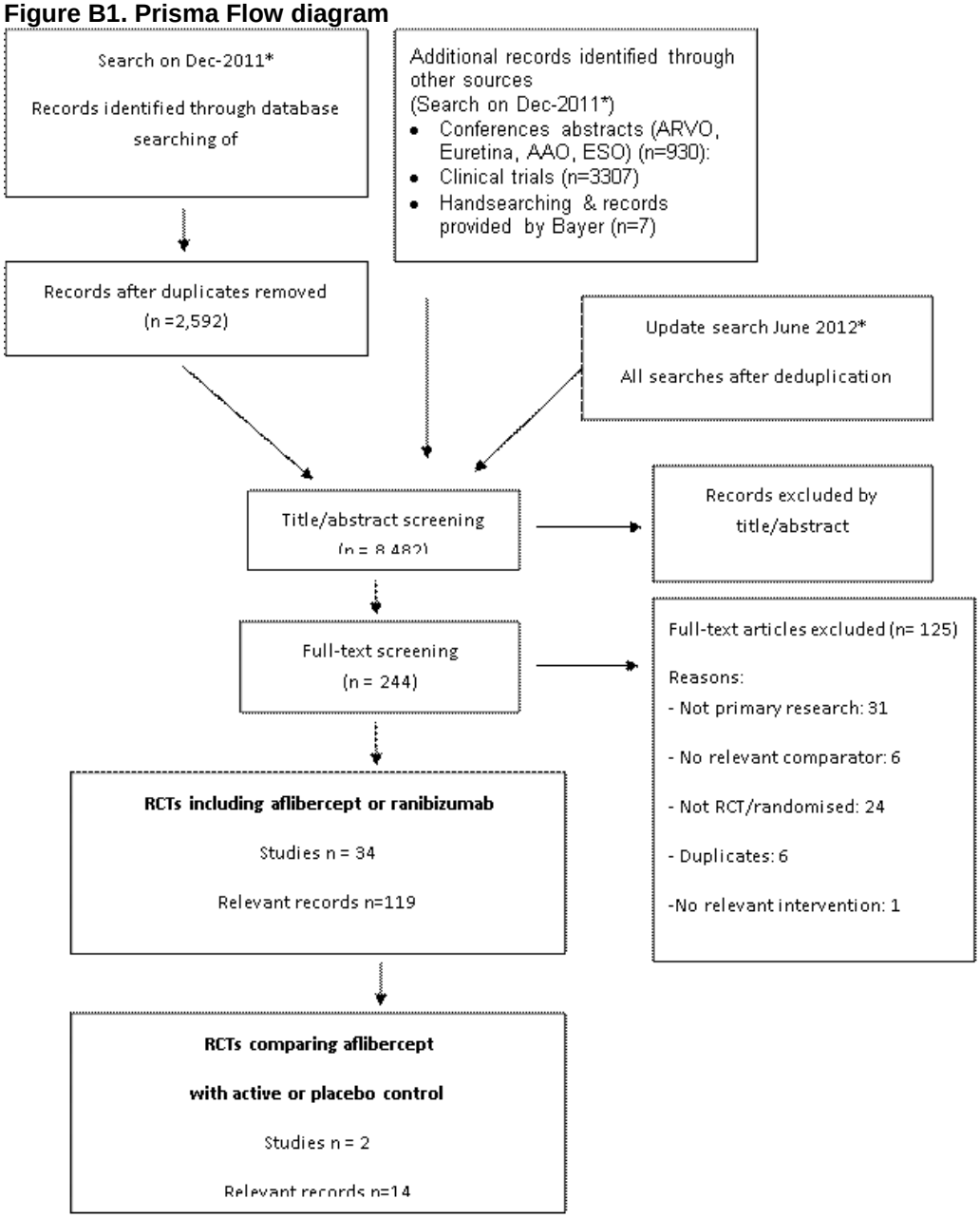
The inclusion and exclusion criteria were as wide as possible to reflect the relevant patient population.

Table B1 Eligibility criteria used in search strategy

Inclusion Criteria	
Study design	Randomised controlled clinical trials
Population	Patients with wet AMD (neovascular or exudative AMD) Patients with Retinal Angiomatous Proliferation (RAP) Patients with submacular haemorrhage secondary to age - related macular degeneration
Interventions	VEGF Trap Eye (Aflibercept®) Ranibizumab/ Lucentis® [Drug dose and regimen had to be reported]
Outcomes	Number of injections Best corrected visual acuity (BCVA) (Mean change from baseline, as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) score) Visual acuity (% of patients who gain/ lose outcome vs. baseline): loss of < 15 letters in ETDRS score loss of > 30 letters in ETDRS score (severe vision loss) loss of > 15 letters in ETDRS score (moderate vision loss) gain of > 15 letters in ETDRS score 20/40 vision or better (Snellen chart) 20/200 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 disc area area of lesion size of leakage greatest linear dimension Fluid on Optical coherence tomography (OCT) Presence of dye leakage Eyes with dry lesion Change in total lesion size Change in central foveal thickness HR-QOL (NEI VFQ-25, EQ-5D, other scales) Treatment discontinuations Serious adverse effects (events that are fatal, life threatening, or require hospitalisation), morbidity and mortality rates
Language	Any
Exclusion Criteria	
Study design	Animal studies

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

Figure B1. Prisma Flow diagram



Abbreviations: MEDLINE = Medical Literature Analysis and Retrieval System Online; EMBASE = Excerpta Medica Database; CENTRAL = Cochrane Central Register of Controlled Trials; NIH = National Institutes of Health; ARVO= Association for Research in Vision and Ophthalmology, AAO = American Academy of Ophthalmology, ESO= European Society of Ophthalmology; Euretina = European Society of Retina Specialists; RCT = randomised controlled trial.

* Precise search dates detailed in Appendix 10.2.

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Multiple publications

The systematic literature review identified multiple reports of two studies directly comparing aflibercept to ranibizumab (see Table B2):

VIEW 1: Vascular Endothelial Growth Factor VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD

VIEW 2: A randomised, double masked, active controlled, phase 3 study of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF Trap-Eye in subjects with neovascular AMD

Publications in bold in Table B2 are used as key sources of evidence throughout Section 6. The 1-year VIEW 1 and VIEW 2 study results were published during preparation of this submission (Heier 2012)(51).

Table B2. Relevant Studies and publications identified during literature search

Trial name	Publications
VIEW 1	Heier 2012 (51) Clinical Study Report (CSR) (unpublished) (52) 2-year VIEW 1 & VIEW 2 summary (unpublished) (53) Heier 2011 (abstract from EURETINA 2011) Brown 2011 (abstract/poster from AAO 2011) Heier 2012 (abstract from ARVO 2012) (6) Freund 2012 (abstract from ARVO 2012) NCT00509795 (clinical trial record) [www.clinicaltrials.gov]
VIEW 2	Heier 2012 (51) Clinical Study Report (CSR) (unpublished) (54) 2-year VIEW 1 & VIEW 2 summary (unpublished) (53) Staurenghi 2010 (abstract from EURETINA 2010) Korobelnik 2011 (abstract from EURETINA 2011) Brown 2011 (abstract/poster from AAO 2011) Schmidt-Erfurth 2011 (abstract from ARVO 2011) Heier 2012 (abstract from ARVO 2012) (6) Freund 2012 (abstract from ARVO 2012) NCT00637377 (clinical trial record) [www.clinicaltrials.gov]

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form.

Table B3. List of relevant head-to-head RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
VIEW 1 (VGFT-OD-0605 311523)	Primary phase Aflibercept 0.5mg given intravitreally every 4 weeks (0.5mg Q4 intravitreal (IVT) injection) 2mg given intravitreally every 4 weeks (2mg Q4 IVT) 2mg given intravitreally every 8 weeks (after 3 initial 4-weekly doses) (2mg Q8 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)	Primary phase 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)	Active primary subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye	Heier 2012 (51) VIEW 1 & VIEW 2 Clinical summary report (53)
VIEW 2 (311523)				Heier 2012 (51) VIEW 1 & VIEW 2 Clinical summary report (53)

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

Selected: Both VIEW 1 and VIEW 2 compare aflibercept with ranibizumab in a relevant population and at a relevant dose range, applicable to the UK population and the current decision problem in this submission.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is

transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

With reference to section 6.2.5, no studies have been excluded from further discussion.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

Given that sufficient, robust clinical evidence relevant to the decision problem was available from RCTs (the preferred source of clinical data), it was not considered relevant to include non-RCTs in the search strategy for clinical effectiveness.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments.

Summary of methodology of relevant RCTs

As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in

confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

Background and objectives

Aflibercept solution for injection is a new potent specific inhibitor of VEGF, designed and formulated to interfere with the growth of new blood vessels that lead to retinal oedema, ischaemia and haemorrhage. Aflibercept is a fully human fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1. It binds to all known VEGF-A isoforms and also PlGF, and has substantially increased binding affinity to VEGF-A when compared to that of ranibizumab(1;2). Mathematical modelling has suggested therefore that aflibercept might still be active in the eye for 10 to 12 weeks after a single intravitreal injection, with the binding activity of 2 mg aflibercept at 83 days, estimated to be comparable to the activity of 0.5 mg ranibizumab at 30 days(3).

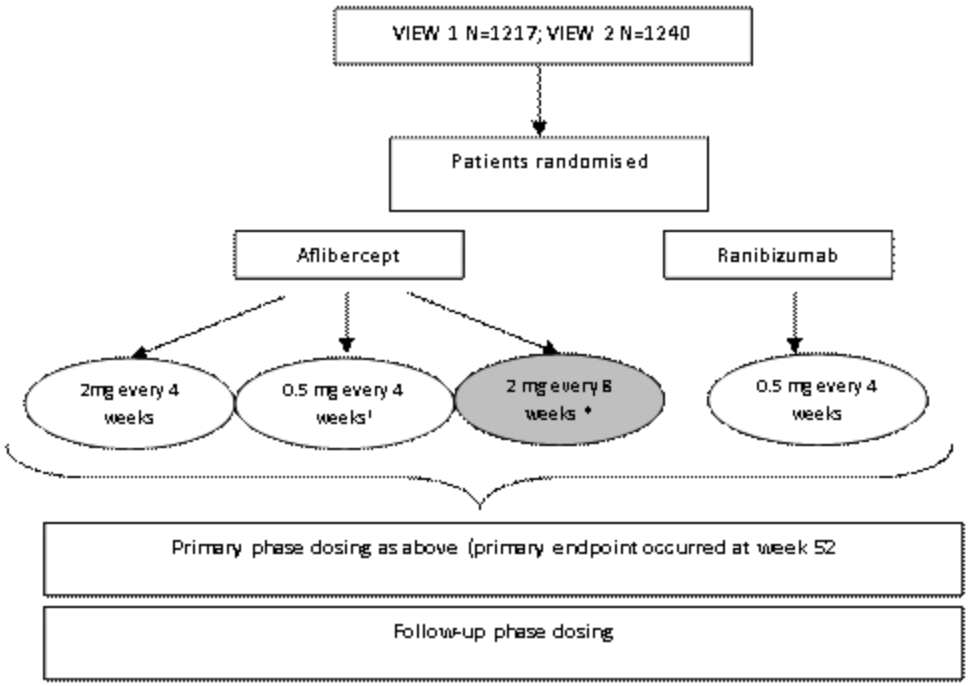
Given its higher affinity for VEGF as compared with ranibizumab, and its ability to be administered at higher doses, studies involving aflibercept have been designed to assess whether aflibercept, at any of 3 dose regimens, can offer at least non-inferior efficacy to existing approved anti-VEGF therapy i.e. monthly ranibizumab (0.5mg Q4) in the treatment of wet AMD, including maintenance of vision over a 52 week treatment period.

The VIEW studies were designed primarily to test whether 2mg aflibercept given every 8 weeks after 3 monthly loading doses (2mg Q8) was non-inferior to monthly ranibizumab (RQ4). This comparator was chosen in agreement with the relevant regulatory authorities in participating countries, because ranibizumab had not been formally tested or approved using an every 2 months dosing regimen and monthly dosing was recommended by the ranibizumab label in some countries. Dose groups of 0.5mg and 2mg aflibercept every 4 weeks (0.5mg Q4 and 2mg Q4) were also included, with 1:1:1:1 randomisation(51).

By including a further 44 weeks of treatment in an exploratory extension study (hereon described as the ‘follow-up phase’), the VIEW studies also aimed to evaluate criteria-based dosing for maintaining vision long-term and potential gains in visual acuity over a longer dosing interval than with the comparator treatment. Potentially, this could reduce the risks associated with a monthly injection procedure. Moreover, it could offer a treatment regimen with the potential for reduction of the monthly monitoring of patients, needed with ranibizumab and PRN dosing.

The safety and tolerability of repeated intravitreal administration of aflibercept over the entire period of 96 weeks was also an objective for study. Evidence is thus presented from two phase 3 studies, VIEW 1 and VIEW 2, on the efficacy, safety and tolerability of aflibercept, when compared with ranibizumab in the treatment of adults with all sub-types of wet (or neovascular) AMD(51). Key features of VIEW 1 and VIEW 2 are summarised in **Figure** 2 and **Table** 6.

Figure B2. VIEW 1 and VIEW 2 study design



*Following 3 initial monthly doses every 4 weeks
with additional evaluation visits up to week 96
+ not a licensed dose (2mg is the license dose of aflibercept)

Table B4. Key features of aflibercept comparative, randomised, double-masked studies investigating primary outcomes in treatment of wet AMD

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 2Q8 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		

Methods

Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

VIEW 1: Vascular Endothelial Growth Factor VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD

VIEW 2: A randomised, double masked, active controlled, phase 3 study of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF Trap-Eye in subjects with neovascular AMD

Design

VIEW 1 and VIEW 2 were pivotal, international, multicentre, randomised, double-masked, parallel-group, active-controlled, phase III non-inferiority studies. The studies were nearly identical in design (see **Figure** 2) so that the data could be pooled. The VIEW study programme represents the largest randomised cohort in wet AMD published to date.

For VIEW 1, study enrolment started in July 2007 and was completed in July 2011, during which time 1,217 patients were randomised to treatment. Study enrolment started for VIEW 2 in April 2008 and was completed in August 2011, during which time 1,240 patients were randomised to treatment(51).

Only one eye per patient was enrolled in the study. If a patient's fellow (non-study) eye required treatment for AMD at study entry, or during the patient's participation in the study, the fellow eye was allowed to receive any approved treatment (this was not allowed for the study eye apart from treatment that did not interfere with evaluation of study drug). Although the fellow eye may have received treatment, it was not considered an additional study eye. Safety of the fellow eye was monitored, and systemic adverse events (AEs) were collected.

The study had two phases, including 1) a primary phase (from randomisation to week 48) where treatment was given 'per protocol' and 2) a follow-up phase involving modified PRN dosing through week 92 and additional evaluation visits (see **Figure** 2, and 'Follow-up')(51).

Discontinuation of study treatment or withdrawal from the study occurred upon occurrence of rhegmatogenous retinal detachment or stage 3 or 4 macular holes; treatment failure (i.e. decrease from baseline by 15 or more letters at two consecutive assessments, 4 weeks apart, during the first 52 weeks of the study); if alternative treatment for AMD in the study eye was required; at the patient's, sponsor's or investigator's request; noncompliance with the protocol (i.e. patient lost to follow-up); or if there were safety concerns (e.g. relevant laboratory abnormality or serious adverse event (SAE)). Patients terminating the study prematurely, who did not meet the criteria for treatment failure, were considered drop-outs. Patients were allowed to discontinue treatment without discontinuing from the study, maintaining their original clinic visit schedule. After the 96 week study period, or earlier if patients discontinued from the study prematurely, patients were not restricted in pursuing any treatments available for AMD.

Method of randomisation

VIEW 1: Patients from the United States and Canada (154 trial sites), were randomised by an interactive voice response system (IVRS) according to a central randomisation scheme with balanced allocation (1:1:1:1 ratio with a fixed block size) to one of four treatment groups(51).

VIEW 2: patients were randomised by country to one of the above four treatment arms, again, randomly assigned by central randomisation group, in a 1:1:1:1 ratio with a fixed block size (51).

Masking

Patients were masked as to treatments. Sham injections were given to maintain masking of longer dosing intervals in the aflibercept 2mg Q8 treatment arm during the primary phase of treatment, where all other treatment arms had monthly injections. Sham injections were not necessary in the extension treatment phase. The sham kits were identical to the aflibercept treatment kits except they had no drug product or needles. Sham injections used the same preparation procedure as for the study drug and used a mock procedure of placing pressure on the eye exerted by a syringe without a needle(51).

There was a strict distribution of responsibilities between masked and unmasked personnel both at the study sites and at the sponsor (see Table B5). Study drug or sham injection was performed by an unmasked physician. A separate physician was assigned to

the role of masked evaluator and all other study site personnel were masked to treatment assignment in order to allow for an unbiased assessment of visual acuity, safety, and ancillary study measures throughout 96 weeks and until database lock and authorisation of data release(51). In the event of a medical emergency, the investigator could unmask the study drug for that patient. Breaking of the mask automatically disqualified the patient from further study participation. OCT images were read by masked readers at independent reading centres (IRC)(51).

Table B5. Masked / unmasked status and roles of study site personnel

Role	Primary responsibility
Masked Principal Investigator	Oversee entire conduct of study Responsible for all aspects of study conduct
Masked Physician / Masked certified designee	Obtains medical history Evaluates vital signs, performs physical exams Performs ophthalmic exams at all study visits (except intravitreal (IVT) injection and immediately post injection exams) Evaluates all safety, including review of images for safety concerns at the site (except those immediately post IVT injection) Refraction and BCVA testing Contact with sponsor regarding medical information not delegated to study coordinator
Unmasked Physician	Injection of study drug Assess safety at 30-60 minute post IVT injection Checks intraocular pressure (IOP) pre- and post-dose Checks indirect ophthalmoscopy post-dose
Unmasked Physician or their unmasked designee	Receives study drug Preparation of study injection Ranibizumab supply reconciliation and reimbursement Study drug accountability Call interactive voice response system (IVRS)for randomisation
Masked Photographer / Fluorescein Angiography Technician / OCT Technician	Acquire OCT images, fundus photographs and / or angiographic images Assure transfer of images to reading centres when required Assure proper archiving of imaging
Masked Study Coordinator	Primary responsibility for administrative and logistical aspects of study conduct Primary point of contact with contract resource organisation (CRO) and sponsor for all non-medical matters Coordinate randomisation with masked and unmasked physicians

Intervention and comparator

Enrolled patients were randomised to one of four treatment regimens containing aflibercept or ranibizumab. During the primary phase of treatment, patients received treatment according to randomisation arm, with patients in the aflibercept 2mg Q8 arm receiving sham injections when no active treatment was due. Injection frequency in the primary phase (up to 52 week primary endpoint) was entirely protocol-driven according to randomisation, and was not determined by the outcome of monthly monitoring.

Primary phase

'Aflibercept'

- 0.5mg Q4 group (n=304) received aflibercept 0.5mg injected intravitreally every 4 weeks (unlicensed dose in the UK)
- 2mg Q4 group (n=304) received aflibercept 2mg injected intravitreally every 4 weeks
- 2mg Q8 group (n=303) (the dose of most interest to the decision problem) received aflibercept 2mg injected intravitreally every 8 weeks (after 3 initial monthly doses) and a sham injection at interim monthly visits thereafter

Aflibercept was supplied in sealed 3 mL single-use vials each with a "withdrawable" volume of approximately 0.5 mL at a concentration of 10 mg/mL or 40 mg/mL (53).

'Ranibizumab'

- 0.5mg Q4 group (n=304)

Received ranibizumab 0.5mg injected intravitreally every 4 weeks

In the follow-up, exploratory, extension phase, patients continued to be evaluated every 4 weeks and remained in their allocated treatment groups, but intravitreal (IVT) injections were given as needed, as frequently as every 4 weeks, but no less frequently than every 12 weeks. The interval at which treatment was administered was determined by specific strict criteria for re-dosing (investigator assessed):

- Increase in CRT of ≥ 100 µm compared to the lowest previous value as measured by OCT, or

- A loss of ≥ 5 ETDRS (Early Treatment Diabetic Retinopathy Study) letters from the best previous letter score in conjunction with recurrent fluid as indicated by OCT, or
- New or persistent fluid as indicated by OCT, or
- New onset classic neovascularisation, or
- New or persistent leak on fluorescence angiography (FA), or
- New macular haemorrhage, or
- 12 weeks have elapsed since the previous injection.

Sham injections were not given in the extension treatment phase of the study.

The volume of injection was 50 µL (0.05 mL). The study drug was withdrawn from the delivered vial using aseptic technique through an 18 gauge filter needle attached to a 1 mL syringe. The needle was discarded after withdrawal of the vial contents and was not used for IVT injection. The needle was replaced by a sterile 30 gauge needle for the IVT injection. The content was expelled until the plunger was aligned with the line that marks 0.05 mL on the syringe.

Injections of study medication were withheld in the presence of active or suspected ocular or periocular infections, active severe intraocular inflammation (i.e. 4+ anterior chamber cell / flare or 4+ vitritis). In addition, as per commercial labelling of ranibizumab doses of aflibercept or ranibizumab were withheld and treatment not resumed earlier than the next scheduled treatment in the event of:

- a decrease in BCVA of ≥ 30 letters compared with the last VA assessment,
- of ≥ 30mmHg,
- a retinal break,
- subretinal haemorrhage involving the centre of the fovea or if the size of the haemorrhage is ≥ 50% of the total lesion area,
- or performed or planned intraocular surgery within the past or next 28 days.

Where an IVT injection could not be given at the scheduled time, withholding of one dose did not constitute reason for patient's withdrawal from study medication.

In both studies, treatment compliance during the first 52 weeks was >97% in all treatment groups. As all drugs were administered by site personnel, compliance with study drug dosing was monitored by review of patient files.

Follow-up

Regardless of assigned treatment, all patients were examined on the day of treatment and assessed every 4 weeks thereafter. Administration of the next dose was protocol driven in all arms during the first 52 weeks. There was additional safety assessment one week after the first treatment - subsequent safety assessments occurred by telephone(51).

Each 4-week visit included BCVA assessment and anterior/posterior segment examination (with IOP determination) before injection (active or sham) and posterior segment examination with IOP determination 30 to 60 minutes after injection. For the 2Q8 treatment group, no treatment decisions were made at the interim monthly visits in the first 52 weeks. A quality of life assessment, the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), occurred at screening and weeks 12, 24, 36, 52, 72 and 96 and, in VIEW 2 only, assessment of patients' general health status using the EQ5D Health Questionnaire (screening, weeks 52 and 96). Adverse events and concomitant medications information were recorded at every visit, and vital signs were measured(51).

Fundus photography and fluorescein angiography (FA) were performed at screening and weeks 24, 52, 72 and 96, and evaluated by an independent centre (Digital Angiography Reading Center, New York). OCT was performed using time domain Stratus machines (Carl Zeiss Meditec, Jena, Germany) and evaluated by an independent centre (VIEW 1: OCT Reading Center at Duke, Durham, NC; VIEW 2: Vienna Reading Center, Austria). Visual acuity examiners were certified to ensure consistent measurement of BCVA. 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 (i.e. every 4 weeks). Areas of visible CNV (classic or occult) were identified when angiographic analyses showed evidence of late leakage or pooling of dye(51).

The 'End of study' visit, which included post-treatment safety follow-up, was, in VIEW 1, performed at week 96, irrespective of the time of the last injection. In VIEW 2, the 'End of study' visit was performed at Week 96 in patients who hadn't received an injection within the previous 8 weeks, or at Week 100 in patients who received an injection at Week 92

(i.e. previous clinic visit). The entire study duration was 96 weeks(VIEW 1) or 96/100 weeks (VIEW 2) [VIEW 1 - up to 92 weeks of treatment plus the screening period and 4-week safety follow-up period; VIEW 2 – up to 92 weeks of treatment plus the screening period and a 4-week or 8-week safety follow-up period depending on the timing of the last study injection]. Hereon, for simplicity, the end of study will be described as 96 weeks.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Inclusion and exclusion criteria (See Table B6).

Eligible patients had to have subfoveal CNV secondary to AMD. “Subfoveal” CNV was defined as the presence of subfoveal neovascularisation, including juxtafoveal lesions that affect the fovea, documented through confirmed FA by an independent reading centre(51).

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 VA was selected as the study eye. If both eyes had equal VA, the eye with the clearest lens and ocular media and least amount of subfoveal scar or geographic atrophy was selected. If there was no objective basis for selecting the study eye, factors such as ocular dominance, other ocular pathology and patient preference were considered in making the selection.

Ophthalmic eligibility criteria apply to the study eye only unless otherwise specified. During screening (Day –21 to Day 0), patients who signed the informed consent underwent physical and ophthalmic examinations.

Table B6. Eligibility criteria in VIEW 1 and VIEW 2 studies.

Trial: VIEW 1 and VIEW 2	
Inclusion criteria	Exclusion criteria
Signed informed consent Age ≥ 50 years Active subfoveal CNV lesions secondary to AMD, including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye Area of CNV must occupy at least 50% of total lesion ETDRS best-corrected visual acuity of: 20/40 to 20/320 (letter score of 73 to 25) in the study eye Willing, committed, and able to return for all clinic visits and complete all study-related procedures Able to read (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member), understand and willing to sign the informed consent form	Prior ocular (in the study eye) or systemic treatment (including prior or concomitant therapy with another investigational or anti-VEGF agent) or surgery for wet AMD, except dietary supplements or vitamins Prior (within 3 months prior to the first study dose) or concomitant treatment with anti-VEGF therapy in the fellow eye with an investigational agent (not approved e.g. bevacizumab) [Prior treatment with an approved anti-VEGF therapy in the fellow eye is allowed] Prior (within 3 months of first study dose) or concomitant systemic anti-VEGF therapy, investigational or approved Total lesion size >12 disc areas (30.5mm^2, including blood, scars and neovascularisation) as assessed by FA in the study eye Subretinal haemorrhages that are either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. If blood under fovea, then fovea must be surrounded by 270 degrees by visible CNV) Scar or fibrosis making up 50% of the total lesion in the study eye Scar, fibrosis or atrophy involving the centre of the fovea in the study eye Presence of retinal pigment, epithelial tears or rips involving the macula in the study eye History of any vitreous haemorrhage in the study eye within 4 weeks prior to Visit 1 Presence of other causes of CNV in the study eye Prior vitrectomy in the study eye History of retinal detachment or treatment or surgery for retinal detachment in the study eye Any history of macular hole ≥ stage 2 in the study eye Any intraocular or periocular surgery within 3 months of day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of Day 1, as long as it is unlikely to interfere with the injection Prior trabeculectomy or other filtration surgery in the study eye Uncontrolled glaucoma (IOP ≥ 25mmHg despite treatment with antiglaucoma medication) in the study eye Aphakia or pseudophakia with absence of posterior capsule (unless resulting from an yttrium aluminium garnet (YAG) posterior capsulotomy) in the study eye Previous therapeutic radiation in the region of the study eye History of corneal transplant or corneal dystrophy in the study eye Significant media opacities, including cataract, in the study eye, which might interfere with visual acuity, assessment of toxicity or fundus photography History or clinical evidence of diabetic retinopathy, diabetic macular oedema or any retinal vascular disease other than AMD in either eye Active intraocular, extraocular and periocular inflammation or infection in either eye Any ocular or periocular infection within 2 weeks prior to screening in either eye Any history of uveitis in either eye

	Presence of scleromalacia in either eye Concurrent intraocular condition in the study eye that could require either medical or surgical intervention during the 96-week study period Concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the patient safety or which otherwise may interfere with evaluation of efficacy or safety History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug Participation in any clinical study within 12 weeks prior to Day 1 Any systemic or ocular treatment with an investigational agent within 3 months prior to Day 1 Long acting steroids, either systemically or intraocularly, within 6 months prior to Day 1 History of allergy to povidone iodine Known serious allergy to fluorescein sodium for injection in angiography Contraindication to ranibizumab Pregnancy or lactation Women of child-bearing age unwilling to practice adequate contraception throughout the study

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Baseline demographics - patient characteristics

Patient characteristics entering primary treatment phase

In general, for both studies, baseline characteristics were similar across treatment groups (see Table B7 and Table B8) (51). In both VIEW 1 and VIEW 2, results of baseline demographic and disease characteristics for the ‘per protocol set (PPS)’ were similar to those of the Full Analysis set (FAS), with no relevant differences between the two analysis sets.

VIEW 1 – Demographic characteristics were similar across treatment groups. The mean age ranged from 77.7 to 78.4 years across treatment groups. Most patients were white (1169 / 1210 [96.6%]) and non Hispanic or Latino (96.6%). Approximately half of the participants were female (711/1210, 58.8%; pairwise comparison vs. ranibizumab in total column [Chi-Square test] p=0.3793). Most patients had non-dark eye colour (793/1210

[65.5%]). The overall mean body mass index (BMI) was 27.40 kg/m^2, the mean weight was 75.39kg and the mean height was 165.60cm(51;55).

The disease characteristics of the study eye were balanced among the study groups at baseline. In the FAS, the total mean baseline BCVA (BCVA letter score) was 55.1. The most commonly represented lesion type was occult, and the distribution of types within each treatment group was as expected for this patient population. The mean CNV area was 6.6mm^2. Mean baseline NEI VFQ-25 total score was 70.7 out of a total of 100 possible points(51).

VIEW 2 – Overall the four treatment groups were homogenous with regard to demographic characteristics, except for gender distribution in the 0.5Q4 group, where the proportion of males to females was nearly identical (50.3% and 49.7%, respectively). Pairwise comparisons of the gender distribution in this group with that of RQ4 resulted in p=0.04 (both in Chi-square and the region-adjusted Cochran–Mantel–Haenszel tests)(51).

The FAS consisted of 535 (44.5%) male and 667 (55.5%) female patients. The mean age ranged from 73.0 to 74.7 years across treatment groups. The majority of patients were white (72.8%) and over 20% were of Asian race due to the geographical location of the trial. Eye colour was predominantly dark (60.1%). Mean weight was 70.1 ± 14.5kg and mean BMI was 26.3 ± 4.7kg/m^2(51).

Patients had a mean baseline BCVA score of 52.4 ± 13.9, which ranged from 10 to 83 (median: 55). BCVA was highest in the RQ4 group (53.8 ± 13.5) and lowest in the 0.5mg Q4 and 2mg Q8 groups (51.6 ± 14.2 and 51.6 ± 13.9, respectively). Pairwise comparisons of the two aflibercept groups with the ranibizumab 0.5mg Q4 group resulted in p= 0.06 (ANOVA, with or without region-adjustment)(51).

Lesion type in the study eye was ‘occult’ in 38.4% patients, ‘minimally classic’ in 35.4% and ‘predominantly classic’ in 25.8% patients, with similar distribution among the treatment groups. Mean total lesion size was 8.28 ± 5.82, the mean area of CNV was 7.83 ± 5.48mm^2, and the mean retinal thickness was 332.5 ± 118.0µm. For vision-related quality of life (QoL), the mean total NEI VFQ-25 score was 72.1 ± 18.99 points (range 7.8; 98.2) and the mean EQ-5D score was 0.8 ± 0.21 points.

Analysis of disease characteristics in the different subgroups did not indicate any relevant imbalances among the treatment groups. There were minor regional differences, by

geographic region, but overall balanced among treatment groups within the different regions.

Comparing baseline characteristics across the two studies, mean CRT was lower at baseline in VIEW 1 (313-324µm) than in VIEW 2 (326-343µm). Differences in size of CNV (VIEW 1 - 6.5-6.6 mm^2; VIEW 2 – 7,6-8.3mm^2) and mean area of lesion (VIEW 1 - 7mm^2; VIEW 2 – 8-8.7mm^2) were also observed.

Table B7. Baseline demographic characteristics of patients entering primary treatment phase for VIEW 1, VIEW 2 and pooled datasets [FAS]

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
Entered 1	N=304	N=291	N=595	N=304	N=309	N=613	N=301	N=296	N=597	N=301	N=306	N=607
Age (s)												
Mean (SD)	78.2 (7.6)	73.0 (9.0)	75.6 (8.7)	77.7 (7.9)	74.1 (8.5)	75.4 (8.4)	78.4 (8.1)	74.7 (8.6)	76.5 (8.5)	77.9 (8.4)	73.8 (8.6)	75.8 (8.8)
Median	79.0	74.0		79.0	75.0		80.0	76.0		79.0	75.0	
Min; Max	{56; 99]	[50; 92]		[51; 94]	[50; 93]		[50; 94]	[51; 93]		[49*; 94]	[50; 93]	
P-value a/ P-value b				-	0.10 / 0.06		-	0.02 / 0.01		-	0.26 / 0.16	
Sex (n[%])												
Male	132 (43.4)	122 (41.9)	254 (42.7)	110 (36.2)	133 (43.0)	243 (39.6)	134 (44.5)	149 (50.3)	283 (47.4)	123 (40.9)	131 (42.8)	254 (41.8)
Female	172 (56.6)	169 (58.1)	341 (57.3)	194 (63.8)	176 (57.0)	370 (60.4)	167 (55.5)	147 (49.7)	314 (52.6)	178 (59.1)	175 (57.2)	353 (58.2)
P-value c/ P-value d				0.0683	0.78 / 0.86		0.7857	0.04 / 0.04		0.5242	0.83 / 0.91	
Race (n[%])												
White	296 (97.4)	213 (73.2)	509 (85.5)	295 (97.0)	226 (73.1)	521 (85.0)	291 (96.7)	219 (74.0)	510 (85.4)	287 (95.3)	217 (70.9)	504 (83.0)
Black	1 (0.3)	1 (0.3)#	2 (0.3) #	1 (0.3)	0 (0.0)#	1 (0.2) #	0 (0.0)	1 (0.3)#	1 (0.2) #	1 (0.3)	2 (0.7)#	3 (0.5) #
Asian	0 (0.0)	60 (20.6)	60 (10.1)	3 (1.0)	67 (21.7)	70 (11.4)	5 (1.7)	61 (20.6)	66 (11.1)	4 (1.3)	69 (22.5)	73 (12.0)
American Indian	2 (0.7)	-	2 (0.3)	0 (0.0)	-	0 (0.0)	2 (0.7)	-	2 (0.3)	1 (0.3)	-	1 (0.2)
Native Hawaiian	1 (0.3)	-	1 (0.2)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	1 (0.3)	-	1 (0.2)
Not	4 (1.3)	17 (5.8)	21	5 (1.6)	16 (5.2)	21 (3.4)	3 (1.0)	15 (5.1)	18 (3.0)	6 (2.0)	18 (5.9)	24 (4.0)

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
Entered 1	N=304	N=291	N=595	N=304	N=309	N=613	N=301	N=296	N=597	N=301	N=306	N=607
Reported			(3.5)									
Multiple	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	1 (0.3)	-	1 (0.2)
Ethnicity (n[%])												
Not Hisp / Latino	297 (97.7)	239 (82.1)		293 (96.4)	259 (83.8)		290 (96.3)	241 (81.4)		289 (96.0)	251 (82.0)	
Hispanic / Latino	7 (2.3)	52 (17.9)		11 (3.6)	50 (16.2)		11 (3.7)	55 (18.6)		12 (4.0)	55 (18.0)	
Eye colour (n[%])												
Dark (blk / bwn)	101 (33.2)	177 (60.8)		107 (35.2)	117 (57.3)		106 (35.2)	176 (59.5)		99 (32.9)	193 (63.1)	
Other	203 (66.8)	114 (39.2)		195 (64.1)	132 (42.7)		194 (64.5)	120 (40.5)		201 (66.8)	113 (36.9)	
Missing	0 (0.0)	-		2 (0.6)	-		1 (0.3)	-		1 (0.3)	-	
Weight (kg)												
Mean (SD)	75.9 (17.8)	69.8 (15.0)		74.2 (16.3)	70.3 (14.4)		77.0 (17.9)	70.5 (14.4)		74.4 (17.7)	69.6 (14.4)	
Median	74.8	68.0		73.5	69.0		74.8	70.0		72.6	68.0	
Min; Max	[40; 135]	[40; 133]		[41; 137]	[32; 140]		[36; 172]	[37; 125]		[41; 143]	[41; 123]	
P-value a/ P-value b				-	0.69 / 0.64		-	0.55 / 0.56		-	0.82 / 0.90	
Height (cm)												
Mean (SD)	166.4 (9.83)	162.5 (9.38)		164.7(10.01)	163.3 (9.19)		166.3(10.24)	163.8 (9.34)		165.0(10.55)	162.8 (9.22)	
Median	165.1	162.6		165.1	163.0		165.1	163.4		165.1	163.0	

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
Entered 1	N=304	N=291	N=595	N=304	N=309	N=613	N=301	N=296	N=597	N=301	N=306	N=607
Min; Max	[144; 196]	[127; 184]		[135; 191]	[144; 195]		[142; 196]	[140; 198]		[135; 188]	[143; 190]	
P-value a/ P-value b				-	0.31 / 0.29		-	0.11 / 0.11		-	0.75 / 0.71	
BMI (kg/m^2)												
Mean (SD)	27.30 (5.21)	26.34 (4.80)		27.40 (5.50)	26.32 (4.89)		27. 8 (5.66)	26.22 (4.49)		27.2 (5.75)	26.18 (4.51)	
Median	26.8	25.97		26.4	25.59		27.0	25.57		26.6	25.62	
Min; Max	[15; 45]	[15.8; 57.6]		[15; 47]	[14.2; 60.4]		[17; 56]	[15.6; 42.8]		[17; 71]	[17.1; 39.2]	

*Though the inclusion criteria was ≥ 50 s of age, one patient was admitted into the study as he was close to his 50th birthday and all other causes of CNV ruled out, rendering it highly likely that the CNV was age-related; # = includes Black or African American; Hisp = Hispanic; Blk = black (eyes); bwn = brown (eye)s; BMI = Body Mass Index;

a P-value in aflibercept column pair-wise comparison versus ranibizumab and in total column all 4 treatment groups of analysis of variance, treatment group as fixed factor

b P-value in aflibercept column pair-wise comparison versus ranibizumab and in total column all 4 treatment groups of analysis of variance, treatment group and region as fixed factors (VIEW 2 analysis only).

c P-value in aflibercept column pair-wise comparison versus ranibizumab (Chi-square test) and in total column all 4 treatment groups (Chi square-test).

d P-value in aflibercept column CMH-test region adjusted (pair-wise comparison versus ranibizumab) and in total column CMH-test region adjusted (all 4 treatment groups) (VIEW 2 analysis only).

Hatched boxes – integrated analysis not conducted

Table B8. Baseline Disease Characteristics in the study eye of patients entering primary treatment phase for VIEW 1, VIEW 2 and pooled datasets [FAS]

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
Entered 1	N=304	N=291	N=595	N=304	N=309	N=613	N=301	N=296	N=597	N=301	N=306	N=607
BCVA (ETDRS letter score) n	304	291		304	309		301	296		301	306	
Mean (SD)	54.0 (13.4)	53.8 (13.5)	53.9 (13.4)	55.2 (13.2)	52.8 (13.9)	54.0 (13.6)	55.6 (13.1)	51.6 (14.2)	53.6 (13.8)	55.7 (12.8)	51.6 (13.9)	53.6 (13.5)
Median	56.0	56.0		58.0	55.0		58.0	54.0		56.0	52.0	
Min; Max	{10; 78]	[10; 83]		[11; 81]	[10; 79]		[18; 85]	[12; 79]		[15; 83]	[16; 76]	
P-value a/ P-value b				-	0.38 / 0.39		-	0.06 / 0.06		-	0.06 / 0.06	
Central retinal thickness (µm) n	286	290		286	308		281	294		286	302	
Mean (SD)	315.3 (108.3)	325.9 (110.9)	321 (109.7)	313.6 (103.4)	334.6 (119.8)	325 (112.6)	313.2 (106.0)	326.5 (116.5)	320 (111.6)	324.4 (111.2)	342.6 (124.0)	333.4 (118.2)
Median	285.5	309.5		290.0	309.0		291.0	313.5		303.0	327.5	
Min; Max	[144; 683]	[139; 810]		[151;802]	[103; 805]		[141; 739]	[107; 793]		[133;835]	[107; 868]	
P-value a/ P-value b				-	0.37 / 0.37		-	0.95 / 0.95		-	0.08 / 0.09	
Total lesion size (mm^2)												
n	298	290		302	307		300	296		301	305	
Mean (SD)	6.99 (5.5)	8.01 (5.7)	7.5 (5.6)	6.98 (5.4)	8.72 (6.1)	7.9 (5.8)	6.95 (4.7)	8.17 (5.5)	7.5 (5.2)	6.89 (5.2)	8.22 (5.9)	7.6 (5.6)

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
Entered 1	N=304	N=291	N=595	N=304	N=309	N=613	N=301	N=296	N=597	N=301	N=306	N=607
Median	5.52	6.60		5.86	7.30		6.23	7.10		5.64	6.70	
Min; Max	[0.1; 29.0]	[0.1; 28.8]		[0.2; 29.6]	[0.1; 30.0]		[0.2; 24.9]	[0.1; 26.6]		[0.0; 32.6]	[0.0; 26.7]	
P-value a/ P-value b				-	0.14 / 0.13		-	0.74 / 0.73		-	0.67 / 0.68	
Area of CNV (mm^2)												
n	298	291		302	308		300	296		300	305	
Mean (SD)	6.53 (5.2)	7.59 (5.3)		6.59 (5.1)	8.25 (5.8)		6.49 (4.5)	7.70 (5.3)		6.57 (5.1)	7.75 (5.5)	
Median	5.2	6.40		5.6	6.70		5.9	6.85		5.4	6.40	
Min; Max	[0; 29]	[0.1; 28.8]		[0; 30]	[0.1; 26.9]		[0; 25]	[0.1; 26.6]		[0; 33]	[0.0, 24.9]	
P-value a/ P-value b				-	0.14 / 0.14		-	0.81 / 0.80		-	0.71 / 0.72	
Lesion Type n(%)												
Occult	115 (37.8)	116 (39.9)	231 (38.8)	110 (36.2)	123 (39.8)	233 (38.0)	121 (40.2)	113 (38.2)	234 (39.2)	118 (39.2)	110 (35.9)	228 (37.6)
Minimally Classic	101 (33.2)	104 (35.7)	205 (34.5)	105 (34.5)	112 (36.2)	217 (35.4)	97 (32.2)	103 (34.8)	200 (33.5)	110 (36.5)	106 (34.6)	216 (35.6)
Predominantly Classic	82 (27)	70 (24.1)	152 (25.5)	87 (28.6)	72 (23.3)	159 (25.9)	81 (26.9)	80 (27.)0	161 (27.0)	71 (23.6)	88 (28.8)	159 (26.2)
NEI VFQ-25 Total												
n	303	291		300	309		297	295		293	306	
Mean (SD)	(71.8	72.90		70.4	70.3		71.1	74.0		69.6	71.3	

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
Entered 1	N=304	N=291	N=595	N=304	N=309	N=613	N=301	N=296	N=597	N=301	N=306	N=607
	(17.2)	(19.1)		(16.6)	(19.4)		(17.8)	(18.2)		(16.8)	(19.1)	
Median	74.8	78.60		72.1	74.80		74.5	78.40		71.6	73.70	
Min; Max	[25; 99]	[12.0; 98.2]		[25; 99]	[7.8; 98.2]		[7; 100]	[14.8; 98.2]		[21; 97]	[19.4; 98.0]	
P-value a/ P-value b					0.09 / 0.08			0.47 / 0.49			0.30 / 0.32	
EQ-5D score												
n	Not performed	291	-	Not performed	308	-	Not performed	295	-	Not performed	306	-
Mean (SD)	In VIEW 1	0.80 (0.21)		In VIEW 1	0.78 (0.22)		In VIEW 1	0.79 (0.22)		In VIEW 1	0.81 (0.19)	
Median		0.80			0.80			0.80			0.80	
Min; Max		[-0.1; 1.0]			[-0.2; 1.0]			[-0.3; 1.0]			[-0.1; 1.0]	
P-value a/ P-value b					0.24 / 0.22			0.82 / 0.77			0.34 / 0.32	

a P-value in aflibercept column pair-wise comparison versus ranibizumab and in total column all 4 treatment groups of analysis of variance, treatment group as fixed factor.

b P-value in aflibercept column pair-wise comparison versus ranibizumab and in total column all 4 treatment groups of analysis of variance, treatment group and region as fixed factors (VIEW 2 analysis only).

Hatched boxes – integrated analysis not conducted

Patient characteristics entering extension treatment phase

In both studies, approximately 90% of the patients continued treatment in the extension phase and the completion rates over the 96 week study period were high (>80%) in all treatment groups. The most frequent primary reasons for discontinuation from either study were ‘withdrawal by patient’ and ‘adverse event. See section 6.3.8 Participant flow.

In both studies, the demographic characteristics of patients entering the extension treatment phase were nearly identical to those of the FAS, and there were no meaningful differences among the treatment groups. Most patients were white, as is typical for patients with wet AMD, and, expectedly, the proportion of Asians was higher in VIEW 2.

In VIEW 1 and VIEW 2, disease characteristics in the study eye were consistent among treatment groups (VIEW 1: all p-values >0.1; VIEW 2: all p-values ≥0.08 with or without region adjustment; ANOVA) and nearly identical to those of the FAS. As at the beginning of the study, patients in VIEW 2 appeared to have poorer anatomical parameters, with larger total lesion and CNV areas.

VIEW 1 – Demographic characteristics were similar across the treatment groups. Four hundred and sixty two patients were male ([redacted]%) and [redacted]%) were female. Median age of patients was [redacted] years. The majority of patients were of White race ([redacted]%) and not Hispanic or Latino ([redacted]%) ethnic origin. Most ([redacted]%) had non-dark eye colour. Mean weight at baseline entering the extension phase was [redacted] kg and mean BMI was [redacted] kg/m^2 (see Table B9 for data by treatment group).

