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Executive summary

Aflibercept (Eylea®) is a potent specific inhibitor of vascular endothelial growth factor (VEGF) and a fully human fusion protein, consisting of soluble VEGF receptors 1 and 2. Aflibercept is now licensed in the UK for the treatment of adults with visual impairment due to diabetic macular oedema (DMO). The recommended dose is 2 mg equivalent to 50 microlitres.

Treatment is initiated with one intrvitreal injection per month for 5 consecutive doses, followed by one injection every 2 months. There is no requirement for monitoring between injections. After the first 12 months of treatment, the treatment interval may be extended based on visual and anatomic outcomes. The schedule for monitoring should be determined by the treating physician and treatment discontinued if there is no evidence of benefit.

Until recently, laser photocoagulation was the mainstay of DMO treatment. However despite reducing the risk of vision loss in patients with DMO, laser treatment has limited effect on improving vision. Laser treatment also carries the risk of central vision loss - either accidental or from macular scarring - over time with repeated treatment. The limitations of laser treatment have provided the impetus for development of pharmacological therapies for DMO.

The regulatory approval of ranibizumab, another anti-VEGF, for adults with visual impairment due to DMO has changed the standard of care as ranibizumab, unlike laser, is able to improve vision significantly. Treatment is initiated with monthly injections until maximum visual acuity is achieved and/or there are no signs of disease activity. Thereafter, treatment intervals should be determined by the physician based on disease activity, as assessed by visual acuity and/or anatomical parameters. A very recent amendment to the ranibizumab licence (September 2014) now also allows extension of treatment intervals stepwise, for up to one month at a time, until signs of disease activity or visual impairment recur. Monitoring is at the discretion of the physician depending on disease activity; unlike aflibercept, the revised ranibizumab Summary of Product Characteristics (SmPC) does not specify that monitoring between injections is not required in the first year. However,

ranibizumab is only recommended by NICE for restricted use within NHS for patients with a baseline central retinal thickness (CRT) of 400µm or more.

Intravitreal corticosteroids are also licensed options for DMO but their UK marketing authorisations restrict usage to patients insufficiently responsive to other therapies and/or pseudophakic patients (where the natural lens of the eye has been replaced for treatment of cataract). Dexamethasone intravitreal implant has not yet been appraised by NICE and is licensed only in adult patients with visual impairment due to DMO who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy. Dexamethasone is not part of routine NHS practice for DMO and its future place in the treatment pathway is not yet established. Fluocinolone acetonide intravitreal implant is recommended by NICE only in patients with chronic DMO that is insufficiently responsive to available therapies and if the implant is to be used in an eye with an intraocular (pseudophakic) lens. Given the criteria of chronicity, prior cataract surgery, and inadequate response to prior therapies, fluocinolone is positioned further down the treatment pathway, and in a smaller subgroup of patients, than we anticipate the place of aflibercept for DMO.

In two, prospective, randomised, double-masked, controlled, multicentre, trials (VISTA and VIVID), aflibercept, either once every 4 weeks (2Q4) or once every 8 weeks after 5 initial monthly doses (2Q8) demonstrated significant improvements over laser photocoagulation in the primary endpoint - mean change in best corrected visual acuity (BCVA) at week 52 (2Q4 = 12.5, 2Q8 = 10.7, and laser = 0.2 letters gain from baseline). Additional analysis after two years in the VISTA study, shows that in patients receiving aflibercept 2Q4 and 2Q8 regimens, the positive effect is maintained over the longer-term (mean change from baseline in BCVA: 2Q4 =11.5 letters; 2Q8=11.1 letters). Patients in the laser photocoagulation treatment group had a mean change from baseline in BCVA of 0.9 letters.

In a systematically sourced mixed treatment comparison, compared with ranibizumab, aflibercept bi-monthly following five initial monthly injections significantly improved the primary outcome of mean change in BCVA from baseline to 52 weeks, as well as the proportion of patients losing 10 letters or more. Other secondary outcomes analysed (including proportion of patients who gain at least 10 letters, lose at least 10 letters (random effects model), and who lose or gain 15

letters or more) were in favour of aflibercept but were not statistically significant compared with ranibizumab. There was no evidence of significant differences in adverse events between ranibizumab and aflibercept. Any potential indirect comparison with intravitreal steroids was considerably limited as the pivotal studies for steroids (the MEAD and FAME studies) used sham rather than laser as the control arm, as well as there being differences in study outcomes, duration, and other characteristics compared with the VISTA and VIVID studies. Moreover, there was insufficient information to be able to do relevant indirect subgroup analyses. An indirect comparison of VISTA and VIVID with the PLACID study, which had a common laser arm, showed aflibercept to be significantly more effective than dexamethasone plus laser in diffuse patients for the only available outcome which was proportion of patients gaining 10 letters.

With aflibercept, the healthcare system will have the opportunity to benefit from fewer and more predicable appointments than current practice. The fixed regimen in the first year does not require additional monitoring between injections. The patient no longer has the inconvenience of monthly monitoring visits associated with ranibizumab. It is not anticipated that the recent change to the marketing authorisation of ranibizumab to allow the possibility of less than monthly monitoring will have a sudden impact on established NHS practice with ranibizumab. A fixed dosing regimen may also offer opportunities, alongside the ease on capacity of reduced monitoring, for improved service planning. Separate monitoring visits are not required to establish the need for an injection visit (two-stop system). The fixed regimen requires approximately the same number of injections as ranibizumab when compared with the number of ranibizumab injections reported across the studies in the network meta-analysis. Moreover, a fixed regimen ensures that patients in practice have the potential to gain outcomes similar to clinical trials as the regimen is not influenced by practicalities or capacity.

A *de novo* health state transition economic model considering the visual acuity of both eyes demonstrated that aflibercept was a dominant treatment (more effective and less costly) for DMO compared with ranibizumab when including a confidential patient access scheme for aflibercept and incremental discounts for ranibizumab up to 60% and remained cost effective up to 80%. A comparison versus laser also

found aflibercept to be more effective and a less costly use of NHS resources for DMO when including the patient access scheme for aflibercept.

Table 1 Base-case cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]	11.398	7.690				
Laser		11.339	7.300	-2,438	0.059	0.389	Dominated
Ranibizumab		11.384	7.598	-8,911	0.014	0.092	Dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

An exploratory analysis versus intravitreal steroids, limited by the absence of robust comparative efficacy and safety data, and differences and uncertainties with regard to the relative positions in the DMO treatment pathway, also demonstrated aflibercept to be a cost effective use of NHS resources.

As requested in the final scope for this appraisal, subgroup analyses were conducted from the VIVID/VISTA studies for baseline visual acuity, baseline central retinal thickness, prior anti-VEGF therapy, prior laser therapy, and prior cataract surgery. These analyses were *post hoc* except for some pre-specified visual acuity categories. As per the total population, aflibercept was clinically effective across all subgroups compared with laser. There was insufficient information in the literature to be able to conduct robust indirect comparisons with other comparators in the relevant subgroups. This considerably limited any comparisons of clinical and cost effectiveness in subgroups. Exploratory analyses were conducted which demonstrated that aflibercept remained a clinically and cost effective option compared with laser and ranibizumab in the subgroups of patients with both thick and thin retinas.

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.

Aflibercept solution for injection (Eylea®) is a vascular endothelial growth factor (VEGF) inhibitor. Aflibercept 40mg/ml solution for injection in a vial is for intravitreal use only. 1 vial contains enough product for a single 2mg dose injection into the eye.

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

Aflibercept solution for injection treats adults with visual impairment due to diabetic macula oedema (DMO) 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 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) has given positive opinion to aflibercept solution for injection for the treatment of DMO on 26th June 2014. Marketing authorisation was gained in the UK via the centralised European regulatory procedure on 6th August 2014.

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).

An EPAR and Summary of Product Characteristics (SmPC) are attached. It is not expected that there will be special conditions, exceptional circumstances or conditions attached to the marketing authorisation.

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 the treatment of adults with visual impairment due to DMO. Aflibercept is already licensed in the UK for the treatment of adults with neovascular wet age-related macular degeneration (wet AMD) and macular oedema secondary to central retinal vein occlusion (CRVO).

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 two pivotal phase III, randomised controlled clinical trials for aflibercept for the treatment of visual impairment due to DMO are the VISTA-DME (NCT01363440) and VIVID-DME (NCT01331681) studies. Both these studies actively compared aflibercept with laser treatment. 1 year data, the basis of the regulatory submission, have been published (Korobelnik, et al 2014). Additional 2 year data was presented at EURETINA in September 2014.

VIVID-East and VIVID-Japan are also ongoing studies in Asia. VIVID-East (NCT01783886), also versus laser, has an expected completion date of July 2015. VIVID-Japan is a single arm study and completed in September 2013 (primary outcome data).

There is also a phase II study of aflibercept solution for injection for DMO, the Da VINCI study (NCT00789477) which completed in September 2010. However, this study did not include a dosing regimen that is in line with the granted EMA marketing authorisation and does not reflect expected practice in the NHS. The approved

posology includes 5 initial consecutive monthly doses of aflibercept (in line with VIVID/VISTA) in a fixed regimen whereas Da Vinci included only 3 initial doses. As there are two larger pivotal phase III studies that included the regimen relevant to the posology stated in the marketing authorisation and expected use in the NHS, this study has not been included as we do not consider that it will add value to the included evidence.

Diabetic Retinopathy Clinical Research Network (www.DRCR.net, Protocol T) is a US National Institutes of Health (government-funded) study including aflibercept, ranibizumab and bevacizumab. The regimen for aflibercept does not reflect that in the marketing authorisation ('as-needed' compared with a fixed regimen of 5 monthly doses followed by bi-monthly, then extended, intervals). The dose of ranibizumab relates only to the dose available in the USA. Bevacizumab is unlicensed for intravitreal use so there is no licensed treatment regimen for DMO.

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

Not applicable

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

The marketing authorisation process for the UK was centralised through the EMA. Eylea received marketing approval from the Food and Drug Administration (FDA) for DMO in the USA in July 2014 (http://www.fda.gov/Drugs/default.htm). There is now also worldwide approval for wet AMD and CRVO.

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 the treatment of DMO was made on 7th July 2014 with expected publication date 10th November 2014.

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 1. Unit costs of technology being appraised

Pharmaceutical formulation	Eylea 40 mg/ml solution for injection in a vial(5).
Method of administration	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 per vial. A confidential simple patient access scheme is available.
Doses	Aflibercept solution for injection (Eylea) is for intravitreal injection only
Dosing frequency	The recommended dose for aflibercept is 2 mg aflibercept, equivalent to 50 microlitres. The approved posology is that is reflected in the EU SmPC is noted below: The recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitres. Eylea treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections. After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and anatomic outcomes. The schedule for monitoring should be determined by the treating physician. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Eylea should be discontinued.
Average length of a course of treatment	
Average cost of a course of treatment	
Anticipated average interval between courses of treatments	
Anticipated number of repeat courses of treatments	
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?

It is not expected that there will be any additional tests or investigations needed for selection for aflibercept solution for injection compared with current NHS treatment. Ranibizumab, another anti-VEGF, is already recommended by NICE guidance (TA274) for the treatment DMO for patients with a baseline central retinal thickness (CRT) of 400µm or more(1). The requirement for baseline visual acuity, fundus photography, fluorescein angiography and/or optical coherence tomography (OCT) is likely to be similar between anti-VEGF intravitreal injections. Moreover, it is anticipated that monitoring requirements will be less for aflibercept compared with current use of ranibizumab. The fixed treatment regimen with aflibercept in the first year does not require additional monitoring between injections. Monthly monitoring was mandatory with ranibizumab(2) up until a change to the wording of the SmPC in September 2014(3). Although more flexibility was given to physicians with regard to monitoring, it is not anticipated that established practice will change immediately and the ranibizumab SmPC does not state explicitly that monitoring between injections is not required in the first year. It is therefore not yet known whether or to what extent clinicians in England and Wales will change their monitoring of patients receiving ranibizumab for DMO based on the new wording of the SmPC.

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

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

It is not expected that the need for monitoring with aflibercept solution for injection will be over and above that currently required for the treatment of DMO in the NHS. As previously discussed in Section 1.12, aflibercept is expected to have a less

burdensome monitoring requirement compared with ranibizumab as the SmPC states clearly that no monitoring is required between injections in the first year. Monitoring for aflibercept between extended treatment intervals will determined by the treating physician. Therefore, fewer monitoring visits would be anticipated overall with aflibercept compared with the monthly monitoring that has been the basis of the dosing regimen established in NHS practice. Monitoring with laser treatment is determined by clinicians. Guidelines by the Royal College of Ophthalmologists, June 2013(4), maintain a need for regular monitoring with all treatments. Also, regular monitoring, maintenance and replacement of laser equipment needs to be considered.

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 DMO with ranibizumab, 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.

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.

Diabetes mellitus is a common condition and a complication of diabetes is retinopathy. With retinopathy, tiny blood vessels in the retina are damaged, leading to increased vascular permeability and blood and fluid leakage. When this happens in the area of the macula, it is known as macula oedema. Eventually the leaking fluid can cause swelling and scar tissue on the macula and permanent loss of central vision. This is the most common cause of blindness in diabetes.

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.

A recent publication highlights the issues with epidemiological estimates for diabetic retinopathy(5). Minassian et al. estimated 64,725 individuals had clinically significant DMO in England based on 2010 diabetes data(6). An Eye Health Data Summary report in February 2014 by the UK Vision Strategy estimated 748,000 people living with background diabetic retinopathy (early signs) and 85,000 as more advanced non-proliferative and proliferative retinopathy combined in 2010(7). The Diabetic Eye Screening Programme has impacted on the availability of epidemiological data although not all diabetes patients are screened (uptake was 81% in 2011-12)(8).

As considered in previous NICE appraisals (TA294 and TA305)(9;10), aflibercept solution for injection in a vial is also indicated for adults for the treatment of neovascular (wet) AMD. Some estimates suggest that there are an estimated 39 new patients per 100,000 of the population eligible for treatment each year. This equates to 21,840 in the total population of England and Wales. Other estimates suggest 26,000, and the number is growing. For CRVO, there are an estimated 12 new patients with MO secondary to CRVO eligible for treatment per 100,000 of the

population in England and Wales each year. This equates to 6,720 eligible for treatment overall in a population of 56 million (Office of National Statistics - Mid-1971 to Mid-2011 Population Estimates: England, Wales and regions; estimated resident population, April 2013). However, again, estimates of patient numbers vary.

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.

The link between DMO and mortality will be discussed further in the context of the economic modelling. There is evidence of a link between diabetes, visual impairment, and mortality although the exact nature of this relationship is uncertain.

Thiagarajan et al 2005(11) reported the rate ratio for all-cause mortality for elderly 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(12) in a somewhat younger population. The paper estimated the effects of vision loss on mortality using a structural equation modelling approach.

Please see economic section 7 for further discussion on mortality for DMO.

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.

TA301 Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy (rapid review of technology appraisal guidance 271). November 2013:

- 1.1 Fluocinolone acetonide intravitreal implant is recommended as an option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies only if:
    - the implant is to be used in an eye with an intraocular (pseudophakic) lens and

    - the manufacturer provides fluocinolone acetonide intravitreal implant with the discount agreed in the patient access scheme

TA274 Ranibizumab for treating diabetic macular oedema (rapid review of technology appraisal guidance 237). April 2013:

- 1.1 Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if:
    - the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
    - the manufacturer provides ranibizumab with the discount agreed in the patient access scheme revised in the context of this appraisal.
- 1.2 People currently receiving ranibizumab for treating visual impairment due to diabetic macular oedema whose disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop

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.

Ranibizumab, another anti-VEGF, is licensed in the UK for adults for the treatment of visual impairment due to DMO. Ranibizumab is recommended by NICE in England and Wales according to the criteria defined in NICE guidance TA274 which specifies thicker retinas at baseline. Laser treatment is also available to treat suitable DMO patients in England and Wales. Aflibercept solution for injection would be an alternative and additional option to standard of care for the treatment of visual impairment due to DMO.

For those people with ‘chronic’ DMO whose disease is insufficiently responsive to available therapies are eligible for fluocinolone acetonide intravitreal implant, only if the implant is to be used in an eye with an intraocular (pseudophakic) lens. Given the label specification that fluocinolone is indicated for those who are both chronic and inadequately responsive to other available therapies, it is assumed that

aflibercept would qualify as being another available therapy and that aflibercept would precede fluocinolone in the treatment pathway. However, there is currently insufficient experience and evidence to evaluate the impact of the introduction of aflibercept on the subsequent part of the treatment pathway and whether it may be steroid sparing, particularly as only a smaller subgroup of pseudophakic and chronic patients qualify. It is expected that fluocinolone will remain an option for chronic, pseudophakic DMO patients unresponsive to other available therapies following the introduction of aflibercept.

Dexamethasone intravitreal implant only recently (26th August 2014) gained a marketing authorisation for DMO and is, therefore, not currently part of routine practice for the treatment of DMO in the NHS. *Ozurdex is indicated for the treatment of adult patients with visual impairment due to diabetic macular oedema (DME) who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy.* Dexamethasone has not yet been assessed by NICE for DMO and will not have been assessed prior to the submission for aflibercept. The position of dexamethasone in the DMO treatment pathway beyond the licensed indication is, therefore, not yet known.

Bevacizumab is an oncology treatment that has previously been used in an unlicensed manner for the treatment of back-of-the-eye conditions when no licensed treatment has been available. The use of bevacizumab for intravitreal use is contraindicated in its license.

Laser was considered standard of care for decision making (i.e. for which the most plausible incremental cost effectiveness ratio (ICER) was used) in the NICE appraisal of ranibizumab for DMO (TA274). In the NICE appraisal of fluocinolone (TA301), the clinical and cost effectiveness estimate versus best supportive care was the foundation for decision making.

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

The main issue for those involved in the treatment of DMO in the UK is the burden of treatment with current standard of care and its, until recently mandatory, monthly

monitoring in terms of resources required and capacity available in ophthalmology as a whole. With an ageing population, the burden on the NHS is increasing with new patients presenting for back-of the-eye conditions such as wet AMD and DMO, and existing patients continuing on treatment. This subsequently impacts on resources available to treat DMO. Ranibizumab according to its label requires monthly monitoring of visual acuity, and usually, anatomical outcomes using optical coherence tomography (OCT). There is still an unmet need for effective treatments without the burden of monthly monitoring visits.

The efficacy of laser has been shown to be inferior to that of anti-VEGF in randomised trials. However, in addition, the efficacy and safety of laser is variable depending on factors such as the type of machine used, the training and experience of the staff, and the nature of the DMO. More modern laser machines are available (PASCAL, NAVILAS) but require capital investment, maintenance, and additional training. Even so, expert opinion indicates that there remain practical issues such as positioning the patient appropriately and the additional time that is required for this.

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

We consider ranibizumab and laser to be the key comparators for this appraisal as these are the treatments which would potentially be displaced by the introduction of aflibercept for visual impairment due to DMO. Ranibizumab is recommended by NICE for the treatment of adults with visual impairment due to DMO if the eye has a central retinal thickness of 400 micrometres or more at the start of treatment, with guidance published in April 2013. Section 4.3 states that *"The Committee heard from the clinical specialists that the current standard treatment for diabetic macular oedema is focal and/or grid laser photocoagulation."*

For completeness, we have also attempted to make a comparison with steroids as they are listed in the scope for this appraisal. However, we do not believe that they can be truly considered direct comparators for aflibercept or that a credible comparison can be made with aflibercept in DMO for several reasons.

As discussed in Section 2.5, we anticipate that aflibercept and fluocinolone acetonide intravitreal implant occupy different positions in the treatment pathway for

DMO. Fluocinolone is recommended by NICE as an option for treating 'chronic' DMO that is insufficiently responsive to available therapies only if the implant is to be used in an eye with an intraocular (pseudophakic) lens. This suggests, as previously discussed in TA301, that eligible patients for fluocinolone have failed prior laser and anti-VEGF therapy. However, there is insufficient experience and evidence at this time to evaluate the true impact of the introduction of aflibercept on subsequent steroidal use.

Moreover, the credibility and validity of an indirect comparison comparing aflibercept with fluocinolone is restricted by differences between studies, including different baseline characteristics/study population, follow-up times and, most importantly, the lack of a common comparator. The FAME study uses sham as a comparator whereas VIVID, VISTA and RESTORE use laser.

Any indirect comparison would also be complicated by the need to compare complex subgroups as defined by both NICE guidance (TA301) and the marketing authorisation for fluocinolone (a subgroup of chronic, non-responsive, prior cataract patients). There is limited data available on subgroups (as discussed in TA301) and the robustness of any attempted indirect comparison will be limited by the insufficiencies in the evidence.

Dexamethasone has only recently, and more recently than aflibercept, received UK marketing authorisation for DMO and has not been assessed by NICE for DMO. The SmPC indicates adult patients with visual impairment due to DMO who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy. Dexamethasone will not have been assessed by NICE prior to the submission for aflibercept for DMO. Therefore, the future position of dexamethasone in the treatment pathway beyond the licensed indication is not yet known. We also anticipate similar feasibility issues with the available evidence as for fluocinolone.

The final scope for this appraisal also lists bevacizumab as a comparator for some patients. Bevacizumab is an unlicensed treatment that has not been appraised by NICE. Although listed on the scopes in previous appraisals for DMO, a cost-effectiveness comparison with bevacizumab was not used in final decision-making to

establish whether ranibizumab or fluocinolone were considered a cost-effective use of resources in the NHS (TA274 and TA301).

Previously, there were no licensed pharmacological treatments in the UK for the treatment of DMO. Therefore, the options available to clinicians in the NHS were limited to unlicensed treatments, such as bevacizumab, or best supportive care. Now, with licensed, NICE-recommended treatments available, this situation has since changed. The Decision Support Unit (DSU) report for NICE in August 2012 stated that following NICE guidance in favour of the use of ranibizumab in patients with AMD, use of bevacizumab in this patient group rapidly declined(13). We would expect a similar trend with the introduction of two licensed options for DMO. Therefore, we do not consider bevacizumab routine or best practice in the NHS for DMO.

Given their licensed status, previous considerations in NICE appraisals, and preferential efficacy and safety profile compared with the previous options available, ranibizumab and laser may now be considered the most relevant comparators for aflibercept but, for completeness, we have considered steroids as listed in the scope for this appraisal. We do not consider bevacizumab remains a relevant comparator as it is an unlicensed product where several licensed options are now available.

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

The VIEW studies for wet AMD and the subsequent EMA evaluation indicate that aflibercept has a similar safety profile to ranibizumab. Both interventions treat DMO through VEGF inhibition and 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 ranibizumab.

Steroids are generally associated with higher rates of cataract and intraocular pressure compared with anti-VEGF injections. As a result, medicines to treat

intraocular pressure and cataracts will be required to a lesser extent with anti-VEGF than with steroidal treatments. This difference in safety profile has led to the restrictions in EMA approval, opinion and NICE guidance for steroids. This topic is discussed in more depth in the context of economic modelling in Section 7.

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 with aflibercept takes place in specialist ophthalmologist clinics. 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.

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. Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (inflammation due to infection (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.

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 visual acuity and anatomical outcomes using OCT. However, a reduction in monitoring requirements will potentially enable a more efficient use of the infrastructure that is currently in place.

3 Equality

3.1 Identification of equality issues

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

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

There are no equality issues identified.

3.1.1 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 which current treatments do not. There have been indications in the literature that this leads to an extended duration(14;15).

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.

See response above.

5 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with visual impairment due to DMO	Adults with visual impairment due to DMO	Not applicable.
Intervention	Aflibercept solution for injection	Aflibercept solution for injection	Not applicable
Comparator(s)	Laser photocoagulation alone The following technologies alone or in combination with laser photocoagulation: Ranibizumab Corticosteroids (including fluocinolone acetonide intravitreal implant and dexamethasone) Bevacizumab (for people in whom ranibizumab and fluocinolone acetonide intravitreal implants are unsuitable)	Laser photocoagulation alone The following technologies alone or in combination with laser photocoagulation: Ranibizumab Corticosteroids (including fluocinolone acetonide intravitreal implant and dexamethasone)	As described further in Section 4, for completeness, we have provided an exploratory comparison with intravitreal corticosteroids. However, there is limited evidence available for any indirect comparison. We also do not believe that fluocinolone can be considered a direct comparator for aflibercept given it is positioned for both chronic and pseudophakic patients insufficiently responsive to other available therapies. Dexamethasone has not yet been assessed by NICE and also has restrictions in its license for DMO. Bevacizumab is an unlicensed treatment where several licensed treatments are now available. Bevacizumab was listed in the scope but was not used as a comparator in the cost-effectiveness analysis referred to in the decision making for either ranibizumab (TA274) or fluocinolone in DMO (TA301).
Outcomes	The outcome measures to be considered include: Best corrected visual acuity (affected eye) Best corrected visual acuity (both eyes) Central foveal subfield thickness Contrast sensitivity Mortality Need for cataract surgery Adverse effects of treatment, including cataract formation and glaucoma Health-related quality of life, including the	The outcome measures to be considered include: Best corrected visual acuity (affected eye) Best corrected visual acuity (both eyes) Central retinal thickness Mortality Need for cataract surgery Adverse effects of treatment Health-related quality of life, including the effects of changes in visual acuity.	The outcomes listed in the final scope were amended following the pre-invitation (post workshop) scope, without further consultation. It appears that this was to be consistent with the final scope for the appraisal of dexamethasone for DMO. Therefore, some outcomes, such as the emphasis on cataracts, relate more closely to an appraisal of corticosteroids. Incidence of glaucoma was very low in VIVID/VISTA and lower in the two aflibercept arms compared with laser (see section 6.9). VIVID and VISTA included change in central retinal thickness as a secondary outcome. Contrast sensitivity was not measured.

	effects of changes in visual acuity.		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	Cost effectiveness of treatments will be expressed in terms of incremental cost per quality-adjusted life year. A lifetime horizon for estimating clinical and cost effectiveness is sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. Patient access schemes for aflibercept, ranibizumab and fluocinolone acetonide intravitreal implant will be taken into account.	
Subgroups to be considered	If evidence allows, consideration will be given to subgroups according to: • baseline visual acuity • baseline central retinal thickness • treatment history (including people who have received no prior treatment, and those who have received and/or whose disease is refractory to laser photocoagulation, ranibizumab or bevacizumab) • presence of pseudophakic lens.	If evidence allows, consideration will be given to subgroups according to: • baseline visual acuity • baseline central retinal thickness • treatment history (including people who have received no prior treatment, and those who have received and/or whose disease is refractory to laser photocoagulation, ranibizumab or bevacizumab) • presence of pseudophakic lens.	
Special considerations	None	None	Not applicable

6 Clinical evidence

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 randomised controlled trials (RCTs) investigating the efficacy and safety of aflibercept (in a fixed treatment pattern i.e. five doses of 2mg every four weeks, followed by 2mg every eight weeks,) in the treatment of Diabetic Macular Oedema (DMO). This formed part of a broader search for evidence to support any requirement for indirect comparisons or network meta-analysis (NMA) of clinical studies of anti-VEGF, intravitreal corticosteroids, laser photocoagulation, best standard care (BSC), and sham comparators for the treatment of patients with DMO and to identify data for DMO cost-effectiveness model inputs.

The searches were undertaken initially in October 2013 using MEDLINE, MEDLINE In-Process Citations & Daily Update, EMBASE, and The Cochrane Central Register of Controlled Trials (CENTRAL) and online clinical trial registers (NIH ClinicalTrials.gov, Current Controlled Trials and WHO International Clinical Trials Registry Platform). In addition, various sources of relevant conference abstracts were screened (American Academy of Ophthalmology (AAO), Association for Research in Vision and Ophthalmology (ARVO), American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), European Society of Retina Specialists (EURETINA), European Society of Ophthalmology (ESO), International Society for Pharmacoeconomics and Outcomes Research

(ISPOR)).

Searches were performed without language restriction. Bayer provided unpublished clinical study reports of the VIVID-DMO and VISTA-DMO studies. An update of the clinical and cost effectiveness searches was undertaken in August 2014. Date limits were used to retrieve studies published since the original searches were run in October 2013.

Throughout the programme of work, the literature searches and systematic reviews adhered to published methods including those recommended by the IQWiG methods guide (Version 4.0), the Cochrane Collaboration and CRD (York, UK), in order to reduce the risk of bias and error. Full details of the literature search strategy including search terms employed are provided in Section 10.2, Appendix 2.

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. A suggested format is provided below.

Identified references were downloaded into Endnote software for further assessment and handling. Titles and abstracts identified through electronic database and web searching were independently screened by two reviewers. During this initial phase of the screening process any references which obviously did not meet the inclusion criteria listed below were excluded. During the screening of conference abstracts, only studies which specifically mentioned randomisation and which reported extractable outcome data (or baseline or subgroup data) were included. Full paper copies were obtained for all of the remaining references. These were independently examined in detail by the two reviewers to determine whether they met the criteria for inclusion in the review. All papers excluded at this second stage of the screening process were documented along with the reasons for exclusion. With respect to both

screening stages, any discrepancies between reviewers were resolved through discussion or the intervention of a third reviewer.

A flow diagram of the numbers of records included and excluded at each screening stage is provided in section 6.2.2 Figure 1.

Inclusion and exclusion criteria

Table 1. Eligibility criteria used in search strategy

Criteria	Inclusion	Exclusion
Study design	Published and unpublished randomised controlled prospective clinical trials Dose or frequency comparison trials Ad-hoc analyses of RCT data Crossover RCT's	Systematic or non-systematic reviews and meta-analyses. Pre-clinical studies, retrospective, prognostic studies, case reports. Editorials, commentaries, letters, consensus reports. Pilot studies (if phase not mentioned), Phase I and II RCTs (to be included as second level evidence, if primary evidence is unavailable). Controlled observational studies (to be included as second level evidence, if primary evidence is unavailable). Separate searches will be performed as required. Single dose of intervention studies Studies of less than 3 months follow-up
Population	Patients with diabetic macular oedema	
Interventions	▪ Eylea (VEGF Trap Eye/Aflibercept/AFB) ▪ Anti-VEGF treatments (Any including Ranibizumab/Lucentis/RBZ, bevacizumab/Avastin/BVZ, pegaptanib/macugen) ▪ Intravitreal steroids (Any including Triamcinolone, Fluocinolone (Iluvien), dexamethasone (Ozurdex) and implants) ▪ Laser treatments ▪ NOTE the intervention should be to treat the DME not to treat cataracts ▪ The above interventions can be included if combined with other treatments (e.g. eye drops) except the exclusions.	▪ Systemic treatments (alone or in combination with intervention) ▪ Surgery (alone or in combination with intervention) ▪ Subtenon injections
Comparators	▪ Placebo, best standard care, masked control, sham, eye drops ▪ Any intervention (from those listed as interventions) ▪ NOTE this can be a single treatment/implant	▪ Systemic treatments (alone or in combination with intervention) ▪ Surgery (alone or in combination with intervention)
Clinical Outcomes	▪ No. injections/treatments ▪ No. visits/ assessments	

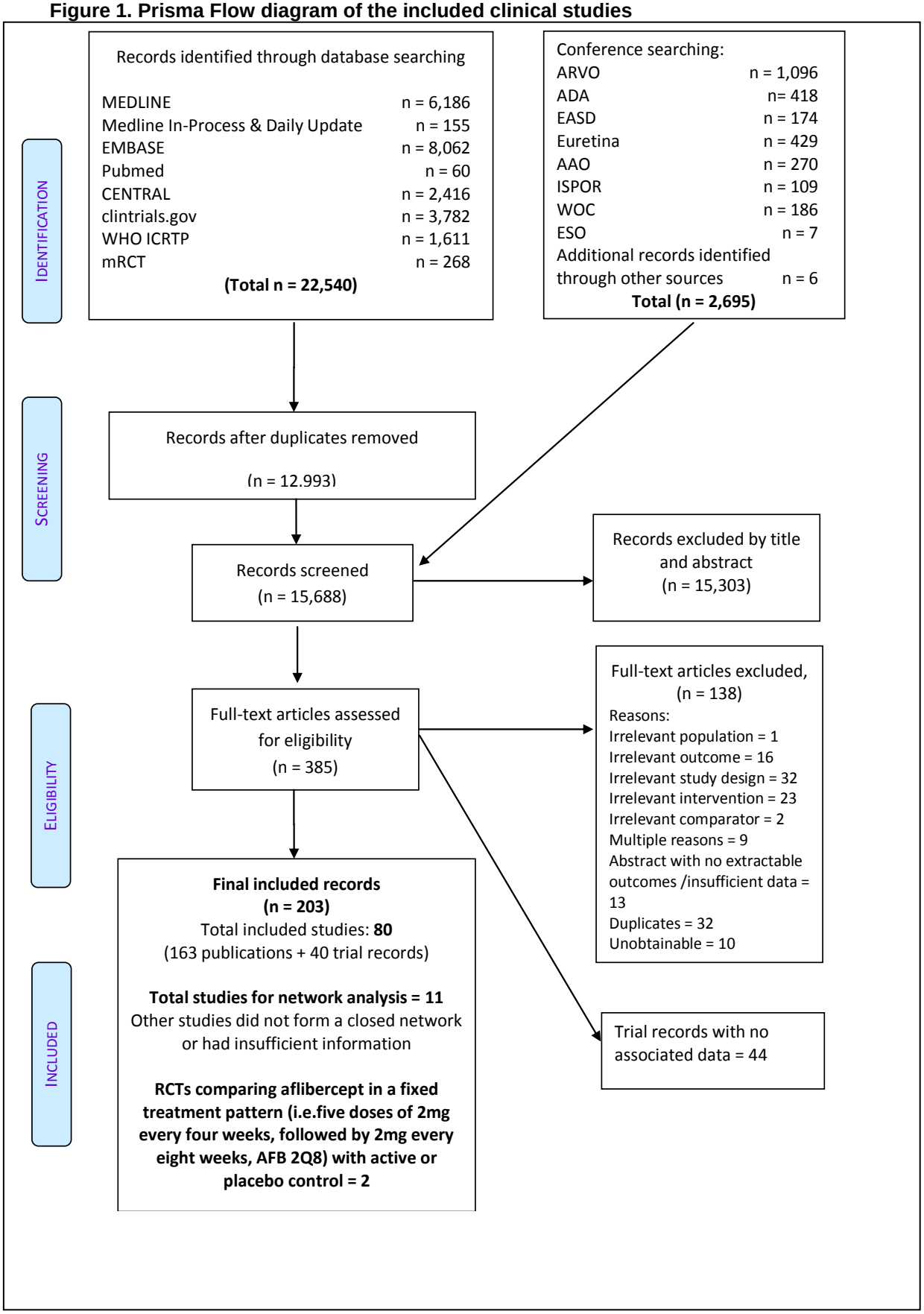
Criteria	Inclusion	Exclusion
	▪ Best corrected visual acuity (BCVA) (Mean change from baseline, mean average change from baseline, as measured by ETDRS score or Snellen equivalent). Visual acuity (% of patients who gain/lose outcome vs. baseline): - loss of ≤ 15 letters in ETDRS score (maintained vision) - loss of ≥ 30 letters ETDRS score (severe vision loss) - loss of ≥ 15 letters ETDRS score (moderate vision loss). - gain of ≥ 15 letters - 20/40 vision or better (Snellen chart) - 20/200 or worse (Snellen chart) - Gain ≥ 0 letters - Gain ≥ 10 letters - Gain ≥ 30 letters ▪ Reduction in laser use ▪ Contrast sensitivity ▪ Change in Choroidal neovascularisation (CNV) ▪ optic disc area ▪ area of lesion ▪ size of leakage ▪ greatest linear dimension ▪ Fluid on OCT ▪ Presence of dye leakage ▪ Eyes with dry lesion ▪ Change in total lesion size ▪ Change in central foveal thickness, mean change from baseline ▪ Health-related quality of life (EQ 5D, NEI VFQ-25, other scales) ▪ Treatment discontinuations ▪ Serious adverse effects (all SAE, all ocular SAE, death, endophthalmitis, uveitis, retinal tear, diabetic macular/retinal oedema, reduced visual acuity, vitreous haemorrhage, corneal abrasion, any others) ▪ Adverse events (all AE, all ocular AE, all non-ocular AE, retinal detachment, retinal ischaemia, lens damage, all grades ocular inflammation, eye pain, increased ocular pressure, retinal degradation, macular oedema, cataract, neovascularisation, any others). ▪ Serious non-ocular adverse events (all, non-fatal cardiac infarction, non-fatal stroke, nonocular haemorrhage, hypertension, serious systemic events, arterial thrombotic events, venous	

Criteria	Inclusion	Exclusion
	thrombotic events).	
Language	▪ Any	

BCVA = Best corrected visual acuity, DME = Diabetic Macular Oedema, ETDRS = Early Treatment Diabetic Retinopathy Study, RCT = Randomised controlled trial, VEGF= Vascular endothelial growth factor.

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. See Figure 1.

Figure 1. Prisma Flow diagram of the included clinical studies



Among the studies excluded from analysis, were the following:

DA VINCI study(16) – this was excluded as it was not a relevant study design e.g. phase II and different aflibercept regimen.

Efficacy and Safety of VEGF Trap Eye in Diabetic Macular Edema (DME) With Central Involvement (VIVID EAST)(NCT01783886) – Bayer / Regeneron, China, Hong Kong, Korea, 375 patients. Expected study completion: July 2015. No data available.

Japanese Safety Study of VEGF Trap-Eye in DME (Diabetic Macular Edema) (VIVID-Japan) (NCT01512966) - Bayer / Regeneron, China, Hong Kong, Korea, 73 patients. Expected study completion: September 2013. Although not yet published, some key data from VIVID-Japan was presented by Hiroko Terasaki at the World Ophthalmology Congress in Tokyo in April 2014 (abstract available at http://www.woc2014.org/pdf/final_program.pdf). However, this was a non-comparative study so was not included in this systematic review.

Protocol T - Comparative Effectiveness Study of Intravitreal Aflibercept, Bevacizumab, and Ranibizumab for DME. National Eye Institute, US Study, 660 patients. Expected study completion is September 2015. Dose of ranibizumab and the treatment regimen for aflibercept not those licensed in the UK.

MEAD studies – These pivotal studies for dexamethasone could not be included in the indirect comparison / network analysis as there was no common comparator.

In DA VINCI, all aflibercept treatment groups (0.5 mg every 4 weeks [0.5Q4], 2 mg every 4 weeks [2Q4], 2 mg every 8 weeks [2Q8], and 2 mg as needed [2PRN]) demonstrated statistically significant improvements in mean change from baseline at 24 and 52 weeks in BCVA and central retinal thickness (CRT) compared to the laser treatment group. The 2Q8 regimen was initiated with 3 monthly doses (as opposed to 5 in the phase III studies – VISTA and

VIVID. Individual patient data suggested that, although mean change in BCVA from baseline to week 24 was not significantly different among the aflibercept groups, fewer patients in the 2 mg treatment group experienced a deterioration of BCVA by more than 5 letters compared to the 0.5 mg aflibercept group.

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 five publications of data from the integrated analyses of the VISTA and VIVID studies comparing aflibercept treatment with laser photocoagulation:

- Korobelnik et al., 2014. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology* Epub 7 Jul 2014 (17). Full publication of the 52-week study results of VISTA and VIVID.

- Nguyen QD and Vista-DME Vivid-DME Study Investigators. Impact of prior therapy for diabetic macular edema (DME) on visual and anatomic outcomes following treatment with intravitreal aflibercept: results from the phase 3 VISTA-DME and VIVID-DME studies. *Invest Ophthalmol Vis Sci* 2014;55(5):5055. Abstract only. (Not used as a data source)

- Lorenz K, Vivid DME and Vista DME study investigators. Evaluation of intravitreal aflibercept for treatment of diabetic macular edema: visual acuity subgroups in VIVID-DME and VISTA-DME. *Invest Ophthalmol Vis Sci* 2014;55(5):5054. Abstract only. (Not used as a data source)

- Brown DM, Vista DME and Vivid DME study investigators. Intravitreal aflibercept injection (IAI) for diabetic macular edema (DME): primary and additional endpoint results from the 12-Month phase 3 VISTA-DME

and VIVID-DME studies. *Invest Ophthalmol Vis Sci* 2014;55(5):5052. Abstract only. (Not used as a data source)

- Schmidt-Erfurth U. Efficacy and safety of intravitreal aflibercept in DME: results of two phase III studies (VIVID-DME and VISTA-DME). Presented at 13th EURETINA congress; 26-29 Sept 2013; Hamburg: Germany. 2013. Abstract and powerpoint presentation (18).

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. A suggested format is presented below.

Table 2. List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
VISTA **[NCT01363440; VGFT-OD-1009]**	n=307 (randomised and received aflibercept) N=155 **2Q4 group:** Aflibercept 2 mg given intravitreally every 4 weeks through to week 144. No sham aflibercept injections. N=152 **2Q8 group:** Aflibercept 2 mg given intravitreally every 8 weeks through to week 144, after 5 initial monthly doses. Sham aflibercept injection given at visits when active treatment not scheduled. **2Q4 and 2Q8 groups:** Sham laser given at baseline and subsequent visits where laser re-treatment criteria met *unless* 'additional treatment' criteria met.	n=154 randomised and received laser photocoagulation at baseline and at visits where laser re-treatment criteria met. **Week 0-96** Sham aflibercept injection given at every visit except when 'additional treatment' criteria are met. **Week 100-148 only:** aflibercept as needed (PRN) according to the aflibercept re-treatment criteria.	DMO secondary to diabetes mellitus involving the centre of the macula.	52-week data: Korobelnik 2014(17)
VIVID **[NCT01331681; Study 91745]**	n=271 (randomised and received aflibercept) N=136	n=133 randomised and received laser photocoagulation at baseline and at visits where laser re-treatment criteria met.		52-week data: Korobelnik 2014 17)

	2Q4 group: Aflibercept 2 mg given intravitreally every 4 weeks through to week 144. No sham aflibercept injections. N=135 **2Q8 group:** Aflibercept 2 mg given intravitreally every 8 weeks through to week 144, after 5 initial monthly doses. Sham aflibercept injection given at visits when active treatment not scheduled. **2Q4 and 2Q8 groups:** Sham laser given at baseline and subsequent visits where laser re-treatment criteria met *unless* 'additional treatment' criteria met.	**Week 0-96** Sham aflibercept injection given at every visit except when 'additional treatment' criteria are met. **Week 100-148 only:** aflibercept as needed (PRN) according to the aflibercept re-treatment criteria.		

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 the VISTA and the VIVID studies compare aflibercept with a relevant comparator (i.e. laser) in a relevant population and dosing regimen, 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 6.2.4 and 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.

No non-RCTs are considered relevant to the decision problem given the availability of RCT evidence which is the preferred study design for NICE appraisal.

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. When there is more than one RCT, the information should be tabulated.

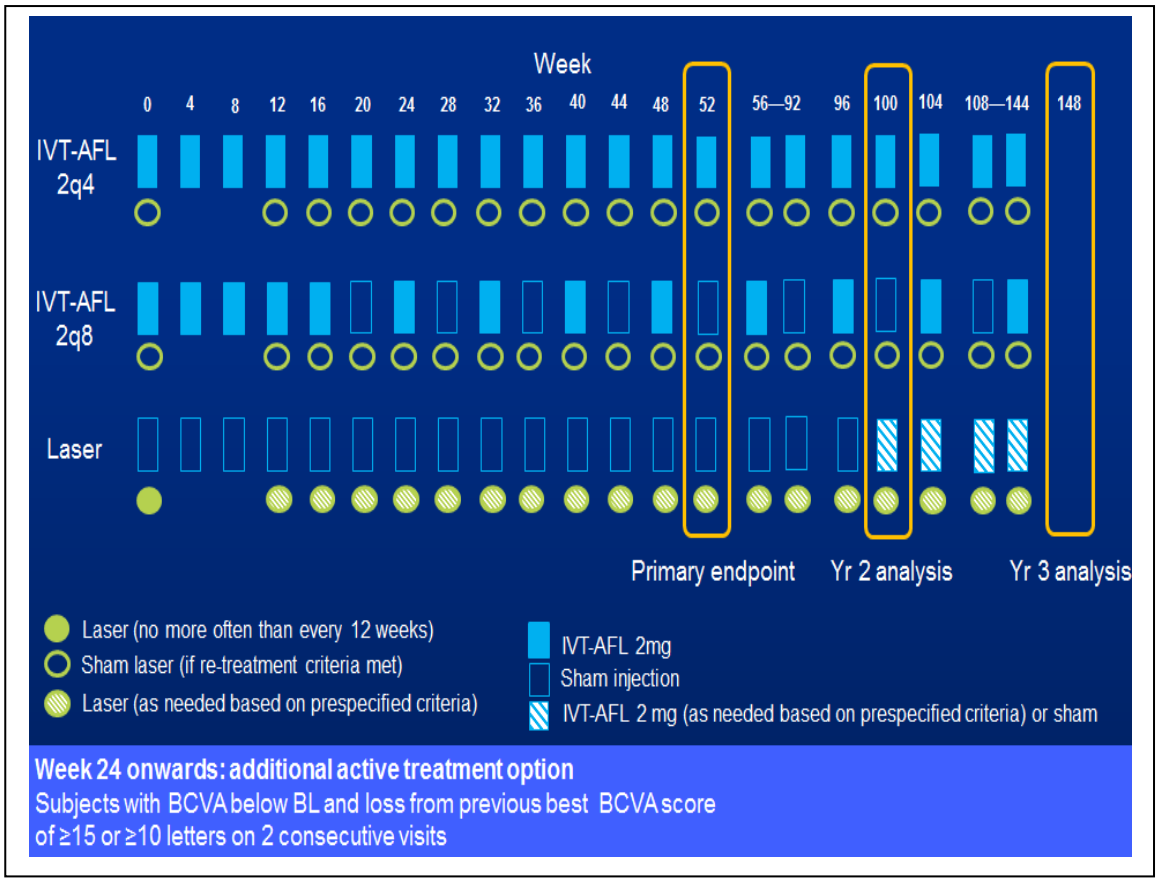
Two large, randomised, controlled studies were designed to assess the efficacy and safety of repeated doses of intravitreal aflibercept in patients with diabetic macular oedema (DMO) with central involvement and a best corrected visual acuity (BCVA) of 20/40 to 20/320 (letter score of 73 to 24). These were named the VISTA and VIVID studies(19;20). The primary objective of VISTA and VIVID was to demonstrate the superiority of aflibercept over laser photocoagulation (laser) on BCVA in eyes with DMO involving the centre of the macula. The key secondary objective was to evaluate the safety and tolerability of aflibercept compared with laser. The standard of care at the time of study design was laser photocoagulation. This is still used as primary therapy in many regions of the world.

The VISTA and VIVID study results at 52-weeks have now been published (17). Data presented in this section are derived where possible from this publication. Supplementary data is provided from protocols(21;22) and clinical study reports(19;20;23;24) and remains academic in confidence (AIC). Study overviews and efficacy results at 52-weeks and also 100-weeks, for both studies, were also presented at the Annual meetings of the European Society of Retina specialists, EURETINA 2013 (52-weeks)(18) and EURETINA 2014 (100-weeks)(25). Also, the European Public Assessment Report (EPAR) has been published, following the European approval of aflibercept (Eylea) for the treatment of diabetic macular oedema(26).

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. The following tables provide a suggested format for when there is more than one RCT.

Figure 2. VISTA and VIVID trial design / treatment schedule



IVT-AFL = intravitreal aflibercept; 2q4 = 2mg aflibercept every 4 weeks; 2q8 = 2mg aflibercept every 8 weeks, after 5 initial monthly doses; Yr = year

Table 3. Comparative summary of methodology of the RCTs

Trial no. (acronym)	VISTA ((18;19;22;26)) [NCT01363440; VGFT-OD-1009]	VIVID ((18;20;21;26)) [NCT01331681; Study 91745]
Design	Prospective, phase III, multicentre, randomised, double-masked, active-controlled superiority study.	Prospective, phase III, multicentre, randomised, double-masked, active-controlled superiority study.
Location	54 sites in the United States (US).	73 sites across Japan, Europe (Austria, Czech Republic, Denmark, France, Germany, Hungary, Italy, Poland, Spain), and Australia.
Duration of study	Overall: 148 weeks (Ongoing) Primary reporting: 52-week data primary endpoint (data obtained between May 2011 and January 2013) Week 100 (2-year data): (data obtained between May 2011 and 18 December 2013)	Overall: 148 weeks (Ongoing). Primary reporting: 52-week primary endpoint (data obtained between May 2011 and June 2013)
Population	DMO secondary to diabetes mellitus involving the centre of the macula. 461 patients randomised and received study medication	DMO secondary to diabetes mellitus involving the centre of the macula. 404 patients randomised and received study medication
Intervention (See Table 4 and Table 5)	n=307 (randomised and received aflibercept) N=155 **2Q4 group:** Aflibercept 2 mg given intravitreally every 4 weeks through to week 144. No sham aflibercept injections. N=152 **2Q8 group:** Aflibercept 2 mg given intravitreally every 8 weeks through to week 144, after 5 initial monthly doses. Sham aflibercept injection given at visits when active treatment not scheduled. **2Q4 and 2Q8 groups:** Sham laser given at baseline and subsequent visits where laser re-treatment criteria met *unless* 'additional treatment' criteria met. Aflibercept was injected in a volume of 50µl.	n=271 (randomised and received aflibercept) N=136 **2Q4 group:** Aflibercept 2 mg given intravitreally every 4 weeks through to week 144. No sham aflibercept injections. N=135 **2Q8 group:** Aflibercept 2 mg given intravitreally every 8 weeks through to week 144, after 5 initial monthly doses. Sham aflibercept injection given at visits when active treatment not scheduled. **2Q4 and 2Q8 groups:** Sham laser given at baseline and subsequent visits where laser re-treatment criteria met *unless* 'additional treatment' criteria met. Aflibercept was injected in a volume of 50µl.
Comparator	Focal/Grid Photocoagulation (modified-ETDRS technique)	

(See Table 4 and Table 5)	n=154 randomised and received laser photocoagulation at baseline and at visits where laser re-treatment criteria met. **Week 0-96** Sham aflibercept injection given at every visit except when 'additional treatment' criteria are met. **Week 100-148 only:** aflibercept as needed (PRN) according to the aflibercept re-treatment criteria.	n=133 randomised and received laser photocoagulation at baseline and at visits where laser re-treatment criteria met. **Week 0-96** Sham aflibercept injection given at every visit except when 'additional treatment' criteria are met. **Week 100-148 only:** aflibercept as needed (PRN) according to the aflibercept re-treatment criteria.
Additional (rescue) treatment	Patients in all groups were also assessed for additional treatment for inadequate responders at each visit starting at week 24, i.e. rescue treatment with aflibercept for laser patients, and laser for the aflibercept patients. (See Table 4 and Table 5)	
Concomitant & disallowed treatment	Patients could not receive any medication for DMO in the study eye, other than study treatment, until they had completed the end of study or early study termination visit. If a pre-treatment concomitant medication was administered [redacted] Any other medication that was [redacted] Systemic anti-angiogenic agents were [redacted] **Fellow eye** - [redacted]	
Criteria for Discontinuation of study treatment	Occurred at patient or investigator request, due to [redacted]	
Method of randomisation	Patients were randomised according to a predetermined central randomisation scheme generated and provided by an interactive voice response system (IVRS) / interactive web response system (IWRS). They were randomised into the 3 treatment groups in a 1:1:1 ratio. One eye per patient was randomised. For patients who meet eligibility criteria in both eyes [redacted]	
	Stratified according to history of myocardial infarction (MI) and/or cerebrovascular accident (CVA) (yes vs. no).	Patients were stratified by geographic region (Japan vs. Europe / Australia).

Method of blinding (care provider, patient and outcome assessor)	In order to maintain masking in the study, sham injections and sham laser were performed throughout the duration of the study whenever active procedures were not indicated or scheduled. Subconjunctival anaesthesia [redacted] The sham laser photocoagulation procedure involved [redacted] Study drug was received, tracked, and prepared by an unmasked individual and study drug injections and sham injections, laser/sham photocoagulation, laser re-treatment, and additional treatment were performed by an unmasked physician. The unmasked physician assessed safety 30 minutes post-injection but took no further part in the study. [redacted] All other site personnel were masked to treatment assignment, including the physician assessing adverse events, supervising the assessment of efficacy and deciding on the need for retreatment or additional treatment. Examiners testing visual acuity and site personnel administering National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) were masked to treatment assignment. At the end of the first year of the studies [redacted] in VIVID or VISTA had been unmasked to treatment. Retinal characteristics were determined by [redacted] All aflibercept and sham treatments were packaged [redacted]
Primary outcome	Change from baseline in Best-Corrected Visual Acuity (BCVA) in ETDRS letter score at week 52.
Main Secondary outcomes	• Proportion of patients gaining ≥ 10 ETDRS letters from baseline to week 52 • Proportion of patients gaining ≥ 15 ETDRS letters from baseline to week 52 • Proportion of patients who achieved ≥2-step improvement on the ETDRS DRSS from baseline to week 52 • Mean change in central retinal thickness (CRT) from baseline to week 52, as assessed on OCT • Vision-related quality of life (QoL): Mean changes in NEI VFQ-25 near activities subscale score from baseline to week 52. • Vision-related quality of life (QoL): Mean changes in NEI VFQ-25 distance activities subscale score from baseline to week 52. • Safety: Ocular and non-ocular adverse events (AEs), and serious adverse events (SAEs), [redacted] • Quality of life : Overall state of health was assessed by EuroQol 5 dimensions health questionnaire (EQ-5D)

Duration of follow-up (& timing of assessments)	Assessments were performed in both studies at regular scheduled clinic visits i.e. day 1, week 4 and every 4 weeks thereafter through to the end of study at week 148. [redacted] A full ocular examination was conducted at each visit[redacted] NEI VFQ-25 (National Eye Institute Visual Functioning Questionnaire-25) and EQ-5D (EuroQoL 5 Dimensions Questionnaire) was administered[redacted] Adverse events and concomitant medications were[redacted] Laboratory assessments were performed [redacted]

Table 4: Description of treatment groups in the VISTA and VIVID studies(18)

	INTERVENTION		COMPARATOR
	Arm 1 **Aflibercept 2Q4**	**Arm 2** **Aflibercept 2Q8**	**Arm 3** **Macular laser photocoagulation**
Aflibercept	2mg every 4 weeks, starting at baseline through to week 144	2mg every 4 weeks, starting at baseline until week 16, thereafter 2mg every 8 weeks through to week 144	**From week 24:** If additional treatment criteria met - aflibercept as per 2Q8 schema (i.e. 5 injections at 4-weekly intervals, then every 8 weeks) **Week 100 - week 148 only:** patients who did not receive additional treatment received aflibercept as needed (PRN) according to the aflibercept re-treatment criteria
Sham injection	None	After week 16, at visits where active aflibercept not scheduled to be administered (i.e. every 8 weeks)	Every visit except when 'additional treatment' criteria are met or visits during year 3 when active injection is scheduled
Laser photocoagulation	None *except* when 'additional treatment' criteria met, then patient receives active laser photocoagulation instead of sham laser according to laser re-treatment guidelines (no more often than every 12 weeks)		Baseline and then at visits where laser re-treatment criteria were met (starting at week 12 and no more often than every 12 weeks) through to week 144
Sham Laser	Baseline and then at visits where laser re-treatment criteria were met (starting at week 12 and no more often than every 12 weeks) *unless* 'additional treatment' criteria met		None

Table 5: Criteria for 'Laser re-treatment', 'Additional treatment' and aflibercept re-treatment(26)

Laser re-treatment guideline	The investigator expects that the patient will benefit from another laser treatment, and at least one of the following: - Thickening of the retina at or within 500 µm of the centre of the macula, or - Hard exudates at or within 500 µm of the centre of the macula, if associated with thickening of adjacent retina, or A zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula
Additional treatment criteria	Patients may be considered for additional treatment from week 24 onwards if one or both of the following conditions is met, and benefit is considered likely, as assessed by the masked personnel: - Loss of ≥ 15 letters from the best previous measurement, but actual BCVA not better than baseline, at any study visit, or - Loss of ≥ 10 letters from the best previous measurement, but actual BCVA not better than baseline, at any study visit, confirmed at a consecutive visit at least 7 days later (may be an unscheduled visit) Patients receiving additional treatment may continue with study visits and receiving randomised treatment up to the final visit.
Aflibercept re-treatment criteria (Laser Photocoagulation treatment arm – Year 3)	Intravitreal aflibercept treatment when any of the following criteria are met: - There is a > 50 µm increase in central retinal thickness (CRT) on optical coherence tomography (OCT) compared to the lowest previous measurement - There are new or persistent cystic retinal changes or sub-retinal fluid on OCT, or persistent diffuse oedema in the central subfield on OCT - A loss of 5 or more letters from the best previous measurement in conjunction with any increase in retinal thickness in the central subfield on OCT - An increase in BCVA between the current and most recent visit of ≥ 5 letters

BCVA=best corrected visual acuity

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

The main inclusion and exclusion criteria are listed here. Please refer to the study protocols(21;22) or supplementary appendix 2 to the Korobelnik 2014 publication(17) for a full list of inclusion and exclusion criteria.

Inclusion criteria

- Age ≥18 years with type 1 or 2 diabetes mellitus
- DMO secondary to diabetes mellitus involving the centre of the macula
- Decrease in vision determined to be primarily the result of DMO
- BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 73 to 24 (20/40 to 20/320)
- Previous laser treatment allowed unless laser scars would prevent any improvement in macular function
- Signed consent and willing and able to comply with site visits and study procedures
- VIVID only: retinal thickness as assessed by OCT of ≥300 µm in the study eye

Main exclusion criteria

The key exclusion criteria from the study protocol include:

- Previous treatment of DMO in the 3 months prior to study entry including laser photocoagulation (panretinal or macular)
- Cataract surgery or any other intraocular surgery in the study eye within 90 days prior to study entry
- Previous vitreoretinal surgery (VIVID only: and/or including scleral buckling), in the study eye
- Patients deemed unlikely to benefit from additional macular photocoagulation
- VIVID only: more than 2 previous macular laser treatments in the study eye
- Prior use of intraocular or periocular corticosteroids in the study eye within 120 days of study entry

- Previous treatment with anti-angiogenic drugs in the study eye (e.g. pegaptanib sodium, bevacizumab, ranibizumab) within 90 days of study entry.

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.

Demographic and baseline including disease characteristics were fairly well balanced among treatment groups in both studies. Differences included the BMI, which was higher in VISTA, CRT values (higher in VIVID), lack of DRSS grading in a quarter of the patients in VIVID (compared to 1.7% in VISTA), higher NEI VFQ-25 scores in VIVID and higher number of pseudophakic patients in VISTA. Reported here are results in the FAS – results in the SAF and PPS were [redacted]

The mean age of patients in VISTA was 62.2 years and in VIVID was 63.6 years. Most patients were white (VISTA: 384/459 [83.7%]; VIVID: 321/403 [79.7%]). The VISTA study included more female patients (VISTA: 209/459 [45.5%]) than VIVID (154/403 [38.2 %). In VISTA, the overall mean BMI was [redacted], the mean weight [redacted], and the mean height [redacted]. In VIVID, the overall mean BMI was [redacted], the mean weight [redacted], and the mean height [redacted].

Mean baseline HbA1c was similar in VISTA (7.8%) and VIVID (7.7%), although in VIVID, the proportion of patients with HbA1c > 8% at baseline was slightly higher in the aflibercept 2Q4 group (40.4% compared to 32.6% in the 2Q8 group and 31.8% in the laser group). Patients had been diagnosed with diabetes for an average of 17.1 years in VISTA and 14.3 years in VIVID, with most having type 2 diabetes [redacted]. Prior treatment with intravitreal anti-VEGF was reported in 42.9% patients in the VISTA study and 8.9% in VIVID. This difference largely reflects a relative limitation of availability to anti-VEGF treatments in countries where the VIVID

study was conducted. However, in both studies, the distribution of these patients was generally balanced across treatment groups.

Total mean baseline BCVA letter score in the study eye was 60.1 in VIVID and 59.3 in VISTA. The majority of patients in all treatment groups/both studies had a Diabetic Retinopathy Severity Scale (DRSS) score between 43 and 53. In VISTA, mean CRT was 482.6 µm and mean IOP was [redacted]. In VIVID, mean CRT was 520.0 µm – the laser group having a higher mean than the aflibercept 2Q4 and 2Q8 groups (540.3 µm versus 501.9 µm and 518.4 µm, respectively) - and mean IOP was 15.9 mmHg.

Ocular and non-ocular medical and surgical history was typical of this patient population and similar among treatment groups – nearly 85% (VISTA) and 72.8% (VIVID) patients had hypertension / hypertensive disorders at baseline, approximately 40% (VISTA) and 24.3% (VIVID) hypercholesterolaemia, and 20% (VISTA) and 15.8% (VIVID) hyperlipidaemia. In VISTA almost [redacted] patients had a history of ischaemic heart disease compared with 12.6% patients in VIVID.

Mean NEI VFQ-25 total score, near activities subscale score, and distance activities subscale score were 69.6, 58.3 and 65.3, respectively.

Table 6: Baseline demographic characteristics of patients entering VISTA and VIVID studies [FAS](18-20)

	Laser		Aflibercept			
			2mg Q4		2mg Q8	
	VISTA	VIVID	VISTA	VIVID	VISTA	VIVID
	N=154	N=132	N=154	N=136	N=151	N=135
Age						
Mean (SD)	61.7 (8.7)	63.9 (8.6)	62.0 (11.2)	62.6 (8.6)	63.1 (9.4)	64.2 (7.8)
Median	[redacted]					
Min; Max	[redacted]					
Sex (n[%])						
Male	85 (55.2)	78 (59.1)	87 (56.5)	83 (61.0)	78 (51.7)	88 (65.2)
Female	69 (44.8)	54 (40.9)	67 (43.5)	53 (39.0)	73 (48.3)	47 (34.8)
Race (n[%])						
White	131 (85.1)	106 (80.3)	128 (83.1)	109 (80.1)	125 (82.8)	106 (78,5)
Black	16 (10.4)	1 (0.8)	16 (10.4)	0 (0.0)	19 (12.6)	1 (0.7)
Asian	3 (1.9)	25 (18.9)	5 (3.2)	27 (19.9)	2 (1.3)	27 (20.0)
Other	4 (2.6)	0 (0.0)	5 (3.2)	0 (0.0)	5 (3.3)	1 (0.7)
Ethnicity (n[%])						
Not Hisp / Latino	[redacted]					

	Laser		Aflibercept			
			2mg Q4		2mg Q8	
	VISTA	VIVID	VISTA	VIVID	VISTA	VIVID
	N=154	N=132	N=154	N=136	N=151	N=135
Hispanic / Latino						
Glycosylated Haemoglobin (HbA1c), %						
Mean (SD)	7.6 (1.68)	7.7 (1.26)	7.9 (1.65)	7.8 (1.46)	7.9 (1.56)	7.7 (1.43)
≤ 8% (n[%])						
> 8% (n[%])	45 (29.2)	42 (31.8)	57 (37.0)	55 (40.4)	57 (37.7)	44 (32.6)
Duration of diabetes (years)						
Mean (SD)	17.2 (9.55)	14.5 (9.8)	16.5(9.94)	14.3 (9.2)	17.6 (11.46)	14.1 (8.9)
Median						
Min; Max[a]						
Prior intravitreal anti-VEGF (in study eye)	63 (40.9)	11 (8.3)	66 (42.9)	7 (5.1)	68 (45.0)	14 (10.4)
Prior laser photocoagulation (in study eye)						

[a] Three patients had a diagnosis of diabetes for less than 0.5 year, which was rounded to 0
2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 4 weeks by intravitreal injection; SD=standard deviation;

Table 7: Baseline disease characteristics of patients entering VISTA and VIVID studies [FAS](18-20)

	Laser		Aflibercept			
			2mg Q4		2mg Q8	
	VISTA	VIVID	VISTA	VIVID	VISTA	VIVID
	N=154	N=132	N=154	N=136	N=151	N=135
BCVA letters						
Mean (SD)	59.7 (10.9)	60.8 (10.6)	58.9 (10.8)	60.8 (10.7)	59.4 (10.9)	58.8 (11.2)
Median						
Min; Max						
CRT (µm)						
Mean (SD)	483 (153)	540 (142)	485 (157)	502 (144)	479 (154)	518 (147)
Median						
Min; Max						
Mean Baseline IOP (mmHg)						
NEI-VFQ mean (SD)						
Total	68.7 (18.1)	77.5 (15.2)	69.5 (19.9)	77.3 (16.2)	70.5 (17.1)	71.2 (17.8)
Distance	63.7 (23.3)	77.0 (20.9)	65.3 (23.5)	76.7 (21.8)	66.8 (22.5)	67.8 (22.9)
Near	56.6 (23.1)	67.4 (22.2)	60.1 (23.9)	68.0 (22.9)	58.1 (22.9)	60.8 (23.5)

2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 4 weeks by intravitreal injection; BCVA=best corrected visual acuity; CRT=Central retinal thickness; DRSS=Diabetic retinopathy severity scale; ETDRS=Early Treatment Diabetic Retinopathy Study; IOP=intraocular pressure; NEI VFQ-25=National Eye Institute Visual Functioning Questionnaire-25.
[a] DRSS levels are defined as follows: none (level 10), mild to moderate non-proliferative DR (levels 14,15,20,35 and 43), moderately severe / severe non-proliferative DR (levels 47 AND 53), mild/moderate/high-risk/advanced proliferative DR (levels 61, 65, 71,75,81 and 85)

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 VISTA and VIVID studies had similar primary and secondary endpoints (see Table 8), all of which were relevant to the disease and matched the requirements of the decision problem.

Reliability/ validity/ current use in clinical practice - All efficacy and safety parameters assessed in VISTA and VIVID, and the methods to measure them are standard variables and methods in clinical studies for DMO, and in ophthalmic practice. 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.

Compliance – As study drug was administered on site (for both studies), compliance with the study drug dosing was monitored by [redacted] All drug compliance records were [redacted]

Table 8: Primary and Secondary endpoints of VISTA and VIVID studies

Endpoint	VISTA	VIVID	Measure
Primary Endpoint			
Change from baseline in Best-Corrected Visual Acuity (BCVA) in ETDRS letter score at week 52.	[redacted]		Visual function or BCVA was using the 4 metre ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group, 1985). The ETDRS letter score as a measure of VA, is widely accepted by regulatory authorities. The VA examiner was masked to treatment [redacted]
Secondary Endpoints			
Proportion of patients gaining ≥ 10 ETDRS letters from baseline to week 52	Assessments performed at day 1, week 4 and every 4 weeks thereafter to week 52		The ETDRS 4m protocol
Proportion of patients gaining ≥ 15 ETDRS letters from baseline to week 52			
Proportion of patients who achieved ≥2-step improvement on the ETDRS DRSS from baseline to week 52	[redacted]		[redacted] The DRSS scale relates presence of retinopathy according to the following scores: -level 10 None -levels 14, 15, 20, 35, 43 Mild to moderate non-proliferative diabetic retinopathy -levels 47 and 53 Moderately severe/severe non-proliferative diabetic retinopathy -levels 61, 65, 71, 75, 81, and 85 Mild/moderate/high-risk/advanced proliferative diabetic retinopathy
Mean change in central retinal thickness (CRT) from baseline to week 52, as assessed on OCT	[redacted]		[redacted] read at a masked independent reading centre.
Vision-related quality of life (QoL): Mean changes in NEI VFQ-25 near activities subscale score from baseline to week 52.	[redacted]		[redacted] masked interviewer [redacted] Near activities: difficulty reading ordinary print in newspapers, performing work or hobbies requiring near vision, or finding something on a crowded shelf. Distance activities: reading street signs or names on stores, and going down stairs, steps or curbs.
Vision-related quality of life (QoL): Mean changes in NEI VFQ-25 distance activities subscale score from baseline to week 52.			
Safety: Ocular and non-ocular adverse events (AEs), and serious adverse events (SAEs), [redacted]	[redacted]		Adverse events were summarised using the Medical Dictionary for Regulatory Activities (MedRA) version 16.0

CRT=Central retinal thickness; DRSS= diabetic retinopathy severity scale; ETDRS=Early Treatment Diabetic Retinopathy Study; FP=Fundus photography; NEI VFQ-25=National Eye Institute Visual Functioning Questionnaire-25; OCT=Optical coherence tomography;

Additional efficacy variables (analysed at week 52) included(26):

- Proportion of patients who gained ≥ 0 and ≥ 5 ETDRS letters from baseline
- Proportion of patients who lost ≥5, ≥10, and ≥15 ETDRS letters from baseline
- Time to first gain of ≥15 ETDRS letters from baseline
- Time to first confirmed gain of ≥15 ETDRS letters from baseline
- Proportion of patients with a ≥ 2- or ≥ 3-step worsening, or a ≥ 3-step improvement from baseline in the ETDRS DRSS score as assessed on fundus photography (FP)
- Change from baseline in the NEI VFQ-25 total score and subscales over time

Patients' overall quality of life was assessed using the EuroQol 5 dimension (EQ-5D) questionnaire.

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.

Analysis populations

The following populations were used for statistical analyses:

Table 9: Definition of Analysis populations in VISTA and VIVID studies

Analysis	Population	VISTA	VIVID
Primary Efficacy	**Full Analysis set (FAS)**	All randomised patients who received any study medication and had a baseline assessment and at least 1 BCVA assessment after baseline. Analysed as randomised.	
Supportive	**Per Protocol (PPS)**	The primary endpoint was also evaluated on the PPS. All patients in the FAS who did not have any major protocol violations during the first 52 weeks. Analysed as treated.	
		Secondary endpoints were also evaluated using [redacted]	Only the primary endpoint was evaluated using [redacted]
Safety	**Safety (SAF)**	All randomised patients who received any study medication (active or sham). Analysed as treated.	

BCVA=best corrected visual acuity

All efficacy endpoints were analysed using the FAS.

In both studies, the proportion of patients included in the FAS and SAF was very similar across the treatment groups (see Table 10). The vast majority of randomised patients were valid for both safety and efficacy analyses.

Table 10: Sample size and Efficacy analysis sets for VISTA, VIVID & integrated analysis(18-20;26;27)

Study	Screened	Treatment group	Randomised Treatment Assigned	Safety Analysis Set (SAF) n (%)	Full Analysis Set (FAS) n (%)	Per Protocol Set (PPS) n (%)	Completed Week 52 n (%)
VISTA	687	Total	466	461 (98.9)	459 (98.5)	[redacted]	435 (93.3)
		Laser	156	154 (98.7)	154 (98.7)		145 (92.9)
		VTE2Q4	156	155 (99.4)	154 (98.7)		146 (93.6)
		VTE2Q8	154	152 (98.7)	151 (98.1)		144 (93.5)
		VTE combined	310	307 (99.0)	305 (98.4)		290 (93.5)
VIVID	604	Total	406	404 (99.5)	403 (99.3)		360 (88.7)
		Laser	135	133[a] (98.5)	132 (97.8)		115 (85.2)
		VTE2Q4	136	136 (100)	136 (100)		125 (91.9)
		VTE2Q8	135	135 (100)	135 (100)		120 (88.9)
		VTE combined	271	271 (100)	271 (100)		245 (90.4)
Integrated Analysis – Week 52	1291	Total	872	865 (99.2)	862 (98.9)		795 (91.2)
		Laser	291	287 (98.6)	286 (98.3)		260 (89.4)
		VTE2Q4	292	291 (99.7)	290 (99.3)		271 (92.8)
		VTE2Q8	289	287 (99.3)	286 (99.0)		264 (91.4)
		VTE combined	581	578 (99.5)	576 (99.1)		535 (92.1)

VTE=aflibercept by intravitreal injection; 2Q4=2mg every 4 weeks; 2Q8=2mg every 8 weeks

[a] One patient only received sham injection. The patient left the study before receiving any laser.

Statistical Analysis Plan

Analysis of data from VISTA and VIVID was determined based on 2 statistical analysis plans (SAPs) for each study: a global SAP and a US SAP (agreed with the US Federal Drugs Agency [FDA]) (see Table 11). The primary variables are the same in both SAPs, however, the designation, timing, and hierarchical test sequence for the secondary endpoints differs. The integrated analysis follows the same approach(26).

Table 11: Status and statistical approach in the global and US statistical analysis plans(18;27)

Endpoint	Global SAP		US SAP	
	Status	Test order[a]	Status	Test order[a]
Change in BCVA by ETDRS letter score from baseline to week 52	Primary	-	Primary	-
Proportion of patients who gained ≥10 ETDRS letters from baseline to week 52	Secondary	1	Exploratory	-
Proportion of patients who gained ≥15 ETDRS letters from baseline to week 52	Secondary	2	Secondary	1
Proportion of patients who achieved ≥2-step improvement on the ETDRS DRSS from baseline to week 52	Secondary	3	Exploratory	-
Change in CRT from baseline to week 52, as assessed by OCT	Secondary	4	Exploratory	-
NEI VFQ-25 near activities subscale change from baseline to week 52	Secondary	5	Exploratory	-
NEI VFQ-25 distance activities subscale change from baseline to week 52	Secondary	6	Exploratory	-

SAP=Statistical analysis plan; US=United States; BCVA=best corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; DRSS= diabetic retinopathy severity scale; CRT=Central retinal thickness; OCT=Optical coherence tomography; NEI VFQ-25=National Eye Institute Visual Functioning Questionnaire-25.

Table 12. Summary of statistical analyses in VISTA and VIVID(17;19;20;26)

	VISTA	VIVID
Primary Hypotheses or hypothesis objective	• The primary hypothesis is [redacted]	

Statistical Analysis	• The primary analysis was a statistical evaluation of superiority of aflibercept treatment to laser treatment in the FAS population, censoring measurements after additional (rescue) treatment was given due to vision loss.The primary analysis used a 2-sided test at the 2.5% significance level, using Bonferroni adjustment for the 2 comparisons (1 - aflibercept 2Q4 versus laser; 2 - aflibercept 2Q8 versus laser) on the primary efficacy endpoint.
	
	• The analysis used an analysis of covariance (ANCOVA) model. The ANCOVA model used treatment as the main effect, history of MI and/or CVA (VISTA only) and geographic region as a fixed factors, and baseline BCVA measurement as the covariate.
	
	• The primary analysis was performed on both the FAS [redacted] The FAS analysis was considered the primary one.
	
	• An integrated analysis of the pooled data of VISTA and VIVID studies with regard to the primary efficacy variable at 52 weeks was also performed.
	
	• Secondary endpoint analysis: If either aflibercept treatment group was shown to be superior to laser for the primary endpoint, the analyses of secondary endpoints was performed in the FAS population, using a hierarchical testing procedure (see Table 11) for superiority of aflibercept treatment over the laser group. The hierarchical method ensured the overall type I error rate of 5% for the study using Bonferroni multiplicity adjustment in the same principles as used for the primary analysis of the primary efficacy variable. P-values were reported for all comparisons; however a superiority claim could only be made for a given endpoint if all preceding endpoint comparisons in the hierarchy are shown to be statistically significant at a 2.5%, 2-sided significance level.
	
	• The same LOCF approach for missing measurements was used in the primary efficacy endpoint and secondary variable analyses.
	
	• Several sensitivity analyses (on primary and secondary endpoints) were performed to address the impact of missing data due to drop-outs or receipt of additional treatment:
	  ○ **Observed case (OC) analysis**: Only observed, non-censored values used for analysis; measurements taken after additional treatment was given were censored.
	  ○ **Including data after additional treatment:**
	  ▪ **aLOCF**: Missing data were imputed by LOCF; data obtained after the initiation of additional treatment were included.
	  ▪ **aOC**: all observed values were used for the analysis, including measurements taken after additional treatment was given.
	  ○ Repeated measurement model (to account for missing data)
	  ○ Multiple imputation analysis
	
	• Additional efficacy variables were analysed descriptively at each scheduled visit from baseline to week 52.	

<table>
<tr><th></th><th>VISTA</th><th>VIVID</th></tr>
<tr><td rowspan="2">Power calculation / Sample size</td><td colspan="2">• The sample size calculation was based on the primary endpoint ‘change from baseline in BCVA in ETDRS letters to week 52’ in 2 comparisons: 2Q4 aflibercept vs. laser and 2Q8 aflibercept vs. laser.

• Under the assumption that the changes in BCVA from baseline were normally distributed, and that the true difference in the mean change in BCVA for each comparative group is 7, with an expected standard deviation for each aflibercept group of 10 and laser of 16, a sample size of 92 patients per group was needed to provide 90% power for rejecting each of the null hypotheses with a 2-sided t-test at the 2.5% (5%/2) significance level.</td></tr>
<tr><td>The planned sample size of 402 patients was based on a dropout rate of 30%, approximately 134 patients per group.</td><td>Assuming a drop-out rate up to 25%, approximately 125 patients per group were required. Of these 375 total patients, approximately 83 were planned to be randomised in Japan.</td></tr>
<tr><td>Data management / Patient withdrawals / censoring methods</td><td colspan="2">A total of 435 (93.3%) and 360 (88.7%) patients completed the first year of the VISTA and VIVID studies, respectively.

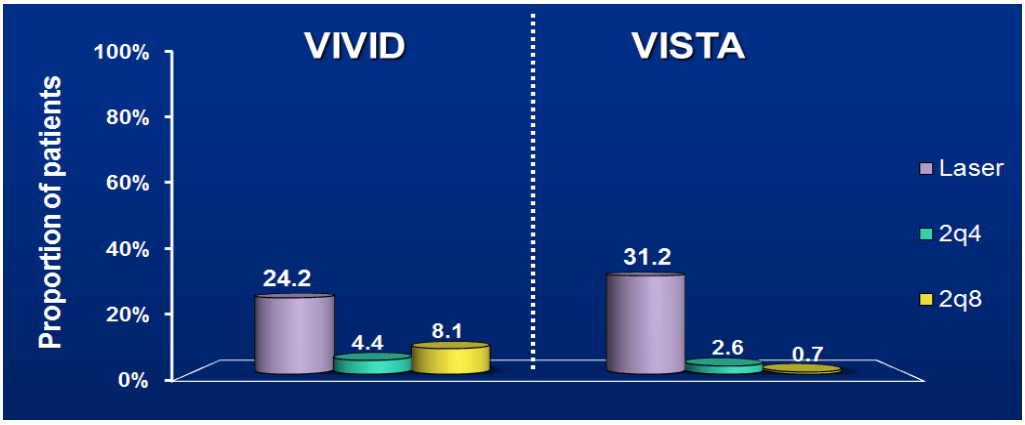
In VISTA, 31 (6.7%) patients prematurely discontinued the study, the main reason being ‘withdrawal by the subject’ (n=14 [3%]). There were a higher number of premature study discontinuations in VIVID (n=46 [11.3%]). The primary reason was “AE” for 18 (4.4%) patients followed by “withdrawal by the subject” for 12 (3%) patients. Three (0.6%)(1 in the laser group and 2 in the 2Q4 group) [VISTA] and 4 (1.0%) (all in the 2Q8 group) [VIVID] patients died.

Management of missing data:
In both studies, measurements obtained after the initiation of additional treatment were censored. Missing or censored values were imputed using the last non-censored value (last observation carried forward [LOCF]). Baseline values were not carried forward. Several sensitivity analyses were performed to address the impact of missing data due to drop-outs or receipt of additional treatment. The same LOCF approach for missing measurements was used in the primary efficacy endpoint and secondary variable analyses.

○ Observed case (OC) analysis: Only observed, non-censored values used for analysis; measurements taken after additional treatment was given were censored.
○ Including data after additional treatment:
▪ aLOCF: Missing data were imputed by LOCF; data obtained after the initiation of additional treatment were included.
▪ aOC: all observed values were used for the analysis, including measurements taken after additional treatment was given.
○ Repeated measurement model (to account for missing data)
○ Multiple imputation analysis

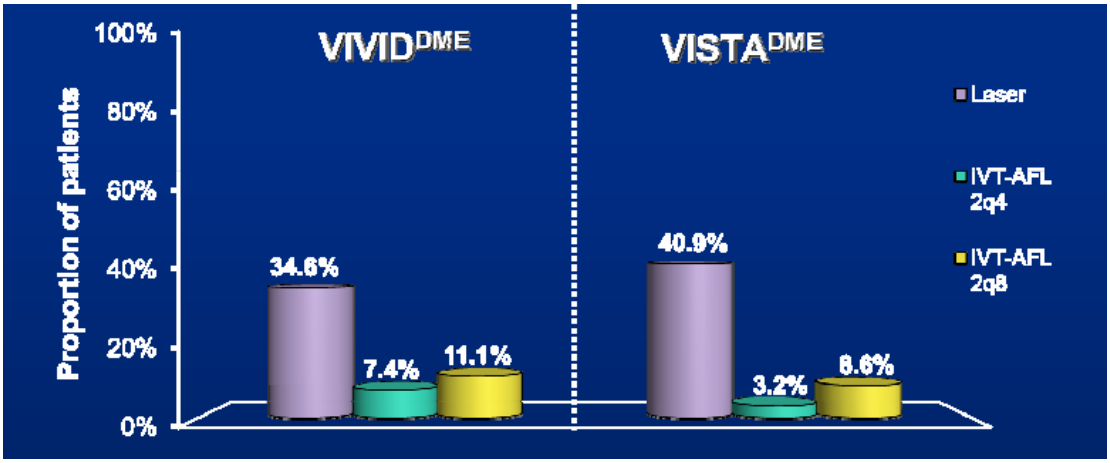
The proportion of patients requiring additional treatment from week 24 onwards was highest in the laser treatment arms of both VISTA (31.2%) and VIVID (24.2%).</td></tr>
</table>

Figure 3: Proportion of patients receiving Additional Treatment in VISTA and VIVID (from week 24 to week 52)(18)



2Q4=2mg aflibercept every 4 weeks by intravitreal injection; 2Q8=2mg aflibercept every 8 weeks by intravitreal injection

Figure 4: Proportion of patients receiving Additional Treatment in VISTA and VIVID (from week 24 to week 100)(25)



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.

In both studies, the pre-planned subgroup analyses were conducted by

- gender,
- age (<55 years, ≥55 to <65 years, ≥65 to <75 years, ≥75 years),

- race (VISTA: White, Black, African American, Other; VIVID: White, Asian),
- geographic region (VIVID: Japan, Europe/Australia)
- ethnicity (Hispanic or Latino no/yes),
- HbA1c (≤8%, >8%),
- baseline VA category (efficacy analyses only: < 40 letters, ≥ 40 to < 55 letters, ≥55 to <65 letters, ≥ 65 letters),
- history of hypertension,
- history of CVA/stroke,
- history of ischaemic heart disease,
- renal function,
- hepatic impairment.

Additional *post hoc* subgroup analyses were carried out in order to respond appropriately to the NICE scope / decision problem, and aid comparison with previous NICE appraisals. These were by:

- *baseline central retinal thickness (CRT),*
- *prior laser,*
- *prior cataract surgery (presence of pseudophakic lens), and*
- *prior anti-VEGF therapy (yes / no)*

No subgroup analysis was possible for loss of 10 or 15 letters. Losing 10 or 15 letters was extremely rare in the aflibercept treatment groups – across the aflibercept 2Q8 arms of VIVID and VISTA, only 5 patients (1.7%) lost 10 or more letters.

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.

See Figure 5, Figure 6, and Figure 7.

Figure 5: Patient disposition for VISTA (19;24;25)

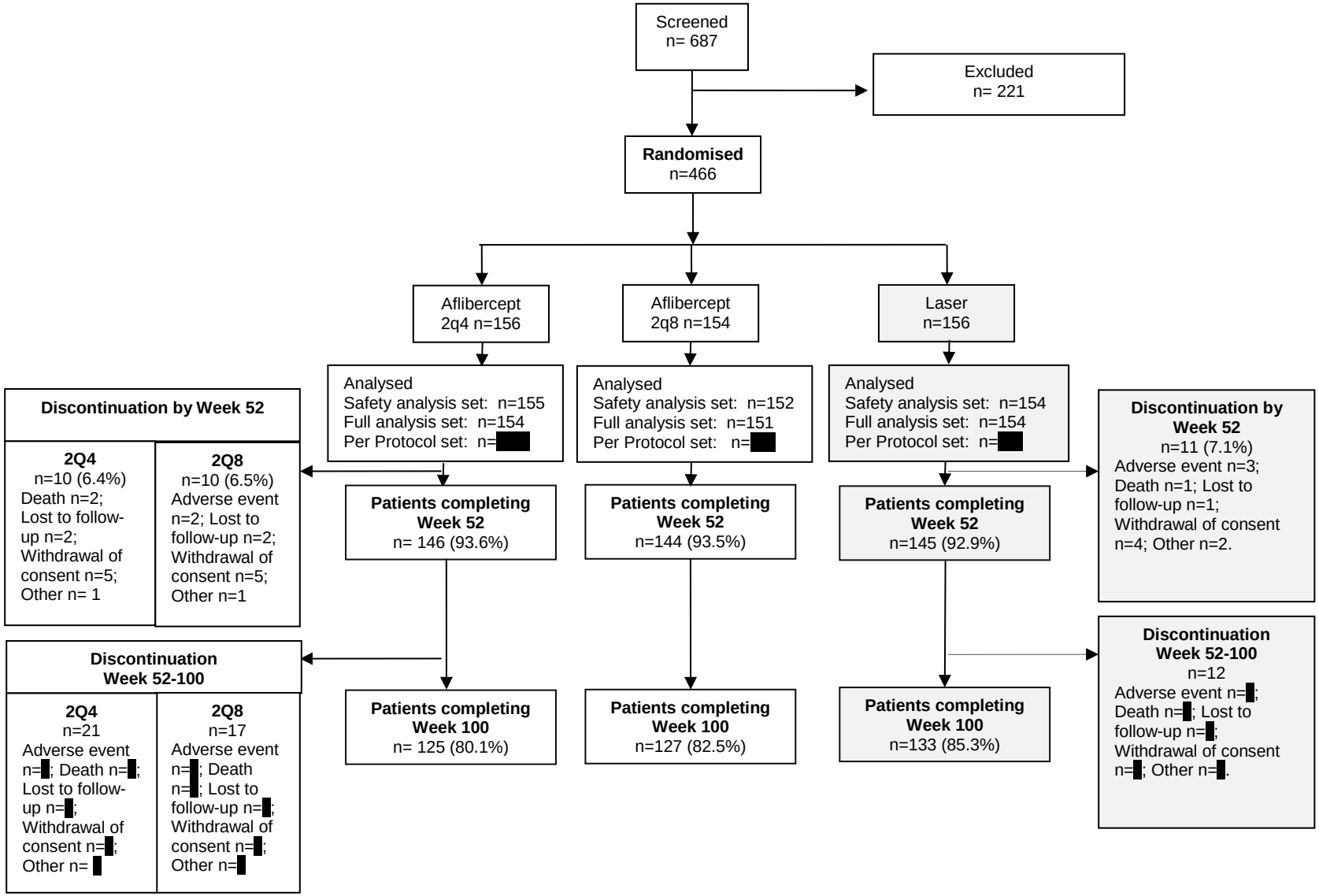


Figure 6: Patient disposition for VIVID (20;23;25)

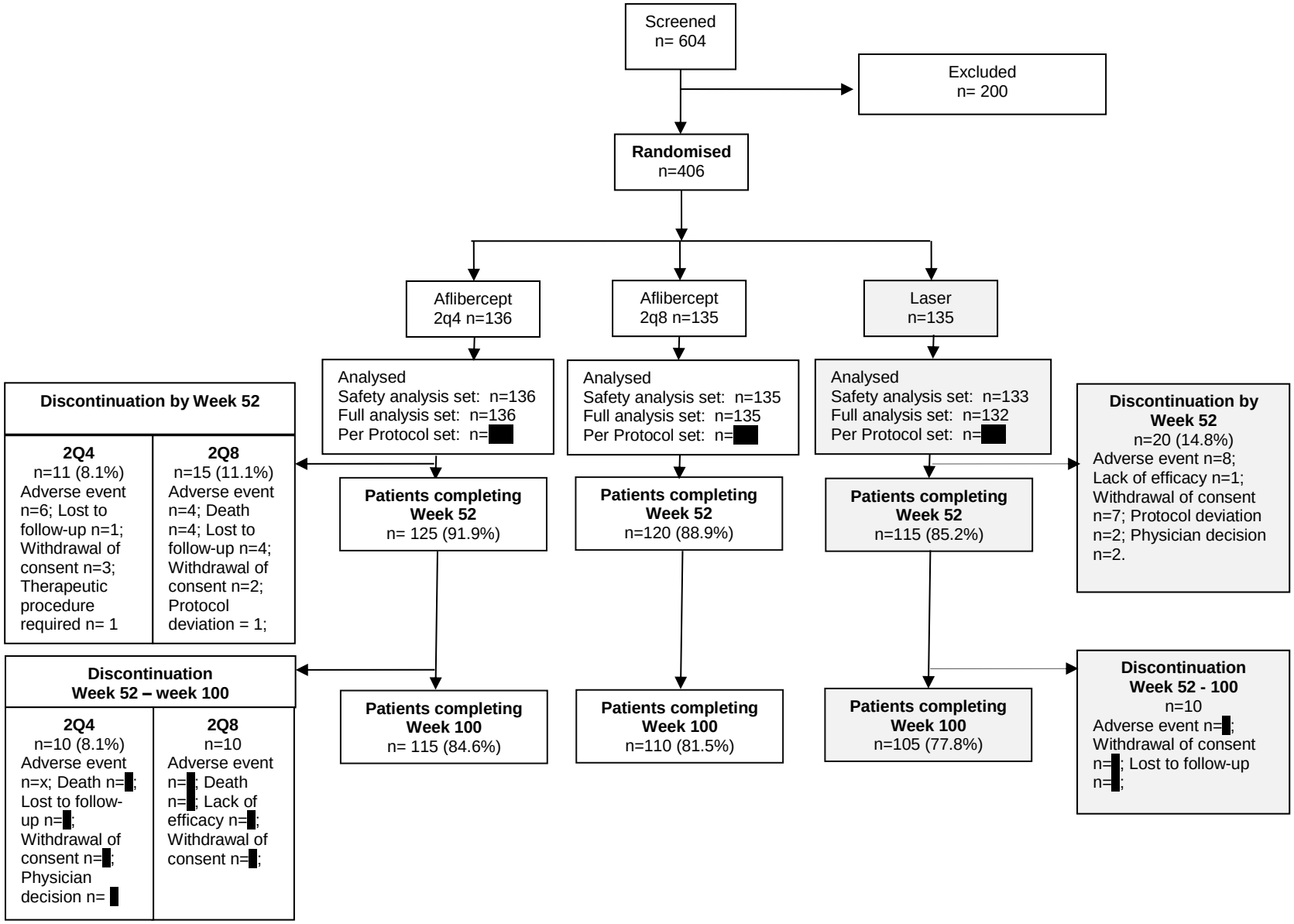
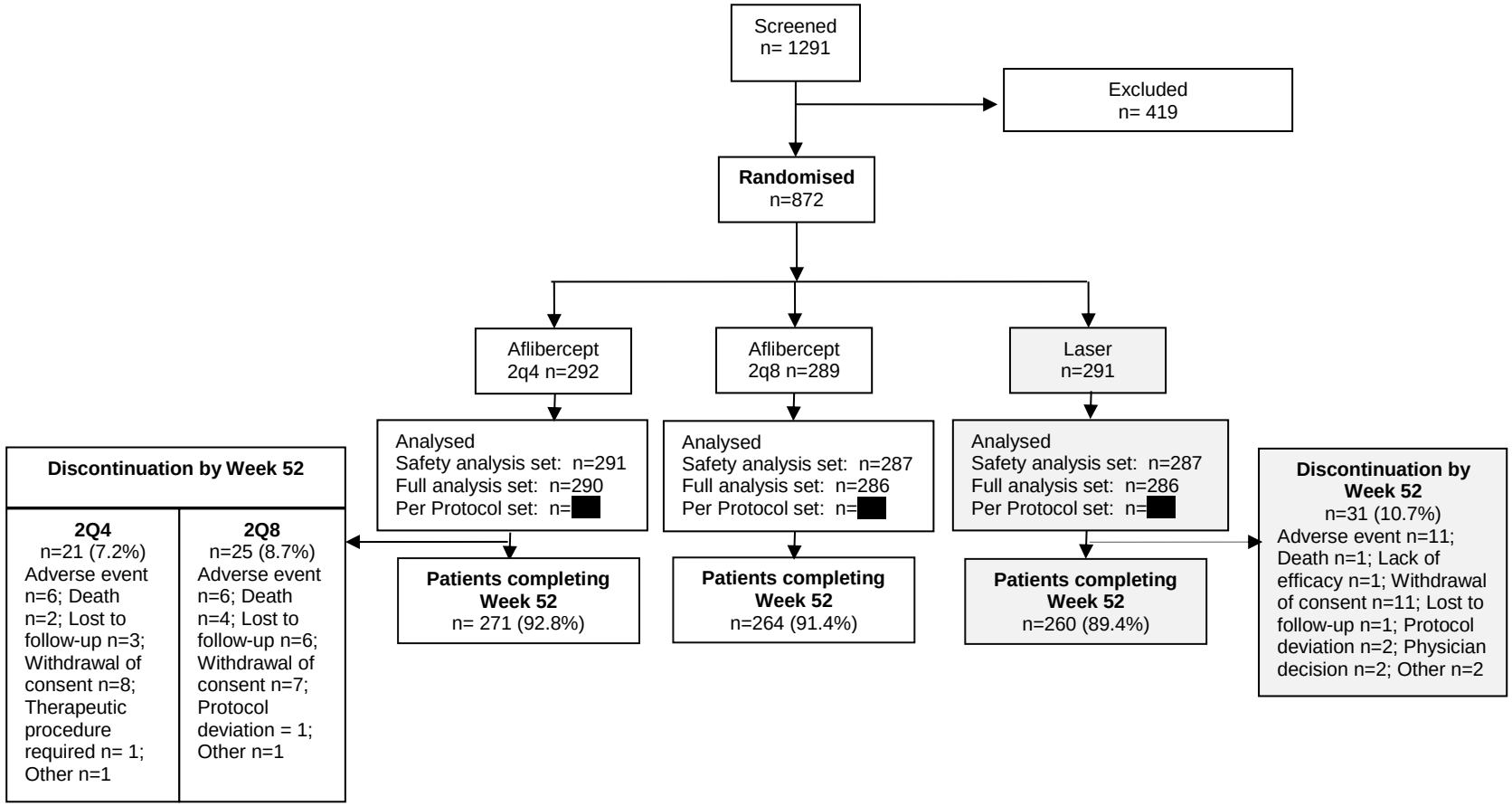


Figure 7: Patient disposition for the integrated analysis at week 52 of VISTA and VIVID studies (19;20)



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.

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 13. Quality assessment results for RCTs

Trial no. (acronym)	**VISTA**	**VIVID**
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 sets were reported (includes all randomised patients who received any study medication and had a baseline assessment and at least 1 BCVA assessment after baseline). Analysed as randomised. Missing or censored values were imputed using the last non-censored value (last observation carried forward [LOCF]). Several sensitivity analyses were performed to address the impact of missing data due to drop-outs or receipt of additional treatment.	

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 following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.

- Discuss and justify definitions of any clinically important differences.

Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

The efficacy results were positive and comparable across studies, and in the integrated analysis.

Of note, efficacy results in all pre-specified evaluable subgroups in each study and in the integrated analysis were consistent with the results in the overall populations. The same holds true for the full analysis set (FAS) versus the *per protocol* set (PPS) results which, where assessed, were very consistent.

Primary efficacy endpoint

Change from baseline in BCVA in ETDRS letter score at week 52

In both studies (VISTA and VIVID), aflibercept, administered as either a 2Q4 or 2Q8 regimen, was shown to be superior to laser treatment for the change from baseline in mean ETDRS letter score at week 52 (see Figure 8). The statistically significant improvements in BCVA compared to the laser group, were considered clinically meaningful (see Table 14).

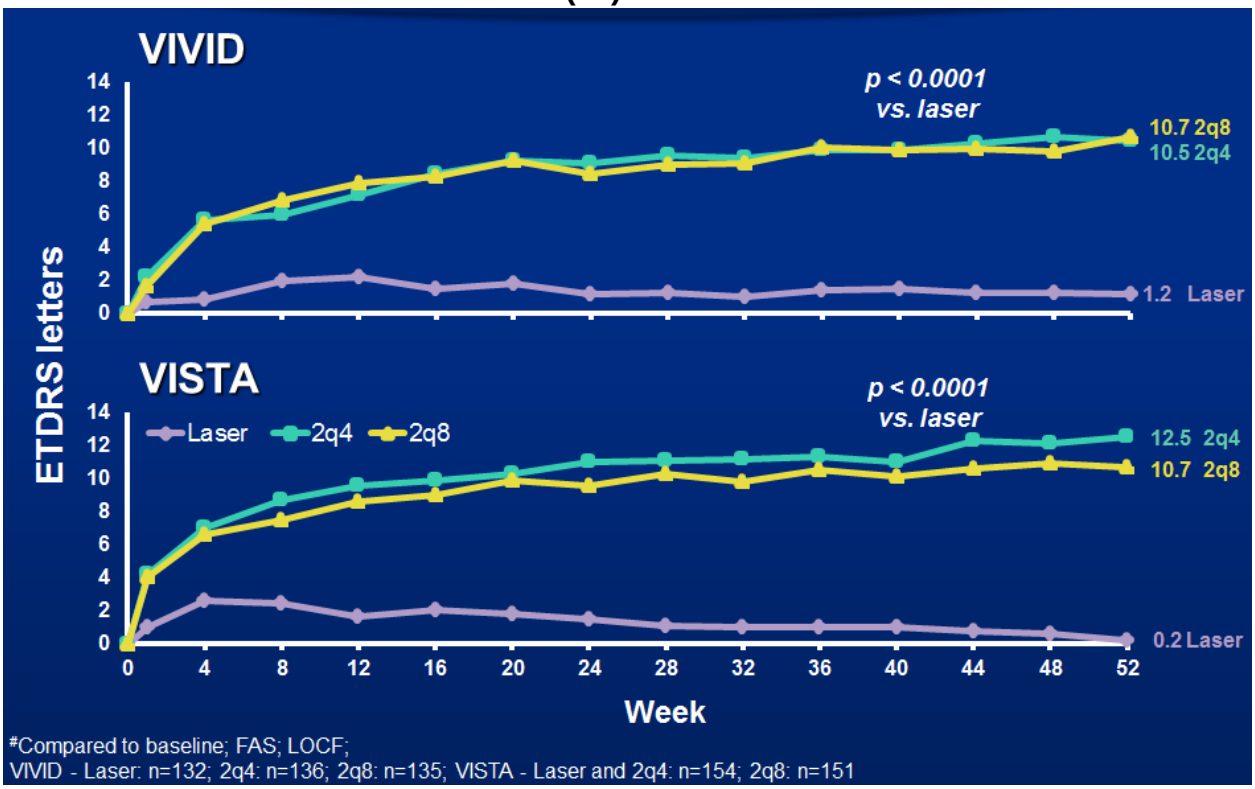
Improvement in BCVA was seen as early as day 3/week 1 in all treatment groups. There was sustained efficacy over the course of the 52 weeks with no decrease over time in the aflibercept groups, while the laser group plateaued by week 8. Notably, the mean number of letters gained in both of the aflibercept groups was similar at 6 months and 12 months, with no decrement during the second half of the study period.

VISTA: the mean changes were 12.5 letters in the 2Q4 group, 10.7 letters in the 2Q8 group, and 0.2 letters in the laser group. The 2Q4 and 2Q8 groups both received monthly doses through week 16 and showed similar efficacy through week 4, after which (except for the 20-week evaluation) the 2Q4 group showed a larger change from baseline through week 52. The differences seen through week 16, during which time both groups were dosed

identically, suggest that the slightly different response to treatment is not due to the effect of the drug regimen. The laser group showed improvement through week 8, and then gradually returned to the baseline value by week 52.

VIVID: the mean changes were 10.5 letters in the 2Q4 group, 10.7 letters in the 2Q8 group, and 1.2 letters in the laser group. The 2Q4 and 2Q8 groups had similar improvements through 52 weeks. The laser group showed improvement through week 12, and then gradually stabilised through week 52.

Figure 8: Mean change from baseline in BCVA in ETDRS letter score at week 52 for VISTA and VIVID studies (18)



INTEGRATED: As expected, in view of the robust and reproducible results from the individual studies, the pre-specified integrated analysis on the pooled data from both studies provided similar results (see Table 14) (26).

Figure 9: Mean change from baseline in BCVA in ETDRS letter score at week 52 for the integrated analysis of the VISTA and VIVID studies [FAS;LOCF] (27)

[IMAGE DELETED – ACADEMIC IN CONFIDENCE]

BCVA=best corrected visual acuity; VTE = intravitreal aflibercept; 2Q4 = 2mg aflibercept every 4 weeks; 2Q8 = 2mg aflibercept every 8 weeks, after 5 initial monthly doses;

Sensitivity analyses of primary efficacy endpoint
(To evaluate the impact of missing data and additional treatment)

All supportive sensitivity analyses conducted to assess the robustness of these results (i.e. PPS, OC, aLOCF, aOC) confirmed the findings of the primary analysis: Treatment with 2mg aflibercept, either once every 4 weeks or once every 8 weeks, provides similar levels of efficacy in the mean change in BCVA in patients with DMO. Both aflibercept treatments are superior to laser treatment. Few eyes (<10%) in the 2Q4 and 2Q8 groups required laser rescue and data from the time rescue laser was given was censored for the primary analysis (LOCF), thus eliminating any confounding influence from laser photocoagulation. When data after additional treatment was included in the analysis (aLOCF), similar improvements were observed in the mean BCVA for these groups, despite the fact that patients in the laser group improved substantially after initiating treatment with aflibercept.[redacted]

[redacted] See Table 15, Table 16, Table 17, and Table 18.

Table 14: Primary efficacy analysis of change in BCVA from baseline to week 52 (VISTA, VIVID and integrated analyses)[FAS, LOCF) (26)

Study	Treatment group	Baseline Means (SD)	Mean change (SD)	LS Mean Change (SE)	Contrast	P Value[1]	Estimate for comparison & 97.5% CI (LS mean)[1]
VISTA	VTE 2Q4 N=154	58.9 (10.77)	12.5 (9.54)	12.3 (0.76)	VTE 2Q4 vs. Laser	<0.0001	12.19 (9.35, 15.04)
	VTE 2Q8 N=151	59.4 (10.89)	10.7 (8.21)	10.6 (0.69)	VTE 2Q8 vs. Laser	<0.0001	10.45 (7.73, 13.17)
	Laser N=154	59.7 (10.95)	0.2 (12.53)	0.1 (1.03)			
VIVID	VTE 2Q4 N=136	60.8 (10.74)	10.5 (9.55)	10.2 (0.89)	VTE 2Q4 vs. Laser	<0.0001	9.25 (6.49, 12.02)
	VTE 2Q8 N=135	58.8 (11.23)	10.7 (9.32)	10.0 (0.85)	VTE 2Q8 vs. Laser	<0.0001	9.05 (6.35, 11.76)
	Laser N=132	60.8 (10.61)	1.2 (10.65)	0.9 (1.00)			
Integrated	VTE 2Q4 N=290	59.8 (10.78)	11.5 (9.58)	11.5 (0.55)	VTE 2Q4 vs. Laser	<0.0001	10.78 (8.79, 12.77)
	VTE 2Q8 N=286	59.1 (11.03)	10.7 (8.74)	10.6 (0.50)	VTE 2Q8 vs. Laser	<0.0001	9.85 (7.92, 11.77)
	Laser N=286	60.2 (10.79)	0.7 (11.69)	0.8 (0.70)			

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection

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

Table 15: Summary of Sensitivity analyses of change in BCVA from baseline to week 52 (FAS; integrated)

Study	Treatment group	Baseline Means (SD)	Mean change (SD)	LS Mean Change (SE)	Contrast	P Value[1]	Estimate for comparison & 97.5% CI (LS mean)[1]
LOCF	VTE 2Q4 N=290	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8 N=286				VTE 2Q8 vs. Laser		
	Laser N=286						
OC[2]	VTE 2Q4 N=251				VTE 2Q4 vs. Laser		
	VTE 2Q8 N=243				VTE 2Q8 vs. Laser		
	Laser N=179						
aLOCF[3]	VTE 2Q4 N=290				VTE 2Q4 vs. Laser		
	VTE 2Q8 N=286				VTE 2Q8 vs. Laser		
	Laser N=286						
aOC[4]	VTE 2Q4 N=261				VTE 2Q4 vs. Laser		
	VTE 2Q8 N=254				VTE 2Q8 vs. Laser		
	Laser N=253						

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection

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

[2] OC: observed case, censoring measurements after additional treatment was given.

[3] aLOCF: last observation carried forward, including measurements after additional treatment was given.

[4] aOC observed case, including measurements after additional treatment was given.

Table 16: Sensitivity analysis of change in BCVA from baseline to week 52 (VISTA, VIVID and integrated analyses)[FAS, OC[1])

Study	Treatment group	Baseline Means (SD)	Mean change (SD)	LS Mean Change (SE)	No of patients	Contrast	P Value[1]	Estimate for comparison & 97.5% CI (LS mean)[2]
VISTA	VTE 2Q4 N=154	[redacted]				VTE 2Q4 vs. Laser	[redacted]	
	VTE 2Q8 N=151					VTE 2Q8 vs. Laser		
	Laser N=154							
VIVID	VTE 2Q4 N=136					VTE 2Q4 vs. Laser	[redacted]	
	VTE 2Q8 N=135					VTE 2Q8 vs. Laser		
	Laser N=132							
Integrated	VTE 2Q4 N=290					VTE 2Q4 vs. Laser	[redacted]	
	VTE 2Q8 N=286					VTE 2Q8 vs. Laser		
	Laser N=286							

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection

[1] OC: observed case, censoring measurements after additional treatment was given.

[2] The CI with p-value for integrated study is based on treatment difference (aflibercept group vs. Laser) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment and Study as fixed factors.

Table 17: Sensitivity analysis of change in BCVA from baseline to week 52 (VISTA, VIVID and integrated analyses)[FAS, aLOCF[1])

Study	Treatment group	Baseline Means (SD)	Mean change (SD)	LS Mean Change (SE)	No of patients	Contrast	P Value[1]	Estimate for comparison & 97.5% CI (LS mean)[2]
VISTA	VTE 2Q4 N=154	[redacted]				VTE 2Q4 vs. Laser	[redacted]	
	VTE 2Q8 N=151					VTE 2Q8 vs. Laser		
	Laser N=154							
VIVID	VTE 2Q4 N=136					VTE 2Q4 vs. Laser	[redacted]	
	VTE 2Q8 N=135					VTE 2Q8 vs. Laser		
	Laser N=132							
Integrated	VTE 2Q4 N=290					VTE 2Q4 vs. Laser	[redacted]	
	VTE 2Q8 N=286					VTE 2Q8 vs. Laser		
	Laser N=286							

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection

[1] aLOCF: last observation carried forward, including measurements after additional treatment was given.
[2] The CI with p-value for integrated study is based on treatment difference (aflibercept group vs. Laser) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment and Study as fixed factors.

Table 18: Sensitivity analysis of change in BCVA from baseline to week 52 (VISTA, VIVID and integrated analyses)[FAS, aOC[1])

Study	Treatment group	Baseline Means (SD)	Mean change (SD)	LS Mean Change (SE)	No of patients	Contrast	P Value[1]	Estimate for comparison & 97.5% CI (LS mean)[2]
VISTA	VTE 2Q4 N=154	[redacted]				VTE 2Q4 vs. Laser	[redacted]	
	VTE 2Q8 N=151					VTE 2Q8 vs. Laser		
	Laser N=154							
VIVID	VTE 2Q4 N=136					VTE 2Q4 vs. Laser	[redacted]	
	VTE 2Q8 N=135					VTE 2Q8 vs. Laser		
	Laser N=132							
Integrated	VTE 2Q4 N=290					VTE 2Q4 vs. Laser	[redacted]	
	VTE 2Q8 N=286					VTE 2Q8 vs. Laser		
	Laser N=286							

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection
[1] aOC observed case, including measurements after additional treatment was given.
[2] The CI with p-value for integrated study is based on treatment difference (aflibercept group vs. Laser) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment and Study as fixed factors.

Subgroup analyses of the primary endpoint

Generally, results of the pre-specified evaluable subgroups on the change in BCVA from baseline to week 52 were [redacted] with those of the overall populations in both studies, and the integrated analysis. Some subgroups were [redacted]

For the integrated analysis, subgroup analyses of the primary and secondary endpoints are presented in detail by baseline VA category (pre-specified)(< 40 letters, ≥ 40 to < 55 letters, ≥55 to <65 letters, ≥ 65 letters), and (post hoc) baseline central retinal thickness (CRT), prior laser, prior cataract surgery

(presence of pseudophakic lens), and by prior anti-VEGF therapy (yes / no) *[see after results of secondary and additional efficacy endpoints]*.

In terms of baseline VA, there were only [redacted] patients across both studies with baseline VA ≥75 ETDRS letters.

Figure 10: Pre-specifed subgroup analysis of change in BCVA from baseline to week 52 (Integrated analysis; FAS; LOCF) (27)

[FIGURE DELETED – ACADEMIC IN CONFIDENCE]

[Figure deleted - CONTINUED]

Secondary & Tertiary endpoints

The results for all visual acuity and anatomic secondary efficacy variables (i.e. proportion of patients gaining ≥10 ETDRS letters from baseline (Figure 11), proportion of patients gaining ≥15 ETDRS letters from baseline (Figure 11), support the conclusion drawn from the primary variable that treatment with 2 mg aflibercept once every 4 weeks, or once every 8 weeks following 5 initial monthly doses, is superior to laser treatment.

As described in Table 11, statistical testing was performed sequentially according to the order that the variables were defined to control for multiplicity and to preserve an alpha size of 0.025. For the global SAP, all secondary variables were characterised in hierarchical manner as secondary endpoints. For the US SAP, the only secondary endpoint at week 52 was the proportion of subjects who gained ≥15 ETDRS letters from baseline - all other secondary variables were analysed in an exploratory manner at week 52. Integrated analyses of secondary variables were all considered exploratory, with no control for multiplicity.

In the VISTA and VIVID studies, clinically and statistically significant differences in favour of aflibercept treatment as compared with laser treatment were seen for the first 4 secondary variables (Table 19). With the exception of the near activities subscale for the 2Q4 group in the VISTA study, the analysis of the NEI VFQ-25 subscales was the first secondary endpoint at which the secondary efficacy analyses were no longer statistically significant. As a result, the hierarchical testing procedure of statistical hypothesis tests for superiority of aflibercept was [redacted]

In the integrated analysis, superior efficacy was also [redacted] aflibercept treatment as compared with laser treatment, for the first [redacted] secondary variables (Table 19).

Improvement in the **proportion of patients who gained ≥ 10 ETDRS letters** and **proportion of patients who gained ≥ 15 ETDRS letters** was seen [redacted] in the aflibercept treatment groups, and for the laser group, [redacted]

In all treatment groups, **a ≥ 2-step improvement on the DRSS** was seen [redacted] This is a meaningful outcome for patients. It has been shown that patients with worsened DRSS are significantly more likely to develop proliferative diabetic retinopathy (DR) and associated vision-threatening events (28). A slowing or reversing of the progression of DR, as demonstrated by an improvement in DRSS, should reduce the risk of significant vision loss.

The aflibercept groups demonstrated a robust and quick **reduction in CRT** beginning at the first post-baseline measurement at week 4 that [redacted] At baseline, CRT (as measured by OCT) was comparable among treatment groups in the FAS in the VISTA study and slightly higher in the laser group than the aflibercept groups in the VIVID study. Small fluctuations were observed in the mean change from baseline in

CRT (ranging from 12 - 22µm [VISTA] and 16.3 - 35.5µm [VIVID]) once 2Q8 administration began; despite these fluctuations, mean change in BCVA from week 20 to week 52 for the 2Q8 groups in both studies were similar to that in the 2Q4 groups. Similar fluctuations in CRT have been observed in other studies where aflibercept was administered in a 2Q8 regimen, with no material impact on ultimate visual improvements (29).

All treatment groups, except the 2Q4 and laser groups in VIVID, experienced a clinically meaningful **change in the scores for NEI VFQ-25 near and distance activities subscales** (approximately 5 or more points in mean change from baseline) at week 52 (Figure 12). Mean changes from baseline in the NEI VFQ-25 near activities subscale and in the NEI VFQ-25 distance activities subscale mostly showed trends in favour of aflibercept in both studies (except the 2Q4 group in VIVID); and the 2Q4 group in the VISTA study had a statistically significant difference compared with laser.

EQ5D data was collected mainly for the purposes of economic evaluation for health technology assessments (HTA) that have a preference for generic-based quality of life measures. The mean change total score from baseline to 52 weeks in VIVID, the European arm of the study, was [redacted] in the laser, 2Q4 and 2Q8 groups respectively. Some data was collected for VISTA but not analysed as part of the clinical analyses. The EQ5D results and their limitations are further discussed in the context of the economic modelling in this submission.

Sensitivity analyses of the secondary endpoints

(To evaluate the impact of missing data and additional treatment)

All sensitivity analyses including OC, aLOCF, and aOC, showed [redacted] o the FAS LOCF analyses for the aflibercept groups. The laser group had [redacted] in the proportion of patients experiencing an increase in ETDRS letter score of at least 10 letters at week 52 using these methods compared to the LOCF method.

For the change in CRT, in both the aLOCF and aOC analyses, [redacted] between aflibercept groups and the laser group [redacted] results were [redacted] the aflibercept groups.

Subgroup analyses of the secondary endpoints

Results for the evaluable prespecified subgroups were also [redacted] with those of the overall population. Some subgroups were [redacted] to provide the necessary power to draw conclusions.

For the integrated analysis, subgroup analyses of the primary and secondary endpoints are presented in detail by baseline VA category (pre-specified)(< 40 letters, ≥ 40 to < 55 letters, ≥55 to <65 letters, ≥ 65 letters), and (post hoc) baseline central retinal thickness (CRT), prior laser, prior cataract surgery (presence of pseudophakic lens), and by prior anti-VEGF therapy (yes / no) *[see after results of secondary and additional efficacy endpoints]*.

Note: No subgroup analysis was possible for loss of 10 or 15 letters. Losing 10 or 15 letters was extremely rare in the aflibercept treatment groups – across the aflibercept 2Q8 arms of VIVID and VISTA, only 5 patients (1.7%) lost 10 or more letters.