Patients had a mean baseline visual acuity letter score (as determined by ETDRS letter chart) of [redacted], which ranged from [redacted] (median: [redacted]). Mean total lesion size was [redacted]mm^2 and mean area of CNV was [redacted]mm^2. Mean CRT was [redacted]µm (see Table B10 for data by treatment group).

VIEW 2 – Demographic characteristics were similar across the treatment groups, except for the distribution of males / females. The proportion of male and females was identical in the 0.5mg Q4 group, while in all other groups, more females participating. Overall in the study, [redacted] patients were male ([redacted]%) and [redacted]%) were female. Median age of patients was [redacted] years. The majority of patients were of White race ([redacted]%) and not Hispanic or Latino ([redacted]%) ethnic origin. The predominant eye colour was dark

([redacted]%). Mean weight at baseline entering the extension treatment phase was [redacted] kg and mean BMI was [redacted] kg/m^2 (see Table B9 for data by treatment group).

Patients had a mean baseline visual acuity letter score of [redacted] ± [redacted], which ranged from [redacted] to [redacted] (median: [redacted]). It was the highest in the RQ4 group ([redacted] ± [redacted]) and lowest in the 0.5mg Q4 and 2mg Q8 groups ([redacted] ± [redacted] and [redacted] ± [redacted], respectively). Pairwise comparisons of these two aflibercept groups with the ranibizumab 0.5mg Q4 group resulted in p=0.06 and p=0.07 (ANOVA, with or without region-adjustment).

Mean total lesion size was [redacted]mm^2 and mean area of CNV was [redacted]mm^2. Mean CRT was [redacted]µm (see Table B10 for data by treatment group).

POOLED – As described in the single study analyses, more females than males entered the extension treatment phase ([redacted]%). Median age of patients was [redacted] years. The majority of patients were of white race ([redacted]) and not Hispanic or Latino ([redacted]%) ethnic origin. The proportion of patients who were of Asian race was [redacted]% (see Table B10 for data by treatment group).

Table B9. Baseline demographic characteristics of patients entering extension treatment phase for VIEW 1, VIEW 2 and pooled datasets

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
Entered 2	[redacted]											
Age (s)												
Mean (SD)												
Median												
Min; Max												
P-value a/ P-value b												
Sex (n[%])												
Male												
Female												
P-value c/ P-value d												
Race (n[%])												
White												
Black												
Asian												
American Indian												
Native Hawaiian												
Not Reported												
Multiple												
Ethnicity (n[%])												
Not Hisp / Latino												

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
Entered 2	[redacted]											
Hispanic / Latino												
Eye colour (n[%])												
Dark (blk / bwn)												
Other												
Missing												
Weight (kg)												
Mean (SD)												
Median												
Min; Max												
P-value a/ P-value b												
Height (cm)												
Mean (SD)												
Median												
Min; Max												
P-value a/ P-value b												
BMI (kg/m^2)												
Mean (SD)												
Median												
Min; Max												
P-value a												

= includes Black or African American; Hisp = Hispanic; Blk = black (eyes); bwn = brown (eye)s; BMI = Body Mass Index;

a P-value in aflibercept column pair-wise comparison versus ranibizumab and in total column all 4 treatment groups of analysis of variance, treatment group as fixed factor.

b P-value in aflibercept column pair-wise comparison versus ranibizumab and in total column all 4 treatment groups of analysis of variance, treatment group and region as fixed factors (VIEW 2 analysis only).

c P-value in aflibercept column pair-wise comparison versus ranibizumab (Chi-square test) and in total column all 4 treatment groups (Chi square-test).

d P-value in aflibercept column CMH-test region adjusted (pair-wise comparison versus ranibizumab) and in total column CMH-test region adjusted (all 4 treatment groups) (VIEW 2 analysis only).

Table B10. Baseline disease characteristics in the study eye for patients entering extension treatment phase for VIEW 1, VIEW 2 and pooled datasets

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
Entered 2	[redacted]											
BCVA (ETDRS letter score) n												
Mean (SD)												
Median												
Min; Max												
P-value a/ P-value b												
CRT (µm)												
n												
Mean (SD)												
Median												
Min; Max												
P-value a/ P-value b												
Total lesion size (mm^2)												
n												
Mean (SD)												
Median												
Min; Max												
P-value a/ P-value b												
Area of CNV (mm^2)												

n	[redacted]
Mean (SD)	
Median	
Min; Max	
P-value a/ P-value b	

a P-value in aflibercept column pair-wise comparison versus ranibizumab and in total column all 4 treatment groups of analysis of variance, treatment group as fixed factor.

b P-value in aflibercept column pair-wise comparison versus ranibizumab and in total column all 4 treatment groups of analysis of variance, treatment group and region as fixed factors (VIEW 2 analysis only).

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

The primary efficacy endpoint in both VIEW 1 and VIEW 2 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.

Visual function, or BCVA was assessed every 4 weeks, in the study eye and fellow eye, using the 4 metre ETDRS protocol (56). The VA examiner was masked to treatment and certified to ensure consistent measurement of BCVA.

Secondary endpoints were:

- Mean change from baseline in BCVA as measured by ETDRS letter score at week 52
- Proportion of patients gaining at least 15 letters of vision from baseline to week 52
- Change in total NEI VFQ-25(57) score from baseline to week 52
- Change in CNV area from baseline to week 52

The NEI VFQ-25 measured vision-related QOL and was administered at screening, weeks 12, 24, 36, 52, 72 and 96. The questionnaire was administered in a quiet room in the local language of the study participant. Total score and subscales (i.e. near activities, distance activities, and vision dependency) of the questionnaire were assessed. The possible range of the NEI VFQ-25 total score is between 0 (worst) and 100 (best). A change in NEI VFQ-25 total score of 4-6 points corresponds to a 15-letter gain in BCVA and is considered clinically meaningful in published studies.

Change in CNV area was assessed by Fundus photography and FA, undertaken at screening (baseline), weeks 24, 52, 72) and the End of Study visit. Fundoscopic examination evaluated the anatomical state of the retinal vasculature. Images were sent to an independent reading centre (IRC) for analysis and adjudication. Readers at the centre were ‘masked’ to treatment.

Reliability/ validity/ current use in clinical practice - All efficacy and safety parameters assessed in VIEW 1 and VIEW 2, and the methods to measure them are standard variables and methods in clinical studies, and in ophthalmic practice (30). They are widely used and generally recognised as valid, reliable, accurate and relevant. In addition, all evaluations were in accordance with Good Clinical Practice (GCP) to ensure safety of patients participating in research.

Other analyses

The primary and secondary efficacy variables were also analysed at Week 96 and were considered the most important variables for evaluation of persistence of efficacy.

For the analysis of the extension treatment period alone, the changes from Week 52 values to Week 96 (VIEW 1) and/or Week 96/100 (VIEW 2) for the primary and secondary endpoints as previously described, were analysed in the population of patients entering the 2nd year. The analysis population of “patients entering extension treatment phase” consists of all patients of the FAS, in whom the re-treatment criteria were assessed at Week 52 and/or a visit later than Week 52 is present and in addition that the patients has not withdrawn from study medication before Week 52.

The safety and tolerability of aflibercept when compared with ranibizumab was also a focus of study. Hence data on all AE were collected at each study visit, according to standard ICH definitions. The term AE was only used to refer to treatment-emergent AEs, i.e. AEs which occurred or worsened after the first administration of study drug. All AEs were assessed for seriousness, intensity, pattern, study drug action, drug treatment, causal relationship to study drug, and causal relationship to the injection procedure.

Other exploratory analyses included at week 52 and at week 96 included:

- Mean change from baseline in CRT as measured by OCT

- Proportions of patients requiring re-treatment within the first 12 weeks of the second phase of treatment
- Proportions of patients who gained ≥ 0 letters , ≥ 10 letters and >30 letters of vision from baseline on the ETDRS chart
- Proportions of patients losing > 15 letters or > 30 letters of vision (BCVA score of 15) from baseline using ETDRS protocol
- Proportions of patients showing complete resolution of FA leakage
- Mean change from baseline in scores for NEI VFQ-25 subscales (near activities, distance activities, vision dependency)
- Mean change from baseline in total lesion area and area of Fluorescein leakage as assessed by FA
- Change from baseline in greatest linear diameter of lesion on FA (VIEW 2 only)
- Proportion of patients with VA of 20/40 or better
- Proportion of patients with VA of 20/200 or worse
- Mean number of doses given in second phase of treatment
- Change in EQ-5D questionnaire scores from screening (VIEW 2 only)
- Change from baseline in classic CNV area

OCT data were read and interpreted by independent reading centres for each study. The VIEW 1 and VIEW 2 data presented in this submission reflects the centre subfield approach.

The EQ-5D questionnaire (58), administered at screening, weeks 52 and 96, provided feedback on patient's overall state of health (from the patient's perspective). It consists of five dimensions: Mobility, Self-care, Usual activities, Pain / discomfort, Anxiety/depression, with each dimension reflecting 'no health problems'(level 1), 'moderate health problems' and 'extreme health problems'(level 3).

Substudies

Patients participating in VIEW 1 and VIEW 2 studies had the option of participating in a pharmacogenetic substudy, to detect any alterations in genotypes associated with AMD, and also explore response to treatment with aflibercept or ranibizumab. In addition, VIEW 2 included a pharmacokinetics study to evaluate systemic exposure, and a nasomucosal

(ENT) substudy to evaluate potential naso-mucosal side-effects. Details of substudies are not discussed any further in this submission.

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

The primary endpoint analysis - non-inferiority of the intravitreal aflibercept treatment regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing < 15 ETDRS letters) - non-inferiority margins and definitions were established in discussion with the FDA, EMA and other regulatory authorities, to preserve constancy with the ranibizumab pivotal trials (51).

Analysis populations

The following populations for analysis were defined based on 52 week data and were used for all statistical analysis:

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 PPS was used for primary analysis (statistical evaluation of non-inferiority). For completeness, confidence intervals were constructed using the FAS. The FAS was used for all hypothesis tests of superiority. Analysis of superiority using the PPS was also done for supportive analyses. Efficacy analysis included patients as randomised. For the PPS,

at maximum one incorrect injection was allowed. Patients treated differently from ‘as randomised’ were listed.

Safety analysis was performed in the population of patients valid for safety. Safety analysis included patients as treated.

The FAS was partitioned into patients who completed the study (completers) and patients who did not complete the study (dropouts). A ‘completer’ was defined as a patient who received treatment for at least 36 weeks and had efficacy data (VA letter score) for at least 36 weeks during the primary phase of the study. For measures that were proportions of responders (i.e., vision gainers or vision maintainers) a patient who withdrew from the study before Week 36 due to treatment failure was considered a non-responder. Otherwise, the last observation carried forward (LOCF) approach was used to impute missing data for all efficacy variables. Baseline values were not carried forward. 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 (in FAS).

In both studies, the treatment groups were well balanced with regard to group sizes. Overall, the different analysis sets were similar with regard to sizes of the 4 treatment groups (see Table B11 and Table B12).

The vast majority of randomised patients were valid for both safety and efficacy analyses. The proportions of patients continuing treatment in the extension treatment phase were >90% and sufficient to assess long-term safety and the maintenance of the efficacy observed in the primary phase after the change in treatment regimen.

Table B11. VIEW 1: Definitions of analysis sets and patient validity / exclusion (all randomised patients)

Analysis set	Ranibizumab 0.5mg Q4 (N=306)	Aflibercept 2mg Q4 (N=304)	Aflibercept 0.5mg Q4 (N=304)	Aflibercept 2mg Q8 (N=303)	Total (N=1217)
Patients randomised	306	304	304	303	1217
SAF received at least one dose of study drug	304	304	304	303	1215
FAS received at least one dose of study drug and had baseline and ≥ 1 post-baseline assessment	304	304	301	301	1210
Patients entering extension treatment phase (as randomised) a	281	290	275	274	1120
Patients entering extension treatment phase (as treated) b	280	290	276	274	1120
Patients completing extension treatment phase	259	273	257	249	1038
Patients completing extension treatment phase under treatment with study medication c	257	273	256	249	1035

a Analysis population used for the analysis of efficacy data, exposure data, and demographic and other Baseline characteristics

b Analysis population used for the analysis of safety data

c The 2 patients who were randomised but not treated are excluded in this category

Table B12. VIEW 2: Definitions of analysis sets and patient validity / exclusion (all randomised patients)

Analysis set	Ranibizumab 0.5mg Q4 (N=303)	Aflibercept 2mg Q4 (N=313)	Aflibercept 0.5mg Q4 (N=311)	Aflibercept 2mg Q8 (N=313)	Total (N=1240)
Patients randomised	303	313	311	313	1240
SAF received at least one dose of study drug	291	309	297	307	1204
FAS received at least one dose of study drug and had baseline and ≥ 1 post-baseline assessment	291	309	296	306	1202
Patients entering extension treatment phase	276	281	274	284	1115
Patients completing extension treatment phase	260	256	245	264	1025
Patients completing extension treatment phase under treatment with study medication	256	256	243	262	1017

Primary hypothesis under investigation

The corresponding hypotheses for the binomially distributed primary efficacy variables are:

- null hypothesis Hi: pi ≤ pc-Δ versus the alternative hypothesis Ki: pi > pc-Δ
- Where pii is the success probability of the aflibercept treatment regimen i, pc is the success probability of the control group ranibizumab, and Δ is the pre-specified non-inferiority margin of 10 %.

Statistical test in primary analysis of primary outcome

The primary analysis was an evaluation of the non-inferiority of aflibercept to ranibizumab at week 52, which was part (comparison 1-3) of a conditional sequence involving 15 a-priori ordered hypotheses (comparisons 4-15 were for superiority testing using secondary endpoints):

- Comparison 1: aflibercept 2mg Q4 versus ranibizumab
- Comparison 2: aflibercept 0.5mg Q4 versus ranibizumab
- Comparison 3: aflibercept 2mg Q8 versus ranibizumab

The non-inferiority margin in individual VIEW 1 and VIEW 2 studies was 10%, and those margins were considered primary in the pooled analysis. Based upon feedback from regulatory agencies the analysis of data pooled from both studies is discussed in an exploratory fashion using a non-inferiority margin of 7% as well as 5%.

The final statistical analysis of the 52-week data was performed as soon as the data of all patients were available and cleaned,. While the study was unmasked by the statistical analyst and the study statistician, investigators, patients, study monitors and data manager remained masked to the individual patient treatment assignments.

Power calculation and sample size

Assuming that 90% of patients treated with 0.5 mg ranibizumab or any aflibercept dose would maintain vision (defined as losing fewer than 15 letters of visual acuity) at Week 52 compared to baseline, a two-sided alpha level of 0.049 (0.05 for VIEW 2), and a non-inferiority margin to be 10%, the sample size estimation resulted in 191 (191 for VIEW 2) patients per treatment group. Assuming a dropout rate of 30% (a high dropout rate is assumed because of the availability of competing, approved therapies), enrolment of 300 patients per group was calculated to provide adequate power to achieve the studies objectives under the stated assumptions.

Supportive analyses of primary outcome

As supportive analysis of the primary efficacy analysis, two-sided 95% Cochran-Mantel-Haenszel intervals adjusted (for region, VIEW 2) were calculated for each of the pair-wise primary efficacy comparisons. To check appropriateness of the calculation of the Mantel-Haenszel weighted confidence intervals, a Breslow-day test was performed to test the homogeneity of odds ratios across geographic regions (VIEW 2). If the test indicated a treatment by geographic region interaction (i.e. $p < 0.05$), exploratory analyses were done to find the source of the interaction.

To identify important factors to the maintenance of vision a stepwise logistic regression was performed with maintaining vision at week 52 as dependent no/yes-variable and age, sex, baseline ETDRS letter score, baseline retinal thickness, baseline CNV area, baseline NEI VFQ-25 total score, baseline EQ-5D score, type of CNV (classic, classic and occult, occult) and treatment group as independent factors (with $p \leq 0.05$ as entry as well as removal criterion for an independent factor to be added or to be deleted from the model).

As supportive analysis a meta-analysis of the pooled data of VIEW 1 and VIEW 2 studies with regard to the primary efficacy variable was also performed.

Further supportive analyses involved the repetition of the primary analyses in the FAS population.

Statistical analysis – secondary and other endpoints

If all three aflibercept groups were shown to be non-inferior to ranibizumab on the primary endpoint, additional comparisons of aflibercept groups to ranibizumab were made using a hierarchical sequence analyses with respect to the secondary endpoints testing for superiority of aflibercept over ranibizumab (mean change in BCVA, then proportion of patients who gain ≥ 15 letters, then mean change in total NEI-VFQ-25 score). As per the primary analysis, the comparison between 2mg Q4 and ranibizumab was tested first. If these analyses were superior, the 0.5mg Q4 dose was tested, and next the 2mg Q8 dose vs. ranibizumab. If superiority was demonstrated for each dose of aflibercept in the above-listed secondary endpoints, each dose was compared with ranibizumab with respect to 'mean change in CNV lesion area from baseline to week 52. The secondary efficacy analysis was conducted in the FAS population.

Table B13. Statistical analysis of secondary endpoints

	VIEW 1	VIEW 2
Analysis of proportions	Pearson's Chi-Square test for the pair-wise comparisons of aflibercept 2mg Q4, 0.5mg Q4, and 2mg Q8 to ranibizumab 0.5mg Q4	Cochran-Mantel-Haenszel tests, adjusted for region, including a Breslow-Day test for homogeneity of odds ratios across regions. A two-sided 95% Cochran-Mantel-Haenszel intervals adjusted for region was calculated
Analysis of continuous variables	Analysis of covariance (ANCOVA) with a main effects model with baseline measure as covariate and treatment as fixed factor.	Two-way analysis of covariance (ANCOVA) main effects model with baseline measure as a covariate and treatment group and region as fixed factors
Pair-wise comparisons of each aflibercept group versus ranibizumab	By corresponding CONTRAST statements and a point-estimate, as well as calculation of two-sided 95% confidence intervals for the treatment difference of each aflibercept treatment group minus ranibizumab	

Additional Efficacy Analyses

All primary and secondary endpoint analyses performed on the 52 week data were repeated for the data covering the whole 96 week study period. These were considered the most important variables for evaluation of persistence of efficacy. All analyses were exploratory and analysed descriptively.

Visual Acuity data at Weeks 52 and 96 were to be used to classify patients who gained vision (i.e. 15 letters or more gained), lost vision (i.e. 15 letters or more lost) and patients with stable vision (all others) with the descriptive analysis done according to dose group.

An assessment of 'Duration of treatment effect' during the extension treatment phase was planned through a review of the dosing data, with the aim of identifying characteristics of patients requiring dosing more often than the protocol specified maximum interval of 12 weeks.

Pooled analysis

As well as separate analysis of VIEW 1 and VIEW 2 data, a pooled analysis of the primary and secondary endpoints was planned. Additional analyses of the pooled data regarding study drug exposure were made for the dosing subgroups using the quartiles of the numbers of injections in the second phase. This analysis was based on the population of patients who completed the study under treatment with study medication.

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Subgroup analyses

Pre-planned subgroup analyses by age, gender, race, renal function, hepatic impairment, baseline VA, lesion size and baseline CNV type were performed for the following variables at Week 52:

- Proportion of patients who maintained vision (<15 letters lost)(PPS and FAS)
- Change from baseline in BCVA at week 52 (FAS)
- Proportion of patients who gain at least 15 letters of vision at week 52 (FAS)
- Change from baseline in total NEI VFQ-25 score (FAS)
- Change from baseline in CNV area at week 52 (FAS)

- Change from baseline in CRT by OCT at week 52 (FAS)

Also, in VIEW 2, due to the number of countries participating, centres were pooled by 8 geographic regions for subgroup analyses. The UK was grouped with North Western Europe, Israel and Australia.

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure B3. Patient disposition for VIEW 1

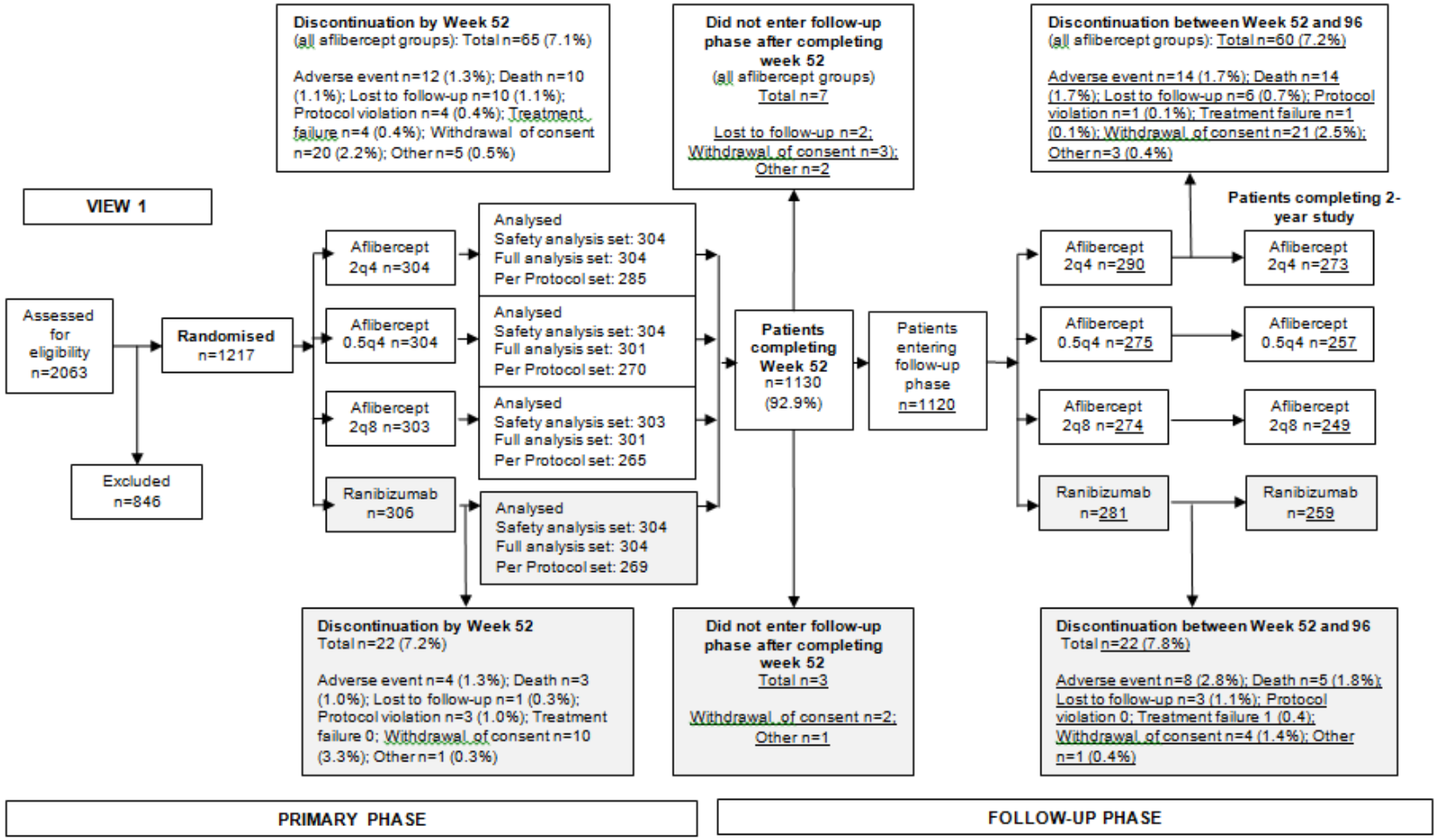


Figure B4. Patient disposition for VIEW 2

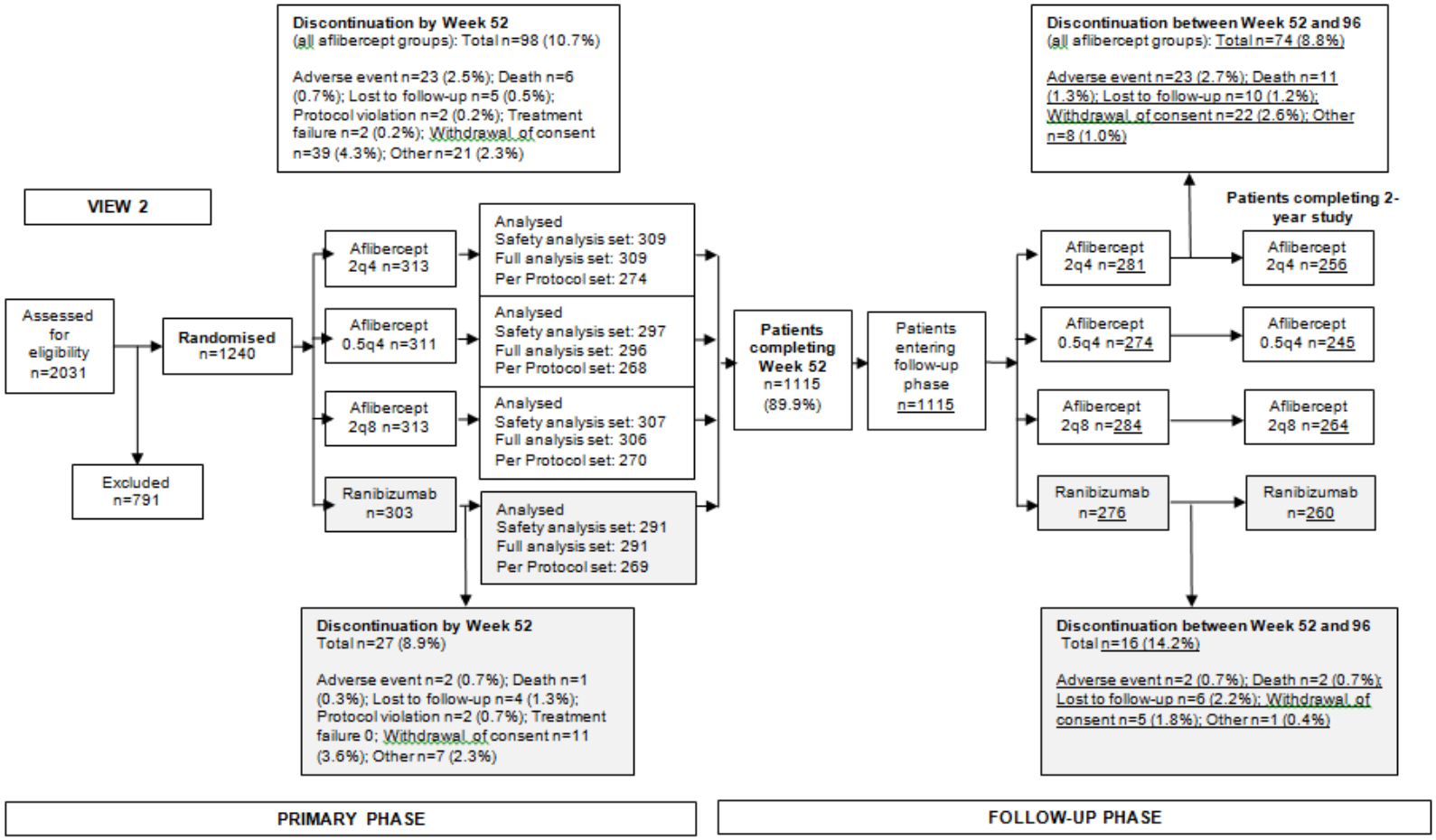
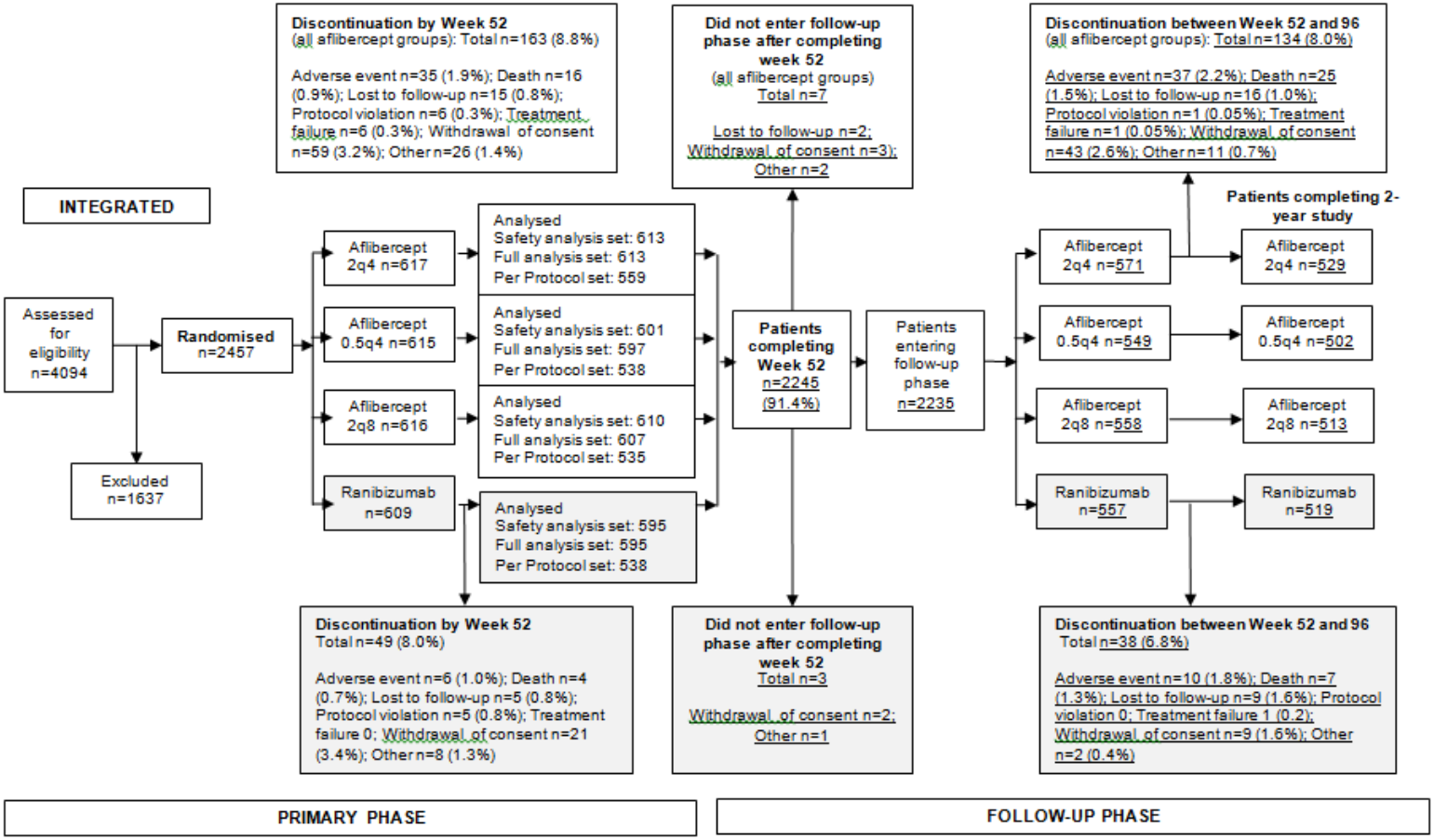


Figure B5. Patient disposition for the integrated analysis of VIEW 1 and VIEW 2



6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A

suggested format for the quality assessment results is shown below.

Table B14. Quality assessment of RCTs

	VIEW 1	VIEW 2
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No Full analysis set used as a sensitivity analysis (includes all randomised patients who received any study drug and had a baseline and at least one post-baseline assessment)	

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the information specified in the submission template should be provided.

Primary efficacy endpoint

Proportion of patients who maintained vision (losing <15 ETDRS letters from baseline)

At Week 52

In both studies, the proportion of patients maintaining vision was similar among treatment groups in the PPS and FAS and all aflibercept groups were statistically non-inferior compared with ranibizumab every 4 weeks.

VIEW 1 - The proportion of patients in the PPS (n=1089) maintaining vision at week 52 was >94% in all treatment groups. It was the highest in the aflibercept 0.5mg Q4 group (95.9%) followed by the 2mg Q4 and 2mg Q8 groups (95.1%) and the lowest in the comparator (ranibizumab) group (94.4%) (see Table B15). Non-inferiority to ranibizumab (as per primary endpoint statistical plan) was therefore demonstrated for all aflibercept groups because the upper limits of the confidence intervals for the differences in proportions between the respective aflibercept groups and ranibizumab were consistently below the pre-specified boundary of 10% and the point estimates of the differences in means favoured aflibercept in all dose groups (see Table B15).

The corresponding proportions of patients in the FAS maintaining vision at week 52 were 95.1% (aflibercept 2mg Q4), 95.0% (0.5 mg Q4), 94.4% (2mg Q8) and 93.8% (ranibizumab 0.5mg Q4). The non-inferiority to ranibizumab was confirmed in this supportive analysis and further confirmed in sensitivity analyses.

VIEW 2 - The proportion of patients in the PPS (n=1081) maintaining vision at week 52 was >94% in all treatment groups. It was the highest in the aflibercept 0.5mg Q4 group (96.3%) followed by the aflibercept 2mg Q4 and 2mg Q8 groups (95.6%) and the lowest in the comparator (ranibizumab 0.5mg Q4) group (94.4%) (see Table B15). Non-inferiority to ranibizumab was demonstrated for all aflibercept groups.

The corresponding proportions of patients in the FAS maintaining vision at week 52 were 94.5% (aflibercept 2mg Q4), 95.3% (0.5mg Q4), 95.4% (2mg Q8) and 94.8% (ranibizumab 0.5mg Q4). The non-inferiority to ranibizumab was confirmed in this supportive analysis, with adjustment for region, and further confirmed in sensitivity analyses.

The aflibercept regimens also met the pre-specified 5% margin for clinical equivalence compared with ranibizumab in each VIEW study. Results of multiple imputation analyses were consistent with those using the LOCF.

POOLED – All aflibercept regimens also met the pre-specified 7% non-inferiority margin in the pre-specified integrated analysis at week 52 combining both VIEW studies.

At Week 96

In both studies, the proportion of patients maintaining vision at week 96 was still ≥90% in all treatment groups, with non-inferiority between all aflibercept groups and ranibizumab still demonstrated (see Table B15). In VIEW 2, homogeneity testing of odds ratios across geographical regions by a Breslow-Day test did not indicate any relevant regional differences (all p-values >0.4). Sensitivity analysis yielded consistent results. The largest differences between the two studies were the treatment differences of the pairwise comparisons between ranibizumab 0.5mg Q4 and aflibercept 2mg Q4 in VIEW 2. Results of corresponding analyses using observed values only were more comparable between the studies.

POOLED – Results from the integrated analysis regarding the maintenance of vision over 2 years, reflect results seen in the single study analyses. Homogeneity testing of the results of the two studies by a Breslow-Day test did not indicate any relevant differences between the respective results of the studies. The results of the integrated analysis confirm the conclusion from the individual studies that, overall, the 4 treatment groups behaved similarly with respect to maintenance of vision, even with more prolonged intervals between treatment injections (see Table B15).

Table B15. Summary of results for the primary endpoint (proportion of patients maintaining vision after 52 and 96 weeks)

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
Week 52 (PPS)	N=269	N=269	N=538	N=285	N=274	N=559	N=270	N=268	N=538	N=265	N=270	N=535
Patients maintaining vision n (%)[1]	254 (94.4)	254 (94.4)	508 (94.42)	271 (95.1)	262 (95.6)	533 (95.4)	259 (95.9)	258 (96.3)	517 (96.1)	252 (95.1)	258 (95.6)	510 (95.3)
Difference (%) (95.1%CI) [2][3]				-0.7 (-4.4, 3.1)	-1.2 (-4.86, 2.46)	-0.9 (-3.5, 1.7)	-1.5 (-5.1, 2.1)	-1.84 (-5.40, 1.71)	-1.7 (-4.2, 0.9)	-0.7 (-4.5, 3.1)	-1.13 (-4.81, 2.55)	-0.9 (-3.5, 1.7)
Week 96 (FAS)	N=304	N=291	N=595	N=304	N=309	N=613	N=301	N=296	N=597	N=301	N=306	N=607
Patients maintaining vision n (%)[1]	273 (89.8)	272 (93.5)	545 (91.6)	283 (93.1)	282 (91.3)	565 (92.2)	271 (90.0)	275 (92.9)	546 (91.5)	275 (91.4)	286 (93.5)	561 (92.42)
Difference (%) (95.1%CI)[2][3]				-3.3 (-7.7, 1.2)	2.2 (-2.0, 6.5)	-0.6 (-3.6, 2.5)	-0.2 (-5.1, 4.6)	0.6 (-3.5, 4.6)	0.2 (-3.0, 3.3)	-1.6 (-6.2, 3.1)	0.0 (-4.0, 4.0)	-0.8 (-3.8, 2.3)
P-value (Breslow-Day test)[4]						0.08			0.79			0.67

1.Last observation carried forward (Baseline values were not carried forward)

2.Difference is ranibizumab minus aflibercept; CI=confidence interval, was calculated using a normal approximation

3.For pooled analysis only: Difference is ranibizumab minus aflibercept; CI=Cochran-Mantel-Haenszel confidence interval adjusted by study for each subgroup and adjusted by study and subgroup for overall CI

4.Testing the homogeneity of odds ratios across studies

Subgroup analyses of primary endpoint

Efficacy results in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, lesion type, lesion size) in each study and in the combined analysis were consistent with the results in the overall populations.

Secondary endpoints - Mean change in BCVA as measured by ETDRS letter score from baseline at Week 52 and Week 96.

At Week 52

In both studies, mean BCVA was comparable among treatment groups, and was seen as early as Week 1 in all treatment groups, with the steepest increase in mean ETDRS letter score being seen within the first 12 weeks.

VIEW 1 – By week 52, mean ETDRS letter score had increased in all treatment groups by approximately 7-11 letters. On the basis of the hierarchical testing sequence, the change from baseline in BCVA for the aflibercept 2mg Q4 group was significantly greater than for the ranibizumab 0.5mg Q4 group (LS mean difference = 3.15; 95.1% CI = 0.92 to 5.37; p = 0.0054). There were no meaningful treatment differences between the other aflibercept groups and the ranibizumab group (RQ4).

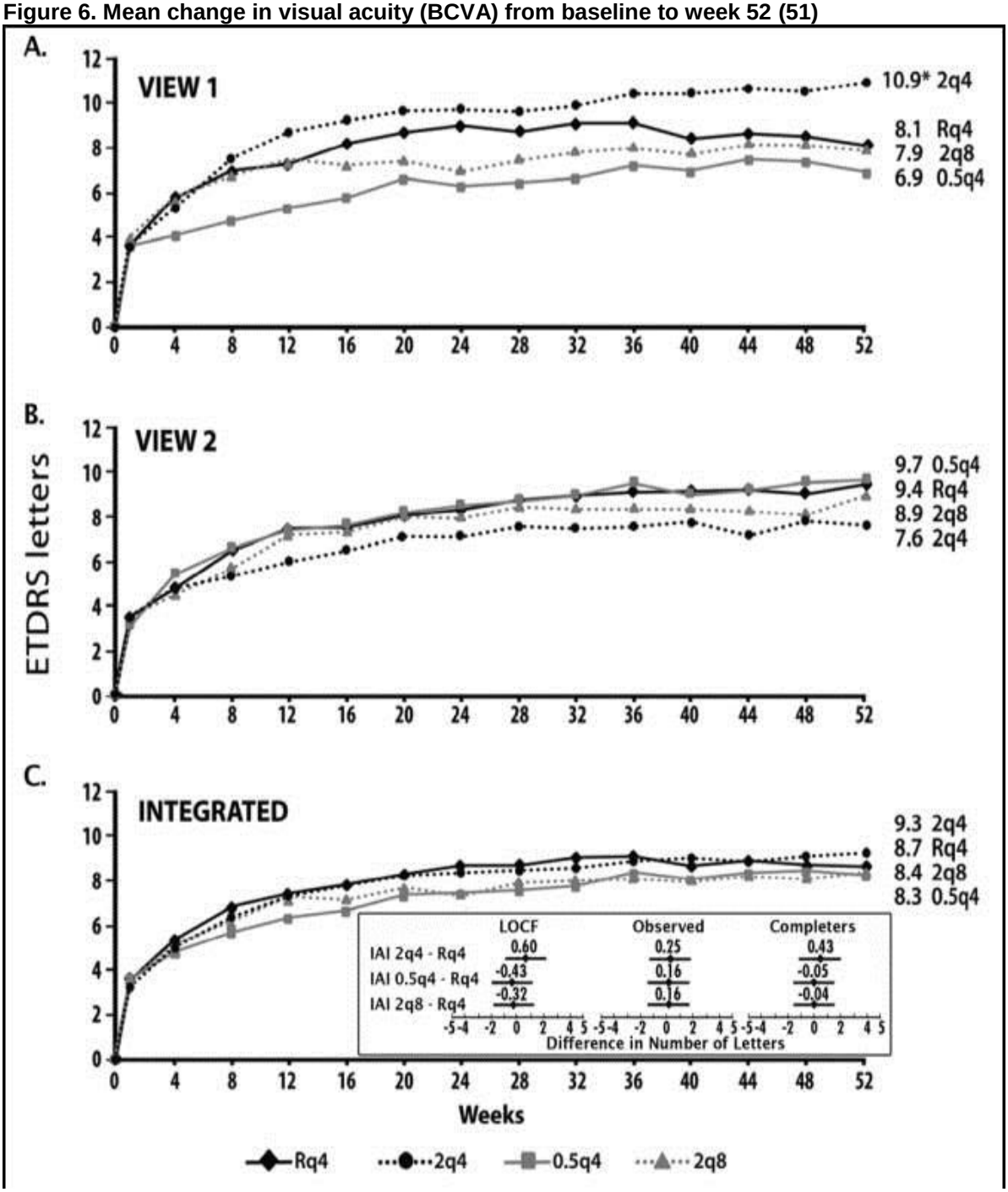
VIEW 2 - By week 52, mean ETDRS letter score had increased in all treatment groups by approximately 8 - 10 letters. Using the LSmeans from the ANCOVA (main effect model), the differences between the 3 aflibercept groups and the ranibizumab group were numerically slightly in favour of the ranibizumab treatment (maximum difference: 1.95 letters in the comparison of aflibercept 2mg Q4 vs. ranibizumab 0.5mgQ4). However, the 95% CIs for the treatment differences consistently included zero and all p-values were >0.05.

The conditional sequence of statistical hypothesis tests for superiority of aflibercept was interrupted at this point in the analysis for VIEW 2.

POOLED - Regardless of whether the analysis was by LOCF, by multiple imputations, by assessing completers, or by using actual observed data, intravitreal aflibercept dosed every 2 months achieved a mean VA score

within 0.3 letters of monthly ranibizumab in the integrated analysis, with a CI of less than 2 letters (see Figure 6).

Figure 6. Mean change in visual acuity (BCVA) from baseline to week 52 (51)



The panel inset (integrated analysis) shows the difference in VA between each IVT aflibercept arm and ranibizumab (least-square mean with 95% confidence interval [CI]) at week 52, using 3 different analyses: by LOCF,

using observed case data, and by assessing completers. Rq4=0.5 mg ranibizumab monthly; 0.5q4=0.5 mg aflibercept monthly; 2q4= 2 mg aflibercept monthly; 2q8= 2 mg aflibercept every 2 months after 3 initial monthly doses.

At Week 96

In both studies, the improvements observed during the primary phase were largely maintained during the extension phase in all treatment groups. Overall, the mean ETDRS letter score decreased during the extension phase by approximately 1-2 letters in each group.

VIEW 1 – At week 96, the improvement in mean ETDRS letter score still amounted to [redacted] letters in all groups - highest in the aflibercept 2mg Q4 group ([redacted] ± [redacted] letters) and lowest in the aflibercept 0.5mg Q4 group ([redacted] letters). The difference in favour of the aflibercept 2mg Q4 over the ranibizumab 0.5mg Q4 group was maintained at week 96.

VIEW 2 – By Week 96, the improvement in mean ETDRS score still amounted to [redacted] letters in the aflibercept 0.5mg Q4, 2mg Q8 and ranibizumab 0.5mg Q4 groups. In the aflibercept 2mg Q4 group, the mean change from baseline was [redacted] letters. Notable this was also the group showing the lowest improvement during year 1.

Minor differences were observed for the change in ETDRS letter score from baseline to Week 96 (see Table B16). The disparate 2mg Q4 results between studies seem to reflect the range of variability within the data. Consistent with this interpretation, patients treated with lower doses of aflibercept or with overall fewer aflibercept injections had numerically greater increases in BCVA over the 96 weeks of the study than did patients in the 2mg Q4 group.

Pooling the data from VIEW 1 and VIEW 2, confirms the impression from the individual studies that, overall, the 4 treatment groups behaved similarly over 96 weeks with respect to change in ETDRS letter score.