Table 19: Secondary efficacy variables – Results from baseline to week 52 in VISTA, VIVID and the integrated analyses of both studies (FAS; LOCF) (18;26;27)

Variable	Laser			Aflibercept					
				2Q4			2Q8		
	VISTA	VIVID	Integrated	VISTA	VIVID	Integrated	VISTA	VIVID	Integrated
Patients gaining ≥ 10 letters									
n	154	132	286	154	136	290	151	135	286
Number (%) gaining ≥ 10 letters	30 (19.5)	34 (25.8)	64 (22.4)	100 (64.9)	74 (54.4)	174 (60.0)	88 (58.3)	72 (53.3)	160 (55.9)
Adjusted difference vs. Laser[1]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(97.5% confidence interval) [1]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p value				<0.0001	<0.0001	[redacted]	<0.0001	<0.0001	[redacted]
Patients gaining ≥ 15 letters[2]									
n	154	132	286	154	136	290	151	135	286
Number (%) gaining ≥ 15 letters	12 (7.8)	12 (9.1)	24 (8.4)	64 (41.6)	44 (32.4)	108 (37.2)	47 (31.1)	45 (33.3)	92 (32.2)
Adjusted difference vs. Laser[1]				34.2	23.3	[redacted]	23.3	24.2	[redacted]
(97.5% confidence interval) [1]				(24.1, 44.4)	(12.6, 33.9)	[redacted]	(13.5, 33.1)	(13.5, 34.9)	[redacted]
p value				<0.0001	<0.0001	[redacted]	<0.0001	<0.0001	[redacted]
Patients with ≥ 2-step ETDRS improvement									
n	154	132	286	154	136	290	151	135	286
Number (%) with ≥ 2-step ETDRS improvement[3]	22/154 (14.3)	6/80 (7.5)	28/234 (12.0)	52/154 (33.8)	27/81 (33.3)	79/235 (33.6)	44/151 (29.1)	23/83 (27.7)	67/234 (28.6)
Adjusted difference vs. Laser[1]				19.7	25.8	[redacted]	14.9	19.3	[redacted]
(97.5% confidence interval) [1]				(9.0, 30.4)	(12.2, 39.4)	[redacted]	(4.4, 25.4)	(6.6, 32.1)	[redacted]
p value				<0.0001	<0.0001	[redacted]	0.0017	0.0006	[redacted]
Change in CRT (by OCT)									
n	154	132	286	154	136	290	151	135	286
Mean change in µm in CRT (SE)	-73.3 (176.72)	-66.2 (138.99)	[redacted]	-186 (150.68)	-195.0 (146.59)	[redacted]	-183 (153.50)	-192 (149.89)	[redacted]
LS mean change in µm in CRT (SE)	-73.3 (12.09)	-53.1 (14.14)	[redacted]	-184.1 (6.57)	-210.1 (7.45)	[redacted]	-186.8 (6.90)	-196.0 (9.64)	[redacted]
Estimate for contrast vs. Laser				-110.78	-156.98	[redacted]	-113.47	-142.82	[redacted]

Variable	Laser			Aflibercept					
				2Q4			2Q8		
	VISTA	VIVID	Integrated	VISTA	VIVID	Integrated	VISTA	VIVID	Integrated
(97.5% confidence interval)				(-141.34, -80.22)	(-190.89, -123.07)	[redacted]	(-144.19, -82.75)	(-179.31, -106.33)	[redacted]
p value				<0.0001	<0.0001	[redacted]	<0.0001	<0.0001	<0.0001
Change in NEI VFQ-25 near activities score									
n	154	132	286	154	136	290	151	135	286
n Evaluable	151	120	271	146	128	274	146	134	280
Mean change in near activities score (SD)	5.4 (20.44)	3.5 (16.77)	[redacted]	9.0 (20.60)	5.7 (18.93)	[redacted]	9.4 (18.50)	5.3 (19.06)	[redacted]
LS mean change in near activities score (SE)	3.7 (1.55)	2.8 (1.52)	[redacted]	8.9 (1.58)	5.2 (1.55)	[redacted]	8.1 (1.44)	1.6 (1.64)	[redacted]
Estimate for contrast vs. Laser				5.19	2.41	[redacted]	4.36	-1.21	[redacted]
(97.5% confidence interval)				(0.33, 10.04)	(-2.01, 6.82)	[redacted]	(-0.21, 8.93)	(-5.79, 3.37)	[redacted]
p value				0.0168	0.2208	[redacted]	0.0323	0.5537	[redacted]
Change in NEI VFQ-25 distance activities score									
n	154	132	286	154	136	290	151	135	286
n Evaluable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in distance activities score (SD)	6.7 (19.85)	2.3 (15.92)	[redacted]	8.6 (20.99)	0.9 (16.49)	[redacted]	7.3 (19.32)	5.3 (18.47)	[redacted]
LS mean change in distance activities score (SE)	4.9 (1.44)	0.7 (1.46)	[redacted]	7.7 (1.57)	-0.5 (1.38)	[redacted]	6.5 (1.48)	0.3 (1.57)	[redacted]
Estimate for contrast vs. Laser				2.86	-1.19	[redacted]	1.65	-0.37	[redacted]
(97.5% confidence interval)				(-1.82, 7.54)	(-5.29, 2.91)	[redacted]	(-2.83, 6.13)	(-4.79, 4.05)	[redacted]
p value				0.1702	0.5138	[redacted]	0.4067	0.8498	[redacted]

2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection; CRT=Central retinal thickness; DRSS=Diabetic retinopathy severity scale; ETDRS=Early Treatment Diabetic Retinopathy Study; IOP=intraocular pressure; LS = least squared; NEI VFQ-25=National Eye Institute Visual Functioning Questionnaire-25; OCT=Optical coherence tomography.

[1]Difference with CI is calculated using Mantel-Haenszel weighting scheme

[2]This is the only secondary endpoint defined for the US SAP

[3]Denominator is number of evaluable patients

Figure 11: Proportion of patients gaining ≥10 and ≥15 letters in the VISTA and VIVID studies (18)

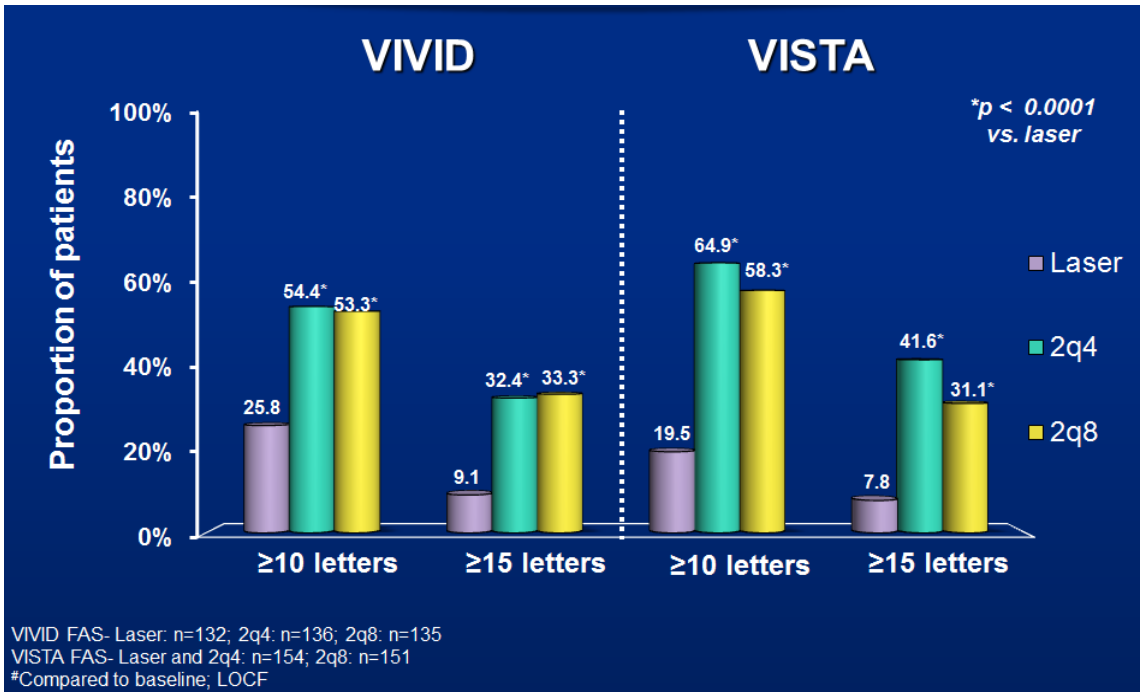


Figure 12: Mean change in NEI VFQ-25 scale for near and distance subscale scores (VISTA and VIVID) (18)

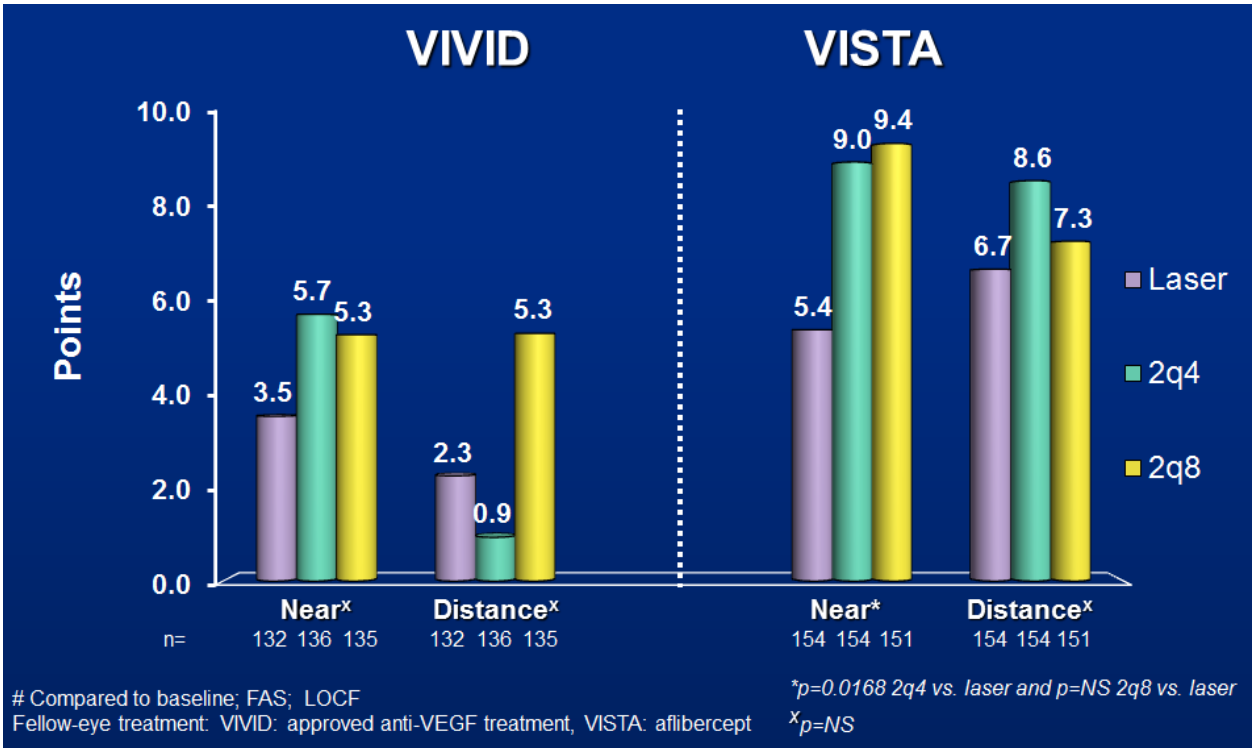


Table 20: Summary of Sensitivity analyses of Proportion of patients gaining ≥ 10 letters in BCVA from baseline at week 52 (FAS; VISTA, VIVID) *

Analysis	Treatment group		Patients gaining ≥ 10 letters at Week 52 n (%)		Adjusted difference (%) (97.5% C.I.)[1]		CMH test[2] p-value	
	VISTA	VIVID	VISTA	VIVID	VISTA	VIVID	VISTA	VIVID
LOCF	VTE 2Q4 N=154	VTE 2Q4 N=136	100 (64.9)	74/136 (54.4)	[redacted]	[redacted]	<0.0001	<0.0001
	VTE 2Q8 N=151	VTE 2Q8 N=135	88 (58.3)	72/135 (53.3)	[redacted]	[redacted]	<0.0001	<0.0001
	Laser N=154	Laser N=132	30 (19.5)	34/132 (25.8)				
OC[3]	VTE 2Q4 N=154	VTE 2Q4 N=136	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0182
	VTE 2Q8 N=151	VTE 2Q8 N=135	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0013
	Laser N=154	Laser N=132	[redacted]	[redacted]				
aLOCF[3]	VTE 2Q4 N=154	VTE 2Q4 N=136	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8 N=151	VTE 2Q8 N=135	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser N=154	Laser N=132	[redacted]	[redacted]				
aOC[4]	VTE 2Q4 N=154	VTE 2Q4 N=136	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8 N=151	VTE 2Q8 N=135	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser N=154	Laser N=132	[redacted]	[redacted]				

*Note: sensitivity analysis of the integrated data was undertaken for regulatory purposes and did not cover all secondary outcomes.
VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection
[1] Difference with confidence interval (C.I.) is calculated using Mantel-Haenszel weighting scheme adjusted by VISTA: medical history of MI or CVA, VIVID: geographical region
[2] P-value is calculated using 2-sided Cochran-Mantel-Haenszel (CMH) test adjusted VISTA: medical history of MI or CVA, VIVID: geographical region
[3] OC: observed case, censoring measurements after additional treatment was given.
[3] aLOCF: last observation carried forward, including measurements after additional treatment was given.
[4] aOC observed case, including measurements after additional treatment was given.

Additional efficacy variables

A number of additional efficacy variables were analysed in support of the results for the primary and secondary variables of the pivotal studies.

Overall, the results for these additional variables were consistent between studies and with the integrated analysis. All aflibercept treatment groups showed beneficial effects in terms of efficacy, with little difference between groups. Taken together, the results for the additional efficacy variables support the findings obtained from the primary and secondary efficacy variables.

Table 21 presents the results for **the proportion of patients gaining ≥0 and ≥5 letters** and **the proportions of patients losing ≥5, ≥10, and ≥15 ETDRS letters from baseline**. At week 52, the 2Q4 and 2Q8 groups in both studies showed greater proportion of patients gaining ≥ 0 and ≥ 5 ETDRS letters compared to the laser group. At week 52, the 2Q4 and 2Q8 groups in both studies showed a smaller proportion of patients losing ≥ 5, ≥ 10, and ≥ 15 ETDRS letters compared to the laser group.

The 2Q4 and 2Q8 treatment groups were numerically superior to the laser group in the NEI VFQ-25 Total score at week 52 in both VISTA and VIVID (see Table 21), although the differences in the change from baseline in the NEI VFQ-25 total score at week 52 compared to the laser group were not significant.

There were minimal **changes from baseline in EQ-5D Total score** in each of the treatment groups (see Table 21).

Note: No subgroup analysis was possible for loss of 10 or 15 letters. Losing 10 or 15 letters was extremely rare in the aflibercept treatment groups – across the aflibercept 2Q8 arms of VIVID and VISTA, only 5 patients (1.7%) lost 10 or more letters.

Table 21: Additional efficacy endpoints – Results from baseline to week 52 in VISTA, VIVID and the integrated analyses of both studies (FAS; LOCF) (19;20;27)

Variable	Laser			Aflibercept					
				2Q4			2Q8		
	VISTA	VIVID	Integrated	VISTA	VIVID	Integrated	VISTA	VIVID	Integrated
Patients gaining ≥ 0 ETDRS letters									
n	154	132	286	154	136	290	151	135	286
Number (%) gaining ≥ 0 letters									
Adjusted difference vs. Laser[1]									
(97.5% confidence interval) [1]									
p value[2]									
Patients gaining ≥ 5 letters									
n	154	132	286	154	136	290	151	135	286
Number (%) gaining ≥ 5 letters									
Adjusted difference vs. Laser[1]									
(97.5% confidence interval) [1]									
p value[2]									
Patients losing ≥ 5 letters									
n	154	132	286	154	136	290	151	135	286
Number (%) losing ≥ 5 letters									
Adjusted difference vs. Laser[1]									
(97.5% confidence interval) [1]									
p value[2]									
Patients losing ≥ 10 letters									
n	154	132	286	154	136	290	151	135	286
Number (%) losing ≥ 10 letters									
Adjusted difference vs. Laser[1]									
(97.5% confidence interval) [1]									
p value[2]									
Patients losing ≥ 15 letters									
n	154	132	286	154	136	290	151	135	286
Number (%) losing ≥ 15 letters									
Adjusted difference vs. Laser[1]									
(97.5% confidence interval) [1]									

Variable	Laser			Aflibercept					
				2Q4			2Q8		
	VISTA	VIVID	Integrated	VISTA	VIVID	Integrated	VISTA	VIVID	Integrated
p value[2]									
Patients with a ≥2-step worsening on DRSS									
n	154	80	234	154	81	235	151	83	234
Number (%) worsening ≥ 2 steps on DRSS									
Adjusted difference vs. Laser[1]									
(97.5% confidence interval) [1]									
p value[2]									
Patients with a ≥3-step worsening on DRSS									
n	154	80	234	154	81	235	151	83	234
Number (%) worsening ≥ 3 steps on DRSS									
Adjusted difference vs. Laser[1]									
(97.5% confidence interval) [1]									
p value[2]									
Patients with a ≥3-step improvement on DRSS									
n	154	80	234	154	81	235	151	83	234
Number (%) improving ≥ 3 steps on DRSS									
Adjusted difference vs. Laser[1]									
(97.5% confidence interval) [1]									
p value[2]									
Change in NEI VFQ-25 Total score									
N	154	132	286	154	136	290	151	135	286
n Evaluable									
Mean change in Total score (SD)									
LS mean change in Total score (SE)									
Estimate for contrast vs. Laser									
(97.5% confidence interval)									
p value									

Variable	Laser			Aflibercept					
				2Q4			2Q8		
	VISTA	VIVID	Integrated	VISTA	VIVID	Integrated	VISTA	VIVID	Integrated
Change in EQ-5D Total score									
N	154	132		154	136		151	135	
n Evaluable									
Mean change from baseline (SD)									
Median									
Min - Max									

2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection; DRSS=Diabetic retinopathy severity scale; ETDRS=Early Treatment Diabetic Retinopathy Study; LS = least squared; NEI VFQ-25=National Eye Institute Visual Functioning Questionnaire-25; NR=not reported; SD=standard deviation

[1]Difference with CI is calculated using Mantel-Haenszel weighting scheme

[2] p-value was calculated using 2-sided Cochran-Mantel-Haenszel test

Subgroup analyses in integrated data from the VISTA and VIVID studies

Where available, for the integrated analysis, subgroup analyses of the primary and secondary endpoints are presented in detail (by endpoint) for baseline VA category (< 40 letters, ≥ 40 to < 55 letters, ≥55 to <65 letters, ≥ 65 letters), baseline CRT (≤400µm, >400µm), prior laser, prior cataract surgery (presence of pseudophakic lens), and by prior anti-VEGF therapy (yes / no). Analyses by baseline VA was a pre-specified subgroup analysis. Analyses by baseline CRT, prior laser, cataract surgery or anti-VEGF therapy were post hoc analyses.

Generally, results consistent with analyses in the overall population are seen in the subgroup analyses. Caution should be applied in interpretation of results where subgroups are small. For example, there were only [redacted] across the VISTA and VIVID studies with a baseline BCVA ≥ 75 letters.

Visual and anatomic improvements over laser with both aflibercept regimens in **subgroups of patients with and without prior anti-VEGF** therapy were similar and as robust as those seen in the total patient population. In the individual studies this was also the case; although in the VIVID study the subgroup of patients who had received prior anti-VEGF therapy was small, reflecting a relative limitation of access to anti-VEGF treatments in countries where the VIVID study was conducted(24).

Table 22: Subgroup Analysis of primary endpoint (Change in BCVA from baseline to week 52) [integrated analysis of VISTA and VIVID studies, FAS; LOCF] (27)(data on file)

Population	Treatment group	Number of patients	Baseline Means (SD)	Mean change (SD)	LS Mean Change (SE)	Contrast	P Value[1]	Estimate for comparison & 95% CI (LS mean) [2]
Overall population	VTE 2Q4	N=290	59.8 (10.78)	11.5 (9.58)	11.5 (0.55)	VTE 2Q4 vs. Laser	<0.0001	10.78 (8.79, 12.77)
	VTE 2Q8	N=286	59.1 (11.03)	10.7 (8.74)	10.6 (0.50)	VTE 2Q8 vs. Laser	<0.0001	9.85 (7.92, 11.77)
	Laser	N=286	60.2 (10.79)	0.7 (11.69)	0.8 (0.70)			
BCVA < 40	VTE 2Q4	[redacted]	For analysis of primary endpoint by BCVA category, see Forest plots following this table (Figure 13)					
	VTE 2Q8	[redacted]						
	Laser	[redacted]						
BCVA ≥ 40 - < 55	VTE 2Q4	[redacted]						
	VTE 2Q8	[redacted]						
	Laser	[redacted]						
BCVA ≥ 55 - < 65	VTE 2Q4	[redacted]						
	VTE 2Q8	[redacted]						
	Laser	[redacted]						
BCVA ≥ 65	VTE 2Q4	[redacted]						
	VTE 2Q8	[redacted]						
	Laser	[redacted]						
Baseline CRT <400µm	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser	[redacted]	[redacted]	[redacted]	[redacted]			
Baseline CRT ≥400µm	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser	[redacted]	[redacted]	[redacted]	[redacted]			
Prior laser	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser	[redacted]	[redacted]	[redacted]	[redacted]			
No prior laser	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser	[redacted]	[redacted]	[redacted]	[redacted]			
Prior cataract surgery (pseudophakic)	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser	[redacted]	[redacted]	[redacted]	[redacted]			
No prior cataract surgery (phakic)	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser	[redacted]	[redacted]	[redacted]	[redacted]			
Prior anti-VEGF therapy	VTE 2Q4	N=74	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	11.8 (7.6, 15.9)
	VTE 2Q8	N=83	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	11.7 (8.1, 15.4)

Population	Treatment group	Number of patients	Baseline Means (SD)	Mean change (SD)	LS Mean Change (SE)	Contrast	P Value[1]	Estimate for comparison & 95% CI (LS mean) [2]
			[redacted]		[redacted]			
	Laser	N=76	[redacted]	[redacted]	[redacted]			
No prior anti-VEGF therapy	VTE 2Q4	N=216	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	10.5 (8.2, 12.8)
	VTE 2Q8	N=203	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	9.2 (6.9, 11.4)
	Laser	N=210	[redacted]	[redacted]	[redacted]			

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection
1 F-test, H0: No difference between treatment groups.
2 The contrast is VTE group – Laser. ANCOVA model with baseline measurement as covariable and treatment group, study, subgroup and treatment group*subgroup as fixed factors was used.

Figure 13: Analysis of primary endpoint by baseline VA category subgroups (integrated data from VISTA and VIVID studies)(FAS; LOCF) (Pre-specified analysis)

[IMAGE DELETED – ACADEMIC IN CONFIDENCE]

Table 23: Subgroup Analysis of the proportion of patients gaining ≥ 10 letters from baseline at week 52) [integrated analysis of VISTA and VIVID studies, FAS; LOCF] (27)(data on file)

Population	Treatment group	Number of patients	Number (%) gaining ≥ 10 letters	Adjusted difference vs. Laser[1]	(97.5% confidence interval) [1]	p value[2]
Overall population	VTE 2Q4	N=290	174 (60.0)	[redacted]	[redacted]	[redacted]
	VTE 2Q8	N=286	160 (55.9)	[redacted]	[redacted]	[redacted]
	Laser	N=286	64 (22.4)			
BCVA < 40	VTE 2Q4	[redacted]	For analysis of this endpoint by BCVA category, see Forest plots following this table (Figure 14)			
	VTE 2Q8	[redacted]				
	Laser	[redacted]				
BCVA ≥ 40 - < 55	VTE 2Q4	[redacted]				
	VTE 2Q8	[redacted]				
	Laser	[redacted]				
BCVA ≥ 55 - < 65	VTE 2Q4	[redacted]				
	VTE 2Q8	[redacted]				
	Laser	[redacted]				
BCVA ≥ 65	VTE 2Q4	[redacted]				
	VTE 2Q8	[redacted]				
	Laser	[redacted]				
Baseline CRT <400µm	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
Baseline CRT ≥400µm	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
Prior laser	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
No prior laser	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
Prior cataract surgery (pseudophakic)	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
No prior cataract surgery (phakic)	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
Prior anti-VEGF therapy	VTE 2Q4	N=74	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	N=83	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	N=76	[redacted]			

Population	Treatment group	Number of patients	Number (%) gaining ≥ 10 letters	Adjusted difference vs. Laser[1]	(97.5% confidence interval) [1]	p value[2]
No prior anti-VEGF therapy	VTE 2Q4	N=216	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	N=203	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	N=210	[redacted]			

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection
[1]Difference with CI is calculated using Mantel-Haenszel weighting scheme.
[2] Cochran-Mantel-Haenszel test controlling for study for each subgroup and controlling for study and subgroup for overall test

Figure 14: Analysis of secondary endpoint - proportion of patients gaining ≥10 letters from baseline at week 52 - by baseline VA category subgroups (integrated data from VISTA and VIVID studies)(FAS; LOCF) (Pre-specified analysis)

[IMAGE DELETED – ACADEMIC IN CONFIDENCE]

Table 24: Subgroup Analysis of the proportion of patients gaining ≥ 15 letters from baseline at week 52 [integrated analysis of VISTA and VIVID studies, FAS; LOCF] (27)(data on file)

Population	Treatment group	Number of patients	Number (%) gaining ≥ 10 letters	Adjusted difference vs. Laser[1]	(97.5% confidence interval) [1]	p value[2]
Overall population	VTE 2Q4	N=290	108 (37.2)	[redacted]	[redacted]	[redacted]
	VTE 2Q8	N=286	92 (32.2)	[redacted]	[redacted]	[redacted]
	Laser	N=286	24 (8.4)			
BCVA < 40	VTE 2Q4	[redacted]	For analysis of this endpoint by BCVA category, see Forest plots following this table (Figure **15**)			
	VTE 2Q8	[redacted]				
	Laser	[redacted]				
BCVA ≥ 40 - < 55	VTE 2Q4	[redacted]				
	VTE 2Q8	[redacted]				
	Laser	[redacted]				
BCVA ≥ 55 - < 65	VTE 2Q4	[redacted]				
	VTE 2Q8	[redacted]				
	Laser	[redacted]				
BCVA ≥ 65	VTE 2Q4	[redacted]				
	VTE 2Q8	[redacted]				
	Laser	[redacted]				
Baseline CRT <400µm	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
Baseline CRT ≥400µm	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
Prior laser	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
No prior laser	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
Prior cataract surgery (pseudophakic)	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			

Population	Treatment group	Number of patients	Number (%) gaining ≥ 10 letters	Adjusted difference vs. Laser[1]	(97.5% confidence interval) [1]	p value[2]
No prior cataract surgery (phakic)	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
Prior anti-VEGF therapy	VTE 2Q4	N=74	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	N=83	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	N=76	[redacted]			
No prior anti-VEGF therapy	VTE 2Q4	N=216	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	N=203	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	N=210	[redacted]			

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection
[1]Difference with CI is calculated using Mantel-Haenszel weighting scheme.
[2] Cochran-Mantel-Haenszel test controlling for study for each subgroup and controlling for study and subgroup for overall test

Figure 15: Analysis of secondary endpoint - proportion of patients gaining ≥15 letters from baseline at week 52 - by baseline VA category subgroups (integrated data from VISTA and VIVID studies)(FAS; LOCF) (Pre-specified analysis)

[IMAGE DELETED – ACADEMIC IN CONFIDENCE]

Table 25: Subgroup Analysis of the patients with ≥ 2-step ETDRS improvement [integrated analysis of VISTA and VIVID studies, FAS; LOCF] (27)(data on file)

Population	Treatment group	Number of patients	Number (%) gaining ≥ 10 letters	Adjusted difference vs. Laser[1]	(97.5% confidence interval) [1]	p value[2]
Overall population	VTE 2Q4	N=290	79/235 (33.6)	[redacted]	[redacted]	[redacted]
	VTE 2Q8	N=286	67/234 (28.6)	[redacted]	[redacted]	[redacted]
	Laser	N=286	28/234 (12.0)			
BCVA < 40	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
BCVA ≥ 40 - < 55	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
BCVA ≥ 55 - < 65	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
BCVA ≥ 65	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
Baseline CRT <400µm	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
Baseline CRT ≥400µm	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
Prior laser	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
No prior laser	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
Prior cataract surgery (pseudophakic)	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			

Population	Treatment group	Number of patients	Number (%) gaining ≥ 10 letters	Adjusted difference vs. Laser[1]	(97.5% confidence interval) [1]	p value[2]
No prior cataract surgery (phakic)	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	[redacted]	[redacted]			
Prior anti-VEGF therapy	VTE 2Q4	N=74	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	N=83	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	N=76	[redacted]			
No prior anti-VEGF therapy	VTE 2Q4	N=216	[redacted]	[redacted]	[redacted]	[redacted]
	VTE 2Q8	N=203	[redacted]	[redacted]	[redacted]	[redacted]
	Laser	N=210	[redacted]			

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection
[1] Difference with CI is calculated using Mantel-Haenszel weighting scheme.
[2] p-value is calculated using 2-sided Cochran-Mantel-Haenszel (CMH) test adjusted by Study for integrated analysis

Table 26: Subgroup Analysis of change in CRT from baseline at week 52 [integrated analysis of VISTA and VIVID studies, FAS; LOCF] (27)(data on file)

Population	Treatment group	Number of patients	Baseline Means (SD)	Mean change (SD)	LS Mean Change (SE)	Contrast	P Value[1]	Estimate for comparison & 95% CI (LS mean) [2]
Overall population	VTE 2Q4	N=290	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8	N=286	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser	N=286	[redacted]	[redacted]	[redacted]			
BCVA < 40	VTE 2Q4	[redacted]	Not reported					
	VTE 2Q8	[redacted]						
	Laser	[redacted]						
BCVA ≥ 40 - < 55	VTE 2Q4	[redacted]						
	VTE 2Q8	[redacted]						
	Laser	[redacted]						
BCVA ≥ 55 - < 65	VTE 2Q4	[redacted]						
	VTE 2Q8	[redacted]						
	Laser	[redacted]						
BCVA ≥ 65	VTE 2Q4	[redacted]						
	VTE 2Q8	[redacted]						
	Laser	[redacted]						
Baseline CRT <400µm	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser	[redacted]	[redacted]	[redacted]	[redacted]			
Baseline CRT ≥400µm	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]

Population	Treatment group	Number of patients	Baseline Means (SD)	Mean change (SD)	LS Mean Change (SE)	Contrast	P Value[1]	Estimate for comparison & 95% CI (LS mean) [2]
	Laser	[redacted]	[redacted]	[redacted]	[redacted]			
Prior laser	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser	[redacted]	[redacted]	[redacted]	[redacted]			
No prior laser	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser	[redacted]	[redacted]	[redacted]	[redacted]			
Prior cataract surgery (pseudophakic)	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser	[redacted]	[redacted]	[redacted]	[redacted]			
No prior cataract surgery (phakic)	VTE 2Q4	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser	[redacted]	[redacted]	[redacted]	[redacted]			
Prior anti-VEGF therapy	VTE 2Q4	N=74	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	-107.37 (-143.14; -71.60)
	VTE 2Q8	N=83	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	-116.79 (-151.55; -82.03)
	Laser	N=76	[redacted]	[redacted]	[redacted]			
No prior anti-VEGF therapy	VTE 2Q4	N=216	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	-139.96 (-161.23;-118.69)
	VTE 2Q8	N=203	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	-129.68 (-151.26;-108.11)
	Laser	N=210	[redacted]	[redacted]	[redacted]			

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection

1 F-test, H0: No difference between treatment groups.

2 The contrast is VTE group – Laser. ANCOVA model with baseline measurement as covariable and treatment group, study, subgroup and treatment group*subgroup as fixed factors was used.

2-year (week 100) results

At the time of drafting this submission, the full 2-year analyses for the VISTA and VIVID studies were not finalised. However, initial 2-year results of VISTA and VIVID were presented at EURETINA in September 2014 (25) and 2-year clinical study reports of both studies are [redacted] (23;24).

Mean change in BCVA from baseline up to week 100 (see Table 27)

VISTA (24;30): In total [redacted] of the randomised patients completed Week 100. Proportions for laser patients [redacted] as for aflibercept combined [redacted] Patients receiving aflibercept 2Q4 and 2Q8 showed a sustained improvement from baseline in BCVA at week 100, when compared to patients in the laser photocoagulation treatment arm. After two years, patients receiving aflibercept 2Q4 had a mean change from baseline in BCVA of 11.5 letters (12.5 letters at 52 weeks). Patients receiving aflibercept 2Q8 had a mean change from baseline in BCVA of 11.1 letters (10.7 letters at 52 weeks). Patients in the laser photocoagulation treatment group had a mean change from baseline in BCVA of 0.9 letters (0.2 letters at 52 weeks).

VIVID (23): In total, [redacted] f the randomised patients completed Week 100. Improvement in BCVA was seen as early as day 3 in all treatment groups, with further improvement continuing to week 52 for the 2Q4 and 2Q8 groups and essentially maintained through week 92. Patients in the 2Q4 group had a larger improvement in VA compared to the 2Q8 group at week 100. The laser group showed improvement through week 12, and then gradually declined through week 100.

Figure 16. Mean change in BCVA through week 100 for VISTA and VIVID studies (25)

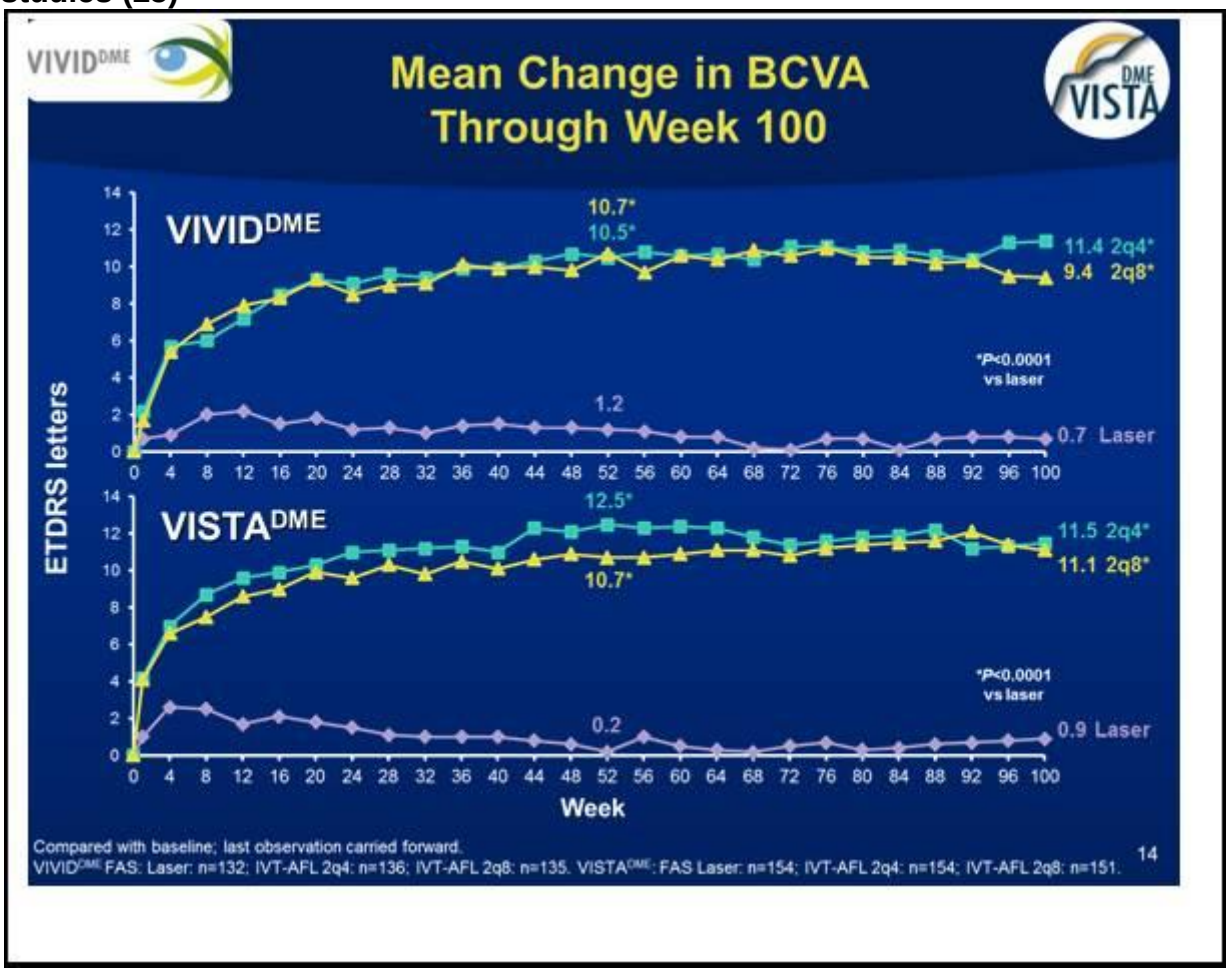


Table 27: Primary efficacy analysis of change in BCVA from baseline to week 100 (VISTA and VIVID)[FAS, LOCF) (23-25)

Study	Treatment group	Baseline Means (SD)	Mean change (SD) Week 52	Mean change (SD) Week 100	LS Mean Change (SE) Baseline to week 100	Contrast	P Value[1]	Estimate for comparison & 97.5% CI (LS mean)[1]
VISTA	VTE 2Q4 N=154	[redacted]	12.5 [redacted]	*11.5* [redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8 N=151	[redacted]	10.7 [redacted]	11.1 [redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser N=154	[redacted]	0.2 [redacted]	0.9 [redacted]	[redacted]			
VIVID	VTE 2Q4 N=136	[redacted]	10.5 [redacted]	11.4 [redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8 N=135	[redacted]	10.7 [redacted]	9.4 [redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser N=132	[redacted]	1.2 [redacted]	0.7 [redacted]	[redacted]			

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection

[1] The confidence interval (CI) with p-value is based on treatment difference (VTE group vs. Laser) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment and VISTA: medical history of MI or CVA, and VIVID: region, as fixed factors.

Sensitivity Analyses of mean change in BCVA from baseline up to week 100 (23;24)

(To evaluate the impact of missing data and additional treatment)

Sensitivity analyses were performed on the change in BCVA from baseline to week 100 in the FAS using the same ANCOVA model (OC, aOC, and aLOCF) as well as repeated measurement model and multiple imputation methods (OC only). The aOC, aLOCF, repeated measurements model, and multiple imputation method analyses demonstrated [redacted] The OC results were [redacted] between aflibercept and laser (Table 28). However, it should be noted that, in the laser group, patients received additional treatment [redacted] and, in the OC analysis, had their post-additional treatment data censored such that the OC analysis includes complete data only from those patients who did not lose the requisite amount of vision to qualify for additional treatment. In both the aLOCF and aOC analyses, which include data after additional treatment was given, results were [redacted]

Table 28: Sensitivity analysis of change in BCVA from baseline to week 100 (VISTA, VIVID)[FAS, OC[1]) (23;24)

Study	Treatment group	Mean change at week 100 (SD)	LS Mean Change (SE)	No of patients	Contrast	P Value[1]	Estimate for comparison & 97.5% CI (LS mean)[2]
VISTA	VTE 2Q4 N=154	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8 N=151	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser		[redacted]
	Laser N=154	[redacted]	[redacted]	[redacted]			
VIVID	VTE 2Q4 N=136	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8 N=135	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser		[redacted]
	Laser N=132	[redacted]	[redacted]	[redacted]			

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection

[1] OC: observed case, censoring measurements after additional treatment was given.

[2] The CI with p-value for integrated study is based on treatment difference (aflibercept group vs. Laser) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment and Study as fixed factors.

Table 29: Sensitivity analysis of change in BCVA from baseline to week 100 (VISTA, VIVID)[FAS, aLOCF[1]) (23;24)

Study	Treatment group	Mean change at week 100 (SD)	LS Mean Change (SE)	No of patients	Contrast	P Value[1]	Estimate for comparison & 97.5% CI (LS mean)[2]
VISTA	VTE 2Q4 N=154	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8 N=151	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser N=154	[redacted]	[redacted]	[redacted]			
VIVID	VTE 2Q4 N=136	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8 N=135	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser N=132	[redacted]	[redacted]	[redacted]			

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection

[1] aLOCF: last observation carried forward, including measurements after additional treatment was given.

[2] The CI with p-value for integrated study is based on treatment difference (aflibercept group vs. Laser) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment and Study as fixed factors.

Table 30: Sensitivity analysis of change in BCVA from baseline to week 52 (VISTA, VIVID)[FAS, aOC[1]) (23;24)

Study	Treatment group	Mean change (SD)	LS Mean Change (SE)	No of patients	Contrast	P Value[1]	Estimate for comparison & 97.5% CI (LS mean)[2]
VISTA	VTE 2Q4 N=154	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8 N=151	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser N=154	[redacted]	[redacted]	[redacted]			
VIVID	VTE 2Q4 N=136	[redacted]	[redacted]	[redacted]	VTE 2Q4 vs. Laser	[redacted]	[redacted]
	VTE 2Q8 N=135	[redacted]	[redacted]	[redacted]	VTE 2Q8 vs. Laser	[redacted]	[redacted]
	Laser N=132	[redacted]	[redacted]	[redacted]			

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection

[1] aOC observed case, including measurements after additional treatment was given.

[2] The CI with p-value for integrated study is based on treatment difference (aflibercept group vs. Laser) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment and Study as fixed factors.

Subgroup Analyses (mean change in BCVA from baseline to week 100)

In general, results of the evaluable pre-specified subgroups on the change in BCVA from baseline to week 100 in the VISTA and VIVID studies[redacted](23;24)

Summary of secondary endpoints (to week 100)(23-25)

In both studies, for the gain of[redacted]and ≥ 2-step improvement in ETDRS DRSS endpoints, the sustained favourable differences to laser at Week 100 were statistically significant for both aflibercept dose groups. Changes in CRT showed a stable course during the second year of treatment for all treatment arms.

In VISTA, all treatment groups experienced a [redacted]change in the scores for NEI VFQ-25 near activities and NEI VFQ-25 distance activities subscales (approximately 5 or more points in mean change from baseline) at week 100. At week 100, both the 2Q4 and the 2Q8 groups were [redacted]to the laser group in the VISTA study for both NEI VFQ-25 near and distance activities.

In VIVID also, all treatment groups experienced a [redacted]in the scores for NEI VFQ-25 near activities subscales (approximately 5 or more points in mean change from baseline) at week 100. The 2Q4 and laser groups were [redacted]to the 2Q8 group at week 100. For NEI VFQ-25 distance activities, only the 2Q8 group[redacted]at week 100[redacted]but the score Was[redacted]

In general, results of the evaluable pre-specified subgroups on all secondary endpoints in both studies from baseline to week 100 [redacted]

Table 31: Secondary efficacy variables – Results from baseline to week 100 in VISTA, VIVID (FAS; LOCF) (23-25)

Variable	Laser		Aflibercept			
			2Q4		2Q8	
	VISTA	VIVID	VISTA	VIVID	VISTA	VIVID
Patients gaining ≥ 10 letters						
n	154	132	154	136	151	135
Number (%) gaining ≥ 10 letters at 52 weeks	30 (19.5)	34 (25.8)	100 (64.9)	74 (54.4)	88 (58.3)	72 (53.3)
Number (%) gaining ≥ 10 letters at 100 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted difference vs. Laser[1]			[redacted]	[redacted]	[redacted]	[redacted]
(97.5% confidence interval) [1]			[redacted]	[redacted]	[redacted]	[redacted]
p value			<0.0001	<0.0001	<0.0001	<0.0001
Patients gaining ≥ 15 letters[2]						
n	154	132	154	136	151	135
Number (%) gaining ≥ 15 letters at 52 weeks	12 (7.8)	12 (9.1)	64 (41.6)	44 (32.4)	47 (31.1)	45 (33.3)
Number (%) gaining ≥ 15 letters at 100 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted difference vs. Laser[1]			[redacted]	[redacted]	[redacted]	[redacted]
(97.5% confidence interval) [1]			[redacted]	[redacted]	[redacted]	[redacted]
p value			<0.0001	<0.0001	<0.0001	0.0001
Patients with ≥ 2-step ETDRS improvement						
n	154	132	154	136	151	135
Number (%) with ≥ 2-step ETDRS improvement at week 52[3]	22/154 14.3)	6/80 (7.5)	52/154 33.8)	27/81 (33.3)	44/151 (29.1)	23/83 (27.7)
Number (%) with ≥ 2-step ETDRS improvement at week 100[3]	24 (15.6)	7/85 (8.2)	57 (37.0)	24/82 (29.3)	56 (37.1)	28/86 (32.6)
Adjusted difference vs. Laser[1]			[redacted]	[redacted]	[redacted]	[redacted]
(97.5% confidence interval) [1]			[redacted]	[redacted]	[redacted]	[redacted]
p value			[redacted]	[redacted]	[redacted]	[redacted]
Change in CRT (by OCT)						
n	154	132	154	135	151	135
Mean change in µm in CRT (SD) at 52 weeks	-73.3 [redacted]	-66.2 [redacted]	-186 [redacted]	-195.0 [redacted]	-183 ([redacted]	-192 ([redacted]
Mean change in µm in CRT (SD) at 100 weeks	-83.9 [redacted]	-85.7 [redacted]	-191.4 [redacted]	-211.8 [redacted]	-191.1 ([redacted]	-195.8 [redacted]
LS mean change in µm in CRT (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimate for contrast vs. Laser			[redacted]	[redacted]	[redacted]	[redacted]
(97.5% confidence interval)			[redacted]	[redacted]	[redacted]	[redacted]
p value			<0.0001	<0.0001	<0.0001	<0.0001

Variable	Laser		Aflibercept			
			2Q4		2Q8	
	VISTA	VIVID	VISTA	VIVID	VISTA	VIVID
Change in NEI VFQ-25 near activities score						
n	154	132	154	136	151	135
n Evaluable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in near activities score (SD) at week 52	5.4 [redacted]	3.5 [redacted]	9.0 [redacted]	5.7 [redacted]	9.4 [redacted]	5.3 [redacted]
Mean change in near activities score (SD) at week 100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change in near activities score (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimate for contrast vs. Laser			[redacted]	[redacted]	[redacted]	[redacted]
(97.5% confidence interval)			[redacted]	[redacted]	[redacted]	[redacted]
p value			[redacted]	[redacted]	[redacted]	[redacted]
Change in NEI VFQ-25 distance activities score						
n	154	132	154	136	151	135
n Evaluable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in distance activities score (SD) at week 52	6.7 [redacted]	2.3 [redacted]	8.6 [redacted]	0.9 [redacted]	7.3 [redacted]	5.3 [redacted]
Mean change in distance activities score (SD) at week 100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change in distance activities score (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimate for contrast vs. Laser			[redacted]	[redacted]	[redacted]	[redacted]
(97.5% confidence interval)			[redacted]	[redacted]	[redacted]	[redacted]
p value			[redacted]	[redacted]	[redacted]	[redacted]

2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection; CRT=Central retinal thickness; DRSS=Diabetic retinopathy severity scale; ETDRS=Early Treatment Diabetic Retinopathy Study; IOP=intraocular pressure; LS = least squared; NEI VFQ-25=National Eye Institute Visual Functioning Questionnaire-25; OCT=Optical coherence tomography.

[1]Difference with CI is calculated using Mantel-Haenszel weighting scheme

[2]This is the only secondary endpoint defined for the US SAP

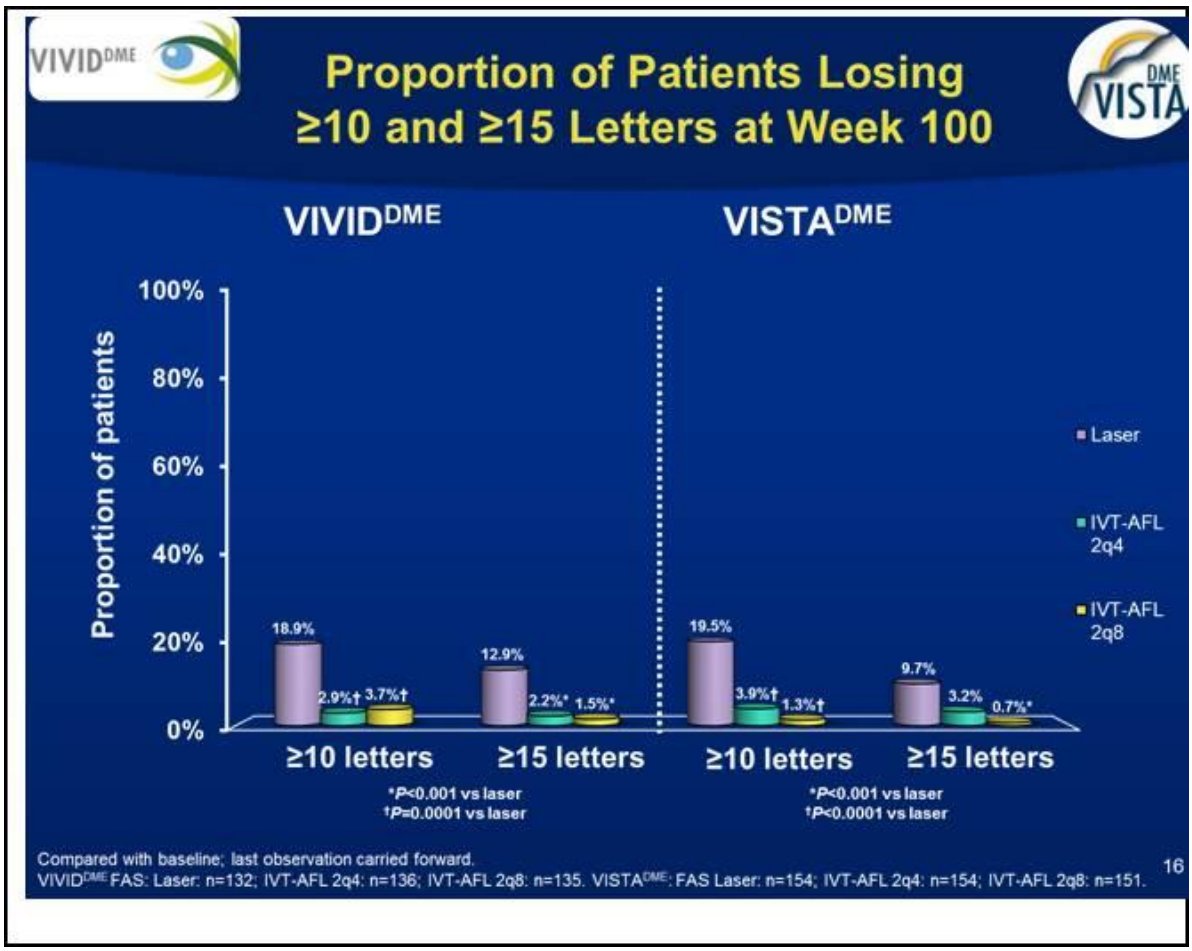
[3]Denominator is number of evaluable patients

Additional efficacy variables (at Week 100) (23-25)

In both studies, the results for the additional efficacy variables supported the findings obtained from the primary and secondary efficacy variables at week 100.

At week 100, the 2Q4 and 2Q8 groups contained a [redacted] of patients who experienced a gain of ≥0 and ≥5 ETDRS letters compared to the laser group; and contained a [redacted] of patients experiencing a loss in vision of ≥5, ≥10, and ≥15 ETDRS letters compared to the laser group.

Figure 17. Proportion of patients losing ≥10 and ≥15 letters at week 100 (25)



There were [redacted] who experienced a ≥2- or ≥3-step worsening and more patients who achieved a ≥3-step improvement on the DRSS in the 2Q4 and 2Q8 groups as compared to the laser group.

Also, the 2Q4 and 2Q8 groups were [redacted] the laser group for mean NEI VFQ-25 total score in the VISTA study: mean increases of[redacted]in the laser, 2Q4, and 2Q8 groups, respectively. In VIVID, the mean total NEI VFQ-25 scores were [redacted]at baseline for the laser and 2Q4 groups; the 2Q8 group was [redacted] at week 100,[redacted] in the laser, 2Q4, and 2Q8 groups, respectively).

The mean changes in the EQ-5D Index Score from baseline results at week 52 were [redacted]those at week 100 - in the VISTA study (FAS) at week 52, the mean changes (SD) in the EQ-5D Index Score from baseline were[redacted]in the laser group, the 2Q4 group, and the 2Q8 group, respectively[redacted]from baseline in EQ-5Q Total score at each post-baseline time point in each of the treatment groups was also reported in the VIVID study.

Efficacy Conclusions

Analyses of VISTA and VIVID demonstrated that aflibercept, either once every 4 weeks or once every 8 weeks, was effective and superior to laser photocoagulation in the treatment of visual impairment due to diabetic macular oedema, in treatment-naive patients as well as patients who had previously received other anti-VEGF therapy. Results of the primary analyses were robust, and were independently verified in the separate studies. The primary conclusions are further supported by extensive sensitivity analyses and by the consistency and convergence of results with secondary variables. Results in the predefined subgroups generally supported those seen in the overall population. Aflibercept treatment remained superior to laser even in sensitivity analyses that included data obtained after the initiation of additional 'rescue' treatment, despite the fact that patients in the laser group improved substantially after initiating aflibercept as additional treatment.

Both aflibercept groups demonstrated significant improvements over laser photocoagulation in the primary endpoint - mean change in BCVA at week 52 - with immediate improvements in BCVA seen as early as day 3 / week 1. Such improvements were maintained over the longer-term (i.e. through week 100), with a mean of 21.3 and 13.5 injections over 100 weeks of the study in the 2Q4 and 2Q8 groups, respectively.

Higher proportions of patients gaining ≥ 10 ETDRS and ≥ 15 ETDRS letters at weeks 52 and 100 were also reported compared to laser photocoagulation. Both aflibercept treatments were effective in treating diabetic retinopathy, based on significant improvements over laser photocoagulation in the proportion of patients achieving ≥2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) at weeks 52 and 100. In addition, a greater number of patients in the aflibercept groups also had an improvement of ≥3-steps, and fewer had ≥2- and ≥3-step worsening in this parameter over 100 weeks compared to the laser group. Significant and sustained improvements in mean CRT were also seen, compared to laser treatment.

With the exception of the NEI VFQ-25 near activities subscale in the 2Q4 group, there were no statistically significant differences in the NEI VFQ-25 near or distance subscales among the treatment groups in the quality of life assessments at week 52. In VISTA, the change from baseline to week 100 for the near activities subscale was significantly greater for the 2Q8 group only, and the change from baseline to week 100 for the distance activities subscale was significantly greater for the 2Q4 group only. In VIVID, all treatment groups experienced a clinically meaningful change in scores (approximately 5 or more points) at week 100 in the NEI VFQ-25 near subscale.results, although the NEI VFQ-25 near and distance subscales analyses for the 2Q4 and 2Q8 groups compared to laser photocoagulation were not statistically significant.

On the basis of these clinical data, the European Medicines Agency (EMA), have approved aflibercept for use in the treatment of visual impairment due to diabetic macular oedema (DMO), using the 2Q8 posology from the VISTA and VIVID studies for the first twelve months, with the possibility of extending the treatment interval according to visual and anatomic outcomes thereafter. There is no requirement for monitoring between injections – patients in the 2Q8 groups in VISTA and VIVID were not permitted to be dosed at intervening visits, which suggested monitoring every month was not necessary.

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

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

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the 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).

See responses below

6.6.2 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.

VISTA and VIVID were similarly designed studies (17), in order that their data could be pooled for integrated or 'meta-analysis'. The integrated data and analyses of the studies have been presented alongside the individual study data throughout sections 6.3 to 6.5.

For the purposes of indirect comparison, a network meta-analyses (NMA) was performed on the 12-month data (see section 6.7). Efficacy Outcomes assessed in the NMA were:

- Change in BCVA at 12 months
- Proportion of patients gaining ≥ 10 letters of BCVA from baseline at 12 months
- Proportion of patients gaining ≥ 15 letters of BCVA from baseline at 12 months

- Proportion of patients losing ≥ 10 letters of BCVA from baseline at 12 months
- Proportion of patients losing ≥ 15 letters of BCVA from baseline at 12 months
- Treatment discontinuation

The pooled estimate for aflibercept was used in the indirect comparisons with ranibizumab, and dexamethasone, described in section 6.7. The results for aflibercept trials are presented in **Table 32** to **Table 34**.

The pooled estimates indicate that:

There is a greater gain in mean BCVA from baseline to 12 months with aflibercept, when compared with laser

- a higher proportion of patients treated with aflibercept achieve a gain of ≥ 10 letters or ≥15 letters, from baseline to 12 months, when compared with laser photocoagulation;

- a lower proportion of patients treated with aflibercept lose ≥15 letters or ≥ 10 letters, from baseline to 12 months, when compared with laser treatment;

all the results are statistically significant.

Table 32. Meta-analysis - Effect estimates by inverse variance fixed and random effects models for continuous efficacy outcomes

BCVA Mean Change from baseline									
Study ID	**Aflibercept**			**Laser**			**Weight**	**Mean Difference**	**Mean Difference**
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**		**IV, Fixed 95% CI**	**IV, Random 95% CI**
VISTA-DME	10.7	8.21	151	0.2	12.53	154	50.6%	10.50 [8.13, 12.87]	10.50 [8.13, 12.87]
VIVID-DME	10.7	9.32	135	1.2	10.65	132	49.4%	9.50 [7.10, 11.90]	9.50 [7.10, 11.90]
Total			**286**			**286**	**100%**	**10.01 [8.32, 11.69]**	**10.01 [8.32, 11.69]**

Table 33. Meta-analysis - Effect estimates by mantel-haenszel fixed effects model for dichotomous efficacy outcomes

Gain of ≥10 ETDRS letters								
Study ID	Aflibercept		Laser		Risk Ratio		Odds Ratio	
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Weight	M-H, Fixed, 95% CI
VISTA-DME	88	151	30	154	46.4%	2.99 [2.11, 4.24]	43.6%	5.77 [3.45, 9.65]
VIVID-DME	72	135	34	132	53.6%	2.07 [1.49, 2.88]	56.4%	3.29 [1.97, 5.52]
Total		286		286	100%	2.50 [1.97, 3.17]	100%	4.37 [3.04, 6.29]
Loss of ≥10 ETDRS letters								
Study ID	Aflibercept		Laser		Risk Ratio		Odds Ratio	
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Weight	M-H, Fixed, 95% CI
VISTA-DME	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID-DME	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gain of ≥15 ETDRS letters								
Study ID	Aflibercept		Laser		Risk Ratio		Odds Ratio	
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Weight	M-H, Fixed, 95% CI
VISTA-DME	47	151	12	154	49.5%	3.99 [2.21, 7.23]	50.3%	5.35 [2.70, 10.58]
VIVID-DME	45	135	12	132	50.5%	3.67 [2.03, 6.61]	49.7%	5.00 [2.50, 10.00]

Total		286		286	100%	3.83 [2.52, 5.82]	100%	5.17 [3.18, 8.42]
Loss of ≥15 ETDRS letters								
Study ID	Aflibercept		Laser		Risk Ratio		Odds Ratio	
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Weight	M-H, Fixed, 95% CI
VISTA-DME	1	151	14	154	48.6%	0.07 [0.01, 0.55]	48.5%	0.07 [0.01, 0.51]
VIVID-DME	0	135	14	132	51.4%	0.03 [0.00, 0.56]	51.5%	0.03 [0.00, 0.51
Total		286		286	100%	0.05 [0.01, 0.27]	100%	0.05 [0.01, 0.25]
Treatment Discontinuation								
Study ID	Aflibercept		Laser		Risk Ratio		Odds Ratio	
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Weight	M-H, Fixed, 95% CI
VISTA-DME	10	154	11	156	35.3%	0.92 [0.40, 2.11]	36.5	0.92 [0.38, 2.22]
VIVID-DME	15	135	20	135	64.7	0.75 [0.40, 1.40]	63.5	0.72 [0.35, 1.47]
Total		289		291	100%	0.81 [0.49, 1.33]	100%	0.79 [0.45, 1.38]

Table 34. Meta-analysis - Effect estimates by Mantel-Haenszel random effects model for dichotomous efficacy outcomes

Gain of ≥10 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	88	151	30	154	48.8%	2.99 [2.11, 4.24]	50.1%	5.77 [3.45, 9.65]
VIVID-DME	72	135	34	132	51.2%	2.07 [1.49, 2.88]	49.9%	3.29 [1.97, 5.52]
Total		**286**		**286**	**100%**	**2.48 [1.73, 3.56]**	**100%**	**4.36 [2.52, 7.56]**
Loss of ≥10 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID-DME	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gain of ≥15 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	47	151	12	154	49.7%	3.99 [2.21, 7.23]	50.8%	5.35 [2.70, 10.58]
VIVID-DME	45	135	12	132	50.3%	3.67 [2.03, 6.61]	49.2%	5.00 [2.50, 10.00]
Total		**286**		**286**	**100%**	**3.83 [2.52, 5.81]**	**100%**	**5.17 [3.18, 8.41]**
Loss of ≥15 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	1	151	14	154	66.0%	0.07 [0.01, 0.55]	65.8%	0.07 [0.01, 0.51]
VIVID-DME	0	135	14	132	34.0%	0.03 [0.00, 0.56]	34.2%	0.03 [0.00, 0.51]
Total		**286**		**286**	**100%**	**0.06 [0.01, 0.29]**	**100%**	**0.05 [0.01, 0.27]**
Treatment Discontinuation								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	10	154	11	156	36.4	0.92 [0.40, 2.11]	39.5%	0.92 [0.38, 2.22]
VIVID-DME	15	135	20	135	63.6	0.75 [0.40, 1.40]	60.5%	0.72 [0.35, 1.47]
Total		**289**		**291**	**100%**	**0.81 [0.49, 1.33]**	**100%**	**0.79 [0.45, 1.38]**

6.6.3 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.

Not applicable.

6.7 Indirect and mixed treatment comparisons

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

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.

Data on the relative efficacy and safety of aflibercept in relation to the main comparator in clinical practice, ranibizumab, in the treatment of DMO is not available from active-controlled trials. There are also no comparative trials between aflibercept and other therapies for the treatment of DMO, such as fluocinolone acetonide implants or dexamethasone implants.

In the absence of head-to-head data a network meta-analysis (NMA) was conducted in order to assess the relative treatment difference between aflibercept (in a fixed treatment pattern of five doses of 2mg every 4 weeks followed by 2mg every eight weeks; AFB 2Q4/2Q8), ranibizumab (0.5mg treatment as needed (p.r.n.); 0.5 PRN RBZ or 0.2µg/day fluocinolone acetonide implants or dexamethasone implants on visual acuity and safety outcomes.

Bucher indirect and Bayesian mixed treatment comparison analyses (fixed and random effect models) were used to synthesise efficacy and safety data reported in clinical studies. These studies were identified by a systematic review of the literature ensuring that all available evidence was used.

The search undertaken to identify relevant clinical data on ranibizumab (0.5mg treatment as needed (p.r.n.); 0.5 PRN RBZ or 0.2µg/day fluocinolone acetonide implants or dexamethasone implants was the main part of the broader systematic review described in section 6.1, 6.2 and appendix 10.2. 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.

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.

A network diagram of all the studies identified as relevant in the systematic review was developed. To more precisely identify which studies would inform the comparative analyses between aflibercept and ranibizumab, dexamethasone, or fluocinolone acetonide, 1) studies that were connected by one arm only and did not form a closed network unless they included comparators of interest, 2) studies which formed loops but did not lie along the path between 2Q8 AFB versus 0.5 PRN RBZ,3) studies which were more than three steps apart from AFB and 4) studies which did not report 12 or 24 month outcomes were removed. This generated a 12 month network of studies (see Figure 18). A 24 month network demonstrated that no mixed treatment comparison analyses were possible for the key comparators.

A comparison between aflibercept and fluocinolone acetonide implants was not possible at 12 months because the included trial (*FAME*) did not have a common comparator to allow an indirect analysis as a network could not be formed. This study compared 0.2µg/day fluocinolone versus sham injection with laser six weeks later if treatment criteria were met.

In order to identify which indirect analyses were possible for which outcomes, all the outcomes for all studies with 12 month follow-up were summarised (Table 41). This resulted in a final list of 11 relevant trials that provided sufficient data to analyse using direct, Bucher indirect and MTC analyses to explore the efficacy and safety of aflibercept in relation to ranibizumab, and dexamethasone.

Studies identified for use in the indirect analyses comparing aflibercept vs. ranibizumab (*VIVID-DME (17), VISTA (17), RESTORE (31), REVEAL (32), RELATION (33), LRT for DME (34), LRT for DME for PRP (35), LUCIDATE (36), IBETA (37), Maia 2009 (38))* and aflibercept vs. dexamethasone (*VIVID, VISTA and PLACID)* were assessed for clinical similarity in terms of study characteristics, risk of bias, patient baseline characteristics and treatment regimens.

Methodology of included studies

Details of the aflibercept trials (VISTA and VIVID) have already been described in Sections 6.1 to 6.5.

Study designs (see Table 35)

Eight trials were multicentre (36-90 centres), only three were single centre (*LUCIDATE, IBETA, Maia 2009*). Nearly all the trials were phase III, except for *LUCIDATE* which was phase IV and *Maia 2009* which was phase II/III. *PLACID* was the only phase II trial included since there were no phase III trials found for dexamethasone implants. Most trials were described as double blind, except *LUCIDATE* and *IBETA* which were open label and *Maia 2009* which was single blind. Six trials had three arms and were randomised 1 to 1 to 1 (*VIVID, VISTA, IBETA, RESTORE, REVEAL, LRT for DME for PRP).* One trial had four arms and was randomised 1 to 1 to 1 to 1 (*LRT for DME).* Four trials had two arms and were randomised 1 to 1 *(PLACID, Maia 2009)* or 2 to 1 *(LUCIDATE, RELATION).* All trials had a follow-up of 12 months, except *LUCIDATE* which reported 11 months follow-up. Patients were randomised according to eye *(IBETA, LRT for DME, LRT for DME for PRP, Maia 2009)* or patient *(VIVID, VISTA, RESTORE, REVEAL, RELATION, LUCIDATE, PLACID).* Most trials included only one eye per patient in the trial, however one trial included both eyes *(Maia 2009),* and two trials included one or two eyes *(IBETA, LRT for DME)* and only one trial did not report this information *(RELATION).* A CONSORT diagram was reported for only three trials (*RESTORE, RELATION, PLACID*). The statistical

analysis method used for the primary outcome was not reported in five trials (*IBETA, REVEAL, LRT for DME for PRP, LUCIDATE, Maia 2009*). The remaining trials all used intention to treat (ITT) analysis with last observation carried forward (LOCF) to impute missing data. Three trials did not report the method used for measuring the main efficacy outcome, visual acuity (*IBETA, LUCIDATE, PLACID*). Three trials reported using an ETDRS chart at four metres (*VIVID, VISTA, RESTORE)*, two at three metres (*LRT for DME, LRT for DME for PRP)* and three used an ETDRS chart but did not report a distance use *(REVEAL, RELATION, Maia 2009).*

Overall the trials had similar study designs, except for IBETA, LUCIDATE, Maia 2009 which stood out as being dissimilar in terms of being single centred, with a lack of blinding, including more than one eye per patient and not reporting the method used for measuring visual acuity.

Eligibility criteria and Concomitant medications (see Table 36)

Trials included patients with clinically significant DMO (*IBETA*), DMO (*RELATION*), diffuse DMO (*RESTORE, PLACID*), DMO secondary to diabetes involving the centre of the macula (*VIVID, VISTA*), focal or diffuse DMO and type 1 or 2 diabetes (*REVEAL*), retinal thickening due to DMO (*LUCIDATE, LRT for DME, LRT for DME for PRP*) or clinically significant macula oedema in patients with diabetic retinopathy (*Maia 2009*). Three trials reported that patients were included if they were on stable management for diabetes (*RESTORE, REVEAL, RELATION*). Trials reported that visual acuity had to be 20/40 or worse (*IBETA, VIVID, VISTA*) or 20/32 or worse (*RESTORE, REVEAL*) or have a BCVA letter score of 34-70 (*PLACID*) 39-78 at four metres (*RESTORE, REVEAL*) or 24 to 73/78 (*VIVID, VISTA, LRT for DME, LRT for DME for PRP*), 55-79 at one metre (LUCIDATE). Trials reported that central macula thickness had to be greater than 250µm (*Maia 2009, LRT for DME, LRT for DME for PRP*) or 275µm (*IBETA, PLACID*) or 300µm (*VIVID, LUCIDATE*). No VEGF treatment in the preceding three months (*LUCIDATE*).

Principal exclusion criteria for all included; cataract or major surgery within six months, history of glaucoma or hypertension or ocular inflammation, loss of vision due to other causes, systemic corticosteroids, severe systemic disease other than diabetes. Laser treatment within three months of study (*RESTORE, VIVID, VISTA, REVEAL, RELATION, LUCIDATE, LRT for DME, PLACID*). Anti VEGF treatment or dexamethasone within three months of study (*RESTORE, VIVID, VISTA, LUCIDATE, PLACID*). Previous treatment for

DME (*LRT for DME, LRT for DME for PRP*) or anti-angiogenic (*VIVID, VISTA, LUCIDATE*) drugs were excluded. Six trials did not report information regarding allowed and disallowed concomitant medications (*RESTORE, RELATION, Maia 2009, LRT for DME, LRT for DME for PRP, PLACID*).

Table 35. Summary of study designs for RCTs included in indirect comparative analyses (see section 6.3 for aflibercept data [VISTA and VIVID])

	Country (ies)	Centres (number of centres)	Phase	Blinding	Randomisation ratio	Follow-up time(s) months	n refers to eye or patient	N eyes studied/ patient	Was a consort flow diagram provided?	Statistical Analysis (primary outcome)	Method for VA
IBETA	Brazil	Single centre (1)	III	Open	1 to 1 to 1	1, 2, 3, 4, 6, 9, 12	eye	1 or 2	No	NR	NR. Mean BCVA (LogMAR) intra-individual difference to baseline
RESTORE	Australia, Belgium, Canada, France, Germany, Greece, Hungary, Italy, Netherlands, Spain, Turkey, United Kingdom	Multi-Centre (73)	III	Double-blind	1 to 1 to 1	12	patient	1	Yes but in reduced form.	LOCF	ETDRS chart at a starting distance of 4m.
REVEAL	China, Hong Kong, Japan, South Korea, Singapore, Taiwan	Multi-centre (52)	III	Double-blind	1 to 1 to 1	12	patient	1	No	NR	ETDRS chart.
RELATION	Germany	Multi-centre (36)	III	Double-blind	2 to 1	12	patient	NR	Yes	LOCF	ETDRS chart with certified VA assessors.
LRT for DME	US	Multi-centre (52)	III	Double-blind	1 to 1 to 1 to 1	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,12, 24, 36.	eye	1 or 2	No	LOCF	BCVA letter score was measured in the study eye at 3m by a certified tester using the E-ETDRS visual acuity test.

	Country (ies)	Centres (number of centres)	Phase	Blinding	Randomisation ratio	Follow-up time(s) months	n refers to eye or patient	N eyes studied/ patient	Was a consort flow diagram provided?	Statistical Analysis (primary outcome)	Method for VA
LRT for DME for PRP	US	Multi-centre (48)	III	Double-blind	1 to 1 to 1	0, 1, 3, 6, 12	eye	1	No	unclear	BCVA letter score was measured in the study eye at 3m by a certified tester using the E-ETDRS visual acuity test.
LUCIDATE	UK	Single centre (1)	IV	Open	2 to 1	11	patient	1	No	NR	NR
Maia 2009	Brazil	Single centre (1)	II/III	Single-blind	1 to 1	3, 6, 9, 12	eye	2	No	NR	Measurement of BCVA was performed according to a standardized refraction protocol using a retroilluminated Lighthouse for the Blind distance VA test chart (using modified ETDRS charts 1, 2, and R).
PLACID	USA, Canada	Multi-centre (48)	II	Double-blind	1 to 1	4,6,9,12	patient	1	yes	LOCF	NR

LOCF= last observation carried forward; NR= not reported; BCVA= best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study

Table 36. Eligibility criteria and concomitant medications for RCTs included in indirect comparative analyses (see section 6.3.2 and section 6.3.3 for aflibercept data [VISTA and VIVID])

	Inclusion criteria	Exclusion criteria (study eye)	Concomitant Medications Allowed	Concomitant Medications Disallowed
REVEAL	Patients with Type 1 or Type 2 diabetes mellitus with HbA1c not more than 10.0% at screening (Visit 1). Patients should be on diet, exercise, and/or pharmacological treatment for diabetes. Patients with visual impairment due to focal or diffuse DME in at least one eye who are eligible for laser treatment in the opinion of the investigator. If both eyes are eligible, the one with the worse VA, as assessed at Visit 1, will be selected for study treatment unless, based on medical reasons, the investigator deems the other eye the more appropriate candidate for study treatment. The study eye must fulfil the following criteria at Visit 1: BCVA score between 78 and 39 letters, using ETDRS chart-like visual acuity testing charts at a testing distance of 4 meters (approx. Snellen equivalent of 20/32 to 20/160). Decrease in vision is due to DME and not due to other causes, in the opinion of the investigator. Medication for the management of diabetes must have been stable within 3m prior to randomization and is expected to remain stable during the course of the study.	Ocular concomitant conditions/ diseases: Concomitant conditions in the study eye which could, in the opinion of the investigator, prevent the improvement of visual acuity on study treatment. Active intraocular inflammation in either eye. Any active infection in either eye. History of uveitis in either eye. Uncontrolled glaucoma in either eye. Ocular treatments: Panretinal laser PC in the study eye within 6 m prior to or during the study. Focal/grid laser PC in the study eye within 3 m prior to study entry. Systemic conditions or treatments: History of stroke, Renal failure requiring dialysis or renal transplant or renal insufficiency with creatinine level > 2.0 mg/dL. Untreated diabetes mellitus Blood pressure systolic > 160 mmHg or diastolic > 100 mmHg Compliance/ Administrative: Pregnant or nursing (lactating) women Other protocol-defined inclusion/exclusion criteria may apply	no	Panretinal laser photocoagulation in the study eye within 6 months prior to or during the study & Focal/grid laser photocoagulation in the study eye within 3 months prior to study entry.
RESTORE	(1) stable medication for the management of diabetes within 3 months before randomization and expected to remain stable during the study; (2) visual impairment due to focal or diffuse DME in at least 1 eye that was eligible for laser treatment in the opinion of the investigator; (3) BCVA letter score between 78 and 39, both inclusive, based on ETDRS-like VA testing charts administered at a starting distance of 4 meters (approximate Snellen equivalent 20/32–	(1) concomitant conditions in the study eye that could prevent the improvement in VA on the study treatment in the investigator's opinion; (2) active intraocular inflammation or infection in either eye; (3) uncontrolled glaucoma in either eye (e.g., IOP >24 mmHg on medication, or from the investigator's judgment); (4) panretinal laser photocoagulation (within 6 months) or focal/grid laser photocoagulation (within 3 months) before study entry; (5) treatment with antiangiogenic drugs in the study eye within 3 months before randomization; (6) history of stroke; and (7) systolic blood pressure (BP) >160 mmHg or diastolic BP >100 mmHg, untreated hypertension, or change in antihypertensive treatment within 3 months preceding baseline.	NR	NR

	Inclusion criteria	Exclusion criteria (study eye)	Concomitant Medications Allowed	Concomitant Medications Disallowed
	20/160); and (4) decreased vision due to DME and not other causes, in the investigator's opinion (at visit 1).			
RELATION	Visual acuity impairment caused by macular oedema in at least one eye; Type 1 or type 2 diabetes mellitus & Stable medication of diabetes in past 3 months.	Patients with uncontrolled systemic or ocular diseases; Laser photocoagulation in the study eye for the last 3 months; Any history of any intraocular surgery in the study eye within the past 3 months; Blood pressure > 160/100 mmHg & Other protocol defined inclusion/exclusion criteria may apply.	NR	NR
LRT for DME	At least 18 years old with type 1 or 2 diabetes. The major eligibility criteria for a study eye included the following: (1) best-corrected Electronic-Early Treatment Diabetic Retinopathy Study (E-ETDRS Visual Acuity Test) visual acuity letter score 78 to 24 (20/32–20/320), (2) definite retinal thickening due to DME on clinical examination involving the center of the macula assessed to be the main cause of visual loss, and (3) retinal thickness measured on time domain OCT >=250 µm in the central subfield.	(1) treatment for DME within the prior 4 months, (2) panretinal photocoagulation within the prior 4 months or anticipated need for panretinal photocoagulation within the next 6 months, (3) major ocular surgery within the prior 4 months, (4) history of open-angle glaucoma or steroid-induced intraocular pressure (IOP) elevation that required IOP-lowering treatment, and (5) IOP >= 25 mmHg. Patients were excluded if their systolic blood pressure was >180 mmHg or diastolic blood pressure was >110 mmHg, or if a myocardial infarction, other cardiac event requiring hospitalization, cerebrovascular accident, transient ischemic attack, or treatment for acute congestive heart failure occurred within 4 months before randomization.	NR	NR
LRT for DME for PRP	At least 18 years old with Type 1 or Type 2 diabetes and without substantial renal disease or uncontrolled hypertension. The major eligibility criteria for a study eye included the following: 1) presence of severe NPDR or PDR, 2) presence of center-involved DME on clinical examination and central subfield thickness on time-domain OCT (Stratus; Carl Zeiss Meditec, Dublin, CA) >=250 µm, and 3) best-corrected Electronic-ETDRS (EETDRS visual acuity test) visual acuity letter score >=24 (approximate Snellen equivalent, 20/320 or better).	Principal exclusion criteria included the following: 1) previous PRP that was sufficiently extensive that the investigator did not believe that >=1200 additional burns were needed or possible, 2) treatment for DME within the previous 4 months, 3) history of open-angle glaucoma or steroid-induced intraocular pressure (IOP) elevation that required IOP lowering treatment, and 4) IOP >= 25 mmHg.	NR	NR

	Inclusion criteria	Exclusion criteria (study eye)	Concomitant Medications Allowed	Concomitant Medications Disallowed
LUCIDATE	Diagnosis of diabetes mellitus (type 1 or type 2); retinal thickening due to DME involving the centre of the macula and OCT central subfield ≥ 300 microns; best corrected visual acuity in the study eye between 55 and 79 ETDRS letters at 1 metre (Snellen equivalent ≥ 6/24 and ≤ 6/9); media clarity, pupillary dilation, and subject cooperation sufficient for adequate fundus photographs; Intraocular pressure less than 30 mmHg; ability to return for study visits; visual acuity in fellow eye ≥ 2/60; fellow eye has received no anti-VEGF treatment within the past 3 months and no expectation of such treatment in next 12 months; no previous laser within 3 months of randomisation; ability to give informed consent throughout the duration of the study.	Macular ischaemia; Macular oedema from a cause other than diabetic macular oedema; Co-existent ocular disease; Presence of an ocular condition such that visual acuity would not improve from resolution of macular oedema; Presence of an ocular condition that might affect macular oedema or alter visual acuity during the course of the study; A substantial cataract that is likely to be decreasing visual acuity by 3 lines or more; History of treatment for diabetic macular oedema at any time in the past 3 months; History of panretinal scatter photocoagulation (PRP) within 3 months prior to randomisation; Anticipated need for PRP in the 6 months following randomisation; Proliferative diabetic retinopathy in the study eye; A condition that, in the opinion of the investigator, would preclude participation in the study; Haemoglobin A1c > 11.0 %; A past medical history of significant renal disease, defined as a history of chronic renal failure requiring dialysis or kidney transplant; Blood pressure >170/100 mmHg; Myocardial infarction, other cardiac event requiring hospitalisation, stroke, transient ischaemic attack, or treatment for acute congestive heart failure within 6 months prior to randomisation; Major surgery within 28 days prior to randomisation or major surgery planned during the next 12 months at baseline; Participation in an investigational trial within 30 days of randomisation that involved treatment with any drug that has not received regulatory approval at the time of study entry; Systemic anti-VEGF or pro-VEGF treatment within 3 months prior to randomisation; Pregnant or lactating women or women intending to become pregnant within the study period including 3 months after study cessation and History of major ocular surgery (including cataract extraction, scleral buckle, any intraocular surgery) within prior 3 months or anticipated within the next 6 months following randomisation. Aphakia. Uncontrolled glaucoma. External ocular infection, including conjunctivitis, chalazion, or severe blepharitis. Known allergy to fluorescein dye or to any component of the study drug.	unclear	History of treatment for diabetic macular oedema at any time in the past 3 months; systemic anti-VEGF or pro-VEGF treatment within 3 months prior to randomisation and history of major ocular surgery (including cataract extraction, scleral buckle, any intraocular surgery) within prior 3 months or anticipated within the next 6 months following randomisation.

	Inclusion criteria	Exclusion criteria (study eye)	Concomitant Medications Allowed	Concomitant Medications Disallowed
PLACID	At least 18 years of age. Diagnosis of type 1 or type 2 diabetes mellitus. Mean retinal thickness =>275 µm by OCT in the 1-mm central macular subfield due to diffuse DME not amenable to laser at stand-alone treatment (at screening). Diffuse macular capillary bed leakage evident on FA BCVA =>34 and =<70 letters (approximately 20/200 and 20/40 Snellen) using the ETDRS method (at screening and baseline).	Uncontrolled systemic disease. Use of systemic corticosteroid within 12 weeks prior to baseline or anticipated use during the study. Active ocular infection (either eye). Glaucoma (either eye). History of an IOP increase =>10 mm Hg or to =>25 mm Hg in response to corticosteroid treatment that required multiple IOP-lowering medications or laser or surgical treatment (either eye). History or presence of venous occlusive disease, uveitis, Irvine-Glass syndrome, or any condition other than diabetic retinopathy that could contribute to macular oedema Epiretinal membrane or vitreomacular traction that in the opinion of the investigator is the primary cause of the macular oedema. History of pars plana vitrectomy. Active optic disc or retinal neovascularization History of intravitreal corticosteroid use except dexamethasone or =< 4 mg triamcinolone dosed at least 13 weeks prior to baseline. Use of periocular corticosteroid within 26 weeks prior to baseline or topical nonsteroidal anti-inflammatory or corticosteroid within 4 weeks prior to baseline. Active ocular infection or history of herpetic infection in eye or adnexa. Aphakia or pseudophakia (unless there is angiographic evidence of diabetic retinopathy and cataract surgery was performed more than 3 months prior to baseline) Any intraocular injection, surgery, or laser within 13 weeks prior to baseline or anticipated need for ocular surgery during the study. Any condition or disease that in the opinion of the investigator would prevent 10-letter improvement in BCVA (e.g., severe macular ischemia, media opacity). IOP >23 mm Hg if untreated, or >21 mm Hg if treated with 1 medication. Current treatment with 2 or more IOP lowering medications.	NR	NR
Maia 2009	Patients were included if they had: 1) new vessels elsewhere >=0.5 disc area in one or more quadrants or new vessels on or within 1 disc diameter of the optic disc <0.25 to 0.33 disc area, and CSME by biomicroscopic evaluation in both eyes, 2) “symmetric” disease (defined for this study as the presence of the aforementioned characteristics [ETDRS severity level 65] in the absence of high-risk PDR in each eye), and 3) central macular thickness (CMT) > 250 um on OCT evaluation.	1) aphakia, 2) cataract surgery in the past 12 months or anticipated need for cataract surgery in the subsequent 12 months, 3) history of glaucoma or ocular hypertension, 4) loss of vision as a result of other causes, 5) systemic corticosteroid therapy, 6) severe systemic disease other than diabetes mellitus, and 7) any condition affecting follow-up or documentation (including preretinal or vitreous haemorrhage).	NR	NR

	Inclusion criteria	Exclusion criteria (study eye)	Concomitant Medications Allowed	Concomitant Medications Disallowed
IBETA	Clinically significant DME - by biomicroscopic evaluation with generalized breakdown of the inner blood-retina barrier with diffuse fluorescein leakage involving the foveal center and most of the macular area on fluorescein angiography; Snellen logarithm of minimum angle of 20/40 or worse; CMT > 275 µm on OCT.	Glycosylated haemoglobin rate above 10%; History of glaucoma or ocular hypertension; Systemic corticoid therapy; History of thromboembolic event (including myocardial infarction or cerebral vascular accident); Major surgery within the prior 6 months or planned within the next 28 days; Uncontrolled hypertension; Severe systemic disease; Any condition affecting documentation or follow-up.	NR	Systemic corticoid therapy

IOP= intraocular pressure; OCT= optical coherence tomography; YAG = Yttrium-aluminium-garnet; PC = photocoagulation; VA = visual acuity; DME = diabetic macular oedema; CNV = choroidal neovascularisation; HbA1c= glycosylated haemoglobin; BP=blood pressure; m=months; PDR= Active proliferative diabetic retinopathy; CMT= Central macular thickness; ETDRS = Early Treatment Diabetic Retinopathy Study

Treatment regimen (see Table 37**)**

Re-treatments were assessed from 12 weeks (*VIVID, VISTA, REVEAL, RESTORE, LUCIDATE*) or 16 weeks (LRT for DME, PLACID) or from 20-24 weeks (*VIVID, VISTA, IBETA*). Re-treatment was not reported in RELATION. Re-treatment criteria for laser was: thickening of retina *(VIVID, VISTA),* according to ETDRS guidelines *(RESTORE),* oedema involving the centre of the macula *(LRT for DME),* and clinically significant macula oedema *(LUCIDATE, Maia 2009).* Retreatment criteria for drug was: loss of ≥15 letters *(VIVID, VISTA),* central subfield thickness ≥275um *(IBETA),* stable vision *(REVEAL, RESTORE),* complex *(LRT for DME, PLACID),* not clearly described *(LRT for DME for PRP).*

Patients received a mean of 8.7 2Q4/2Q8 AFB injections (*VIVID*) or 8.4 2Q4/2Q8 AFB injections (*VISTA*). Note that patients in the laser arm of VIVID and VISTA received 4.2-4.4 AFB injections as rescue treatment. There were 9 injections in LRT for DME but for PRP it is unclear as it included other treatments, as well as ranibizumab.

Patients received a mean of 2.1-2.7 active laser treatments plus sham injections (number received not reported) in *VIVID* and *VISTA.* Patients received 1.5-3 active laser treatments plus 7.3-11 sham injections in *REVEAL, RESTORE, LRT for DME and LRT for DME for PRP (RELATION* did not report these outcomes).

In *RESTORE* and *REVEAL* patients received a mean of 6.8-7.8 RBZ injections plus 1.5-1.9 sham laser treatments (*LUCIDATE* did not report this outcome). Patients received a mean of 1.67 dexamethasone implants in *PLACID* and 2.5 laser treatments plus 1.64 sham injections.

Overall treatment regimens were similar for trials of the same drug but variable between drug trials. Timing and definitions for retreatment criteria were different between all trials.

For the analysis of AFB 2Q4/2Q8 versus 0.5 PRN RBZ: Patients receiving AFB had more active treatment injections than RBZ. Patients in AFB trials received similar numbers of active laser treatments to that of RBZ trials but the numbers of additional sham injections could not be compared.

For the analysis of AFB 2Q4/2Q8 versus 0.7 DEX + laser: Number of injections versus number of implant was not comparable, however patients in the AFB trials received similar

numbers of active laser treatments to that of the dexamethasone trials but the numbers of additional sham injections could not be compared.

Additional Laser treatment

All studies in the mixed treatment comparison included some degree of combination treatment, however, the nature of this combination regimen varied between studies. Patients receiving anti-VEGF treatment could receive rescue laser, prompt laser, or deferred laser. The systematic review allowed the inclusion of studies of ranibizumab or steroid monotherapy, ranibizumab or steroid combination therapy with laser, and studies including rescue laser.

Give that PLACID (laser versus dexamethasone in combination with laser) was the only study available for the MTC for dexamethasone, no comparison with dexamethasone monotherapy is therefore available.

Potential sources of bias may arise from patients receiving additional/rescue treatments (VIVID-DME, VISTA-DME, LRT for DME for PRP). In the VIVID-DME, VISTA-DME trials 4-8% patients randomised to aflibercept also received laser, and up to 32% of patients randomised to laser received aflibercept (mean of 4.2 injections). However, sensitivity analyses were conducted for VISTA/VIVID (see section 6.5.3) which showed similar results across the different populations used, with and without additional treatment.

In the RESTORE study, no differences in efficacy between the arm receiving ranibizumab and sham and the arm receiving a combination of ranibizumab and laser were identified.

The Bucher analyses tested the impact of the additional laser by comparing aflibercept monotherapy (VISTA/VIVID excluding rescue laser) versus ranbizumab therapy (RESTORE). This did not change the overall conclusions of the indirect comparison

Table 37: Comparison of treatment regimens

Study	Treatment group	n	Detailed regimen	PRN retreatment criteria for drug	Laser regimen (dose and energy) PRN criteria for laser	Mean injections received at 12 months (SD)		No. Scheduled injections
						including sham	excluding sham	
RELATION	0.5RBZ + prompt laser Fixed Q4 then PRN	85	Active laser PC at baseline. 0.5 mg RBZ at baseline, 30, 60 and 90 days, then PRN	NR Retreatment reapplied at intervals no shorter than 28 days from last treatment.	focal/grid photocoagulation Retreatment was applied at no shorter than 3 months from the last treatment. Number of laser treatments received was NR.	NR(NR)	NR(NR)	4
	laser + sham injections Fixed Q4 then PRN	43	Active laser PC procedure at baseline. Sham intravitreal injections at baseline, 30, 60 and 90 days, then PRN.			NR(NR)	NR(NR)	4
REVEAL	0.5RBZ + sham laser Fixed Q4 then PRN		RBZ/sham injections were given on day 1, month 1 and month 2 then pro-re-nata	If stable vision not reached at month 3, one injection per month continued until stable vision was reached. Intravitreal injections re-initiated if needed. No further details.	Active/sham laser photocoagulation was performed according to ETDRS guidelines at ≥3 month intervals. Active/sham laser given to treatment arms: RBZ + sham = 1.5, RBZ + laser=1.5, laser + sham = 1.9.	NA	7.8(NR)	3
	0.5RBZ + prompt laser Fixed Q4 then PRN					NA	7(NR)	3
	laser + sham injections Fixed Q4 then PRN					7.4(NR)	NA	3
RESTORE	laser + sham injections Fixed Q4 then PRN	111	3 monthly RBZ injections (or sham) at months 0-2. Further monthly injections according to retreatment criteria. Laser treatment regimen not reported.	From month 3, 1 injection/ month was to be continued if stable VA was not reached. Treatment was suspended if either of the following criteria were met: (1) no (further) BCVA improvement was attributable to treatment with intravitreal injection at the last 2 consecutive visits, (2) BCVA letter score 84 was observed at the last 2 consecutive	NR. Decisions on retreatment with laser/sham were independent of decisions to administer ranibizumab/sham injections and vice versa. Retreatment was according to ETDRS guidelines. Patients receiving retreatment with active or sham laser continued to be treated with monthly ranibizumab or sham injections as long as the treatment criteria for intravitreal injection were fulfilled. From month 3-11 patients received 0.9 sham laser in RBZ arm, 0.7 active laser in RBZ arm and 1.1 in laser + sham injection arm.	7.3(3.22) sham only	NA	3
	0.5RBZ + sham laser Fixed Q4 then PRN	116				NA	7(2.81)	3
	0.5RBZ + laser Fixed Q4 then PRN	118				NA	6.8(2.95)	3

Study	Treatment group	n	Detailed regimen	PRN retreatment criteria for	Laser regimen (dose and energy) PRN criteria for laser	Mean injections received at 12 months (SD)		No. Scheduled
				visits. Injections could be resumed PRN if there was a decrease in BCVA due to DME progression. Retreatments were given at intervals > 3 months from the previous treatment if deemed necessary.	From baseline -12 months, mean number of laser/sham laser treatments received: RBZ = 1.9±1.07 (sham), RBZ + laser = 1.7±0.89 (active), Laser = 2.1±1.04 (active).			
LRT for DME	Prompt laser + sham injections Fixed Q4 then PRN	293	Laser (1 week after first sham) + sham injections every 4 weeks to 12-weeks study visit. PRN from 16-weeks.	Retreatment assessed from 16 wk study visit. Drug was given unless deemed a 'success' (VA letter score 84 (20/20) or OCT central subfield thickness <250 microns since last injection / baseline for the sham prompt laser group. From the 24-wk study visit and thereafter retreatment was if the study visit was deemed 'no improvement'. Treatment for DME other than the randomization-assigned regimen) was permitted (VA ≥ 10 or letters worse than baseline, OCT central subfield thickness 250 µm, DME judged to be the cause of visual acuity loss, and at least 13 weeks since 'complete laser' had been given with 'no improvement). Retreatment with RBZ could be every 4 weeks; IVTA every 16 wks.	The laser treatment 'session' should generally be completed in a single 'sitting'. Focal/grid photocoagulation administered using modified ETDRS protocol. Subsequent laser treatment following an injection, if needed. PRN if there was 'edema involving the center of the macula' or 'edema threatening the center of the macula' (defined as: OCT central subfield thickness >= 250 µm) and if 'complete laser' had not been given (defined as: Direct treatment to all microaneurysms within areas of macular edema and grid treatment to all other areas of macular edema), provided that it had been at least 13 weeks since the last focal/grid laser application. Deferred laser treatment only given if eye was not improving from RBZ. Eyes assigned to sham + prompt laser could receive sham injections every 4 weeks. Median laser treatments: prompt laser + sham = 3, RBZ + prompt laser = 2, IVTA + prompt laser = 2.	11(NR)	NA	4
	0.5RBZ + prompt laser Fixed Q4 then PRN	187	RBZ injections every 4 weeks to 12-weeks study visit. PRN from 16-weeks. Laser given 7-10 days after first RBZ.			NA	8(NR)	4
	0.5RBZ + deferred laser Fixed Q4 then PRN	188	RBZ injections every 4 weeks to 12-weeks study visit. PRN from 16-weeks. Laser given 24 days after first RBZ.			NA	9(NR)	4
	4IVTA + laser Fixed Q4 then PRN	186	4 mg IVTA at randomization plus laser 1 week post-injection, repeated every 16 weeks with sham at 4-wk intervals in-between. PRN from 16 wk.			8(NR)	3	1

Study	Treatment group	n	Detailed regimen	PRN retreatment criteria for	Laser regimen (dose and energy) PRN criteria for laser	Mean injections received at 12 months (SD)		No. Scheduled
LRT for DME for PRP	laser + sham injections Fixed then PRN	123	Two injections (RBZ/sham) were given, one at baseline and one at 4 weeks. After the 14 week visit, varied additional treatments were at the investigator's discretion (including BVZ).	At the investigator's discretion	The focal/grid laser technique was modified from the original ETDRS protocol. Panretinal photocoagulation consisted of 1200 to 1600 burns given over 1 sitting to 3 sittings, with completion of the regimen within 49 days of randomization. Focal/grid laser for DME was performed 3 days to 10 days after the injection for all treatment groups. Panretinal photocoagulation could be initiated immediately after the focal/grid laser or on a subsequent day but was to be initiated within 14 days of the baseline injection and fully completed within 49 days of randomization. Additional PRP was performed only if the size or amount of neovascularization increased after completion of the study-required PRP. Median number of focal/grid laser treatments: RBZ + prompt laser = 2, RBZ + deferred laser = 0, IVTA + prompt laser = 2.	NR(NR)	NR(NR)	2
	0.5RBZ + laser Fixed then PRN	113				NR(NR)	NR(NR)	2
	4IVTA + laser Fixed then PRN	109	One injection IVTA was given at baseline and a sham injection at 4 weeks. After the 14-week visit, additional treatment was at the investigator's			NR(NR)	NR(NR)* *Studies reported number of eyes receiving additional treatments, but not mean injections.	1 + 1 sham
LUCIDATE	0.5RBZ Fixed Q4 then PRN		Intravitreal injection at baseline, 4 and 8 weeks then four-weekly as required to 44 weeks.	NR	Argon laser therapy to the macula in accordance with the modified ETDRS protocol. PRN every 12 weeks if CSME present. Number of laser treatments received was NR.	NR(NR)	NR(NR)	3
	Laser Fixed then PRN		Argon laser at baseline, 12, 24 and 36 weeks.			NR(NR)	NR(NR)	0
PLACID	0.7 DEX + laser Fixed then PRN	127	Dex at baseline (single-use applicator with a 22-gauge needle was used to place implant in the vitreous cavity	Retreatment was evaluated at months 4, 6, and 9. Patients had to meet all 4 of the following criteria: (1) mean retinal thickness in the 1-mm central macular subfield of	Modified ETDRS focal (direct/grid) laser photocoagulation using yellow- or green-wavelength laser. Laser treatment was applied to all areas of the retina that had been determined to be thickened or leaking based on the results of the clinical examination, OCT, and FA performed at the	1.67(NR)	1.67(NR)	1

Study	Treatment group	n	Detailed regimen	PRN retreatment criteria for	Laser regimen (dose and energy) PRN criteria for laser	Mean injections received at 12 months (SD)		No. Scheduled
			through the pars plana). One month later patients received laser.	the study eye of =>250 on time-domain OCT; (2) a min interval between treatments of at least 3 m for laser retreatment and at least 6 m for DEX implant/ sham retreatment; (3) patient not at significant risk from retreatment; and (4) patient may benefit from retreatment. Patients could receive up to 3 additional laser treatments and 1 additional DEX implant or sham treatment (at month 6 or 9).	screening visit. Average laser treaments received/patient; DEX=2.25, sham injection=2.5			
	Laser + sham injection Fixed then PRN	126	Sham injection at baseline (an applicator was pressed against the conjunctiva). One month later patients received laser.			1.64(NR) sham only	0(NR)	1 (sham)
IBETA	Laser Fixed + PRN	23	Focal / grid PC (no other detail reported)	Retreatment was performed at weeks 20 and 40 if central subfield macular thickness higher than 275 µm.	Focal / grid photocoagulation for diabetic macular edema according to ETDRS guidelines. Number of laser treatments received was NR.	NR(NR)	NR(NR)	0
	1.5mg BVZ + laser PC Fixed + PRN	21	Intravitreal bevacizumab (1.5 mg). 4 weeks later focal PC given.			NR(NR)	NR(NR)	1
	4mg IVTA+laser Fixed + PRN	20	Intravitreal preservative-free triamcinolone (4 mg) given at baseline. 4 weeks later focal PC given.			NR(NR)	NR(NR)	1
Maia 2009	Laser Fixed then PRN	22	After completion of the bilateral PRP session at week 3, one eye (per patient) was randomly assigned to receive one IVTA (IVTA group), and fellow eyes received no	NR – assumed this was a single injection.	Laser PC consisted of fullscatter PRP treatment performed in three episodes (at weeks 1, 2, and 3) according to ETDRS guidelines. 400-600 x 500 µm spots were performed/ PRP episode, at the discretion of the treating investigator. Macular (focal and/or grid) laser PC guided by FA findings was performed at the first laser treatment (wk 1) for all patients. Additional macular (grid and/or focal) laser treatment was permitted if CSME and	NR(NR)	NR(NR)	0
	4IVTA + laser Fixed then PRN	22				NR(NR)	NR(NR)	1

Study	Treatment group	n	Detailed regimen	PRN retreatment criteria for	Laser regimen (dose and energy) PRN criteria for laser	Mean injections received at 12 months (SD)		No. Scheduled
			additional treatment (control group).		treatable lesions on FA were still present at any follow-up study visit. Focal leaks > 500 µm from the center of the macula were also treated, and grid treatment was not usually reapplied to areas that had been treated previously. Additional laser given to 13 patients in control group and 2 patients of IVTA group.			

NE = Not Evaluable; SD = standard deviation; NR = not reported; CRT = central retinal thickness; SE = standard error; HRQOL = health related quality of life; HbA1c = Glycosylated haemoglobin; AFB = aflibercept; BCVA=best-corrected visual acuity; BVZ = Bevacizumab; DEX = Dexamethasone; Log MAR = logarithm of minimal angle of resolution; OCT = Optical coherence tomography; PRN. = pro re nata; RBZ = ranibizumab; PC = photocoagulation; IVTA = intravitreal triamcinolone acetonide; ETDRS = Early Treatment Diabetic Retinopathy Study; mths = months; wks = weeks; 2Q8 = 2.0 mg intravitreal injections every eight weeks; 2Q4 = 2.0 mg intravitreal injections every four weeks; m = month; mg = Milligrams; N/A = not applicable; VA= visual acuity; AE = adverse events; CMT = central macular thickness; CRT = central retinal thickness; FA = fluorescein angiography;

Baseline characteristics (see Table 38)

All four trials which were reported as abstracts poorly reported their baseline characteristics (*IBETA*, *RELATION, REVEAL, LUCIDATE*), preventing a detailed comparison of their characteristics. Within trials, treatment arms were evenly matched.

A comparison of the different trials indicated that they differed considerably in size. *VIVID, VISTA, RESTORE, REVEAL, LRT for DME, LRT for DME for PRP, PLACID* had 109 to 293 patients per treatment arm, whereas *LUCIDATE, Maia 2009 and IBETA* had less than 25 patients per arm. *RELATION* had 43-85 patients/arm. The mean patient age was between 60 and 64 years except for *LRT for DME for PRP* where patients had a median age of 54-58 years. The proportion of men in the trials ranged from 49% to 65%, except in Maia 2009 which had 45.5% of men overall. Ethnicity was reported by five trials (*VIVID, VISTA, LRT for DME for PRP, PLACID),* each trial reported different ethnic groups but overall the groups were predominantly white (56-85%), followed by variable proportions of Black or African/American (1-17%), Asian (1-20%) or Hispanic/Latino (8-25%). Patients predominantly had type 2 diabetes (82-100%) in five trials (*VISTA, RESTORE, LRT for DME, LRT for DME for PRP, Maia 2009)* and the average duration of diabetes was 9-18 years, as reported in six trials *(VIVID, VISTA, RESTORE LRT for DME, LRT for DME for PRP, Maia 2009).* The average glycosylated haemoglobin (HbA1c) was 7.2 to 8.1% *(VIVID, VISTA, RESTORE LRT for DME, LRT for DME for PRP),* but was higher in *Maia 2009* at 9.6% in both groups overall. The type of DMO was reported by four trials; in one trial (*RESTORE*) there was predominantly focal DMO (48-58%) and in three trials (*LRT for DME, LRT for DME for PRP, PLACID*) there was predominantly diffuse DMO (42-100%).

Central retinal thickness, where reported, varied between studies from 412 (*RESTORE*) to 540µm (*VIVID*); central macula subfield varied from 352µm (*LRT for DME for PRP*) to 421µm (*IBETA*). 'Choroidal thickness at the central macula' was also reported by *LUCIDATE* and varied from 244µm to 265µm and 'central macular thickness' was reported by *Maia 2009* and varied from 332µm to 360µm. It was unclear if these measurements are physiologically equivalent.

Mean ETDRS score at baseline varied from 57-58 letters (*PLACID*), 59-61 (*VIVID, VISTA*), 62-65 (*RESTORE*). Some trials reported visual acuity as a mean Log MAR of 0.63-0.68, equivalent to 31.5-34 letters (*IBETA*) and 0.38-0.44, equivalent to 19-22 letters (Maia

2009). *LRT for DME* and *LRT for DME for PRP* only reported mean Snellen equivalents of 65-68. (Note 5 letters = 0.1 logMAR).

HRQOL scores (NEI-VFQ-25) were only reported by *VIVID, VISTA* and *RESTORE*, mean values varied from 68-77. Four trials reported previous therapy for DME, including anti-VEGF and laser (*VISTA, LRT for DME, LRT for DME for PRP, PLACID),* for two of these trials this was an exclusion criteria *(LRT for DME, LRT for DME).*

Overall it was difficult to compare baseline characteristics due to the lack of reporting of these items.

For the analysis of AFB 2Q4/2Q8 versus 0.5 PRN RBZ: Of all the trials *LUCIDATE, Maia 2009 and IBETA* were most dissimilar to the others in terms of size, and baseline ETDRS score and potentially macula thickness. For the analysis of AFB 2Q4/2Q8 versus 0.7 DEX + laser: *VIVID-DME, VISTA-DME and PLACID* all had similar baseline characteristics where reported, CRT and ETDRS were broadly equivalent.

Table 38: Summary of patient baseline characteristics for RCTs included in indirect comparative analyses (see section 6.3.4 for aflibercept data [VISTA and VIVID])

Study	**RELATION**		**LUCIDATE**	
Treatment group	**0.5RBZ+ prompt laser Fixed Q4 then PRN**	**laser + sham injections Fixed Q4 then PRN**	**0.5Ranibizumab Fixed Q4 then PRN**	**laser Fixed then PRN**
n randomised	**85**	**43**	**11**	**11**
Age: Mean (SD)	63.5(9.3)	63.5(10.5)	NR(NR)	NR(NR)
Median (range)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)
Gender: Males %	62.3	62.8	NR	NR
Ethnicity (%)	NR	NR	NR	NR
Diabetes				
Type 1 (%)	NR	NR	NR	NR
Type 2 (%)	NR	NR	NR	NR
Duration of diabetes (yrs): Mean (SD)	NR(NR)	NR(NR)	NR	NR
Median (range)	NR(NR)	NR(NR)	NR(NR)	NR(NR)
% HbA1c: Mean (SD)	NR(NR)	NR(NR)	NR(NR)	NR(NR)
Median (range)	NR(NR)	NR(NR)	NR(NR)	NR(NR)
Type DMO			NR(NR)	NR(NR)
Predominantly focal (%)	NR	NR		
Neither focal or diffuse is predominant (%)	NR	NR	NR	NR
Predominantly diffuse (%)	NR	NR	NR	NR
Not specified (%)	NR	NR	NR	NR
CRT µm: Mean (SD) or *median* **Definition:**	NR(NR)	NR(NR)	243.5(58.8) Choroidal thickness at central macula.	264.6(51.8) Choroidal thickness at central macula.
ETDRS score: Mean (SD)	NR(NR)	NR(NR)	NR	NR
Median (range)	NR(NR-NR)	NR(NR-NR)	NR(NR)	NR(NR)
LogMAR, mean (SD) *SE*	NR(NR)	NR(NR)	NR(NR-NR)	NR(NR-NR)
Approx. Snellen equivalent: Median	NR	NR	NR(NR)	NR(NR)
20/200 or worse (%)	NR	NR	NR	NR
20/200 -20/40 (%)	NR	NR	NR	NR
20/40 or better (%)	NR	NR	NR	NR
HRQOL (NEI VFQ-25 score): Mean (SD)	NR(NR)	NR(NR)	NR	NR
Median (range)	NR(NR-NR)	NR(NR-NR)	NR(NR)	NR(NR)
Previous DMO therapy	NR	NR	NR(NR-NR)	NR(NR-NR)

Study	RESTORE			REVEAL		
Treatment group	**laser + sham injections Fixed Q4 then PRN**	**0.5RBZ+sham laser Fixed Q4 then PRN**	**0.5RBZ+ laser Fixed Q4 then PRN**	**0.5RBZ+sham laser Fixed Q4 then PRN**	**0.5RBZ+ prompt laser Fixed Q4 then PRN**	**laser + sham injections Fixed Q4 then PRN**
n randomised	**111**	**116**	**118**	**133**	**132**	**131**
Age: Mean (SD)	63.5(8.81)	62.9(9.29)	64(8.15)	60.7(9.37)	61.2(10.52)	61.5(9.68)
Median (range)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)
Gender: Males %	52.3	62.9	59.3	60.9	50.75	57.25
Ethnicity (%)	NR	NR	NR	NR	NR	NR
Diabetes						
Type 1 (%)	11.7	11.2	12.7	NR	NR	NR
Type 2 (%)	87.4	88.8	86.4	NR	NR	NR
Uncertain/NR (%)	0.9	0	0.8	NR	NR	NR
Duration of diabetes (yrs): Mean (SD)	12.93(9.02)	15.23(9.91)	14.62(9.84)	NR(NR)	NR(NR)	NR(NR)
Median (range)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)
% HbA1c: Mean (SD)	7.28(1.11)	7.23(1.08)	7.5(1.1)	NR(NR)	NR(NR)	NR(NR)
Median (range)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)
Type DMO						
Predominantly focal (%)	47.7	55.2	57.6	NR	NR	NR
Neither focal or diffuse is predominant (%)	NR	NR	NR	NR	NR	NR
Predominantly diffuse (%)	46.8	38.8	39	NR	NR	NR
Not specified (%)	5.4	6	3.4	NR	NR	NR
CRT µm: Mean (SD) or *median* **Definition:**	412.4(123.95) central retinal	426.6(118.01) central retinal	416.4(119.91) central retinal	NR(NR)	NR(NR)	NR(NR)
ETDRS score: Mean (SD)	62.4(11.11)	64.8(10.11)	63.4(9.99)	NR(NR)	NR(NR)	NR(NR)
Median (range)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)
LogMAR, mean (SD) *SE*	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)
Approx. Snellen equivalent: Median	20/63	20/50	20/50	NR	NR	NR
20/200 or worse (%)	NR	NR	NR	NR	NR	NR
20/200 -20/40 (%)	NR	NR	NR	NR	NR	NR
20/40 or better (%)	NR	NR	NR	NR	NR	NR
HRQOL (NEI VFQ-25 score): Mean (SD)	73.5(18.2)	72.8(16.9)	74.1(18.1)	NR(NR)	NR(NR)	NR(NR)
Median (range)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)
Previous DMO therapy	NR	NR	NR	NR	NR	NR

Study	LRT for DME			
Treatment group	**laser + sham injections Fixed Q4 then PRN**	**0.5RBZ+ prompt laser Fixed Q4 then PRN**	**0.5RBZ+ deferred laser Fixed Q4 then PRN**	**4IVTA+laser Fixed Q4 then PRN**
n randomised	**293**	**187**	**188**	**186**
Age: Mean (SD)	NR(NR)	NR(NR)	NR(NR)	NR(NR)
Median (range)	63(NR-NR)	62(NR-NR)	64(NR-NR)	62(NR-NR)
Gender: Males %	58	55	59	54
Ethnicity (%)	White 69%; African-American 17%; Hispanic or Latino 12%; Asian 1%; More than one race <1%; Unknown /NR <1%	White 70%; African-American 16%; Hispanic or Latino 11%; Asian 1%; Hawaiian/ Pacific Islander 1%; More than one race 1%; Unknown/NR 1%	White 71%; African-American 13%; Hispanic or Latino 13%; Asian 1%; More than one race 1%; Unknown/NR 1%	White 72%; African-American 17%; Hispanic or Latino 8%; Asian 2%; Unknown/NR 1%
Diabetes				
Type 1 (%)	9	6	8	8
Type 2 (%)	89	92	90	89
Uncertain/NR (%)	3	2	2	3
Duration of diabetes (yrs): Mean (SD)	NR(NR)	NR(NR)	NR(NR)	NR(NR)
Median (range)	16(NR)	18(NR)	17(NR)	17(NR)
% HbA1c: Mean (SD)	NR(NR)	NR(NR)	NR(NR)	NR(NR)
Median (range)	7.3(NR)	7.3(NR)	7.5(NR)	7.4(NR)
Type DMO				
Predominantly focal (%)	27	32	36	28
Neither focal or diffuse is predominant (%)	24	25	22	26
Predominantly diffuse (%)	49	43	42	46
CRT µm: Mean (SD) or *median* **Definition:**	407*(NR) central subfield	371*(NR) central subfield	382*(NR) central subfield	374*(NR) central subfield
ETDRS score: Mean (SD)	NR(NR)	NR(NR)	NR(NR)	NR(NR)
Median (range)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)
LogMAR, mean (SD) *SE*	NR(NR)	NR(NR)	NR(NR)	NR(NR)
Approx. Snellen equivalent: Median	65	66	66	66
20/200 or worse (%)	3	6	2	5
20/200 -20/40 (%)	56	57	61	55
20/40 or better (%)	40	37	37	40
HRQOL (NEI VFQ-25 score): Mean (SD)	NR(NR)	NR(NR)	NR(NR)	NR(NR)
Previous DMO therapy	Panretinal PC 16%; laser 59%;	Panretinal PC 19%; laser 54%; IVT	Panretinal PC 16%; laser 54%;	Panretinal PC 20%; laser 61%;

	IVT 13%; vitrectomy 5%; peribulbar triamcinolone 4%; anti-VEGF 8%	12%; vitrectomy 4%; peribulbar triamcinolone 5%; anti-VEGF 13%	IVT 19%; vitrectomy 3%; peribulbar triamcinolone 3%; anti-VEGF 11%	IVT 17%; vitrectomy 6%; peribulbar triamcinolone 3%; anti-VEGF 11%

Study	**LRT for DME for PRP**		
Treatment group	**laser + sham injections** **Fixed**	**0.5RBZ+ laser** **Fixed**	**4IVTA+laser** **Fixed**
n randomised	**123**	**113**	**109**
Age: Mean (SD)	NR(NR)	NR(NR)	NR(NR)
Median (range)	54(NR-NR)	57(NR-NR)	58(NR-NR)
Gender: Males %	64.2	57.5	59.6
Ethnicity (%)	White 62%, African American 9%, Hispanic or Latino 25%, Asian 2%, American Indian/Alaskan Native 1%, Unknown/NR 1%	White 64%, African American 13%, Hispanic or Latino 23%, Asian 1%, Native Hawaiian/Other Pacific Islander 1%, Unknown/NR 1%	White 56%, African American 17%, Hispanic or Latino 25%, Asian 2%, American Indian/ Alaskan Native 1%
Diabetes			
Type 1 (%)	16	12	11
Type 2 (%)	82	82	87
Uncertain/NR (%)	2	6	2
Duration of diabetes (yrs): Median (range)	15(NR)	15(NR)	15(NR)
% HbA1c: Mean (SD)	NR(NR)	NR(NR)	NR(NR)
Median (range)	7.9(NR)	8.1(NR)	8.1(NR)
Type DMO			
Predominantly focal (%)	30	17	25
Neither focal /diffuse is predominant (%)	15	22	13
Predominantly diffuse (%)	55	61	62
CRT µm: Mean (SD) or *median* **Definition**	355*(NR) central subfield	352*(NR) central subfield	359*(NR) central subfield
ETDRS score: Mean (SD)	NR(NR)	NR(NR)	NR(NR)
Median (range)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)
LogMAR, mean (SD) *SE*	NR(NR)	NR(NR)	NR(NR)
Approx. Snellen equivalent: Median	67	68	67
20/200 or worse (%)	11.4	4.4	5.5
20/200 -20/40 (%)	40.7	46.9	51.4
20/40 or better (%)	48	48.7	43.1
HRQOL (NEI VFQ-25 score): Mean (SD)	NR(NR)	NR(NR)	NR(NR)
Median (range)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)
Previous DMO therapy	Laser 33%, ITCL 1%, Vitrectomy 2%, Peribulbar TCL 1%, Anti-VEGF 5%	Laser 29%, ITCL 8%, Vitrectomy 0%, Peribulbar TCL 0%, Anti-VEGF 1%	Laser 33%, ITCL 3%, Vitrectomy 0%, Peribulbar TCL 1%, Anti-VEGF 3%

Study	PLACID	
Treatment group	**0.7 DEX + laser Fixed then PRN**	**Laser + sham injection Fixed then PRN**
n randomised	**126**	**127**
Age: Mean (SD)	61.8(11.1)	61.3(9.3)
Median (range)	NR(25-93)	NR(30-86)
Gender: Males %	49.2	52
Ethnicity (%)	White: n=82 (65.1%), Hispanic: n=26 (20.6%), Black: n=11 (8.7%), Asian: n=3 (2.4%), Other: n=4 (3.2%).	White: n=73 (57.5%), Hispanic: n=27 (21.3%), Black: n=14 (11.0%), Asian: n=4 (3.1%), Other: n=9 (7.1%).
Diabetes		
Type 1 (%)	NR	NR
Type 2 (%)	NR	NR
Uncertain/NR (%)	NR	NR
Duration of diabetes (yrs): Mean (SD)	NR(NR)	NR(NR)
Median (range)	NR(NR)	NR(NR)
% HbA1c: Mean (SD)	NR(NR)	NR(NR)
Median (range)	NR(NR)	NR(NR)
Type DMO		
Predominantly focal (%)	0	0
Neither focal or diffuse is predominant (%)	0	0
Predominantly diffuse (%)	126(100)	127 (100)
CRT µm: Mean (SD) or *median* **Definition**	438 (134) Central retinal	430 (131) Central retinal
ETDRS score: Mean (SD)	57(9.4)	57.5(9.5)
Median (range)	NR(NR-NR)	NR(NR-NR)
LogMAR, mean (SD) *SE*	NR(NR)	NR(NR)
Approx. Snellen equivalent: Mean	NR	NR
20/200 or worse (%)	NR	NR
20/200 -20/40 (%)	NR	NR
20/40 or better (%)	NR	NR
HRQOL (NEI VFQ-25 score):	NR(NR)	NR(NR)
Previous DMO therapy	3.2% received medical treatment(in both arms), 64% had received laser (unclear if this is for DME).	NR

Study	IBETA			Maia 2009	
Treatment group	**Laser Fixed then PRN**	**1.5mgBVZ+ laser PC Fixed then PRN**	**4mgIVTA+laser Fixed then PRN**	**laser Fixed then PRN**	**4IVTA+laser Fixed then PRN**
n randomised	**23**	**21**	**20**	**22**	**22**
Age: Mean (SD)	NR(NR)	NR(NR)	NR(NR)	61.9(5.3)	
Median (range)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)
Gender: Males %	NR	NR	NR	45.5	

Study	IBETA			Maia 2009	
Treatment group	**Laser Fixed then PRN**	**1.5mgBVZ+ laser PC Fixed then PRN**	**4mgIVTA+laser Fixed then PRN**	**laser Fixed then PRN**	**4IVTA+laser Fixed then PRN**
Ethnicity (%)	NR	NR	NR	NR	NR
Diabetes					
Type 1 (%)	NR	NR	NR	0	
Type 2 (%)	NR	NR	NR	100	
Duration of diabetes (yrs): Mean (SD)	NR(NR)	NR(NR)	NR(NR)	NR	
Median (range)	NR(NR)	NR(NR)	NR(NR)	8.9(5.4)	
% HbA1c: Mean (SD)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	
Median (range)	NR(NR)	NR(NR)	NR(NR)	9.6(1.4)	
Type DMO					
Predominantly focal (%)	NR	NR	NR	NR	NR
Neither focal or diffuse is predominant (%)	NR	NR	NR	NR	NR
Predominantly diffuse (%)	NR	NR	NR	NR	NR
Not specified (%)	NR	NR	NR	NR	NR
CRT µm: Mean (SD) or *median* **Definition:**	421.4(NR) central subfield macula thickness	410.2(NR) central subfield macula thickness	402.3(NR) central subfield macula thickness	331.68(78.88) Central macula	360.05(84.85) Central macula
ETDRS score: Mean (SD)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)
Median (range)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)
LogMAR, mean (SD) *SE*	0.65(0.08)*	0.63(0.07)*	0.68(0.06)*	0.38(0.17)	0.44(0.17)
Approx. Snellen equivalent: Median	NR	NR	NR	20/50+1	20/50+2
20/200 or worse (%)	NR	NR	NR	NR	NR
20/200 -20/40 (%)	NR	NR	NR	NR	NR
20/40 or better (%)	NR	NR	NR	NR	NR
HRQOL (NEI VFQ-25 score): Mean (SD)	NR(NR)	NR(NR)	NR(NR)	NR(NR)	NR(NR)
Median (range)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)	NR(NR-NR)
Previous DMO therapy	NR	NR	NR	NR	NR

SD = standard deviation; NR= not reported; CRT= central retinal thickness; SE= standard error; HRQOL= health related quality of life; HbA1c = Glycosylated haemoglobin; PC=photocoagulation.