Figure B7. Mean change in visual acuity at the end of 96 weeks (integrated data)

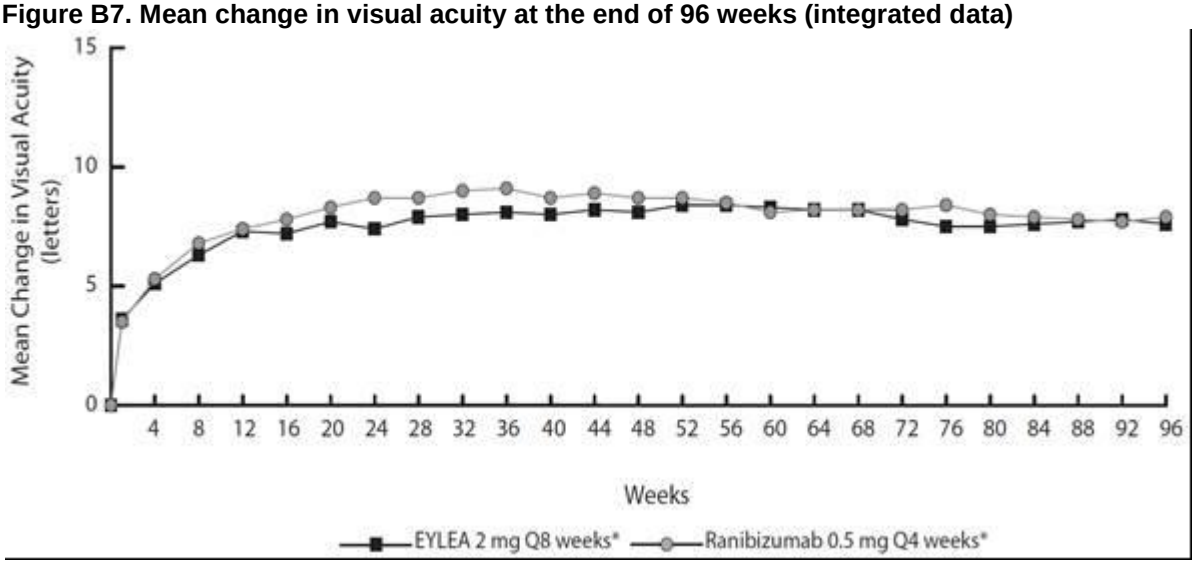


Table B16. Change from baseline to Week 52 and Week 96 in ETDRS letter score in the study eye (FAS)

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
	N=304	N=291	N=595	N=304	N=309	N=613	N=301	N=296	N=597	N=301	N=306	N=607
Baseline												
Mean (SD)	54.0 (13.4)	53.8 (13.5)	53.9 (13.4)	55.2 (13.2)	52.8 (13.9)	54.0 (13.6)	55.6 (13.1)	51.6 (14.2)	53.6 (13.8)	55.7 (12.8)	51.6 (13.9)	53.6 (13.5)
Median	56.0	56.0	56.0	58.0	55.0	56.0	58.0	54.0	55.0	56.0	52.0	55.0
Min: Max	[10; 78]	[10; 83]	[10; 83]	[11; 81]	[10; 79]	[10; 81]	[18; 85]	[12; 79]	[12; 85]	[15; 83]	[16; 76]	[15; 83]
Week 52												
Mean (SD)	62.1 (17.7)	63.1 (16.6)		66.1 (16.2)	60.4 (18.3)		62.4 (16.5)	61.3 (17.8)		63.6 (16.9)	60.5 (17.5)	
Median	67.0	67.0		71.0	65.0		65.0	65.0		68.0	64.0	
Min: Max	[0; 88]	[8; 90]		[8; 98]	[4; 92]		[11; 89]	[0; 89]		[11; 93]	[7; 93]	
Week 52 (change from baseline)												
Mean (SD)	8.1 (15.3)	9.4 (13.5)	8.74(NR)	10.9 (13.8)	7.6 (12.6)	9.3 (NR)	6.9 (13.4)	9.7 (14.1)	8.3 (NR)	7.9 (15)	8.9 (14.4)	8.4 (NR)
Median	9.0	10.0		11.0	8.0		7.0	10.0		9.0	9.0	
Min: Max	[-75.0; 56.0]	[-47; 56]		[-37.0; 61.0]	[-37; 42]		[-46.0; 56.0]	[-52; 45]		[-48; 54.0]	[-63; 50]	
LS means difference[1]				3.15	-1.95	0.60	-0.80	-0.06	-0.43	0.26	-0.90	-0.32
95.1% CI for difference				(0.92, 5.37)	(-4.10, 0.20)	(-0.94, 2.14)	(-3.03, 1.43)	(-2.24, 2.12)	(-1.99, 1.12)	(-1.97, 2.49)	(-3.06, 1.26)	(-1.87, 1.23)
				0.0054	0.076	(NR)	0.4793	0.956	(NR)	0.8179	0.413	(NR)

P-value vs. RQ4 [2]												
[redacted]												

[1] Difference is aflibercept minus ranibizumab; CI = confidence interval, was calculated using normal approximation [2] ANCOVA main

Proportion of patients who gained at least 15 letters of BCVA from baseline to Week 52 and to Week 96.

In both studies, the sustained efficacy of all aflibercept dose groups with regard to BCVA was also demonstrated in the proportions of patients with a vision gain of ≥ 15 letters. Irrespective of the treatment, the proportion of patients with a vision gain of ≥ 15 letters at Week 52 remained nearly constant by the end of 96 weeks.

At Week 52

VIEW 1 – By Week 52, 37.5% of the patients in the aflibercept 2mg Q4 group, 30.9% in the ranibizumab 0.5mg Q4 group, 30.6% in the aflibercept 2mg Q8 group and 24.9% in the 0.5mg Q4 group had gained 15 letters or more in the ETDRS letter score. The proportion of patients who experienced a gain in vision of ≥ 15 letters at week 52 was slightly higher in the aflibercept 2mg Q4 group compared to the ranibizumab 0.5mg Q4 group (114 [37.5%] versus 94 [30.9%]), however pairwise comparisons between the different aflibercept groups and ranibizumab group did not show any meaningful treatment differences. The conditional sequence of statistical hypothesis tests for superiority of aflibercept was interrupted at this point in the analysis for VIEW 1.

VIEW 2 – By Week 52, 34.0% patients in the ranibizumab 0.5mg Q4 group, 29.4% in the aflibercept 2mg Q4 group, 34.8% in the 0.5mg Q4 group and 31.4% in the 2mg Q8 group had gained 15 letters or more in the ETDRS letter score, with no meaningful treatment differences.

At Week 96

VIEW 1 –.The effect was largely maintained through Week 96, when still [redacted]% patients in the aflibercept 2mg Q4 group, [redacted]% in the 2mg Q8 group, [redacted]% in the ranibizumab 0.5mg Q4 group and [redacted]% in the aflibercept 0.5mg Q4 group had a vision gain of ≥ 15 letters compared to baseline. No meaningful treatment differences were noted in the pairwise comparisons between 2mg aflibercept treatment groups and ranibizumab, however, the

comparison of ranibizumab and the 0.5mg Q4 aflibercept group was statistically in favour of ranibizumab treatment. A similar trend, although less pronounced, was already observed during the primary phase.

VIEW 2 – As in VIEW 1, the effect was largely maintained through Week 96, with [redacted]% patients (ranibizumab 0.5mgQ4), [redacted]% in the aflibercept 2mg Q4 group, [redacted]% in the 0.5mg Q4 group and [redacted]% in the 2mg Q8 group still having vision gain of ≥ 15 letters compared to baseline.

Integrated analysis – As already noted in the single studies the proportions of patients gaining ≥ 15 letters of vision up to Week 96 were also comparable among treatment groups in the integrated analysis of pooled data. Homogeneity testing of the results across the studies by a Breslow-Day test, however, indicated a difference for the individual results of the pairwise comparisons of ranibizumab 0.5mg Q4 and aflibercept 2mg Q4. In VIEW 1, the proportion of patients gaining 15 letters or more was higher in the aflibercept 2mg Q4 group than in the ranibizumab 0.5mg Q4 group, which was the reverse in VIEW 2 (see Table B17). As a consequence, the respective proportions of patients were nearly identical in all treatment groups in the integrated analysis.

Table B17. Proportion of patients gaining ≥ 15 letters of vision in the ETDRS letter score in the study eye at Week 52 and at Week 96 (FAS)

	Ranibizumab 0.5mh Q4			Aflibercept 2mg Q4			Aflibercept 0.5mg Q4			Aflibercept 2mg Q8		
	VIEW 1 N=304	VIEW 2 N=291	Pooled N=595	VIEW 1 N=304	VIEW 2 N=309	Pooled N=613	VIEW 1 N=301	VIEW 2 N=296	Pooled N=597	VIEW 1 N=301	VIEW 2 N=306	Pooled N=607
Patients gaining ≥15 letters at Week 52 (n[%])	94 (30.9)	99 (34.0)	193 (32.44)	114 (37.5)	91 (29.4)	205 (33.4)	75 (24.9)	103 (34.8)	178 (29.8)	92 (30.6)	96 (31.4)	NR (30.97)
Difference (%)[1]				6.58	-4.57	1.0	-6	0.78	2.7	-0.36	-2.65	-1.5
95.1% CI				(-0.98, 14.14)	(-12.02, 2.88)	(-4.3, 6.3)	(-13.17, 1.16)	(-6.91, 8.46)	(-7.9, 2.6)	(-7.74, 7.03)	(-10.18, 4.88)	(-6.8, 3.8)
P-value vs. RQ4 [2]				0.1042	0.229	NR	0.1037	0.843	NR	0.93	0.490	NR
Patients gaining ≥15 letters at Week 96 (n[%])			188 (31.6)			191 (31.2)			168 (28.1)			
Difference (%)[1][3]												
95.1% CI												
P-value (Breslow-Day test)[4]												

[1] Difference is aflibercept minus ranibizumab; CI = confidence interval, was calculated using normal approximation

[2] Pearson's Chi-Squared Test (2-sided)

[3] Pooled analysis only: Mantel-Haenszel estimate for the difference is aflibercept minus ranibizumab. CI =confidence interval was calculated using normal approximation for each study and Cochran-Mantel-Haenszel confidence interval adjusted by study for pooled data

[4] Testing the homogeneity of odds ratios across studies

Change in NEI VFQ-25 total score from baseline

In both studies, vision-related QoL improved in parallel to vision improvement during the primary phase, and was maintained during the extension phase of the studies. The changes were nearly identical in all treatment groups.

At Week 52

VIEW 1 – At week 52, the mean NEI VFQ-25 total score had improved in all groups (from 69-71 points at baseline) by 4-6 points. This level of improvement is generally deemed to be clinically relevant. The rank order of the groups for NEI VFQ-25 was consistent with the BCVA data, with the greatest change from baseline in the 2mg Q4 aflibercept group.

VIEW 2 – The mean NEI VFQ-25 total score had improved in all groups (from 70-74 points at baseline) by 5-6 points. A difference in favour of the ranibizumab 0.5mg Q4 treatment was observed with a mean (95% CI of difference) of -2.79 (-4.89, -0.69) when compared with the 2mg Q4 aflibercept treatment group. The other aflibercept groups did not appear to be different from ranibizumab 0.5mg Q4.

At Week 96

In both studies - The improvements in NEI VFQ-25 total score and the absence of any clinically meaningful treatment differences between the aflibercept groups and the ranibizumab-treated group were further confirmed in the analysis of the whole 96 week treatment period. In all treatment groups, the mean NEI VFQ-25 total score had improved from baseline to week 96 by [redacted] points. In VIEW 2 – The difference between ranibizumab 0.5mgQ4 and aflibercept 2mg Q4 persisted in the 96 week data.

In the integrated analysis, the mean total score improved during the entire study period in all treatment groups by a clinically meaningful extent by approximately [redacted] points. In all treatment groups the improvements had already occurred during the first 52 weeks of treatment and were largely maintained during the extension phase.

Table B18. Change from baseline to Week 52 and Week 96 in NEI VFQ-25 total score (FAS)

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
	N=304	N=291	N=595	N=304	N=309	N=613	N=301	N=296	N=597	N=301	N=306	N=607
Baseline (n)	303	291	594	300	309	609	297	295	592	293	306	599
Mean (SD)	71.8 (17.2)	72.9 (19.1)	72.4 (18.1)	70.4 (16.6)	70.3 (19.4)	70.3 (18.1)	71.1 (17.8)	74.0 (18.2)	72.6 (18.0)	69.6 (16.8)	71.3 (19.1)	70.5 (18.0)
Median	74.8	78.6	76.7	72.1	74.8	73.6	74.5	78.4	76.4	71.6	73.7	72.6
Min: Max	[25; 99]	[12; 98]	[12; 99]	[25; 99]	[8; 98]	[8; 99]	[7; 100]	[15; 98]	[7; 100]	[21; 97]	[19; 98]	[19; 98]
Week 52 (n)	300	287		302	304		292	291		299	299	
Mean (SD)	76.8 (16.)	79.5 (16,7)		77.0 (16.92)	74.6 (19.2)		75.4 (17.37)	79.1 (16.8)		74.6 (17.68)	76.4 (19.3)	
Median	79.7	84.3		80.4	80.4		77.8	84.1		78.2	81.8	
Min: Max	[25.7; 100.0]	[24; 100]		[18.5; 100.0]	[8; 99]		[20.3; 99.4]	[15; 100]		[15.7; 100.0]	[10; 100]	
Week 52 (change from baseline) (n)	300	287		298	304		289	290		292	299	
Mean (SD)	4.9 (14.0)	6.3 (14.8)	5.6 (NR)	6.7 (13.5)	4.5 (15.0)	5.6 (NR)	4.5 (11.9)	5.1 (13.7)	4.8 (NR)	5.1 (14.7)	4.9 (14.7)	5.0 (NR)
Median	3.2	4.7		5.0	3.2		3.9	3.1		3.8	2.8	
Min: Max	[-34.3; 59.2]	[-33; 54]		[-45.9; 52.5]	[-64; 49]		[-33.3; 43.5]	[-57; 63]		[-32.0; 50.5]	[-47; 62]	
LSmeans difference[1]				1.28	-2.79	0.75	-0.67	-0.93	-0.79	-0.60	-1.95	-1.26
95.1% CI for difference				(-0.73, 3.28)	(-4.90, 0.68)	(-2.2, 0.71)	(-2.69, 1.35)	(-3.07, 1.20)	(-2.26, 0.67)	(-2.61, 1.42)	(-4.07, 0.17)	(2.72, 0.2)
				0.2090	0.010		0.5128	0.392	NR	0.5579	0.072	

P-value vs. RQ4						NR						(NR)
Week 96 (n)	[redacted]											
Mean (SD)												
Median												
Min: Max												
Week 96 (change from baseline) (n)												
Mean (SD)												
Median												
Min: Max												
LSmeans difference[1]												
95.1% CI for difference												

[1] Difference is aflibercept minus ranibizumab; CI = confidence interval, was calculated using normal approximation. ANCOVA main effect model.

Change in CNV area from baseline

In both studies, all groups demonstrated a comparable decrease in the secondary end point of change in area of active CNV. The decrease in mean CNV area achieved during the primary phase of treatment was largely maintained through the extension phase in all treatment groups.

At Week 52

VIEW 1 – By week 52, mean CNV area had decreased from approximately 6.5 mm^2 to 2-3mm^2 in all groups. The mean decrease was least in the aflibercept 0.5mg Q4 group (-3.5 ± 5.3mm^2) and greatest in the 2mg Q4 group (-4.6 ± 5.5mm^2). Pairwise comparisons of the 0.5mg Q4 and 2mg Q8 groups with ranibizumab 0.5mg Q4, with regard to changes from baseline, indicated treatment differences in favour of the ranibizumab Q4 treatment.

VIEW 2 – By the Week 52 visit, mean CNV area had decreased from approximately > 7.5 mm^2 to < 3mm^2 in all groups. The mean decrease was least in the ranibizumab 0.5mg Q4 group (-4.2 ± 6.1mm^2) and greatest in the aflibercept 2mg Q4 group (-6.0 ± 6.1mm^2). Using LSmeans from the exploratory ANCOVA (main effect model), the difference between these two groups was -1.18mm^2 (95% CI: -1.98 to -0.38mm^2). No meaningful differences between other groups were detected.

At Week 96

VIEW 1 – Up to Week 96, the decreases in mean CNV area observed during the primary phase were roughly maintained in all groups. Pairwise comparisons of the aflibercept 0.5mg Q4 and 2mg Q8 groups with ranibizumab 0.5mg Q4, with regard to changes from baseline, indicated treatment differences in favour of the ranibizumab 0.5mg Q4 treatment. Treatment differences in favour of ranibizumab, when compared with the 0.5mg Q4 or 2mg Q8 aflibercept treatment groups, were observed, similarly to the primary treatment phase.

VIEW 2 – Up to Week 96, the decreases in mean CNV area observed during the primary phase were maintained in all groups and the magnitude of the difference between the aflibercept 2mg Q4 and ranibizumab 0.5mg Q4 groups narrowed.

In the ‘Integrated analysis’, analysis of the pooled data showed a reduction in mean CNV area from baseline to Week 96/100 by [redacted]% in all treatment groups. The seeming difference between the ranibizumab 0.5mgQ4 and the aflibercept 0.5mg Q4 and 2mg Q8 groups, respectively, with regard to these changes, was no longer detectable in this analysis.

Subgroup analyses of secondary efficacy endpoints – results were generally qualitatively consistent with results seen in the overall population.

Table B19. Change from baseline to Week 52 and Week 96 in CNV area (FAS)

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
	N=304	N=291	N=595	N=304	N=309	N=613	N=301	N=296	N=597	N=301	N=306	N=607
Baseline (n)	298	291	589	302	308	610	300	296	596	300	305	605
Mean (SD)	6.53 (5.2)	7.59 (5.3)	7.049 (5.316)	6.59 (5.1)	8.25 (5.8)	7.426 (5.485)	6.49 (4.5)	7.70 (5.3)	7.089 (4.905)	6.57 (5.1)	7.75 (5.5)	7.165 (5,359)
Median	5.2	6.410	5.750	5.6	6.670	6.095	5.9	6.825	6.210	5.4	6.360	5,870
Min: Max	[0.1; 29]	[0.09; 28.79]	[0.09; 28.97]	[0.2; 29.6]	[0.12; 26.86]	[0.12; 29.60]	[0.0; 24.9]	[0.07; 26.57]	[0.00; 26.57]	[0.0; 32.6]	[0.00; 24.85]	[0.00; 32.63]
Week 52 (n)	292	278		298	295		288	287		286	290	
Mean (SD)	2.2 (4.06)	3.198 (4.977)		1.9 (4.21)	2.339 (5.035)		3.0 (4.82)	3.497 (5.903)		3.1 (5.13)	2.597 (4.860)	
Median	0.0	0.000		0.0	0.000		0.0	0.000		0.0	0.000	
Min: Max	[0;19.6]	[0; 25.89]		[0.0; 22.7]	[0.0; 32.23]		[0.0; 22.2]	[0.0; 36.93]		[0.0; 32.6]	[0.0; 23.71]	
Week 52 (change from baseline)	288	278		296	294		287	287		286	289	
Mean (SD)	-4.2 (5.6)	-4.16 (5.90)	-4.21 (NR)	-4.6 (5.5)	-5.95 (6.12)	-5.3 (NR)	-3.5 (5.3)	-4.24 (6.13)	-3.86 (NR)	-3.4 (6.0)	-5.16 (5.87)	-4.28 (NR)
Median	-3.3	-3.46		-3.7	-4.61		-2.7	-3.75		-2.3	-4.11	
Min: Max	[-29.0; 10.7]	[-27.79; 16.38]		[-29.6; 11.9]	[26.86; 10.99]		[-24.9; 18.6]	[-23.72; 18.68]		[-32.6; 26.4]	[-24.48; 14.43]	
LSmeans difference[1] 95.1% CI for				-0.33 (-1.04, 0.38)	-1.18 (-1.979, -0.382)	-0.74 (-1.27, -0.21)	0.71 (-0.01, 1.42)	0.170 (-0.632, 0.972)	0.45 (-0.08, 0.99)	0.86 (0.15, 1.58)	-0.733 (-1.534, 0.068)	0.08 (-0.46, 0.61)

difference P-value vs. RQ4				0.3575	0.004	(NR)	0.0507	0.678	(NR)	0.0173	0.073	(NR)
Week 96 (n)												
Mean (SD)												
Median												
Min: Max												
Week 96 (change from baseline) (n)												
Mean (SD)												
Median												
Min: Max												
LSmeans difference[1]												
95.1% CI for difference												

[1] Difference is aflibercept minus ranibizumab; CI = confidence interval, was calculated using normal approximation. ANCOVA main effect model.

Additional endpoints efficacy analysis

Summary of extent of vision gain and loss (see Table B20)

Several additional efficacy endpoints referred to certain categories of vision gain and vision loss from baseline as measured by the ETDRS letter score. A summary of these results can be found in Table B20. In both studies, it can be seen that vision gain and vision loss were similar in all treatment groups. Long-term treatment with aflibercept was as efficacious regarding changes to VA as treatment with ranibizumab. Notably, the aflibercept 2mg Q8 group achieved clinically equivalent results over 96 weeks while requiring 5.3 fewer doses on average, albeit the difference was protocol driven.

At week 52, approximately 80% of patients in each group had not lost any letters from their baseline ETDRS letter score and approximately 40-50% of patients in each group had experienced a vision gain of at least 10 letters. These proportions remained nearly constant throughout the whole study period. Extreme vision gains i.e. by ≥ 30 letters, occurred in 2.9% to 7.6% of patients. Severe vision loss (loss by ≥ 30 letters) was rare.

In the integrated analysis, pairwise comparisons between the respective proportions in the ranibizumab 0.5mg Q4 and the aflibercept groups were made. The only relevant numerical difference was found in the pairwise comparison of the aflibercept 0.5mg Q4 and ranibizumab Q4 group with regard to the proportion of patients with a vision gain of [redacted] letters, which was [redacted]% lower in the aflibercept 0.5mg Q4 than in the ranibizumab Q4 group. All other comparisons did not indicate any major differences. With a few exceptions, homogeneity testing of odds ratios across studies demonstrated the consistency of the results of both studies.

Change from baseline in CRT

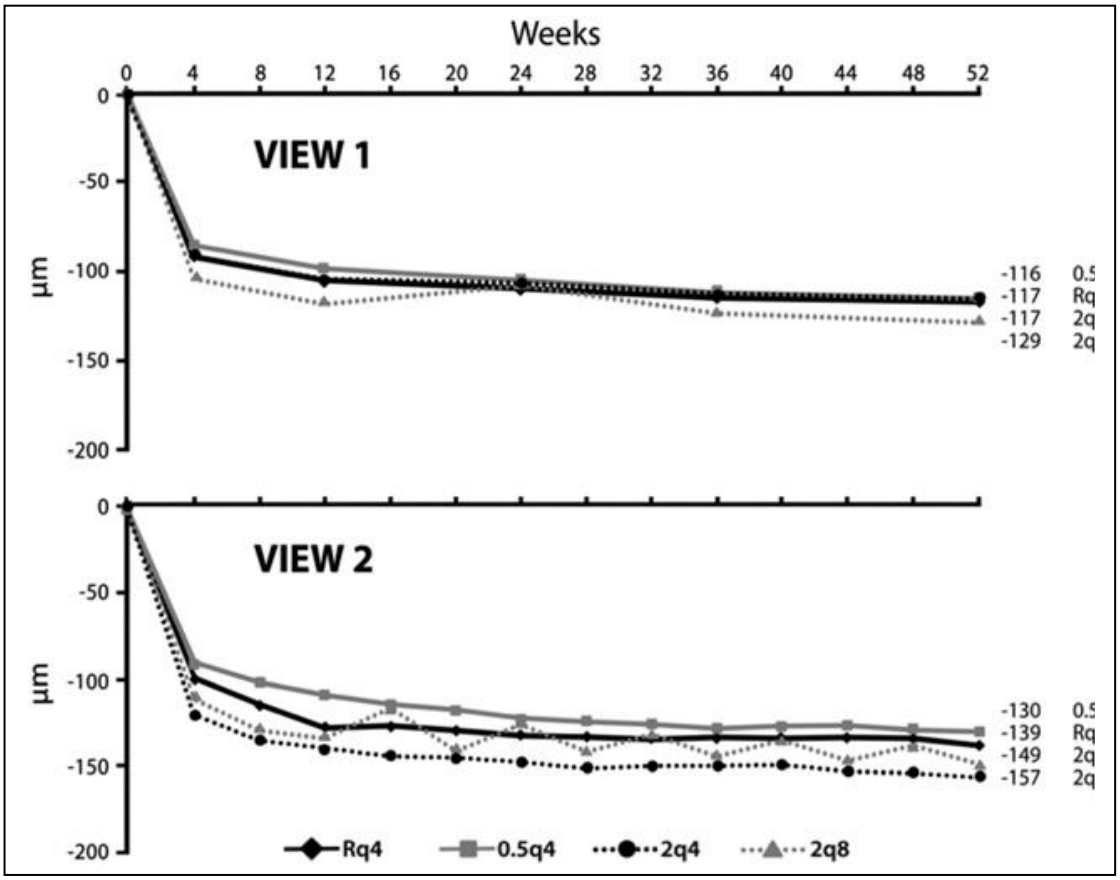
In both studies, mean CRT decreased markedly in all treatment groups during the primary phase (>35-40%), with reduction noticeable even after the first intravitreal injection. The effect was largely maintained through the extension treatment phase. Although the absolute decreases were clinically relevant in

both studies, they were numerically more pronounced in VIEW 2. Although the decreases in mean CRT were numerically slightly greater for aflibercept than for ranibizumab at Week 96, these differences may represent variability in the data. Using the LS means from the exploratory ANCOVA, the point estimates for the differences between aflibercept groups and the RQ4 group in the changes in CRT from baseline to week 96 did not reveal any meaningful treatment differences.

Table B20. Proportion of patients with different extents of vision gain or loss at week 96 [FAS]

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
	N=304	N=291	N=595	N=304	N=309	N=613	N=301	N=296	N=597	N=301	N=306	N=607
Proportion of patients: n (%)	[redacted]											
Gaining ≥ 0 letters												
Gaining ≥ 5 letters												
Gaining ≥ 10 letters												
Gaining ≥ 15 letters												
Gaining ≥ 30 letters												
Proportion of patients: n (%)												
Losing any letters												
Losing ≥ 5 letters												
Losing ≥ 10 letters												
Losing ≥ 15 letters												
Losing ≥ 30 letters												

Figure B8. Mean change from baseline in central retinal thickness (51)



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

A post hoc analysis was performed to determine the percentage of patients who had fluid-free retinas, which were defined, on OCT, by the absence of both cystic intraretinal oedema and subretinal fluid.

At Week 52

All intravitreal aflibercept groups were similar to the monthly ranibizumab group in terms of this end point, with numerically higher percentages of dry retinas seen in the 2mg Q4 and 2mg Q8 aflibercept regimens largely driven by VIEW 2

Table B21. Proportion of patients with Dry Retina at week 52 (observed case, full analysis set)

	Ranibizumab	Intravitreal Aflibercept		
	0.5mg Q4	2mg Q4	0.5mg Q4	2mg Q8
VIEW 1, % (n)	63.6% (171/269)	64.8% (184/284)	56.7% 148/261	63.4% (168/265)
VIEW 2, % (n)	60.4% (162/268)	80.3% (220/274)	63.9% (170/266)	71.9% (197/274)
Integrated, % (n)	62.0% (333/537)	72.4% (404/558)	60.3% (318/527)	67.7% (365/539)

At Week 96

All treatment groups declined in the proportion of patients who were dry from Week 52 to Week 96 suggesting that the fixed dosing employed in the first 52 weeks of the study is better in terms of disease control than the modified quarterly dosing regimen employed in the extension phase. In both studies, retinal fluid was still present in up to 50% of patients at the end of the extension phase. While the results in VIEW 2 still favoured the aflibercept 2 mg treatment when compared to ranibizumab 0.5mg Q4, the proportions of patients with detectable retinal fluid were similar across treatment groups in VIEW 1.

In the integrated analysis, the aflibercept 2 mg groups showed better results than the 0.5mg Q4 and ranibizumab 0.5mg Q4 groups.

Proportion of patients receiving re-treatment within the first 12 weeks of the extension phase of the study

The last mandatory IVT injection during the primary phase was to be performed at Week 48. All subsequent injections were to be performed either when at least one of the re-treatment criteria was met or after 12 weeks had passed since the previous injection. In the second phase of both studies, [redacted] patients in the 2 mg aflibercept groups than in the ranibizumab 0.5mg Q4 group received their first treatment prior to the mandatory 12-week treatment interval.

Subgroup analyses (by dosing subgroup)

Analyses of dosing subgroups were performed on BCVA (changes in ETDRS letter score) and OCT data (changes in CRT and retinal fluid status), both for the single studies and for the pooled data (integrated analyses).

In order to further analyse the impact of the actual frequency of injections during the extension treatment phase on efficacy outcomes the following post-hoc determined dosing subgroups in the extension treatment study medication completers were generated:

- patients with ≤ 3 injections during week 52 to week 96/100
- patients with 4-6 injections week 52 to week 96/100
- patients with ≥ 7 injections week 52 to week 96/100
- patients with re-treatment always in the interval of 8 or 12 weeks in the extension treatment phase. This subgroup was considered only in the integrated analysis.

Analysis of the changes in BCVA from baseline to Week 96 in the different dosing subgroups did not reveal any meaningful differences among treatment groups and subgroups.

In accordance with the results of the analysis of changes in BCVA in the different subgroups, the distribution of the different categories of vision gain and loss was similar in all subgroups, and no meaningful difference between the ranibizumab and the aflibercept groups was detectable in any of the subgroups

The decreases in CRT from baseline to Week 96 as seen in the whole treatment groups were also seen in all dosing subgroups. In all treatment groups, patients who received [redacted] injections in the extension treatment phase or patients who received re-treatment always every 8 or 12 weeks had the [redacted] decreases in mean CRT during the study. The extent of decreases was similar in all treatment groups. As already described for the whole treatment groups, the decreases occurred mostly during the first 52 weeks of study, and “new or persistent fluid as indicated by OCT” was one of the most frequent reasons for re-treatment. This corresponds to the finding that patients

receiving [redacted] injections in the extension treatment phase also showed the lowest mean decreases in CRT.

The subgroups of patients who received [redacted] injections in the extension treatment phase and those who received re-treatment always every 8 or 12 weeks also included the highest proportions of patients without detectable retinal fluid at Week 52 ([redacted]% in all treatment groups). This trend continued through Week 96/100. At the end of the entire study period, the proportions of patients with dry retina were still the highest in these 2 dosing subgroups (approximately [redacted]% in all treatment groups) and the lowest in the subgroup of subjects who received [redacted] injections during the extension treatment.

Injection Frequency

For all analyses (VIEW 1, VIEW 2 and integrated), the mean total number of injections administered over the entire study period (not counting the sham injections during primary phase in study arm for aflibercept 2mg Q8) was clearly lower in the aflibercept 2mg Q8 group than in the other treatment groups (see **Table** 25), albeit the difference was protocol driven.

The three most common reasons for re-injection in the extension treatment phase were ‘new or persistent fluid as indicated by OCT’, ’12 weeks have elapsed since the last injection’, ‘loss from the best previous letter score of ≥ 5 letters [in conjunction with recurrent fluid as indicated by OCT]’.

VIEW 1 – From week 52 to week 96, most patients (58.8% to 66.6% across the treatment groups) exclusively received injections every 8 or 12 weeks. Mean times between injections were not noticeably different between treatment groups.

VIEW 2 – Consistent with the analyses of mean number of injections over the entire study period, the mean times between injections were slightly longer in the groups of patients treated with the 2mg aflibercept dose (Q4 and Q8) compared to other groups. From week 52 to Week 96 more patients in the aflibercept Q4 or Q8 groups (73.0% and 66.5 % respectively) compared to the

ranibizumab 0.5mg Q4 group (53.6%) exclusively received injections every 8 or 12 weeks.

POOLED - Overall, the average number of injections in the extension treatment phase was lower in the 2mg aflibercept groups (Q4: 4.1 ± 1.8 injections, Q8: 4.2 ± 1.7 injections) than in the ranibizumab or aflibercept 0.5mg Q4 groups. This difference was driven by the fact that fewer patients in the aflibercept 2mg groups needed more intense therapy.

26.5% patients treated with ranibizumab and 24% patients from the aflibercept 0.5mg Q4 group, required ≥6 injections in the extension phase of treatment (almost double compared with only 14% patients in the 2mg Q4 group and 15.9% patients in the 2mg Q8 group).

In addition, [redacted] patients in the 2mg treatment arms were given injections in extension phase of treatment because ‘12 weeks interval from the last injection had lapsed’ (see Table B22, Proactive quarterly). Similar to the single study results, these findings may suggest better durability of the treatment effects of the 2mg dose compared to the other treatment arms. As patients were required to receive an injection ≤ 12 weeks in extension phase of treatment, there was no opportunity to test any further the difference between treatment arms among patients with the least disease activity and who rarely met the protocol-based re-treatment criteria.

Table B22. Injection frequency by dosing subgroup

	Dosing		
	Proactive quarterly	Predominantly every other month	Reactive
Injections (max = 11)	[redacted]		
Aflibercept 2mg Q8			
Ranibizumab 0.5mg Q4			

In patients with the greatest disease activity i.e. those who met the protocol-based requirements to receive more frequent injections, an additional analysis applying quartile splits on the distribution of the number of injections administered in the extension phase of treatment (in study treatment completers) revealed that, in the [redacted]% patients requiring the most intense therapy (i.e. those with the greatest number of injections, 4th quartile), the ranibizumab 0.5mg Q4 group received a mean of [redacted] more injections ([redacted] ± [redacted] injections) compared with the aflibercept 2mg Q8 group ([redacted] ± [redacted] injections). An ANCOVA model (including 'treatment group' and 'study' as fixed factors) for the test of differences in these numbers of injections between ranibizumab and the respective aflibercept dose groups within the 4th quartile revealed p-values of p[redacted] for the contrasts 'aflibercept 2mg Q4 vs. ranibizumab 0.5mg Q4' or 'aflibercept 2mg Q8 vs. ranibizumab 0.5mg Q4' while 'aflibercept 0.5mg Q4 vs. ranibizumab 0.5mg Q4' was not significant (p=[redacted]).

Overall, the exposure analyses revealed that, in the extension treatment phase, patients treated with 2mg aflibercept (compared to those treated with the 0.5 mg dose or ranibizumab) showed a numerical trend towards:

- A longer time to the administration of the first injection after the fixed dose regimen,
- More prolonged treatment intervals and
- Somewhat fewer injections administered (i.e., required), particularly in terms of the proportion of patients receiving a high number of injections.

The difference in number of injections was most pronounced in patients with a presumably high VEGF load, i.e., those requiring more re-injections under the modified quarterly dosing schedule.

Patients who might otherwise need more frequent injections in a ranibizumab PRN regime might be as well maintained with fewer injections of aflibercept 2mg.

Table B23. Injection frequency data [SAF]

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
	N=304	N=291	N=595	N=304	N=309	N=613	N=304	N=297	N=601	N=303	N=307	N=610
Mean total number of injections over entire study period (SD)	16.1 (3.8)	16.8 (3.7)	16.5 (3.7)	16.3 (2.6)	15.7 (3.7)	16.0 (3.2)	16.1 (4.0)	16.3 (3.9)	16.2 (4.0)	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)	73.1 (17.3)	74.4 (17.6)	73.7 (17.4)	68.3 (19.3)	68.0 (20.3)	68.2 (19.8)	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=529			N=499			N=511
No of injections from Week 52 To Week 96/100 n(%)												
1	[redacted]											
2												
3												
4												
5												

6	[redacted]											
7												
8												
9												
10												
11												
Mean number of injections Week 52 to Week 96/100			4.7 (2.2)			4.1 (1.8)			4.6 (2.2)			4.2 (1.7)

EFFICACY SUMMARY

Aflibercept has been studied versus ranibizumab in two pivotal multicentre, randomised, double-masked, phase III trials. VIEW 1 and VIEW 2 were of nearly identical design. VIEW 1, involved 1217 participants from the United States and Canada and VIEW 2, involved 1240 participants from across Europe, Asia-Pacific and Latin-America(51).

The non-inferiority of 0.5mg or 2mg aflibercept administered every 4 weeks or 2mg aflibercept administered every 8 weeks (after 3 loading doses) (hereon described as 2mg Q8) compared to ranibizumab (0.5mg administered every 4 weeks) (hereon described as 0.5mg Q4) for the prevention of moderate vision loss was established at the end of 52 weeks.

After a further 44 weeks with all groups receiving a modified PRN regimen (with a minimum of an injection every 12 weeks), analysis of the changes in BCVA from baseline to Week 96 in the different dosing subgroups did not reveal any meaningful differences among treatment groups and subgroups.

The marked functional and morphological improvements achieved in all treatment groups during the first 52 weeks of proactive treatment were largely maintained over the extension phase of treatment using a modified quarterly retreatment schedule. These improvements included stabilisation of vision or improvement in visual function, reduction in CNV area, and reduction in CRT.

2 mg Q8 aflibercept proved to be as efficacious as ranibizumab in the management of patients with wet AMD with an average of 5 fewer injections over the treatment duration of 96 weeks of the study, although the number of injections was protocol driven. The 2mg Q8 aflibercept group received a median of 11 injections compared to 16 injections in the ranibizumab group.

In the follow up phase, the 2mg Q8 aflibercept group received an average of 4.2 injections while the ranibizumab group received 4.7 injections. The quartile of patients requiring the most intense therapy (in terms of injection frequency) had 1.4 fewer injections with aflibercept (2mg Q8 group) than ranibizumab-treated patients.

The proportion of patients requiring frequent injections (6 or more injections) in the extension phase of treatment (week 52 to week 96) was higher in the ranibizumab group (26.5%) compared to aflibercept 2mg Q8 group (15.9%).

Vision-related quality of life, as measured by NEI VFQ-25, improved in all treatment groups and was maintained during the extension phase of the studies. During the first 52 weeks, the mean NEI VFQ-25 total score had improved in all groups by a clinically meaningful extent by approximately 4-6 points.

The slight decrease in visual acuity and an increase in patients with fluid on OCT observed when switching from a proactive treatment (fixed dosing) schedule (primary phase) to a modified quarterly dosing schedule with a reactive ‘as needed’ component (extension phase) suggests that fixed, proactive dosing may provide better AMD control in any of the treatment arms than the modified quarterly dosing schedule / reactive “as needed” treatment component, although the VA drop was not clinically meaningful.

Based on the anatomical data from the VIEW 1 and VIEW 2 trials, approximately 50% of 2mg aflibercept Q8 patients had no evidence of fluid on OCT compared to approximately 46% of 0.5mg Q4 ranibizumab patients at 96 weeks.

6.6 Meta-analysis

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

VIEW 1 and VIEW 2 were similarly designed studies, in order that their data could be pooled for integrated or 'meta-analysis'. The integrated data and analyses of the VIEW 1 and VIEW 2 studies have been presented alongside the individual study data throughout sections 6.3 to 6.5.

Data on the clinical benefits and adverse effects of aflibercept in wet AMD in comparison to ranibizumab, the main licensed comparator treatment used in clinical practice in England and Wales were available from active-controlled trials. However, the active-controlled studies used a dosing regimen of ranibizumab that was used in clinical studies and is not typically used in clinical practice (discussed in more detail in section 6.10.2). It is also different to the approved dosing schedule for ranibizumab. The European label for ranibizumab now defines a 'treat-to–target' scheme i.e. monthly treatment until the patient's VA is stable for 3 consecutive months(14), with re-treatment, in a similar way, upon loss of VA (with a minimum of two injections).

A mixed treatment comparison was therefore carried out to assess the effects on VA outcomes of fixed dose aflibercept (2mg every 8 weeks over 52 and 96 weeks) compared with 0.5mg ranibizumab in a 'reactive dosing' (or treatment as needed) regimen.

6.7 Indirect and mixed treatment comparisons

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

The search undertaken to identify relevant clinical data on ranibizumab given in a PRN or 'reactive dosing' regimen, was the main part of the broader search, introduced and described in section 6.1, 6.2 and appendix 10.2. The systematic review was to examine published literature for data on the effects of aflibercept in a fixed treatment pattern (2mg Q8, every eight weeks) compared with 0.5mg ranibizumab treatment as needed (PRN) on VA outcomes, while at the same time identifying any aflibercept RCTs and more specifically, any RCTs comparing aflibercept directly with ranibizumab.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Please refer to section 6.1, section 6.2 and appendix 10.2 for details of the search strategy, inclusion and exclusion criteria used in the search strategy and the Prisma flow diagram of the numbers of studies included and excluded at each stage.

The systematic review identified 34 RCTs involving either ranibizumab or aflibercept, from 118 records. Thirty one studies (MARINA, ANCHOR, PIER, SAILOR, EXCITE, HATZ, Bashshur, VIEW 1, VIEW 2, CATT, Mont Blanc, Harbor, Jabbour, Jabbour 2008, EXTEND-1, FOCUS, Rouvas, Subramanian, Vallance, APEC-0031, Chan, Hughes, Detail, Moon, Marin-Lambies, Biswas,

Heier, Soderberg, NCT00436553, IVAN, Flaxel) investigated ranibizumab and five trials investigated aflibercept (VIEW 1, VIEW 2, CLEAR-IT 1, CLEAR-AMD 1, CLEAR-IT 2). Sixteen of these trials used ranibizumab, and four used aflibercept in a fixed treatment regimen and 21 used ranibizumab and one aflibercept in a PRN treatment regimen. Two trials investigated both ranibizumab and aflibercept (VIEW 1 and VIEW 2), with ranibizumab at a fixed treatment regimen for the first 12 months, followed by a PRN treatment regimen until 24 months. For the ranibizumab trials, outcomes were measured at 5, 6, 12, 24 and 36 months, the aflibercept trials measured outcomes at 12 and 24 months. No published trials were identified for ranibizumab treat-to-target regimens. Key study characteristics of these 34 studies are summarised in the full report on the indirect comparison (see reference(59)).

From these studies, a network of all included interventions and their comparisons was generated. To identify which of these studies would inform the research question the following studies were removed:

- all disconnected studies,
- all studies which were more than three steps from aflibercept.
- studies which did not inform the network (were connected by one arm only)
- studies which included bevacizumab as the only comparator

This led to the production of three final networks which presented data at 6 months or 12 months or 24 months for the following comparison ‘Fixed aflibercept 2mg Q8 vs. PRN ranibizumab 0.5mg, with PRN dosing (dashed lines) or fixed dosing (solid lines) included. Only EXTEND-1 Rouvas (35 and 36 months) reported outcomes at time points beyond 24 months.

At six months, no data were available for aflibercept and therefore no analyses were possible. Ten studies were included in the network of outcomes at 1 year - VIEW 1 and VIEW 2 presented data at 52 weeks, this was assumed to be 12 months in line with the other studies.. For analysis at 24 months, only trials that involved a switch treatment of fixed aflibercept 2mg Q8 to PRN aflibercept 2mg Q8 (aflibercept fixed/PRN) were available and

network analyses was not possible. Therefore, two step indirect analyses were used to compare aflibercept fixed/PRN to 0.5mg ranibizumab fixed/PRN. Three trials were found for the outcome of maintained vision. VIEW 1 and VIEW 2 presented data at 96 weeks, this was assumed to be 24 months in line with the other studies.

For the ten studies, details on study characteristics (design, comparators, patient numbers, outcomes studied), Baseline characteristics, Inclusion and exclusion criteria, permitted and disallowed concomitant medications, Intervention and comparators, frequency of treatment and monitoring, and primary and secondary outcomes can be found in reference(59).

Quality assessment of RCTs

The Cochrane Collaboration quality assessment checklist was used to assess the methodological quality of each included study. Each study was awarded a ‘yes’, ‘no’ or ‘unclear/unknown’ rating for each individual item in the checklist. Any additional clarifications or comments were also included. An overall rating was included to aid the comparison of trials/studies of any indirect analyses. The results of the quality assessment were used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. A summary of the quality assessment results is presented here (**Table** 26), with more detail presented in Appendix 10.

Table B24. Quality Assessments/ Risk of bias of Stage 2 studies

Study	Adequate randomisation	Adequate concealment	Patient blinding	Physician blinding	Outcome assessor blinding	Attrition/exclusion reported	Appropriate data analysis	Incomplete outcome data adequately addressed	Results for all specified outcomes reported	Other sources of bias	Overall rating of bias
View 1	yes	yes	yes	yes	yes	yes	PP, LOCF	Mixed	yes	Industry funding	Low
View 2	yes	yes	yes	yes	yes	yes	PP, LOCF	Mixed	yes	Industry funding	Low
CATT	NR	yes	no	yes	yes	yes	mixture	no	yes	NR	High
DETAIL	NR	NR	no	no	no	no	NR	NR	yes	NR	High
Harbor	NR	NR	yes	yes	no	yes	LOCF	unclear	yes	Industry funding	Unclear
Moon	NR	NR	no	no	no	no	NR	NR	NR	NR	High
MARINA	NR	NR	yes	yes	yes	yes	ITT	yes	yes	Industry funding	Low
PIER	yes	NR	yes	yes	yes	yes	ITT	yes	yes	Industry funding	Low
EXCITE	NR	NR	yes	NR	NR	yes	ITT, PP	mixed	yes	Industry funding	Unclear
EXTEND-1	NR	NR	NR	NR	NR	yes	ITT, PP, LOCF	no	yes	Industry funding	Unclear

ITT= intention-to-treat analysis; NR = not reported; PP= per protocol analysis; LOCF = last observation carried forward. Overall rating was given to the predominant rating within each study, but randomisation and incomplete data analysis were given further importance. Clear=unclear risk of bias; green = low risk of bias; orange = high risk of bias

Overall five studies (CATT, DETAIL, Harbor, Moon and EXTEND) included at least one source of high risk of bias and five studies (VIEW 1, VIEW 2, MARINA, PIER, and EXCITE) had no source of high risk of bias (see Table B24). All studies were randomised, however only three (VIEW 1, VIEW 2, and

PIER) provided methodological details to confirm that this was adequate. Allocation concealment was adequate in three studies (VIEW 1, VIEW 2, and CATT). The other studies did not report about concealment of randomisation. Most of the studies provided sufficient methodologically detail to judge, whether blinding was adequate. Exceptions to this were; the EXCITE trial blinding of physicians and outcome assessors was not reported and in the EXTEND trial, blinding of physicians, outcome assessors, and patient blinding was not reported. Therefore these studies were judged to have an unclear risk of bias. Three studies were open-label studies (EXTEND, Moon and DETAIL) and were therefore judged to have a high risk of bias. CATT did not have patient blinding. The other studies were judged to have a low risk of bias due to adequate blinding.