Quality assessment of included RCTs

A summary of quality assessment of the trials is shown in Table 39 and detailed critical appraisals are provided in Appendix 10.5.

Overall six trials (*VIVID, VISTA, IBETA, RESTORE, LRT for DME for PRP, Maia 2009*) were rated as being at a high risk of bias for at least one domain. There were five trials (*REVEAL, RELATION, LRT for DME, LUCIDATE and PLACID*) that were at low or unclear risk of bias in all domains. All trials were randomised, however only four (*VIVID, VISTA, RESTORE and PLACID*) provided methodological details to confirm that this was adequate. Allocation concealment was adequate in three trials (*VIVID, VISTA and PLACID*). The other trials did not report any details of allocation concealment. Two trials were open-label studies (*LUCIDATE and IBETA*), four further trials were judged to have a high risk of bias due to inadequate blinding of personnel (*VIVID, VISTA, RESTORE*) or patients (*Maia 2009)*. Only one trial was judged to have a high risk of bias due to a lack of assessment blinding *(RESTORE*). Two trials were judged to have a high risk of incomplete data; one appeared to report data only for eyes completing the trial *(IBETA*) and one trial had excluded three eyes from the analysis due to adverse events (*Maia 2009*). Six trials (*VIVID, VISTA, RESTORE, RELATION, LRT for DME, PLACID*) were judged to be associated with a low risk of bias because they applied ITT analysis with LOCF to impute missing data and therefore incomplete outcome data were adequately addressed. Only one trial had a high risk of bias due to selective reporting of outcomes (*IBETA*).

Other sources of bias arose from patients receiving additional/rescue treatments (*VIVID, VISTA, LRT for DME for PRP*). In the *VIVID, VISTA* trials 4-8% patients randomised to VEGF also received laser, and up to 32% of patients randomised to laser received VEGF (mean of 4.2 injections). IBETA was judged to have a high risk of other bias because there was inconsistent reporting of the 'number of eyes' between the different abstract publications. In addition six trials were noted to have industry funding (*VIVID, VISTA, RESTORE, REVEAL, RELATION, PLACID*) and three had mixed funding (*LRT for DME, LRT for DME for PRP, LUCIDATE).*

In total four trials were published as abstracts only (*IBETA, REVEAL, RELATION, LUCIDATE*), with a lack of information, and this generally explained the reason for high (*IBETA*) or unclear (*REVEAL, RELATION, LUCIDATE*) risk of bias in these studies.

Overall the studies were not similar with regards to risk of bias.

For the analysis of AFB 2Q4/2Q8 vs. 0.5 PRN RBZ: *VIVID, VISTA, IBETA, RESTORE, LRT for DME for PRP, Maia 2009* all had a high risk of bias for at least one domain, whilst *REVEAL, RELATION, LRT for DME, LUCIDATE* had no high risk of bias in any domain.

For the analysis of AFB 2Q4/2Q8 vs. 0.7 DEX + laser: *VIVID, VISTA* both had a high risk of bias in two domains, whilst *PLACID* had no high risk of bias in any domain.

Table 39: Summary of the risk of bias

Study	Random Sequence Generation	Allocation Concealment	Blinding Participants/Personnel	Blinding Outcome Assessment	Incomplete Outcome data	Selective Reporting	Other
VIVID-DME	L	L	H	L	L	L	H
VISTA-DME	L	L	H	L	L	L	H
IBETA	U	U	H	U	H	H	H
RESTORE	L	U	H	H	L	L	U
REVEAL	U	U	U	U	U	L	U
RELATION	U	U	U	U	L	U	U
LRT for DME	U	U	U	L	L	L	L
LRT for DME for PRP	U	U	U	L	U	L	H
LUCIDATE	U	U	U	U	U	U	U
Maia 2009	U	U	H	L	H	U	L
PLACID	L	L	L	L	L	L	U

Risk of Bias: L = Low, U = Unclear, H = High

Results of the included studies

Aflibercept: VISTA-DME and VIVID-DME – see section 6.5.

Ranibizumab:

- RESTORE(31). Ranibizumab alone and combined with laser were superior to laser monotherapy in improving mean average change in BCVA letter score from baseline to month 1 through 12 (+6.1 and +5.9 vs +0.8; both P<0.0001). The mean change ± SD in BCVA letter score from baseline to month 12 was 6.8 ± 8.3 (*P*<0.0001) in the ranibizumab arm, 6.4 ± 11.8 (*P* < 0.0004) in the ranibizumab plus laser arm, and 0.9

± 11.4 in the laser arm. At month 12, a significantly greater proportion of patients gained a ≥15 and ≥10 BCVA letter score and BCVA letter score with ranibizumab (22.6% and 37.4%, respectively) and ranibizumab + laser (22.9% and 43.2%) versus laser (8.2% and 15.5%). Conversely, a lower proportion of patients lost ≥10 and ≥15 letters in both the ranibizumab arms compared with the laser arm.

- The REVEAL study compared ranibizumab (0.5 mg) with ranibizumab plus laser and laser alone (32). At 12 months, both ranibizumab arms resulted in a statistically significantly better improvement in BCVA compared to laser alone.

- LRT for DME (34). The 1-year mean change (±SD) in the visual acuity letter score from baseline was significantly greater in the ranibizumab + prompt laser group (+9±11, P<0.001) and ranibizumab + deferred laser group (+9±12, P<0.001) but not in the triamcinolone + prompt laser group (+4±13, P=0.31) compared with the sham + prompt laser group (+3±13).

- LRT for DME for PRP (35). Mean changes (±SD) in visual acuity letter score from baseline were significantly better in the ranibizumab (+1 ± 11; P < 0.001) and triamcinolone (+2 ± 11; P < 0.001) groups compared with those in the sham group (-4 ± 14) at the 14-week visit, mirroring retinal thickening results. These differences were not maintained when study participants were followed for 56 weeks for safety outcomes.

- LUCIDATE (36). Ranibizumab-treated patients gained 6.0 ETDRS letters while laser subjects lost 0.9 letters (p=0.008) at 48 weeks.

Dexamethasone:

- PLACID (39). Patients were randomised to dexamethasone implant at baseline plus laser or sham implant and laser. Although a greater improvement in mean BCVA was seen at 1–9 months in the dexamethasone plus laser group compared with laser alone, there was no statistically significant difference at 12 months.

The IBETA (37), RELATION (33) and MAIA (38) studies contributed results of focal / grid photocoagulation for diabetic macular oedema.

Limitations of the review

One of the main limitations of the review was the quality (risk of bias) of the included studies. All of the included studies had unclear or high risk of bias in at least one domain of the Cochrane risk of bias tool (Table 39). Typically, this was either because trials were only available as abstracts or because methodological details were poorly reported. The most common issue was inadequate blinding of patients and of study personnel/outcome assessors (*VIVID, VISTA, RESTORE, IBETA, Maia 2009*). In *VIVID, VISTA* and in *RESTORE* some personnel involved in the trial were unblinded, therefore this carries the risk that treatment assignment may have been revealed. *IBETA* was an open label study with no blinding of participants or personnel. *Maia 2009* compared 4mg IVTA + laser versus laser with no sham injections in the laser group, therefore the patients in this trial could not be blinded to their treatment assignment. Blinding of those personnel delivering the intravitreal treatments is difficult in this type of trial as the sham injection procedure typically involves pressing a syringe with no needle against the eye compared to syringe with needle for the active treatment.

Patient baseline characteristics were often poorly reported which made it difficult to compare populations between trials, particularly for those trials which were only reported as abstracts. Variation between trials in the definition of parameters (e.g. central macular thickness) also contributed to this issue.

The application of additional or rescue treatments other than the randomly assigned treatment was also an issue. The time at which these treatments became available and the criteria for further treatment varied between trials. The use of additional treatments is clearly justified ethically for those patients whose disease is worsening. The differences in how this is implemented in different trials means that comparisons between trials must be interpreted with this in mind.

The follow-up period of the aflibercept (*VIVID, VISTA*) and dexamethasone (*PLACID*) studies was relatively short at 12 months compared to the ranibizumab trials which had up to three years follow-up in some cases. This is largely because aflibercept and dexamethasone are relatively new treatments and few studies have yet been published. This situation is expected to improve as the existing trials mature and new studies become available.

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.

Two trials (VISTA and VIVID) investigated aflibercept compared with laser photocoagulation (VISTA and VIVID). Six studies (RELATION, RESTORE, REVEAL, LRT for DME, LRT for DME for PRP, and LUCIDATE) investigated ranibizumab compared with laser photocoagulation. No trials investigated both ranibizumab and aflibercept. The review additionally identified one study comparing bevacizumab or triamcinolone in combination with laser vs. laser (IBETA), one study comparing triamcinolone plus laser with laser alone (Maia 2009) and one study involving a comparison between dexamethasone plus laser versus laser plus sham injections (PLACID).

The indirect analyses within the submission will consider the comparisons between aflibercept and ranibizumab and aflibercept and dexamethasone intravitreal implant, as stated in Section 4, although the comparison versus dexamethasone is limited as it excludes the MEAD study due to a different control arm being in each study.

Table 40. Summary of the trials used to conduct the indirect comparison

No. trials	STUDY	Intervention	Comparator(s)
1	VISTA (17)	Aflibercept	Laser photocoagulation (laser)
2	VIVID (17)	Aflibercept	Laser photocoagulation
3	IBETA (37)	Laser photocoagulation	Bevacizumab (1.5mg) + laser Triamcinolone (4mg) + laser
4	RELATION (33)	Ranibizumab + prompt laser	Laser photocoagulation + sham injections
5	RESTORE (31)	Ranibizumab + laser	Laser + sham injections Ranibizumab + sham laser
6	REVEAL (32)	Ranibizumab + laser	Laser + sham injections Ranibizumab + sham laser
7	LRT for DME (34)	Ranibizumab + prompt laser Ranibizumab + deferred laser	Laser + sham injections Triamcinolone + laser
8	LRT for DME for PRP (35)	Laser + sham injections	Ranibizumab + laser Triamcinolone + laser
9	LUCIDATE (36)	Ranibizumab	Laser
10	Maia 2009 (38)	Triamcinolone + laser	Laser
11	PLACID (39)	Dexamethasone + laser	Laser + sham injections

A summary of the NMA are presented in the Network of evidence diagram below. As highlighted in section 6.7.2 the comparison between aflibercept and fluocinolone acetonide implants was not possible because the included fluocinolone trials (FAME) did not have a common comparator to allow an indirect analysis and a network could not be formed.

Results for key common trial efficacy and safety endpoints were reported and used as inputs for the NMA as presented in Table 41.

Figure 18. The overall feasible network at 12 months, showing direct comparisons by drug, comparator and dose

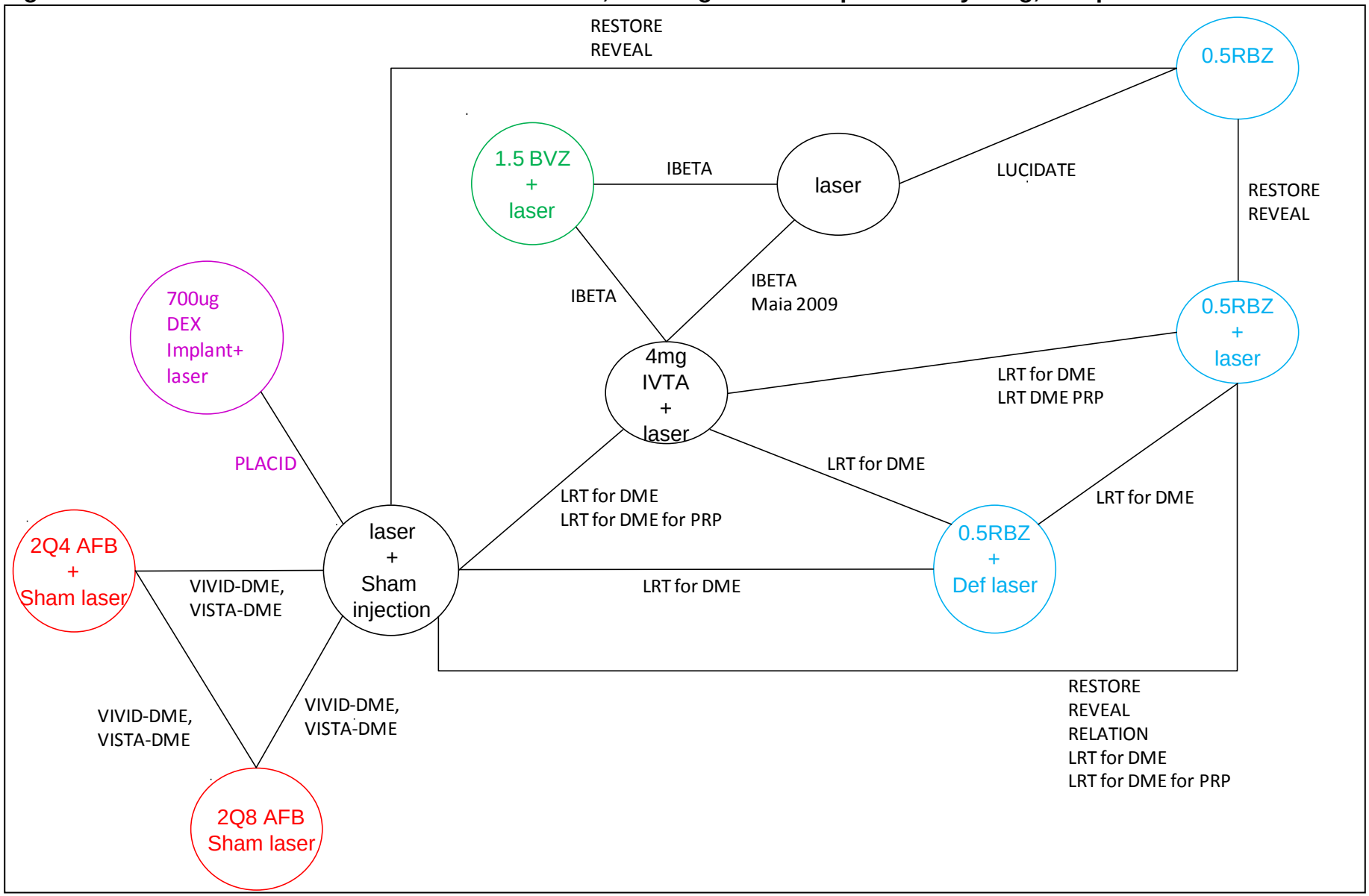


Table 41: Endpoints for which indirect analyses could be performed

Endpoints	Aflibercept vs ranibizumab	Aflibercept vs. dexamethasone
Mean Change in BCVA from baseline at 12 months	Yes	No
Mean Average Change in BCVA from baseline at 12 months	Yes	No
Proportion of patients gaining ≥ 10 letters of BCVA from baseline at 12 months	Yes	Yes
Proportion of patients losing ≥ 10 letters of BCVA from baseline at 12 months	Yes	No
Proportion of patients gaining ≥ 15 letters of BCVA from baseline at 12 months	Yes	No
Proportion of patients losing ≥ 15 letters of BCVA from baseline at 12 months	Yes	No
Treatment discontinuation	Yes	Yes
All serious adverse events	Yes	No
All serious ocular adverse events	Yes	No
All serious non-ocular adverse events	Yes	No
All non-ocular adverse events	Yes	No
All adverse events	Yes	No
All ocular adverse events	Yes	No
Eye pain	Yes	Yes
Hypertension	Yes	No
Cataract	Yes	Yes
All-cause mortality	Yes	No
Macular Oedema	No	Yes
Reduced visual acuity	No	Yes
Vitreous haemorrhage	No	Yes
Increased intraocular pressure	No	Yes

There were a number of additional adverse events for which quantitative analysis was not possible between aflibercept and ranibizumab. This was primarily due to either differences in outcome definition between studies (e.g. ‘serious’ versus ‘any’ vitreous haemorrhage) or insufficient events in one or more treatment groups. As stated in the decision problem, glaucoma had not been considered as rates were so low in the VISTA/VIVID study.

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

The results of both fixed and random effects models were evaluated. The results of the direct meta-analyses are reported below as forest plots based on the fixed effects model for each evaluable endpoint / treatment.

Overall the results showed that the choice of fixed versus random effects did not significantly alter the effect estimate in any analysis. Therefore, we have presented the fixed effect model in more detail here with a summary of the random effects data at the end of the section.

- **BCVA Mean Change from Baseline**

The *VIVID* and *VISTA* trials measured mean change from baseline in best corrected visual acuity in patients treated with 2Q8 AFB + sham laser or in patients treated with laser photocoagulation + sham injection. The results of a direct comparison of 2Q8 AFB + sham laser versus laser + sham injection are presented in Figure 19**.** The mean difference (MD) was 10.01 [95%CI 8.32-11.69, p<0.00001].

BCVA mean change from baseline was also measured in patients treated with 0.5mg PRN RBZ + sham laser or laser photocoagulation + sham injection in the *RESTORE* and *REVEAL* trials. The results of a direct analysis are shown in Figure **20**. The MD was 5.19 [95%CI 3.63-6.75, p<0.00001].

In both analyses there was a statistically significant effect in which showed a benefit of the anti-VEGF based treatments (AFB or RBZ) compared to laser treatment. The magnitude of this effect was greater for AFB treated patients than for RBZ treated patients. Both analyses were found to be statistically homogeneous (I^2 = 0%).

Figure 19: AFB 2Q8+sham laser vs. laser+sham injection: BCVA mean change from baseline

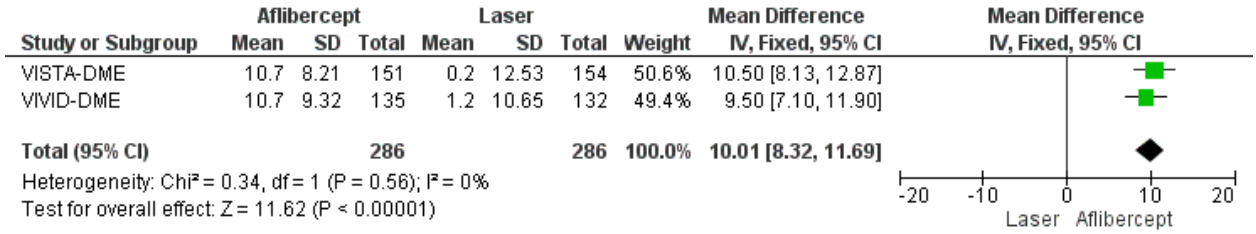
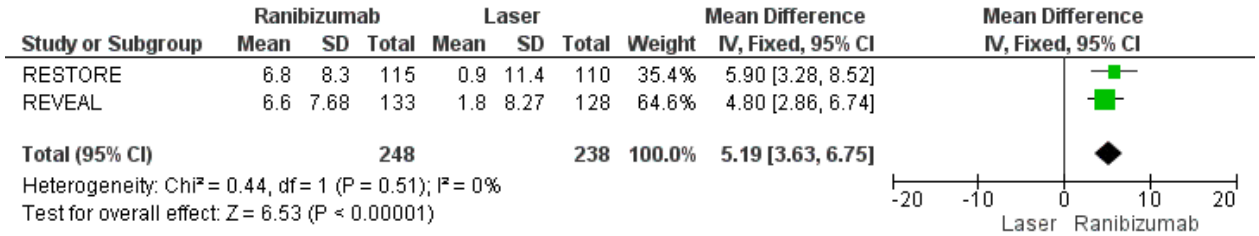


Figure 20: 0.5 PRN RBZ+sham laser vs. laser+sham injection: BCVA mean change from baseline



- **BCVA Mean Average Change from Baseline**

The *VIVID* and *VISTA* trials measured mean average change from baseline in best corrected visual acuity in patients treated with 2Q8 AFB + sham laser or in patients treated with laser photocoagulation + sham injection. The results of a direct comparison of 2Q8 AFB + sham laser versus laser + sham injection are presented in Figure 21**.** The mean

difference (MD) was 6.69 [95%CI 5.51-7.88, p<0.00001], when using results derived from aLOCF (missing values replaced by last observed post baseline value prior to missing value). The mean difference (MD) was 7.75 [95%CI 6.43-9.06, p<0.00001], when using results derived from LOCF (missing values replaced by last observed post baseline value prior to missing value or additional treatment), Figure 22..

BCVA mean change from baseline was also measured in patients treated with 0.5mg PRN RBZ + sham laser or laser photocoagulation + sham injection in the *RESTORE* and *REVEAL* trials. The results of a direct analysis are shown in Figure 23. For the RESTORE trial LOCF analyses for comparability with the other trials was used. The MD was 4.80 [95%CI 3.59-6.00, p<0.00001].

In both analyses there was a statistically significant effect which showed a benefit of the anti-VEGF based treatments (AFB or RBZ) compared to laser treatment. The magnitude of this effect was greater for AFB treated patients than for RBZ treated patients. Both analyses were found to be statistically homogeneous (I^2 = 0%).

Figure 21: AFB 2Q8+sham laser vs. laser+sham injection: BCVA mean average change from baseline (aLOCF)

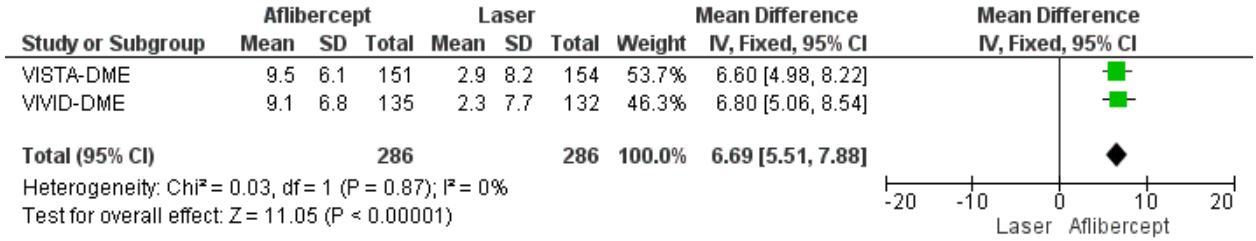


Figure 22: AFB 2Q8+sham laser vs. laser+sham injection: BCVA mean average change from baseline (LOCF)

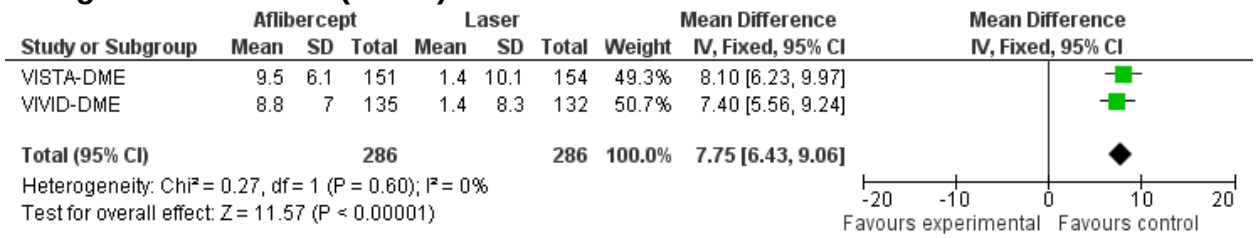
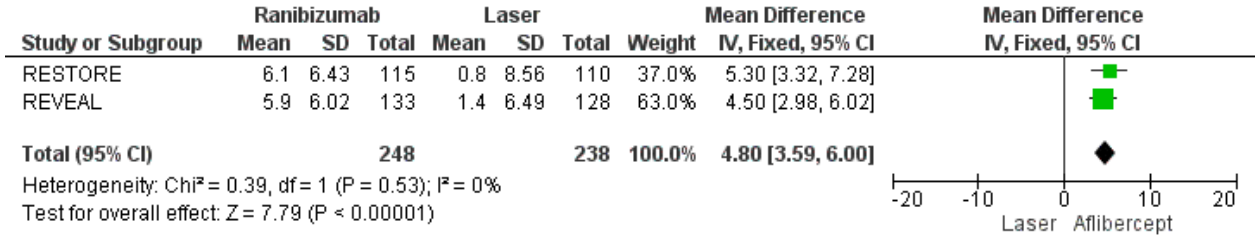


Figure 23: 0.5 PRN RBZ+sham laser vs. laser+sham injection: BCVA mean average change from baseline (LOCF)



- **Gain of ≥10 ETDRS letters**

VIVID and *VISTA* reported data to allow a direct analysis of the comparison between 2Q8 AFB + sham laser versus laser + sham injection for the outcome 'Gain of ≥10 ETDRS letters' which gave a RR of 2.50 [95%CI 1.97-3.17, p<0.00001](The PLACID study was the only trial which reported gain of ≥10 ETDRS letters for the comparison of 0.7DEX + laser versus laser + sham injection therefore no direct meta-analysis was possible. The RR from the *PLACID* study was 1.18 [95%CI 0.77-1.79] (Figure 26).

Figure 24). This analysis showed moderate heterogeneity (I^2=56%) which indicates that this result should be interpreted with caution. The same outcome was reported in the *RESTORE* and *REVEAL* trials for the comparison between 0.5 PRN RBZ + sham laser versus laser + sham injection which gave an RR of 2.48 [95%CI 1.74-3.54, p<0.00001](Figure 25). In both cases there was a significant difference in favour of the anti-VEGF based treatment compared to laser treatment.

The PLACID study was the only trial which reported gain of ≥10 ETDRS letters for the comparison of 0.7DEX + laser versus laser + sham injection therefore no direct meta-analysis was possible. The RR from the *PLACID* study was 1.18 [95%CI 0.77-1.79] (Figure 26).

Figure 24: AFB 2Q8+sham laser vs. laser+sham injection: gain of ≥10 ETDRS letters

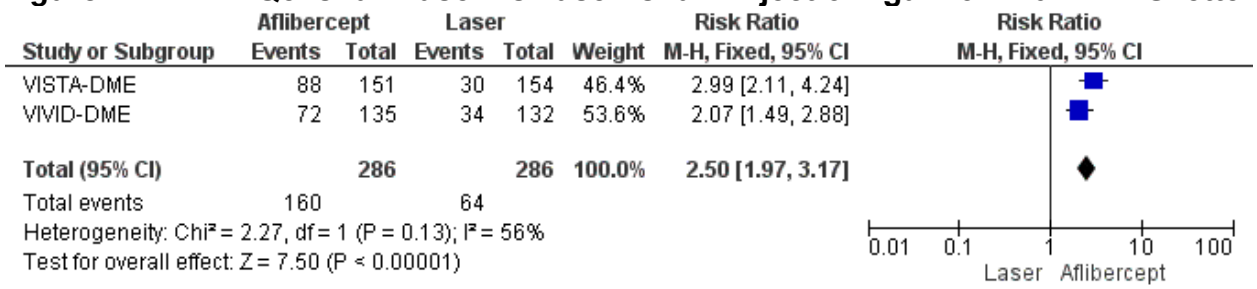


Figure 25: 0.5 PRN RBZ+sham laser vs. laser+sham injection: gain of ≥10 ETDRS letters

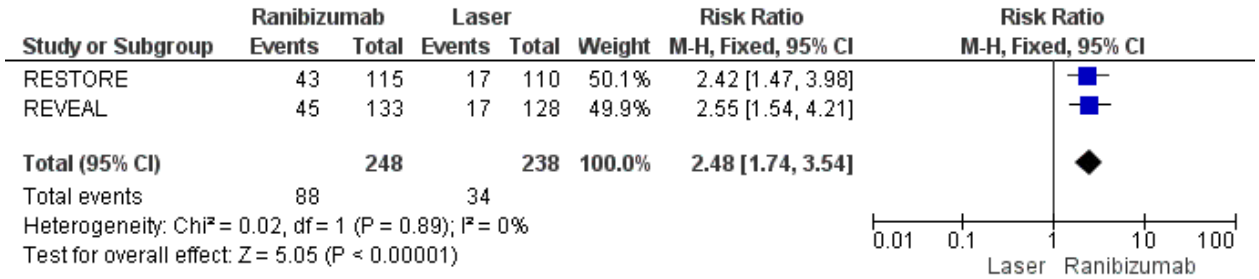
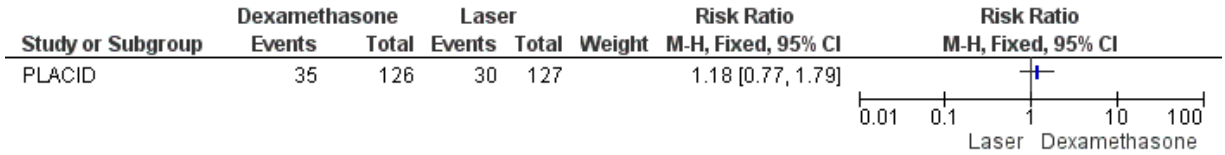


Figure 26: 0.7DEX + laser vs. laser + sham injection: gain of ≥10 ETDRS letters



- **Loss of ≥10 ETDRS letters**

VIVID and *VISTA* were combined in a direct analysis of 2Q8 AFB + sham laser versus laser + sham injection for the outcome 'Loss of ≥10 ETDRS letters'. Similarly, *RESTORE* and *REVEAL* were combined in a direct analysis of 0.5 PRN RBZ + sham laser versus laser + sham injection for the same outcome.

The combined analysis of *VIVID* + *VISTA* is presented in Figure 27. The RR was [redacted] The corresponding analysis of *RESTORE* + *REVEAL* is presented in Figure **28**. The RR for this analysis was 0.35 [95%CI 0.16-0.77, p=0.009]. In both analyses there was evidence showing a significant effect of anti-VEGF treatment. These results show that patients receiving anti-VEGF treatment were significantly less likely to experience vision loss ≥10 ETDRS letters compared to patients receiving laser treatment. The magnitude of this effect was larger in the comparison of 2Q4/2Q8 AFB + sham laser versus laser + sham injection than in the comparison of 0.5 PRN RBZ + sham laser versus laser + sham injection. Both analyses were found to be statistically homogeneous (I^2 = 0%).

Figure 27: AFB 2Q8+sham laser vs. laser+sham injection: loss of ≥10 ETDRS letters

[FIGURE DELETED]

Figure 28: 0.5 PRN RBZ+sham laser vs. laser+sham injection: loss of ≥10 ETDRS letters

- **Gain of ≥15 ETDRS letters**

VIVID and *VISTA* were combined in a direct analysis of 2Q8 AFB + sham laser versus laser + sham injection for the outcome 'Gain of ≥15 ETDRS letters'. Similarly, *RESTORE* and *REVEAL* were combined in a direct analysis of 0.5 PRN RBZ + sham laser versus laser + sham injection for the same outcome.

The combined analysis of *VIVID* + *VISTA* is presented in Figure 29. The RR was 3.83 [95% CI 2.52-5.82, p<0.00001]. The corresponding analysis of *RESTORE* + *REVEAL* is presented in Figure 30. The RR for this analysis was 2.58 [95%CI 1.57-4.23, p=0.0002]. In both analyses there was evidence of a significant effect of anti-VEGF treatment indicating that patients receiving anti-VEGF treatment were significantly more likely to experience an improvement in visual acuity ≥15 ETDRS letters compared to patients receiving laser treatment. Both analyses were found to be statistically homogeneous (I^2 = 0%).

Figure 29: AFB 2Q8+sham laser vs. laser+sham injection: gain of ≥15 ETDRS letters

Study or Subgroup	Aflibercept Events	Aflibercept Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
VISTA-DME	47	151	12	154	49.5%	3.99 [2.21, 7.23]
VIVID-DME	45	135	12	132	50.5%	3.67 [2.03, 6.61]
Total (95% CI)		**286**		**286**	**100.0%**	**3.83 [2.52, 5.82]**
Total events	92		24			

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 6.29 (P < 0.00001)

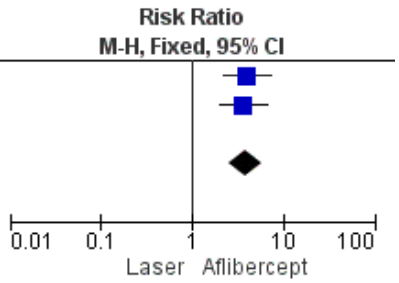
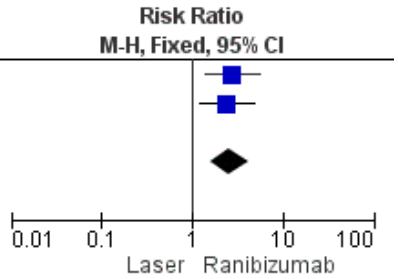


Figure 30: 0.5 PRN RBZ+sham laser vs. laser+sham injection: gain of ≥15 ETDRS letters

Study or Subgroup	Ranibizumab Events	Ranibizumab Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTORE	26	115	9	110	47.4%	2.76 [1.36, 5.63]
REVEAL	25	133	10	128	52.6%	2.41 [1.20, 4.81]
Total (95% CI)		**248**		**238**	**100.0%**	**2.58 [1.57, 4.23]**
Total events	51		19			

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 3.74 (P = 0.0002)



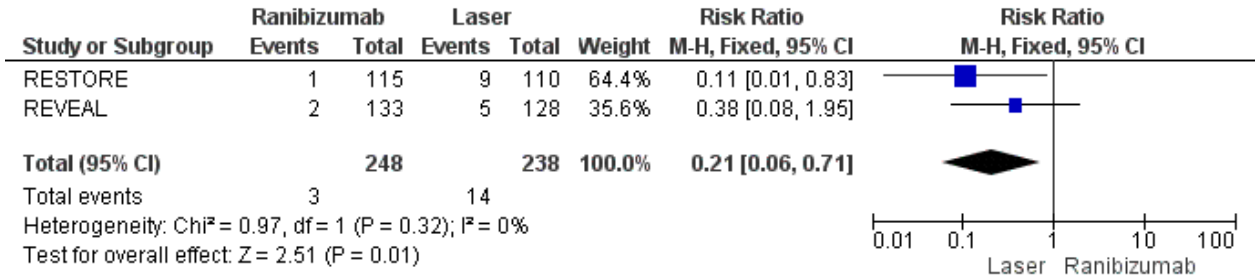
- **Loss of ≥15 ETDRS letters**

VIVID and VISTA were combined in a direct analysis of 2Q8 AFB + sham laser versus laser + sham injection for the outcome 'Loss of ≥15 ETDRS letters'. Similarly, *RESTORE* and *REVEAL* were combined in a direct analysis of 0.5 PRN RBZ + sham laser versus laser + sham injection for the same outcome.

The combined analysis of *VIVID* + *VISTA* is presented in Figure 31. The RR was 0.05 [95% CI 0.01-0.27, p<0.0004]. The corresponding analysis of *RESTORE* + *REVEAL* is presented in Figure **32**. The RR for this analysis was 0.21 [95%CI 0.06-0.71, p=0.01]. In both analyses there was evidence of a significant effect of anti-VEGF treatment. The magnitude of this effect was larger in the comparison of 2Q4/2Q8 AFB + sham laser versus laser + sham injection (Figure 31) than in the comparison of 0.5 PRN RBZ + sham laser versus laser + sham injection (Figure **32**). These results show that patients receiving anti-VEGF treatment were less likely to experience a loss of visual acuity ≥15 ETDRS letters compared to patients receiving laser treatment. Both analyses were found to be statistically homogeneous (I^2 = 0%).

Figure 31: AFB 2Q8+sham laser vs. laser+sham injection: loss of ≥15 ETDRS letters

Figure 32: 0.5 PRN RBZ+sham laser vs. laser+sham injection: gain of ≥15 ETDRS letters



- **Treatment discontinuation**

VIVID-DME and VISTA-DME reported data to allow a direct analysis of the comparison between 2Q8 AFB + sham laser versus laser + sham injection for the outcome 'Treatment Discontinuation' which gave a RR of 0.81 [95%CI 0.49-1.33, p=0.41] (Figure 33). Therefore fewer discontinutations occurred after 2Q8 AFB treatment than with laser, but it wasn't a significant result. The analysis was found to be statistically homogeneous (I^2=0%). The same outcome was reported in the RESTORE and REVEAL trials for the comparison between 0.5 PRN RBZ + sham laser versus laser + sham injection which gave an RR of 0.65 [95%CI 0.40-1.05, p<0.08] (Figure 34). This analysis showed moderate heterogeneity (I^2=66%) which indicates that this result should be interpreted with caution.

The PLACID study was the only trial which reported treatment discontinuation for the comparison of 0.7DEX + laser versus laser + sham injection therefore no direct meta-analysis was possible. The RR from the PLACID study was 0.70 [95%CI 0.44-1.13] (Figure 35).

Discontinuation was reported as 'all discontinuations for all studies'.

Figure 33: AFB 2Q8+sham laser vs. laser+sham injection: Treatment Discontinuation

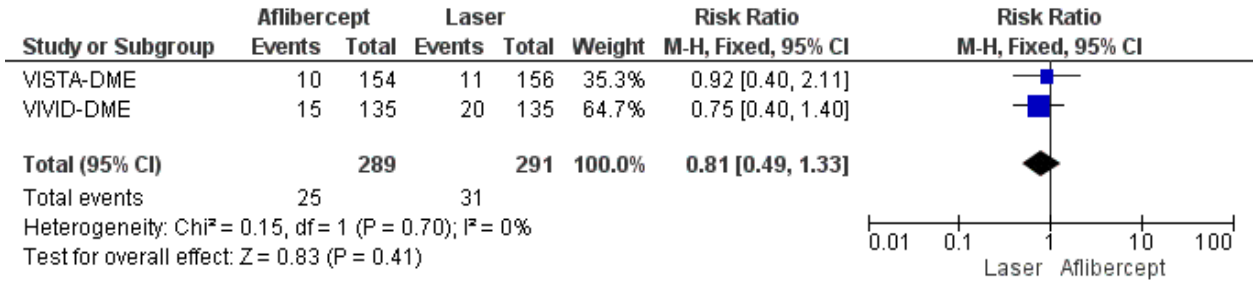
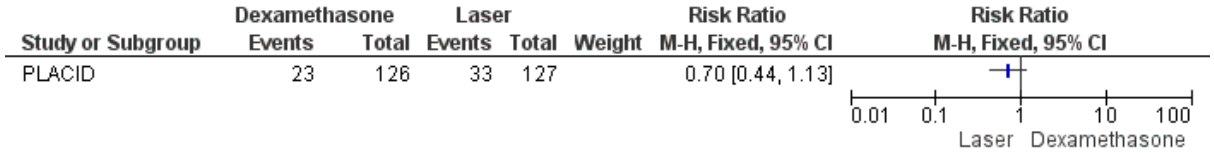


Figure 34: 0.5 PRN RBZ+sham laser vs. laser+sham injection: Treatment Discontinuation

Figure 35: 0.7DEX + laser vs. laser + sham injection: Treatment Discontinuation



- **All serious adverse events**

The *VIVID and VISTA* trials reported All Serious Adverse Events in patients treated with 2Q8 AFB + sham laser or in patients treated with laser photocoagulation + sham injection. The results of a direct comparison of 2Q8 AFB + sham laser versus laser + sham injection are presented in Figure 36**.** The RR was 0.93 [95%CI 0.70-1.22, p=0.58].

All serious adverse events were also measured in patients treated with 0.5mg PRN RBZ + sham laser or laser photocoagulation + sham injection in the *RESTORE and REVEAL*

trials. The results of a direct analysis are shown in Figure **37**. The RR was 1.17 [95%CI 0.78-1.75, p=0.44].

Figure 36: AFB 2Q8 + sham laser vs. Laser + sham injection: all serious adverse events

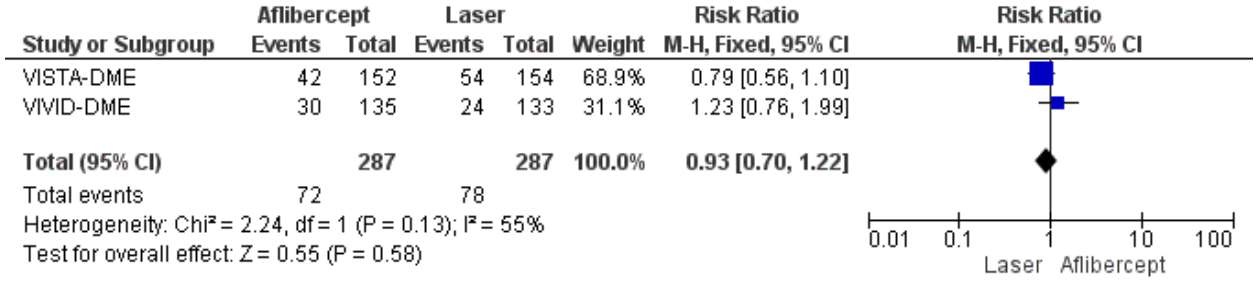
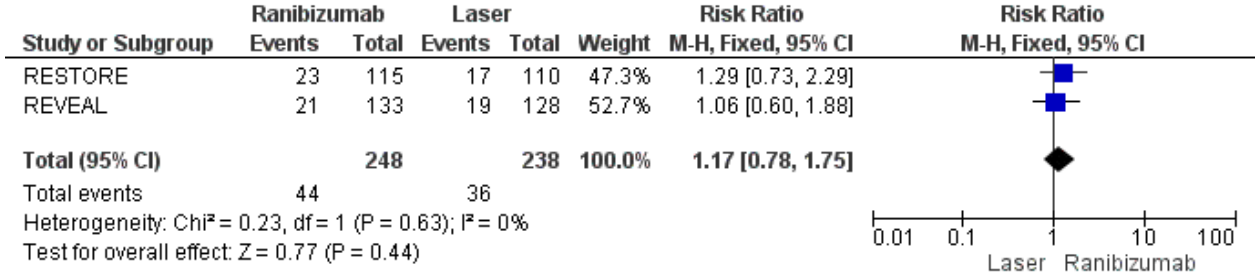


Figure 37: 0.5 PRN RBZ+sham laser vs. laser+sham injection: all serious adverse events



- **All Serious Ocular Adverse Events**

VIVID and VISTA reported data to allow a direct analysis of the comparison between 2Q8 AFB + sham laser versus laser + sham injection for the occurrence of 'All Serious Ocular Adverse Events' which gave a risk ratio of 0.42 [95%CI 0.15-1.17, p=0.1](**Figure 38**). The same outcome was reported in the *RESTORE and REVEAL* trials for the comparison between 0.5 PRN RBZ + sham laser versus laser + sham injection which gave an RR of 1.81 [95%CI 0.59-5.62, p=0.30](**Figure 39**). This analysis showed moderate heterogeneity (I^2=67%) which indicates this result should be interpreted with caution. In both cases there was no significant difference in the frequency of adverse events between treatments.

Figure 38: AFB 2Q8+sham laser vs. laser+sham injection: all serious ocular adverse events

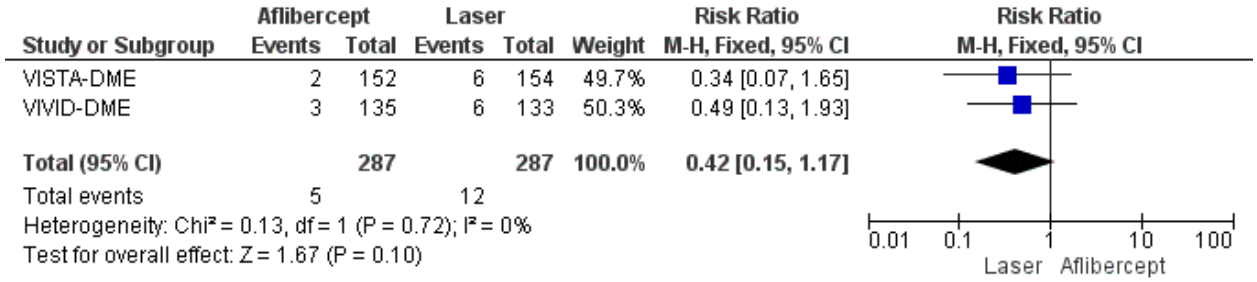
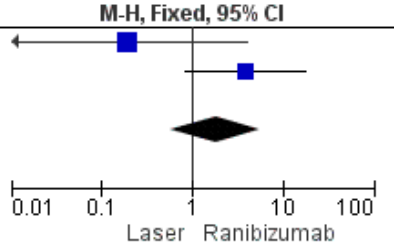


Figure 39: 0.5 PRN RBZ+sham laser vs. laser+sham injection: all serious ocular adverse events

Study or Subgroup	Ranibizumab Events	Ranibizumab Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTORE	0	115	2	110	55.6%	0.19 [0.01, 3.94]
REVEAL	8	133	2	128	44.4%	3.85 [0.83, 17.78]
Total (95% CI)		**248**		**238**	**100.0%**	**1.81 [0.59, 5.62]**
Total events	8		4			

Heterogeneity: Chi² = 3.05, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 1.03 (P = 0.30)



- **All Serious Non-Ocular Adverse Events**

VIVID and VISTA were combined in a direct analysis of 2Q8 AFB + sham laser versus laser + sham injection for the outcome 'All Serious Non-Ocular Adverse Events'. The RR was 0.99 [95%CI 0.73-1.34, p=0.94](Figure 40). This analysis showed moderate heterogeneity (I^2=52%). This outcome was only reported by the *RESTORE* trial for the comparison of 0.5 PRN RBZ + sham laser versus laser + sham injection therefore no meta-analysis was possible for this comparison. The point estimate from the *RESTORE* trial is shown in Figure 41 (RR = 1.47, 95%CI 0.81-2.66).

Figure 40: AFB 2Q8+sham laser vs. laser+sham injection: all serious non-ocular adverse events

Study or Subgroup	Aflibercept Events	Aflibercept Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
VISTA-DME	39	152	47	154	72.0%	0.84 [0.59, 1.21]
VIVID-DME	25	135	18	133	28.0%	1.37 [0.78, 2.39]
Total (95% CI)		**287**		**287**	**100.0%**	**0.99 [0.73, 1.34]**
Total events	64		65			

Heterogeneity: Chi² = 2.09, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 0.08 (P = 0.94)

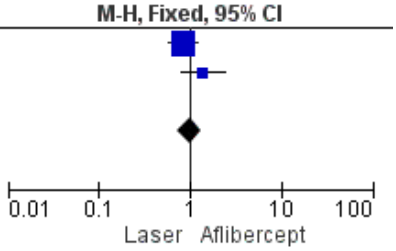
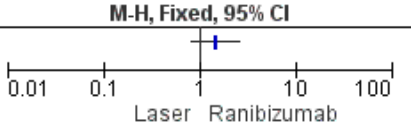


Figure 41: 0.5 PRN RBZ+sham laser vs. laser+sham injection: all serious non-ocular adverse events

Study or Subgroup	Ranibizumab Events	Ranibizumab Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTORE	23	115	15	110		1.47 [0.81, 2.66]



- **All Adverse Events**

VIVID and VISTA were combined in a direct analysis of 2Q8 AFB + sham laser versus laser + sham injection for the outcome 'Adverse Events'. Similarly, *RESTORE and REVEAL* were combined in a direct analysis of 0.5 PRN RBZ + sham laser versus laser + sham injection for the same outcome.

The combined analysis of *VIVID-DME* + *VISTA-DME* is presented in Figure 42. The RR was 1.00 [95% CI 0.95-1.06, p=0.98]. This analysis showed moderate heterogeneity (I^2 = 55%). The corresponding analysis of *RESTORE* + *REVEAL* is presented in Figure 43. The RR for this analysis was 1.41 [95%CI 0.95-2.09, p=0.09]. In both analyses there was no significant difference in the frequency of adverse events between treatment arms.

Figure 42: AFB 2Q8+sham laser vs. laser+sham injection: all adverse events

Study or Subgroup	Aflibercept Events	Aflibercept Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
VISTA-DME	139	152	146	154	56.2%	0.96 [0.91, 1.03]
VIVID-DME	119	135	112	133	43.8%	1.05 [0.95, 1.15]
Total (95% CI)		**287**		**287**	**100.0%**	**1.00 [0.95, 1.06]**
Total events	258		258			

Heterogeneity: Chi² = 2.23, df = 1 (P = 0.14); I² = 55%
Test for overall effect: Z = 0.02 (P = 0.98)

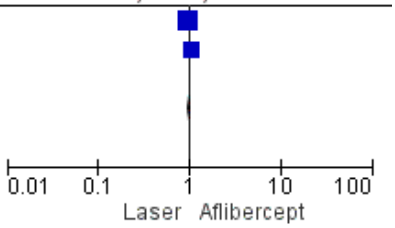
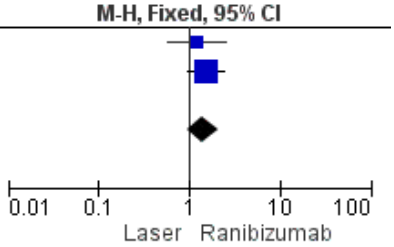


Figure 43: 0.5 PRN RBZ+sham laser vs. laser+sham injection: all adverse events

Study or Subgroup	Ranibizumab Events	Ranibizumab Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTORE	14	115	11	110	32.4%	1.22 [0.58, 2.56]
REVEAL	36	133	23	128	67.6%	1.51 [0.95, 2.39]
Total (95% CI)		**248**		**238**	**100.0%**	**1.41 [0.95, 2.09]**
Total events	50		34			

Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.09)



- **All Ocular Adverse Events**

VIVID and VISTA were combined in a direct analysis of 2Q8 AFB + sham laser versus laser + sham injection for the outcome 'All Ocular Adverse Events'. The RR was 0.90 [95%CI 0.79-1.03, p=0.12](Figure **44**) and the two trials were statistically homogeneous (I^2 = 0%). This outcome was only reported by the *RESTORE* trial for the comparison of 0.5 PRN RBZ + sham laser versus laser + sham injection therefore no meta-analysis was possible for this comparison. The point estimate from the *RESTORE* trial is shown in Figure 45 (RR = 1.09, 95%CI 0.80-1.49).

Figure 44: AFB 2Q8+sham laser vs. laser+sham injection: all ocular adverse events

Study or Subgroup	Aflibercept Events	Aflibercept Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
VISTA-DME	87	152	103	154	55.3%	0.86 [0.72, 1.02]
VIVID-DME	80	135	82	133	44.7%	0.96 [0.79, 1.17]
Total (95% CI)		**287**		**287**	**100.0%**	**0.90 [0.79, 1.03]**
Total events	167		185			

Heterogeneity: Chi² = 0.75, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 1.53 (P = 0.12)

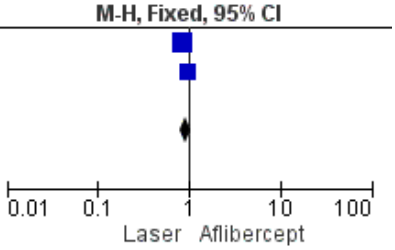
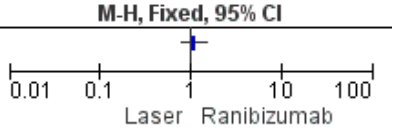


Figure 45: 0.5 PRN RBZ+sham laser vs. laser+sham injection: all ocular adverse events

Study or Subgroup	Ranibizumab Events	Ranibizumab Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTORE	49	115	43	110		1.09 [0.80, 1.49]



- **All Non-ocular adverse events**

VIVID and VISTA were combined in a direct analysis of 2Q8 AFB + sham laser versus laser + sham injection for the outcome 'All Non-Ocular Adverse Events'. The RR was 1.02 [95%CI 0.93-1.12, p=0.68](Figure 46) and the two trials were statistically homogeneous (I^2 = 0%). This outcome was only reported by the *RESTORE* trial for the comparison of 0.5 PRN RBZ + sham laser versus laser + sham injection therefore no meta-analysis was possible for this comparison. The point estimate from the *RESTORE* trial is shown in Figure 47 (RR = 0.94, 95%CI 0.76-1.17).

Figure 46: AFB 2Q8+sham laser vs. laser+sham injection: all non-ocular AEs

Study or Subgroup	Aflibercept Events	Aflibercept Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
VISTA-DME	119	152	132	154	61.6%	0.91 [0.82, 1.02]
VIVID-DME	98	135	81	133	38.4%	1.19 [1.00, 1.41]
Total (95% CI)		**287**		**287**	**100.0%**	**1.02 [0.93, 1.12]**
Total events	217		213			

Heterogeneity: Chi² = 7.39, df = 1 (P = 0.007); I² = 86%
Test for overall effect: Z = 0.42 (P = 0.68)

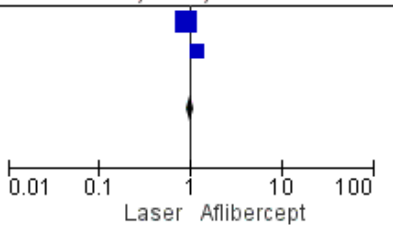
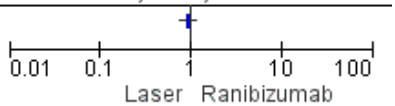


Figure 47: 0.5 PRN RBZ +sham laser vs. laser+sham injection: all non-ocular AEs

Study or Subgroup	Ranibizumab Events	Ranibizumab Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RESTORE	67	115	68	110		0.94 [0.76, 1.17]



- **Eye Pain**

VIVID and VISTA were combined in a direct analysis of 2Q8 AFB + sham laser versus laser + sham injection for the outcome 'Eye Pain'. The RR was 1.18 [95%CI 0.65-2.14, p=0.59](Figure 48), indicating that a greater proportion of patients receiving 2Q4/2Q8 AFB experienced eye pain compared to those receiving laser treatment. The two trials were statistically homogeneous (I^2 = 0%) This effect was not statistically significant. This outcome was only reported by the *RESTORE* trial for the comparison of 0.5 PRN RBZ + sham laser versus laser + sham injection therefore no meta-analysis was possible for this

comparison. The point estimate from the *RESTORE* trial is shown in Figure 49 (RR = 1.04, 95%CI 0.48-2.27).

The comparison of 0.7DEX + laser versus Laser + sham injection was only reported in a single study (*PLACID*), therefore, no direct analysis was possible for this comparison. The RR from the *PLACID* study was 1.47 [95%CI 0.65-3.31], Figure 50.

Figure 48: AFB 2Q8+sham laser vs. laser+sham injection: eye pain

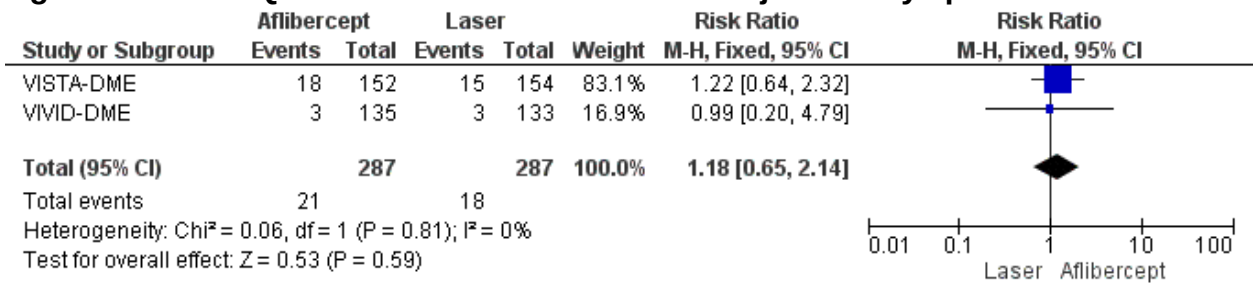


Figure 49: 0.5 PRN RBZ+sham laser vs. laser+sham injection: eye pain

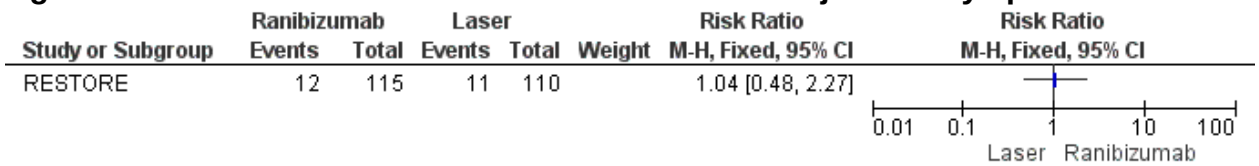
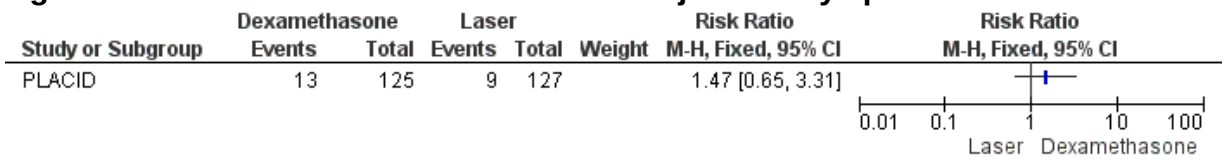


Figure 50: 0.7DEX + laser vs. laser + sham injection: eye pain



- **Hypertension**

VIVID and VISTA were combined in a direct analysis of 2Q8 AFB + sham laser versus laser + sham injection for the outcome 'Hypertension'. The RR was 0.92 [95%CI 0.64-1.32, p=0.67](**Figure 51**), indicating that a slightly smaller proportion of patients receiving 2Q4/2Q8 AFB experienced hypertension compared to those receiving laser treatment. This effect was not statistically significant.

The same outcome was in both the *RESTORE and REVEAL* trials for the comparison of 0.5 PRN RBZ + sham laser versus laser + sham injection. The results of the direct analysis are shown in Figure 52 (RR = 0.96, 95%CI 0.48-1.91). As for the AFB analysis the results showed that slightly smaller but non-significant proportion of patients receiving 0.5PRN RBZ experienced hypertension compared to the laser group. Both analyses were statistically homogeneous (I^2 = 0%).

Figure 51: AFB 2Q8+sham laser vs. laser+sham injection: hypertension

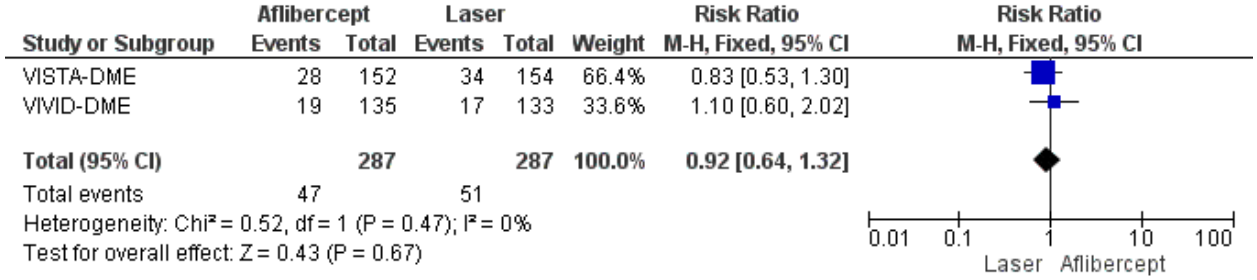
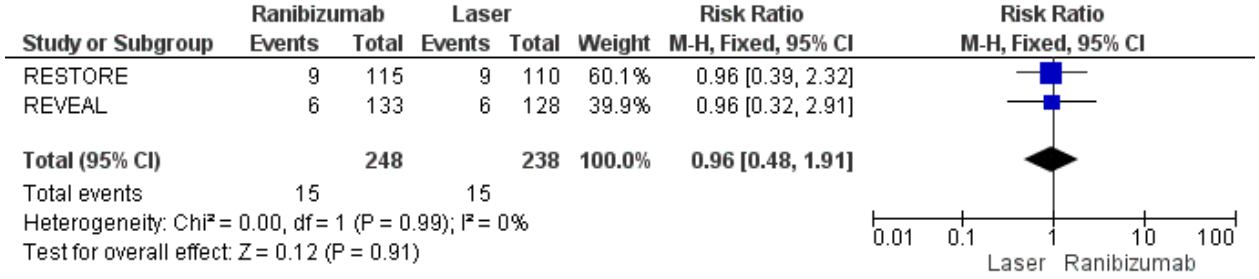


Figure 52: 0.5 PRN RBZ+sham laser vs. laser+sham injection: hypertension



- **Cataract**

VIVID and VISTA were combined in a direct analysis of 2Q8 AFB + sham laser versus laser + sham injection for the outcome 'Cataract'. The RR was 0.93 [95%CI 0.46-1.90, p=0.85](Figure 53) indicating that a slightly smaller proportion of patients receiving 2Q8 AFB experienced cataracts compared to those receiving laser treatment, however, this effect was not statistically significant, some heterogeneity was evident (I^2=38%). Only the *RESTORE* trial reported this outcome for the comparison of 0.5 PRN RBZ + sham laser versus laser + sham injection therefore no meta-analysis was possible for this comparison. The point estimate from the *RESTORE* trial is shown in **Figure 54** (RR = 0.27, 95%CI 0.06, 1.29).

The comparison of 0.7DEX + laser versus Laser + sham injection was only reported in a single study (*PLACID*), therefore, no direct analysis was possible for this comparison. The RR from the *PLACID* study was 2.20 [95%CI 0.86-5.61], Figure 55.

Figure 53: AFB 2Q8+sham laser vs. laser+sham injection: cataract

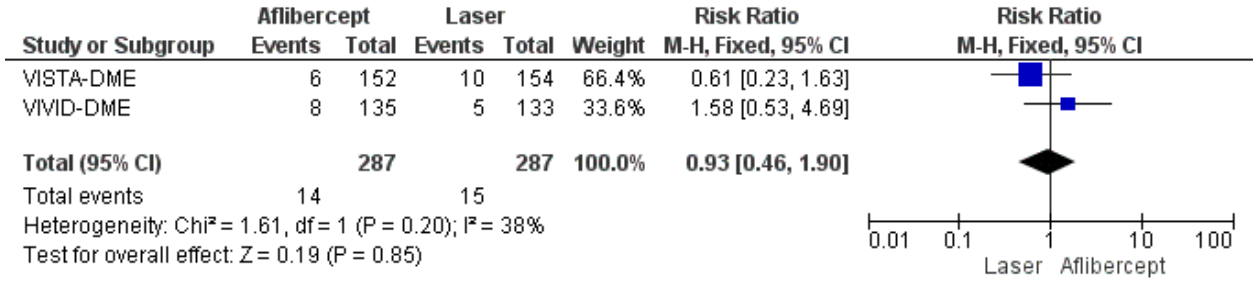


Figure 54: 0.5 PRN RBZ+sham laser vs. laser+sham injection: cataract

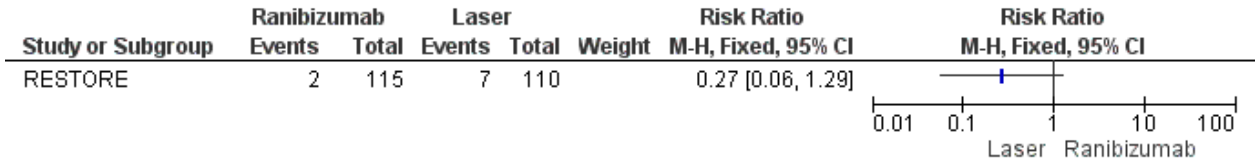
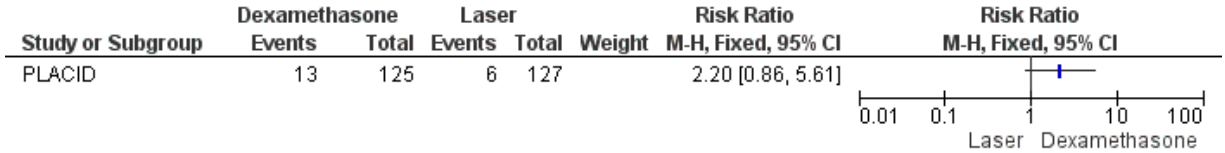


Figure 55: 0.7DEX + laser vs. laser + sham injection: cataract



- **All Cause Mortality**

VIVID and VISTA were combined in a direct analysis of 2Q8 AFB + sham laser versus laser + sham injection for the outcome 'All Cause Mortality'. The RR was 2.19 [95%CI 0.49-9.73, p=0.30](Figure 56), indicating that more patients receiving 2Q8 AFB died compared to those receiving laser treatment but this result was not significant. There is a high degree of uncertainty in this estimate. The 95% confidence intervals ranged from 0.49 to 9.73 and the deaths were reported exclusively in the VIVID-DME study. This showed moderate heterogeneity (I^2=47%).

This outcome was only reported in the *RESTORE* trial for the comparison of 0.5 PRN RBZ + sham laser versus laser + sham injection therefore no meta-analysis was possible for this comparison. The point estimate from the *RESTORE* trial is shown in Figure 57. There was almost no difference in the number of deaths reported in each arm for this study (two each) with a RR of 0.96 (95%CI 0.14-6.67).

Figure 56: AFB 2Q8+sham laser vs. laser+sham injection: mortality

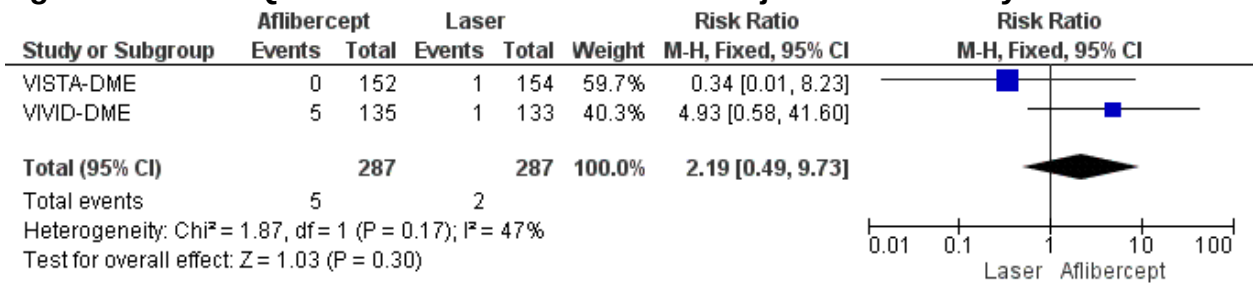
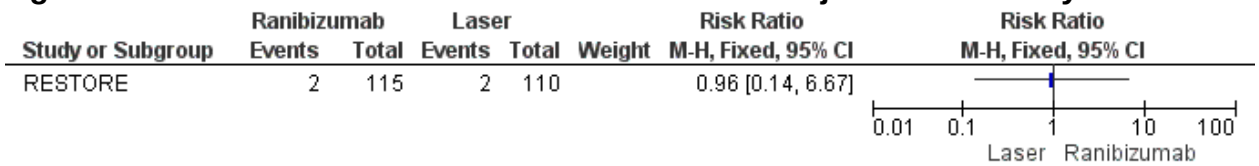


Figure 57: 0.5 PRN RBZ+sham laser vs. laser+sham injection: mortality



- **Macular Oedema**

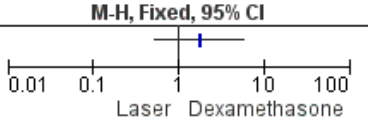
Macular Oedema was only reported in a single study each for the comparison of either 2Q8 AFB + sham laser versus Laser + sham injection (*VIVID*) or 0.7DEX + laser versus Laser + sham injection (*PLACID*). Direct meta-analysis was not possible for this outcome for either comparison. The RR from the *VIVID* study was [redacted], Figure 58. The RR from the *PLACID* study was 1.78 [95%CI 0.53-5.92], Figure 59.

Figure 58: AFB 2Q8 + sham laser vs. laser + sham injection: macular oedema

[FIGURE DELETED]

Figure 59: 0.7DEX + laser vs. laser + sham injection: macular oedema

Study or Subgroup	Dexamethasone Events	Dexamethasone Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PLACID	7	125	4	127		1.78 [0.53, 5.92]



- **Reduced Visual Acuity**

VIVID and VISTA reported data to allow a direct analysis of the comparison between 2Q8 AFB + sham laser versus laser + sham injection for the outcome 'Reduced visual acuity' which gave a RR of 0.60 [95%CI 0.32-1.10] (Figure 60). This analysis found no heterogeneity (I^2=0%). The *PLACID* study was the only trial which reported gain of ≥10 ETDRS letters for the comparison of 0.7DEX + laser versus laser + sham injection therefore no direct meta-analysis was possible. The RR from the *PLACID* study was 0.94 [95%CI 0.45-1.98],

Figure **61**.

Figure 60: AFB 2Q8 + sham laser vs. laser + sham injection: reduced visual acuity

Study or Subgroup	Aflibercept Events	Aflibercept Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
VISTA-DME	5	152	8	154	31.7%	0.63 [0.21, 1.89]
VIVID-DME	10	135	17	133	68.3%	0.58 [0.28, 1.22]
Total (95% CI)		**287**		**287**	**100.0%**	**0.60 [0.32, 1.10]**
Total events	15		25			

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.65 (P = 0.10)

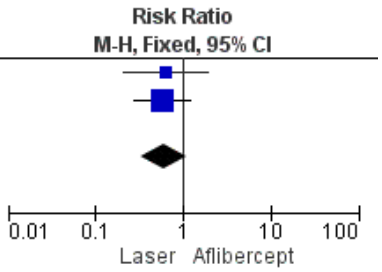
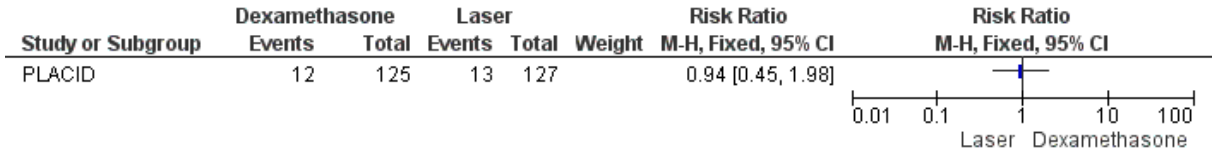


Figure 61: 0.7DEX + laser vs. laser + sham injection: reduced visual acuity

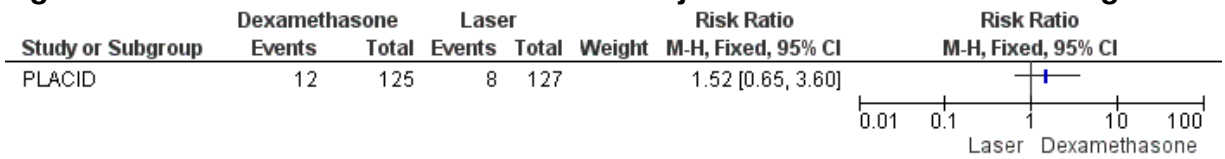


- **Vitreous Haemorrhage**

VIVID and VISTA reported data to allow a direct analysis of the comparison between 2Q8 AFB + sham laser versus laser + sham injection for the adverse event outcome 'Vitreous Haemorrhage' which gave a RR of 0.36 [0.12 to 1.13, p=0.08] (Figure 62). This analysis showed moderate heterogeneity (I^2=60%) which indicates that this result should be interpreted with caution. The comparison of 0.7DEX + laser versus Laser + sham injection was only reported in a single study (*PLACID*), therefore, no direct analysis was possible for this comparison. The RR from the *PLACID* study was 1.52 [95%CI 0.65-3.60] (Figure 63).

Figure 62: AFB 2Q8 + sham laser vs. laser + sham injection: vitreous haemorrhage

Figure 63: 0.7DEX + laser vs. laser + sham injection: vitreous haemorrhage



- **Increased Intraocular Pressure**

VIVID and VISTA reported data to allow a direct analysis of the comparison between 2Q8 AFB + sham laser versus laser + sham injection for the adverse event outcome 'Increased Intraocular Pressure' which gave a RR of 1.19 [0.53 to 2.71, p=0.67] (Figure **64**). This analysis showed moderate-high heterogeneity (I^2=73%) which indicates that this result includes a high degree of uncertainty and should be interpreted with caution. The comparison of 0.7DEX + laser versus Laser + sham injection was only reported in a single study (*PLACID*), therefore, no direct analysis was possible for this comparison. The RR from the *PLACID* study was 12.70 [95%CI 3.07-52.49], Figure 65**.** This indicates a significant increase in the number of patients with intraocular pressure due to dexamethasone.

Figure 64: AFB 2Q8 + sham laser vs. laser + sham injection: increased intraocular pressure

Study or Subgroup	Aflibercept Events	Aflibercept Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
VISTA-DME	6	152	1	154	9.9%	6.08 [0.74, 49.90]
VIVID-DME	6	135	9	133	90.1%	0.66 [0.24, 1.79]
Total (95% CI)		**287**		**287**	**100.0%**	**1.19 [0.53, 2.71]**
Total events	12		10			

Heterogeneity: Chi² = 3.65, df = 1 (P = 0.06); I² = 73%
Test for overall effect: Z = 0.42 (P = 0.67)

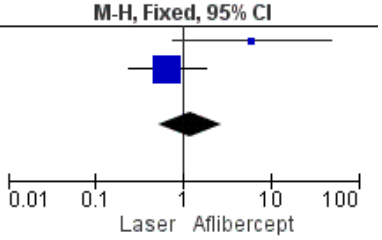


Figure 65: 0.7DEX + laser vs. laser + sham injection: increased intraocular pressure

Study or Subgroup	Dexamethasone Events	Dexamethasone Total	Laser Events	Laser Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PLACID	25	125	2	127		12.70 [3.07, 52.49]

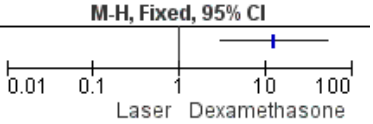


Table 42. Effect estimates by inverse variance fixed and random effects models for continuous efficacy outcomes

BCVA Mean Change from baseline									
Study ID	**Aflibercept**			**Laser**			**Weight**	**Mean Difference**	**Mean Difference**
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**		**IV, Fixed 95% CI**	**IV, Random 95% CI**
VISTA-DME	10.7	8.21	151	0.2	12.53	154	50.6%	10.50 [8.13, 12.87]	10.50 [8.13, 12.87]
VIVID-DME	10.7	9.32	135	1.2	10.65	132	49.4%	9.50 [7.10, 11.90]	9.50 [7.10, 11.90]
Total			**286**			**286**	**100%**	**10.01 [8.32, 11.69]**	**10.01 [8.32, 11.69]**
Study ID	**Ranibizumab**			**Laser**			**Weight**	**Mean Difference**	**Mean Difference**
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**		**IV, Fixed 95% CI**	**IV, Random 95% CI**
RESTORE	6.8	8.3	115	0.9	11.4	110	35.4%	5.90 [3.28, 8.52]	5.90 [3.28, 8.52]
REVEAL	6.6	7.68	133	1.8	8.27	1.28	64.6%	4.80 [2.86, 6.74]	4.80 [2.86, 6.74]
Total			**248**			**238**	**100%**	**5.19 [3.63, 6.75]**	**5.19 [3.63, 6.75]**
BCVA Mean Average Change from baseline									
Study ID (aLOCF)	**Aflibercept**			**Laser**			**Weight**	**Mean Difference**	**Mean Difference**
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**		**IV, Fixed 95% CI**	**IV, Random 95% CI**
VISTA-DME	9.5	6.1	151	2.9	8.2	154	53.7	6.60 [4.98, 8.22]	6.60 [4.98, 8.22]
VIVID-DME	9.1	6.8	135	2.3	7.7	132	46.3	6.80 [5.06, 8.54]	6.80 [5.06, 8.54]
Total			**286**			**286**	**100%**	**6.69 [5.51, 7.88]**	**6.69 [5.51, 7.88]**
Study ID (LOCF)	**Aflibercept**			**Laser**			**Weight**	**Mean Difference**	**Mean Difference**
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**		**IV, Fixed 95% CI**	**IV, Random 95% CI**
VISTA-DME	9.5	6.1	151	1.4	10.1	154	49.3	8.10 [6.23, 9.97]	8.10 [6.23, 9.97]
VIVID-DME	8.8	7	135	1.4	8.3	132	50.7	7.40 [5.56, 9.24]	7.40 [5.56, 9.24]
Total			**286**			**286**	**100%**	**7.75 [6.43, 9.06]**	**7.75 [6.43, 9.06]**
Study ID	**Ranibizumab**			**Laser**			**Weight**	**Mean Difference**	**Mean Difference**
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**		**IV, Fixed 95% CI**	**IV, Random 95% CI**
RESTORE	6.1	6.43	115	0.8	8.56	110	37.1	5.30 [3.32, 7.28]	5.30 [3.32, 7.28]
REVEAL	5.9	6.02	133	1.4	6.49	128	62.9	4.50 [2.98, 6.02]	4.50 [2.98, 6.02]
Total			**248**			**238**	**100%**	**4.80 [3.59, 6.00]**	**4.80 [3.59, 6.00]**

Table 43. Effect estimates by Mantel-Haenszel random effects model for dichotomous efficacy outcomes

Gain of ≥10 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	88	151	30	154	48.8%	2.99 [2.11, 4.24]	50.1%	5.77 [3.45, 9.65]
VIVID-DME	72	135	34	132	51.2%	2.07 [1.49, 2.88]	49.9%	3.29 [1.97, 5.52]
Total		**286**		**286**	**100%**	**2.48 [1.73, 3.56]**	**100%**	**4.36 [2.52, 7.56]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
RESTORE	43	115	17	110	50.5%	2.42 [1.47, 3.98]	48.7%	3.27 [1.72, 6.20]
REVEAL	45	133	17	128	49.5%	2.55 [1.54, 4.21]	51.3%	3.34 [1.79, 6.23]
Total		**248**		**238**	**100%**	**2.48 [1.74, 3.53]**	**100%**	**3.30 [2.11, 5.17]**
Study ID	**Dexamethasone**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
PLACID*	35	126	30	127		1.18 [0.77, 1.79]		1.24 [0.71, 2.19]
Loss of ≥10 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID-DME	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
RESTORE	4	115	14	110	54.2%	0.27 [0.09, 0.80]	53.4%	0.25 [0.08, 0.78]
REVEAL	4	133	8	128	45.8%	0.48 [0.15, 1.56]	46.6%	0.47 [0.14, 1.58]
Total		**248**		**238**	**100%**	**0.35 [0.16, 0.78]**	**100%**	**0.33 [0.14, 0.77]**

Gain of ≥15 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	47	151	12	154	49.7%	3.99 [2.21, 7.23]	50.8%	5.35 [2.70, 10.58]
VIVID-DME	45	135	12	132	50.3%	3.67 [2.03, 6.61]	49.2%	5.00 [2.50, 10.00]
Total		**286**		**286**	**100%**	**3.83 [2.52, 5.81]**	**100%**	**5.17 [3.18, 8.41]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
RESTORE	26	115	9	110	48.6%	2.76 [1.36, 5.63]	48.0%	3.28 [1.46, 7.37]
REVEAL	25	133	10	128	51.4%	2.41 [1.20, 4.81]	52.0%	2.73 [1.25, 5.95]
Total		**248**		**238**	**100%**	**2.57 [1.57, 4.23]**	**100%**	**2.98 [1.70, 5.23]**
Loss of ≥15 ETDRS letters								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	1	151	14	154	66.0%	0.07 [0.01, 0.55]	65.8%	0.07 [0.01, 0.51]
VIVID-DME	0	135	14	132	34.0%	0.03 [0.00, 0.56]	34.2%	0.03 [0.00, 0.51]
Total		**286**		**286**	**100%**	**0.06 [0.01, 0.29]**	**100%**	**0.05 [0.01, 0.27]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
RESTORE	1	115	9	110	38.5%	0.11 [0.01, 0.83]	38.9%	0.10 [0.01, 0.79]
REVEAL	2	133	5	128	61.5%	0.38 [0.08, 1.95]	61.1%	0.38 [0.07, 1.97]
Total		**248**		**238**	**100%**	**0.23 [0.07, 0.84]**	**100%**	**0.22 [0.06, 0.82]**

Treatment Discontinuation								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	10	154	11	156	36.4	0.92 [0.40, 2.11]	39.5%	0.92 [0.38, 2.22]
VIVID-DME	15	135	20	135	63.6	0.75 [0.40, 1.40]	60.5%	0.72 [0.35, 1.47]
Total		**289**		**291**	**100%**	**0.81 [0.49, 1.33]**	**100%**	**0.79 [0.45, 1.38]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
RESTORE	14	116	13	111	49.8%	1.03 [0.51, 2.09]	49.6%	1.03 [0.46, 2.31]
REVEAL	10	133	23	131	50.2%	0.43 [0.21, 0.86]	50.4%	0.38 [0.17, 0.84]
Total		**249**		**242**	**100%**	**0.66 [0.28, 1.57]**	**100%**	**0.63 [0.24, 1.66]**
Study ID	**Dexamethasone**			**Laser**		**Risk Ratio**		**Odds Ratio**
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
PLACID*	23	126	33	127		0.70 [0.44, 1.13]		0.64 [0.35, 1.16]

Table 44. Effect estimates by Mantel-Haenszel random effects model for dichotomous safety outcomes

All Serious Adverse Events								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	42	152	54	154	57.7%	0.79 [0.56, 1.10]	54.4%	0.71 [0.44, 1.15]
VIVID-DME	30	135	24	133	42.3%	1.23 [0.76, 1.99]	45.6%	1.30 [0.71, 2.36]
Total		**287**		**287**	**100%**	**0.95 [0.62, 1.47]**	**100%**	**0.93 [0.52, 1.69]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
RESTORE	23	115	17	110	50.1%	1.29 [0.73, 2.29]	48.9%	1.37 [0.69, 2.73]
REVEAL	21	133	19	128	49.9%	1.06 [0.60, 1.88]	51.1%	1.08 [0.55, 2.11]
Total		**248**		**238**	**100%**	**1.17 [0.78, 1.76]**	**100%**	**1.21 [0.75, 1.96]**
All Serious Ocular Adverse Events								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	2	152	6	154	42.6%	0.34 [0.07, 1.65]	43.1%	0.33 [0.07, 1.66]
VIVID-DME	3	135	6	133	57.4%	0.49 [0.13, 193]	56.9%	0.48 [0.12, 1.96]
Total		**287**		**287**	**100%**	**0.42 [0.15, 1.18]**	**100%**	**0.41 [0.14, 1.18]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
RESTORE	0	115	2	110	40.3%	0.19 [0.01, 3.94]	40.7%	0.19 [0.01, 3.96]
REVEAL	8	133	2	128	59.7%	3.85 [0.83, 17.78]	59.3%	4.03 [0.84, 19.36]
Total		**248**		**238**	**100%**	**1.15 [0.06, 20.98]**	**100%**	**1.16 [0.06, 22.61]**

All Ocular Adverse Events								
All Serious Non-Ocular Adverse Events								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	39	152	47	154	59.8%	0.84 [0.59, 1.21]	56.4%	0.79 [0.48. 1.30]
VIVID-DME	25	135	18	133	40.2%	1.37 [0.78, 2.39]	43.6%	1.45 [0.75, 2.81]
Total		**287**		**287**	**100%**	**1.02 [0.64, 1.64]**	**100%**	**1.03 [0.57, 1.87]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
RESTORE*	23	115	15	110		1.47 [0.81, 2.66]		1.58 [0.78, 3.22]
All Adverse Events								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	139	152	146	154	56.2%	0.96 [0.91, 1.03]	44.1%	0.59 [0.24, 1.46]
VIVID-DME	119	135	112	133	43.8%	1.05 [0.95, 1.15]	55.9%	1.39 [0.69, 2.81]
Total		**287**		**287**	**100%**	**1.00 [0.92, 1.08]**	**100%**	**0.95 [0.41, 2.21]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
RESTORE	14	115	11	110	27.9%	1.22 [0.58, 2.56]	33.3%	1.25 [0.54, 2.88]
REVEAL	36	133	23	128	72.1%	1.51 [0.95, 2.39]	66.7%	1.69 [0.94, 3.06]
Total		**248**		**238**	**100%**	**1.42 [0.96, 2.10]**	**100%**	**1.53 [0.94, 2.48]**
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	87	152	103	154	55.3%	0.86 [0.72, 1.02]	52.6%	0.66 [0.42, 1.05]
VIVID-DME	80	135	82	133	44.7%	0.96 [0.79, 1.17]	47.4%	0.90 [0.55, 1.48]
Total		**287**		**287**	**100**	**0.90 [0.79, 1.03]**	**100%**	**0.77 [0.55, 1.08]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
RESTORE*	49	115	43	110		1.09 [0.80, 1.49]		1.16 [0.68, 1.97]
All Non-Ocular Adverse Events								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	119	152	132	154	53.0%	0.91 [0.82, 1.02]	48.9%	0.60 [0.33, 1.09]

VIVID-DME	98	135	81	133	47.0%	1.19 [1.00, 1.41]	51.1%	1.70 [1.02, 2.84]
Total		**287**		**287**	**100**	**1.04 [0.79, 1.36]**	**100%**	**1.02 [0.37, 2.83]**
Study ID	**Ranibizumab**		**Laser**			**Risk Ratio**		**Odds Ratio**
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
RESTORE*	67	115	68	110		0.94 [0.76, 1.17]		0.86 [0.51, 1.47]
Eye Pain								
Study ID	**Aflibercept**		**Laser**			**Risk Ratio**		**Odds Ratio**
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	18	152	15	154	85.7%	1.22 [0.64, 2.32]	83.3%	1.24 [0.60, 2.57]
VIVID-DME	3	135	3	133	14.3%	0.99 [0.20, 4.79]	16.7%	0.98 [0.20, 4.97]
Total		**287**		**287**	**100%**	**1.18 [0.65, 2.15]**	**100%**	**1.20 [0.62, 2.32]**
Study ID	**Ranibizumab**		**Laser**			**Risk Ratio**		**Odds Ratio**
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
RESTORE*	12	115	11	110		1.04 [0.48, 2.27]		1.05 [0.44, 2.49]
Study ID	**Dexamethasone**		**Laser**			**Risk Ratio**		**Odds Ratio**
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
PLACID*	13	125	9	127		1.47 [0.65, 3.31]		1.52 [0.63, 3.70]

Hypertension								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	28	152	34	154	65.0%	0.83 [0.53, 1.30]	61.2%	0.80 [0.46, 1.39]
VIVID-DME	19	135	17	133	35.0%	1.10 [0.60, 2.02]	38.8%	1.12 [0.55, 2.26]
Total		**287**		**287**	**100%**	**0.92 [0.64, 1.32]**	**100%**	**0.91 [0.59, 1.41]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
RESTORE	9	115	9	110	60.9%	0.96 [0.39, 2.32]	59.1%	0.95 [0.36, 2.50]
REVEAL	6	133	6	128	39.1%	0.96 [0.32, 2.91]	40.9%	0.96 [0.30, 3.06]
Total		**248**		**238**	**100%**	**0.96 [0.48, 1.91]**	**100%**	**0.96 [0.46, 2.01]**
Cataract								
Study ID	**Aflibercept**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	6	152	10	154	53.1%	0.61 [0.23, 1.63]	53.0%	0.59 [0.21, 1.67]
VIVID-DME	8	135	5	133	46.9%	1.58 [0.53, 4.69]	47.0%	1.61 [0.51, 5.06]
Total		**287**		**287**	**100%**	**0.95 [0.37, 2.41]**	**100%**	**0.95 [0.36, 2.53]**
Study ID	**Ranibizumab**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
RESTORE*	2	115	7	110		0.27 [0.06, 1.29]		0.26 [0.05, 1.28]
Study ID	**Dexamethasone**		**Laser**		**Risk Ratio**		**Odds Ratio**	
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
PLACID*	13	125	6	127		2.20 [0.86, 5.61]		2.34 [0.86, 6.37]

* Only reported in a single study. No meta-analysis possible. Point estimates are reported for completeness

Macular Oedema								
Study ID	**Aflibercept**		**Laser**			**Risk Ratio**		**Odds Ratio**
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VIVID-DME*	[redacted]							
Study ID	**Dexamethasone**		**Laser**			**Risk Ratio**		**Odds Ratio**
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
PLACID*	7	125	4	127		1.78 [0.53, 5.92]		1.82 [0.52, 6.39]
Reduced Visual Acuity								
Study ID	**Aflibercept**		**Laser**			**Risk Ratio**		**Odds Ratio**
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	5	152	8	154	31.6%	0.63 [0.21, 1.89]	34.1%	0.62 [0.20, 1.94]
VIVID-DME	10	135	17	133	68.4%	0.58 [0.28, 1.22]	65.9%	0.55 [0.24, 1.24]
Total		**287**		**287**	**100%**	**0.60 [0.32, 1.10]**	**100%**	**0.57 [0.29, 1.11]**
Study ID	**Dexamethasone**		**Laser**			**Risk Ratio**		**Odds Ratio**
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
PLACID*	12	125	13	127		0.94 [0.45, 1.98]		0.93 [0.41, 2.13]
Vitreous Haemorrhage								
Study ID	**Aflibercept**		**Laser**			**Risk Ratio**		**Odds Ratio**
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	1	152	8	154	44.8%	0.13 [0.02, 1.00]	45.1%	0.12 [0.01, 0.98]
VIVID-DME	3	135	3	133	55.2%	0.99 [0.20, 4.79]	54.9%	0.98 [0.20, 4.97]
Total		**287**		**287**	**100%**	**0.39 [0.05, 3.07]**	**100%**	**0.38 [0.05, 3.12]**
Study ID	**Dexamethasone**		**Laser**			**Risk Ratio**		**Odds Ratio**
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
PLACID*	12	125	8	127		1.52 [0.65, 3.60]		1.58 [0.62, 4.01]
Increased IOP								
Study ID	**Aflibercept**		**Laser**			**Risk Ratio**		**Odds Ratio**
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
VISTA-DME	6	152	1	154	41.4%	6.08 [0.74, 49.90]	41.8%	6.29 [0.75, 52.86]
VIVID-DME	6	135	9	133	58.6%	0.66 [0.24, 1.79]	58.6%	0.64 [0.22, 1.85]
Total		**287**		**287**	**100%**	**1.65 [0.18, 14.83]**	**100%**	**1.66 [0.18, 15.74]**
Study ID	**Dexamethasone**		**Laser**			**Risk Ratio**		**Odds Ratio**
	Events	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Weight**	**M-H, Random, 95% CI**
PLACID*	25	125	2	127		12.70 [3.07, 52.49]		15.63 [3.61, 67.56]

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

All ‘head-to-head’ comparisons of comparator treatments were performed following methods recommended by the Cochrane Handbook. Forest plots of effect sizes were prepared for each of the outcomes in Cochrane Review Manager Version 5.2 (RevMan 5.2). Dichotomous outcomes (e.g. number of patients with a gain of ≥10 ETDRS letters) were reported as relative risks (RRs) with 95% confidence intervals (CIs), continuous outcomes as mean differences (MDs) with 95% CI. To allow comparison, odds ratios were also reported. Pooled effect sizes (RRs/weighted mean difference (WMD)) and 95% CIs were calculated using fixed effect and random effects models using inverse variance or Mantel-Haenszel methods. Data were only pooled where trials were considered to be clinically and statistically homogeneous (see section 6.7.7).

Data were synthesised using Bucher indirect and Bayesian mixed treatment comparison (MTC) analyses (fixed and random effect models), consistent with ISPOR taskforce recommendations for the conduct of direct and indirect meta-analysis.

Indirect meta-analysis was performed using Microsoft Excel 2010 according to the method developed by Bucher 1997. Results were presented as odds ratios (OR) and risk ratios (RR) for binary outcomes and as mean differences (MD) with 95% CIs for continuous outcomes using results from the direct fixed and random effects meta-analysis.

If at least one ‘head-to-head’ trial was found then a MTC (using a network of both ‘head-to-head’ and indirect comparisons) was performed using Bayesian methods in WinBUGS version 1.4.3 (http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml). RRs and ORs with 95% credible intervals (CrI) were calculated for each outcome and available treatment comparison using random effects models. WinBUGS codes are available in an Appendix.

Issues of heterogeneity and consistency were investigated using the I2 statistic for heterogeneity and the Deviance Information Criterion (DIC) for Bayesian model fit. To evaluate the assumptions underlying indirect and MTC analyses, a narrative discussion concerning the feasibility and appropriateness of indirect comparisons was provided using the criteria of homogeneity, similarity and consistency. Issues of similarity were considered by investigating the trial designs, conduct, treatment details and patient

characteristics. Consistency was not assessed as for the treatment comparisons of interest there was no direct ‘head-to-head’ trial evidence.

Aflibercept (2mg every 4 weeks for the first 5 months followed by 2mg every 8 weeks) and 0.5mg ranibizumab PRN could be compared via a common comparator of laser + sham injection. After completing the assessment of clinical similarity the included studies were considered sufficiently similar to employ a fixed effects model in the analysis. The results of both fixed and random effects models were estimated. All possible direct analyses were performed to assess statistical heterogeneity before performing indirect and mixed treatment comparison (MTC) analyses. The results of the direct meta-analyses are reported as forest plots based on the fixed effects model (see section 6.7.4). The direct analyses estimated the risk ratio based on data from those trials which directly compared 2Q8 AFB versus laser + sham (*VIVID, VISTA*) or 0.5 PRN RBZ versus laser + sham (*RESTORE, REVEAL*) or dexamethasone implant versus laser +sham.

6.7.6 Please present the results of the analysis.

Results of the network meta-analysis (NMA) showed a significant improvement in visual acuity outcomes (‘BCVA mean change from baseline’ and ‘loss ≥10 ETDRS letters’) for AFB 2Q8 in comparison to 0.5 PRN RBZ. There was no significant difference between aflibercept and ranibizumab in alternative visual acuity (‘gain ≥15 ETDRS letters’, ‘loss ≥15 ETDRS letters’, ‘gains ≥10 ETDRS letters’) or safety outcomes. For each of the nine safety outcomes where quantitative analysis was possible, patients receiving aflibercept experienced fewer adverse events than those receiving ranibizumab but as these results are based on a small number of studies they should be interpreted with caution. AFB 2Q8 significantly improved the visual acuity ‘gain ≥10 ETDRS letters’ and reduced ‘increased intraocular pressure’ in comparison to 0.7mg dexamethasone, but did not significantly influence other visual acuity or safety outcomes. A comparison of AFB 2Q8 to 0.2µg/day fluocinolone acetonide implants was not possible.

Efficacy outcomes

Bucher indirect analysis of 12-month efficacy outcomes

- **2Q8 AFB versus 0.5 RBZ**

The results showed that 2Q8 AFB improved BCVA mean change from baseline by significantly more than 0.5PRN RBZ (MD = 4.82, 95%CI 2.52 to 7.12) and BCVA mean average change from baseline using aLOCF (MD = 1.89, 95% CI 0.20 to 3.58) and BCVA mean average change from baseline using LOCF (MD = 2.95, 95% CI 1.17 to 4.73). For all other outcomes (except discontinuation) the results showed a trend in favour of 2Q8 AFB but these effects were not significant.

Table 45: Indirect meta-analysis of 2Q8 AFB vs. 0.5PRN RBZ for 12 month efficacy outcomes

Outcome	No. Trials	FE: Effect Size (95% CI)	RE: Effect Size (95%CI)
BCVA Mean Change from baseline	4 studies, Total N = 1611 (VIVID-DME, VISTA-DME, RESTORE, REVEAL)	MD = 4.82 (2.52 to 7.11)	MD = 4.82 (2.52 to 7.11)
BCVA Mean Average Change from baseline (aLOCF)	4 studies, Total N = 1611 (VIVID-DME, VISTA-DME, RESTORE, REVEAL)	MD = 1.89 (0.20 to 3.58)	MD = 1.89 (0.20 to 3.58)
BCVA Mean Average Change from baseline (LOCF)	4 studies, Total N = 1611 (VIVID-DME, VISTA-DME, RESTORE, REVEAL)	MD = 2.95 (1.17 to 4.73)	MD = 2.95 (1.17 to 4.73)
Gain ≥10 EDTRS letters	4 studies, Total N = 1611 (VIVID-DME, VISTA-DME, RESTORE, REVEAL)	RR = 0.993 (0.65 to 1.52) OR = 1.32 (0.74 to 2.35)	RR = 1.00 (0.60 to 1.66) OR = 1.32 (0.65 to 2.68)
Loss ≥10 EDTRS letters	4 studies, Total N = 1611 (VIVID-DME, VISTA-DME, RESTORE, REVEAL)	[redacted]	[redacted]
Gain ≥15 EDTRS letters	4 studies, Total N = 1611 (VIVID-DME, VISTA-DME, RESTORE, REVEAL)	RR = 1.49 (0.78 to 2.85) OR = 1.74 (0.83 to 3.65)	RR = 1.49 (0.78 to 2.85) OR = 1.74 (0.83 to 3.65)
Loss ≥15 EDTRS letters	4 studies, Total N = 1611 (VIVID-DME, VISTA-DME, RESTORE, REVEAL)	RR = 0.24 (0.03 to 1.90) OR = 0.23 (0.03 to 1.86)	RR = 0.26 (0.03 to 2.11) OR = 0.23 (0.03 to 1.86)
Treatment Discontinuation	4 studies, Total N = 1611 (VIVID-DME, VISTA-DME, RESTORE, REVEAL)	RR = 1.22 (0.60 to 2.47) OR = 1.27 (0.58 to 2.81)	RR = 1.23 (0.45 to 3.37) OR = 1.25 (0.41 to 3.83)

FE = Fixed Effects, RE = Random Effects, MD = Mean Difference, RR = Risk Ratio, OR = Odds Ratio, CI = Confidence Interval

There was some concern whether the *REVEAL* trial could be considered comparable to the other studies included in this analysis as this trial was conducted in an Asian population whereas the other studies were conducted in predominantly Caucasian populations. A sensitivity analysis was performed to investigate the effects of excluding this study on efficacy outcomes (Table 46).

Table 46: Indirect meta-analysis of 2Q8 AFB vs. 0.5PRN RBZ for 12 month efficacy outcomes: sensitivity analysis

Outcome	No. Trials	FE: Effect Size (95% CI)	RE: Effect Size (95%CI)
BCVA Mean Change from baseline	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	MD = 4.11 (0.99 to 7.22)	MD = 4.11 (0.99 to 7.22)
BCVA Mean Average Change from baseline (aLOCF)	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	MD = 1.39 (-0.92 to 3.71)	MD = 1.39 (-0.92 to 3.71)
BCVA Mean Average Change from baseline (LOCF)	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	MD = 2.45 (0.07 to 4.82)	MD = 2.45 (0.07 to 4.82)
Gain ≥10 EDTRS letters	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 1.02 (0.59 to 1.77) OR = 1.34 (0.64 to 4.79)	RR = 1.03 (0.55 to 1.90) OR = 1.33 (0.57 to 3.10)
Loss ≥10 EDTRS letters	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	[redacted]	[redacted]
Gain ≥15 EDTRS letters	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 1.39 (0.61 to 3.16) OR = 1.58 (0.61 to 4.06)	RR = 1.39 (0.61 to 3.16) OR = 1.58 (0.61 to 4.05)
Loss ≥15 EDTRS letters	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 0.52 (0.04 to 7.27) OR = 0.52 (0.04 to 7.39)	RR = 0.55 (0.03 to 8.77) OR = 0.50 (0.03 to 7.72)
Treatment Discontinuation	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 0.78 (0.33 to 1.87) OR = 0.79 (0.33 to 1.89)	RR = 0.76 (0.29 to 2.03) OR = 0.77 (0.29 to 2.05)

FE = Fixed Effects, RE = Random Effects, MD = Mean Difference, RR = Risk Ratio, OR = Odds Ratio, CI = Confidence Interval

- **2Q4/2Q8 AFB versus 0.7 dexamethasone**

Indirect analyses of 2Q8 AFB versus 0.7DEX for the outcome 'Gain of ≥10 ETDRS letters' included three trials. *VIVID-DME* and *VISTA-DME* compared 2Q8 AFB + sham laser versus laser + sham injection. *PLACID* compared 0.7DEX + sham laser with laser + sham injection. The results showed that significantly more patients receiving 2Q8 AFB gained ≥10 ETDRS letters compared to those receiving 0.5PRN RBZ (RR = 2.10, 95%CI 1.29 to 3.40). There was no significant difference in the number of patients who discontinued

treatment for 2Q8 AFB + sham laser vs. 0.7DEX + sham laser (RR = 1.15, 95%CI 0.58 to 2.29).

Table 47: Bucher Indirect analysis of 2Q8 AFB vs. 0.7DEX for gain of ≥10 ETDRS letters

Outcome	No. Trials	FE: Effect Size (95% CI)	RE: Effect Size (95%CI)
Gain ≥10 EDTRS letters	3 studies, Total N = 1123 (VIVID-DME, VISTA-DME, PLACID)	RR = 2.10 (1.29 to 3.40) OR = 3.51 (1.79 to 6.88)	RR = 2.10 (1.21 to 3.66) OR = 3.52 (1.60 to 7.72)
Treatment Discontinuation	3 studies, Total N = 1123 (VIVID-DME, VISTA-DME, PLACID)	RR = 1.15 (0.58 to 2.29) OR = 1.24 (0.55 to 2.82)	RR = 1.16 (0.57 to 2.34) OR = 1.23 (0.54 to 2.80)

MTC analysis of 12-month efficacy outcomes

No networks were feasible for 2Q8 AFB versus 0.7DEX.

- **All treatments compared with laser + sham injection**

Table 48: All treatments compared with laser + sham injection (treatment 1) for random effects models

Treatment (code in the analysis)	Mean change in BCVA Median (95% CrI)	Mean average change in BCVA Median (95% CrI)- aLOCF VIVID/VISTA	Mean average change in BCVA Median (95% CrI)- LOCF VIVID/VISTA	Gain ≥ 15 letters RR (95% CrI)	Loss ≥ 15 letters RR (95% CrI)	Gain ≥ 10 letters RR (95% CrI)	Loss ≥ 10 letters RR (95% CrI)	Treatment Discontinuation RR (95% CrI)
RBZ + laser (2) RBZ (3) IVTA + laser (4) BVZ + laser (5) Laser (6) AFB2Q4 + sham laser(7) AFB2Q4/8 + sham laser(8) RBZ + deferred laser (9)	5.13 (3.54, 6.58) 5.26 (3.28, 7.10) 1.12 (-1.19, 3.47) -0.29 (-11.86, 10.98) -2.65 (-8.64, 3.26) 10.71 (8.59, 12.97) 9.91 (7.70, 12.0) 5.72 (3.12, 8.25)							1.11 (0.73, 1.70) 0.74 (0.38, 1.36) 0.99 (0.54, 1.71) 1.23 (0.29, 3.40) 1.04 (0.28, 2.99) 0.70 (0.35, 1.35) 0.80 (0.42, 1.55) 0.82 (0.33, 1.75)
IVTA + laser (2) RBZ (3) RBZ + laser (4) RBZ + deferred laser (5) AFB2Q4 + sham laser(6) AFB2Q4/8 + sham laser(7)				1.43 (0.92, 2.13) 2.19 (1.47, 3.13) 2.09 (1.51, 2.82) 1.87 (1.20, 2.76) 3.45 (2.50, 4.57) 3.09 (2.20, 4.21)	1.00 (0.49, 1.96) 0.19 (0.03, 0.63) 0.56 (0.28, 1.02) 0.32 (0.07, 1.10) 0.06 (0.007, 0.24) 0.03 (0.001, 0.16)	1.18 (0.82, 1.60) 1.74 (1.36, 2.17) 1.80 (1.50, 2.14) 1.64 (1.18, 2.12) 2.17 (1.79, 2.57) 2.07 (1.68, 2.48)	[redacted]	
RBZ + laser (2) RBZ (3) AFB2Q4 + sham laser(4) AFB2Q4/8 + sham laser(5)		4.58 (2.74, 6.47) 4.80 (3.09, 6.61) 7.23 (5.43, 9.02) 6.72 (4.92, 8.39)	4.61 (2.76, 6.54) 4.87 (3.05, 6.66) 8.34 (6.40, 10.27) 7.71 (5.80, 9.59)					

FE = Fixed Effects, RE = Random Effects, RR = Risk Ratio, OR = Odds Ratio, CrI = Credible Interval

- **2Q8 AFB versus 0.5 RBZ**

The results showed that 2Q8 AFB significantly improved BCVA mean change from baseline (MD = 4.67, 95% CrI 2.45 to 6.87), mean average change from baseline in BCVA aLOCF (MD = 1.87, 95% CrI 0.22 to 3.57), and mean average change from baseline in BCVA LOCF (MD = 2.88, 95% CrI 1.16 to 4.66) compared with 0.5PRN RBZ. There was also a significant reduction in the proportion of patients with a loss of 10 or more letters (RR = [redacted]) for the fixed effect model. However this reduction was not significant in the random effects model due to the wider 95% CrI. For all other outcomes the results showed a trend in favour of 2Q8 AFB but the results were not significant (Table 49).

There were no direct analyses of 2Q8 AFB versus RBZ, therefore it was not possible to evaluate consistency between the direct and indirect results.

Table 49: MTC analyses of 2Q8 AFB compared with 0.5PRN RBZ for 12 month efficacy outcomes

Outcome	No. Trials	FE: Effect Size (95% CrI)	RE: Effect Size (95%CrI)
BCVA Mean Change from baseline	10 studies, Total N = 3060 (RESTORE, REVEAL, RELATION, LRT for DME, LRT for DME/PRP, VIVID-DME, VISTA-DME, IBETA, LUCIDATE, Maia 2009)	MD = 4.67 (2.45 to 6.87) DIC = 109.9	MD = 4.67 (1.85 to 7.52) DIC = 111.49
BCVA Mean Average Change from baseline (aLOCF)	4 studies, Total N = 1611 (VIVID-DME, VISTA-DME, RESTORE, REVEAL)	MD = 1.87 (0.22 to 3.57) DIC = 29.46	MD = 1.93 (-0.65 to 4.34) DIC = NR
BCVA Mean Average Change from baseline (LOCF)	4 studies, Total N = 1611 (VIVID-DME, VISTA-DME, RESTORE, REVEAL)	MD = 2.88 (1.16 to 4.66) DIC = 29.46	MD = 2.81 (0.24 to 5.44) DIC = 30.95
Gain ≥10 EDTRS letters	6 studies. Total N = 2810 (RESTORE, REVEAL, LRT for DME, LRT for DME/PRP, VIVID-DME, VISTA-DME)	RR = 1.32 (0.98 to 1.78) OR = 1.64 (0.97 to 2.78) DIC = NR	RR = 1.19 (0.90 to 1.57) OR = 1.59 (0.75 to 3.35) DIC = 131.59
Loss ≥10 EDTRS letters	6 studies. Total N = 2810 (RESTORE, REVEAL, LRT for DME, LRT for DME/PRP, VIVID-DME, VISTA-DME)	[redacted]	[redacted]
Gain ≥15 EDTRS letters	6 studies. Total N = 2810 (RESTORE, REVEAL, LRT for DME, LRT for DME/PRP, VIVID-DME,	RR = 1.78 (0.96 to 3.29) OR = 1.90 (0.95 to 3.75) DIC = 117.47	RR = 1.42 (0.93 to 2.24) OR = 1.87 (0.87 to 4.16) DIC = 119.25

Outcome	No. Trials	FE: Effect Size (95% CrI)	RE: Effect Size (95%CrI)
	VISTA-DME)		
Loss ≥15 EDTRS letters	6 studies. Total N = 2810 (RESTORE, REVEAL, LRT for DME, LRT for DME/PRP, VIVID-DME, VISTA-DME)	RR = 0.13 (0.004 to 1.35) OR = 0.13 (0.004 to 1.35) DIC = 95.94	RR = 0.14 (0.007 to 1.52) OR = 0.14 (0.006 to 1.53) DIC = 96.0
Treatment Discontinuation	9 studies. Total N = 2956 (RESTORE, REVEAL, LRT for DME, LRT for DME for PRP, VIVID-DME, VISTA-DME, IBETA, LUCIDATE, Maia 2009)	RR = 1.12 (0.55 to 2.30) OR = 1.14 (0.52 to 2.49)	RR = 1.09 (0.44 to 2.77) OR = 1.10 (0.39 to 3.29)

FE = Fixed Effects, RE = Random Effects, MD = Mean Difference, RR = Risk Ratio, OR = Odds Ratio, CrI = Credible Interval; DIC = Deviance Information Criterion

There was some concern whether the *LRT for DME for PRP* study was sufficiently similar to the other studies included in the analysis due to differences in the treatment protocol compared to other studies. In this study, treatment was only scheduled up to 12 weeks, beyond this point patients received only PRN 'rescue' treatment with the randomly assigned intervention. From week 14-56 only ~50% of included patients received further treatment. A sensitivity analysis was performed to investigate the effect of excluding this study from the MTC. The results of this analysis are reported in Table 50. Exclusion of *LRT for DME for PRP* did not change the results of the analysis.

Table 50: MTC analyses of 2Q8 AFB compared with 0.5PRN RBZ for 12 month efficacy outcomes: Sensitivity Analysis

Outcome	No. Trials	FE: Effect Size (95% CrI)	RE: Effect Size (95%CrI)
BCVA Mean Change from baseline	9 studies, Total N = 2715 (RESTORE, REVEAL, RELATION, LRT for DME, VIVID-DME, VISTA-DME, IBETA, LUCIDATE, Maia 2009)	MD = 4.58 (2.38 to 6.76)	MD = 4.61 (1.78 to 7.82)
Gain ≥10 EDTRS letters	5 studies. Total N = 2465 (RESTORE, REVEAL, LRT for DME, VIVID-DME, VISTA-DME)	RR = 1.26 (0.95 to 1.66) OR = 1.55 (0.91 to 2.62)	RR = 1.16 (0.86 to 1.53) OR = 1.54 (0.63 to 3.40)
Loss ≥10 EDTRS letters	5 studies. Total N = 2465 (RESTORE, REVEAL, LRT for DME, VIVID-DME, VISTA-DME)	[redacted]	[redacted]
Gain ≥15 EDTRS letters	5 studies. Total N = 2465 (RESTORE, REVEAL, LRT for DME, VIVID-DME, VISTA-DME)	RR = 1.56 (0.97 to 2.54) OR = 1.87 (0.96 to 3.69)	RR = 1.39 (0.85 to 2.19) OR = 1.86 (0.73 to 4.26)
Loss ≥15	5 studies. Total N = 2465	RR = 0.15 (0.01 to 1.51)	RR = 0.14 (0.01 to 1.92)

Outcome	No. Trials	FE: Effect Size (95% CrI)	RE: Effect Size (95%CrI)
EDTRS letters	(RESTORE, REVEAL, LRT for DME, VIVID-DME, VISTA-DME)	OR = 0.15 (0.01 to 1.51)	OR = 0.14 (0.004 to 1.93)
Treatment Discontinuation	8 studies. Total N = 2611 (RESTORE, REVEAL, LRT for DME, VIVID-DME, VISTA-DME, IBETA, LUCIDATE, Maia 2009)	RR = 1.17 (0.61 to 2.24) OR = 1.20 (0.56 to 2.63)	RR = 1.18 (0.42 to 3.11) OR = 1.21 (0.36 to 3.76)

Safety

Bucher indirect analysis of 12 month safety outcomes

- **2Q8 AFB versus 0.5 RBZ**

The analyses revealed no statistically significant results. The results showed that patients receiving 2Q8 AFB had a trend towards an increased risk of all cause mortality (RR = 2.25, 95%CI 0.16-31.26), and cataract (RR = 3.42, 95%CI 0.62-18.95); however, none of these effects were statistically significant. For all other safety outcomes patients receiving 2Q8 AFB experienced fewer adverse events than those receiving 0.5PRN RBZ but these effects were not statistically significant (Table 51).