Exclusion of patients was reported in all, except for the DETAIL and Moon studies. Data analysis was judged to be associated with an unclear risk of bias in eight of the ten trials. Two trials (MARINA, PIER) were judged to be associated with a low risk of bias because they applied intention-to-treat analysis and therefore incomplete outcome data were adequately addressed. In contrast, two studies (CATT and EXTEND) were judged to have high risk of bias due to inadequate incomplete outcome data assessment. CATT had imbalanced dropout rates between treatment arms, per protocol analysis was used for all outcomes of interest to this review and therefore the analysis did not address dropout and the studies judged to have a high risk of bias. EXTEND presented inconsistent and confusing results which were therefore deemed to be unreliable. The Harbor study used last observation carried forward to impute missing data. The other studies had an unclear risk of bias for incomplete data because it was not reported (DETAIL, Moon), a mix (VIEW 1, VIEW 2, EXCITE) or unclear (Harbor). Most studies were free of selective outcome reporting, except for Moon where it was unclear. The most common other source of risk of bias was from industry funding in eight of the ten trials, no other source of bias could be identified based on what was reported for the three remaining trials (CATT, DETAIL, and Moon).

All the studies were given an overall assessment of quality. Four studies were given a low risk of bias (VIEW 1, VIEW 2, MARINA, PIER), three had an unclear risk of bias (Harbor, EXCITE, EXTEND) and three were given a high risk of bias (CATT, DETAIL, Moon). The four studies judged to have a low risk were large randomised trials which were well reported. The high risk trials were either: small poorly reported studies (Moon, DETAIL) of abstracts or on the clinicaltrials.gov website or were incompletely analysed (CATT). . All the trials with unclear risk of bias were full publications apart from Harbor for which there was an abstract and presentation slides. Studies are required to have similar levels of bias to allow valid indirect analyses.

Four of the trials allowed treatment switches and after 12 months the patients switched from fixed dosing regimen to PRN (VIEW 1, VIEW 2, CATT, EXTEND). PIER allowed crossover of treatments after 12 months and the proportions of patients switching was high (62-72%), this therefore invalidated the 24 month data and meant that PIER was excluded from 24 month analysis.

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

A brief summary of the trials used in the network analysis at 12 months is provided below (Table B25) [Shading indicates the trials also used in the indirect analysis at 24 months].

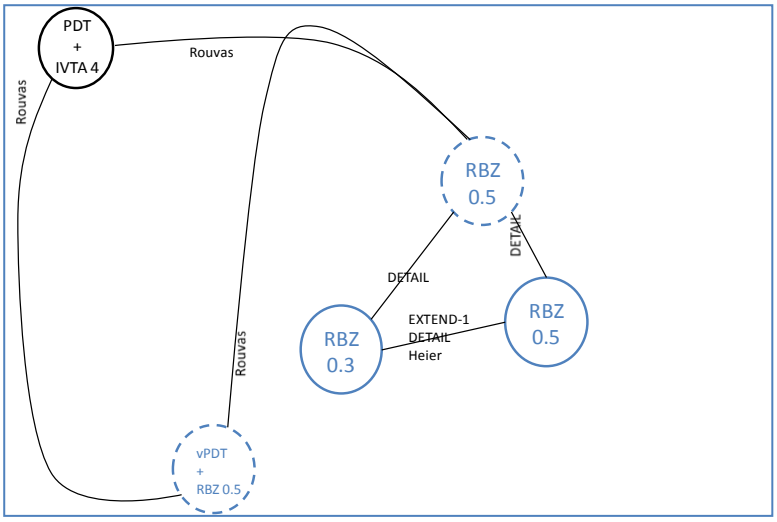
The IVAN trial was not included in the network analysis because the outcomes were combined for PRN and fixed dosing (the author was contacted to try and access the separate data, and they informed of their intention not to publish the data separately until the 24 month data were ready in 2013). Similarly, ANCHOR included photodynamic therapy.

Table B25. Summary of the trials used to conduct the network meta analyses (59)

Study name / Acronym (primary ref)	Aflibercept			Ranibizumab					
	2mg Q4	0.5mg Q4	2mg Q8	0.3mg Q4 (fixed)	0.3mg PRN	0.5mg Q4 (fixed)	0.5mg PRN	2mg (fixed)	2mg PRN
VIEW 1 (51;53)	✓ To 52 weeks then PRN (Q4-12 weeks to week 96)	✓ To 52 weeks then PRN (Q4-12 weeks to week 96)	✓ To 52 weeks ✓ then PRN (Q4-12 weeks to week 96)			✓ To 52 weeks then PRN (Q4-12 weeks to week 96)			
VIEW 2 (51;53)									
CATT (60)						✓ For 12 months	✓ For 12 months		
Harbor (61)						✓ To 12 months	✓ Monthly x 3 then PRN to 12 months	✓ To 12 months	✓ Monthly x 3 then PRN to 12 months
Moon (62)						✓ Monthly to 12 months			✓ Monthly x4 then PRN
DETAIL (63)				✓ Monthly x 6	✓ Monthly x 3 then PRN	✓ Monthly x 6	✓ Monthly x 3 then PRN		
MARINA (64)				✓ To 12 and 24 months		✓ To 12 and 24 months Also a sham injection arm			
PIER (65;66)				✓ Monthly x 3 then Every 3 months to 12 and 24 months		✓ Monthly x 3 then Every 3 months Also a sham injection arm			
EXCITE (67)				✓ To 12 months		✓ Monthly x 3 then			

Study name / Acronym (primary ref)	Aflibercept			Ranibizumab					
	2mg Q4	0.5mg Q4	2mg Q8	0.3mg Q4 (fixed)	0.3mg PRN	0.5mg Q4 (fixed)	0.5mg PRN	2mg (fixed)	2mg PRN
				✓ Monthly x 3 then Every 3 months		Every 3 months			
EXTEND-1 (68;69)				✓ Monthly x12	then PRN to months 24 and 35	✓ Monthly x12	then PRN to months 24 and 35		

Figure B9. Network comparisons of 2mg fixed Q8 aflibercept compared to PRN ranibizumab regimens at six months



RBZ = ranibizumab; PDT = photodynamic therapy; IVTA= intravitreal triamcinolone acetonide. Numbers indicate drug dose in mg. Dashed line = PRN, solid line = fixed dosing regimen.

Figure B10. Network comparisons of 2mg fixed Q8 aflibercept compared to PRN ranibizumab regimens at 12 months

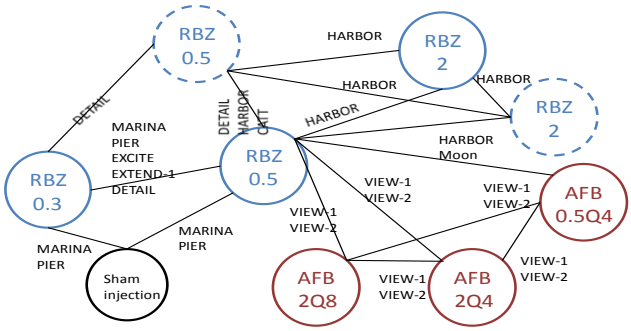
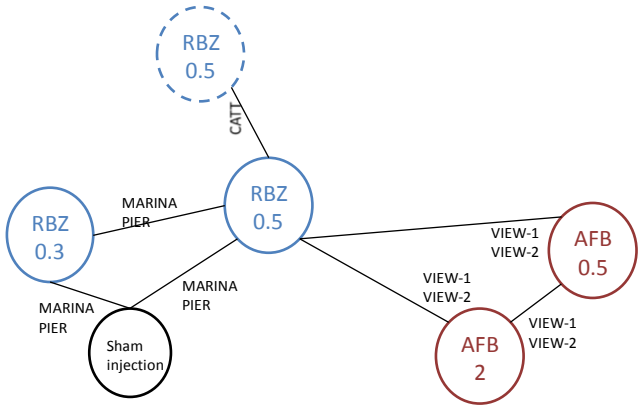


Figure B11. Network comparisons of 2mg fixed Q8 aflibercept compared to PRN ranibizumab regimens at 24 months



6.7.4 For the selected trials, provide a summary of the data used in the analysis.

From Appendix 12 reference(59). Study data to inform the network analyses (Bayesian and frequentist)

Table B26. Maintained vision

		A		B		C		H		I	
Direct	**Study**	**Fixed AFB 2mg Q8**		**Fixed RBZ 0.5mg**		**Prn RBZ 0.5mg**		**Fixed AFB 0.5mg Q4**		**Fixed AFB 2mg Q4**	
		R	N	R	N	R	N	R	N	R	N
AB (2)	View 1	28	30	28	30						
	View 2	29	30	27	29						
BC (1)	CATT			26	28	27	28				
	Harbor			26	27	26	27				
AI (2)	View 1	28	30							28	304
	View 2	29	30							29	309
AH (2)	View 1	28	30					28	30		
	View 2	29	30					28	29		
HI (2)	View 1							28	30	28	304
	View 2							28	29	29	309
BI (2)	View 1			28	30					28	304
	View 2			27	29					29	309
BH (2)	View 1			28	30			28	30		
	View 2			27	29			28	29		

Table B27. BCVA mean change from baseline

Direct	Study	A			B			C			H			I			F			G			K		
		Fixed AFB 2Q8 AFB 2Q8			Fixed RBZ 0.5 RBZ 0.5			Prn RBZ 0.5 RBZ 0.5			Fixed AFB 2Q0.5 AFB 2Q0.5			Fixed AFB 2Q4 AFB 2Q4			Fixed RBZ 2 RBZ 2			Prn RBZ 2 RBZ 2			Fixed RBZ 0.3 RBZ 0.3		
		R	N	sd	R	N	sd	R	N	sd	R	N	sd	R	N	sd	R	N	sd	R	N	sd	R	N	sd
AB (2)	View 1	7.9	301	15	8.1	304	15.3																		
	View 2	8.9	306	14.4	9.4	291	13.5																		
BC (3)	CATT				8.5	284	14.1	6.8	285	13.1															
	DETAIL*SD				1	20	14.1	11.5	18	13.1															
	Harbor SD				10.1	275	15.3	8.2	275	17.1															
BG (2)	Harbor SD				10.1	275	15.3													8.6	273	18.2			
	Moon				5.2	30	17													7.9	40	7			
BF (1)	Harbor SD				10.1	275	15.3										9.2	274	51.3						
CF (1)	Harbor SD							8.2	275	18.2							9.2	274	51.3						
CG (1)	Harbor SD							8.2	275	18.2										8.6	273	18.2			
FG (1)	Harbor SD																9.2	274	51.3	8.6	273	18.2			
AI (2)	View 1	7.9	301	15										10.9	304	13.8									
	View 2	8.9	306	14.4										7.6	309	12.6									
AH (2)	View 1	7.9	301	15							6.9	301	13.4												
	View 2	8.9	306	14.4							9.7	296	14.1												
HI (2)	View 1										6.9	301	13.4	10.9	304	13.8									
	View 2										9.7	296	14.1	7.6	309	12.6									
BI (2)	View 1				8.1	304	15.3							10.9	304	13.8									
	View 2				9.4	291	13.5							7.6	309	12.6									
BH (2)	View 1				8.1	304	15.3				6.9	301	13.4												
	View 2				9.4	291	13.5				9.7	296	14.1												
BK (5)	MARINA SD				7.2	240	22																6.5	238	16.8
	PIER SD				-0.2	61	11.1																-1.6	60	8.5
	EXCITE**				3.8	88	13.3																4.9	104	13.1
	EXTEND-1				10.5	41	11.4																9.5	35	12.8
	DETAIL SD				1	20	13.1																0	20	13.1
CK (1)	DETAIL* SD							11.5	18	3.3													0	20	13.1

* combined prn regimens (treat until macular fluid absent and treat until macular fluid and PED absent). SD standard deviations were imputed (using CATT for DETAIL, Moon for Harbor, Excite for Marina & Pier). ** ITT analysis, 6 scheduled injections (11 scheduled injections also reported for 0.3 RBZ fixed, but not calculated here).

Table B28. Gain > 15 letters

		A		B		C		H		I		F		G	
Direct	**Study**	**Fixed AFB 2mg Q8**		**Fixed RBZ 0.5mg**		**Prn RBZ 0.5mg**		**Fixed AFB 0.5mg Q4**		**Fixed AFB 2Q4**		**Fixed RBZ 2mg**		**prn RBZ 2mg**	
		R	N	R	N	R	N	R	N	R	N	R	N	R	N
AB	View 1	9	30	9	30										
	View 2	9	30	9	29										
BC	CATT			9	28	7	28								
	Harbor			9	27	8	27								
BG	Harbor			9	27									90	273
BF	Harbor			9	27							99	27		
CF	Harbor					8	27					99	27		
CG	Harbor					8	27							90	273
FG	Harbor											99	27	90	273
AI (2)	View 1	9	30							11	30				
	View 2	9	30							91	30				
AH	View 1	9	30					75	30						
	View 2	9	30					10	29						
HI (2)	View 1							75	30	11	30				
	View 2							10	29	91	30				
BI (2)	View 1			9	30					11	30				
	View 2			9	29					91	30				
BH	View 1			9	30			75	30						
	View 2			9	29			10	29						

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

See reference(59) for full details. All 'head to head' analyses i.e. of intervention vs. comparator (A vs. B) were performed in line with the Cochrane Handbook. Three forms of indirect analysis were used; simple 'Bucher' analysis, frequentist network analysis and Bayesian network analysis.

Indirect comparison (ITC) - ITCs were performed using the methods and principles of Bucher et al 1997 originally developed for odds ratios (ORs). ORs and relative risks (RRs) were calculated using the adaptation of Wells et al 2009(70). All simple indirect analyses were performed in Excel using results from direct random effects models.

Network meta-analysis (NMA) - NMAs were used to compare more than two treatments in the same analysis. NMA allows direct and indirect comparisons in one analysis. Both frequentist methods and Bayesian methods were used for analysis. Frequentist analyses were performed using STATA (STATA™ for Windows, version 10, Stata Corp; College Station, TX) and Bayesian analyses were performed with WinBUGS 1.4.3 (MRC Biostatistics Unit Cambridge and Imperial College School of Medicine at St Mary's, London). All results were presented as point estimates (e.g. OR or RR, OR values only for the frequentist method) with either 95% confidence intervals (frequentist approach) or 95% credible intervals (Bayesian approach). The frequentist method is a fixed effect only model whilst the Bayesian method was run as a random effects model to allow for the fact that some trials had multiple treatment groups (up to four) and the analysis needed to account for correlation within a trial.

Dichotomous outcomes (frequentist) - Based on 2 × 2 tables (or 3 × 2 tables) from each study, as many data entries with respective coding for treatment and outcome (e.g. maintained vision) were created as there were patients in the respective cell.

A logistic regression analysis with the dichotomous outcome (e.g. maintained vision) as the dependent variable and the different treatment groups as independent variables was performed. One treatment was identified as the reference group to which the other treatments were compared. To preserve randomisation within each trial, a dummy variable was included for each of the trials. This dummy variable also adjusted for differences in risk profiles and study setup between trials.

Continuous outcomes (frequentist) - Mean change in VA as a continuous outcome (mean change from baseline) was used. Studies were excluded from the analysis if they did not report a baseline measurement or did not present mean change data. As many entries were created for a study as there were participants. For each participant the adjusted outcome, assuming a normal distribution, was estimated. As the normal distribution gives slightly deviating values based on chance, these values were corrected using the following

formula “adjusted outcome = (xq-meqq)* sdq/sdqq+ meanq” (where xq = new mean based on normal distribution, meqq = adjustment for mean, sdq = new sd based on normal distribution, sdqq = adjustment for sd, meanq = original mean outcome). A linear regression model was then used to model this adjusted outcome and used to compare treatment groups.

Bayesian network analyses - The WinBUGS codes used for dichotomous outcomes are described in (insert cross-ref to where WINBUGS codes are in submission). One Markov chain was used and initial values were loaded into the package as described in the code or generated automatically by WinBUGs. A burn-in of 20,000 iterations was used to check convergence then results were collected for a further 100,000 iterations. To check that the winBUGS codes were performing as expected, WinBUGS was used to perform a network analysis only on the studies included in the simple/ ‘Bucher’ indirect analyses. If an SD was not reported, this was imputed using values from other studies.

A narrative discussion concerning the feasibility and appropriateness of indirect comparisons was presented using the criteria of homogeneity, similarity and consistency as described by Song et al 2009(71). A comparison of population traits, study characteristics, interventions, follow-up, and outcome results enabled a straight-forward assessment of study variation.

Forest plots were prepared to compare the results from the simple ‘Bucher’ indirect method of analysis to the frequentist network and the Bayesian Network.

6.7.6 Please present the results of the analysis.

Based on ten trials (6193 patients) and ITCs, no significant differences between a fixed dosing regimen of aflibercept 2Q8 and 0.5mg ranibizumab PRN were found for the outcomes of maintaining vision, improving vision or improving BCVA.

To compare aflibercept 2mg Q8 to 0.5mg ranibizumab PRN four trials were found for the outcome of maintained vision (the proportion of patients losing ≤

15 letters ETDRS scale) at 12 months. No significant difference was found between the treatments using Bayesian (OR, 1.51 [95% CrI, 0.42 to 5.94]) or frequentist network analysis (OR, 1.44 [95% CI, 0.68 to 3.09]). Ten trials were used to analyse the change in BCVA at 12 months, but no significant differences were seen between treatments by both Bayesian (MD, -2.87 [95% CrI, -10.02 to 4.3]) or frequentist networks (MD, 0.83 [95% CI, -1.57 to 3.23]). Four trials were used to analyse improved vision (the proportion of patients gaining ≥15 letters ETDRS) at 12 months. No difference was found between the treatments using Bayesian (OR, 1.28 [95% CrI, 0.45 to 3.68]) or frequentist network analysis (OR, 1.29 [95% CI, 0.91 to 1.83]). Two step indirect analyses were performed and these revealed the same overall results.

At 24 months, network analysis was not possible due to switch treatments of fixed aflibercept 2mg Q8 to PRN (aflibercept fixed/PRN). Two step indirect analyses were used to compare aflibercept fixed/PRN to 0.5mg ranibizumab PRN. Three trials were found for the outcome of maintained vision (OR, 0.91, [95% CI, 0.36 to 2.34]), change in best corrected visual acuity (MD 0.31 [95% CI, -4.33 to 3.71]) and improved vision (OR, 0.84 [95% CI, 0.50 to 1.42]). No significant difference was found between the treatments.

There were concerns regarding the validity of the indirect analyses as heterogeneity was present, three studies had a high risk of bias and several of the studies had dissimilar baseline characteristics (in terms of ETDRS score, definition of PRN retreatment criteria, % males, central retinal thickness and received different numbers of injections). Sensitivity analyses were performed with regard to the heterogeneity and this did not alter the final result. Insufficient trials were available to further explore the baseline characteristics. No direct analyses were possible.

Please see reference(59) section 5.7 to 5.15 for in-depth presentation of the results of all analyses.

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Heterogeneity was assessed by measuring the degree of inconsistency in the studies' results (I^2). This measure (I^2) describes the percentage of total variation across studies that were due to heterogeneity rather than the play of chance. The value of I^2 can lie between 0% and 100%. Low, moderate and high I^2 values correspond to 25%, 50%, and 75%, respectively.

If important heterogeneity was identified, it was explored by investigating the effects of the following pre-specified factors: methodological quality of the primary studies, definition of wet AMD, duration of AMD, baseline characteristics, and co-morbidities such as cardiovascular diseases or diabetes. Results were presented in a narrative manner.

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Three trials (CATT, DETAIL, Harbor) comparing 0.5mg ranibizumab fixed vs. 0.5mg ranibizumab PRN were combined for the outcome ‘mean change of ETDRS letters from baseline in BCVA’ at 12 months. The result indicated that 0.5mg ranibizumab PRN improved, on average, BCVA by 0.01 letters [95% CI -3.95, 3.92] more than 0.5mg RBZ fixed, the result was not statistically significant (p = 0.99), however there was high heterogeneity between the included studies, I^2 = 73%. The heterogeneity is undoubtedly explained by the results of the DETAIL study, which were completely the opposite to the results of the CATT and Harbor. A sensitivity analysis was performed by removing the results for DETAIL in the analysis, this found that 0.5mg ranibizumab fixed improved BCVA by 1.78 letters [95% CI 0.06, 3.51] more than 0.5mg ranibizumab PRN and the trials are homogenous (I^2 = 0%). Analysis of DETAIL alone indicated that 0.5mg RBZ PRN improved, on average, BCVA by 10.50 letters [95%CI 8.27, 12.73].

Bucher indirect analysis for fixed aflibercept 2mg Q8 vs. 0.5mg ranibizumab PRN and the outcome ‘mean change of ETDRS letters from baseline in BCVA’ at 12 months included the DETAIL trial therefore a sensitivity analysis was also performed. Bucher analysis using all trials (View 1, View 2, CATT,

Detail, Harbor) found that fixed aflibercept 2mg Q8 improved mean change in BCVA by 0.37 letters more [95% CI -4.63, 3.89] than 0.5mg ranibizumab PRN and indicated no significant effect between the two treatments. Indirect analysis performed with data from DETAIL, VIEW 1 and VIEW 2 produced a result of MD = -10.36 [95% CI -19.66 to -2.06], whilst data from CATT, Harbor VIEW 1 and VIEW 2 produced a result of MD =1.42 [95% CI -0.96 to 3.89].

Network analysis for fixed aflibercept 2mg Q8 vs 0.5mg ranibizumab PRN and the outcome of BCVA mean change at 12 months found no significant differences between treatments. The frequentist network analysis favoured fixed aflibercept 2mg Q8 and showed a mean increase of 0.83 letters [95%CI -1.57, 3.23], compared with the Bayesian network analysis which found a mean decrease of -2.87 letters [95% CrI -10.02 to 4.30]. Since the analysis of BCVA mean change was influenced by the results of the DETAIL trial we also performed a sensitivity analysis, by excluding the data from DETAIL from the analysis. The frequentist network analysis (-DETAIL) again favoured fixed AFB 2Q8 and showed a mean increase of 1.35 [95%CrI -1.08 to 3.77] and the Bayesian network analysis (-DETAIL) found a mean increase of 1.15 [95%CrI -3.92 to 6.09]. All the analyses found no significant differences between the treatments.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Discussion of DETAIL and possible explanations for the heterogeneity:

The patients of DETAIL appear to have responded differently to the treatments compared to the other patient study groups. DETAIL carried a high risk of bias but close analysis of the reasons for this indicated that the study was open label and was not clearly reported (it was reported as an abstract and as online trial information). These are not reasons to discount the results.

The PRN dosing regimen for the DETAIL study was a combined result of two reported regimens, one regimen was to treat until macular fluid was absent and the other was to treat until macular fluid and retinal pigment epithelial

detachment was absent. Combination of the PRN regimens was considered acceptable as no other PRN regimens were reported by separate diagnostic criteria. Both DETAIL PRN regimens were identified by OCT, which was the defined method used by most other PRN regimens. However close analysis of the results for the two DETAIL PRN regimens indicated that the 'treat until macular fluid and retinal pigment epithelial detachment was absent' showed the largest improvement in VA (20 letters) of any trial. 'Treat until macular fluid was absent' showed an increase of three letters, whilst the fixed regimens in DETAIL only showed an increase of 0 and 1 letters. The large improvement of BCVA due to treatment until macular fluid and retinal pigment epithelial detachment was absent was largely responsible for the heterogeneity seen in the analyses, despite its small study size (n=58). It is unclear if this regimen is used by other trials, since the reporting of the retreatment criteria was often unclear, however no other trials directly report such a regimen, therefore it is likely that different PRN retreatment criteria will influence the effect.

Another area of concern for the DETAIL study is its size, we assumed that the study size was 58 from the information provided but this was not clear. Analysis of the baseline characteristics for DETAIL was difficult because of the lack of reporting; however baseline BCVA, age, and central retinal thickness were broadly in line with Harbor and CATT. While patients had received previous treatments for wet AMD in the DETAIL study this was not the case in the other studies and may represent a source of heterogeneity. As a source of heterogeneity the DETAIL study is important because it makes the indirect analyses invalid. Sensitivity analyses were performed for all outcomes which used the currently available DETAIL study data. Until DETAIL is described in a full report we can neither be certain of its results nor decide whether it should be included or excluded from our analyses.

Discussion of similarity and inconsistency:

Comparisons of trial similarity, indicated that the trials were dissimilar with regards to their baseline patient characteristics, how PRN retreatment was defined and by the number of injections given (and therefore drug dose).

Several studies (Harbor, DETAIL, Moon, EXTEND-1) were poorly reported or were limited reports, thereby precluding our ability to compare study similarity.

Comparisons of the consistency between Bucher indirect analyses and network mixed treatment comparisons indicated all that all the models found that there were no significant differences between the different treatments. There were no direct studies of fixed dosing aflibercept 2mg Q8 vs. PRN dosing ranibizumab 0.5mg with which to check the consistency of our indirect results.

Overall although our analyses were found to be consistent, the assumption of similarity maybe flawed.

6.7.10 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable

6.7.11 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

See previous

6.8 Non-RCT evidence

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in ‘Systematic reviews: CRD’s guidance for undertaking reviews in health care’

(www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

Given that robust clinical evidence relevant to the decision problem was available from RCTs (the preferred source of clinical data), and an indirect comparison, it was not considered relevant to include non-RCTs in the search strategy for clinical effectiveness.

6.9 Adverse events

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

Neither VIEW 1 nor VIEW 2 included safety outcomes as a primary analysis.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Evidence of the safety and tolerability profile of aflibercept when compared to ranibizumab, in the treatment of wet AMD, is provided by safety analyses and

adverse event reporting from two international, multicentre, randomised, double-masked, active-controlled, phase III non-inferiority studies of near-identical design (VIEW 1 and VIEW 2). The design, methodology, descriptions of all endpoints, and efficacy results from VIEW 1 and VIEW 2 are detailed in Section 6.1 to 6.5.

The safety and tolerability of repeated intravitreal administration of aflibercept when compared with ranibizumab for a period of up to 96 weeks, was included as a secondary objective in the VIEW 1 and VIEW 2 studies. Data on all AE were collected at each study visit (i.e. every 4 weeks), according to standard ICH definitions. The term AE was only used to refer to treatment-emergent AEs, i.e. AEs which occurred or worsened after the first administration of study drug. All AEs were assessed for seriousness, intensity, pattern, study drug action, drug treatment, causal relationship to study drug, and causal relationship to the injection procedure. Other safety procedures included the documentation of pregnancy (in a female patient or female partner of a male study patient), laboratory evaluations including determination of antibodies to aflibercept, electrocardiography, measurement of vital signs, IOP measurements, indirect ophthalmology and slit lamp biomicroscopy.

The SAF included patients who had received any study drug at all. The total number of patients valid for the safety analyses from VIEW 1 and VIEW 2 was 2419. The breakdown of this population is detailed further in Table B29

Table B29. Safety analysis population – VIEW 1, VIEW 2 and POOLED

	Study Arms				**TOTAL (n)**
	Ranibizumab	Aflibercept			
	0.5mg Q4 (n)	2mg Q4 (n)	0.5mg Q4 (n)	2mg Q8 (n)	
VIEW 1	304	304	304	303	1215
VIEW 2	291	309	297	307	1204
POOLED	595	613	601	610	2419

In both VIEW 1 and VIEW 2, the summary of the safety data did not identify any clinically meaningful differences between aflibercept and ranibizumab

(see Table B30). The integrated analysis of the pooled data did not indicate any meaningful differences among the treatment groups either. Incidences of all reported event types were quite similar among the treatment groups. No dose-response was observed among the patients treated with aflibercept. Thus, the safety profile of aflibercept over 96 weeks in all dose groups was similar to the safety profile observed for ranibizumab.

A total of 1177 patients (96.9%) in VIEW 1, 1134 (94.2%) in VIEW 2, and 2311 (95.5%) patients in the integrated analysis experienced at least one treatment-emergent adverse event (TEAE) during the entire study period. In the integrated analysis, no differences ≥ 5.0% between the ranibizumab group and the aflibercept combined group were noted in TEAEs experienced over 96 weeks, and in the single studies any differences ≥5.0% noted were always in favour of aflibercept (VIEW 1: "any injection-related ocular TEAEs" [ranibizumab: 62.5% vs. aflibercept combined: 56.6%], "injection-related ocular TEAEs in the study eye" [ranibizumab: 62.2% vs. aflibercept combined: 55.4%], and "any SAEs" [ranibizumab: 34.9% vs. aflibercept: 29.7%]; VIEW 2: "any non-ocular TEAEs" [ranibizumab: 76.6% vs. aflibercept combined: 81.8%]).

Overall, the incidence and types of AEs for ocular, non-ocular and injection-related AEs were similar between the treatment groups. The most common adverse reactions (in at least 5% of patients treated with aflibercept) were conjunctival haemorrhage (26.7%), eye pain (10.3%), vitreous detachment (8.4%), cataract (7.9%), vitreous floaters (7.6%), and increased intraocular pressure (7.2%).

Ocular TEAEs and Serious Adverse Events (SAEs)

The frequency and type of ocular TEAEs and SAEs reported over 96 weeks in the study eye were similar between aflibercept (at any dose) and ranibizumab in VIEW 1 and VIEW 2 (see Table B30). TEAEs and SAEs were consistent with what might be expected with the nature of underlying disease, disease progression or attributable to the injection procedure, and occurred at similar rates across all treatment groups (see Table B31 for ocular TEAEs). The 5

most common ocular study eye TEAEs in the pooled total study population (N=2419) were "conjunctival haemorrhage" (27.5%), "retinal haemorrhage" (14.5%), "visual acuity reduced" (12.3%), "eye pain" (10.3%), and "macular degeneration" (8.8%). The most commonly reported ocular SAEs in the study eye, occurring in no more than 3 (1.0%) patients in any dose group, were endophthalmitis, VA reduced, and retinal haemorrhage. Overall, cases of endophthalmitis (TEAEs and SAEs)(VIEW 1: n=5 ranibizumab, n=4 aflibercept; VIEW 2: n=1 2mg Q4) or uveitis (VIEW 1: n=1 aflibercept 0.5mg Q4; VIEW 2: n=1 2mg Q4) were infrequent. In the VIEW studies (96 weeks data) the endophthalmitis rates for aflibercept were 0.02% per injection and for ranibizumab were 0.05% per injection.

Drug-related (solely based on the site investigator's assessment) ocular TEAEs occurred in 7% of the total patients (see Table B30). In both VIEW 1 and VIEW 2, there were no clinically meaningful differences between aflibercept and ranibizumab in either the frequency or types of drug-related ocular TEAEs occurring in the study eye. Analysis of the integrated data, as with the single studies, did not indicate meaningful differences between ranibizumab and aflibercept or across the different aflibercept dose groups. Drug-related ocular study eye SAEs over 96 weeks were very infrequent (8 patients in total in the integrated study pool involved; 3 patients from VIEW 1 and 5 patients from VIEW 2) [cataract n=2, pseudoendophthalmitis n=1, retinal haemorrhage n=1, retinal pigment epithelial tear n=2, VA reduced n=2] with, as far as assessable due to low absolute numbers of events, no meaningful differences among the treatment groups.

Fellow eye

TEAEs seen in the fellow eye were typical of the disease process or the injection procedure and qualitatively similar to the TEAEs seen in the study eye. There were no meaningful between-group differences. The incidence of ocular TEAEs in the fellow eye across the study pool (N=2419) over 96 weeks was 60.0% in the ranibizumab 0.5mg Q4 group, 56.9% in the 2mg Q4 group, 55.6% in the 0.5mg Q4 group, and 56.1% in the 2mg Q8 group. The 3 most common TEAEs in the fellow eye in the pooled total study population were

"retinal haemorrhage" (10.1%), "age-related macular degeneration" (6.9%), and "visual acuity reduced" (6.6%).

In both VIEW 1 (n=14 [1.2%]) and VIEW 2 (n=23 [1.9%]), the incidence rate of patients with SAEs in the fellow eye was similar to that of patients treated in the study eye with either aflibercept or ranibizumab. Analysis of the integrated data showed similar results. Many of the reported events were probably attributable to the additional presence of AMD in the contralateral eye and/or associated approved treatments (including ranibizumab) in the fellow eye (as permitted by study protocol).

In the fellow eye (which was not allowed to receive treatment with aflibercept or other unapproved investigational drugs, but was allowed to receive approved drugs such as ranibizumab), study drug-related ocular TEAEs were infrequent during the entire study period of 96 weeks. In VIEW 1, two patients were involved (one case of "vitreous floaters" in each of aflibercept 2mg Q4 and 2mg Q8 groups) and in VIEW 2, only 8 patients (0.7%; n=2 ranibizumab Q4, n=3 aflibercept 2mg Q4, n=2 0.5mg Q4, n=1 2mg Q8) were deemed to have study drug-related TEAEs in the fellow eye, including ‘cataract’, ‘macular degeneration’, ‘retinal haemorrhage’, ‘retinal oedema’, ‘subretinal fibrosis’, ‘visual impairment’, ‘injection site erythema’, ‘injection site pain’, and ‘intraocular pressure increased’. No study drug-related SAEs affecting the fellow eye were reported.

Table B30. Summary of safety data TEAEs during the entire study period

	Ranibizumab			Aflibercept								
	0.5mg Q4			2mg Q4			0.5mg Q4			2mg Q8		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
	N=304 n (%)	N=291 n (%)	N=595 n (%)	N=304 n (%)	N=309 n (%)	N=613 n (%)	N=304 n (%)	N=297 n (%)	N=601 n (%)	N=303 n (%)	N=307 n (%)	N=610 n (%)
Any TEAE			567 (95.3)			587 (95.8)			566 (94.2)			591 (96.9)
Non-ocular (systemic)			494 (83.0)			522 (85.2)			501 (83.4)			519 (85.1)
Ocular (study eye)			486 (81.7)			475 (77.5)			467 (77.7)			483 (79.2)
Any study drug-related AE												
Ocular (study eye)												
Non-ocular												
Any injection-related AE												
Any AE causing treatment discontinuation			21 (3.5)			26 (4.2)			39 (6.5)			30 (4.9)
Any AE-related death			15 (2.5)			12 (2.0)			16 (2.7)			18 (3.0)
Any SAE			170 (28.6)			158 (25.8)			168 (28.0)			177 (29.0)
Non-ocular (systemic)			146 (24.5)			131 (21.4)			152 (25.3)			154 (25.2)
Ocular (study eye)			26 (4.4)			22 (3.6)			19 (3.2)			24 (3.9)
Any study drug-related SAE												
Any injection-related SAE (study eye)												

NB. POOLED analysis for deaths is 'Any Death' not any AE-related death

Table B31. Integrated analysis: Ocular TEAEs in the study eye occurring in ≥5.0% of patients at preferred term level in any treatment group during entire study period (Baseline to Week 96)(SAF)

MedDRA preferred term	Ranibizumab	Aflibercept			
	0.5mg Q4 (N=595) n (%)	2mg Q4 (N=613) n (%)	0.5mg Q4 (N=601) n (%)	2mg Q8 (N=610) n (%)	Combined (N=1824) n (%)
Any ocular TEAE (study eye)	486 (81.7)	475 (77.5)	467 (77.7)	483 (79.2)	1425 (78.1)
Conjunctival haemorrhage	178 (29.9)	145 (23.7)	171 (28.5)	171 (28.0)	487 (26.7)
Retinal haemorrhage	85 (14.3)	85 (13.9)	82 (13.6)	99 (16.2)	266 (14.6)
VA reduced	67 (11.3)	76 (12.4)	76 (12.6)	79 (13.0)	23 (12.7)
Eye pain	62 (10.4)	74 (12.1)	60 (10.0)	54 (8.9)	188 (10.3)
Macular degeneration	49 (8.2)	54 (8.8)	52 (8.7)	57 (9.3)	163 (8.9)
Vitreous detachment	48 (8.1)	61 (10.0)	46 (7.7)	47 (7.7)	154 (8.4)
Cataract	37 (6.2)	53 (8.6)	51 (8.5)	40 (6.6)	144 (7.9)
Vitreous floaters	58 (9.7)	59 (9.6)	40 (6.7)	39 (6.4)	138 (7.6)
Increased IOP	64 (10.8)	48 (7.8)	37 (6.2)	47 (7.7)	132 (7.2)
Retinal oedema	23 (3.9)	21 (3.4)	27 (4.5)	42 (6.9)	90 (4.9)
Retinal degeneration	27 (4.5)	32 (5.2)	26 (4.3)	23 (3.8)	81 (4.4)
Maculopathy	32 (5.4)	23 (3.8)	37 (6.2)	19 (3.1)	79 (4.3)
Ocular hyperaemia	31 (5.2)	24 (3.9)	23 (3.8)	14 (2.3)	61 (3.3)

IOP=intraocular pressure

Note: Preferred terms are sorted in descending order by frequency in the aflibercept combined group.

Injection-related TEAEs and SAEs

Injection-related TEAEs in the study eye (solely based on the site investigator's assessment) were reported more frequently in VIEW 1 than VIEW 2. An on-site evaluation revealed that the mode of periprocedural anaesthesia (drop anaesthesia or subconjunctival infiltration) was handled differently in the two studies (i.e. more sites in VIEW 1 than in VIEW 2 employed the more burdensome subconjunctival anaesthesia using a needle for injection of the anaesthetic under the conjunctiva), and this may have

contributed to the observed incidence difference. Overall, there were no clinically meaningful differences in patients treated with aflibercept or ranibizumab in terms of frequencies or pattern of the reported injection-related TEAEs and events seemed to mainly include mild, uncomplicated and transient conditions.

The incidence of injection-related TEAEs was also higher in the primary phase of treatment (to week 52) than the extension treatment phase (week 52 to week 96/100) in both studies. This was as expected, because of the treatment regimen in the primary phase by which injections were given at fixed intervals of 4 weeks (including sham injections in the 2mg Q8 group) and in the extension treatment phase, treatment-free intervals of up to 12 weeks were permitted. The pattern of injection-related events, however, appeared to be similar in both phases of treatment.

Injection-related SAEs in the study eye were low, reported in 24 patients (12 in each study). Numerically, the event rate was slightly higher in the ranibizumab group than in any of the aflibercept groups, but overall (and given the low event numbers) no meaningful treatment group differences were observed. More cases of endophthalmitis were reported in VIEW 1, while more cases of cataract development were documented in VIEW 2.

Although no study-specific injections were to be applied to the fellow eye, there were reports of injection-related ocular TEAEs in the fellow eye during the two- study period [aggregated incidence: [redacted]% in the ranibizumab 0.5mg Q4 group, [redacted]% in the aflibercept 2mg Q4 group, [redacted]% in the 0.5mg Q4 group, and [redacted]% in the 2mg Q8 group]. As mentioned earlier, the fellow eye was allowed to receive any regionally approved treatment (e.g. open-label ranibizumab) for the management of AMD in accordance with the treating physician's decision and this might be a reasonable explanation for why some patients had injection-related events in the fellow eye. However, only two patients (from VIEW 1, both ‘endophthalmitis’) had injection-related ocular SAEs in the fellow eye.

Non-ocular TEAEs and SAEs

Non-ocular AEs reported over the entire study period covered a broad range of medical conditions (see Table B32) for aggregated non-ocular TEAEs applying an incidence cut of ≥2.5%). Many events were associated with respiratory infections. TEAEs potentially related to systemic VEGF inhibition, such as non-ocular haemorrhages or proteinuria remained uncommon throughout the study and similarly distributed among treatment groups in both VIEW 1 and VIEW 2 and in the integrated analysis. In VIEW 1, a difference in the incidence of transient ischaemic attacks (TIAs) was noted (2.0% [n=18 combined aflibercept group] versus 0.3% [n=1 ranibizumab]). In VIEW 2, the incidence of TIA was 0.7% (2 patients) in the ranibizumab 0.5mg Q4 group and 0.3% (3 patients) in the aflibercept combined group. Thus, the imbalance observed in VIEW 1 in terms of TIA occurrence was not apparent in VIEW 2 and a comprehensive analysis of arterial thromboembolic events, revealed an overall similar incidence and overall pattern between the groups.

The incidence of study drug-related non-ocular TEAEs was low in either study (see Table B30 and Table B32) and the type of events was consistent with those expected in this patient population. Overall, the number of non-ocular study drug-related TEAEs was driven by patients with events reported from VIEW 2 (42 patients vs. VIEW 1: 10 patients) but overall, the pattern / frequency of distribution of events were similar among treatment groups in analysis of the single studies and in the integrated analysis, with no apparent dose-relationship noted.

The incidence of non-ocular SAEs in both VIEW 1 and VIEW 2 was similar in patients treated with aflibercept and ranibizumab. Although some chance imbalances were noted sometimes favouring ranibizumab (VIEW 1: TIA) and sometimes favouring aflibercept (VIEW 1: myocardial infarction, coronary artery disease, pneumonia), the overall pattern of non-ocular SAEs and the lack of a dose-related trend, suggested that there were no meaningful differences in patients treated with one drug or the other. Numerically, the incidence of non-ocular SAEs over 96 weeks was slightly higher in VIEW 1 ([redacted]%) compared to VIEW 2 ([redacted]%) - in particular in the ranibizumab group

with an SAE incidence of [redacted]% [VIEW 1] vs. [redacted]% [VIEW 2] - but event patterns seemed to be similar.

In VIEW 1, only [redacted] patient (2mg Q8 group) experienced a non-ocular SAE considered drug-related ("cerebrovascular accident" of moderate intensity with resolution after 12 days of its occurrence). [redacted] patients ([redacted]%) in VIEW 2 had non-ocular SAEs deemed study drug-related during the complete course of the study ([redacted] patients [[redacted]%] in the 2mg Q4 group, X patient [[redacted]%] in the 0.5mg Q4 group, and [redacted] patients [[redacted]%] in the 2mg Q8 group). Apart from one case with renal failure (2mg Q8), all remaining cases were associated with cerebral or cardiac artery vessel disorders. The absolute number of events was small and therefore, this imbalance might have occurred simply by chance. Overall, the data did not support that treatment with aflibercept might be associated with an increased risk of non-ocular SAEs compared to treatment with ranibizumab.

Table B32. Integrated analysis of Non-ocular TEAEs occurring in ≥2.5% of patients in any treatment group during entire study period from baseline to Week 96 (SAF)

System organ class **MedDRA preferred term**	**Ranibizumab**	**Aflibercept**			
	0.5mg Q4 (N=595) n (%)	**2mg Q4 (N=613) n (%)**	**0.5mg Q4 (N=601) n (%)**	**2mg Q8 (N=610) n (%)**	**Combined (N=1824) n (%)**
Any non-ocular TEAE	[redacted]				
Infections and infestations					
Nasopharyngitis					
Bronchitis					
Urinary tract infection					
Influenza					
Upper respiratory tract infection					
Pneumonia					
Sinusitis					
Cystitis					
Investigations					
Blood glucose increased					
Protein urine present					
Urine protein / creatinine ratio increased					

Blood urine present Blood pressure increased Blood creatinine increased	[redacted]
Cardiac disorders Atrioventricular block first degree Atrial fibrillation Bundle branch block left	
Musculoskeletal and connective tissue disorders Back pain Arthralgia Osteoarthritis Pain in extremity	
Gastrointestinal disorders Diarrhoea Nausea Constipation Gastrooesophageal reflux disease Vomiting	
Injury, poisoning & procedural complications Fall Contusion	
Nervous system disorders Headache Dizziness	
Vascular Disorders Hypertension*	
Respiratory, Thoracic & Mediastinal disorders Cough Chronic obstructive pulmonary disease Dyspnoea	
Metabolism & Nutrition disorders Diabetes mellitus	

Hypercholesterolaemia	[redacted]
General disorders & administration site conditions Pyrexia	
Skin & subcutaneous disorders	
Neoplasms, benign, malignant, & unspecified (incl. Cysts / polyps) Basal cell carcinoma	
Renal & urinary disorders	
Psychiatric disorders Depression Anxiety	
Blood & Lymphatic system disorders Anaemia	
Immune system disorders Seasonal allergy	
Ear & labyrinth disorders Vertigo	
Reproductive system & Breast disorders	

* This is the single preferred term ‘hypertension’ Note: System organ classes (SOC) are sorted in descending order by frequency in the aflibercept combined group, preferred terms are sorted within each SOC in descending order by frequency in the aflibercept combined group

In general for SAEs, whilst the aflibercept groups had numerically higher incidences than the ranibizumab groups, the 2Q4 group had fewer events than the 2Q8 group, meaning that a causal relation to aflibercept is implausible (higher total dose with 2Q4 but fewer SAEs).

Deaths

In both VIEW 1 and VIEW 2, mortality was similar in patients treated with aflibercept or ranibizumab and the causes of death were consistent with the aged study population, including 20 from cardiac disorders and 17 from

malignancies. There was no indication of any relevant hazards associated with the administration of aflibercept at any dose as compared to ranibizumab. Deaths suspected to be drug-related by site investigators were very infrequent with a total of 2 patients involved, and, upon further investigation, reasonable alternative explanations for the fatal events could be identified. Overall, the analyses of deaths yielded consistent results across the 2 studies. Consequently, the aggregated mortality across the 2 studies was 2.8%, with no relevant imbalances among the 4 treatment groups (see Table B30).

Intraocular pressure (IOP)

Generally, the analyses of IOP measurements in the study eye over 96 weeks yielded consistent results across the 2 studies. There were no signs of sustained IOP increases found over the 96 week study period and comparison of study eye IOP data with a ‘reference group’ (i.e. fellow eye IOP in patients with uninjected fellow eye) did not reveal meaningful differences. It can thus be concluded that the injections did not affect the course of the study eye IOP as compared to the uninjected fellow eye and that intravitreal treatment with aflibercept at any dose over a period of up to 96 weeks is not accompanied by sustained increases in IOP.

Immunogenicity

During both studies, very low levels of treatment-emergent immunogenicity to aflibercept were exhibited, and minimal to no neutralising activity. Positive responses in the antidrug antibody (ADA) assay were detected mainly within the first 52 weeks of the studies, with minimal increases in either incidences or titres observed during the extension treatment phase. Many of the patients that were positive in the ADA assay exhibited a positive response at Baseline, prior to the first administration of drug, or were in the ranibizumab cohort and never even exposed to aflibercept. These results appear to be due to pre-existing immunoreactivity in the serum samples from the patients. Furthermore, the percentage of patients positive in the ADA assay at Baseline in each treatment group (approximately [redacted]% to [redacted]%) is similar to the apparent rate of treatment-emergent responses observed in each group. This suggests

that the actual immunogenicity rate may be [redacted] than those indicated by the ADA assay. The exploratory subgroup analyses of AEs and VA revealed no clinically meaningful differences between patients positive and negative in the ADA assay, indicating that the detection/presence of ADA to aflibercept did not impact safety or efficacy during the study period.

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

- A total of 1,824 patients constituted the safety population in the two phase 3 studies with up to 96 weeks of exposure to aflibercept, of which 1,223 patients were treated with the 2mg dose (n=610 2mg Q8).
- In terms of safety, aflibercept was well tolerated over 96 weeks of treatment with a similar safety profile to ranibizumab in relation to ocular and non-ocular AEs.
- The most common AEs were typical of injection procedure or underlying disease.
- Serious adverse events related to the injection procedure have occurred in less than 1 in 1,000 intravitreal injections with aflibercept and included endophthalmitis, traumatic cataract and transient increased intraocular pressure.
- Aflibercept injection only transiently increases IOP, the rate of IOP-related AEs in all aflibercept groups being in line with the ranibizumab arm.
- AEs potentially, or theoretically, related to systemic VEGF inhibition were uncommon and equally distributed among the four treatment groups.
- Consistent results were observed between the safety analyses of VIEW 1 and VIEW 2 except some chance findings, likely due to the small numbers of affected patients, that occurred in VIEW 1 and not VIEW 2.
- The 5 most common ocular study eye TAE (at least 5% treated with aflibercept) in the pooled total safety population up to 96 weeks were conjunctival haemorrhage (26.7%), eye pain (10.3%), vitreous detachment (8.4%), cataract (7.9%), vitreous floaters (7.6%) and increased IOP(7.2%).

AEs potentially, or theoretically, related to systemic VEGF inhibition were uncommon and equally distributed among the four treatment groups – Arterial thromboembolic events, including nonfatal myocardial infarction, nonfatal stroke, or vascular death (including deaths of unknown cause) occurred in 3.3% (60 out of 1,824) in the combined group of patients treated with aflibercept compared with 3.2% (19 out of 595) patients treated with ranibizumab in VIEW1 and VIEW2 during the 96 weeks study duration.

Consistent results were observed between the safety analyses of VIEW 1 and VIEW 2, indicating the validity of the safety results for aflibercept across a large study cohort and in a trial population that was similar in terms of ethnicity and age to the wet AMD population in England and Wales.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Clinical benefit of aflibercept

Aflibercept has been tested in double-masked, controlled RCTs (VIEW 1, VIEW 2), where administration of 2mg aflibercept (3 initial monthly doses then fixed 8-weekly injections over 52 weeks) provided comparable (statistically non-inferior) efficacy, in terms of prevention of moderate vision loss, to ranibizumab injections (every 4 weeks over 52 weeks). Both interventions were then given as needed during an extension phase to 96 weeks, but ‘capped’ such that all patients received at least one injection every 12 weeks. Stabilisation or improvement in visual function was maintained over the 96-week study period.

Other improvements, achieved during the first 52 weeks of proactive treatment, such as reduction in CNV area, reduction in CRT, and vision-related quality of life (as measured by NEI VFQ-25) were generally maintained during the reactive dosing (extension) phase of treatment.

Subgroup analyses showed that there are no restrictions regarding efficacy of 2mg aflibercept in relation to organ function such as renal impairment, liver function or diabetes status.

In the follow up phase, the 2mg Q8 aflibercept group received an average of 4.2 injections while the ranibizumab group received 4.7 injections. Of patients requiring the most intense therapy (in terms of injection frequency), 1.4 fewer injections were administered in the aflibercept 2mg Q8 group than ranibizumab-treated patients. The proportion of patients requiring frequent injections (≥6 injections) in the extension phase of treatment (week 52 to week 96) was higher in the ranibizumab group ([redacted]%) compared to aflibercept 2mg Q8 group ([redacted]%) and more patients in the 2mg aflibercept-treatment arms were given injections in the extension phase of treatment because the 12 weeks interval from the last injection had lapsed (aflibercept 2mg Q8 [redacted]%; ranibizumab 0.5mg Q4 [redacted]%).

Harms

Aflibercept was well tolerated, with a similar safety profile to ranibizumab, with regard to ocular and non-ocular adverse effects. The most common AEs were typical of injection procedure or underlying disease (conjunctival haemorrhage, eye pain, vitreous detachment, cataract, vitreous floaters, and increased IOP).

Serious adverse events related to the injection procedure were rare (8 patients in total over 96 weeks in VIEW 1/2). AEs that could relate to systemic VEGF inhibition e.g. arterial thromboembolic events (ATEs) were reported in 3.3% of aflibercept patients and 3.2% of patients treated with ranibizumab.

Summary of benefits and harms

The VIEW 1 and VIEW 2 studies demonstrated the efficacy and favourable safety profile of 2mg aflibercept IVT given every two months (after 3 initial monthly injections). These studies also provided evidence demonstrating that a 2-monthly injection regimen can occur without the need for monthly monitoring. Therefore, a clear positive benefit / risk balance is shown.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Quality of the clinical evidence base

The safety and efficacy of aflibercept were assessed in two large, prospective, randomised, double-masked, active-controlled, multicentre, studies (VIEW I and 2) against an active comparator, ranibizumab. This kind of rigorous study design is of wide international acceptance and use, and RCT design is generally considered the 'gold standard'. All efficacy and safety parameters assessed in VIEW 1 and VIEW 2, and the methods to measure them are standard variables and methods in clinical studies, and in UK ophthalmic practice. They are widely used and generally recognised as valid, reliable, accurate and relevant. All evaluations were in accordance with GCP to ensure safety of patients participating in research and quality of data.

In both pivotal studies (VIEW 1, VIEW 2), all three aflibercept dosing regimens were numerically similar and consistently shown to be non-inferior to ranibizumab with regard to the pre-specified primary efficacy analysis, i.e., the proportion of subjects maintaining vision after 52 weeks of treatment. In fact, in each study and for all comparisons, the actual upper limit of the CI of the difference between ranibizumab and aflibercept (≤ 3.1%) was substantially below the pre-specified, clinically meaningful non-inferiority margin of 10% and also below 5%. All sensitivity analyses conducted to assess the robustness of these results confirmed the findings of the primary analysis. The validity of these findings is further supported by the fact that, as is desirable for non-inferiority studies, the active comparator in VIEW 1 and VIEW 2 behaved in a manner entirely consistent with its clinical experience: i.e., the active comparator ranibizumab yielded success rates for the primary efficacy variable (94.4% of all subjects maintained vision in both VIEW 1 and VIEW 2) that were very similar to those obtained with monthly ranibizumab treatment in the pivotal studies ANCHOR(72) and MARINA(64) that had been used to support the registration of ranibizumab. In addition to VA outcomes, all 3 aflibercept dosing regimens, including 2 mg aflibercept dosed every 8 weeks, also similarly improved anatomic outcomes as compared to monthly

ranibizumab and, in both studies, vision-related QOL improved in parallel to vision improvement during the primary treatment phase, and was maintained during the second phase of the studies.

Capacity of clinical evidence to capture benefits of aflibercept

A benefit of fixed-dose aflibercept in the first year removes the uncertainty around treatment for wet AMD - eye care services can more easily plan their workloads and manage demand for services. It also enables patients to know in advance whether they are to receive an injection or not. Within current posology for ranibizumab, apart from when patients are receiving their second or third ‘stabilising’ injection, they do not know when a routine monitoring visit may turn into a further indication for treatment.

Employing a double masked design and using sham injections in the 2mg Q8 aflibercept arm, may have restricted the full practical advantages over monthly ranibizumab injections in the first 52 weeks of the studies. In other words, the impact of products with differing injection frequency on quality of life and healthcare resources e.g. removing the need for regular clinic appointments, reducing patient apprehension & experience of the injection procedure and reduced preparatory work for injections in the clinic, was not able to be directly measured or experienced, particularly in terms of health related quality of life (HRQL) measures such as the EQ5D. PRN dosing was also capped at 12 weeks meaning some patients were receiving injections earlier than may have been dictated by ‘clinical criteria’ for re-treatment. The trial may therefore underestimate such benefits that may be seen in clinical practice in England and Wales.

Disparity between clinical evidence and licensed regimens

Table B33: shows that there are disparities in the dosing schedule of aflibercept and ranibizumab applied in the VIEW study programme to that in the product labelling of ranibizumab(14) and the labelling for aflibercept and to the way ranibizumab is currently used in clinical practice.

Table B33: Comparison of posology of aflibercept and ranibizumab across the VIEW study programme, product labelling and clinical practice.

	Aflibercept	Ranibizumab
VIEW 1 & VIEW 2	2mg given intravitreally every 8 weeks (after 3 initial monthly doses) for the first 52 weeks. In the extension treatment phase (week 52 to week 96), dosing was determined by specific-dosing criteria with injections a minimum of 4 weeks apart and a maximum of 12 weeks apart	0.5mg given intravitreally every 4 weeks for the first 52 weeks. In the extension treatment phase (week 52 to week 96), dosing was determined by specific-dosing criteria with injections a minimum of 4 weeks apart and a maximum of 12 weeks apart
Approved product labelling in the UK (5;14)	The recommended dose for aflibercept is 2 mg aflibercept, equivalent to 50 microlitres. Aflibercept treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections. After the first 12 months of treatment with aflibercept, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections.	0.5mg intravitreal injection given monthly and continued until maximum VA is achieved i.e. the patient`s VA is stable for three consecutive monthly assessments performed while on ranibizumab treatment. Thereafter patients should be monitored monthly for VA. Treatment is resumed when monitoring indicates loss of VA due to wet AMD. Monthly injections should then be administered until stable VA is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month. Modelling for the regulatory assessment for the revised posology following a concept of individualized PRN treatment driven by monitoring of stability indicated an average of 8.4 injections for treat-to-target(73) which is similar to that previously modelled for VA guided administration (8.1 injections in the first year) and low threshold retreatment (8.4 injections in the first year)(74;75).
Clinical Practice	Not applicable	Clinicians in England and Wales prescribe ranibizumab on an individualised ‘as needed’ basis.

Aflibercept posology

The 2-monthly fixed dosing schema, following 3 initial monthly doses, with extended dosing intervals after 12 months is approved as the standard posology in the European licence. Results of the VIEW studies presented

earlier in Section 6, established that all 3 aflibercept dose regimens, and, in particular, 2 mg Q8 aflibercept (dosed every 8 weeks after 3 initial monthly loading doses), provided efficacy that was clinically equivalent (statistically non-inferior) to ranibizumab 0.5 mg Q4 (dosed every 4 weeks) at 52 weeks. This is in alignment with the US FDA-approved(10) and Australian label for aflibercept (Eylea®)(11).

The marketing authorisation for aflibercept does not require monthly monitoring. The 2-monthly fixed dosing in the first 52 weeks of the VIEW studies was per protocol and not driven by monthly monitoring, such as is routinely required for ranibizumab. The aim of introducing a fixed dosing schema was to decrease the need for this monthly monitoring, Therefore, because data from follow-up examinations conducted at non-dosing visits in the 2mg Q8 arm were only collected for analytic purposes and not used for clinical decision making (other than for withdrawal of patients), the results demonstrate that these efficacy benefits can be achieved with aflibercept 2mg Q8 without the need for between-visit monitoring. Also, there is a concern with treatment regimens involving reactive dosing in that, while some patients can achieve periods of apparent quiescence after initial anti-VEGF therapy, the disease can unpredictably recur with catastrophic manifestations such as submacular haemorrhage; these catastrophic events do not appear to be predicted by regular monitoring, but have been reported to occur if the patient is not continuing to receive regular anti-VEGF treatment(76;77). It is a reasonable assumption that a fixed dosing paradigm of demonstrated efficacy would not only serve to maintain initial vision gains, but might also reduce the risk of rare catastrophic events such as submacular haemorrhages.

In addition, aflibercept treatment can be extended after 12 months based on visual and anatomical outcomes. Some patients who did not need injections every 2 months received injections at 12-weekly intervals based on the capped design of the PRN extension treatment phase of VIEW 1 and VIEW 2 (47.4%), with efficacy still being maintained. Evidence is not yet available for longer intervals than 12 weeks between injections after 12 months.

Ranibizumab posology

The VIEW trials included a fixed monthly regimen of ranibizumab in the first 52 week period. Initial trials of ranibizumab, including some pivotal to its licensing in AMD(64;72), used a monthly dosing of intravitreal ranibizumab. During design of the VIEW study programme, available results from these ranibizumab trials indicated this regimen to be the most relevant comparator for any new active-controlled studies in wet AMD, hence the inclusion of monthly ranibizumab in the primary phase of VIEW 1 and VIEW 2 studies (78). However, current UK practice is based on a reactive and individualised form of 'as needed' dosing of ranibizumab, whereby the decision of whether to administer an injection is driven by regular monthly hospital monitoring visits.

The current EMA-approved posology for ranibizumab was revised in September 2011 based on a reanalysis of data from completed wet AMD studies which demonstrated that the originally approved PRN posology for ranibizumab, based on re-treatment in the case of a 5-letter loss of VA, was suboptimal(14;79). The revised posology follows a concept of individualised PRN treatment which is driven by monitoring of stability. The current posology still requires monthly monitoring. Monthly injections administered until no further improvement is observed and re-treatment initiated when there is a loss of VA due to disease activity). This also brought recommendations for dosing in wet AMD into line with recommendations for the additional DMO and RVO indications for ranibizumab.

Modelling for the regulatory authorities indicated an additional 2 injections (a total of 8.4) are required in the first year of individualised PRN ranibizumab treatment based on the stability concept compared to 5 letter loss VA-guided PRN(14). 8.1 and 8.4 injections for low threshold retreatment have also been estimated for the first year elsewhere(74;75).

Recent studies (including the CATT and IVAN studies) indicate that an 'as needed' schedule based on monthly review demonstrates reduced efficacy compared to a monthly schedule of ranibizumab injections(45;46;46). However, an 'as needed' regimen has the benefit of reducing risk of injection-related adverse events and enhancing patient convenience, by removing monthly injections(78). Patients are still required to attend hospital monthly to

be monitored for VA, and, usually, anatomical features, including the use of OCT(80). This requirement means that a reactive regimen with monthly monitoring still places significant burden on patients and already stretched healthcare services and finances, despite the lower frequency of injections(29). During the ranibizumab licence application process, results from the PIER study became available(65), indicating that the beneficial effect of ranibizumab on VA was reached after three monthly injections, when a plateau in VA was observed in responders. Even though a slight, approximately 2-letter additional VA gain was observed after the first three months, this was considered to be of low clinical relevance.

Nevertheless, increased demand on eye care services and cost containment has meant that in clinical practice, the monthly monitoring requirements of individualised PRN treatment, as stated in the label for ranibizumab, are increasingly difficult to achieve, and practice can be extremely variable between centres, depending on capacity(29). In addition, some local audit data indicate a lower number of injections in practice for patients with relatively good baseline VA compared to the average wet AMD population(81).

Some centres have a ‘two-stop’ system whereby assessments and injections are administered at separate visits, thereby increasing the number of monitoring visits for the patient in practice to two per month. As previously mentioned, recent evidence indicates that less frequent dosing (PRN or quarterly) is associated with lower VA outcomes compared with monthly(45;45). However, more evidence is needed to understand the full impact of how fewer injections and monitoring visits, driven primarily by resource availability, impacts on visual outcomes in practice compared to trial data.

In summary, it appears that despite alternative dosing regimens of ranibizumab not achieving the same efficacy as monthly ranibizumab, the general consensus is to treat with fewer injections in order to minimise the inconvenience of a monthly injection procedure and also to contain costs. It remains to be seen whether the new patient access scheme involving the

supply of discounted ranibizumab to the NHS will lead to any changes in clinical practice. As can be seen from the efficacy results, presented earlier in Section 6, the introduction of aflibercept provides the opportunity to treat with fewer injections than monthly ranibizumab whilst obtaining comparable efficacy, and to schedule fewer monitoring visits than current clinical practice.

Therefore, with regard to efficacy of 2-monthly aflibercept in comparison with ranibizumab at the currently approved dosing or its dosing in clinical practice, it is surmised that since fewer ranibizumab injections are administered in these schedules compared to the number of injections of ranibizumab administered in VIEW 1 and VIEW 2 (approximately 12 injections) in the first 52 weeks, aflibercept would remain at least non-inferior to ranibizumab.

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Evidence to support the use of aflibercept for the treatment of wet AMD is provided by results from VIEW 1 and VIEW 2. These were well designed trials i.e. large, prospective, randomised, double-masked, active-controlled, multicentre, and adequately powered, demonstrating the non-inferiority of aflibercept when compared with ranibizumab. These study characteristics, in addition to those described below, demonstrate the credibility and relevance of the evidence base to the decision problem.

Population

Adults with wet AMD' was the key inclusion criterion for VIEW 1 and VIEW 2 study entry. Therefore the population included within the clinical studies is reflective of the population within this appraisal. The demographic and baseline characteristics were representative of a population of patients with wet AMD. Approximately 89% (1,616/1,817) of the patients randomised to treatment with aflibercept across the VIEW studies were 65 years of age or older and approximately 63% (1,139/1,817) were 75 years of age or older.

The benefits of aflibercept were consistent across all subgroups (age, gender, race, renal function, hepatic impairment, baseline VA, lesion size and baseline CNV type) and geographical regions, demonstrating that a wide range of patients, typical of those presenting in clinical practice in England and Wales, can benefit from aflibercept. These analyses also showed that there are no restrictions regarding efficacy of 2mg aflibercept in relation to organ function such as renal impairment, liver function or diabetes status.

Comparators

Ranibizumab is the treatment used routinely in England and Wales within the NHS and was the comparator in VIEW 1 and VIEW 2. Ranibizumab was accepted by NICE for the treatment of wet AMD (with specific treatment criteria attached) in August 2008(20). NICE guidance was adopted by the SMC for Scotland(82). This NICE guidance was re-issued in May 2012(21). As discussed in section 6.10.2, there are disparities in the dosing schedule of aflibercept and ranibizumab applied in the VIEW study programme to that in the product labelling of ranibizumab(14) and to the way ranibizumab is currently used in UK clinical practice.

Intervention

The marketing authorisation for aflibercept does not require monthly monitoring, yet patients receiving the 2-monthly aflibercept fixed dosing in the first 52 weeks of the VIEW studies were required to attend follow-up examinations conducted at non-dosing visits in the 2mg Q8 arm. This was to preserve masking, and any monitoring data collected in the first 52 weeks were for analytic purposes only and not used for clinical decision making (other than for withdrawal of patients).

The VIEW studies evaluated various dosing schedules in terms of dose and frequency of injection, in order that an optimum dosing schedule for aflibercept that delivered at least comparable efficacy to ranibizumab with, if possible, fewer than monthly injections, could be determined. This is of direct benefit to the patient in clinical practice because of the anticipated reduced risk to patient safety due to fewer than monthly injections and a reduced

number of clinic visits but similar efficacy. In practice, comparing a fixed aflibercept 2mg Q8 regimen to ranibizumab PRN (including monthly monitoring), a treatment that does not require monthly monitoring visits is of benefit to the healthcare system, due to a reduction in the number of healthcare professional appointments and less demand for OCT assessments.

Outcomes

Wet AMD is characterised by abnormal CNV and retinal oedema that leads to loss of vision, with aetiology of the disease linked to VEGF, which promotes vascular growth and permeability.

In studies assessing the effects of anti-VEGF agents, therefore, it would be of direct relevance to include outcome measures involved with the assessment of treatment effects on vision and also assessment of aflibercept's ability to halt or slow disease progression.

The main impact of the disease is the loss or change in vision. With this in mind, the primary efficacy endpoint in VIEW 1 and VIEW 2 was an assessment of how frequently aflibercept was able to maintain visual function (or VA) i.e. the proportion of patients who maintain vision at Week 52. Maintenance of vision was determined if patients had lost fewer than 15 letters in the ETDRS letter score compared to baseline. During assessment, letters are read from standard eye-charts, commonplace worldwide. Eye charts are used routinely in 'eye tests' in clinical practice in the UK.

In both pivotal studies (VIEW 1, VIEW 2), all three aflibercept dosing regimens were numerically similar and consistently shown to be non-inferior to ranibizumab with regard to the pre-specified primary efficacy analysis, i.e., the proportion of subjects maintaining vision after 52 weeks of treatment. The validity of these findings is further supported by the fact that, as is desirable for non-inferiority studies, the active comparator in VIEW 1 and VIEW 2 behaved in a manner entirely consistent with the clinical experience with monthly ranibizumab treatment in the pivotal studies ANCHOR(72) and MARINA(64), used to support the registration of ranibizumab.

Change in visual acuity in the VIEW studies was measured in terms of the study eye. This is consistent with other clinical trials for wet AMD, such as those reviewed in the systematic review. However, VA (the whole person), as stated in the scope for this appraisal, has been addressed in the context of cost effectiveness (section 7.3).

Secondary and other exploratory endpoints which further assessed the effects of aflibercept on vision included: change in VA as measured by ETDRS letter score; proportions of patients gaining or losing ≥ 15 or 30 letters from baseline to week 52 and 96; proportions of patients gaining ≥ 0 or 10 letters of vision; proportions of patients with VA of 20/40 or better and VA of 20/200 or worse. Again, these utilised the ETDRS chart which are valid clinical measures of visual function in practice (alongside the Snellen chart).

In addition to VA outcomes, all 3 aflibercept dosing regimens, including 2 mg aflibercept dosed every 8 weeks, also similarly improved anatomic outcomes as compared to monthly ranibizumab. In respect of assessing anatomic correction of the disease and the decrease in retinal swelling and fluid, outcomes assessed included ‘change in CNV area’, ‘Mean change from baseline in CRT as measured by OCT’, ‘Proportions of patients showing complete resolution of FA leakage’, ‘mean change from baseline in total lesion area and area of Fluorescein leakage as assessed by FA’, ‘Change from baseline in greatest linear diameter of lesion on FA (VIEW 2 only)’ and ‘Change from baseline in classic CNV area’. Fundus photography, FA and OCT are routine procedures for retinal imaging and results of these assessments are directly applicable to observing the extent of disease progression in wet AMD. The extensive number of variables examined in VIEW 1 and VIEW 2, provide a very robust and compelling demonstration of the efficacy of aflibercept and since the primary and secondary efficacy variables in the VIEW study programme were also analysed at Week 96, evaluation of persistence of efficacy of aflibercept over a longer term was possible. This is useful since, in practice, patient requirements for treatment will not be limited to 12 months.

The safety profile and patient tolerability were also evaluated at 4-weekly intervals over the entire study period (up to 96 weeks) – important features for any new product before it can be accepted for use in a broader population, and integrated into standard clinical practice. All AEs were assessed for seriousness, intensity, pattern, study drug action, drug treatment, causal relationship to study drug, and causal relationship to the injection procedure. Aflibercept was found to be well tolerated with an acceptable safety profile and without notable differences compared to ranibizumab 0.5mg Q4 in ocular and non-ocular TEAEs.

The most common ocular AEs were typical of injection procedure or underlying disease and occurred at similar rates across all treatment groups. Overall, cases of endophthalmitis were infrequent. Injection-related TEAEs seemed to mainly include mild, uncomplicated and transient conditions. As injection-related TEAEs in the study eye were reported more frequently in VIEW 1 than VIEW 2, it is worth highlighting that the mode of periprocedural anaesthesia was different across the studies - more sites in VIEW 1 than in VIEW 2 employed the more burdensome subconjunctival anaesthesia using a needle for injection of the anaesthetic under the conjunctiva versus drop anaesthesia). This may have contributed to the observed incidence difference.

There is low systemic exposure after intravitreal injection with aflibercept. This was borne out in the low incidence of non-ocular SAEs and non-ocular drug-related TEAEs reported in the studies.

AEs potentially, or theoretically, related to systemic VEGF inhibition (e.g. non-ocular haemorrhages or proteinuria) were uncommon and equally distributed among the treatment groups, as was the incidence of adjudicated arterial thromboembolic events (non-fatal myocardial infarctions, non-fatal strokes, and fatal vascular events) based on the definition used by the Anti-Platelet Trialists' Collaboration (APTC). APTC events are the most clinically important arterial thromboembolic events because they represent irreversible morbidity or mortality.

It can be concluded from the safety analysis that as one of the main safety risks associated with the treatment of wet AMD is the intravitreal injection procedure itself, safety issues should decrease with less frequent than monthly injections.

Patient reported outcomes were also included in VIEW 1 and VIEW 2. These assessments are important as they are reported and/or scored directly by the patient, free of interpretation by a clinician. It is an account of how the patient functions or feels relative to a health condition or therapy and a useful indicator as to how patients might experience the treatment in clinical practice and how the therapy impacts on aspects of daily living and health related quality of life. 'Change in total NEI VFQ-25 score from baseline to week 52' was a secondary endpoint measuring vision-related QOL. Total score and subscales (i.e. near activities, distance activities, and vision dependency) of the questionnaire were assessed. In both studies, vision-related quality of life improved in parallel to vision improvement during the primary treatment phase, and was maintained during the second phase of the studies. The changes were nearly identical in all treatment groups - the mean NEI VFQ-25 total score had improved from baseline to week 96 (week 96/100 VIEW 2) by 4-6 points. A change in NEI VFQ-25 total score of 4-6 points corresponds to a 15-letter gain in BCVA and is considered clinically meaningful. This is an important benefit for a person with wet AMD, as an improved vision-related QOL can mean the difference between being independent and dependent, improved wellbeing, and also mean they are less at risk of falls due to visual problems(83-85).

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The results of the VIEW 1 and VIEW 2 trials are directly applicable to the population of wet AMD patients in England and Wales who are eligible for anti-VEGF treatment. There is no evidence to suggest that the efficacy and safety of aflibercept would be different in this, or a wider UK population.

VIEW 1 and VIEW 2 studies were conducted mainly in patients described as of 'White race' (84.8% patients) in the integrated analysis of the two studies, which reflects the population in England and Wales(86).

Similarly the average age in the VIEW trials (76 years) is similar to the UK wet AMD population, where the majority of patients are over 70 years of age(85). Those included in the VIEW trials had not received prior therapy but the treatment of these patients is not excluded from the anticipated marketing authorisation and there is growing experience of treatment in these patients in other countries(87).

Ranibizumab (as PRN dosing) is the treatment used most commonly in England and Wales within the NHS. Ranibizumab was the comparator in VIEW 1 and VIEW 2. As discussed in section 6.10.2, there are disparities in the dosing schedule of ranibizumab applied in the VIEW study programme to that in the product labelling of ranibizumab(14) and to the way ranibizumab is currently used in UK clinical practice (see section 6.10.2 for a full discussion around this aspect). In addition, recent studies (CATT and IVAN (45;46)) have indicated that efficacy of monthly 0.5mg ranibizumab is better than the PRN dosing.

With regard to efficacy of 2-monthly aflibercept in comparison with ranibizumab at the currently approved dosing (TTT) or its dosing in clinical practice (PRN), it is surmised that since fewer ranibizumab injections are administered in these schedules compared to the number of injections of ranibizumab administered in VIEW 1 and VIEW 2 (approximately 12 injections) in the first 52 weeks, aflibercept would remain at least non-inferior to ranibizumab.

The benefits of aflibercept over ranibizumab i.e. less monitoring visits and non-inferior efficacy when compared to monthly ranibizumab (with fewer

injections) will mean that wet AMD patients can now receive a proven treatment and dosing schedule without a compromise in efficacy. Both clinician (and patient) can be confident that they are giving (and receiving) per-protocol treatment.

Fixed-dose aflibercept in the first year also removes the uncertainty around treatment for wet AMD. Eye care services can more easily plan their workloads and manage demand for services. It also enables patients to know in advance whether they are to receive an injection or not. Within current posology for ranibizumab, apart from when patients are receiving their second or third ‘stabilising’ injection, they do not know when a routine monitoring visit may turn into a further indication for treatment.

Also, in contrast to ‘as needed’ PRN regimens which require complex treatment decisions during monthly monitoring visits, the fixed every 2-monthly regimen in the first year does not depend on making such treatment decisions.

Current guidelines for ranibizumab treatment of wet AMD include monthly monitoring, with injections as needed, in order to improve and maintain VA. The variable and resource intensive treatment regimens and the need for continuous monthly monitoring impact on service organisation, resource availability and budgets(29). These monthly visits can be lengthy, causing inconvenience not only for the patient but also their caregiver, especially in terms of travel time and costs but also missed work days. This inconvenience is heightened when, in some areas, injections and monitoring are scheduled in separate clinics, requiring up to two visits in every month that an injection is required. As well as the impact on healthcare services this creates, if inadequately treated, patients with wet AMD often become high users of healthcare, community support and social welfare services as a result of sight loss causing falls, social isolation and loss of independence(29). Hence, there is an unmet need for effective therapies that reduce the burden of mandatory monthly monitoring visits(88;89).

The fixed 2-monthly dosing schedule for aflibercept in the first year and the opportunity for extended treatment intervals beyond 12 months, without the need for additional monthly monitoring, is expected to reduce per patient resource use of eye care services, upon implementation of aflibercept treatment in England and Wales. The size of the reduction (compared with if just ranibizumab was being used) will depend on current ranibizumab treatment schedules used within each hospital in England and Wales - market research suggests wide variation in injection frequency and also in adherence to the monthly monitoring guidelines associated with ranibizumab.

An additional advantage around the potential for fewer injections when compared with monthly ranibizumab and also compared with numbers of injections required in some trials of ranibizumab PRN such as the CATT study(45) is a reduction in the risk for the patient, associated with each intravitreal procedure. During the clinical studies it was apparent that a large part of the adverse event reporting was driven by the injection procedure itself. With each intravitreal administration, there are serious risks of endophthalmitis, retinal detachments, traumatic cataract, and increased. It is also suggested that regular fixed dosing may reduce the risk of rare catastrophic events such as submacular haemorrhage, reported with treatment regimens involving PRN dosing.

The trials may have underestimated benefits that may be seen in clinical practice in England and Wales. As highlighted in Section 6.10.2, the double masked design and sham injections in the 2mg Q8 aflibercept arm, and capped PRN dosing for all groups at 12 weeks (extension phase), may have restricted experience of the full practical advantages of aflibercept 2mg Q8 fixed-dosing, on quality of life and healthcare resources e.g. removing the need for regular clinic appointments, reducing patient apprehension and experience of the injection procedure, reduced preparatory work for injections in the clinic.

Based on the clinical evidence presented, the introduction of aflibercept can:

- Provide a more predictable dosing schedule and hence more predictable drug costs and service planning when compared with PRN ranibizumab.
- Remove the need for patients to attend hospital every month regardless of whether or not they need an injection;
- Introduce more certainty around treatment efficacy than is possible with PRN regimens.
- Have the potential to decrease resource use within eye care services per patient through. freeing of clinic capacity as a result of the reduced monitoring requirements
- However, the introduction of fixed dose aflibercept may require a short term change of service planning to gain the long term benefit of reduced monitoring.

Patient selection – use of aflibercept in clinical practice

It is not anticipated that there will be any additional tests or investigations required for selection of patients appropriate for aflibercept, over and above the current routine assessments of wet AMD. Moreover, it is expected to reduce this burden by reducing the frequency of assessments.

Although no specific studies in patients with hepatic and/or renal impairment were conducted with aflibercept, subgroup analyses of study data showed that there are no restrictions regarding efficacy of 2mg aflibercept in relation to organ function such as renal impairment, liver function or diabetes status. Hence, available data do not suggest a need for a dose adjustment with aflibercept in these patients.

Aflibercept must be administered by a qualified ophthalmologist experienced in intravitreal injections. The injection procedure would be similar to that of ranibizumab, already in use in England and Wales. Therefore, it is not expected that additional training of healthcare personnel would be required.

What proportion of the evidence base is for the dose(s) given in the SPC?

The evidence base included 0.5mg Q4, 2mg Q4 and 2mg Q8 doses of aflibercept. The dose selected to take forward to licensing / marketing authorisation is the 2mg Q8 dose given in the SmPC.

7 Cost effectiveness

Summary

- The economic evaluation of aflibercept for wet AMD is based on a de novo economic model. Publications of models found in the systematic search did not specifically address the decision problem for this appraisal.
- A Markov model which incorporates the VA of both eyes was developed, as defined in the scope and as preferred in previous NICE eye appraisals(40-42), in a series of 31 health states.
- Transition probabilities are based on data from the ITC including the VIEW and CATT studies which was not able to demonstrate any significant differences between aflibercept fixed and ranibizumab as needed based on monthly evaluations. Although the ITC was limited substantially by the evidence available, which varied in terms of baseline characteristics, retreatment criteria and number of injections, this was the best evidence available to address the decision problem as the pivotal VIEW trials compared aflibercept every two months, after three initial monthly doses, to monthly (not PRN) ranibizumab in the first 52 weeks for non-inferiority.
- Frequency of injections and monitoring for both aflibercept and ranibizumab are based on the regimens specified in the UK marketing authorisations.
  - Ranibizumab dosing is a reactive regimen based on monthly monitoring
  - Aflibercept is administered initially for three monthly doses, then every other month in a fixed regimen without monitoring in between. After the first 12 months, dosing may be less frequent and there is no requirement for monthly monitoring.
  - This led to a considerable reduction in cost of monitoring for aflibercept compared with ranibizumab
- Adverse events were not included given the low rates of relevant adverse events and similar safety profiles for aflibercept and ranibizumab.
- Given the lack of evidence for latter years of treatment, a conservative approach has been taken with regard to making similar assumptions for aflibercept and ranibizumab with regard to frequency of injection, monitoring, discontinuation and treatment effect.

- Utilities have been taken from EQ5D values from VIEW 2 (not in VIEW 1) as this is the preferred NICE method and can be linked to data on the VA of both the study eye and the fellow eye, for which data was collected.
  - These utility values capture the benefits of treating the worse-seeing eye but were not able to capture the benefits of reduced monitoring as patients had monthly assessments for safety/masking purposes.
- The economic evaluation demonstrated that aflibercept is a cost effective option compared with ranibizumab for the treatment of wet AMD.

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

A systematic literature review was performed in order to identify existing cost-effectiveness studies in the treatment of wet AMD. Additional to the cost-effectiveness evaluations this search was also designed to identify utilities, resource use and cost estimates in wet AMD (see section 7.3).

The review of the literature covered both electronic medical databases and the Internet. The search included bibliographic reference lists of included studies and formal health technology assessment (HTA) documents. The original review focused on studies published between 1995 and 2010 in Europe and the United States. An update of the original review was carried out in 2012. Papers published before 1995 were considered not to be relevant to the purpose of the search on the assumption that economic evaluations of currently used wet AMD treatments would not be published before that time, and resource use and cost estimates published more than 15 years ago are

unlikely to be relevant. Conference abstracts were searched for the previous two years. It was expected that abstracts submitted before that would have been published within two years. There were no date restrictions on the searches for HTA documentation. No language restrictions were applied in the search strategy.

The full search string is reported in Appendix 10 and includes: population, interventions, outcomes, study type and limits. Inclusion and exclusion criteria for the electronic search are reported below (criteria include search for utilities, resource use and cost estimates additional to the economic evaluations):

The study types included were; studies performed in Europe and the United States, economic analyses of wet AMD treatments (including economic models and analyses alongside clinical trials), utility studies for wet AMD or VA health states or relevant AEs, resource use and cost studies (e.g., cost of illness estimates) relevant to wet AMD, visual impairment, or pre-specified adverse events. Reviews, letters or comment articles that discuss costs but in which cost estimates are not evidence-based were excluded.

The patient population of interest for inclusion was patients with wet AMD (including patients with sub macular hemorrhage secondary to AMD). Studies of patients with dry AMD, AMD of undefined stage or type, polypoidal choroidal vasculopathy, retinal vein occlusion-related macular edema, chronic cystoid macular edema, idiopathic macular telangiectasia, CNV secondary to causes other than AMD, DMO and neovascular secondary to central exudative chorioretinopathy were excluded.

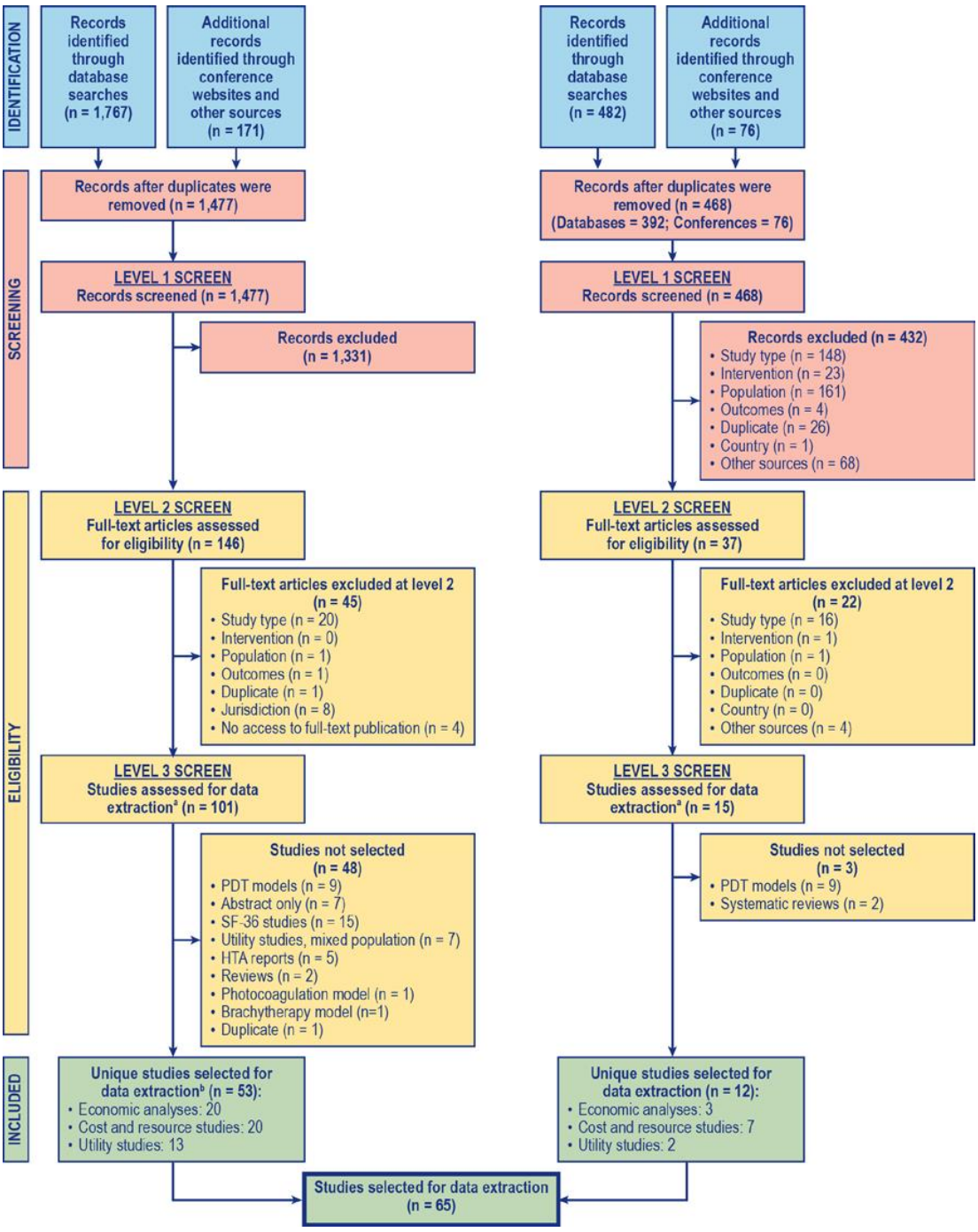
The initial search of economic evaluations *was of a wider scope than the decision problem for this appraisal*. Studies of aflibercept (VEGF Trap-Eye, Eylea), ranibizumab (Lucentis), pegaptanib (Macugen), bevacizumab (Avastin), verteporfin (Visudyne) PDT, and laser photocoagulation were originally included. Therefore, following screening by title and abstracts and then full text, economic analyses evaluating other treatments were deprioritised because ranibizumab has become the standard of care following

its recommendation by NICE for wet AMD and these comparators are no longer relevant to the decision problem. Studies where only an abstract was available were excluded and utility, resource use, and cost studies were not subject to inclusion and exclusion criteria for study interventions.
Supporting documents for the NICE technology appraisal for pegaptanib and ranibizumab for the treatment of AMD (TA155) were excluded because the manufacturer models had already been published(19).

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) diagram, adapted from Moher et al 2009(90), reporting included and excluded studies is shown below (the diagram also reports utilities and cost/resource use studies).

Figure B12 PRISMA Diagram for Study Inclusion and Exclusion: Original Review (Left Diagram) and Review Update (Right Diagram)

HTA = health technology assessment; PDT = photodynamic therapy; SF-36 = Short-Form 36-Item Health Survey. Diagram includes search for utilities and cost and resource use.



Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

20 unique economic studies were included in the data extraction phase. Smiddy 2009(91) was an update of Smiddy 2007(92;93) and there was the poster version of the full-text publication, therefore they were excluded and 18 articles were extracted into this report. At the review update, 3 articles were included for data extraction.

The majority of the 21 economic evaluations were Markov models; time horizons ranged from 1 year (Cohen et al 2008(94)) to lifetime (Hernández-Pastor et al 2010(95); Javitt et al 2008(96)). The majority of studies used QALYs as the main measure of benefit; other benefit measures included line years, vision years (years with VA > 20/200), the proportion of patients with VA improvement; and the proportion of patients with legal blindness avoided. Of the 21 unique economic studies that were extracted, 17 evaluated ranibizumab and one evaluated aflibercept(91). The study reported a cost-effectiveness model evaluating the cost per line-year of life expectancy (cost per line-year) of patients with wet AMD in the United States.

Study quality was generally poor, with overall quality ratings below 50% for all but 2 studies (Javitt et al 2008(96) and Wolowacz et al 2007(97)), using the checklist reported by Zimovetz et al(98) and presented at ISPOR in 2009.

Given that none of the evaluations address the decision problem, a detailed description of each economic evaluation is reported in Appendix 10.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated

instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

The quality assessment of cost-effectiveness studies was conducted using the checklist reported by Zimovetz et al(98). The full assessment for each study is reported in Appendix 11.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The base case analysis considers the population from the VIEW 2 trial. As outlined in section 1.6 patients included in the VIEW trials were adults with neovascular (wet) AMD. Specifically this analysis uses data derived from the VIEW 2 trial for the calculation of health state utilities, given the inclusion of the EQ5D, and for the VA distribution of the model cohort at baseline, year 1 and year 2.

As outlined in section 1.3 aflibercept solution for injection has gained marketing authorisation for a similar population to that described in the VIEW studies. As such the patient population in this analysis represents both the

[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.
[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

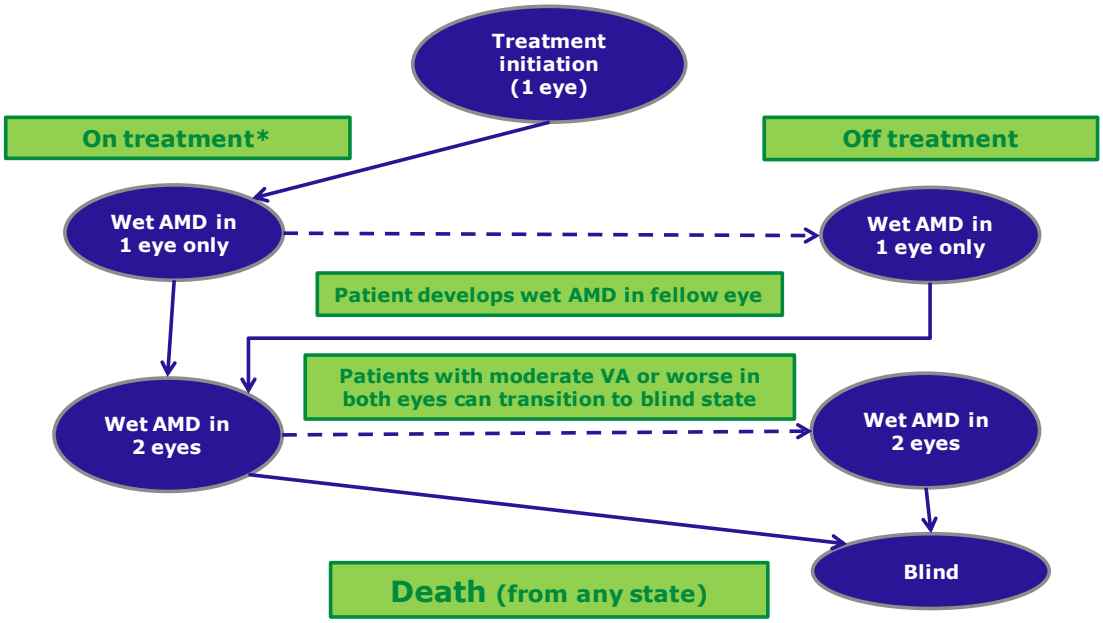
licensed indication, the population from the VIEW 2 trial and the population specified in the scope for this appraisal.