Table 51: Indirect analysis of 2Q8 AFB vs. 0.5PRN RBZ for 12 month safety outcomes

Outcome	No. Trials	FE: Effect Size (95% CI)	RE: Effect Size (95%CI)
All Serious AE	4 studies, Total N = 1611 (VIVID-DME, VISTA-DME, RESTORE, REVEAL)	RR = 0.78 (0.48 to 1.27) OR = 0.74 (0.40 to 1.37)	RR = 0.81 (0.45 to 1.47) OR = 0.77 (0.36 to 1.64)
All Serious Ocular AE	4 studies, Total N = 1611 (VIVID-DME, VISTA-DME, RESTORE, REVEAL)	RR = 0.20 (0.04 to 1.11) OR = 0.19 (0.03 to 1.11)	RR = 0.39 (0.02 to 7.34) OR = 0.38 (0.02 to 8.03)
All Serious Non-Ocular AE	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 0.66 (0.34 to 1.29) OR = 0.62 (0.28 to 1.40)	RR = 0.70 (0.33 to 1.48) OR = 0.65 (0.26 to 1.64)
All AE	4 studies, Total N = 1611 (VIVID-DME, VISTA-DME, RESTORE, REVEAL)	RR = 0.70 (0.47 to 1.04) OR = 0.66 (0.32 to 1.38)	RR = 0.70 (0.47 to 1.05) OR = 0.62 (0.23 to 1.63)
All Ocular AE	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 0.83 (0.59 to 1.16) OR = 0.66 (0.35 to 1.25)	RR = 0.83 (0.59 to 1.16) OR = 0.66 (0.35 to 1.25)
All Non-Ocular AE	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 1.04 (0.83 to 1.32) OR = 1.26 (0.65 to 2.45)	RR = 1.11 (0.78 to 1.57) OR = 1.19 (0.38 to 3.73)

Outcome	No. Trials	FE: Effect Size (95% CI)	RE: Effect Size (95%CI)
Eye Pain	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 1.13 (0.42 to 3.01) OR = 1.14 (0.39 to 3.39)	RR = 1.14 (0.43 to 3.03) OR = 1.14 (0.39 to 3.40)
Hypertension	4 studies, Total N = 1611 (VIVID-DME, VISTA-DME, RESTORE, REVEAL)	RR = 0.96 (0.44 to 2.09) OR = 0.95 (0.40 to 2.25)	RR = 0.96 (0.44 to 2.09) OR = 0.95 (0.40 to 2.23)
Cataract	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 3.42 (0.62 to 18.95) OR = 3.57 (0.61 to 20.97)	RR = 3.52 (0.58 to 21.23) OR = 3.65 (0.55 to 24.23)
All Cause Mortality	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 2.25 (0.16 to 31.26) OR = 2.28 (0.16 to 32.83)	RR = 1.77 (0.07 to 44.10) OR = 1.78 (0.07 to 46.70)

FE = Fixed Effects, RE = Random Effects, MD = Mean Difference, RR = Risk Ratio, OR = Odds Ratio, CI = Confidence Interval

There was some concern whether the *REVEAL* trial could be considered comparable to the other studies included in this analysis as this trial was conducted in an Asian population whereas the other studies were conducted in predominantly Caucasian populations. A sensitivity analysis was performed to investigate the effects of excluding this study on the four safety outcomes that included the *REVEAL* study (All SAE, All SOAE, All AE, Hypertension). No significant results were found for the sensitivity analyses.

Table 52: Indirect analysis of 2Q8 AFB vs. 0.5PRN RBZ for 12 month safety outcomes – Sensitivity analysis

Outcome	No. Trials	FE: Effect Size (95% CI)	RE: Effect Size (95%CI)
All Serious AE	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 0.71 (0.37 to 1.33) OR = 0.66 (0.30 to 1.44)	RR = 0.74 (0.36 to 1.51) OR = 0.68 (0.37 to 1.68)
All Serious Ocular AE	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 2.19 (0.09 to 3.94) OR = 2.17 (0.09 to 54.81)	RR = 2.21 (0.09 to 52.16) OR = 2.16 (0.09 to 51.63)
All AE	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 0.81 (0.38 to 1.71) OR = 0.81 (0.30 to 2.21)	RR = 0.82 (0.39 to 1.73) OR = 0.76 (0.23 to 2.49)
Hypertension	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 0.96 (0.37 to 2.50) OR = 0.95 (0.33 to 2.75)	RR = 0.96 (0.37 to 2.51) OR = 0.96 (0.33 to 2.77)

FE = Fixed Effects, RE = Random Effects, MD = Mean Difference, RR = Risk Ratio, OR = Odds Ratio, CI = Confidence Interval

- **2Q4/2Q8 AFB versus 0.7 dexamethasone**

None of the analyses found any significant results; all showed a trend for fewer adverse events when treated with 2Q4/2Q4 AFB + sham laser in comparison to 0.7DEX + sham laser.

Table 53: Indirect analysis of 2Q8 AFB vs. 0.7DEX for 12 month safety outcomes

Outcome	No. Trials	FE: Effect Size (95% CI)	RE: Effect Size (95% CI)
Macular Oedema	2 studies, Total N = 657 (VIVID-DME, PLACID)	[redacted]	[redacted]
Reduced Visual Acuity	3 studies, Total N = 1123 (VIVID-DME, VISTA-DME, PLACID)	RR = 0.64 (0.24 to 1.67) OR = 0.61 (0.21 to 1.77)	RR = 0.64 (0.17 to 2.40) OR = 0.61 (0.21 to 1.77)
Vitreous Haemorrhage	3 studies, Total N = 1123 (VIVID-DME, VISTA-DME, PLACID)	RR = 0.30 (0.07 to 1.39) OR = 0.28 (0.06 to 1.38)	RR = 0.18 (0.02 to 1.65) OR =0.16 (0.02 to 1.54)
Eye Pain	3 studies, Total N = 1123 (VIVID-DME, VISTA-DME, PLACID)	RR = 0.80 (0.29 to 2.21) OR = 0.79 (0.26 to 2.38)	RR = 0.78 (0.27 to 2.21) OR = 0.76 (0.24 to 2.38)
Increased Intraocular Pressure	3 studies, Total N = 1123 (VIVID-DME, VISTA-DME, PLACID)	RR = 0.08 (0.02 to 0.42) OR = 0.07 (0.01 to 0.37)	RR = 0.13 (0.01 to 1.79) OR = 0.11 (0.01 to 1.54)
Cataract	3 studies, Total N = 1123 (VIVID-DME, VISTA-DME, PLACID)	RR = 0.42 (0.13 to 1.39) OR = 0.40 (0.11 to 1.40)	RR = 0.43 (0.12 to 1.63) OR = 0.41 (0.10 to 1.64)

MTC analysis of 12 month safety outcomes

No networks were feasible for 2Q8 AFB versus 0.7DEX.

- **All treatments compared with laser + sham injection**

Table 54: All treatments compared with laser + sham injection (treatment 1) for random effects models

Treatment (code in the analysis)	All SAE RR (95% CrI)	All serious ocular AE RR (95% CrI)	All AE RR (95% CrI)	All ocular AE RR (95% CrI)	All serious non-ocular AE RR (95% CrI)	All non-ocular AE RR (95% CrI)	Cataract RR (95% CrI)
RBZ + laser (2)	1.10 (0.77, 1.56)	1.23 (0.36, 4.01)	1.08 (0.88, 1.23)	1.12 (0.91, 1.32)	1.30 (0.67, 2.32)	0.87 (0.51, 1.09)	0.80 (0.17, 3.06)
RBZ (3)	1.15 (0.77, 1.69)	1.23 (0.26, 4.21)	1.12 (0.92, 1.28)	1.09 (0.78, 1.31)	1.50 (0.69, 2.61)	0.97 (0.65, 1.13)	0.25 (0.025, 1.39)
AFB2Q4 + sham laser(4)	0.96 (0.62, 1.40)	0.38 (0.09, 1.37)	0.98 (0.72, 1.19)	0.92 (0.67, 1.14)	1.01 (0.53, 1.70)	1.00 (0.80, 1.11)	0.98 (0.34, 2.60)
AFB2Q4/8 + sham laser(5)	0.94 (0.62, 1.40)	0.38 (0.09, 1.43)	0.99 (0.73, 1.19)	0.92 (0.66, 1.13)	1.01 (0.54, 1.72)	1.01 (0.81, 1.12)	0.96 (0.34, 2.57)

- **2Q8 AFB versus 0.5 RBZ**

The results showed that there were no significant differences between 2Q8 AFB and 0.5PRN RBZ for any of the safety outcomes at 12 months although there was a trend towards an increased risk of mortality and cataract with 2Q8 AFB.

Table 55: MTC analyses of 2Q8 AFB compared with 0.5PRN RBZ for 12 month safety outcomes

Outcome	No. Trials	FE: Effect Size (95% CrI)	RE: Effect Size (95%CrI)
All Serious AE	5 studies, Total N = 1739 (RESTORE, REVEAL, RELATION, VIVID-DME, VISTA-DME)	RR = 0.76 (0.47 to 1.26) OR = 0.71 (0.39 to 1.32)	RR = 0.82 (0.47 to 1.42) OR = 0.74 (0.31 to 1.72)
All Serious Ocular AE	5 studies, Total N = 1739 (RESTORE, REVEAL, RELATION, VIVID-DME, VISTA-DME)	RR = 0.28 (0.06 to 1.24) OR = 0.27 (0.05 to 1.25)	RR = 0.30 (0.05 to 2.49) OR = 0.28 (0.05 to 2.58)
All AE	5 studies, Total N = 1739 (RESTORE, REVEAL, RELATION, VIVID-DME, VISTA-DME)	RR = 0.79 (0.55 to 1.10) OR = 0.61 (0.29 to 1.26)	RR = 0.88 (0.64 to 1.15) OR = 0.58 (0.18 to 1.82)
All Ocular AE	4 studies, Total N = 1343 (RESTORE, RELATION, VIVID-DME, VISTA-DME)	RR = 0.75 (0.54 to 1.05) OR = 0.60 (0.32 to 1.09)	RR = 0.85 (0.58 to 1.25) OR = 0.58 (0.16 to 1.87)
All Serious Non-Ocular AE	4 studies, Total N = 1343 (RESTORE, RELATION, VIVID-DME, VISTA-DME)	RR = 0.60 (0.32 to 1.14) OR = 0.53 (0.24 to 1.17)	RR = 0.67 (0.29 to 1.66) OR = 0.53 (0.12 to 2.11)
All Non-Ocular AE	3 studies, Total N = 1215 (VIVID-DME, VISTA-DME, RESTORE)	RR = 1.09 (0.87 to 1.40) OR = 1.27 (0.65 to 2.42)	RR = 1.03 (0.80 to 1.56) OR = 1.22 (0.23 to 6.18)
Eye Pain	4 studies, Total N = 1343 (RESTORE, RELATION, VIVID-DME, VISTA-DME)	RR = 0.98 (0.38 to 2.70) OR = 0.97 (0.34 to 2.94)	RR = 0.96 (0.23 to 3.91) OR = 0.95 (0.17 to 4.75)
Hypertension	4 studies, Total N = 1343 (RESTORE, REVEAL, VIVID-DME, VISTA-DME)	RR = 0.95 (0.44 to 2.07) OR = 0.95 (0.40 to 2.22)	RR = 0.95 (0.37 to 2.55) OR = 0.94 (0.28 to 3.14)
Cataract	3 studies, Total N = 1215 (RESTORE, VIVID-DME, VISTA-DME)	RR = 3.93 (0.77 to 32.74) OR = 4.09 (0.76 to 34.86)	RR = 3.83 (0.52 to 43.72) OR = 4.16 (0.49 to 50.98)
All Cause Mortality	3 studies, Total N = 1215 (RESTORE, VIVID-DME, VISTA-DME)	RR = 2.90 (0.20 to 50.4) OR = 3.06 (0.18 to 60.01)	RR = 2.76 (0.13 to 79.02) OR = 2.83 (0.11 to 85.27)

FE = Fixed Effects, RE = Random Effects, MD = Mean Difference, RR = Risk Ratio, OR = Odds Ratio, CrI = Credible Interval

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.

Issues of heterogeneity and consistency were investigated using the I^2 statistic for heterogeneity and the Deviance Information Criterion (DIC) for Bayesian MTC model fit.

I^2 statistic measures the degree of inconsistency between the study results and describes the percentage of total variation across studies due to heterogeneity rather than the play of chance. The value of I^2 lies between 0% and 100%. For the purposes of this review (and as often used), a simplified categorisation of heterogeneity was used: low (0 to 25%), moderate (26 to 75%), and high (>75%)[9]. Studies were only considered to be sufficiently similar for the purposes of pooling if I^2<75%.

The DIC (deviance information criterion) statistic was assessed as an estimate of goodness of fit for the MTC model. Overall, this shows that there is very little difference between the Fixed effects and Random effects models. The DIC models are very similar in each case indicating that the goodness of fit for the models is almost the same in both cases (see Table 49).

To evaluate the assumptions underlying indirect and MTC analyses, a narrative discussion concerning the feasibility and appropriateness of indirect comparisons was provided using the criteria of homogeneity, similarity and consistency. Issues of similarity were considered by investigating the trial designs, conduct, treatment details and patient characteristics. Consistency was not assessed as for the treatment comparisons of interest there was no direct 'head-to-head' trial evidence.

For all comparators and analyses the clinical similarity of the studies was first assessed and then all possible direct analyses were performed to assess statistical heterogeneity before performing any indirect and MTC analyses. This allowed the identification of any dissimilar studies that may have required further exploration using sensitivity analysis.

There was very little statistical heterogeneity detected between the combined studies in the comparisons of 2Q8 AFB + sham laser versus laser + sham injection or 0.5 PRN RBZ + sham laser versus laser + sham injection. The I^2 statistic was 0% for all efficacy outcomes except 'gain of ≥10 ETDRS letters' where *VIVID-DME* and *VISTA-DME* showed 56% heterogeneity and 'discontinuation' where *RESTORE* and *REVEAL* showed 66%.

There was considerable heterogeneity for increased intraocular pressure (I^2 = 73%) (VISTA, VIVID). *VIVID-DME* and *VISTA-DME* both had two domains with high risk of bias in the Cochrane risk of bias tool and in both cases of heterogeneity the issues were the involvement of unblinded personnel and the availability of treatments other than the randomly assigned treatment.

Moderate heterogeneity was observed in the direct analysis of several safety outcomes. This may be because the frequency of adverse events was low in all studies, therefore, the analysis of safety outcomes was based a small number of events with a high degree of uncertainty.

The lack of statistical heterogeneity identified in the direct analyses indicated that fixed effect models can be used for the indirect analyses. However, results from the random effects analyses were also tabulated, to show that they provided similar results. A gain of ≥10 letters and discontinuation were the only efficacy outcomes to indicate heterogeneity in the direct analyses, but the results show that similar indirect results were obtained using both fixed and random effect models (see Table 49). Both RR and OR are reported to allow comparison with direct and MTC analyses.

A statistical test of heterogeneity was not included in the MTC analyses as it was believed that it would have been under powered and, as such, presents a weak argument. The purpose of such tests is to give some indication of whether it is appropriate to conduct the MTC at all. As the tests are often underpowered a significant result may be a cause for concern but a non-significant result cannot be interpreted as evidence for the absence of heterogeneity. It is still a value judgement how much heterogeneity is too much and different people will apply different thresholds. Thus, we elected to present the evidence from the MTC and consider the effects of the heterogeneity in the discussion rather than declare the evidence valid/invalid based on a p-value from an under powered test.

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.

Where concerns were held over the suitability of some trials for inclusion in the analyses, sensitivity analyses were performed. These are presented alongside the results in section 6.7.6.

The *REVEAL* trial was conducted in an Asian population whereas the other studies were conducted in predominantly Caucasian populations. A sensitivity analysis was performed to investigate the effects of excluding this study on efficacy outcomes (Table 46) and four safety outcomes that included the *REVEAL* study (All SAE, All SOAE, All AE, Hypertension). No significant results were found for the sensitivity analyses.

There was also some concern whether the *LRT for DME for PRP* study was sufficiently similar to the other studies included in the analysis due to differences in the treatment protocol compared to other studies. In this study, treatment was only scheduled up to 12 weeks, beyond this point patients received only PRN 'rescue' treatment with the randomly assigned intervention. From week 14-56 only ~50% of included patients received further treatment. A sensitivity analysis was performed to investigate the effect of excluding this study from the MTC. The results of this analysis are reported in Table 50. Exclusion of *LRT for DME for PRP* did not change the results of the analysis.

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

Heterogeneity has been discussed in section 6.7.7.

There were no direct analyses of 2Q8 AFB versus RBZ or 2Q8 AFB versus dexamethasone implant, therefore it was not possible to evaluate consistency between direct and indirect results.

6.8 Non-RCT evidence

There are no relevant non-RCTs included in this submission.

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 VISTA nor VIVID included safety outcomes as a basis for 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 laser photocoagulation in the treatment of DMO, is provided by safety analyses and adverse event reporting from two ongoing international, multicentre, randomised, double-masked, phase III superiority studies of near-identical design (VISTA and VIVID). The ongoing studies are still masked. This submission reports on safety analyses to week 100. The design, methodology, descriptions of all endpoints, and efficacy results from VISTA and VIVID are detailed in Section 6.1 to 6.5. The safety and tolerability of intravitreal administration of aflibercept every 4 weeks (2Q4) and every 8 weeks (2Q8) when compared with laser photocoagulation for a period of up to three years, was included as a secondary objective in the VISTA and VIVID studies. Data on all AE were collected at each study visit The term AE was only used to refer to

All AEs were assessed for

[redacted]Other safety procedures included [redacted]

The safety analysis population included all patients who had received any study drug. The total number of patients valid for the integrated safety analysis from VISTA and VIVID was 865. The breakdown of this population is detailed further in Table 56.

Table 56: Safety analysis population – VISTA, VIVID and Integrated

	Study Arms			TOTAL (n)
	Laser photocoagulation (n)	Aflibercept		
		2Q4 (n)	2Q8 (n)	
VISTA	154	155	152	461
VIVID	133	136	135	404
Integrated	287	291	287	865

2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection

Approximately 90% of patients in all groups completed 52 weeks of treatment and over 80% patients completed 100 weeks treatment. Actual exposure for aflibercept was consistent with the planned exposure. The mean number of active injections during the first 2 years of aflibercept treatment for patients in the 2Q4 and 2Q8 groups was 21.3 (5.83) and 13.5 (2.88) in VISTA and 22.6 (5.8) and 13.6 (2.9) in VIVID.

The mean (SD) number of active laser treatments was [redacted] in the VISTA study and [redacted] in the VIVID study.

A total of 427 patients (92.6%) in VISTA, 350 (86.6%) in VIVID, and 777 (89.8%) patients in the integrated analysis experienced at least one treatment-emergent adverse event (TEAE) during the first 52 weeks of the study periods (Table 57). [redacted] had experienced at least one treatment-emergent adverse event (TEAE).

In general, the pattern of TEAEs at 52 and 100 weeks [redacted] the pivotal studies; however, VISTA had [redacted] of TEAEs, [redacted] a higher incidence of non-ocular TEAEs, and a higher incidence of SAEs, [redacted] compared with VIVID. The incidence of study drug-related TEAEs was [redacted] It should be noted that patients in the laser group could receive aflibercept in the study eye, and the aflibercept groups could receive laser in the

study eye beginning at week 24 as additional treatment. All patients could be treated with anti-VEGF (primarily aflibercept) in the fellow eye.

Incidences of all reported event types were similar among the treatment groups (Table 57), although drug-related or injection-related TEAEs[redacted] in the aflibercept groups than in the laser group and laser-related TEAEs [redacted]in the laser group than in the aflibercept group. This is consistent with the treatment assignments. Most TEAEs were of [redacted]however [redacted] patients in the laser group reported ocular TEAEs of greater than mild severity in the study eye (Integrated analysis weeks 0-52:[redacted]This observation was [redacted]week 100 in both studies. There was a[redacted]study eye SAEs in the laser group than in the aflibercept groups in weeks 0 to 52[redacted]

Overall, the safety data indicate that aflibercept, compared to laser therapy, is well tolerated, both locally and systemically, and has a favourable safety profile out to at least 2 years in the DMO patient population (25). The safety profile is also consistent with that observed in the AMD and CRVO trial populations.

Table 57: Summary of safety data TEAEs during the first 52 weeks of VISTA and VIVID (SAF)(18;27)

	Laser photocoagulation			Aflibercept					
				2Q4			2Q8		
	VISTA	VIVID	Integrated	VISTA	VIVID	Integrated	VISTA	VIVID	Integrated
	N=154 n (%)	N=133 n (%)	N=287 n (%)	N=155 n (%)	N=136 n (%)	N=291 n (%)	N=152 n (%)	N=135 n (%)	N=287 n (%)
Any TEAE	**146 (94.8)**	**112 (84.2)**	**258 (89.9)**	**142 (91.6)**	**119 (87.5)**	**261 (89.7)**	**139 (91.4)**	**119 (88.1)**	**258 (89.9)**
Non-ocular (systemic)	132 (85.7)	81 (60.9)	213 (74.2)	125 (80.6)	92 (67.6)	217 (74.6)	119 (78.3)	98 (72.6)	217 (75.6)
Ocular (study eye)	103 (66.9)	82 (61.7)	185 (64.5)	96 (61.9)	76 (55.9)	172 (59.1)	87 (57.2)	80 (59.3)	167 (58.2)
Any study drug-related AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular drug-related (study eye)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any injection-related AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection-related ocular AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any laser-related AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Laser-related ocular AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AE causing treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular (study eye)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-ocular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE	**54 (35.1)**	**24 (18.0)**	**78 (27.2)**	**53 (34.2)**	**23 (16.9)**	**76 (26.1)**	**42 (27.6)**	**30 (22.2)**	**72 (25.1)**
Non-ocular (systemic)	47 (30.5)	18 (13.5)	65 (22.6)	48 (31.0)	19 (14.0)	67 (23.0)	39 (25.7)	25 (18.5)	64 (22.3)
Ocular (study eye)	6 (3.9)	6 (4.5)	12 (4.2)	3 (1.9)	2 (1.5)	5 (1.7)	2 (1.3)	3 (2.2)	5 (1.7)
Drug-related ocular SAE (study eye)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any injection-related SAE (study eye)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

VTE=aflibercept; 2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection
Note: A patient is counted only once within each preferred term or system organ class.

Ocular TEAEs and Serious Adverse Events (SAEs)

A summary of ocular TEAEs occurring in the study eye is shown in Table 58**.**. Ocular TEAEs in the study eye were generally consistent either with disease progression (particularly in the laser group) e.g. diabetic retinopathy, diabetic retinal oedema, macular oedema, retinal neovascularisation and visual acuity reduction or abnormal tests, vitreous or retinal haemorrhage; or consistent with the expected adverse consequences of the injection procedure (particularly in the aflibercept groups) e.g. conjunctival haemorrhage, eye pain, increased intraocular pressure, increased lacrimation and injection site pain.

The number of patients experiencing at least 1 ocular TEAE in the study eye was[redacted]in the laser group compared to the 2Q4 group and the 2Q8 group. [redacted]dose-response between the 2Q4 and 2Q8 groups[redacted] For the aflibercept treatment groups, the most common ocular TEAEs (occurring in ≥ 10% patients at week 52 or 100) in the study eye were conjunctival haemorrhage,[redacted]For the laser treatment group, the most common ocular TEAEs in the study eye were [redacted]of endophthalmitis occurred in either VISTA or VIVID in the first 100 weeks of study.

The incidence of serious ocular TEAEs in the study eye was low and similar across treatment groups (by Week 52: n=12 [4.2%] in the laser group, 5 (1.7%) 2Q4 group, and 5 (1.7%) in the 2Q8 group; [redacted]

The most commonly reported serious ocular TEAEs in the study eye were [redacted] In line with ocular TEAEs, most reported ocular SAEs were those known to be typically related to the injection procedure or the underlying disease.

In VISTA, the overall incidence of drug-related ocular TEAEs in the study eye was [redacted] In the VIVID study, drug-related ocular TEAEs in the study eye were [redacted] in the aflibercept groups [redacted] than in the laser group [redacted]

The most frequently reported study drug-related ocular TEAEs in the study eye for the aflibercept combined group were [redacted] in the 2Q8 arm of the VISTA study experienced increased intraocular pressure in the study eye. This TEAE along with cataract in [redacted] were deemed to be a drug-related SAEs.

Fellow eye

At weeks 52 [redacted], TEAEs seen in the fellow eye were typical of the disease process or the injection procedure, consistent across all treatment groups and of similar pattern to the TEAEs seen in the study eye. For all 3 treatment groups, the most common ocular TEAE (≥10%) in the fellow eye in the integrated study population were conjunctival haemorrhage and diabetic retinal oedema. Ocular drug related TEAEs in the fellow eye were [redacted] Likewise, the incidence of ocular SAEs in the fellow eye was also [redacted] and considered to be drug-related in [redacted] This patient also had [redacted] An SAE of endophthalmitis occurred in 1 patient in the laser group after receiving an injection of ranibizumab in the fellow eye.

Table 58: Integrated analysis: Ocular TEAEs in the study eye
Week 0-52: occurring in ≥1.0% of patients in any treatment group (SAF)
Week 0-100: occurring in ≥2.0% of patients in any treatment group (SAF)

MedDRA preferred term	Laser photocoagulation (N=287) n (%)		Aflibercept 2Q4 (N=291) n (%)		Aflibercept 2Q8 (N=287) n (%)		Aflibercept Combined (N=578) n (%)	
	Week 0-52	Week 0-100	Week 0-52	Week 0-100	Week 0-52	Week 0-100	Week 0-52	Week 0-100
Any ocular TEAE (study eye)	185 (64.5)	[redacted]	172 (59.1)	[redacted]	167 (58.2)	[redacted]	339 (58.7)	[redacted]
Blepharitis	4 (1.4)	[redacted]	1 (0.3)	[redacted]	9 (3.1)	[redacted]	10 (1.7)	[redacted]
Blindness transient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cataract	15 (5.2)	[redacted]	15 (5.2)	[redacted]	14 (4.9)	[redacted]	29 (5.0)	[redacted]
Cataract cortical	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cataract nuclear	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cataract subcapsular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctival haemorrhage	50 (17.4)	[redacted]	89 (30.6)	[redacted]	73 (25.4)	[redacted]	162 (28.0)	[redacted]
Conjunctival hyperaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis allergic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corneal abrasion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corneal erosion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cystoid macular oedema	10 (3.5)	[redacted]	1 (0.3)	[redacted]	6 (2.1)	[redacted]	7 (1.2)	[redacted]
Diabetic retinal oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetic retinopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry eye	11 (3.8)	[redacted]	15 (5.2)	[redacted]	4 (1.4)	[redacted]	19 (3.3)	[redacted]
Eye inflammation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye irritation	10 (3.5)	[redacted]	12 (4.1)	[redacted]	10 (3.5)	[redacted]	22 (3.8)	[redacted]
Eye pain	18 (6.3)	[redacted]	31 (10.7)	[redacted]	21 (7.3)	[redacted]	52 (9.0)	[redacted]
Eye Pruritus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MedDRA preferred term	Laser photocoagulation (N=287) n (%)		Aflibercept 2Q4 (N=291) n (%)		Aflibercept 2Q8 (N=287) n (%)		Aflibercept Combined (N=578) n (%)	
	Week 0-52	Week 0-100	Week 0-52	Week 0-100	Week 0-52	Week 0-100	Week 0-52	Week 0-100
Eyelid oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Foreign body sensation in eyes	9 (3.1)	[redacted]	9 (3.1)	[redacted]	9 (3.1)	[redacted]	18 (3.1)	[redacted]
Glaucoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intraocular pressure increased	10 (3.5)	[redacted]	17 (5.8)	[redacted]	12 (4.2)	[redacted]	29 (5.0)	[redacted]
Keratitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lacrimation increased	5 (1.7)	[redacted]	12 (4.1)	[redacted]	6 (2.1)	[redacted]	18 (3.1)	[redacted]
Macular cyst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Macular fibrosis	12 (4.2)	[redacted]	7 (2.4)	[redacted]	13 (4.5)	[redacted]	20 (3,5)	[redacted]
Macular oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maculopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular hyperaemia	12 (4.2)	[redacted]	8 (2.7)	[redacted]	11 (3.8)	[redacted]	19 (3.3)	[redacted]
Ocular hypertension	0	[redacted]	10 (3.4)	[redacted]	3 (1.0)	[redacted]	13 (2.2)	[redacted]
Optic atrophy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Optic disc haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Photophobia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Photopsia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Posterior capsule opacification	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Punctate keratitis	3 (1.0)	[redacted]	9 (3.1)	[redacted]	8 (2.8)	[redacted]	17 (2.9)	[redacted]
Retinal aneurysm	5 (1.7)	[redacted]	5 (1.7)	[redacted]	9 (3.1)	[redacted]	14 (2.4)	[redacted]
Retinal exudates	16 (5.6)	[redacted]	11 (3.8)	[redacted]	13 (4.5)	[redacted]	24 (4.2)	[redacted]
Retinal haemorrhage	21 (7.3)	[redacted]	9 (3.1)	[redacted]	12 (4.2)	[redacted]	21 (3.6)	[redacted]
Retinal neovascularisation	13 (4.5)	[redacted]	3 (1.0)	[redacted]	2 (0.7)	[redacted]	5 (0.9)	[redacted]

MedDRA preferred term	Laser photocoagulation (N=287) n (%)		Aflibercept 2Q4 (N=291) n (%)		Aflibercept 2Q8 (N=287) n (%)		Aflibercept Combined (N=578) n (%)	
	Week 0-52	Week 0-100	Week 0-52	Week 0-100	Week 0-52	Week 0-100	Week 0-52	Week 0-100
Retinal pigment epitheliopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Retinal vascular disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Retinopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sjogren's syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual acuity reduced	25 (8.7)	[redacted]	7 (2.4)	[redacted]	15 (5.2)	[redacted]	22 (3.8)	[redacted]
Visual acuity tests abnormal	23 (8.0)	[redacted]	6 (2.1)	[redacted]	9 (3.1)	[redacted]	15 (2.6)	[redacted]
Visual impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous adhesions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous detachment	10 (3.5)	[redacted]	9 (3.1)	[redacted]	11 (3.8)	[redacted]	20 (3.5)	[redacted]
Vitreous floaters	9 (3.1)	[redacted]	21 (7.2)	[redacted]	13 (4.5)	[redacted]	34 (5.9)	[redacted]
Vitreous haemorrhage	11 (3.8)	[redacted]	10 (3.4)	[redacted]	4 (1.4)	[redacted]	14 (2.4)	[redacted]

2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection; NR = not reported

Injection-related TEAEs and SAEs

The incidence of injection-related ocular TEAEs in the study eye was [redacted] consi stent with the expected adverse consequences of the injection procedure. The most frequent injection-related TEAEs (occurring in ≥10% of patients in any treatment group) were [redacted] The incidence of injection-related SAEs was [redacted]

Patients were allowed to receive aflibercept in the fellow eye starting at week [redacted] Injection procedure-related TEAEs in the fellow eye [redacted] than those in the study eye. [redacted] eported in the study eye. During the first 100 weeks of study, there were [redacted] ocular injection procedure-related SAEs reported in the fellow eye in any treatment group in VISTA or VIVID.

Laser-related TEAEs and SAEs

Ocular laser procedure-related TEAEs of the study eye were [redacted] patients in the 2Q8 group. In the laser treatment group, the most frequent laser-related TEAEs in the study eye was [redacted] In the aflibercept treatment groups, the most frequent laser-related TEAE was [redacted] laser-related SAEs were reported in the fellow eye in either study during the first 100 weeks.

Non-ocular TEAEs and SAEs

The number of patients experiencing at least 1 non-ocular TEAE was [redacted] between treatment groups at week 100 (laser 85.4%; 2Q4 87.6%; 2Q8 88.5%). In general, the pattern of TEAEs was [redacted] however, the incidences of reported TEAEs were [redacted] overall incidence of TEAEs [redacted] every system organ class (SOC). Most non-ocular TEAEs had a [redacted] For all 3 treatment groups, the most common non-ocular TEAEs [redacted]

The incidence of study drug-related non-ocular TEAEs was [redacted] both studies [redacted] With the exception of hypertension [redacted] patients in the VISTA laser group [redacted] and cerebrovascular accident (CVA) [redacted] patient in the VISTA laser group and [redacted] in the VISTA 2Q4 group [redacted] non-ocular drug-related TEAEs occurred in [redacted]

In the VISTA study, the number of patients experiencing at least 1 non-ocular SAE in the first 100 weeks was [redacted] The overall frequency of non-ocular SAEs was [redacted] The reported non-ocular SAEs occurred across a broad range of [redacted]

[redacted]

Table 59: Integrated analysis: Non-ocular TEAEs
Week 0-52 occurring in ≥3% of patients in any treatment group (SAF)
Week 0-100: occurring in ≥5% of patients in any treatment group (SAF)

System organ class MedDRA preferred term	Laser photocoagulation (N=287) n (%)		Aflibercept 2Q4 (N=291) n (%)		Aflibercept 2Q8 (N=287) n (%)		Aflibercept Combined (N=578) n (%)	
	Week 0-52	Week 0-100	Week 0-52	Week 0-100	Week 0-52	Week 0-100	Week 0-52	Week 0-100
Any non-ocular TEAE	**213 (74.2)**	[redacted]	**217 (74.6)**	[redacted]	**217 (75.6)**	[redacted]	**434 (75.1)**	[redacted]
Blood & Lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	7 (2.4)		15 (5.2)		13 (4.5)		28 (4.8)	
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure congestive								
Ear & labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	9 (3.1)		9 (3.1)		6 (2.1)		15 (2.6)	
Diarrhoea	9 (3.1)		13 (4.5)		7 (2.4)		20 (3.5)	
Nausea	8 (2.8)		11 (3.8)		8 (2.8)		19 (3.3)	
Vomiting	8 (2.8)		9 (3.1)		6 (2.1)		15 (2.6)	
General disorders & administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	8 (2.8)		15 (5.2)		11 (3.8)		26 (4.5)	
Immune system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	12 (4.2)		14 (4.8)		5 (1.7)		19 (3.3)	
Influenza	9 (3.1)		7 (2.4)		10 (3.5)		17 (2.9)	
Nasopharyngitis	33 (11.5)		37 (12.7)		31 (10.8)		68 (11.8)	

System organ class MedDRA preferred term	Laser photocoagulation (N=287) n (%)		Aflibercept 2Q4 (N=291) n (%)		Aflibercept 2Q8 (N=287) n (%)		Aflibercept Combined (N=578) n (%)	
	Week 0-52	Week 0-100	Week 0-52	Week 0-100	Week 0-52	Week 0-100	Week 0-52	Week 0-100
Urinary tract infection	13 (4.5)	[redacted]	13 (4.5)	[redacted]	18 (6.3)	[redacted]	31 (5.4)	[redacted]
Sinusitis	11 (3.8)	[redacted]	10 (3.4)	[redacted]	9 (3.1)	[redacted]	19 (3.3)	[redacted]
Pneumonia	4 (1.4)	[redacted]	10 (3.4)	[redacted]	5 (1.7)	[redacted]	15 (2.6)	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning & procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fall	7 (2.4)	[redacted]	7 (2.4)	[redacted]	9 (3.1)	[redacted]	16 (2.8)	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood glucose increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood pressure increased	5 (1.7)	[redacted]	[redacted]	[redacted]	6 (2.1)	[redacted]	16 (2.8)	[redacted]
Blood urea increased	9 (3.1)	[redacted]	10 (3.4)	[redacted]	8 (2.8)	[redacted]	18 (3.1)	[redacted]
Glycosylated haemoglobin increased	6 (2.1)	[redacted]	9 (3.1)	[redacted]	4 (1.4)	[redacted]	13 (2.2)	[redacted]
Blood creatinine	8 (2.8)	[redacted]	10 (3.4)	[redacted]	9 (3.1)	[redacted]	19 (3.3)	[redacted]
phosphokinase increased	9 (3.1)	[redacted]	3 (1.0)	[redacted]	2 (0.7)	[redacted]	5 (0.9)	[redacted]
Metabolism & Nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes mellitus	14 (4.9)	[redacted]	8 (2.7)	[redacted]	16 (5.6)	[redacted]	24 (4.2)	[redacted]
Hyperglycaemia	11 (3.8)	[redacted]	2 (0.7)	[redacted]	3 (1.0)	[redacted]	5 (0.9)	[redacted]
Hypercholesterolaemia	9 (3.1)	[redacted]	4 (1.4)	[redacted]	3 (1.0)	[redacted]	7 (1.2)	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	9 (3.1)	[redacted]	9 (3.1)	[redacted]	4 (1.4)	[redacted]	13 (2.2)	[redacted]
Back pain	8 (2.8)	[redacted]	11 (3.8)	[redacted]	5 (1.7)	[redacted]	16 (2.8)	[redacted]
Neoplasms, benign, malignant, & unspecified (incl. Cysts / polyps)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

System organ class MedDRA preferred term	Laser photocoagulation (N=287) n (%)		Aflibercept 2Q4 (N=291) n (%)		Aflibercept 2Q8 (N=287) n (%)		Aflibercept Combined (N=578) n (%)	
	Week 0-52	**Week 0-100**	**Week 0-52**	**Week 0-100**	**Week 0-52**	**Week 0-100**	**Week 0-52**	**Week 0-100**
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	15 (5.2)	[redacted]	16 (5.5)	[redacted]	8 (2.8)	[redacted]	24 (4.2)	[redacted]
Dizziness	6 (2.1)	[redacted]	9 (3.1)	[redacted]	3 (1.0)	[redacted]	12 (2.1)	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Renal & urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, Thoracic & Mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	10 (3.5)	[redacted]	15 (5.2)	[redacted]	10 (3.5)	[redacted]	25 (4.3)	[redacted]
Skin & subcutaneous disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	51 (17.8)	[redacted]	54 (18.6)	[redacted]	47 (16.4)	[redacted]	101 (17.5)	[redacted]

2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection

Deaths

A total of 26 deaths were reported during the first 100 weeks of study: 11 deaths in VIVID and 15 deaths in VISTA. [redacted] deaths [redacted] were judged by the investigator to be drug-related. [redacted] death in VISTA [redacted] between intravitreal administration of study drug to event onset. In VIVID [redacted] aflibercept treatment [redacted] serious TEAEs while on study. However, [redacted] assessed as unrelated to the study drug. Concomitant medications at the time of the event are listed as [redacted]

Table 60: Deaths during weeks 0-100 of the VISTA and VIVID studies (SAF) (25)

	Laser photocoagulation	Aflibercept		
	n (%)	2Q4	2Q8	Combined
		n (%)	n (%)	n (%)
VISTA (n)	N=154	N=155	N=152	N=307
Death	***3 (1.9)***	***8 (5.2)***	***4 (2.6)***	***12 (3.9)***
Arteriosclerosis	0	0	1 (0.6)	1 (0.3)
Cardiac Arrest	1 (0.6)	1 (0.6)	2 (1.3)	3 (1.0)
Cardiac failure acute	0	1 (0.6)	0	1 (0.3)
Cerebrovascular accident	0	1 (0.6)	1 (0.6)	2 (0.7)
Death (aetiology unknown)	0	1 (0.6)	0	1 (0.3)
Multi-organ failure	1 (0.6)	0	0	0
Myocardial Infarction	0	1 (0.6)	0	1 (0.3)
Pneumonia	0	1 (0.6)	0	1 (0.3)
Pulseless electrical activity	0	1 (0.6)	0	1 (0.3)
Renal failure chronic	0	1 (0.6)	0	1 (0.3)
Sudden cardiac death	1 (0.6)	0	0	0
VIVID (n)	133	136	135	271
Death	***1 (0.8)***	***4 (2.9)***	***6 (4.4)***	***10 (3.7)***
Acute MI	1 (0.8)	0	0	0
Brain herniation	0	1 (0.7)	0	1 (0.4)
Cardiac failure	0	0	1 (0.7)	1 (0.4)
Colon cancer	0	1 (0.7)		1 (0.4)
Hypertensive heart disease	0	0	1 (0.7)	1 (0.4)
Lung neoplasm	0	0	1 (0.7)	1 (0.4)
B-cell lymphoma	0	0	1 (0.7)	1 (0.4)
Myocardial infarction	0	2 (1.5)	1 (0.7)	3 (1.1)
Ventricular arrhythmia	0	0	1 (0.7)	1 (0.4)

2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection

X

Additional Adverse Events of interest: Arterial Thromboembolic Events Based on Anti-Platelet Triallists' Collaboration (APTC) endpoint

ATEs, as defined by APTC criteria, include non-fatal myocardial infarction, non-fatal ischaemic or haemorrhagic stroke, or vascular death (including deaths of unknown cause). APTC events are the most clinically important arterial thromboembolic events because they can represent irreversible morbidity or mortality. Potential ATEs were evaluated by a masked adjudication committee according to criteria formerly applied and published by the APTC (40). The overall incidence of APTC events in VISTA and VIVID was low.

Table 61: APTC Defined Arterial Thromboembolic Events during year 1 in the VISTA and VIVID studies (Integrated analysis; SAF)(25)

	Laser photocoagulation	Aflibercept		
	n (%)	2Q4	2Q8	Combined
		n (%)	n (%)	n (%)
	N=287	N=291	N=287	N=578
Any APTC event	***12 (4.2)***	***21 (7.2)***	***16 (5.6)***	***37 (6.4)***
Non-Fatal Myocardial Infarction	7 (2.4)	9 (3.1)	5 (1.7)	14 (2.4)
Non-Fatal Stroke	3 (1.1)	7 (2.4)	6 (2.1)	13 (2.2)
Vascular death	3 (1.1)	6 (2.1)	6 (2.1)	12 (2.1)

APTC=Antiplatelet Triallists' Collaboration
2Q4=2mg every 4 weeks by intravitreal injection; 2Q8=2mg every 8 weeks by intravitreal injection

Intraocular pressure (IOP)

Generally, the analyses of IOP measurements in the study eye yielded [redacted] across the treatment groups. Mean pre-injection IOP in the study eye was [redacted] all treatment groups at baseline, [redacted] rom baseline to week 100 in all treatment groups.

Immunogenicity

Overall, the results suggest that intravitreal administration of aflibercept is associated with a low risk of immunogenicity; furthermore, the data did not demonstrate any clinically meaningful difference between safety in patients with positive or negative responses in the ADA (anti-drug antibodies) assay.

A total of [redacted] were positive in the ADA assay at any time in the first 100 weeks of study [redacted] were positive only at baseline, suggesting preexisting immunoreactivity rather than a treatment-emergent response.

Thus [redacted] patients demonstrated a treatment-emergent positive response in the ADA assay at week 100 [redacted] patient positive in the ADA assay [redacted] in the neutralising antibody assay.

Other investigations

[redacted] changes in laboratory values, vital signs, ECGs, or pre-injection IOP were seen in any of the treatment groups.

Adverse events leading to withdrawal

In both studies, the incidence of ocular and non-ocular TEAEs leading to withdrawal from the study drug [redacted] discontinuations due to TEAEs [redacted]

Subgroup analyses

[redacted]

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

Overall, the safety data demonstrate that aflibercept has a favourable safety profile, both ocular and systemically. The safety profile is also consistent with that already seen in studies with patients with neovasuclar AMD - directly comparing aflibercept with ranibizumab (VIEW (29)) - and CRVO (COPERNICUS, GALILEO(41-44)), and suggests no association with increased risk for fatalities, APTC events, or SAEs.

Aflibercept is well tolerated in patients with DMO over 52 weeks and 100 weeks with no notable differences between 2Q4 and 2Q8 regimens or compared with laser photocoagulation in the incidence of ocular or non-ocular TEAEs.

In general, TEAEs consistent with the injection procedure were [redacted] in the aflibercept groups e.g. conjunctival haemorrhage and eye pain, whereas TEAEs consistent with disease worsening were [redacted] in the laser group (e.g. visual acuity tests abnormal). Most ocular TEAEs had a

maximum intensity of [redacted] cases of endophthalmitis occurred in the VISTA or VIVID studies during the first 100 weeks of study.

The most common non-ocular TEAEs [redacted] The overall frequency of APTC events was low with no notable differences among treatment groups and no evidence of a dose response across treatment groups. Also, of the 26 deaths reported across the two studies over the first 100 weeks, all but two were considered unrelated to the study drug. [redacted]
Safety outcomes with aflibercept were consistent with those reported in aflibercept studies in wet AMD and CRVO, confirming the validity of the safety results for aflibercept across larger cohorts.

Other than the comparison with laser photocoagulation, no direct comparison was available with active agents used to treat DMO in clinical practice was included in VISTA or VIVID. An indirect comparison was therefore conducted to explore safety between aflibercept and ranibizumab, fluocinolone acetate and dexamethasone (see section 6.7). A comparable safety profile between aflibercept 2Q8 and ranibizumab has already been demonstrated in wet AMD, and alongside the safety profile of aflibercept demonstrated in VIVID and VISTA, it is anticipated that aflibercept will also have a comparable safety profile to ranibizumab in the treatment of DMO. In the indirect comparison accompanying this submission, there was no significant difference between aflibercept and ranibizumab in the safety outcomes at 12 months (all serious adverse events, all serious ocular adverse events, all adverse events, all ocular adverse events, all non-ocular adverse events, all serious non-ocular adverse events, eye pain, hypertension, cataract and all-cause mortality).

With regard to other comparators listed in the decision problem, a comparison of aflibercept with fluocinolone acetonide implants was not possible because the identified trials did not have a common comparator to allow an indirect analysis. Three trials were included in the analysis of ‘increased intraocular pressure’ at 12 months for the aflibercept/dexamethasone comparison. Significantly fewer events occurred with aflibercept treatment. Bucher indirect

analysis was also possible for the safety outcomes: macular oedema, reduced visual acuity, vitreous haemorrhage, eye pain and cataract at 12 months and no significant differences between aflibercept and dexamethasone were noted for these outcomes. However, as acknowledged in the Diabetic Retinopathy guidelines (4), and also the Summary of Product Characteristics for both fluocinolone acetonide and dexamethasone implants, the high rate of increased IOP and cataract does need to be considered when using intravitreal steroid preparations. Consequently, these treatments are only recommended in patients who have been insufficiently responsive to prior treatment with laser photocoagulation or other available non-corticosteroid therapies for diabetic macular oedema or who are pseudophakic.

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.

Evidence to support the use of aflibercept for the treatment of DMO is provided by results from VISTA and VIVID, two well-designed trials i.e. large, prospective, randomised, double-masked, controlled, multicentre, adequately powered, demonstrating the superiority of aflibercept when compared with laser photocoagulation.

Analyses of VISTA and VIVID demonstrated that aflibercept, either monthly or every 8 weeks, was effective and superior to laser photocoagulation in the treatment of visual impairment due to diabetic macular oedema. Both aflibercept groups demonstrated significant improvements over laser photocoagulation in the primary endpoint - mean change in BCVA at week 52 - with immediate improvements in BCVA seen as early as day 3 / week 1. Improvements were maintained over the longer-term (i.e. through week 100).

Higher proportions of patients gaining ≥ 10 ETDRS and ≥ 15 ETDRS letters at weeks 52 and 100 were also reported compared to laser photocoagulation. An

improvement of ≥15 letters in BCVA is clinically important and relevant to patients, and has been correlated with significant improvements in functional activities such as reading, cooking, watching television, and driving(45). A gain or loss of 10 letters was also previously considered clinically significant by NICE(1).

Both aflibercept treatments were effective in treating diabetic retinopathy, based on significant improvements over laser photocoagulation in the proportion of patients achieving ≥2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) at weeks 52 and 100. In addition, a greater number of patients in the aflibercept groups also had an improvement of ≥3-steps, and fewer had ≥2- and ≥3-step worsening in this parameter over 100 weeks compared to the laser group. Significant and sustained improvements in mean CRT were also seen, compared to laser treatment, with improvement seen as early as week 1, further demonstrating the anatomical improvements that aflibercept can bring about.

Both regimens produced similar visual acuity outcomes, but the 2Q8 group achieved this improvement with fewer injections. A significant beneficial finding is that the dosing interval of aflibercept injections can be prolonged to 8 weeks without specifically no requirement for monitoring between injections and without compromising efficacy. This allows a ‘proactive’ dosing approach. This contrasts with ranibizumab, for which a more ‘reactive’ dosing approach is recommended, whereby patients will need regular monitoring in order to assess whether maximum visual acuity has been achieved and/or for signs of disease activity. This is particularly important for a chronic disease like DMO, affecting patients often still in their working years. Fewer ophthalmology clinic visits translates to fewer absences from work, and should translate to a relative increase in productivity. It may also relieve financial and caseload burden on the healthcare system. A further advantage of the fixed every 8-week dosing paradigm recommended for aflibercept over variable dosing regimens is that treatment is delivered on a proactive basis and not in response to recurrence of disease. Multiple recurrences of disease may lead

to irreversible loss of retinal function, particularly in photoreceptors, limiting patients' capacity to regain and/or maintain good visual function.

The beneficial clinical profile of aflibercept was accompanied by an acceptable safety profile. Aflibercept was well tolerated in patients with DMO over 52 weeks [redacted] with no notable differences between 2Q4 and 2Q8 regimens or compared with laser photocoagulation in the incidence of ocular or non-ocular TEAEs. Ocular TEAEs were consistent with those expected with the nature of underlying disease, disease progression, or attributable to the injection procedure. The most common non-ocular TEAEs were [redacted]The risk profile of aflibercept is consistent with that already seen in patients with neovascular AMD or CRVO, and suggests no association with increased risk for fatalities, APTC events, or SAEs.[redacted]

The efficacy and safety of aflibercept was corroborated across key visual acuity and anatomic endpoints and all pre-specified subgroup and sensitivity analyses conducted, indicating the robustness of the results in a broad spectrum of patients.

DMO as a manifestation of diabetic retinopathy is the most common cause of blindness in diabetes(46), and in people of working age in England, Wales and Scotland(47). A key objective for treatment of DMO is the improvement of vision accompanied by a favourable safety profile. Based on the current evidence and taking into account the severity and the burden of untreated DMO, it can be concluded that the benefits of aflibercept clearly outweigh risks arising from its use.

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

A key strength of the evidence base is that the efficacy and safety of aflibercept in the treatment of DMO was corroborated in two independent, international RCTs, and across the subgroup and sensitivity analyses

conducted, indicating the robustness of the results in a broad spectrum of patients. Sensitivity analyses demonstrated that overall results were not affected by missing data or additional treatment (rescue laser). Study eligibility criteria were designed to include a representative sample of diabetic patients with DMO, including those who had received prior therapy e.g.anti-VEGF treatment, laser photocoagulation, cataract surgery. Subgroup analyses included those predefined and all those specified in the decision problem.

All efficacy and safety assessments in VISTA and VIVID are standard variables and methods in clinical studies for DMO, and in ophthalmic practice (4;48). They are widely recognised as valid, reliable, accurate and relevant to the assessment of DMO. Studies were conducted according to the highest standards of International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP), and in line with advice from regulatory authorities.

The two different dosing (and monitoring) intervals studied for aflibercept i.e. monthly or 8-weekly also provides information on the viability of a longer interval between monitoring and/or dosing. The burden of treatment and monitoring, in terms of resources required and capacity available within Ophthalmology departments is an ongoing issue in the UK, and with an ageing population the number of patients presenting with back-of –the-eye conditions is increasing. Current standard of care, ranibizumab, requires monitoring of VA as often as every month, and usually, anatomical outcomes using OCT. Hence, an opportunity to extend the injection interval without the burden of any additional monitoring between injections in the first year would be a key benefit in the introduction of aflibercept for the treatment of DMO.

A limitation to the evidence is that laser photocoagulation was the only ‘active’ comparator in both studies, whereas in clinical practice, ranibizumab, another intravitreal anti-VEGF treatment, is now more commonly used as ‘standard of care’ in the NHS, particularly in patients with eyes with central retinal thickness of 400 micrometres or more at the start of treatment. At the time of study design, although several treatment modalities were under investigation, there were no approved pharmacological treatments for DMO and the

mainstay of treatment was laser photocoagulation. Hence its selection for the comparator arm in VISTA and VIVID.

An indirect comparison with ranibizumab (0.5mg PRN [as needed]) has been included in this submission [see 6.7], in order to put the results of VISTA and VIVID into the context of current clinical practice. Results of the network meta-analysis (NMA) showed a significant improvement in visual acuity outcomes ('BCVA mean change from baseline' and 'loss ≥10 ETDRS letters') for aflibercept 2mg (given every 4 weeks for the first five months and then every 8 weeks i.e. the 2Q8 dosing regimen in VISTA and VIVID studies) in comparison to 0.5mg ranibizumab administered on a PRN basis, although a limitation to the evidence could be that the loss of ≥ 10 letters was only significant in the fixed effects MTC model. Despite favouring aflibercept, there was no significant difference between aflibercept and ranibizumab in alternative visual acuity ('gain ≥15 ETDRS letters', 'loss ≥15 ETDRS letters', 'gains ≥10 ETDRS letters') or safety outcomes. For each of the nine safety outcomes where quantitative analysis was possible, patients receiving aflibercept experienced fewer adverse events than those receiving ranibizumab - these results are based on a small number of studies and they should be interpreted with caution. For completeness, results were also significantly in favour of aflibercept versus dexamethasone implant (0.7mg) for the visual acuity 'gain ≥10 ETDRS letters' and reduced 'increased intraocular pressure' but did not significantly influence other visual acuity or safety outcomes. A limitation to the comparison with dexamethasone is that the pivotal studies for dexamethasone in DMO could not be included in the MTC as there was no common comparator. A comparison of aflibercept with fluocinolone acetonide implants was not possible because identified trials did not have a common comparator to allow an indirect analysis.

A general limitation to the evidence base on treatments for DMO is the lack of long-term data with all treatments. However some studies are still ongoing e.g. VISTA and VIVID, or are yet to report longer-term data and it is anticipated that this is only a short-term limitation.

The VIVID/VISTA studies fairly represent the fixed regimen specified in the first 12 months in the SmPC. However, the SmPC allows treatment extension beyond 12 months to avoid any potential over treatment of patients. Similarly, the SmPC for ranibizumab states a 'treat-to-target' regimen that differs somewhat to regimens in the studies included in the mixed treatment comparison. Moreover, treatment in real life may be influenced by practical aspects of clinical practice.

As can be seen from the results of VISTA and VIVID, laser photocoagulation inconsistently attenuates disease progression and has limited effect on improving vision. The Royal College of Ophthalmologists Diabetic Retinopathy guidelines suggest that 'in clinical practice, the outcome of laser photocoagulation for DMO is not as good as in research studies due to a number of factors such as laser equipment, patient factors and laser operator'(4). Thus, in VISTA and VIVID the efficacy of laser treatment may be exaggerated with a better safety profile than may be seen in practice. Also, although laser photocoagulation can reduce the risk of further vision loss in patients with DMO, the procedure may also cause macular scarring over time with repeated treatment(49;50). This can lead to scotomas in the long term. Such effects of laser treatment may not be easily observable within the context of clinical trials as this is a longer-term effect of treatment.

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.

DMO is a complication of diabetic retinopathy and the most common cause of loss of vision in people with diabetes. With this in mind, outcome measures in VISTA and VIVID, were based around assessment of treatment effects on vision and also the ability of aflibercept to halt or slow disease progression – of direct relevance to the diabetic patient with DMO.

Population

‘Adults with DMO secondary to diabetes mellitus involving the centre of the macula’ was the key inclusion criterion for VISTA and VIVID study entry. Study eligibility criteria were designed to include a representative sample of diabetic patients with DMO, including patients who may or may not have received prior laser and/or anti-VEGF treatment and/or cataract surgery.

Benefits of aflibercept were consistent across subgroups including age, gender, race, baseline HbA1c, baseline BCVA, baseline CRT, and prior anti-VEGF or laser therapy and prior cataract surgery demonstrating that a wide range of patients with DMO, typical of those presenting in clinical practice in England and Wales, can benefit from aflibercept.

Comparators

In the VISTA and VIVID studies, aflibercept treatment was compared with the best standard of care at the time of study design i.e. laser photocoagulation. This is one of the comparators stated in the decision problem. Since then, as discussed in Section 6.3, new treatments have been introduced: ranibizumab, fluocinolone acetate, and dexamethasone intravitreal implant.

As discussed in section A, we consider laser photocoagulation and ranibizumab to be the most appropriate comparators. A comparison with steroids has been included for completeness, as they are listed in the final scope, however, it is considered these treatments, in line with their licensed indications, are used after anti-VEGF treatments in the management pathway.