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

The economic model was developed to assess the lifetime clinical and economic consequences of using aflibercept to treat adults with wet AMD. The model is a Markov state-transition cohort model that includes 30 health states for patients who are on treatment and a similar set of health states exist for patients who are not receiving active anti-VEGF treatment. These health states are based on the concept of a two-eye model (treated eye and fellow eye) where each health state is defined by the combination of VA in both eyes i.e. each eye may have NVI, mild, moderate, severe or blind VA (see 7.2.4). The treated eye is also sometimes referred to as the 'first eye'. The fellow eye is also referred to as the 'second eye'.

Figure 13: Diagram of the model structure



Five of the 30 health states are for patients who have not developed wet AMD in the fellow eye and the remaining 25 are for patients who developed wet

AMD in the fellow eye. For each health state patients may be either on or off active anti-VEGF treatment. In addition for health states where wet AMD is present in both eyes patients can be either treated in one or both eyes.. All health states are represented in Table B34.

Table B34: Combinations of VA levels in the two eye model
Stated number as a function of VA in treated and fellow eye

	Visual acuity in treated eye				
Visual acuity in fellow eye	**No vision impairment**	**Mild vision impairment**	**Moderate vision impairment**	**Severe vision impairment**	**Blind**
No vision impairment and no wet AMD*	1	2	3	4	5
No vision impairment	6	7	8	9	10
Mild vision impairment	11	12	13	14	15
Moderate vision impairment	16	17	18	19	20
Severe vision impairment	21	22	23	24	25
Blind	26	27	28	29	30

* In other rows wet AMD is present in the fellow eye as well as the treated eye

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

A state transition Markov model was developed in Microsoft Excel. The model has the ability to simulate the movement of a cohort of patients who transition through a number of defined health states over time, and capture the different costs and outcomes that patients experience when they are given alternative interventions. Wet AMD is a chronic progressive condition and the model is designed to simulate disease progression over a life time horizon where 99% of the model cohort have died within 25 years of treatment initiation.

One-month Markov cycles are used throughout the model timeframe. Given that individualised PRN treatment with ranibizumab requires monthly

monitoring according to its SmPC, and this is more frequent than the monitoring for aflibercept or the treatment administration for both aflibercept and ranibizumab, this is an appropriate cycle to capture costs and benefits.

This simulation incorporates the concept of a two-eye model by taking account of the VA of both eyes. Economic models based on the BSE have been criticised by reviewers for NICE and the SMC for being over-optimistic and unrealistic. Therefore, despite a two-eye model being potentially more complex in design and more difficult to populate with data, a model that incorporates the BCVA of both eyes have been designed. Given that, in real life, people have two eyes and their HRQL is affected by the BCVA of both eyes, this better represents reality. In addition, wet AMD can be a bilateral disease and a two-eye model enables consideration of the impact of the second eye being affected and how it is managed.

The following sections outline in further detail the rationale for each of the key health states in the model.

7.2.4 Please define what the health states in the model are meant to capture.

Health states in the model and previously presented in Table B34: are designed to capture the visual acuity of both the treated and the fellow eye for patients with wet AMD. Each eye is able to have one of five possible VA levels, defined by an ETDRS letter range. The levels and their definitions are as follows:

- (1) No vision impairment (NVI) >80;
- (2) Mild vision impairment 80-66 Letters;
- (3) Moderate vision impairment 65-51 Letters;
- (4) Severe vision impairment 50-36 Letters; and
- (5) Blind <36 Letters

The definition of the health states represent a logical combination of the definition of blindness in terms of VA, the available evidence reported as gains

and losses of letters from baseline in available RCTs and the need to have consistent transitions between the median value of health state ranges:

- Blindness is defined as having a visual acuity of 3/60 (35 ETDRS letters) or worse based on based on the definition for severe sight impairment (blindness) used by the UK department of health and NHS. This definition of visual impairment was used to anchor the blind state(99).
- The other states were set to have a width of 15 letters as the available RCTs provided data on either gaining or losing 15 or 30 letters of VA.
- Patients were assumed to have the median visual acuity of each range and transition to the median value of either the adjacent state or the state two levels higher, based on the number of letters gained or lost. For example a patient with moderate visual impairment who gained either 15 or 30 letters would transition to either the mild or NVI health state respectively.

The model reported here is a two-eye model where the VA of both eyes is used to define each health state. There are a total of 30 different health states composed of the 25 possible combinations of the 5 levels of VA for the treated and fellow eye (Table B34:). The first 5 health states are composed of the five VA levels in the treated eye and no wet AMD developed in the fellow eye – where the fellow eye is assumed to have no visual impairment as long as it does not develop wet AMD. In addition to the 30 health states representing different visual acuity levels there is also an additional absorbing health state of death which patients can transition from any other health state.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

Wet AMD is a chronic, progressive condition that directly affects vision and this, in turn, can impact on the HRQL of patients. In clinical trials, the efficacy

of treatment is primarily measured in terms of improving or maintaining visual acuity. By defining health states that represent the different levels of BCVA in each eye, patients are able to either loose or gain visual acuity by transitioning to health states with either a higher or lower median value of ETDRS letters.

If inadequately treated, patients with wet AMD can develop severe vision loss and even blindness. Disease progression (natural history) in the model is defined by two parameters which specify the probability that patients either lose 15 or 30 letters of vision. These probabilities are derived from a meta-analysis by Wong et al(50) and define the change in VA during the natural history of patients with wet AMD, this is the definition of disease progression that is used for patients in the best supportive care arm (BSC) arm of the model, when patients are not on active treatment. In addition patients with wet AMD in the treated eye have a risk of developing wet AMD in the fellow eye.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table B35: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	25 years	A lifetime horizon was used to quantify the full impact of costs and outcomes for the different treatments. 99% of patients with wet AMD die within this timeframe.	NICE Methods of Technology Appraisal 2008
Cycle length	1 month	The cycle length is based on the monitoring frequency for ranibizumab and the likely minimum amount of time that changes in vision would be noticed.	Ranibizumab SmPC(14)
Half-cycle correction	Not applied	Unnecessary when using a short cycle length	Not applicable
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE reference case	NICE Methods of Technology Appraisal 2008
Discount of 3.5% for utilities and costs	3.5%	NICE reference case	As above
Perspective (NHS/PSS)	NHS/PSS Perspective	NICE reference case	As above

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The economic analysis includes the treatments outlined below for the treatment of adults with wet AMD:

- Intervention: aflibercept solution for injection 2 mg
- Comparator: ranibizumab 0.5 mg

Both treatments have been incorporated into the economic evaluation according to their UK marketing authorisations. Both treatments are licensed in the UK for the treatment of neovascular (wet) AMD.

Dosing and monitoring frequency for both aflibercept and ranibizumab has been estimated based on the regimens specified in the SmPCs:

- Aflibercept: *"The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microlitres…Eylea treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections…After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections."(aflibercept SmPC)*
- Ranibizumab: *"The recommended dose for Lucentis is 0.5 mg given monthly as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml…Treatment is given monthly and continued until maximum visual acuity is achieved i.e. the patient`s visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment…Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed when monitoring indicates loss of visual acuity due to wet AMD. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month."(14)*

Treatment with aflibercept in the VIEW trials is generally similar to that described in the SmPC, although trial participants were subject to monthly assessments for safety/masking purposes and the treatment regimen in weeks 52 to 96 as needed was capped at a minimum of every 12 weeks. RCT evidence beyond the trial duration is not available.

Given that the decision to revise the ranibizumab SmPC in September 2011 was based on a post-hoc analysis of the pivotal studies by the regulatory authorities, the inclusion of efficacy data for this specific regimen was not available(79): *"The originally approved posology in wet AMD, based on three initial monthly injections and re-treatment in case of a 5-letter loss of VA, was not optimal…Analyses of the currently available monotherapy data from completed AMD studies (MARINA, ANCHOR, PIER, EXCITE, SUSTAIN, MONT BLANC, DENALI) were carried out. This was the basis for an update of the SPC and Package Leaflet with an alternative posology for the ranibizumab treatment of patients with wet AMD following a concept of an individualised PRN treatment which is driven by monitoring of the stability…The SPC was brought in line with the recommendations for DME and RVO-indications, based on a 'stability concept' (i.e. monthly injections administered until no further improvement is observed and re-treatment initiated when there is a loss of Visual Acuity due to disease activity)."* The regulatory authorities estimated an average of 8.4 injections in the first year with this regimen, which we have included(73).

7.2.8 Has a treatment continuation rule been assumed?

The SmPC for aflibercept does not specify any stopping rules for treatment. No additional treatment continuation rules have been assumed. Please see section 7.3 for assumptions regarding discontinuation.

7.3 Clinical parameters and variables

Please demonstrate how the clinical data were implemented into the model.

7.3.1 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Treatment years 1 and 2

<u>Aflibercept arm</u>

Clinical trial data from the aflibercept 2mg Q8 arm of the VIEW 2 trial was incorporated into the model to define the baseline distribution of the patients throughout the health states at model start. During years one and two of the simulation the distribution of the patients at 52 and 96 weeks from the clinical trial data was reproduced.

The analysis of the trial data was based on the LOCF population. Based on the reported ETDRS letters for the study eye patients were grouped into a VA range aligned to the ranges used in the model (NVI, Mild, Moderate, Severe, Blind) (as reported in section 7.2.4). The analysis was reproduced at three time points: baseline, 52 weeks and 96 weeks.

After grouping patients from the VIEW 2 trial data at baseline into the VA distributions defined in the model, as small proportion of the patient population were classified as having a blind study eye (<36 ETDRS letters). In order to incorporate the VIEW 2 trial data as accurately as possible, patients classified as having a blind study eye were treated in the model for years 1 and 2. For years 3-5 an assumption was made that blind patients would not be treated in their blind eye(s) based on clinical opinion indicating that blind eyes are unlikely to benefit from treatment and would not normally be treated in practice.

Two linear trends were used to populate the monthly model cycles; one for cycles 1 to 12 and the second one for cycles 13 to 24. The first trend was calculated based on the baseline and year one VIEW 2 trial data as starting and end points, respectively; the second trend was calculated using the year one and year two VIEW 2 trial values. The ITC provided 12/24 month data.

The mortality rate at 96 weeks for the aflibercept 2mg Q8 arm was obtained from the VIEW 2 study, which included the EQ5D, and applied to model cycles by assuming a linear trend over the two year period.

A treatment discontinuation rate was also applied based on the average of the discontinuation rates reported for the aflibercept 2mg Q8 arm in the VIEW 2 trial and the 0.5mg ranibizumab PRN arm from the CATT trial, as the VIEW study compared aflibercept 2mg Q8 to ranibizumab monthly in the 52 weeks.

The distributions calculated from the VIEW 2 clinical trial data for the study eye in the aflibercept arm are as follows:

Table B36: Summary of VA distributions derived from VIEW 2 trial data

Health State	Screening	Week 52	Week 96
NVI	[redacted]		
Mild			
Moderate			
Severe			
Blind			
Total	**100.0%**	**100.0%**	**100.0%**

The final VA distributions used in the model after the death rate was applied are:

Table B37: VA distribution used in the model

Health State	Year 1	Year 2
NVI	15.6%	16.7%
Mild	26.6%	23.9%
Moderate	27.9%	25.7%
Severe	18.7%	19.0%
Blind	10.4%	13.2%
Dead	0.8%	1.6%
Total	**100%**	**100%**

<u>Ranibizumab arm</u>

The relative risks for gaining and maintaining vision between baseline and year 1 and between year 1 and year 2 of treatment - derived from an ITC (see section 6.7), as the VIEW study compared aflibercept 2mg Q8 to monthly ranibizumab in the first 52 weeks - were applied to the change in VA observed for patients in the aflibercept 2mg Q8 arm of the VIEW 2 trial. The resulting VA distributions for year one and year two were used for the ranibizumab arm of the model. As with the aflibercept model arm a linear trend was used to populate model cycles between cycles 1 to 12 and cycles 13 to 24.

The death rate and treatment discontinuation rate were applied as in the aflibercept arm. The final VA distributions used in the model for years one and two are as follows:

Table B38: VA distribution for the ranibizumab model arm at year 1 and 2

Health State	Year 1	Year 2
NVI	13.1%	15.1%
Mild	24.6%	22.5%
Moderate	29.1%	26.1%
Severe	20.1%	20.1%
Blind	12.3%	14.6%
Dead	0.8%	1.6%
Total	**100.0%**	**100.0%**

A further scenario analysis was conducted using the same efficacy data (RRs set to 1) for both treatment arms in years 1 and 2.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Treatment efficacy years 3-5

The available RCTs, identified in the systematic literature review provide data for treatment efficacy in years 1 and 2. There is no directly comparative RCT data available after year 2.

Wet AMD is a chronic, progressive condition. Clinical opinion indicates that a proportion of patients will continue to require anti-VEGF treatment beyond the second year. The treatment period in the model extends therefore beyond the two years for which RCT data is available.

For years 3 to 5 the model assumes that patients on active treatment will remain in the same health state that they are in after 24 months. Patients on treatment in years 3 to 5 will incur treatment costs as normal. As there is no evidence of significant differences in the ITC, a conservative approach has been taken and assumptions for years 3 to 5 are identical between arms.

In line with clinical opinion no treatment is assumed after year 5 and all patients follow natural history progression rates.

Clinical efficacy in the fellow eye

Efficacy in the “treated eye” is assumed to be independent of the efficacy of treatment in the fellow eye. Efficacy for the fellow eye while on treatment was calculated with the same methodology as for the “treated eye”.

Treatment discontinuation

Direct comparative data for the discontinuation rates was not available. An assumption was made that the two treatment arms will have the same discontinuation rates given the comparable efficacy and safety profiles. For years 1 and 2 of treatment an average was taken between the discontinuation rate for the aflibercept 2mg Q8 arm in the VIEW 2 trial and the 0.5mg ranibizumab PRN arm (based on monthly evaluation) from the CATT trial, as included in the ITC (as the VIEW study included monthly ranibizumab in the first year). Trial data was not available in years 3 to 5 therefore clinical opinion was used to estimate discontinuation in these years (see section 7.3.7).

Best supportive care (BSC) – no active treatment

The natural history of wet AMD is described in the model using two parameters in the BSC arm. These parameters are the probability of losing either 15 or 30 ETDRS letters. The values for these parameters are derived from a recent meta-analysis by Wong et al(50) which describes the natural history of wet AMD patients receiving no active anti-VEGF treatment. Three year data reported by Wong was converted to one month (per cycle) probabilities(100).

Mortality rates

A systematic literature search was conducted (Appendix 16) to identify mortality rates specific to the wet AMD population. Although there was evidence to show elevated mortality rates for people with impaired vision, the

evidence linking wet AMD, specifically, to mortality is limited due to confounding factors(41).

Therefore in the absence of wet AMD specific mortality, age specific all-cause mortality was obtained from UK life tables as, based on all-cause mortality in all arms of the VIEW trials it is not anticipated that there is any difference between ranibizumab and aflibercept in terms of mortality. Excess mortality was only included for blind patients (both eyes) using the hazard ratio reported by Thiagarajan 2005(25). The Thiagarajan paper was selected since it was conducted in a broad population within the UK setting.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Based on Wong (50) the probability of developing wet AMD in the fellow eye varies as a function of the time spent with wet AMD in the first eye. For the current analysis the second year rate of developing wet AMD in the fellow eye reported in the study was converted to one month (per cycle) probabilities(100).

For the rest of the transition probabilities captured in the model there is no evidence that they should vary as a function of time spent with wet AMD.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Vision loss was directly measured in the trials.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide details[3]:

A small number (3 interviews) of interviews were conducted with consultant ophthalmologists to inform resource use estimates. These interviews were not used to elicit clinical parameters.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table B39: Summary of variables applied in the economic model

Variable	Value	DISTRIBUTION (variation testes)	Reference to section in submission
Relative risks aflibercept vs. ranibizumab - Year 1 compared to baseline			
RR Maintaining vision	1.02	(95%CI: 0.98,1.06) LOGNORM	ITC 7.3.1
RR Gaining 15-29 letters	1.19	(95%CI: 0.93,1.51) LOGNORM	ITC 7.3.1
RR Gaining >= 30 letters	1.19	(95%CI: 0.93,1.51) LOGNORM	ITC 7.3.1
Relative risks aflibercept vs. ranibizumab Year 2 compared to year 1			
RR Maintaining vision	0.99	(95%CI: 0.93,1.07) LOGNORM	ITC 7.3.1
RR Gaining 15-29 letters	0.88	(95%CI: 0.61,1.28) LOGNORM	ITC 7.3.1
RR Gaining >= 30 letters	0.88	(95%CI: 0.61,1.28)	ITC 7.3.1
Probabilities of Adverse Events (as in TA155) - Aflibercept and ranibizumab arms			
Intraocular inflammation	0%	NA	7.4.12
Vitrous hemorrhage	0%	NA	7.4.12
Endophthalmitis	0%	NA	7.4.12
Traumatic lens injury	0%	NA	7.4.12
Retinal detachment	0%	NA	7.4.12
Probabilities of Discontinuation- Aflibercept and ranibizumab arms			
1st year	2.70%	SE 20% of mean BETA	7.3.2
2nd year	3.50%	SE 20% of mean BETA	7.3.2
Years 3-5	18.67%	SE 20% of mean BETA	7.3.2
Annual probability of Change in Visual Acuity Year 1 – Best supportive care			
Improvement	0	NA	7.3.1
Losing 3 lines	6.48%	SE 20% of mean BETA	7.3.1
Losing 6 lines	17.23%	SE 20% of mean BETA	7.3.1
No change	76.29%	Residual	7.3.1
Mean number of Injections per year			
Aflibercept year 1	7	SE 20% of mean GAMMA	7.5.1
Aflibercept year 2	4	SE 20% of mean GAMMA	7.5.1

Variable	Value	DISTRIBUTION (variation testes)	Reference to section in submission
Aflibercept year 3	4	SE 20% of mean GAMMA	7.5.1
Aflibercept year 4	4	SE 20% of mean GAMMA	7.5.1
Aflibercept year 5	4	SE 20% of mean GAMMA	7.5.1
Ranibizumab year 1	8	SE 20% of mean GAMMA	7.5.1
Ranibizumab year 2	6	SE 20% of mean GAMMA	7.5.1
Ranibizumab year 3	4	SE 20% of mean GAMMA	7.5.1
Ranibizumab year 4	4	SE 20% of mean GAMMA	7.5.1
Ranibizumab year 5	4	SE 20% of mean GAMMA	7.5.1
Treated – Eye / Fellow - Eye Model Parameters			
% with wet AMD involvement in both eyes at baseline	0%		7.5.1
% treated in second eye if AMD develops	100%		7.3.1
1-month probability of first-eye patients developing second-eye wet AMD	0.65%		7.3.3
Visual Acuity at Model start (1st eye)			
No visual impairment	[redacted]		7.3.1
Mild	[redacted]		7.3.1
Moderate	[redacted]		7.3.1
Severe	[redacted]		7.3.1
Blind	[redacted]		

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

A state transition model was used to extrapolate from events occurring during the trial period to costs and benefits that occur beyond the trial period. Given the paucity of evidence, a conservative approach has been taken and the same assumptions have been used for aflibercept and ranibizumab.

Data from the aflibercept 2mg Q8 arm of the VIEW 2 clinical trial and relative risks from the ITC provide efficacy values for the first two years of treatment only. Clinical opinion has indicated that patients are likely to continue treatment beyond 24 months; therefore this analysis has included a 5 year treatment period within the lifetime horizon.

Two assumptions have been made in order to specify the treatment efficacy in the model arms for years 3 to 5. Firstly, given that the ITC did not show evidence of a significant difference in treatment efficacy between ranibizumab PRN and aflibercept 2mg Q8/PRN in the first two years, it was assumed that they have identical efficacy in years 3 to 5. Secondly, as no comparative RCT data was available for treatment efficacy beyond two years an assumption was made whereby patients on active treatment in years 3 to 5 would experience the same ‘efficacy’ (change in visual acuity) as those patients in the BSC – no active anti-VEGF treatment arm.

However, while patients on active treatment in years 3 to 5 have the same rate of disease progression as those patients in the BSC arm, patients do receive costs associated with treatment such as IVT injections and monitoring visits, based on values obtained from a physician survey.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table B40: Model assumptions

Model Assumption	Justification
Treatment efficacy in years 3 to 5 is assumed to be the same for both aflibercept and ranibizumab	There is no efficacy evidence for year 3+ and no significant efficacy differences in years 1 and 2.
Patients on treatment in years 3 to 5 in both treatment arms are assumed to stay in the same health state as after 24 months.	In the absence of RCT evidence this is a conservative estimate.
100% patients developing wet AMD in the fellow eye will be treated	Clinical experts advised that this is a case-by-case decision, but a simplification for the model this would be an acceptable assumption to implement.
Patients start developing wet AMD in the fellow eye after year 3	During year 1 and 2 clinical trial data was reproduced for the treated eye and the probability of developing wet AMD in the fellow eye was not included
The treatment discontinuation rate for ranibizumab and aflibercept is assumed to be the same in all years.	Comparative discontinuation rates were not available for the aflibercept 2Q8 and ranibizumab 0.5mg PRN. There is no evidence of significant differences in efficacy or adverse event rates and mode of administration is similar.
Aflibercept is assumed to follow a one-stop model for treatment administration during year 1.	Based on marketing authorisation from EMEA.
50% of the patients treated with ranibizumab follow a two-stop model and 50% follow a one-stop model for treatment administration in years 1 to 5.	Clinical experts advise that this is the current practice for treating wet AMD patients in England
50% of the patients treated with aflibercept follow a two-stop model and 50% follow a one-stop model for treatment administration in years 2 to 5.	Assumed to follow the same clinical practice indicated by the clinical experts for patients in treatment with ranibizumab
The relative risk for improvement is the same for gaining 3 lines as for gaining 6 lines.	Data from the NMA was not separately available for gaining 3 lines and 6 lines.
Eyes that are defined as having a visual acuity of >36 ETDRS letters (blind) are not treated in years 3-5.	This is based on clinical opinion indicating that blind eyes are unlikely to benefit from treatment and would not normally be treated in clinical practice.

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Leakage from the CNV leads to macular oedema and lesions and eventual permanent central vision loss. Wet AMD is associated with a progressive and unremitting loss of vision including distortion and impaired colour vision(30). It is generally known that a decrease in visual function has an impact on HRQL(101). People with wet AMD retain some 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. In particular, there is a link with physical visual function, in particular visually demanding activities such as reading the newspaper and recognising faces are affected, as is reading speed and distance vision(30). There is also a higher proportion of falls in people with lower VA(24). People registered with visual impairment, in particular, are entitled to state assistance(99).

However the exact nature of this relationship between VA and HRQL is somewhat unclear due to comorbidities/confounders in the ageing population(101), difficulties measuring vision-related QOL and HRQL and the variable performance of generic HRQL instruments such as the EQ5D in visual disorders(102). This is also demonstrated by the difficulties(103) in trying to map the NEI-VFQ-25 to the EQ5D which highlights the differences between vision based aspects of quality of life and those on the EQ5D. Also, it is not just VA but also contrast sensitivity affected by wet AMD(30).

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Wet AMD may develop rapidly, causing severe changes to a patient's central vision in a short period of time. Progression of wet AMD can lead to severe vision loss and blindness. In addition severe vision loss is associated with chronic morbidity, increased depression, and increased risk of falls. In turn

these outcomes may lead to diminished quality of life due to high levels of emotional distress(17-19).

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case.

Health related quality of life was measured in the VIEW 2 trial using the EQ5D instrument. The NEI-VFQ-25 (see section 6.5) collected information on vision-related quality of life in both VIEW 1 and VIEW 2. However, the generic EQ5D is the preferred measure in the NICE methods. Measurements were made at baseline, at the end of the first year of treatment and the end of the second year of treatment. Utility values were obtained by applying the UK population tariff(104;105). As such the method of measuring and valuing HRQL match the methods set out in the reference case. The utility values used in the base case are derived from a data set from VIEW 2 trials using all time points and all trial arms. A pooled data set was chosen in order to obtain the largest possible sample size for each visual acuity group due to the high level of variability that is often observed with HRQL data.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide information.

No mapping techniques were performed for the derivation of health-state utility values applied in the cost-utility model described in this Single Technology Appraisal as EQ5D data was measured in the VIEW 2 trial and this is the preferred source according to NICE methods.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria

used. The search strategy used should be provided in section 10.12, appendix 12.

As the systematic review undertaken included resource use and cost estimates as well as economic analyses and utility, refer to section 7.1.1 for details of the review as a whole. Appendix 10 provides details of the search string used in the literature search.

13 quality of life studies were selected for data extraction. One cost study(106) also reported utility estimates, resulting in a total of 14 papers suitable for data extraction. Studies using the SF-36 (15 studies) were not included at the data extraction stage as generic preference-based utility instruments such as the EQ5D are preferred by NICE. The review update for the systematic search found the following two utility studies which were included in the data extraction:

Finger et al 2012(107) reported a patient-preference study in which 55 treatment-naïve patients with wet AMD were treated with ranibizumab and assessed for the impact on patient preferences and vision-related QOL.

Most of the studies used time trade-off (TTO) techniques to estimate utility weights and values were elicited from physicians, patients and the general public. Brown et al 2000(108;109) and Lee et al 2008(110) reported utility weights elicited from physicians and patients using standard gamble (SG) methods. Boland et al(2011), Czoski-Murray(111), Espallargues et al 2005(112), Lotery et al 2007(113), Brown et al 2000(107), Sahel et al 2007(114) and Gower et al 2010 measured estimated utility in patients using the EQ5D; Short-Form 6D Health Status Questionnaire (SF-6D); and Health Utilities Index (HUI) Mark III.

Most of the studies investigated VA in the patient’s better-seeing eye. Sahel et al(114) found that the VA of the worse-seeing eye has little effect on the HUI3 score, however disease-specific measures (NEI-VFQ 25 and MacDQoL scale) did detect a change.

Utility estimates for a number of related AEs including cataracts, retinal detachment, and endophthalmitis were reported by Gower et al 2010(115) and Brown et al 2007(116). Utilities ranged from 0.52 for endophthalmitis to 0.858 for cataracts.

7.4.6 Provide details of the studies in which HRQL is measured.

A detailed explanation of results is provided in Appendix 10. The EQ5D data from the VIEW 2 trial has been used in the model as it is the preferred measure for NICE.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The majority of studies found in the literature search report utility scores according to the VA of the better seeing eye only, however the utilities used in this submission are based on a combination of vision in both eyes. Of the studies found in the literature search, only Brown(108) reports the utilities associated with a specified combination of VA in both eyes. However, Brown only uses the VA in both eyes up to 20/30 to 20/50 in the better eye and <=20/40 in the worse eye, with further reduction in VA states reported only in accordance with the sight in the better eye. Brown used TTO and SG techniques to measure utility from both physicians and patients, with perfect health yielding a score of 1.00. The study reported values ranging from 0.998 given by physicians using SG to 0.89 given by patients using TTO for vision described as 20/20 to 20/25 in the better eye and <=20/40 in the worse eye. Utility values decrease with declining vision, and at the stage reported as “difficulty counting fingers to light perception”, utility was 0.4 for TTO and 0.55 for SG. This pattern of reducing utility with declining vision is reflected by the other studies found in the literature search, despite the description of only one eye.

The utilities in the clinical trial are elicited through the EQ5D and use a value of 0.89 for those with no visual impairment. The pattern of reduction in utility with decreasing VA is similar to that in the studies found in the literature,

however the reduction in utility is lower than that displayed by many of the studies in the literature search; mild visual impairment in one eye having a utility of 0.85 through to blindness in both eyes having a utility of 0.6.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Given the low rates of events in the VIEW trials (in particular, those events specified in the model for TA155) and, in particular, the small relative differences between aflibercept and ranibizumab, the impact of these has not been included in the base case economic model, only as a scenario analysis to account for any uncertainty. Ocular AEs associated with anti-VEGF treatment include vitreous haemorrhage, endophthalmitis, traumatic lens injury, retinal tear/detachment and intraocular inflammation. The major impact of ocular AEs is loss or impaired vision; in addition inflammation may lead to pain and redness of the conjunctiva and the underlying episclera.

Therefore, for the scenario analysis, for AEs utility decrements, the literature review found two papers with information. Of these, one(116) is a QOL study reporting utilities from AMD patients for AEs using TTO techniques. The other paper(115) is a cost-effectiveness analysis for treatment of patients with AMD. As Brown et al 2010 is a study specifically designed to investigate the utility associated with health states and events in patients with AMD, it was favoured when selecting the source of utility decrement for AEs.

Table B41. Summary of utility values associated to AEs (including those specified in TA155, where available)

Adverse event	Utility decrement	CI (low)	CI (high)	Reference	Justification
Retinal hemorrhage	30%	18.2%	41.8%	Conservative estimate: to be equal to highest AE in Brown, 2007(116)	Not found in either papers reporting utilities for AEs
Vitreous hemorrhage	30.5%	18.8%	43.2%	Gower 2010 (115)	Not found in Brown so taken from the only other paper found to report AEs
Endophthalmitis	30%	18.2%	41.8%	Brown 2007	Quality of life study reporting utility for AEs
Cataract	14.2%	8.5%	19.5%	Brown, 2007	See above
Retinal detachment	27%	16.4%	37.6%	Brown, 2007	See above

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table B42: Summary of quality-of-life values for cost-effectiveness analysis

Vision acuity in both eyes	Utility (EQ-5D)	SD	Reference in submission	Justification
None/None	[redacted]	[redacted]	7.4.3	VIEW protocol (117)
None/Mild	[redacted]	[redacted]	7.4.3	VIEW protocol (117)
None/Moderate	[redacted]	[redacted]	7.4.3	VIEW protocol (117)
None/Severe	[redacted]	[redacted]	7.4.3	VIEW protocol (117)
None/Counting Fingers	[redacted]	[redacted]	7.4.3	VIEW protocol (117)
Mild/Mild	[redacted]	[redacted]	7.4.3	VIEW protocol (117)
Mild/Moderate	[redacted]	[redacted]	7.4.3	VIEW protocol (117)
Mild/Severe	[redacted]	[redacted]	7.4.3	VIEW protocol (117)
Mild/Counting Fingers	[redacted]	[redacted]	7.4.3	VIEW protocol (117)
Moderate/Moderate	[redacted]	[redacted]	7.4.3	VIEW protocol (117)
Moderate/Severe	[redacted]	[redacted]	7.4.3	VIEW protocol (117)
Moderate/Counting Fingers	[redacted]	[redacted]	7.4.3	VIEW protocol (117)
Severe/Counting Fingers	[redacted]	[redacted]	7.4.3	VIEW protocol (117)
Severe/Severe	[redacted]	[redacted]	7.4.3	VIEW protocol (117)
Counting Fingers/Counting Fingers	[redacted]	[redacted]	7.4.3	VIEW protocol (117)

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide details[4]:

Utility values were obtained from EQ5D data from the VIEW 2 clinical trial, in line with the NICE preferred reference case.

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The health states are based on the VA in both eyes. This is defined by the number of ETDRS letters that a person can see on a chart. Patients are assumed to have a constant HRQL during their time in a health state, as such HRQL is only affected by changes in VA and not the duration spent in a particular health state.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Previous economic evaluations of ranibizumab in wet AMD(19) have included intraocular inflammation, vitreous haemorrhage, endophthalmitis, traumatic lens injury and retinal detachment. In the VIEW studies, no incidence of any of these AEs was reported for aflibercept. This was reflected in the CLEAR-IT(118) phase II study of aflibercept. The VIEW study found the safety profiles of aflibercept and ranibizumab to be similar but included only a monthly ranibizumab regimen in the first 52 weeks (see section 6.9.2 for details).

For ranibizumab as needed, the risk of AEs was only reported for endophthalmitis in the year 2 results of the CATT trial (0.7%), therefore to provide data on AEs associated with ranibizumab treatment, we reviewed data was from the ranibizumab PRN arm of a phase III study reported by Boyer et al 2009(119). In the Boyer et al study, a large safety study of 4300 subjects with neovascular wet AMD, very low rates of relevant events (between 0,2% and 0.4% per patient year) were reported. Neither study reflects the 'stability concept' retreatment regimen specified in the SmPC.

Table B43. Rates of AEs (as specified in Colquitt et al(19) for TA155)

Event	Intraocular Inflammation	Vitreous Haemorrhage	Endo-phthalmitis	Traumatic Lens Injury	Retinal Detachment	Source
Aflibercept	0.00%	0.00%	0.00%	0.00%	0.00%	VIEW 2 (included EQ5D)
Ranibizumab	0.20%	0.10%	0.40%	0.00%	0.20%	Boyer 2009

In the VIEW trials, AE rates were similar between aflibercept and ranibizumab (see section 6.9.2 for details). The small difference in rates between the VIEW and Boyer data may be due to differences between trials rather than between treatments. Physician experience and practices associated with IVT injections have evolved since the time of the pivotal MARINA/PIER trials(64) for ranibizumab, which may have been prone to injection-related events.

As discussed in section 6.9, the VIEW trials found aflibercept and ranibizumab to have relatively safe profiles as the incidence of ocular and systemic AEs was balanced and low across treatment groups, including 0.5mg ranibizumab monthly/PRN and 2mg aflibercept 2-monthly/PRN. The most frequent ocular AEs being (>10%) patients were conjunctival haemorrhage, eye pain, retinal haemorrhage and VA reduced(51).

Therefore, the evidence based assumptions have been selected. The cost and utility impact of AEs has been assumed as equal for aflibercept and ranibizumab in the base case of the model and, therefore, data on relative differences are not required. A sensitivity analysis included the event rates from Boyer et al 2009(119) for ranibizumab.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

In the base case the model cohort starts the simulation in a range of health states which match the distribution of VA reported in the VIEW 2 trial, which included the EQ5D data. The overall utility value of the cohort at baseline is a weighted sum of this distribution. 0.89 is the mean utility for state NVI-NVI.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL was assumed to be constant over time. No adjustment was made for cohort aging. In the model analysis changes in HRQL over time can only occur due to change in VA. In addition the utility value associated with a particular level of VA/health state was also assumed to be constant over time.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Yes, the utility values for the health states derived from the VIEW 2 clinical trial were amended to impose an assumption that utility monotonically decreases with worsening VA. This assumption reflects both the general view in ophthalmology that a person with worse vision should have worse HRQL and also the results of previous studies examining the relationship between VA and utility caused by wet AMD(108;111). The trial utility values for the different combinations of VA in the first and second eye produced four instances where utility increases when overall VA in both eyes decreases, as highlighted in Table B44.

Table B44. Utility values from VIEW 1 and 2 trials

	NVI	Mild	Moderate	Severe	Blind
NVI	[redacted]				
Mild					
Moderate					
Severe					
Blind					

The highlighted points were amended by taking the average of the value above and below the anomalous data point. For example the amended value for severe-moderate was calculated by taking the average of blind-moderate and moderate-moderate. The final amended values used in the model are shown in Table B45.

Table B45. Amended utility values

	NVI	Mild	Moderate	Severe	Blind
NVI	[redacted]				
Mild					
Moderate					
Severe					
Blind					

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Cost of monitoring and administration

Management of wet AMD with anti-VEGF drugs is conducted by ophthalmologists expert in the administration of IVT medications.

Professional guidelines(30) recommend that management should include:

- clinical examination, OCT and a FA before treatment initiation
- clinical examination and OCT at monitoring visits (section 2.6/10)

It was assumed that clinical examination would incur the cost of an ophthalmologist outpatient visit (see Table B46). On the basis of expert clinical opinion, administration of VEGF therapy is assumed to require:

- If the treatment schedule is variable, that in around half of centres administration of injections would be performed on a *separate visit* from a monitoring visit.

This, according to expert clinical opinion, is currently the case in NHS practice for ranibizumab. Given the absence of evidence for aflibercept, a conservative assumption has been made and it is assumed to be the same as for ranibizumab, despite the differences in the wording of the SmPCs regarding retreatment criteria and monitoring requirements.

If the treatment schedule is fixed (i.e. aflibercept in the first 12 months), a *single visit* for monitoring and administration is assumed to be conducted as monitoring is not required to determine if an injection is needed.

Table B46: Unit costs associated with monitoring visits and treatment

	Cost (£)	HRG	Reference
Ophthal-mologist visit	79.74	All NHS trusts and NHS foundation trusts - Consultant Led: Follow up Attendance Non-Admitted Face to Face: 130 - ophthalmology	Department of Health, 2012(120)
OCT	117.26	NHS trusts and NHS foundation trusts - Outpatient Procedures. HRG code: BZ23Z - Minor Vitreous Retinal Procedures	As above
Fluorescein angiography	117.26	NHS trusts and NHS foundation trusts - Outpatient Procedures. HRG code: BZ23Z - Minor Vitreous Retinal Procedures	As above
Administration visit - outpatient	79.74	All NHS trusts and NHS foundation trusts - Consultant Led: Follow up Attendance Non-Admitted Face to Face: 130 - ophthalmology	As above
Administration visit – day case	402.08	Reference Costs - NHS trusts and NHS foundation trusts - Day Cases. HRG code: BZ23Z - Minor Vitreous Retinal Procedures. Proportion from HES: Main procedures and interventions: 4 character (OPCS-4), 2010-2011 (weighted average of codes: C79.4 and C89.3)	Hospital Episode Statistics (HES), 2012(121)
Administration visit – weighted average	£257.45	Proportions of patients treated as outpatients (44.87%) and day-case (55.13%)	Hospital Episode Statistics (HES), 2012

Frequency of monitoring

Frequency of monitoring in years one and two for ranibizumab is based on the monthly monitoring recommended in the SmPC. Frequency of monitoring for aflibercept in year one and two is also based on the recommended posology stated in its SmPC. In year one no additional monitoring is required between injections and in year two the frequency of monitoring is assumed to remain once every two months, matching the maximum frequency of administration (see section 7.2.7).

Frequency of monitoring visits for treatment after year 2 is uncertain. Expert opinion suggested that, despite the SmPC wording, continuing monthly monitoring with ranibizumab is unlikely for the majority of patients and that 7

visits per year might typically be required(122). A *conservative approach* has been taken for aflibercept and the number of monitoring visits has been assumed the same for both arms, although the SmPC for ranibizumab states monthly monitoring and the SmPC for aflibercept does not state this and, based on the SmPC for years one and two is likely to be six or less.

Table B47: Frequency of monitoring visits
Visits per patient per year, patients on treatment only

	Year 1	Year 2	Year 3	Year 4	Year 5
Aflibercept	7	6	7	7	7
Source	*SmPC*	*SmPC*	*Conservative assumption given lack of evidence – same as ranibizumab*		
Ranibizumab	12	12	7	7	7
Source	*SmPC*	*SmPC*	*Expert opinion*		

Frequency of injections

The frequency of injections used for ranibizumab in year 1 and 2 is in line with what was reported in NICE TA155(21) and the number estimated in the EMA assessment report for the 2011 revision to the SmPC for ranibizumab(73). The frequency of injections used for aflibercept in year 1/2 was also derived from the marketing authorisation and also for year 2 from VIEW 2(123). Number of injections for year 3 to 5 were derived from the physician survey for ranibizumab(122) and, conservatively given the absence of evidence for aflibercept , assumed to be equal for the two treatment arms.

Table B48: Frequency of injections
Administrations per patient per year, patients on treatment only

	Year 1	Year 2	Year 3	Year 4	Year 5
Aflibercept	7	4	4	4	4
Source	*SmPC*	*SmPC/ VIEW 2*	*Conservative assumption given lack of evidence – same as ranibizumab*		
Ranibizumab	8	6	4	4	4
Source	*TA155/ EMA report*		*Expert opinion*		

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS reference costs 2011-12(120) were used in this analysis, as they provide relevant costs and volume that reflect the pattern of care delivered in the NHS. Reference Costs represent the cost burden to the NHS rather than internal reimbursement between NHS organisations and allow for a greater level of granularity to be assessed and are more up-to-date.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources.

The main systematic literature review undertaken included resource use and cost estimates as well as economic analyses and utility. Complete details of the methods for the review have been outlined in section 7.1.1. Appendix 10 provides details of the search string used in the literature search.

Twenty one resource use and cost studies were identified, of which 1 was excluded as it was only available in abstract form. Additionally, a utility study (124) also reported resource use. Therefore resource use and cost data were extracted from 21 studies. These studies are described in appendix 14.

However, none of these studies described the administration and monitoring of aflibercept or ranibizumab according to their SmPCs in the UK (see 7.5.4).

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the specified details[5]:

Input from 3 clinical experts was used to inform analysis where data were not available elsewhere. The experts approached were all consultant ophthalmologists with extensive experience of treating patients with wet AMD in the UK. A total of 16 experts were initially contacted, 3 agreed to participate

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

and a separate phone interview, based on a questionnaire, was performed with each expert. The questionnaire used and the individual answers are available in Appendix 17.

No background information was provided previous to the phone call interviews since the intention was to capture their experience based on their clinical practice.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Unit drug costs

The unit drugs costs discussed in this section are current British National Formulary prices and do not include nationally agreed PAS. Ranibizumab is subject to a simple discount scheme but the details are confidential. Information regarding a PAS for aflibercept are detailed in the PAS submission template.

Table B49: Unit costs associated with the technology in the economic model

Items	Aflibercept	Ranibizumab	Ref. in submission
Technology cost per dose	£816.00	£742.17	BNF 64

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Table B51: List of health states and associated costs in the economic model
Aflibercept annual costs patient on treatment

Health State	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
*NVI-NVI						
Treatment costs	£7,514	£4,294	£4,294	£4,294	£4,294	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£8,452	£5,316	£5,513	£5,513	£5,513	£0
*NVI-MILD						
Treatment costs	£7,514	£4,294	£4,294	£4,294	£4,294	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£8,452	£5,316	£5,513	£5,513	£5,513	£0
*NVI-MOD						
Treatment costs	£7,514	£4,294	£4,294	£4,294	£4,294	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£8,452	£5,316	£5,513	£5,513	£5,513	£0
*NVI-SEV						
Treatment costs	£7,514	£4,294	£4,294	£4,294	£4,294	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£8,452	£5,316	£5,513	£5,513	£5,513	£0
*NVI-BLIND						
Treatment costs	£0	£0	£0	£0	£0	£0
Monitoring costs	£0	£0	£0	£0	£0	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£0	£0	£0	£0	£0	£0
NVI-NVI						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
NVI-MILD						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
NVI-MOD						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0

NVI-SEV						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
NVI-BLIND						
Treatment costs	£7,514	£4,294	£4,294	£4,294	£4,294	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£8,452	£5,316	£5,513	£5,513	£5,513	£0
MILD-NVI						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
MILD-MILD						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
MILD-MOD						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
MILD-SEV						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
MILD-BLIND						
Treatment costs	£7,514	£4,294	£4,294	£4,294	£4,294	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£8,452	£5,316	£5,513	£5,513	£5,513	£0
MOD-NVI						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
MOD-MILD						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0

Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
MOD-MOD						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
MOD-SEV						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
MOD-BLIND						
Treatment costs	£7,514	£4,294	£4,294	£4,294	£4,294	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£8,452	£5,316	£5,513	£5,513	£5,513	£0
SEV-NVI						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
SEV-MILD						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
SEV-MOD						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
SEV-SEV						
Treatment costs	£13,226	£7,558	£7,558	£7,558	£7,558	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£14,164	£8,580	£8,777	£8,777	£8,777	£0
SEV-BLIND						
Treatment costs	£7,514	£4,294	£4,294	£4,294	£4,294	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£8,452	£5,316	£5,513	£5,513	£5,513	£0
BLIND-NVI						

Treatment costs	£7,514	£4,294	£4,294	£4,294	£4,294	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£8,452	£5,316	£5,513	£5,513	£5,513	£0
BLIND-MILD						
Treatment costs	£7,514	£4,294	£4,294	£4,294	£4,294	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£8,452	£5,316	£5,513	£5,513	£5,513	£0
BLIND-MOD						
Treatment costs	£7,514	£4,294	£4,294	£4,294	£4,294	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£8,452	£5,316	£5,513	£5,513	£5,513	£0
BLIND-SEV						
Treatment costs	£7,514	£4,294	£4,294	£4,294	£4,294	£0
Monitoring costs	£938	£1,023	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£8,452	£5,316	£5,513	£5,513	£5,513	£0
BLIND-BLIND						
Treatment costs	£0	£0	£0	£0	£0	£0
Monitoring costs	£0	£0	£0	£0	£0	£0
Blindness	£585	£585	£585	£585	£585	£585
Total	£585	£585	£585	£585	£585	£585

Ranibizumab annual costs patient on treatment

Health State	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
*NVI-NVI						
Treatment costs	£7,997	£5,998	£3,998	£3,998	£3,998	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£10,199	£8,202	£5,218	£5,218	£5,218	£0
*NVI-MILD						
Treatment costs	£7,997	£5,998	£3,998	£3,998	£3,998	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£10,199	£8,202	£5,218	£5,218	£5,218	£0
*NVI-MOD						
Treatment costs	£7,997	£5,998	£3,998	£3,998	£3,998	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£10,199	£8,202	£5,218	£5,218	£5,218	£0
*NVI-SEV						
Treatment costs	£7,997	£5,998	£3,998	£3,998	£3,998	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£10,199	£8,202	£5,218	£5,218	£5,218	£0
*NVI-BLIND						
Treatment costs	£0	£0	£0	£0	£0	£0
Monitoring costs	£0	£0	£0	£0	£0	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£0	£0	£0	£0	£0	£0
NVI-NVI						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
NVI-MILD						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
NVI-MOD						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
NVI-SEV						

Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
NVI-BLIND						
Treatment costs	£7,997	£5,998	£3,998	£3,998	£3,998	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£10,199	£8,202	£5,218	£5,218	£5,218	£0
MILD-NVI						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
MILD-MILD						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
MILD-MOD						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
MILD-SEV						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
MILD-BLIND						
Treatment costs	£7,997	£5,998	£3,998	£3,998	£3,998	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£10,199	£8,202	£5,218	£5,218	£5,218	£0
MOD-NVI						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
MOD-MILD						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0

Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
MOD-MOD						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
MOD-SEV						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
MOD-BLIND						
Treatment costs	£7,997	£5,998	£3,998	£3,998	£3,998	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£10,199	£8,202	£5,218	£5,218	£5,218	£0
SEV-NVI						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
SEV-MILD						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
SEV-MOD						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
SEV-SEV						
Treatment costs	£13,934	£10,451	£6,967	£6,967	£6,967	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£16,136	£12,655	£8,187	£8,187	£8,187	£0
SEV-BLIND						
Treatment costs	£7,997	£5,998	£3,998	£3,998	£3,998	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£10,199	£8,202	£5,218	£5,218	£5,218	£0
BLIND-NVI						
Treatment costs	£7,997	£5,998	£3,998	£3,998	£3,998	£0

Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£10,199	£8,202	£5,218	£5,218	£5,218	£0
BLIND-MILD						
Treatment costs	£7,997	£5,998	£3,998	£3,998	£3,998	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£10,199	£8,202	£5,218	£5,218	£5,218	£0
BLIND-MOD						
Treatment costs	£7,997	£5,998	£3,998	£3,998	£3,998	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£10,199	£8,202	£5,218	£5,218	£5,218	£0
BLIND-SEV						
Treatment costs	£7,997	£5,998	£3,998	£3,998	£3,998	£0
Monitoring costs	£2,202	£2,205	£1,220	£1,220	£1,220	£0
Blindness	£0	£0	£0	£0	£0	£0
Total	£10,199	£8,202	£5,218	£5,218	£5,218	£0
BLIND-BLIND						
Treatment costs	£0	£0	£0	£0	£0	£0
Monitoring costs	£0	£0	£0	£0	£0	£0
Blindness	£585	£585	£585	£585	£585	£585
Total	£585	£585	£585	£585	£585	£585

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Due to the very low incidence of relevant AEs in the VIEW studies, the model assumed no clinically or statistically significant differences between therapies in the incidence of AEs. These costs are used in the sensitivity analysis only.

To estimate unit costs for AEs relevant HRGs were identified using the procedures codes (OPCS-4,(121)). NHS Reference Costs(120) were used to estimate unit costs.

Vitreous haemorrhage: OPCS-4 codes C791 (Vitrectomy using anterior approach, VR Band 3) and C792 (Vitrectomy using pars plana approach, VR Band 4) were identified. These were associated with the HRG: BZ22Z - Vitreous Retinal Procedures - category 2. A weighted average of non-elective inpatient (short stay) HRG data and day cases HRG data was taken

Endophthalmitis: the methodology to cost endophthalmitis was taken from Lyall, 2012(125), who recently completed an observational study to describe the management of post intravitreal anti-VEGF endophthalmitis (PIAE) in patients undergoing treatment for wet AMD in the UK. OPCS-4 code C791 was identified (Vitrectomy using anterior approach, VR Band 3). This was associated with the HRG: BZ22Z - Vitreous retinal procedures - category 2. A weighted average of non-elective inpatient (short stay) HRG data and day cases HRG data was taken. Also an average of the cost of treatment with vancomycin (£174.00) and Amikin® (£310.50)(126) was added to the HRG cost.

Cataract: this was costed using the HRG BZ02Z - Phacoemulsification cataract extraction and lens implant. A weighted average of non-elective inpatient (short stay) HRG data and day cases HRG data was taken

Retinal detachment: the OPCS-4 code C822 (Cryotherapy to lesion of retina, VR Band 1) was identified. This was associated to the HRG: BZ23Z - Vitreous Retinal Procedures - category 1. A weighted average of non-elective inpatient (short stay) HRG data and day cases HRG data was taken

Retinal haemorrhage: A weighted average of the HRGs BZ24A (Non-Surgical Ophthalmology with length of stay 2 days or more, total HRG) and BZ24C (Non-Surgical Ophthalmology with length of stay 1 day or less, total HRG) was taken.

Table B50: Unit cost of adverse events

	Cost (£)	HRG	Reference in submission
Vitreous haemorrhage	1,270.97	BZ22Z - Vitreous Retinal Procedures - category 2; Weighted average of Non-Elective Inpatient (Short Stay) HRG Data and Day Cases HRG Data.	7.4.12
Endophthalmitis	674.91	Calculated from Lyall, 2012. All patients had intravitreal injection of antibiotics (Vancomycin and Amikacin were most common). 16 patients on 47 underwent pars plana vitrectomy. Sources: BNF for drugs and Reference Costs for vitrectomy: HRG: BZ22Z - Vitreous Retinal Procedures - category 2; OPCS: pars plana vitrectomy (C792).	7.4.12
Cataract	851.43	BZ02Z - Phacoemulsification Cataract Extraction and Lens Implant. Weighted average of Non-Elective Inpatient (Short Stay) HRG Data and Day Cases HRG Data.	7.4.12
Retinal Detachment	411.44	BZ23Z - Vitreous Retinal Procedures - category 1. Weighted average of Non-Elective Inpatient (Short Stay) HRG Data and Day Cases HRG Data.	7.4.12
Retinal haemorrhage	474.89	Weighted average of BZ24A Non-Surgical Ophthalmology with length of stay 2 days or more (total HRG) and BZ24C Non-Surgical Ophthalmology with length of stay 1 day or less (total HRG)	7.4.12

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

An annual cost of blindness was used in the cost-effectiveness analysis. Blindness was defined as having a VA of 3/60 (35 ETDRS letters) or worse in both eyes following the definition used by the UK Department of Health(99).

The systematic review of economic evaluations (reported in section 8.1) and a search of recent UK HTA appraisals of ophthalmic drugs(40;42) indicated that models previously developed for the UK setting have estimated the cost of blindness using an observational study by Meads in 2003(127). Meads and

colleagues estimated the cost of blindness in the year 2000 in patients affected by AMD. Costs to the NHS were only were taken into account in this analysis.

Meads et al reported the proportion of patients receiving each blindness component in one year. The unit cost of each component was multiplied by the probability of occurrence and inflated to 2011, using the Hospital & Community Health Services (HCHS) index from the PSSRU 2011(128).

Table B51: Annual cost of blindness

	Proportion of patients receiving service	**Unit cost (£/2000)**	**Weighted cost (£/2000)**	**Weighted cost (£/2012)**
Low vision aids	33.00%	136.33	44.99	65.41
Low vision rehabilitation	11.00%	205.30	22.58	32.83
Depression	38.60%	391.97	151.30	219.98
Hip replacement	5.00%	3,669.00	183.45	266.73
Cost of blindness used in the analysis				**584.95**

7.6 Sensitivity analysis

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The uncertainty around parameters used in the cost-effectiveness model was tested performing sensitivity analyses. One-way sensitivity analysis, scenario analyses and a probabilistic sensitivity analysis were performed.

A number of scenario analyses were performed, described below:

a) Number of injections from trials for year 1 and 2: The number of injections reported in the VIEW 2 trial for aflibercept and CATT trial for ranibizumab were used for the first two years of treatment in this scenario analysis. The base case analysis used values from the labels.

Table 54: Number of injections from trials (scenario analysis)

Year	Aflibercept	Ranibizumab
1	7.7	4.0
2	6.9	5.7

b) Monthly monitoring for ranibizumab and bi-monthly for aflibercept in years 3-5: in year 3 to 5 base case number of monitoring visits was derived for ranibizumab from the physician survey and assumed to be the same for both treatment arms. A different assumption was tested in this scenario analysis which follows the trend of frequency associated with year 1 and 2.

Table B52: Frequency of monitoring (scenario analysis)

Year	Aflibercept	Ranibizumab
1	4	12
2	6	12
3	6	12
4	6	12
5	6	12

c) Cost-minimisation analysis: a scenario was tested using the same efficacy values for both treatments to assess how these would impact the final results. The same proportions of patients gaining/losing VA in the aflibercept arm were assigned to ranibizumab.

Table B53: Efficacy values for aflibercept and ranibizumab (scenario analysis)

Parameter	Relative risk (aflibercept vs ranibizumab)	
	Year 1	Year 2
Maintaining vision	1.0	1.0
Gaining 15-29 letters	1.0	1.0
Gaining >= 30 letters	1.0	1.0

d) Brazier (Czoski-Murray 2009) utility values: As discussed previously, the model base case measures health related quality of life using utility values from the VIEW 2 clinical trial which were derived using the EQ5D instrument. However previous economic analyses for wet AMD using a one eye model have applied alternative utility values. Of the alternative utility values reported, NICE has indicated that those reported by Czoski-Murray et al 2009 were considered the most appropriate(21). Therefore a scenario analysis was performed using the utility values reported in Czoski-Murray(111) and a 0.1 utility decrement for the worse-seeing eye, following the method reported previously(21).

Table B54: Health state utilities from Czoski-Murray (scenario analysis)

State	Utility
NVI	0.71
Mild Impairment	0.69
Moderate Impairment	0.62
Severe Impairment	0.51
Blindness	0.31
Utility Decrement for Worse-Seeing Eye	0.10

e) AEs from Boyer, 2009 are used: The incidence of AE reported for both ranibizumab and aflibercept in the CATT and VIEW 2 trials is low (see 7.4.12) and has not been included in the base case analysis. In a scenario analysis the rate of AEs reported in Boyer et al., 2009(119) has been used. Boyer et al. performed a twelve-month multicenter clinical trial to evaluate the safety and efficacy of IVT ranibizumab in a large population of subjects with AMD.

Table B55: Adverse events from Boyer, 2009 (scenario analysis)

Retinal hemorrhage	Vitreous Hemorrhage	Endophthalmitis	Cataract	Retinal Detachment
0.30%	0.20%	0.10%	0.10%	0.10%

f) Maintenance of benefit in years 3-5: Given the absence of evidence for years 3-5, a scenario was conducted with an assumption of efficacy equivalent to BSC (from Wong et al(50)) in both arms for years 3-5.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

In order to understand the sensitivity of model outputs to changes in the values of different parameters a one-way sensitivity analysis (OWSA) was conducted. The OWSA examined the effect of a viable range of parameter values on the incremental costs, incremental outcomes and the incremental cost-effectiveness ratio (ICER). Parameter ranges used in the OWSA can be found in **Table** B56. The rationale for including parameters in the OWSA is as follows:

- Discounting: A range of 0 - 6% was tested, in accordance with the NICE guide to the methods of technology appraisal
- Efficacy parameters: Probabilities for gaining or losing either 3 or 6 lines of vision with aflibercept and ranibizumab were varied
- Utility values were varied using their associated standard deviations from the VIEW 2 trial data
- Drug costs were varied by ±20%
- Number of injections were varied by ±20%
- Monitoring visits were varied by ±20% in the absence of alternative data
- Time horizon: base case analysis was performed on a lifetime horizon (25 years). This was also tested at 15 and 20 years.

Table B56: Variables included in the one-way sensitivity analysis (OWSA)

	Sensitivity Analysis	Base case values	Low estimate	High estimate	Source
1	Physician Visits aflibercept year 1	7	5.6	8.4	Based on marketing authorisation from EMEA
	OCT aflibercept year 1	7	5.6	8.4	Assumption equal to number of visits
	Physician Visits aflibercept year 2	6	4.8	7.2	Based on marketing authorisation from EMEA
	OCT aflibercept year 2	6	4.8	7.2	Assumption equal to number of visits
	Physician Visits aflibercept year 3	7	5.6	8.4	Based on marketing authorisation from EMEA
	OCT aflibercept year 3	7	5.6	8.4	Assumption equal to number of visits
	Physician Visits aflibercept year 4	7	5.6	8.4	Based on marketing authorisation from EMEA
	OCT aflibercept year 4	7	5.6	8.4	Assumption equal to number of visits
	Physician Visits aflibercept year 5	7	5.6	8.4	Based on marketing authorisation from EMEA
	OCT aflibercept year 5	7	5.6	8.4	Assumption equal to number of visits
2	Physician Visits Ranibizumab year 1	12	9.6	14.4	SmPC(14)
	OCT Ranibizumab year 1	12	9.6	14.4	SmPC(14)
	Physician Visits Ranibizumab year 2	12	9.6	14.4	SmPC(14)
	OCT Ranibizumab year 2	12	9.6	14.4	SmPC(14)
	Physician Visits Ranibizumab year 3	7	5.6	8.4	Expert opinion(122)
	OCT Ranibizumab year 3	7	5.6	8.4	Expert opinion(122)
	Physician Visits Ranibizumab year 4	7	5.6	8.4	Expert opinion(122)
	OCT Ranibizumab year 4	7	5.6	8.4	Expert opinion(122)

	Physician Visits Ranibizumab year 5	7	5.6	8.4	Expert opinion(122)
	OCT Ranibizumab year 5	7	5.6	8.4	Expert opinion(122)
3	Injections aflibercept year 3	4	3.2	4.8	Assumed same as Rbz
	Injections aflibercept year 4	4	3.2	4.8	Assumed same as Rbz
	Injections aflibercept year 5	4	3.2	4.8	Assumed same as Rbz
4	Injections ranibizumab year 3	4	3.2	4.8	Expert opinion(122)
	Injections ranibizumab year 4	4	3.2	4.8	Expert opinion(122)
	Injections ranibizumab year 5	4	3.2	4.8	Expert opinion(122)
5	Discount rate costs	0.035	0.028	0.042	NICE ref case
	Discount rate outcomes	0.035	0.028	0.042	NICE ref case
6	Discontinuation aflibercept year 1	0.002	0.002	0.003	Average between VIEW/CATT (45;117)
	Discontinuation aflibercept year 2	0.003	0.002	0.004	Average between VIEW/CATT (45;117)
	Discontinuation Ranibizumab year 1	0.002	0.002	0.003	Average between VIEW/CATT (45;117)
	Discontinuation Ranibizumab year 2	0.003	0.002	0.004	Average between VIEW/CATT (45;117)
7	Discontinuation aflibercept year 3	0.017	0.014	0.021	Assumed same as Rbz
	Discontinuation Ranibizumab year 3	0.017	0.014	0.021	Expert opinion(122)
8	Drug cost aflibercept	£816	£653	£979	Bayer/list price
9	Drug cost ranibizumab	£742	£594	£891	BNF (126)
10	Year 1 RR Maintain Vision	1.02	0.98	1.06	ITC(59)
11	Year 1 RR Gaining 15-29 letters	1.19	0.93	1.51	ITC(59)
12	Year 1 RR Gaining +=30 letters	1.19	0.93	1.51	ITC(59)

13	Year 2 RR Maintain Vision	0.99	0.93	1.07	ITC(59)
14	Year 2 RR Gaining 15-29 letters	0.88	0.61	1.28	ITC(59)
15	Year 2 RR Gaining +=30 letters	0.88	0.61	1.28	ITC(59)
16	Proportion 1 stop year 1 Rbz	0.50	0.25	0.75	Expert opinion(122)
17	Proportion 1 stop year 2 Rbz	0.50	0.25	0.75	Expert opinion(122)
18	Proportion 1 stop year 3 Rbz	0.50	0.25	0.75	Expert opinion(122)
19	Proportion 1 stop year 4 Rbz	0.50	0.25	0.75	Expert opinion(122)
20	Proportion 1 stop year 5 Rbz	0.50	0.25	0.75	Expert opinion(122)
21	Proportion 1 stop year 2 Aflibercept	0.50	0.25	0.75	Assumed same as Rbz
22	Proportion 1 stop year 3 Aflibercept	0.50	0.25	0.75	Assumed same as Rbz
23	Proportion 1 stop year 4 Aflibercept	0.50	0.25	0.75	Assumed same as Rbz
24	Proportion 1 stop year 5 Aflibercept	0.50	0.25	0.75	Assumed same as Rbz

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of ‘priors’. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA was conducted to simultaneously take into account the uncertainty associated with parameter values. The implementation of PSA involved assigning particular parametric distributions and repeatedly sampling mean parameter values. Sampling was based on point estimates used in the deterministic analysis and standard errors were obtained from literature sources where available or in the absence of supporting data a value equal to 20% of the mean (point estimate) was used as a default.

Each group of samples from all of the parameters included in the PSA generated an estimate for total costs and effects. A total of 1000 different samples were taken from all distributions so that all values of a parameter are likely to have been present in the range of outputs.

Variables and statistical distributions used in the probabilistic sensitivity analyses are reported below.

Table B57: Variables included in the PSA

Parameter name in the model	Definition	Distribution type	Source
Relative risk year 1 gaining vision	Relative risk of gaining vision from baseline to year 1 (Aflibercept vs Ranibizumab)	LOGNORM	Indirect comparison
Relative risk year 1 maintaining vision	Relative risk of maintaining vision from baseline to year 1 (Aflibercept vs Ranibizumab)	LOGNORM	Indirect comparison
Relative risk year 2 gaining vision	Relative risk of gaining vision from year 1 to year 2 (Aflibercept vs Ranibizumab)	LOGNORM	Indirect comparison
Relative risk year 2 maintaining vision	Relative risk of maintaining vision from year 1 to year 2 (Aflibercept vs Ranibizumab)	LOGNORM	Indirect comparison
pDiscont_VTE2q8	Percentage of patients who discontinue treatment with aflibercept in year 1	BETA	CATT (45)
pDiscont2_VTE2q8	Percentage of patients who discontinue treatment with aflibercept in year 2	BETA	CATT (45)
pDiscont3_VTE2q8	Percentage of patients who discontinue treatment with aflibercept in year 3	BETA	CATT (45)
pDiscont_RBZprn	Percentage of patients who discontinue treatment with ranibizumab in year 1	BETA	CATT (45)
pDiscont2_RBZprn	Percentage of patients who discontinue treatment with ranibizumab in year 2	BETA	CATT (45)
pDiscont3_RBZprn	Percentage of patients who discontinue treatment with ranibizumab in year 3	BETA	CATT (45)
NoInj_Y1_VEGF	Number of aflibercept injections in year 1	GAMMA	SmPC
NoInj_Y2_VEGF	Number of aflibercept injections in year 2	GAMMA	SmPC
NoInj_Y3_VEGF	Number of aflibercept injections in year 3	GAMMA	Expert opinion (122)
NoInj_Y4_VEGF	Number of aflibercept injections in year 4	GAMMA	Expert opinion (122)
NoInj_Y5_VEGF	Number of aflibercept injections in year 5	GAMMA	Expert opinion (122)
NoInj_Y1_RbzPRN	Number of ranibizumab injections in year 1	GAMMA	SmPC

Parameter name in the model	Definition	Distribution type	Source
NoInj_Y2_RbzPRN	Number of ranibizumab injections in year 2	GAMMA	SmPC
NoInj_Y3_RbzPRN	Number of ranibizumab injections in year 3	GAMMA	Expert opinion (122)
NoInj_Y4_RbzPRN	Number of ranibizumab injections in year 4	GAMMA	Expert opinion (122)
NoInj_Y5_RbzPRN	Number of ranibizumab injections in year 5	GAMMA	Expert opinion (122)
c_PhysVisit	Cost of an ophthalmologist visit	GAMMA	NHS Ref (120)
c_OCT	Cost of optical coherence tomography scan	GAMMA	NHS Ref (120)
c_FlAngio	Cost of Fluorescein angiography	GAMMA	NHS Ref (120)
NVI_NVIUtil	Utility value of no visual impairment-no visual impairment	BETA	VIEW 2 (123)
NVI_MildUtil	Utility value of no visual impairment-mild impairment	BETA	VIEW 2 (123)
NVI_ModUtil	Utility value of no visual impairment-moderate impairment	BETA	VIEW 2 (123)
NVI_SevUtil	Utility value of no visual impairment-moderate impairment	BETA	VIEW 2 (123)
NVI_BlindUtil	Utility value of no visual impairment-blind/counting fingers	BETA	VIEW 2 (123)
Mild_MildUtil	Utility value of mild-mild impairment	BETA	VIEW 2 (123)
Mild_ModUtil	Utility value of mild-moderate impairment	BETA	VIEW 2 (123)
Mild_SevUtil	Utility value of mild-severe impairment	BETA	VIEW 2 (123)
Mild_BlindUtil	Utility value of mild-blind/counting fingers impairment	BETA	VIEW 2 (123)
Mod_ModUtil	Utility value of moderate-moderate impairment	BETA	VIEW 2 (123)
Mod_SevUtil	Utility value of moderate-severe impairment	BETA	VIEW 2 (123)
Mod_BlindUtil	Utility value of moderate-blind/counting fingers impairment	BETA	VIEW 2 (123)
Sev_SevUtil	Utility value of severe-severe impairment	BETA	VIEW 2 (123)

Parameter name in the model	Definition	Distribution type	Source
Sev_BlindUtil	Utility value of severe-blind/counting fingers impairment	BETA	VIEW 2 (123)
Blind_BlindUtil	Utility value of blind/counting fingers-blind/counting fingers impairment	BETA	VIEW 2 (123)
NPhys_yr1_VEGF	Number of ophthalmologist visits for aflibercept in year 1	GAMMA	SmPC
NOCT_yr1_VEGF	Number of optical coherence tomography scans for aflibercept in year 1	GAMMA	SmPC
NFA_yr1_VEGF	Number of Fluorescein angiography procedures for aflibercept in year 1	GAMMA	Expert opinion (122)
NPhys_yr2_VEGF	Number of ophthalmologist visits for aflibercept in year 2	GAMMA	SmPC
NOCT_yr2_VEGF	Number of optical coherence tomography scans for aflibercept in year 2	GAMMA	SmPC
NPhys_yr3_VEGF	Number of ophthalmologist visits for aflibercept in year 3	GAMMA	Expert opinion (122)
NOCT_yr3_VEGF	Number of optical coherence tomography scans for aflibercept in year 3	GAMMA	Expert opinion (122)
NPhys_yr4_VEGF	Number of ophthalmologist visits for aflibercept in year 4	GAMMA	Expert opinion (122)
NOCT_yr4_VEGF	Number of optical coherence tomography scans for aflibercept in year 4	GAMMA	Expert opinion (122)
NPhys_yr5_VEGF	Number of ophthalmologist visits for aflibercept in year 5	GAMMA	Expert opinion (122)
NOCT_yr5_VEGF	Number of optical coherence tomography scans for aflibercept in year 5	GAMMA	Expert opinion (122)
NPhys_yr1_RbzPRN	Number of ophthalmologist visits for ranibizumab in year 1	GAMMA	SmPC

Parameter name in the model	Definition	Distribution type	Source
NOCT_yr1_RbzPRN	Number of optical coherence tomography scans for ranibizumab in year 1	GAMMA	SmPC
NFA_yr1_RbzPRN	Number of Fluorescein angiography procedures for ranibizumab in year 1	GAMMA	Expert opinion (122)
NPhys_yr2_RbzPRN	Number of ophthalmologist visits for ranibizumab in year 2	GAMMA	SmPC
NOCT_yr2_RbzPRN	Number of optical coherence tomography scans for ranibizumab in year 2	GAMMA	SmPC
NPhys_yr3_RbzPRN	Number of ophthalmologist visits for ranibizumab in year 3	GAMMA	Expert opinion (122)
NOCT_yr3_RbzPRN	Number of optical coherence tomography scans for ranibizumab in year 3	GAMMA	Expert opinion (122)
NPhys_yr4_RbzPRN	Number of ophthalmologist visits for ranibizumab in year 4	GAMMA	Expert opinion (122)
NOCT_yr4_RbzPRN	Number of optical coherence tomography scans for ranibizumab in year 4	GAMMA	Expert opinion (122)
NPhys_yr5_RbzPRN	Number of ophthalmologist visits for ranibizumab in year 5	GAMMA	Expert opinion(122)
NOCT_yr5_RbzPRN	Number of optical coherence tomography scans for ranibizumab in year 5	GAMMA	Expert opinion (122)

7.7 Results

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The outcomes in the decision problem are visual acuity (the affected eye), visual acuity (the whole person), AE of treatment and HRQL.

Table B58: Year 1 summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
	Aflibercept arm	Aflibercept arm
NVI	[redacted]	15.6%
Mild		26.6%
Moderate		27.9%
Severe		18.7%
Blind		10.4%
Dead		0.8%
BCVA*	60.5	60.3

Table B59: Year 2 summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
	Aflibercept	Aflibercept
NVI	[redacted]	16.7%
Mild		23.9%
Moderate		25.7%
Severe		19.0%
Blind		13.2%
Dead		1.6%
BCVA*	59.7	58.9

(Percentage of starting cohort in each visual acuity state, treated eye)
*Based on VA of study eye

At years 1 and 2 in the aflibercept arm distribution of patients across the different levels of VA for the treated eye closely matches the distribution of

patients in the VIEW 2 trial at 52 and 96 weeks, respectively. The slightly lower proportions of the model cohort relative to the clinical trial data is a result of applying a constant mortality rate from the VIEW 2 trial at 96 weeks.

In addition to the cohort VA distribution, it was also possible to compare the cohort BCVA of the study eye versus that reported in the VIEW 2 clinical trial at years one and two. The average level of BCVA obtained in the model outcomes at year 1 and 2 closely matches the average BCVA reported in the VIEW 2 trial at 52 and 96 weeks, respectively. The level of BCVA in the model is calculated by weighting the number of letters (EDTRS) that define each VA level by the percentage of patients at each level of VA. Since the patient distributions are similar between the model outcomes and the trial data it is expected that the BCVA outcomes are similar as well.

It was not helpful to compare the VA distribution of the ranibizumab arm to clinical trial data as the VA ranges used for ranibizumab were calculated applying the relative risks reported in the ITC to the aflibercept values reported in the VIEW 2 trial.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Table B60 show the proportion of the model cohort occupying each health state at each year when on and off treatment (respectively) for the aflibercept arm. The proportion of patients in each health state is presented by year as opposed to be presented at each model monthly cycles in order to simplify the representation of the model cohort over the lifetime horizon.

Figure 14 and Figure 15 illustrates the Markov traces for the aflibercept cohort aggregating health states by patients on and off treatment.

Figure B14. Markov trace: Aflibercept (On and off treatment)

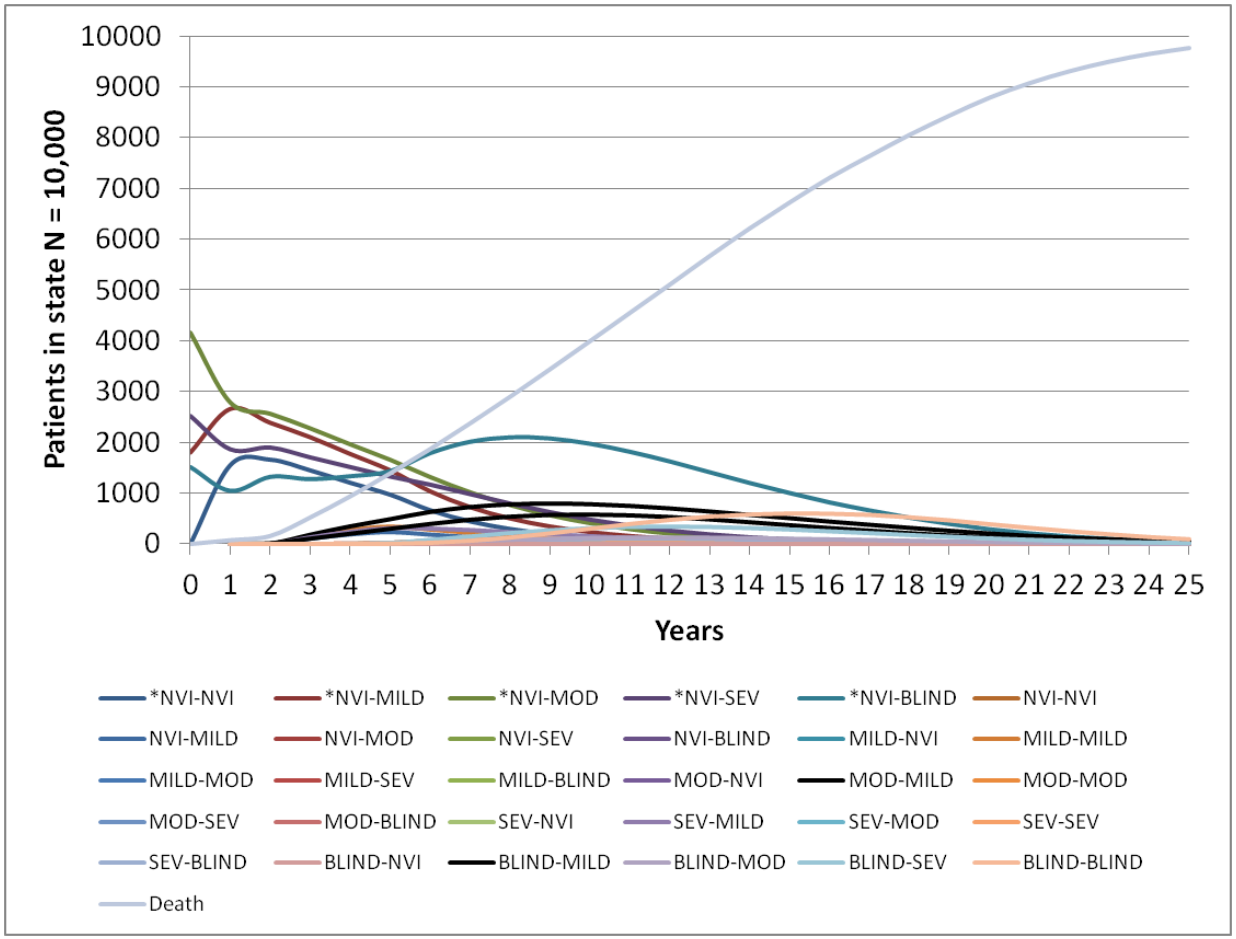


Table B60 Number patients in state on treatment Aflibercept Arm N = 10,000

Health states	Y 1	Y2	Y3	Y4	Y 5	Y 6	Y 7	Y 8	Y 9	Y 10	Y 11	Y 12	Y 13	Y 14	Y 15	Y 16	Y 17	Y 18	Y 19	Y 20	Y 21	Y 22	Y 23	Y 24	Y 25
*NVI-NVI	1518	1608	1190	853	608	412	276	184	121	79	52	33	21	13	8	5	3	2	1	1	0	0	0	0	0
*NVI-MILD	2592	2305	1706	1223	872	617	433	301	207	141	95	64	42	27	17	11	7	4	3	1	1	0	0	0	0
*NVI-MOD	2714	2477	1833	1315	937	745	581	442	329	240	172	0	0	57	38	25	16	10	6	4	2	1	1	0	0
*NVI-SEV	1817	1835	1358	974	694	619	532	438	349	271	204	0	0	77	54	36	25	16	10	6	4	2	1	1	0
*NVI-BLIND	1013	1271	1138	1006	883	1047	1160	1202	1185	1125	1034	0	0	685	572	467	378	296	226	166	120	85	58	38	24
NVI-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NVI-MILD	0	0	90	141	160	123	90	64	44	30	20	13	9	6	3	2	1	1	0	0	0	0	0	0	0
NVI-MOD	0	0	0	0	0	7	9	9	8	6	4	2	0	2	1	1	0	0	0	0	0	0	0	0	0
NVI-SEV	0	0	0	0	0	19	26	26	22	18	13	10	7	5	3	2	1	1	0	0	0	0	0	0	0
NVI-BLIND	0	0	0	0	0	3	8	13	16	16	16	14	12	9	7	5	4	3	2	1	1	0	0	0	0
MILD-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MILD-MILD	0	0	130	202	229	184	140	104	75	53	37	25	17	11	7	5	3	2	1	1	0	0	0	0	0
MILD-MOD	0	0	0	0	0	10	14	14	13	11	8	6	4	3	2	1	1	1	0	0	0	0	0	0	0
MILD-SEV	0	0	0	0	0	28	41	42	38	31	24	18	13	9	6	4	3	2	1	1	0	0	0	0	0
MILD-BLIND	0	0	0	0	0	4	13	21	27	29	29	26	23	19	15	12	9	6	5	3	2	1	1	0	0
MOD-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MOD-MILD	0	0	139	218	246	328	387	421	433	428	412	386	353	316	280	242	208	174	142	112	87	66	49	34	23
MOD-MOD	0	0	0	0	0	1	2	3	4	4	3	3	2	2	1	1	1	0	0	0	0	0	0	0	0
MOD-SEV	0	0	0	0	0	3	7	10	11	11	10	8	6	5	3	2	2	1	1	0	0	0	0	0	0
MOD-BLIND	0	0	0	0	0	1	3	8	12	16	18	19	18	17	14	12	10	7	6	4	3	2	1	1	0
SEV-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SEV-MILD	0	0	103	161	182	172	154	132	108	87	67	51	37	27	19	13	9	6	4	2	1	1	0	0	0
SEV-MOD	0	0	0	0	0	9	15	18	18	17	14	12	9	7	5	4	3	2	1	1	0	0	0	0	0
SEV-SEV	0	0	0	0	0	27	45	53	53	49	43	35	28	21	16	11	8	5	3	2	1	1	0	0	0

SEV-BLIND	0	0	0	0	0	4	14	27	38	46	50	51	48	43	37	31	25	19	14	10	7	5	3	2	1
BLIND-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BLIND-MILD	0	0	78	135	170	225	273	307	326	329	319	299	272	240	207	174	144	115	90	67	49	35	25	16	10
BLIND-MOD	0	0	0	0	0	12	27	41	52	61	65	66	64	60	54	47	41	34	27	21	15	11	8	5	3
BLIND-SEV	0	0	0	0	0	34	75	115	150	175	190	194	190	178	162	143	123	102	82	63	48	35	25	17	11
BLIND-BLIND	0	0	0	0	0	5	23	56	101	154	207	256	294	320	333	332	321	296	263	221	181	143	109	78	53
Death	76	160	525	941	1394	1872	2378	2902	3445	3998	4557	2893	3315	6222	6733	7218	7647	8065	8445	8797	9083	9318	9507	9659	9775

* Patients with wet AMD in one eye only

Table B61: Number patients in state off treatment Aflibercept Arm N = 10,000

Health states	Y 1	Y2	Y3	Y4	Y 5	Y 6	Y 7	Y 8	Y 9	Y 10	Y 11	Y 12	Y 13	Y 14	Y 15	Y 16	Y 17	Y 18	Y 19	Y 20	Y 21	Y 22	Y 23	Y 24	Y 25
*NVI-NVI	42	58	265	357	368	256	171	114	75	49	32	21	13	8	5	3	2	1	1	0	0	0	0	0	0
*NVI-MILD	72	84	399	551	581	421	294	204	140	95	64	43	28	18	12	7	5	3	2	1	1	0	0	0	0
*NVI-MOD	75	90	446	651	724	576	439	327	240	173	123	86	59	39	26	17	11	7	4	3	1	1	0	0	0
*NVI-SEV	50	67	351	544	637	553	454	361	280	212	158	115	82	57	39	27	18	11	7	4	3	2	1	0	0
*NVI-BLIND	28	46	133	322	546	734	844	889	883	841	774	692	601	511	426	348	281	220	168	123	89	63	43	28	18
NVI-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NVI-MILD	0	0	17	49	74	63	48	35	25	17	12	8	5	3	2	1	1	0	0	0	0	0	0	0	0
NVI-MOD	0	0	0	2	4	6	6	5	5	4	3	2	1	1	1	0	0	0	0	0	0	0	0	0	0
NVI-SEV	0	0	1	5	12	17	18	16	13	10	8	6	4	3	2	1	1	0	0	0	0	0	0	0	0
NVI-BLIND	0	0	0	1	3	6	9	11	12	12	11	9	7	6	5	3	2	2	1	1	0	0	0	0	0
MILD-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MILD-MILD	0	0	24	71	112	100	80	61	46	33	23	16	11	7	5	3	2	1	1	0	0	0	0	0	0
MILD-MOD	0	0	0	3	6	9	10	9	8	7	5	4	3	2	1	1	1	0	0	0	0	0	0	0	0
MILD-SEV	0	0	1	8	18	27	29	28	24	20	15	11	8	6	4	3	2	1	1	0	0	0	0	0	0
MILD-BLIND	0	0	0	1	4	10	15	19	21	22	20	18	16	13	10	8	6	4	3	2	1	1	1	0	0
MOD-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MOD-MILD	0	0	33	119	229	290	326	345	349	341	325	303	276	247	217	188	162	135	110	86	67	51	38	27	18
MOD-MOD	0	0	0	0	1	2	2	3	3	2	2	2	1	1	1	0	0	0	0	0	0	0	0	0	0
MOD-SEV	0	0	0	1	3	5	7	8	8	7	6	5	4	3	2	1	1	1	0	0	0	0	0	0	0
MOD-BLIND	0	0	0	0	1	3	6	9	12	14	14	14	13	12	10	8	6	5	4	3	2	1	1	0	0
SEV-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SEV-MILD	0	0	22	69	117	119	110	95	79	63	49	37	27	19	14	9	6	4	3	2	1	1	0	0	0
SEV-MOD	0	0	0	3	7	11	14	14	14	12	10	8	7	5	4	3	2	1	1	0	0	0	0	0	0
SEV-SEV	0	0	1	8	20	33	40	42	40	36	31	25	20	15	11	8	6	4	2	2	1	1	0	0	0
SEV-BLIND	0	0	0	1	5	12	21	30	36	40	41	40	37	32	27	22	18	14	10	7	5	3	2	1	1

BLIND-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BLIND-MILD	0	0	13	53	116	156	192	219	235	239	234	220	200	177	153	129	107	85	67	50	37	26	18	12	8
BLIND-MOD	0	0	0	3	8	17	26	34	41	46	49	49	47	44	40	35	30	25	20	15	11	8	6	4	3
BLIND-SEV	0	0	1	7	22	46	72	97	118	134	143	145	141	132	120	105	91	75	61	47	35	26	18	12	8
BLIND-BLIND	0	0	0	1	6	18	40	70	107	146	185	219	244	260	266	261	250	229	202	169	137	108	82	59	40

Table B62 and Table B63 show the same data for the comparator arm. Figure 15 illustrates the Markov traces for the ranibizumab cohort aggregating health states by patients on and off treatment.

Figure B15: Markov trace: Ranibizumab (on and off treatment)

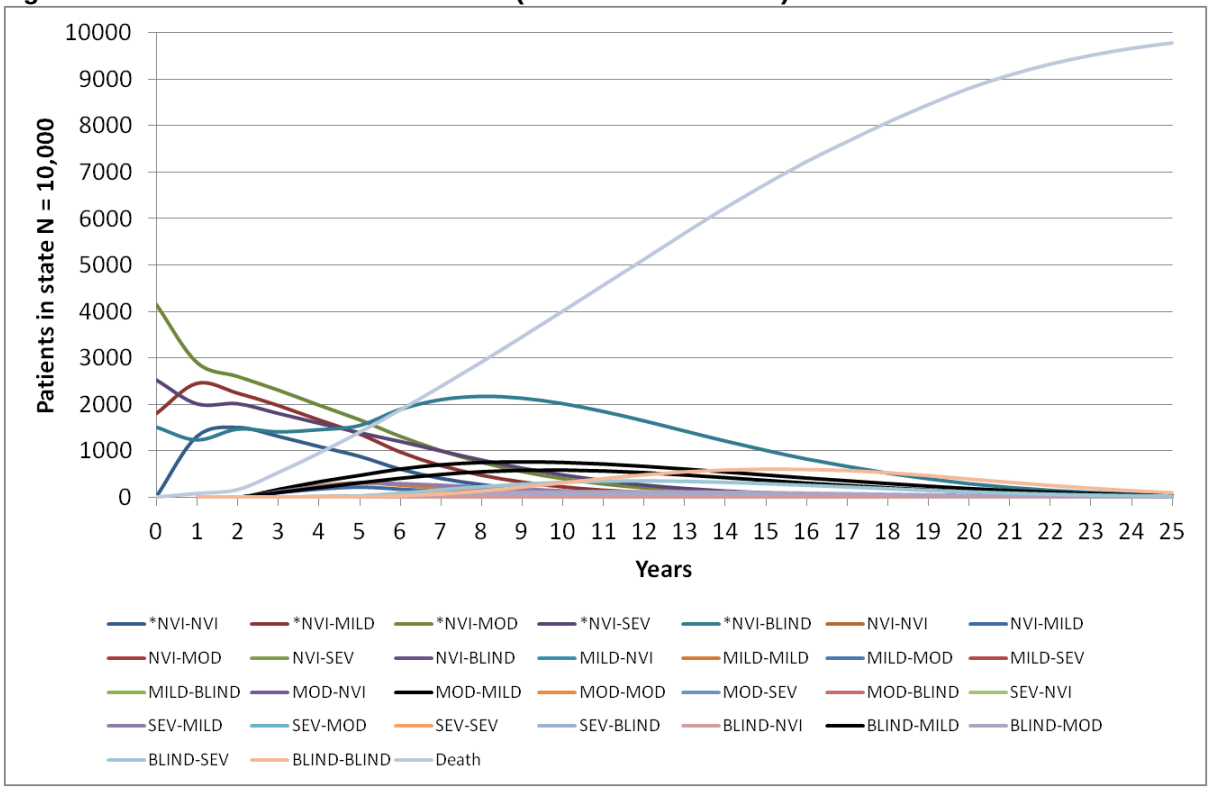


Table B62. Number patients in state on treatment - Ranibizumab Arm N = 10,000

Health states	Y 1	Y2	Y3	Y4	Y 5	Y 6	Y 7	Y 8	Y 9	Y 10	Y 11	Y 12	Y 13	Y 14	Y 15	Y 16	Y 17	Y 18	Y 19	Y 20	Y 21	Y 22	Y 23	Y 24	Y 25
*NVI-NVI	1276	1455	1077	772	550	373	250	166	110	72	47	30	19	12	7	5	3	2	1	1	0	0	0	0	0
*NVI-MILD	2395	2172	1607	1152	821	580	407	282	194	132	89	59	39	25	16	10	6	4	2	1	1	0	0	0	0
*NVI-MOD	2830	2514	1860	1334	951	745	575	433	320	232	166	116	80	54	0	0	15	10	6	3	2	1	1	0	0
*NVI-SEV	1956	1941	1436	1030	734	640	541	441	348	267	201	148	106	75	0	0	24	15	10	6	4	2	1	1	0
*NVI-BLIND	1199	1414	1267	1119	983	1142	1245	1275	1246	1174	1073	956	829	703	0	0	385	301	230	169	122	86	59	39	24
NVI-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NVI-MILD	0	0	82	128	145	111	81	58	40	27	18	12	8	5	3	2	1	1	0	0	0	0	0	0	0
NVI-MOD	0	0	0	0	0	6	8	8	7	5	4	3	2	1	0	0	0	0	0	0	0	0	0	0	0
NVI-SEV	0	0	0	0	0	17	24	23	20	16	12	9	6	4	3	2	1	1	0	0	0	0	0	0	0
NVI-BLIND	0	0	0	0	0	2	7	12	14	15	14	13	10	8	7	5	4	3	2	1	1	0	0	0	0
MILD-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MILD-MILD	0	0	122	191	216	173	131	97	70	50	35	24	16	10	7	4	3	2	1	1	0	0	0	0	0
MILD-MOD	0	0	0	0	0	9	13	14	12	10	8	6	4	3	2	1	1	1	0	0	0	0	0	0	0
MILD-SEV	0	0	0	0	0	27	38	39	35	29	23	17	12	9	6	4	3	2	1	1	0	0	0	0	0
MILD-BLIND	0	0	0	0	0	4	12	20	25	27	27	25	21	18	14	11	8	6	4	3	2	1	1	0	0
MOD-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MOD-MILD	0	0	141	221	250	329	385	417	427	422	404	378	346	310	274	237	204	170	139	109	85	64	47	34	23
MOD-MOD	0	0	0	0	0	1	2	3	4	3	3	2	2	1	1	1	0	0	0	0	0	0	0	0	0
MOD-SEV	0	0	0	0	0	2	7	9	10	10	9	7	6	4	3	2	1	1	1	0	0	0	0	0	0
MOD-BLIND	0	0	0	0	0	0	3	7	11	15	17	17	17	15	13	11	9	7	5	4	2	2	1	1	0
SEV-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SEV-MILD	0	0	109	170	193	179	157	133	108	86	66	50	36	26	18	13	8	6	4	2	1	1	0	0	0
SEV-MOD	0	0	0	0	0	10	16	18	18	16	14	11	9	7	5	3	2	2	1	1	0	0	0	0	0

SEV-SEV	0	0	0	0	0	28	45	53	53	49	42	34	27	20	15	11	8	5	3	2	1	1	0	0	0
SEV-BLIND	0	0	0	0	0	4	14	27	38	45	49	49	46	42	36	30	24	18	14	10	7	4	3	2	1
BLIND-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BLIND-MILD	0	0	87	151	189	248	297	330	346	347	335	312	282	248	213	179	148	118	92	69	50	36	25	17	11
BLIND-MOD	0	0	0	0	0	14	29	44	56	64	68	69	67	62	56	49	42	34	28	21	16	12	8	6	4
BLIND-SEV	0	0	0	0	0	37	81	124	159	185	199	203	197	185	167	147	126	105	84	65	49	36	25	17	11
BLIND-BLIND	0	0	0	0	0	5	25	60	108	162	217	267	306	331	344	342	330	304	269	226	185	146	111	80	55
Death	76	160	525	941	1394	1872	2378	2902	3446	3998	4557	5114	5678	6223	4113	4502	7649	8067	8446	8798	9084	9319	9507	9660	9775

Table B63: Number patients in state off treatment - Ranibizumab Arm N = 10,000

Health states	Y 1	Y2	Y3	Y4	Y 5	Y 6	Y 7	Y 8	Y 9	Y 10	Y 11	Y 12	Y 13	Y 14	Y 15	Y 16	Y 17	Y 18	Y 19	Y 20	Y 21	Y 22	Y 23	Y 24	Y 25
*NVI-NVI	35	53	240	323	333	231	155	103	68	45	29	19	12	7	5	3	2	1	1	0	0	0	0	0	0
*NVI-MILD	66	79	376	518	546	395	276	191	131	89	60	40	26	17	11	7	4	3	2	1	1	0	0	0	0
*NVI-MOD	79	91	449	651	719	567	428	318	231	166	117	82	56	37	25	16	10	7	4	2	1	1	0	0	0
*NVI-SEV	54	70	366	562	653	559	453	358	276	208	154	112	79	55	38	26	17	11	7	4	3	1	1	0	0
*NVI-BLIND	33	51	141	333	559	747	854	896	886	841	772	689	598	507	422	344	278	217	166	121	88	62	42	28	18
NVI-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NVI-MILD	0	0	16	44	67	57	43	32	23	16	11	7	5	3	2	1	1	0	0	0	0	0	0	0	0
NVI-MOD	0	0	0	2	4	5	6	5	4	3	2	2	1	1	1	0	0	0	0	0	0	0	0	0	0
NVI-SEV	0	0	1	5	11	15	16	14	12	9	7	5	4	2	2	1	1	0	0	0	0	0	0	0	0
NVI-BLIND	0	0	0	1	3	6	8	10	11	10	10	8	7	5	4	3	2	2	1	1	0	0	0	0	0
MILD-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MILD-MILD	0	0	22	67	106	93	75	57	43	31	22	15	10	7	4	3	2	1	1	0	0	0	0	0	0
MILD-MOD	0	0	0	3	6	9	9	9	8	6	5	4	3	2	1	1	1	0	0	0	0	0	0	0	0
MILD-SEV	0	0	1	7	17	25	27	26	22	18	14	11	8	5	4	3	2	1	1	0	0	0	0	0	0
MILD-BLIND	0	0	0	1	4	9	14	18	20	20	19	17	14	12	9	7	5	4	3	2	1	1	0	0	0
MOD-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MOD-MILD	0	0	34	119	229	288	322	339	342	334	317	295	269	240	212	183	157	131	107	84	65	49	37	26	18
MOD-MOD	0	0	0	0	1	2	2	3	2	2	2	2	1	1	1	0	0	0	0	0	0	0	0	0	0
MOD-SEV	0	0	0	1	2	5	7	7	7	7	6	5	4	3	2	1	1	1	0	0	0	0	0	0	0
MOD-BLIND	0	0	0	0	1	3	5	8	11	12	13	13	12	11	9	7	6	5	3	2	2	1	1	0	0
SEV-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SEV-MILD	0	0	23	72	120	121	110	95	78	62	48	36	26	19	13	9	6	4	3	2	1	1	0	0	0
SEV-MOD	0	0	0	3	7	12	14	14	13	12	10	8	6	5	3	2	2	1	1	0	0	0	0	0	0
SEV-SEV	0	0	1	8	21	33	40	42	40	36	30	24	19	14	11	8	5	4	2	1	1	1	0	0	0
SEV-BLIND	0	0	0	1	5	12	21	29	36	39	40	39	35	31	26	21	17	13	10	7	5	3	2	1	1

BLIND-NVI	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
BLIND-MILD	0	0	14	58	124	164	198	224	238	242	235	221	200	177	152	128	106	85	66	49	36	26	18	12	8
BLIND-MOD	0	0	0	3	9	17	27	35	42	47	49	50	48	44	40	35	30	25	20	15	11	8	6	4	3
BLIND-SEV	0	0	1	7	23	48	75	100	121	136	145	146	141	132	119	105	90	75	60	46	35	25	18	12	8
BLIND-BLIND	0	0	0	1	6	19	41	72	109	149	187	221	246	261	266	261	250	228	201	168	137	108	82	59	40

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Each health state in the model is assigned a utility value based on the VA of both eyes. Patients in the model transition to different health states over time due to either the effect of treatment or natural disease progression. QALYs are calculated by weighting the time spent in a particular state by the utility value assigned to the state. The cumulative QALYs are based on a cohort of patients with a starting VA distribution derived from the baseline distribution of the patients in the VIEW 2 clinical trial, which is the same as the distribution used in the base case analysis.

Table 64 and Table 65 show the aggregated cumulative QALYs for the intervention and the comparator arm, respectively. QALYs are aggregated for patients on and off treatment within the same treatment arm. QALYs accrued in both treatment arms are also presented by year in order to simplify representation of data over the lifetime (25 years) horizon.

Table B64: Aflibercept Cumulative QALYs per health state per year (Years 1-25)

Health State	Y 1	Y2	Y3	Y4	Y 5	Y 6	Y 7	Y 8	Y 9	Y 10	Y 11	Y 12	Y 13	Y 14	Y 15	Y 16	Y 17	Y 18	Y 19	Y 20	Y 21	Y 22	Y 23	Y 24	Y 25
*NVI-NVI	0.07	0.21	0.34	0.44	0.52	0.58	0.62	0.65	0.66	0.67	0.68	0.68	0.69	0.69	0.69	0.69	0.69	0.69	0.69	0.69	0.69	0.69	0.69	0.69	0.69
*NVI-MILD	0.19	0.39	0.57	0.71	0.83	0.91	0.97	1.01	1.04	1.06	1.07	1.07	1.08	1.08	1.08	1.09	1.09	1.09	1.09	1.09	1.09	1.09	1.09	1.09	1.09
*NVI-MOD	0.29	0.50	0.69	0.85	0.98	1.08	1.16	1.22	1.26	1.29	1.31	1.32	1.33	1.34	1.34	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35
*NVI-SEV	0.18	0.33	0.47	0.59	0.70	0.78	0.86	0.92	0.96	0.99	1.02	1.04	1.05	1.06	1.06	1.07	1.07	1.07	1.07	1.07	1.07	1.07	1.07	1.07	1.07
*NVI-BLIND	0.10	0.20	0.29	0.39	0.49	0.60	0.72	0.86	0.99	1.11	1.22	1.31	1.39	1.46	1.51	1.56	1.59	1.62	1.64	1.65	1.66	1.67	1.67	1.68	1.68
NVI-NVI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
NVI-MILD	0.00	0.00	0.00	0.02	0.03	0.05	0.06	0.06	0.07	0.07	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
NVI-MOD	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
NVI-SEV	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
NVI-BLIND	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
MILD-NVI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MILD-MILD	0.00	0.00	0.01	0.02	0.04	0.06	0.08	0.09	0.10	0.11	0.11	0.11	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
MILD-MOD	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
MILD-SEV	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.02	0.02	0.02	0.02	0.02	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
MILD-BLIND	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
MOD-NVI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MOD-MILD	0.00	0.00	0.01	0.03	0.05	0.09	0.13	0.18	0.23	0.27	0.31	0.35	0.38	0.41	0.44	0.46	0.48	0.49	0.51	0.51	0.52	0.53	0.53	0.53	0.53
MOD-MOD	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MOD-SEV	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
MOD-BLIND	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
SEV-NVI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
SEV-MILD	0.00	0.00	0.00	0.02	0.04	0.05	0.07	0.09	0.10	0.11	0.12	0.12	0.12	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13
SEV-MOD	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
SEV-SEV	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.02	0.02	0.03	0.03	0.03	0.03	0.03	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
SEV-BLIND	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.02	0.02	0.02	0.03	0.03	0.03	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04

BLIND-NVI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
BLIND-MILD	0.00	0.00	0.00	0.01	0.03	0.05	0.08	0.11	0.14	0.17	0.20	0.22	0.25	0.27	0.29	0.30	0.31	0.32	0.33	0.34	0.34	0.34	0.34	0.34	0.35
BLIND-MOD	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.02	0.02	0.03	0.03	0.04	0.04	0.05	0.05	0.05	0.06	0.06	0.06	0.06	0.06	0.06	0.06
BLIND-SEV	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.03	0.05	0.06	0.08	0.09	0.11	0.12	0.13	0.14	0.15	0.15	0.16	0.16	0.16	0.17	0.17	0.17
BLIND-BLIND	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.03	0.04	0.06	0.08	0.10	0.12	0.14	0.16	0.18	0.20	0.21	0.22	0.23	0.23	0.24	0.24

Table B65 Ranibizumab Cumulative QALYs per health state per year (Years 1-25)

Health State	Y 1	Y2	Y3	Y4	Y 5	Y 6	Y 7	Y 8	Y 9	Y 10	Y 11	Y 12	Y 13	Y 14	Y 15	Y 16	Y 17	Y 18	Y 19	Y 20	Y 21	Y 22	Y 23	Y 24	Y 25
*NVI-NVI	0.06	0.18	0.30	0.39	0.47	0.52	0.55	0.58	0.59	0.60	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.62	0.62	0.62	0.62	0.62	0.62
*NVI-MILD	0.18	0.37	0.53	0.67	0.78	0.86	0.92	0.95	0.98	0.99	1.00	1.01	1.02	1.02	1.02	1.02	1.02	1.02	1.02	1.02	1.02	1.02	1.02	1.02	1.02
*NVI-MOD	0.29	0.51	0.70	0.86	1.00	1.10	1.18	1.23	1.27	1.30	1.32	1.34	1.34	1.35	1.35	1.36	1.36	1.36	1.36	1.36	1.36	1.36	1.36	1.36	1.36
*NVI-SEV	0.19	0.35	0.50	0.63	0.73	0.82	0.90	0.96	1.00	1.03	1.06	1.07	1.09	1.09	1.10	1.10	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11	1.11
*NVI-BLIND	0.11	0.22	0.33	0.43	0.54	0.66	0.79	0.93	1.06	1.18	1.30	1.39	1.47	1.54	1.60	1.64	1.68	1.70	1.72	1.74	1.75	1.75	1.76	1.76	1.76
NVI-NVI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
NVI-MILD	0.00	0.00	0.00	0.01	0.03	0.04	0.05	0.06	0.06	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07
NVI-MOD	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
NVI-SEV	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
NVI-BLIND	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
MILD-NVI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MILD-MILD	0.00	0.00	0.01	0.02	0.04	0.06	0.08	0.09	0.09	0.10	0.10	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11
MILD-MOD	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
MILD-SEV	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
MILD-BLIND	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
MOD-NVI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MOD-MILD	0.00	0.00	0.01	0.03	0.05	0.09	0.13	0.18	0.22	0.27	0.31	0.35	0.38	0.41	0.43	0.46	0.47	0.49	0.50	0.51	0.51	0.52	0.52	0.53	0.53
MOD-MOD	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MOD-SEV	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
MOD-BLIND	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
SEV-NVI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
SEV-MILD	0.00	0.00	0.00	0.02	0.04	0.06	0.07	0.09	0.10	0.11	0.12	0.12	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13
SEV-MOD	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
SEV-SEV	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.02	0.02	0.03	0.03	0.03	0.03	0.03	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04

SEV-BLIND	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.02	0.02	0.02	0.03	0.03	0.03	0.03	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
BLIND-NVI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
BLIND-MILD	0.00	0.00	0.00	0.01	0.03	0.05	0.08	0.11	0.15	0.18	0.21	0.24	0.26	0.28	0.30	0.32	0.33	0.34	0.34	0.35	0.35	0.36	0.36	0.36	0.36
BLIND-MOD	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.02	0.02	0.03	0.04	0.04	0.05	0.05	0.05	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
BLIND-SEV	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.03	0.05	0.07	0.08	0.10	0.11	0.13	0.14	0.15	0.15	0.16	0.16	0.17	0.17	0.17	0.17	0.17
BLIND-BLIND	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.03	0.04	0.06	0.08	0.10	0.12	0.15	0.17	0.18	0.20	0.21	0.22	0.23	0.24	0.24	0.25

Each health state in the model is assigned a utility value based on the VA of both eyes. Patients in the model transition to different health states over time due to either the effect of treatment or natural disease progression. QALYs are calculated by weighting the time spent in a particular state by the utility value assigned to the state. The cumulative QALYs shown in Table B64 and Table B65 are based on a cohort with a starting VA distribution derived from the baseline distribution of the patients in the VIEW 2 clinical trial, and is the same as the distribution used in the base case analysis.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Life years and QALYs accrued at each level of VA are presented in a disaggregated manner and by health state for the intervention and the comparator arm in Table B66. Clinical outcomes reported are based on a lifetime (25 years) horizon.

Table B66: Model outputs by clinical outcomes

	LY Aflibercept	LY Ranibizumab	QALY Aflibercept	QALY Ranibizumab
*NVI-NVI	0.78	0.70	0.69	0.62
*NVI-MILD	1.23	1.16	1.09	1.02
*NVI-MOD	1.54	1.55	1.35	1.36
*NVI-SEV	1.25	1.29	1.07	1.11
*NVI-BLIND	2.26	2.36	1.68	1.76
NVI-NVI	0.00	0.00	0.00	0.00
NVI-MILD	0.10	0.09	0.08	0.07
NVI-MOD	0.01	0.01	0.01	0.01
NVI-SEV	0.02	0.02	0.02	0.02
NVI-BLIND	0.02	0.02	0.01	0.01
MILD-NVI	0.00	0.00	0.00	0.00
MILD-MILD	0.15	0.14	0.12	0.11
MILD-MOD	0.01	0.01	0.01	0.01
MILD-SEV	0.04	0.03	0.03	0.03
MILD-BLIND	0.03	0.03	0.02	0.02
MOD-NVI	0.00	0.00	0.00	0.00
MOD-MILD	0.78	0.77	0.53	0.53
MOD-MOD	0.00	0.00	0.00	0.00
MOD-SEV	0.01	0.01	0.01	0.01
MOD-BLIND	0.02	0.02	0.01	0.01
SEV-NVI	0.00	0.00	0.00	0.00
SEV-MILD	0.17	0.17	0.13	0.13
SEV-MOD	0.02	0.02	0.01	0.01
SEV-SEV	0.05	0.05	0.04	0.04
SEV-BLIND	0.06	0.06	0.04	0.04
BLIND-NVI	0.00	0.00	0.00	0.00
BLIND-MILD	0.51	0.52	0.35	0.36
BLIND-MOD	0.09	0.10	0.06	0.06
BLIND-SEV	0.26	0.27	0.17	0.17
BLIND-BLIND	0.41	0.42	0.24	0.25

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Disaggregated incremental clinical and economic outcomes are reported in Table B67, Table B68 and

Table B69 by level of VA in both eyes.

Table B67: Summary of QALY gain by health state

Health State	QALY Aflibercept	QALY Ranibizumab	Increment Aflibercept vs Ranibizumab	Absolute Increment Aflibercept vs Ranibizumab	% Increment Aflibercept vs Ranibizumab
*NVI-NVI	0.689	0.615	0.074	0.074	22%
*NVI-MILD	1.087	1.023	0.064	0.064	19%
*NVI-MOD	1.351	1.361	-0.010	0.010	3%
*NVI-SEV	1.073	1.110	-0.037	0.037	11%
*NVI-BLIND	1.678	1.764	-0.086	0.086	26%
NVI-NVI	0.000	0.000	0.000	0.000	0%
NVI-MILD	0.080	0.072	0.008	0.008	2%
NVI-MOD	0.006	0.005	0.001	0.001	0%
NVI-SEV	0.017	0.015	0.002	0.002	0%
NVI-BLIND	0.013	0.012	0.001	0.001	0%
MILD-NVI	0.000	0.000	0.000	0.000	0%
MILD-MILD	0.118	0.111	0.007	0.007	2%
MILD-MOD	0.009	0.009	0.001	0.001	0%
MILD-SEV	0.027	0.025	0.002	0.002	1%
MILD-BLIND	0.023	0.021	0.002	0.002	0%
MOD-NVI	0.000	0.000	0.000	0.000	0%
MOD-MILD	0.535	0.527	0.008	0.008	2%
MOD-MOD	0.003	0.002	0.000	0.000	0%
MOD-SEV	0.008	0.007	0.001	0.001	0%
MOD-BLIND	0.015	0.014	0.001	0.001	0%
SEV-NVI	0.000	0.000	0.000	0.000	0%
SEV-MILD	0.132	0.134	-0.002	0.002	1%
SEV-MOD	0.014	0.014	0.000	0.000	0%
SEV-SEV	0.037	0.037	0.000	0.000	0%
SEV-BLIND	0.040	0.039	0.001	0.001	0%
BLIND-NVI	0.000	0.000	0.000	0.000	0%
BLIND-MILD	0.345	0.360	-0.015	0.015	4%
BLIND-MOD	0.060	0.062	-0.002	0.002	1%
BLIND-SEV	0.168	0.173	-0.005	0.005	2%
BLIND-BLIND	0.240	0.245	-0.005	0.005	2%

Table B68: Summary of costs by health state

Health State	Costs Aflibercept	Costs Ranibizumab	Increment Aflibercept vs Ranibizumab	Absolute Increment Aflibercept vs Ranibizumab	% Absolute Increment Aflibercept vs Ranibizumab
*NVI-NVI	£2,988	£3,045	-57	57	1%
*NVI-MILD	£5,264	£5,818	-554	554	15%
*NVI-MOD	£6,472	£7,753	-1281	1281	34%
*NVI-SEV	£4,447	£5,461	-1014	1014	27%
*NVI-BLIND	£1,614	£2,353	-739	739	19%
NVI-NVI	£0	£0	0	0	0%
NVI-MILD	£248	£210	39	39	1%
NVI-MOD	£0	£0	0	0	0%
NVI-SEV	£0	£0	0	0	0%
NVI-BLIND	£0	£0	0	0	0%
MILD-NVI	£0	£0	0	0	0%
MILD-MILD	£356	£313	43	43	1%
MILD-MOD	£0	£0	0	0	0%
MILD-SEV	£0	£0	0	0	0%
MILD-BLIND	£0	£0	0	0	0%
MOD-NVI	£0	£0	0	0	0%
MOD-MILD	£383	£362	20	20	1%
MOD-MOD	£0	£0	0	0	0%
MOD-SEV	£0	£0	0	0	0%
MOD-BLIND	£0	£0	0	0	0%
SEV-NVI	£0	£0	0	0	0%
SEV-MILD	£283	£280	4	4	0%
SEV-MOD	£0	£0	0	0	0%
SEV-SEV	£0	£0	0	0	0%
SEV-BLIND	£0	£0	0	0	0%
BLIND-NVI	£0	£0	0	0	0%
BLIND-MILD	£148	£156	-8	8	0%
BLIND-MOD	£0	£0	0	0	0%
BLIND-SEV	£0	£0	0	0	0%
BLIND-BLIND	£2,806	£2,866	-60	60	2%

Table B69: Summary of predicted resource use by category of cost

Item	Cost Aflibercept	Cost Ranibizumab	Increment Aflibercept vs Ranibizumab	Absolute Increment Aflibercept vs Ranibizumab	% Absolute Increment Aflibercept vs Ranibizumab
Drug costs	£18,430	£19,826	-£1,396	£1,396	39%
Physician costs	£923	£1,890	-£967	£967	27%
Monitoring tests	£2,850	£4,033	-£1,184	£1,184	33%
Cost of Blindness	£2,806	£2,866	-£60	£60	2%

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The base case analysis consists of one treatment comparator pair namely aflibercept 2mg Q8/PRN versus ranibizumab 0.5 mg PRN.

In the base case results aflibercept was associated with comparable life expectancy compared with ranibizumab over the lifetime (25 years) horizon. These results are based on the treatment effects calculated based on the VIEW 2 clinical trial outcomes and the relative risks (RRs) calculated through the ITC reported in section 6.7. RRs did not find statistically significant differences between the treatment effects of the interventions. The small differences in QALYs accrued by the interventions in the model are in line with the findings of the ITC. Aflibercept was associated with lower costs compared to ranibizumab (- £3,606 per patient). The base case found aflibercept to reduce costs and improve outcomes compared to ranibizumab in the treatment of patients with wet AMD.

Table B70 : Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	£25,009.19	10.57	7.77				
Ranibizumab	£28,615.22	10.57	7.76	£3,606	-0.001	-0.010	Dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Sensitivity analysis was performed using a net monetary benefit approach since aflibercept was dominant compared to ranibizumab in the base case. The willingness to pay threshold that was used for the analysis was £20,000 as this is the lower end of the NICE threshold range.

The tornado diagrams in Figure B16 shows the 15 one way sensitivity tests which most impacted results. Findings were most sensitive to the drug costs, number of injections and frequency of monitoring, percentage of patients in one-stop or two-stop models followed by the relative risk for gaining or maintaining vision.

Discount rates used for the analysis had relatively little impact on overall cost-effectiveness outcomes.

In all instances tested, aflibercept incurred lower costs versus ranibizumab and accrued more QALYs.

Figure B16: Tornado diagram: deterministic sensitivity analysis

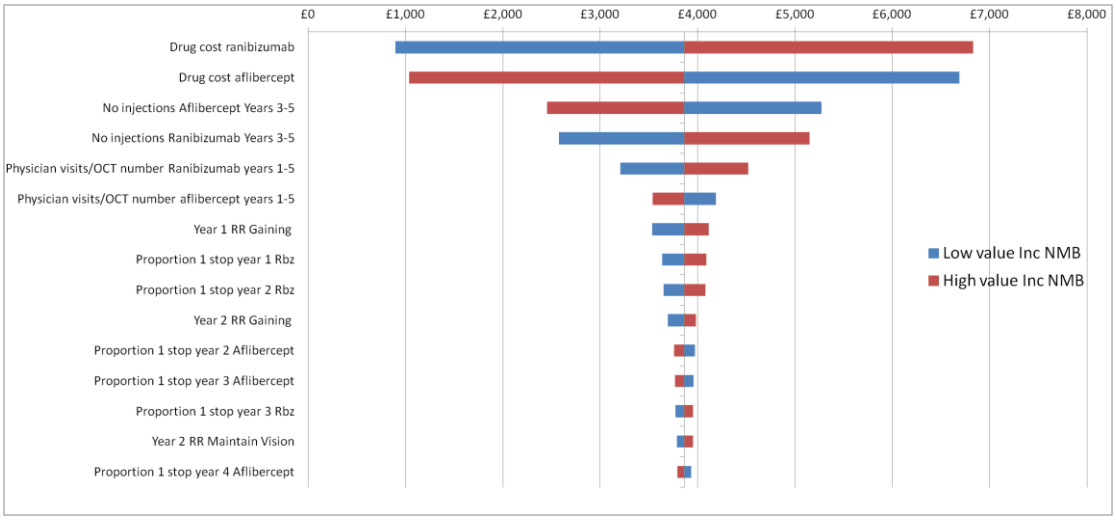


Table B71 Results of the deterministic sensitivity analysis

Variable no.	Parameter	Inc Costs (low)	Inc QALYs (low)	Inc Costs (high)	Inc QALYs (high)	Low value Inc NMB	High value Inc NMB
1	Drug cost ranibizumab	-£645	0.013	-£6,576	0.013	£903	£6,834
2	Drug cost aflibercept	-£6,435	0.013	-£786	0.013	£6,693	£1,044
3	No injections Aflibercept Years 3-5	-£5,019	0.013	-£2,203	0.013	£5,277	£2,460
4	No injections Ranibizumab Years 3-5	-£2,325	0.013	-£4,897	0.013	£2,583	£5,154
5	Physician visits/OCT number Ranibizumab years 1-5	-£2,984	0.013	-£4,238	0.013	£3,241	£4,496
6	Year 1 RR Gaining	-£3,696	-0.008	-£3,546	0.029	£3,530	£4,125
7	Physician visits/OCT number aflibercept years 1-5	-£3,906	0.013	-£3,316	0.013	£4,164	£3,574
8	Proportion 1 stop year 1 Rbz	-£3,383	0.013	-£3,839	0.013	£3,641	£4,096
9	Proportion 1 stop year 2 Rbz	-£3,396	0.013	-£3,825	0.013	£3,654	£4,083

10	Year 2 RR Gaining	-£3,649	0.002	-£3,583	0.020	£3,698	£3,989
11	Proportion 1 stop year 2 Aflibercept	-£3,718	0.013	-£3,504	0.013	£3,976	£3,761
12	Year 2 RR Maintain Vision	-£3,669	0.006	-£3,543	0.021	£3,787	£3,963
13	Proportion 1 stop year 3 Aflibercept	-£3,691	0.013	-£3,531	0.013	£3,949	£3,788
14	Proportion 1 stop year 3 Rbz	-£3,532	0.013	-£3,690	0.013	£3,790	£3,947
15	Proportion 1 stop year 4 Aflibercept	-£3,672	0.013	-£3,550	0.013	£3,930	£3,807

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Probabilistic sensitivity analysis results, derived by sampling from input parameter distributions, indicated that aflibercept is associated with lower costs compared with ranibizumab. The analysis also showed that aflibercept has a probability of 82.4% of achieving higher QOL versus ranibizumab.

In addition, the analysis indicated that aflibercept would be considered cost-effective versus ranibizumab across a range of hypothetical willingness-to-pay thresholds as shown in the cost effectiveness acceptability curve (CEAC).

Table B72: PSA simulations per CE quadrant

Dominant	More effective & more costly	Less effective & less costly	Dominated
82.4%	0%	17.6%	0%

Figure B17: Cost-effectiveness plane

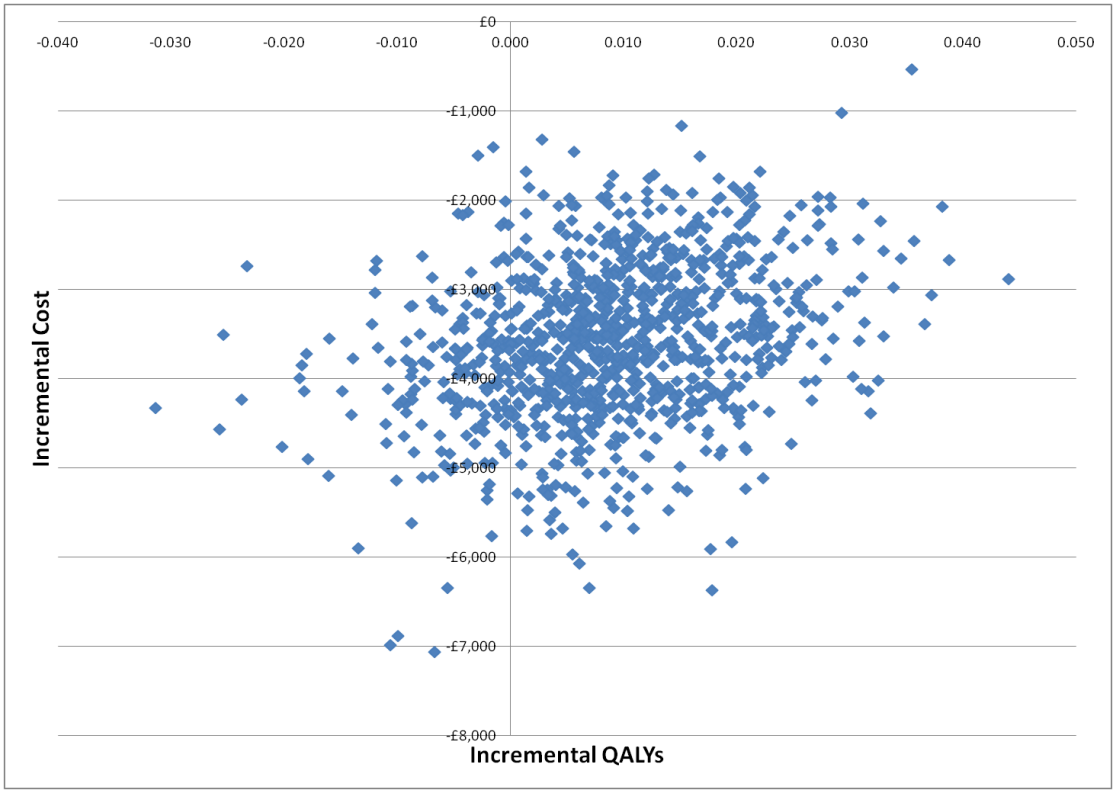
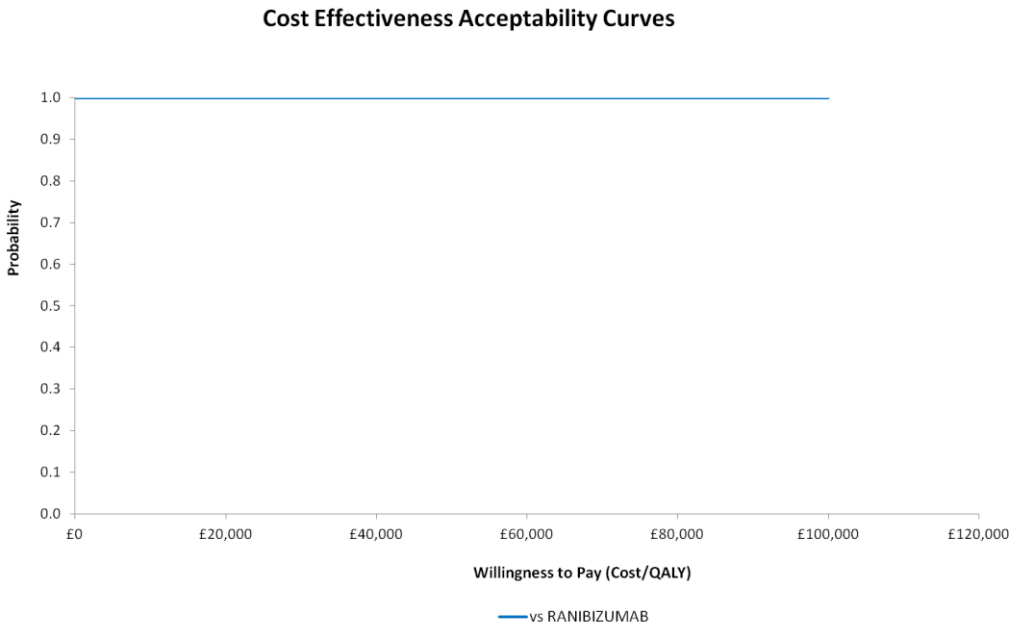


Figure B18: Cost-effectiveness acceptability curve



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

As compared to the base case in the following scenario analysis inclusion of the rates of AEs reported in Boyer et al 2009(119) was tested. Results show, in line with the base case results, that aflibercept is associated with lower costs (- £3,626 per patient) and slightly higher QOL compared to ranibizumab at the end of the time horizon.

Due to the low rates of AEs reported in the clinical trials they were considered not to be relevant for the analysis and therefore excluded from the base case. Results from this scenario analysis show that inclusion of AEs does not have an impact on results.

Table B73: Scenario 1) AEs from Boyer for ranibizumab

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	£25,009	10.57	7.77				
Ranibizumab	£28,636	10.57	7.76	£3,626	-0.001	-0.011	Dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Following previous opinion from the national institute of health and clinical excellence (NICE)(21) the utility values reported by Czoski-Murray et al 2009 (111) and a 0.1 utility decrement for the worse-seeing eye, following the method reported previously(21) were considered in this scenario analysis.

Results show that a different source of utilities has an impact in the QALYs accrued by each of the interventions. Applying the Czoski-Murray et al 2009 utilities decreased the total number of QALYs accrued in both treatment arms by the end of the lifetime horizon. The reason why the differences are generated may be because this alternative source of utilities reports values for a specific level of visual acuity and not for a combination of VAs in both eyes as captured by the utilities generated from the VIEW 2.

When looking at the incremental outcomes results do not change the conclusions from the base case results.

Table B74: Scenario 2) Utilities from Brazier (Czoski-Murray, 2009)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	£25,009	10.57	5.03				
Ranibizumab	£28,615	10.57	4.98	£3,606	-0.001	-0.054	Dominated

Results of the indirect comparison between aflibercept and ranibizumab indicated that there is no evidence of statistically significant differences in the RRs of the treatment effects of both therapies; therefore the following scenario tested the results when the RRs were set to 1 (implying no treatment effect differences between the intervention and the comparator) in order to test the uncertainty about the numerical results from the ITC.

Results showed that aflibercept was associated with lower costs compared to ranibizumab at the end of the time horizon (- £3,679 per patient). The conclusion of this scenario analysis is that aflibercept is a cost-saving therapy for the NHS in the treatment of patients with wet AMD in England and Wales.

Table B75: Scenario 3) Same efficacy in both arms (cost-minimisation analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	£25,009	10.57	7.77				
Ranibizumab	£28,689	10.57	7.77	£3,679	0.000	0.000	More costly

When the number of injections reported in the VIEW 2 trial for aflibercept and CATT trial for ranibizumab are used in the first two years of treatment aflibercept is associated with lower costs compared to ranibizumab at the end of the time horizon (- £1,658 per patient). LYs and QALYs accrued do not change as compared to the base case since the number of injections administered to the patients does not have an impact in the treatment effect

associated to each of the interventions. Results of this scenario analysis show dominance of aflibercept over ranibizumab over a lifetime (25 years) horizon.

Table B76: Scenario 4) Injections in years 1-2 from the trial (Eylea 7.7 and 4.0; Lucentis 6.9 and 5.7)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	£25,679	10.57	7.77				
Ranibizumab	£27,337	10.57	7.76	£1,658	-0.001	-0.010	Dominated

In the following three scenario analyses, the assumptions around the frequency of monitoring and clinical practice around monitoring (one-stop model vs. two-stop model) were tested. In all three scenario analyses results show that aflibercept is associated with lower costs compared to ranibizumab at the end of the time horizon (- £5,460, - £4,778, - £3,611 respectively per patient). LYs and QALYs accrued do not change as compared to the base case since the frequency and clinical practice around monitoring does not have an impact in the treatment effect associated to each of the interventions. Results of all three scenario analyses show dominance of aflibercept over ranibizumab over a lifetime (25 years) horizon.

Table B77: Scenario 5) Monitoring (Eylea 7,6,6,6,6; Lucentis 12,12,12,12,12)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	£24,696	10.57	7.77				
Ranibizumab	£30,156	10.57	7.76	£5,460	-0.001	-0.010	Dominated

Table B78: Scenario 6) Monitoring (Eylea 100% 1 stop model years 1-5; Lucentis 100% 2 stop model years 1-5)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	£24,611	10.57	7.77				
Ranibizumab	£29,389	10.57	7.76	£4,778	-0.001	-0.010	Dominated

Table B79: Scenario 7) Monitoring years 3-5 (Eylea and Lucentis 6,6,6)

Technologies	Total	Total	Total	Incremental	Incremental	Incremental	ICER (£)

	costs (£)	LYG	QALYs	costs (£)	LYG	QALYs	versus baseline (QALYs)
Aflibercept	£24,696	10.57	7.77				
Ranibizumab	£28,307	10.57	7.76	£3,611	-0.001	-0.010	Dominated

Similarly changing the efficacy assumption in years 3-5 to BSC does not change the overall conclusion of dominance from the base case.

Scenario 8 – Assumption of efficacy = to BSC (Wong et al) in both arms for years 3-5

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	£24,879.51	10.41	7.69				
Ranibizumab	£28,530.40	10.41	7.68	£3,651	-0.001	-0.009	Dominated

7.7.10 What were the main findings of each of the sensitivity analyses?

- The deterministic sensitivity analysis has shown that results were most sensitive to the drug costs, number of injections and frequency of monitoring, proportion of patients in one-stop and two-stop models, followed by the relative risk for gaining or maintaining vision

- Scenario analyses were performed to test how assumptions impacted the final results. Inputs tested in the scenarios were using AEs, different utilities, same efficacy in both arms and different assumptions on frequency of injections and monitoring. Results have shown that aflibercept was dominant in all scenarios after testing extreme values and cost-saving when the same efficacy was applied to both arms

- Results from the probabilistic sensitivity analysis have shown that aflibercept is 89.8% likely to dominate ranibizumab and 10.2% likely to be less effective and less costly.

7.7.11 What are the key drivers of the cost-effectiveness results?

The cost-effectiveness results are mainly driven by the following

- The cost of ranibizumab and aflibercept injections
  - The cost of the drugs is a key driver of the base case results, as they are the larger component of the overall cost per patients over the lifetime horizon.
- The RR of gaining vision (aflibercept vs ranibizumab)
  - The RR of gaining vision is a key driver in all analyses comparing aflibercept versus ranibizumab as this determines the differences in the treatment effects between the two therapies.
- Frequency of monitoring
  - Results are driven by the number of monitoring visits for aflibercept and ranibizumab in years one to five and proportion of patients in a one-stop and two-stop model. The uncertainty has been tested in scenario/ sensitivity analyses showing that aflibercept is dominant in all cases.
- The number of injections
  - Number of injections is a key driver of the model since the annual number of injections has a direct impact on the drug cost component which has shown to be another key driver of the base case results.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

A check of internal validity was performed, to ensure that outputs are logical and accurate within the framework set by the model. This was ensured by quality control of the model by the model developers, and a model audit performed by an experienced health economist outside the team of developers.

The model was additionally validated against the underlying trial data.

As previously discussed (Section 7.3.1) the VA distribution of patients in the VIEW 2 clinical trial were used to calibrate estimate the distribution of the model cohort at years one and two.

7.9 Subgroup analysis

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

Subgroup analyses were not part of the current evaluation since the target population includes all those patients with wet AMD requiring anti-VEGF treatment. The scope proposed subgroups according to lesion type. Data to compare aflibercept and ranibizumab in terms of their benefits and harms in these subgroups was not available given the limitation of the ITC for the population as a whole as described in section 6.7. In addition, as described in section 2, ranibizumab has superseded verteporfin and PDT as the standard of care for wet AMD and this has meant that the subgroups that define PDT treatment are no longer as relevant to the management of wet AMD.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable.

7.9.3 Please describe how the statistical analysis was undertaken.

Not applicable

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

Not applicable

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

See 7.9.2.

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

In the economic literature review one cost-effectiveness study including aflibercept was identified(91). The study reported a cost-effectiveness model evaluating the cost per line-year of life expectancy in the United States and was conducted using assumptions before efficacy data for aflibercept were known. This study was not considered further.

No other economic evaluation of aflibercept was identified that is specifically relevant to the decision problem in this appraisal.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

The scope of the appraisal considers adults with wet AMD.

The economic evaluation considered adolts with wet AMD with VA of 36 letters or better at time of treatment, using the characteristics of the VIEW population to define VA at baseline. Patients with VA of less than 36 letters are legally blind, and available utility data does not allow us to reliably estimate the implications of further deterioration in vision in these patients. We believe that these patients would be unlikely to receive VEGF therapy for wet AMD in the UK at present,

The NMA included studies of wet AMD (neovascular or exudative AMD), Retinal Angiomatous Proliferation (RAP) or submacular haemorrhage

secondary to age - related macular degeneration. The studies contributing to the ITC however all considered similar populations of patients with wet AMD.

The VIEW study participants were elderly (mean age 74-78 years according to group), predominantly white, and a majority were female. A recent publication estimating overall prevalence of AMD in the UK suggests no obvious inconsistencies between the modelled population and the prevalent AMD(129).

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The evaluation presented builds on existing evaluations of other interventions in wet AMD. It is consistent with other models in that a Markov process is used, states are defined by VA, extrapolation beyond trial data is used to estimate long term costs and outcomes. In addition to previous work the current model is able to explicitly consider the proportion of patients affected by the disease in one or in both eyes and to model costs and consequences of bilateral treatment.

The main weakness of the evaluation is that no evidence directly compares aflibercept with ranibizumab as currently licensed. Efficacy data were derived from the VIEW trials and an ITC against ranibizumab PRN from a range of different studies.

No RCT data were identified describing treatment with aflibercept and ranibizumab after 2 years. Clinical opinion indicated that it is likely that therapy will continue to be needed after year 2, but the frequency of treatment, benefits and costs of continuing therapy are unclear. In the absence of evidence, simple assumptions were made that did not differentiate between therapies.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Extensive sensitivity and scenario analyses were performed testing parameters and scenario in the model which could have had an impact on the final results. Further evidence generation could improve the robustness of the analyses and the accuracy of the input values. In particular, long-term follow up of treatment frequency and effects after year 2 would be beneficial.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Two populations were used in this Budget Impact analysis:

- Number of eligible patients for wet AMD treatment in the UK
- Number of eligible eyes for wet AMD treatment in the UK.

The rationale behind this lies in the fact that all patients were assumed to be affected by wet AMD in one eye and a proportion of them would develop the disease in the fellow eye, as considered in the economic model. The rate of second eye involvement was calculated using a 4-year probability from a meta-analysis by Wong et al 2008 (26.8%(50)) and converted into an annual rate (7.5%) using the method published by Miller et al in 1994(100). A percentage equal to 7.5% was added to the number of eligible patients in wet AMD each year in England and Wales, providing the number of eligible eyes.

In order to estimate a projected eligible wet AMD population (number of patients and number of eyes) from year 2013 to 2017, the following parameters have been considered:

- Total projected population in England and Wales from 2013 to 2017: Mid-2011 population in England and Wales was used from the Office of National Statistics(130) based on the results of the 2011 Census. To this, an average annual population growth rate for UK was applied, calculated using projections data from the ONS(130)

- Prevalence and incidence of wet AMD in UK as a whole, estimated on 50+ population (males and females) from Owen et al 2012(129), based on a meta-analysis of 30 studies
- Proportion of eligible patients to wet AMD treatment in the UK each year. The estimated proportion of eyes meeting NICE criteria for treatment with ranibizumab was used for this purpose, from the costing template accompanying NICE TA155(21).

The projected number of eligible patients and eyes used in the budget impact analysis calculations are reported in Table C80.

Table C80: Population used in the Budget Impact Analysis

	2013	2014	2015	2016	2017
Population in England and Wales	20,665	21,285	21,923	22,581	23,258
Prevalent population with wet AMD in UK	248	255	263	271	279
Incident population with wet AMD in UK	39	40	42	43	44
Eligible to treatment patients	230	237	244	251	259
Eligible to treatment eyes	247	254	262	270	278

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

To help understand the economic impact of aflibercept uptake and use, cost savings were estimated under two scenarios; a world with aflibercept and a world without aflibercept. The uptake of aflibercept was assumed to be increasing over time and displacing the other medicines currently in the UK market of wet AMD, represented by ranibizumab only (see section 8.3).

8.3 What assumption(s) were made about market share (when relevant)?

The wet AMD market in the UK is currently represented by ranibizumab for the 99.5% of the share and verteporfin for the remaining 0.5%(131). The assumption was made that the world without aflibercept was considered to be described by ranibizumab only (100% of the market for years 2013-2017).

The uptake of aflibercept displaces a portion of ranibizumab share every year. The market shares projections in the world with aflibercept are shown below.

Table C81: Projected market shares: world with aflibercept

	2013	2014	2015	2016	2017
Aflibercept uptake	[redacted]				
Ranibizumab					

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Treatment of wet AMD tends to be expensive as patients require frequent injections and monitoring visits for years(46). Treatment with ranibizumab in the UK is administered on a PRN (per needed) schedule, meaning that patients require monitoring to assess whether they need a treatment injection (14). Treatment with aflibercept for the first 12 months does not require patients to be monitored between injections (SmPC). Furthermore the number of injections required by a patient treated with aflibercept in year 1 (SmPC) and 2(123) is lower than the number of injections required with ranibizumab, leading to a saving on administration costs to the NHS, given that injections are performed by an experienced ophthalmologist (SmPC). More details in section 8.3.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Costs considered in the budget impact analysis were drug costs and costs associated with monitoring assessments. Drug and administration costs are reported below

Table C82: Drug and administration cost

	Cost (£)	Reference in submission
Aflibercept - drug only	816.00	Section 7.5
Ranibizumab – drug only	742.17	Section 7.5
Administration cost	257.45	Section 7.5

As injections have to be performed by a "qualified physician experienced in administering IVT injections"(SmPC), the cost of a consultant ophthalmologist was used from the NHS Reference costs(120) as a weighted average of an outpatient and a day-case procedure based on HES data, as in the economic model.

The number of injections is reported in Table C83; a conservative assumption was made for years 3 to 5 since no data are available where frequency of injections is considered to be the equivalent for aflibercept and ranibizumab (details and sources in section 7.5)

Table C83 Frequency of injections (see Section 7 – economic model)

	2013	2014	2015	2016	2017
Aflibercept	7	4	4	4	4
Ranibizumab	8	6	4	4	4

Monitoring assessment procedures considered in this budget impact analysis were: a visual acuity visit performed by an ophthalmologist and an OCT. Unit costs of monitoring procedures are reported in the table below (more details in section 7.5).

Table C84: Unit costs associated with monitoring visits

	Cost (£)	Reference in the submission
Visual acuity visit	79.74	Section 7.5
OCT	117.26	Section 7.5

The frequency of monitoring is reported in Table C85; as for the frequency of injections the same assumption was made for monitoring where numbers for years 3-5 were assumed to be the same for the two drugs (for more detail refer to section 7.5).

Table C85: Frequency of monitoring

	Year 1	Year 2	Year 3	Year 4	Year 5
Aflibercept	7	6	7	7	7
Ranibizumab	12	12	7	7	7

8.6 Were there any estimates of resource savings? If so, what were they?

Displacement of ranibizumab by aflibercept will be associated in savings due to lower frequency of treatment and monitoring assessments due to treatment injections.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The base case analysis yielded a very small budget impact of aflibercept over the time period 2013-2017 (an overall budget increase of 0.03%). As expected, some savings occur in the first two years given the lower number of injections and monitoring. These numbers were assumed to be the same for aflibercept and ranibizumab in years 3 to 5. The base case results are presented in Table C86.

Table C86: Budget impact of aflibercept (base case results)

Year	Without aflibercept	With aflibercept	Budget impact	%
2013	£2,518,726	£2,518,489	-£237	-0.01%
2014	£2,085,595	£1,995,004	-£90,590	-4.34%
2015	£1,384,083	£1,407,380	£23,296	1.68%
2016	£1,425,606	£1,457,453	£31,847	2.23%
2017	£1,468,374	£1,506,309	£37,935	2.58%
Total	£8,882,383	£8,884,635	£2,251	0.03%

An analysis was performed using the discounted price from the Patient's Access Scheme for aflibercept (see PAS template for details).

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No, no other opportunities have been included in the analysis.

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