A mixed treatment comparison was attempted for aflibercept, ranibizumab, dexamethasone and fluocinolone acetate. As discussed in section 6.7 and 6.10.2, the indirect comparison of efficacy and safety outcomes between aflibercept and ranibizumab in DMO showed a significant improvement in visual acuity outcomes (‘BCVA mean change from baseline’ and ‘loss ≥10

ETDRS letters') for aflibercept 2mg (given every 4 weeks for the first five months and then every 8 weeks. There was no significant difference between aflibercept and ranibizumab in alternative visual acuity ('gain ≥15 ETDRS letters', 'loss ≥15 ETDRS letters', 'gains ≥10 ETDRS letters') or safety outcomes.

Indirect analysis was possible for some endpoints for the comparison of aflibercept versus dexamethasone. Aflibercept significantly improved visual acuity in the Bucher analysis for the outcome of 'the proportion of patients gaining ≥10 ETDRS letters' at 12 months; No significant difference was found between treatment with aflibercept 2Q8 compared to 0.7mg dexamethasone for the outcomes: all discontinuations, macular oedema, reduced visual acuity, vitreous haemorrhage, eye pain and cataract at 12 months. Significantly fewer events occurred with aflibercept treatment in the analysis of 'increased intraocular pressure' at 12 months for the aflibercept/dexamethasone comparison.

A comparison of aflibercept with fluocinolone acetonide implants was not possible because identified trials did not have a common comparator to allow an indirect analysis. Aflibercept and fluocinolone acetonide intravitreal implant occupy different positions in the treatment pathway for DMO. Fluocinolone is recommended by NICE as an option for treating chronic DMO that is insufficiently responsive to available therapies only if the implant is to be used in an eye with an intraocular (pseudophakic) lens, so it is not clear how relevant a comparison would be.

The evidence base in this submission does not address a comparison between bevacizumab and aflibercept. As discussed in Section 2, bevacizumab is an oncology treatment that has previously been used in an unlicensed manner for the treatment of back-of-the-eye conditions when no licensed treatment has been available. Given that there are now several licensed options for visual impairment due to DMO, minimal use of unlicensed preparations is anticipated.

Intervention

Dose per injection in VISTA and VIVID studies was 2mg intravitreally. This is the same dose per injection utilised in aflibercept treatment of wet AMD and CRVO. The dosing regimen in the 2Q8 arms of VISTA and VIVID for the first year is the same as the now licensed regimen for the treatment of visual impairment due to DMO i.e. one injection per month for five consecutive doses, followed by one injection every two months, with 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.

Outcomes

All efficacy and safety assessments in VISTA and VIVID are standard variables and methods in clinical studies for DMO, and in ophthalmic practice (4;48) and are thus highly relevant to the decision problem..

The primary efficacy endpoint in VISTA and VIVID was ‘mean change in BCVA from baseline at 52 weeks’; an assessment of aflibercept’s effect on visual function compared with laser treatment. During assessment, letters are read from standard eye-charts, commonplace worldwide and used routinely in ‘eye tests’ in clinical practice in the UK.

The primary endpoint was met in both studies - aflibercept treatment was found to be significantly superior to laser treatment (VISTA $p<0.0001$; VIVID $p<0.0001$). Improvements in visual acuity were rapid and were evident as early as day 3 /week 1 after the first injection. All sensitivity and subgroup analyses conducted to assess the robustness of these results confirmed the findings of the primary analysis in the overall trial populations. The clinical benefit of treatment with aflibercept was also supported by the analyses of the secondary and additional efficacy endpoints evaluated in VISTA and VIVID (e.g. (i.e. proportion of patients gaining ≥10 ETDRS letters from baseline, proportion of patients gaining ≥15 ETDRS letters from baseline, proportion of patients achieving a ≥2-step improvement on the DRSS from baseline, and

change in CRT from baseline). Notably, gains of ≥15 letters in BCVA were reported in 31.1% to 41.6% of patients in the aflibercept treatment groups across the 2 studies (vs. 7.8% to 9.1% in the laser groups). An improvement of ≥15 letters in BCVA is clinically important and relevant to patients, and has been correlated with significant improvements in functional activities such as reading, cooking, watching television, and driving(45).

The ≥ 2-step improvements in DRSS were seen [redacted] This is a meaningful outcome for patients. It has been shown that patients with worsened DRSS are significantly more likely to develop proliferative diabetic retinopathy (DR) and associated vision-threatening events(28). A slowing or reversing of the progression of DR, as demonstrated by an improvement in DRSS, should reduce the risk of significant vision loss.

There was also a robust and rapid reduction of CRT as measured by OCT in both aflibercept groups, with significant improvements over the laser group. This improvement was seen as early as week 1, further demonstrating the anatomical improvements that aflibercept can bring about.

In addition - although to date (at 100 weeks) in the VISTA and VIVID studies there are no substantial differences between aflibercept and laser treatment - patient reported outcomes were included in both studies. These assessments are important as they are reported and/or scored directly by the patient, free of interpretation by a clinician and provide an account of how the patient functions or feels relative to a health condition or therapy and a useful indicator as to how they might experience the treatment in clinical practice and how the therapy impacts on aspects of daily living and health related quality of life. Changes in near and distance activity NEI VFQ-25 (National Eye Institute 25-item Visual Function Questionnaire) scores from baseline were secondary endpoints. With the exception of the NEI VFQ-25 near activities subscale in the 2Q4 group, there were no statistically significant differences in the NEI VFQ-25 near or distance subscales among the treatment groups in the quality of life assessments at week 52. The results of the NEI VFQ-25 questionnaire should be interpreted with caution, as the scale assesses binocular visual

function with results primarily reflective of the better-seeing eye. As only 1 eye (usually the worse-seeing eye) was eligible for enrolment in the studies, changes in this parameter for a given patient may be muted if the patient had a better seeing fellow eye. Nevertheless, *any* improvement in vision, leading to an improved vision-related quality of life, can mean the difference between independent and dependent living, improved wellbeing or depression, and also mean patients are less at risk of falls or accidents due to visual problems(51-53). Overall quality of life was assessed using the EuroQol 5-dimensions questionnaire, however minimal changes in EQ-5D Total score in each of the treatment groups were reported from baseline to week 52.

The safety profile and patient tolerability of aflibercept is also being evaluated at 4-weekly intervals throughout VISTA and VIVID study durations – a necessity before a treatment is accepted for use in a broader population, and integrated into standard clinical practice. The safety profile of aflibercept is well established and known through its licensed use in its treatment of wet AMD and CRVO. Experience from VISTA and VIVID supports this evidence. 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 well tolerated throughout the first 100 weeks of the studies, without notable differences between 2Q4 and 2Q8 regimens or compared with laser photocoagulation in the incidence of ocular or non-ocular TEAEs. In general, adverse events consistent with the injection procedure were more common in the aflibercept groups, whereas events consistent with disease worsening were more common in the laser group. [redacted] endophthalmitis occurred in the VISTA or VIVID studies during the first 100 weeks of study and the overall frequency of APTC events was low with no notable differences among treatment groups and no evidence of a dose response across treatment groups. Also, of the 26 deaths reported across the two studies over the first 100 weeks, [redacted]

Importantly, the positive effects of aflibercept on all measured efficacy and safety outcomes were shown to be durable throughout the studies (to date,

measured for up to 100 weeks). This is a relevant feature of study considering treatment requirements for patients in practice are likely to extend beyond a year.

Data for the outcome of contrast sensitivity listed in the decision problem was not collected in the VISTA or VIVID studies.

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 VISTA and VIVID trials are directly applicable to the patient population with DMO in England and Wales, who are eligible for anti-VEGF treatment. Although no UK centres participated in the studies, baseline demographics were similar in both studies to that expected in clinical practice in England and Wales e.g. median age ~63 years, slightly more males than females, and over three-quarters of patients described as of 'White race'(54). Extensive subgroup analyses (e.g. age, gender, race, baseline HbA1c, baseline BCVA) within the efficacy and safety outcomes generally support the results for the overall populations; and therefore, confirm aflibercept's applicability to a relevant broad population. This included a mix of patients in the DMO trials who had either type 1 or type 2 diabetes or patients who had not received any prior anti-VEGF therapy, laser treatment, or cataract surgery and those who had, which will be similar to clinical practice, where patients may have received prior ranibizumab, laser or cataract surgery.

The fixed nature of the dosing regimen for aflibercept may mean that outcomes similar to those achieved in trials are conceivable. Whilst clinical trial protocols do include selection criteria different to general practice, the

inclusion of patients with prior therapy and levels of vision of 75 letters and under, may have minimised some of those differences.

Aflibercept solution for injection is an additional and alternative option to currently available treatment, ranibizumab, and superior in efficacy to laser photocoagulation for the treatment of DMO. Ranibizumab is considered standard of care in eyes with central retinal thickness of 400 micrometres or more at the start of treatment.

A direct comparison with ranibizumab is not available for DMO, however, the indirect comparison [see section 6.7] of efficacy and safety outcomes between aflibercept and ranibizumab in DMO showed a significant improvement in visual acuity outcomes ('BCVA mean change from baseline' and 'loss ≥10 ETDRS letters') for aflibercept 2mg (given every 4 weeks for the first five months and then every 8 weeks. There was no significant difference between aflibercept and ranibizumab in alternative visual acuity ('gain ≥15 ETDRS letters', 'loss ≥15 ETDRS letters', 'gains ≥10 ETDRS letters') or safety outcomes. Aflibercept and ranibizumab have previously been shown to have a similar safety profile in the VIEW studies in wet AMD. When compared to ranibizumab, the main benefit of aflibercept treatment is the removal of a requirement / burden of monitoring between doses, at least for the first year, reducing the financial and temporal burden on patients, caregivers, and healthcare systems. This is particularly important for a chronic disease like DMO, affecting patients often still in their working years. Fewer clinic visits translates to less inconvenience, fewer absences from work, and should translate to a relative increase in productivity. In addition, the fixed every 8-week dosing paradigm recommended for aflibercept has an advantage over variable dosing regimens in that treatment is delivered on a proactive basis and not in response to recurrence of disease. Multiple recurrences of disease may lead to irreversible loss of retinal function, particularly in photoreceptors, limiting patients' capacity to regain and/or maintain good visual function. Fixed-dosing of aflibercept has the additional benefit of removing the uncertainty around treatment for DMO - Ophthamology services are able to more easily plan their workloads and manage demand for services, which will

inevitably rise with the ageing population. Patients will also 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.

Laser treatment is also used in clinical practice, especially where anti-VEGF treatment is not appropriate. However, as confirmed by results of VISTA and VIVID, laser photocoagulation inconsistently attenuates disease progression and has limited effect on improving vision. The Royal College of Ophthalmologists Diabetic Retinopathy guidelines suggest that ‘in clinical practice, the outcome of laser photocoagulation for DMO is not as good as in research studies due to a number of factors such as laser equipment, patient factors and laser operator’(4). Thus, in VISTA and VIVID the efficacy of laser treatment may be exaggerated with a better safety profile than may be seen in practice. Also, although laser photocoagulation can reduce the risk of further vision loss in patients with DMO, the procedure may also cause macular scarring over time with repeated treatment(49;50). This can lead to scotomas in the long term. Such effects of laser treatment may not be easily observable within the context of clinical trials as this is a longer-term effect of treatment. In addition, some of the difficulties encountered with laser treatment mean that treatment may not be able to take place, for example if there is too much previous damage or scarring or it is not possible to get the patient in the right position for treatment. An advantage of intravitreal pharmacological treatment of DMO is that it does not carry the same risk of operator/clinical error and sudden or permanent visual loss, avoids the potential destructive effects of laser photocoagulation in the long term, and importantly, repeat treatments are not limited. Moreover, laser requires the maintenance and servicing of machines, replacing of gas and lenses, repair or replacement in the case of breakdown, training and an appointed safety officer.

Other therapies available in clinical practice for the treatment of DMO include dexamethasone and fluocinolone acetate, neither of which has been directly compared with aflibercept in DMO studies. Dexamethasone intravitreal

implant is indicated for the treatment of adult patients with visual impairment due to DMO who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy i.e. *after anti-VEGF therapies*. Nevertheless, an indirect analysis was possible for some endpoints for the comparison of aflibercept versus dexamethasone. Aflibercept significantly improved visual acuity in the Bucher analysis for the outcome of 'the proportion of patients gaining ≥10 ETDRS letters' at 12 months; No significant difference was found between treatment with aflibercept 2Q8 compared to 0.7mg dexamethasone for the outcomes: all discontinuations, macular oedema, reduced visual acuity, vitreous haemorrhage, eye pain and cataract at 12 months. Significantly fewer events occurred with aflibercept treatment in the analysis of 'increased intraocular pressure' at 12 months for the aflibercept/dexamethasone comparison. Aflibercept and fluocinolone acetonide intravitreal implant occupy different positions in the treatment pathway for DMO. Fluocinolone is recommended by NICE as an option for treating chronic DMO that is insufficiently responsive to available therapies only if the implant is to be used in an eye with an intraocular (pseudophakic) lens. A comparison of aflibercept with fluocinolone acetonide implants was not possible because identified trials did not have a common comparator to allow an indirect analysis.

Patient selection – use of aflibercept in DMO in clinical practice

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 for DMO within the NHS. Also, both aflibercept and ranibizumab are already widely used for wet age-related macular degeneration and central retinal vein occlusion. Therefore, no additional training of healthcare personnel would be required and no additional tests or investigations are required for selection or monitoring of patients appropriate for aflibercept, over and above the current routine assessments in DMO.

Although no studies in patients with hepatic and/or renal impairment have been conducted with aflibercept, available data from subgroup analyses of

VISTA and VIVID (DMO) and previous studies in wet AMD, and CRVO do not suggest a need for any dose adjustment with aflibercept in these patients.

As there are no adequate and well-controlled studies in pregnant women, aflibercept is not recommended for use during pregnancy, unless the potential benefit justifies the potential risk to the foetus. As in clinical trials, women of childbearing potential are required to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept.

There is limited experience in patients older than 75 years with DMO, and also in patients with DMO due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy.

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

The entire evidence base relates to the dose of aflibercept to be licensed for use in the treatment of DMO (i.e. 2mg).

7 Cost effectiveness

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 to identify cost-effectiveness analyses was conducted. Only full cost-effectiveness analyses were eligible, including studies based on models or performed alongside clinical trials. General cost of illness, economic burden, cost-minimisation and budget impact studies were excluded. Inclusion and exclusion criteria are shown in Table 62.

Table 62. Inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Study design	▪ Published economic evaluations: Including: alongside RCTs, CUAs	▪ Systematic or non-systematic reviews ▪ Budget impact analyses ▪ Cost of illness analyses ▪ Cost minimization analyses
Population	▪ Patients with diabetic macular oedema	
Interventions	▪ Eylea (VEGF Trap Eye/Aflibercept/AFB) ▪ Anti-VEGF treatments (Ranibizumab/Lucentis/RBZ, bevacizumab/Avastin/BVZ, pegaptanib/macugen) ▪ Intravitreal steroids (Triamcinolone, Fluocinolone, dexamethasone) ▪ Laser treatments	▪ Systemic treatments (alone or in combination with intervention) ▪ Surgery (alone or in combination with intervention)
Comparators	▪ Placebo, best standard care, masked control, sham ▪ Any intervention	
Outcomes	▪ Cost ▪ QALYs ▪ ICERs/whether cost-effective at some ICER threshold.	
Language	▪ Any	

CUA=Cost Utility Analysis; QALY = Quality Adjusted Life Year; ICER = Incremental Cost-effectiveness Analysis.

The search was conducted in literature databases and conference proceedings. Searches were not limited by language or publication status. Search terms are shown in Appendix 10.10.

Literature databases: The following literature databases were searched from inception:

- Medline (OvidSP): 1946 to week 5, July 2014
- Medline In-Process Citations & Daily Update (OvidSP): up to 8 August 2014
- Embase (OvidSP): 1974 to 8 August 2014
- NHS Economic Evaluations Database (NHS EED) (Wiley): Issue 3. July 2014
- Health Economic Evaluation Database (HEED) (Wiley): up to 11 August 2014
- Econlit (EBSCO): 1886 to 1 July 2014

An additional companion PubMed search was undertaken in tandem with Medline via OvidSP to detect the latest 'ahead of print' and 'online first' electronic content.

Conference abstracts: The following conference proceedings were screened for the past 5 years in October 2013:

- Association for Research in Vision and Ophthalmology (ARVO) http://www.iovs.org/search?arvomtgsearch=true
- American Diabetes Association (ADA) http://professional.diabetes.org
- European Association for the Study of Diabetes (EASD) http://www.easd.org/index.php?option=com_content&view=article&id=69&Itemid=509
- European Society of Retina Specialists (EURETINA) http://www.euretina.org/abstracts.asp

- American Academy of Ophthalmology (AAO) https://secure.aao.org/apps/MeetingArchive/tabid/433/Default.aspx
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) http://www.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp
- World Ophthalmology Conference (WOC) – 2012 only http://www.woc2012.org/files/abstract_book_woc2012.pdf
- European Society of Ophthalmology (ESO) – 2013 only http://www.abstractserver.com/soe2013/ebook/index.html

An update performed in August 2014 screened the following proceedings (EASD, EURETINA and ESO proceedings were not rescreened, as the conferences had not yet taken place):

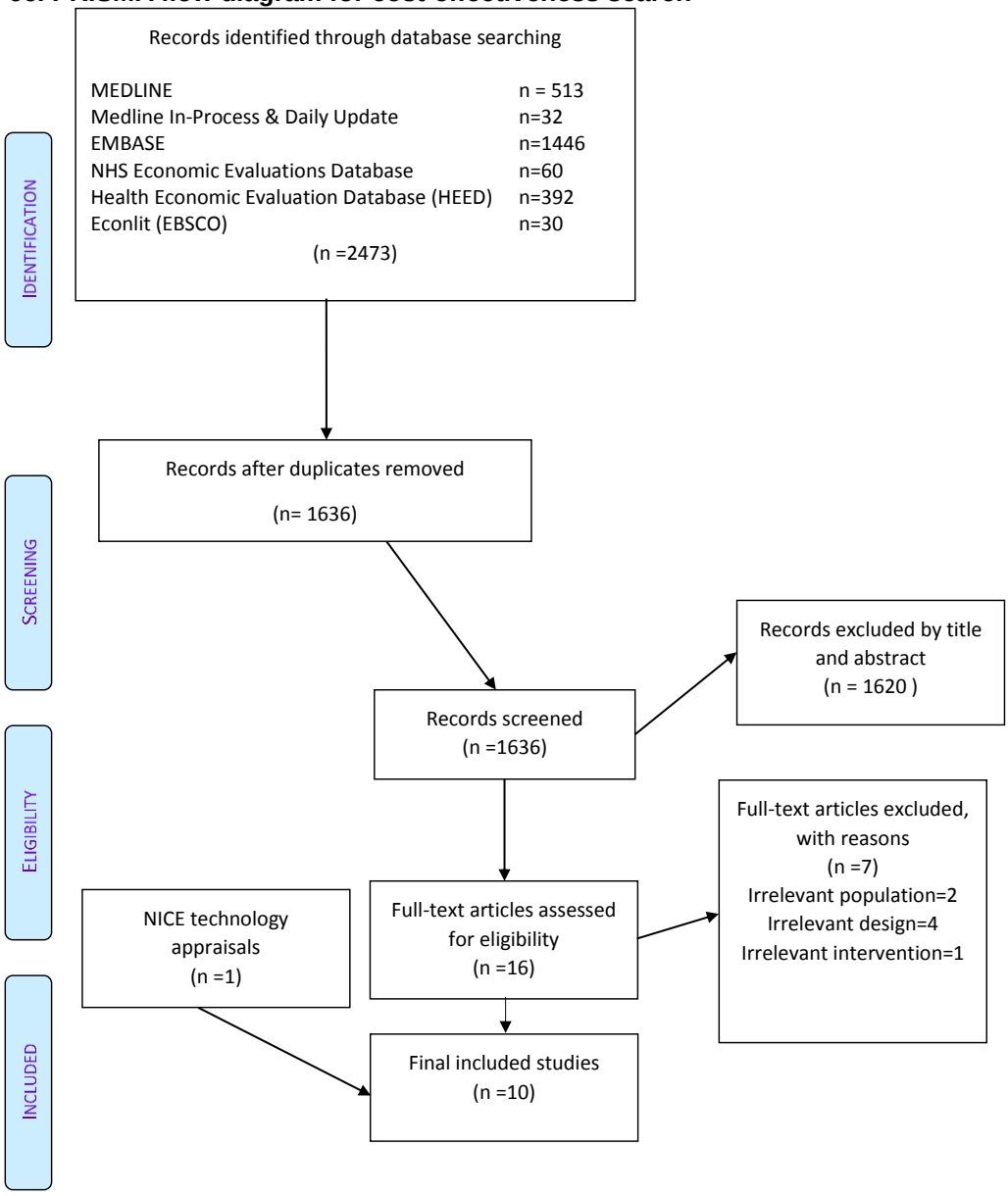
- Association for Research in Vision and Ophthalmology (ARVO) http://www.iovs.org/search?arvomtgsearch=true
- American Diabetes Association (ADA) http://diabetes.diabetesjournals.org/content/63/Supplement_1.toc
- American Academy of Ophthalmology (AAO) https://secure.aao.org/apps/MeetingArchive/tabid/433/Default.aspx
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) http://www.ispor.org/RESEARCH_STUDY_DIGEST/index.asp
- World Ophthalmology Conference (WOC) http://www.woc2014.org/contents/program.html

After removal of duplicates, the titles and abstracts of all references identified from the search were independently reviewed by two researchers. The suitability of the articles was evaluated against the eligibility criteria shown in Table 62. Full texts of the studies selected were reviewed and the same eligibility criteria applied. In the event of disagreement between the two reviewers at both screening stages, a third reviewer was consulted. All papers

included after the full text review were retained for data extraction. Data extraction was carried out by one reviewer and checked by another. Any discrepancies were resolved by discussion or the intervention of a third reviewer.

A total of 2473 hits (including duplicates) were obtained from the search (Figure 66). A total of 16 full text articles and one NICE technology assessment were assessed for eligibility. Ten 10 studies were found to meet exclusion criteria and went forward to data extraction (Figure 66).

Figure 66. PRISMA flow diagram for cost-effectiveness search



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.

The 10 studies that went forward to data extraction are shown in Table 63.

Table 63. All cost-effectiveness studies meeting eligibility criteria

	Year	Title	Journal
(Stein et al., 2013)(55)	2013	Cost-effectiveness of various interventions for newly diagnosed diabetic macular oedema.	Ophthalmology
(Smiddy, 2012)(56)	2012	Clinical applications of cost analysis of diabetic macular oedema treatments.	Ophthalmology
(Smiddy, 2011)(57)	2011	Economic considerations of macular oedema therapies.	Ophthalmology
(Sharma et al., 2000b)(58)	2000	The cost-effectiveness of grid laser photocoagulation for the treatment of diabetic macular oedema: results of a patient-based cost-utility analysis.	Curr Opin Ophthalmol
(Mitchell et al., 2012a)(59)	2012	Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial.	Br J Ophthalmol
(Haig et al., 2011a)(60)	2011	Economic evaluation of ranibizumab for the treatment of diabetic macular oedema in Canada.	Value Health.
(Dewan et al., 2012)(61)	2012	Cost-effectiveness analysis of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular oedema.	Ophthalmology
(Brennig et al., 2011b)(62)	2011	Economic evaluation of ranibizumab in the treatment of visual impairment due to diabetic macular oedema in Austria.	Value Health.
Novartis (NICE, 2013a)(1)	2010/2013	Lucentis ® (ranibizumab) for the treatment of visual impairment due to diabetic macular oedema (DMO).	NICE Single Technology Appraisal TA237/274
(Haig et al., 2013)(63)	2013	A Quebec economic evaluation for 36 months of ranibizumab for the treatment of diabetic macular edema	Value in Health

All studies compared prompt laser (with or without sham injection) to a number of other strategies (Table 64). Sharma compared prompt laser with delayed laser and found prompt laser to be cost-effective at an ICER of US $3,655(58).All other studies compared laser with drug alone or drug plus laser combinations.

Four out of the six studies that compared ranibizumab monotherapy found it to be cost-effective(1;59;60;62). The UK studies(1;59) found that ranibizumab, with an ICER of £24,028 and £15,938 respectively versus prompt laser, was cost-effective at a threshold of £30,000 or £20,000 per QALY in comparison to prompt laser, which was cheapest. Unfortunately, a full incremental analysis was not reported in that ranibizumab plus prompt laser was also compared to prompt laser. However, in both of these studies, the incremental cost was higher and incremental QALYs were lower for ranibizumab plus laser than for ranibizumab monotherapy, which implies that ranibizumab monotherapy would be cost-effective overall. A study in Austria found that ranibizumab monotherapy was cost-effective (although the threshold was not specified), with an ICER of €5,254 versus prompt laser(62). A study in Canada found that ranibizumab monotherapy was cost-effective (once again threshold not specified) with an ICER of Canadian $44,000 per QALY also versus prompt laser(60).

The only two studies that did not find ranibizumab to be cost-effective were those by Smiddy where no technology was reported to be cost-effective largely due to the fact that they did not perform an incremental analysis and only average cost-effectiveness ratios were presented(56;57).

The remaining three studies compared prompt laser to combinations of ranibizumab with adjuvant laser (prompt or delayed). Stein found that ranibizumab plus delayed laser was cost-effective (US $100,000 threshold) with an ICER of US $71,271 versus prompt laser(55). In the same study, triamcinolone plus delayed laser was dominated by (more expensive and less effective than) prompt laser, which was the cheapest strategy. Unfortunately, Stein did not perform a full incremental analysis in that bevacizumab plus laser was not compared directly to ranibizumab. Stein also found that ranibizumab plus delayed laser was cost-effective with an ICER of $71,271

and bevacizumab plus delayed laser was cost-effective with an ICER of $11,138, both versus prompt laser. However, given that bevacizumab plus laser was cheaper than ranibizumab plus laser and assumed to be of equal effectiveness, ranibizumab plus laser could not be cost-effective. Dewan compared three technologies with prompt laser, namely, ranibizumab plus either prompt or delayed laser and triamcinolone plus delayed laser(61). However, only a comparison of QALYs was reported for ranibizumab or triamcinolone without specifying whether each was combined with prompt or delayed laser. A full incremental analysis was conducted, but only in terms of cost per letter for all comparators. An important point to note is that, although not explicitly stated, the technologies labelled as 'ranibizumab' might be equivalent to those labelled as 'ranibizumab plus delayed/deferred laser'. Indeed Mitchell mentions 'laser therapy as required' in year 3 for ranibizumab monotherapy(59).

The other two studies comparing ranibizumab are only available as abstracts and this detail is not reported(60;62). However, if ranibizumab is equivalent to ranibizumab plus delayed laser then seven studies will have compared ranibizumab with prompt laser and four of these found it to be cost-effective although the one by Stein was probably incorrect (see above)(1;55;59;60;62). Only three studies conducted a probabilistic sensitivity analysis. However, neither Mitchell nor the Novartis NICE submission conducted this analysis in a 'fully incremental way' i.e. they only compared two technologies at a time and not all three(1;59) In the study by Novartis it was possible to calculate the probabilities of being cost-effective when all three were compared from Table B52, p.171. Given that combined therapy had a zero probability versus monotherapy, the probability of 60% for monotherapy compared to laser also applies to the comparison of all three. Thus, the probability that laser is cost-effective is 100-60 i.e. 40%. As stated above, Stein did not compare bevacizumab plus laser with ranibizumab plus laser and so found in one analysis that the former had a 91% probability of being cost-effective and, in a separate analysis, that the latter had a 67% probability of being cost-effective(55).

Table 64. Summary of cost-effectiveness studies

Study	Cost year	Country	Study conclusion	Population (inc. subgroup)	Technology	ICER	Comparator	Cost-effective?	ICER threshold	Probability cost-effective (%)
(Sharma et al., 2000b)(58)	2000	United States	Overall, grid laser photocoagulation for diabetic macular oedema is a very cost-effective treatment based on the results of this cost–utility analysis.	DME, bilateral symmetric	Prompt laser	3655	Delayed laser	Yes	20000	NA
					Delayed laser	Cheapest	NA	No		NA
(Smiddy, 2011)(57)	2010		Relative costs and benefits should be considered in perspective when applying and developing treatment strategies.	DME	Bevacizumab	NR	NR	NR	NR	NA
					Prompt laser					NA
					Triamcinolone					NA
					Pegaptanib					NA
					Ranibizumab					NA
(Dewan et al., 2012)(61)			In treatment of phakic patients with DME, ranibizumab with deferred laser provided an additional 6 letters correct compared with triamcinolone with laser at an additional cost of $19 216 over 2 years. That would indicate that if the gain in VA seen at 2 years is maintained in subsequent years, then the treatment of phakic patients with DME using ranibizumab may meet accepted standards of cost-effectiveness. For pseudophakic patients, first-line treatment with triamcinolone seems to be the most cost-effective option.		Triamcinolone + Delayed Laser	Cheapest	NA			NA
					Sham injections + Prompt laser	393/letter	Triamcinolone+ Delayed Laser			NA
					Ranibizumab + Delayed laser	20/letter				NA
					Ranibizumab + Prompt laser	5943 /letter	Sham injections + Prompt laser			NA
				DME, Pseudophakic	Triamcinolone + Delayed Laser	Cheapest	NA			NA
					Sham injections + Prompt laser	Dominated	Triamcinolone+ Delayed Laser			NA
					Ranibizumab + Delayed laser	14690/letter				NA
					Ranibizumab + Prompt laser	Dominated				NA
(Mitchell et al., 2012a)(59)		United Kingdom	Based on RESTORE 1-year follow-up data, ranibizumab monotherapy appears to be cost-effective relative to laser monotherapy, the current standard of care. Cost-	DME in one eye (BCVA <=75 letters)	Prompt laser	Cheapest	NA	No	30000	NR
					Ranibizumab + Prompt laser	36106	Prompt laser			NR
					Ranibizumab	24028		Yes		NR

Study	Cost year	Country	Study conclusion	Population (inc. subgroup)	Technology	ICER	Comparator	Cost-effective?	ICER threshold	Probability cost-effective (%)
			effectiveness of combination therapy is less certain.							
(Brennig et al., 2011b)(62)		Austria	The study suggests that in Austria, ranibizumab treatment for visual impairment resulting from DME is a cost-effective strategy versus the current standard of care, laser coagulation.	DME	Prompt laser	Cheapest	NA	No	NR	NA
					Ranibizumab	5354	Prompt laser	Yes		NA
(Stein et al., 2013)(55)	2011	United States	With bevacizumab and ranibizumab assumed to have equivalent effectiveness and similar safety profiles when used in the management of CSDME, bevacizumab therapy confers the greatest value among the different treatment options for CSDME.	Newly diagnosed clinically significant DME (CSDME)	Bevacizumab + Delayed laser	11138	Prompt laser photocoagulation alone.		100000	91
					Bevacizumab + Prompt laser	Dominated	Bevacizumab+delayed laser	No		8
					Prompt laser	Cheapest	NA			10
					Triamcinolone + Delayed laser	Dominated	Prompt laser photocoagulation alone.			0
					Ranibizumab + Delayed laser	71271		Yes		67
					Ranibizumab + Prompt laser	89903		No		24
Smiddy, 2012(57)			Cost-effectiveness analyses can be clinically relevant and may be considered when formulating and applying treatment strategies for some subsets of patients with DME.	DME	Aflibercept	NR	NR	NR	NR	NA
					Bevacizumab					NA
					Prompt laser					NA
					Triamcinolone					NA
					Ranibizumab					NA
				DME, Poor VA (20/200-20/320)	Prompt laser					NA
					Triamcinolone					NA
				DME, Pseudophakic	Prompt laser					NA
					Triamcinolone + Prompt Laser					NA
					Ranibizumab					NA

Study	Cost year	Country	Study conclusion	Population (inc. subgroup)	Technology	ICER	Comparator	Cost-effective?	ICER threshold	Probability cost-effective (%)
(Haig et al., 2011a)(60)	NR	Canada	Compared to laser photocoagulation, ranibizumab monotherapy shows cost-effectiveness within commonly accepted cost per QALY thresholds.	DME	Prompt laser	Cheapest	NA			NA
					Ranibizumab	44000	Prompt laser	Yes		NA
(NICE, 2013a)(1)	2009	United Kingdom	The probability of ranibizumab monotherapy being cost-effective at a willingness to pay (WTP) threshold of £20,000 was 60%, and at a WTP threshold of £30,000 was 84%.The probabilities for ranibizumab plus laser combination treatment were 28% at a £20,000 threshold and 49% at a £30,000 threshold.	DME (VA <=75 letters)	Prompt laser	Cheapest	NA	No	20000	40
					Ranibizumab + Prompt laser	Dominated	Ranibizumab	No		0
					Ranibizumab	15938	Prompt laser	Yes		60
(Haig et al., 2013)(63)	NR	Canada	Compared to laser photocoagulation, ranibizumab monotherapy and combination therapy for 3 years show cost-effectiveness from health care and societal perspectives.	DME	Prompt laser	Cheapest	NA	No	NR	NR
					Ranibizumab	24345	Laser	Yes		
					Ranibizumab + Prompt laser	36148	Laser			

Mitchell and colleagues evaluated the cost-effectiveness of ranibizumab as monotherapy or combined with laser therapy versus laser monotherapy in patients with visual impairment caused by DMO (Table 65)(59). A Markov model was developed to simulate outcomes and costs of treating DMO in one eye over a 15-year period, from the perspective of the UK healthcare payer. Eight health states defined by BCVA using 10-letter categories were used in the model. Clinical data were obtained from the phase III RESTORE trial. Mortality was estimated by adjusting general UK population death rates according to the increased relative risk of death in patients with DME. Utility scores were based on the EQ-5D questionnaire completed by patients in RESTORE. Costs included the cost of treatment and monitoring and costs associated with blindness.

The model predicted that 48% of patients treated with ranibizumab monotherapy and 47% treated with ranibizumab plus laser therapy would have BCVA >65 letter after 1 year, compared with 38% of patients receiving laser monotherapy(59). Ranibizumab monotherapy was associated with a cost of £4191 and an incremental gain of 0.71 QALYs, corresponding to £24028 per QALY gained relative to laser monotherapy. Corresponding values for ranibizumab plus laser therapy were £4695, 0.13 QALYs and £36106 per QALY gained. Univariate sensitivity analysis showed that costs per QALY gained were most sensitive to changes in the number of injections and the time horizon.

Table 65. Summary of cost-utility analysis of ranibizumab using 1-year data from the RESTORE trial (Mitchell et al., 2012a)(59)

Country	UK
Endpoint	DME in one eye (BCVA ≤75 letters)
Patient age	63 years
Model characteristics	
Type of evaluation	Cost-utility (Markov model)
Intervention	Ranibizumab monotherapy or combined with laser therapy
Comparator	Laser monotherapy
Time horizon	15 years
Description of health states	BCVA 10-letter categories (Snellen)
Adverse events modelled	Assumed to have negligible impact
Perspective	UK healthcare payer perspective
Outcomes	Cost per QALY, costs
Discount rates	Annual 3.5%
Sensitivity analysis	Univariate sensitivity analysis
Category of utility reported	Utility scores calculated for each BCVA health state based on EQ-5D scores
Results	
Total cost for each intervention	Incremental cost versus laser monotherapy: Ranibizumab monotherapy: £4191 Ranibizumab plus laser therapy: £4695
Total health benefit	Percent of patients with BCVA >65 letters after 1 year: Ranibizumab monotherapy: 48% Ranbizumab plus laser therapy: 47% Laser monotherapy: 38%
Incremental health benefit outcome	Ranibizumab monotherapy: 0.17 QALYs gained Ranbizumab plus laser therapy: 0.13 QALYs gained
Incremental outcome ratio	Ranibizumab monotherapy: £24028 per QALY gained Ranbizumab plus laser therapy: £36106 per QALY gained

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.

[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

A full quality assessment based on Drummond and Jefferson is shown in section 10.11, appendix 11. The studies by Brennig and Haig were excluded given that they were only available as abstracts(60;62;63). Overall, the best reported study in terms of number of checklist elements with a 'yes' was the Novartis study, which is not surprising since it was part of a manufacturer submission for a NICE technology appraisal(1). The least well reported study was Dewan which lacked some fundamental information such as clear definition of health states and an explanation of the term 'cumulative utility' (see below)(61). As mentioned in the overview above, Dewan also presented results for technologies, which were not clearly defined i.e. without specifying the timing of concomitant laser. However, all studies suffered from important problems. In particular, no systematic review in order to obtain estimates of effectiveness was conducted and, of the studies that were quality assessed, only Sharma reported a full incremental analysis(58). Indeed, of the remainder, the only two that did report an incremental analysis were both abstracts(60;62). Stein did not compare bevacizumab with ranibizumab treatments, instead producing separate analyses for each(55). Smiddy calculated only average cost-effectiveness ratios in both studies(56;57) and Mitchell and Novartis compared both ranibizumab and ranibizumab plus laser to a single comparator (laser)(1;59).

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.

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decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

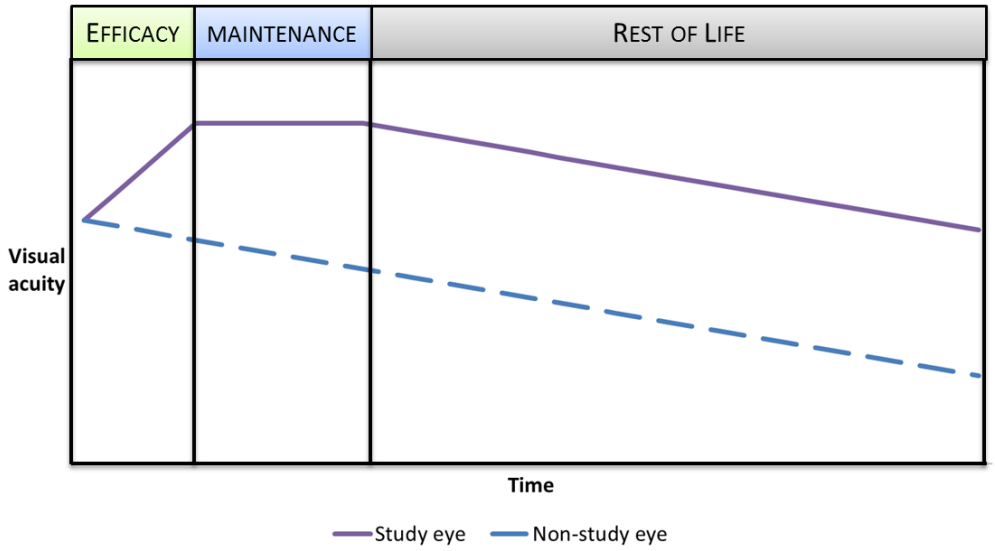
Patients with visual impairment due to DMO are considered in the model. Aflibercept currently holds a UK marketing authorisation for treatment of adults with visual impairment due to diabetic macular oedema.

Model structure

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

A state transition model was developed in Microsoft Excel. The model consists of three distinct and separate phases (Figure 67), starting with the *efficacy phase*, which lasts for 1 year. This is the only phase in which patient vision may improve with treatment. After the efficacy phase, vision among treated patients is assumed to remain stable for 4 years, described as the *maintenance phase*. Following the maintenance phase is the *rest of life* phase, where a long-term decline of vision occurs.

Figure 67. Visual acuity over time - three phases of the model (non-study eye = fellow eye)



BCVA in the fellow eye may vary in the model. This inclusion removes the need to make assumptions about BCVA in the fellow eye and about whether the study eye is the better or worse seeing eye. The fellow eye may be treated in the model. If the fellow eye is treated, the three phases described above are applied to the fellow eye. The second eye may start treatment at the start

of any of the first 5 years of the model. An incidence rate is used to generate the number of fellow eyes initiated.

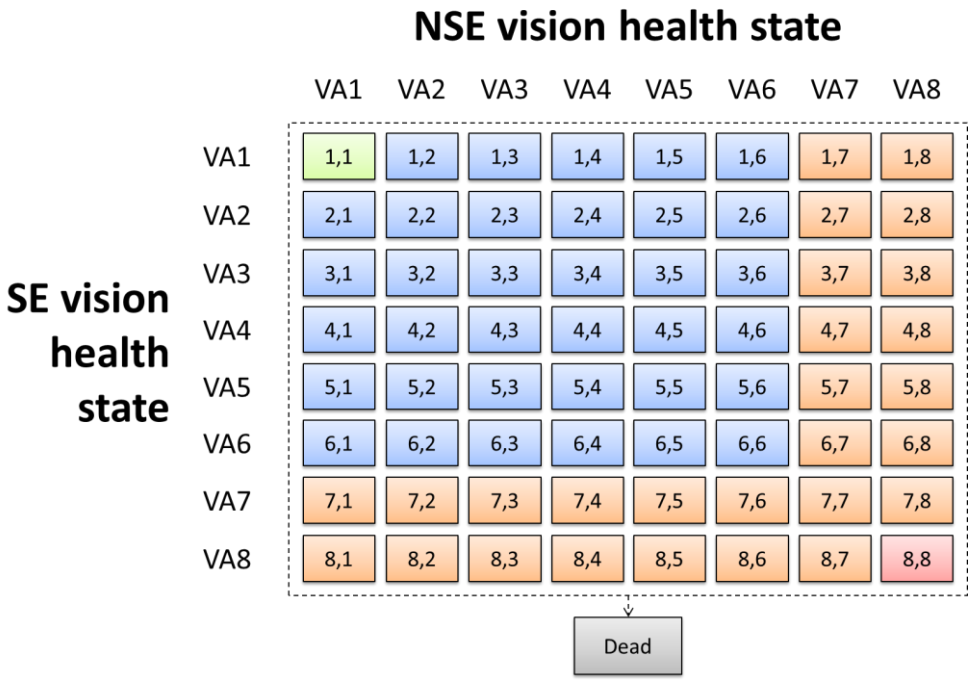
Health states are defined by the visual acuity in both the study eye and fellow eye. At any point in the model, both eyes will fall into one of eight mutually exclusive visual acuity health states, defined by ETDRS letters read (Table 66). The two worst health states, VA7 and VA8, represent blindness, consistent with other models(59;64;65).

Table 66. Categorisation of vision based on EDTRS letters

BCVA category	ETDRS letters read
VA1	86 – 100
VA2	76 – 85
VA3	66 – 75
VA4	56 – 65
VA5	46 – 55
VA6	36 – 45
VA7	26 - 35 (blindness)
VA8	0-25 (blindness)

The model features a total of 65 health states, 64 for each combination of study eye and fellow eye, and one absorbing health state representing death (Figure 68).

Figure 68. Model health states defined by vision in study eye (SE) and fellow eye (NSE) (colour indicates severity of health state)



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

The rationale for the three phase approach is based on the available evidence (VIVID/VISTA trials), expert opinion from clinical practice, and previous HTA submissions for back-of-the-eye conditions. In the VIVID/VISTA trials, vision improvements occurred over the first year and then appeared to plateau over the second year. The one year maintenance phase was used because, although two year data for aflibercept were available from VIVID/VISTA, the equivalent ranibizumab data contained cross over meaning that an indirect comparison of two year outcomes was not possible. The maintenance phase was extended up to the 5-year time point because data from a UK physician survey showed that physicians would continue to treat patients for up to 5 years with the aim of stabilising vision (see Appendix 15: Physician survey). This approach to maintaining vision in the medium term has been accepted in previous HTA submissions(1;1;10). The rest of life phase is based on the assumption that patients' vision declines at a steady rate over the remainder of their life.

A similar three phase approach (efficacy, maintenance and rest of life) was used and accepted in submissions to NICE and the SMC for aflibercept in wet age-related macular degeneration(9).
A two eye approach was chosen because quality of life is a function of both eyes. Initiation of treatment of the fellow eye was limited to the first five years to limit complexity in the model and to reflect uncertainty around treatment priorities in the far future. This simplification was endorsed as reasonable by expert clinical advisors (Appendix 16).
Health state ranges were chosen to be adequately sensitive to changes in vision associated with DMO and its treatment and were typically 10 letters apart. A change in vision of 10 letters or more is considered clinically significant, and is a commonly used endpoint within ophthalmology clinical trials, including the VISTA and VIVID studies. Visual acuity health states defined by 10-letter cut-offs have also featured in previous DMO cost-effectiveness models(55;59) and confirmed by clinical specialists in the Appraisal Committee of a previous NICE submission for ranbizumab(1).

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

Overall vision is a function of the vision in both eyes, and therefore the model considers both the impact of visual acuity in the study eye and the fellow eye on patient outcomes.

Discontinuation is captured by having additional states in which the patient does not receive treatment.

Increase in mortality associated with blindness is captured by transition probabiities from the “blind” states.

Treatment of the first and second eye is captured by separate consideration of efficacy and benefit in each eye.

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.

DMO directly affects visual acuity, which is used to define model health states.

The model's three phases are used to represent:

- A period of potential improvement, justified by good quality trial data
- A period where treatment is expected to continue to maintian vision, supported by some evidence and by clincial opinion
- Long term decline in vision after the effectiveness of treatment is exhausted.

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.

The key features of the model used to conduct the base-case analysis are summarised in Table 67 below.

Table 67. Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime	A lifetime horizon was chosen because DMO is a chronic disease, and time horizons that exceed typical treatment durations are a common feature of previous cost-effectiveness models in DMO.	(55;59)
Cycle length	4-weekly	4-weekly cycles reflect the highest frequency of treatment administration (initial monthly doses of aflibercept and ranibizumab), the monthly monitoring of visual acuity for ranibizumab and to adequately capture changes in vision.	SmPCs
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 2013(66)
Discount of 3.5% for utilities and costs	3.5%	NICE reference case	NICE Methods of Technology Appraisal 2013(66)
Perspective (NHS/PSS)	NHS/PSS	NICE reference case	NICE Methods of Technology Appraisal 2013(66)
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

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 intervention considered is aflibercept 2 mg administered in a fixed-dose regimen that may be extended after the first year, with no requirement for monthly monitoring. According to the SmPC, treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two months. After the first 12 months, the treatment interval may be extended based on visual and anatomical outcomes.The regimen considered in the model is identical to the SmPC (8 fixed doses in year 1).

Treatment with ranibizumab is modelled according to an established ‘treat-to-target’ regimen that requires monthly monitoring of visual acuity, at least in the first year. 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. Treatment is resumed when (monthly) monitoring indicates loss of visual acuity due to DMO. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments(2). The SmPC for ranibizumab changed in September 2013(3), but it is not yet known what impact this may have on future practice.

Treatment with intravitreal steroids was modeled in line with their licensed doses and posologies. Otherwise, the exploratory comparison with steroids is limited by the reasons stated in Section A, and the issues with the available evidence discussed in Section 6.7, 7.3 and 7.9.

As per the scope, the analysis includes ranibizumab and steroid treatment with and without laser. For aflibercept, rescue laser was administered in 4-8% of patients in the VIVID/VISTA trials. However, measurements taken after additional treatment was given were censored in the primary analysis. In the RESTORE study, included in the NMA, one arm included laser and the other did not, even though that study did not show any difference in efficacy between the two arms. Nevertheless, DRCR.net, also included in the NMA, included different criteria for rescue. For dexamethasone, the regimen considered in this de novo analysis was dexamethasone+laser as this was used in the only included study (PLACID). In the FAME study, 41-43% participants were given additional rescue laser in the fluocinolone arm at 3 years (13-18% recieivng off-protocol treatments including anti-VEGF and triamcinolone). Given this, the aflibercept efficacy presented here and in the indirect comparison may be considered conservative as the proportion of patients receiving laser in addition to aflibercept is lower than in the data used for other comparators, additonal treatment was censored in the primary analysis, and additional laser has only been costed in the exploratory dexamethasone analysis where it was clearly reported in the PLACID results.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.

Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

The model allows the user to assume that blind patients stop treatment during the maintenance phase.

Both ranibizumab and aflibercept have similar stopping rules in their SmPCs and, therefore, any impact of this in clinical practice is likely to be similar for both products.

7.3 Clinical parameters and variables

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

Baseline population

The baseline age of patients in the model was 63 years (95% CI: 63.39-64.62) and the proportion of female patients was 42.1% (95% CI: 38.8-45.4). These values were based on the population enrolled in the VIVID/VISTA clinical trials (section 6.5)

The proportion of fellow eye involvement at baseline was taken from a physician survey. On average, the physicians estimated that 46.5% of patients had fellow eye involvement at baseline. An estimate of 35% was used in the appraisal TA274 of ranibizumab for DMO(1).

The starting vision health state distributions for the study eye and the fellow eye were estimated from the integrated VIVID/VISTA trial analyses (Table 68). They are estimated from the full sample, regardless of treatment arm, and are applied to all treatments.

Table 68. Starting distribution of health states

	VA1	VA 2	VA 3	VA 4	VA 5	VA 6	VA 7	VA 8	Total
Study eye	[redacted]								**100%**
Fellow eye	[redacted]								**100%**

Discontinuation

Monthly treatment discontinuation rates were estimated using data from the VIVID/VISTA studies, an NMA (Section 6.7.4) and published sources (Table 69). The relative risks from the NMA were used to estimate discontinuation for aflibercept and ranibizumab to ensure randomisation was not broken.

Table 69. Monthly treatment discontinuation rates

	Relative risk	Monthly probability of discontinuation	Sources
Aflibercept	0.80*	0.00678	NMA (Section 6.7.4)
Laser	-	0.00847	VIVID/VISTA
Ranibizumab	0.74*	0.00627	NMA (Section 6.7.4)

[3] One patient in the clinical trial programme had a BCVA >75 in the study eye; this patient is modelled as observed in the trial but the target patient population of this submission remains patients with a BCVA ≤75 letters

+Compared to aflibercept from VIVID/VISTA

Mortality risk (background and associated with diabetes and poor vision)

Background mortality rates per patient age have been taken from the England and Wales 2010-2012 national life tables(67).

A review of previous NICE appraisal documentation was conducted within the systematic review that was performed to inform choice of epidemiological parameters.

To reflect the additional risk of mortality associated with a diabetic cohort, a relative risk (vs a non-diabetic general population) of 1.95 was applied to the background mortality rates. The mortality rates associated with diabetes have been taken from a large prospective longitudinal study in the US of over 5000 people (The Framingham Heart Study from 1950 to 2005)(68) (Table 70).

A relative risk of mortality associated with poor vision (1.23) has also been applied to individuals who were blind (VA7 or VA8) in one or both eyes(12) (Table 70). This is similar to the estimates used in the NICE appraisal of ranibizumab for DMO(1) that combined estimates of 1.93(69) and 1.27(1;70), and also referenced the Diabetic Retinopathy Programme annual report(4).

A scenario analysis was also considered using a recommendation from the ERG following a review of the decision problem. A relative risk of 1.27 from the ranibizumab submission was applied to the risk of mortality of patients with diabetes to represent the increased likelihood of death in a patient with DMO. The overall RR applied in this scenario was 2.45.

Table 70. Background mortality and relative risk of additional mortality associated with diabetes and blindness

Parameter	Value	95% CI		Source
Background mortality	Various			(ONS, 2014)(67)
Relative risk of mortality (diabetes)	1.95	1.64	2.33	(Preis et al., 2009)(68)
Relative risk of mortality	1.23	1.16	1.31	(Christ et al., 2008)(12)

(one eye blind)				

Efficacy

Laser

Laser efficacy in the model was based on the probabilities of gaining or losing 10 or 15 letters from the VIVID/VISTA studies as described in section 6.5.

Aflibercept and ranibizumab

In the base case, aflibercept and ranibizumab efficacy in the model were based on the probabilities of gaining or losing 10 or 15 letters. These probabilities were estimated by applying the relative risks estimated as part of the NMA (described in section 6.7) to the equivalent probabilities for laser.

Intravitreal corticosteroids

These analyses are considered exploratory for the reasons given in Section A and the limitations in the available evidence described in Section 6.7 and 7.9.

Dexamethasone intravitreal implant

In the base case, dexamethasone efficacy is based on the probability of gaining 10 letters, which was the only outcome available for this comparison. This probability was estimated using the relative risks from the indirect comparison of aflibercept versus dexamethasone using the PLACID study comparing laser to dexamethasone+laser (section 6.7).

It should be noted that in this comparison, aflibercept efficacy was based on the observed probabilities from the VIVID/VISTA trials rather than being based on a relative risk versus laser. This comparison should therefore be considered an exploratory analysis.

The remaining probabilities (gaining or losing fifteen letters and losing ten letters) were set equal to the equivalent values for laser from the VIVID/VISTA studies. A choice was required due to lack of an indirect comparison for these outcomes using PLACID .These values were chosen because

dexamethasone has not demonstrated any benfit over laser for these endpoints.

Given that a full set of comparative relative risks were not available, this comparison is less robust than the comparisons with laser and ranibizumab. Moreover, the pivotal MEAD studies could not be included in the NMA as the control was sham rather than laser, as in VIVID/VISTA.

Finally, the population considered in the model matches that of the VIVID/VISTA trial which differs from the licensed indication of dexamethasone. No indirect comparison comparing aflibercept with dexamethosone was available in the indicated population.

Fluocinolone acetonide intravitreal implant

It was not possible to do an indirect comparison of aflibercept versus fluocinolone in terms of gain or losses of 10 letters as the FAME study had a different control arm (sham) compared with VISTA/VIVID (laser), as well as different study outcomes and study duration (3 years). In the analysis presented, fluocinolone efficacy is based solely on the probability of gaining 15 letters. This probability was taken directly from the trial publication(71). The remaining probabilities (gaining or losing ten letters and losing fifteen letters) were set equal to laser because there was no evidence available to suggest that they were any different. In this comparison, aflibercept efficacy was based on the observed probabilities from the VIVID/VISTA trials. This analysis assumes that patients maintain vision during the efficacy phase unless they gain ten letters or discontinue.

This represents a crude comparison method as randomisation is broken by comparing these treatments without adjusting for study heterogeneity. Moreover, the limitations with the evidence from the FAME study is discussed in depth in NICE guidance TA301. We have also discussed this further in Section 7.9. Given the lack of validity associated with such comparative data, as well as the different places in the treatment pathway, this should be considered an exploratory analysis.

Finally, it should be noted that the population considered in the de novo model presented matches that of the VIVID/VISTA trial which differs from the licensed indication of fluocinolone. Campochiaro et al found that fluocinolone was more effective in this population based on mean change in BCVA over a 24 month period

Safety

The following adverse events were considered in the model: cataracts, endophthalmitis, retinal detachment, vitreous haemorrhage, ocular hypertension. Adverse events were modelled to only occur in patients who were on treatment.

For laser, monthly adverse events rates from the VIVID/VISTA studies were used.

For aflibercept and ranibizumab, monthly adverse event rates were estimated by applying relative risks from the NMA to the relative risks for laser (section 6.7).

Given the absence of a common comparator arm in the pivotal MEAD, FAME, VISTA and VIVID studies to form an indirect comparison, for dexamethasone and fluocinolone, monthly adverse event rates were taken directly from trial publications(71;72). In these comparisons observed aflibercept rates were used. Both were crude comparisons as randomisation was broken.

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.

The model uses the probability of gaining or losing 10 letters to represent a move of one health state, and the probability of gaining or losing 15 letters to represent a move of two health states. Both were secondary endpoints from the VIVID/VISTA trial programme and subsequent NMA.

Ten letters represent a move of one health state because the model health states are divided into groups of 10 letters (with the exception of the top and bottom states). Fifteen letters was used to estimate likelihood of a a move of two health states as it is the only measure of response larger than 10 letter change that could be identified from the NMA. The iimportance of this variable is tested in sensitivity analysis.

Efficacy phase

The following transitions are possible while patients are on treatment during the efficacy phase:

- Remain in the same health state
- Gain one health state
- Gain two health states
- Lose one health state
- Lose two health states
- Discontinue treatment
- Die

The following transitions are possible while patients are off treatment during the efficacy phase:

- Remain in the same health state
- Lose one health state
- Die

Transition probabilities for laser treatment were estimated from the VIVID/VISTA trials (Table 71). Transition probabilities for aflibercept and ranibizumab were estimated by applying relative risks versus laser treatment from the NMA (Table 72).

Table 71. Monthly transition probabilities for laser treatment based on VIVID/VISTA

	Monthly transition probability
Gain 10 letters	0.016971

Lose 10 letters	[redacted]
Gain 15 letters	0.006738
Lose 15 letters	0.007814

Table 72. Relative risks (versus laser treatment) of gaining or losing letters with aflibercept or ranibizumab based on NMA

	≥10 letter gain RR (95% CI)	**≥10 letter loss RR (95% CI)**	**≥15 letter gain RR (95% CI)**	**≥15 letter loss RR (95% CI)**
Aflibercept	2.07 (1.68-2.48)	[redacted]	3.09 (2.20-4.21)	0.03 (0.00-0.16)
Ranibizumab	1.74 (1.36-2.17)	0.37 (0.13-0.92)	2.19 (1.47-3.13)	0.19 (0.03-0.63)

Table 73, Table 74 and Table 75 show the transition matrices for the efficacy phase for aflibercept, ranibizumab and laser treatment, respectively. These matrices incorporate the probabilities of improving vision, losing vision, discontinuing and dying. The green cells represent the probability of improving BCVA. The red cells represent the probability of declining BCVA. The grey cells represent the probability of maintaining BCVA.

Table 73. Transition matrices during the efficacy phase for aflibercept

	On treatment								Off treatment								
	VA1	VA2	VA3	VA4	VA5	VA6	VA7	VA8	VA1	VA2	VA3	VA4	VA5	VA6	VA7	VA8	D
VA1	[redacted]	0.0351	0.0208	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA2	[redacted]	[redacted]	0.0351	0.0208	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA3	0.0002	[redacted]	[redacted]	0.0351	0.0208	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA4	0.0000	0.0002	[redacted]	[redacted]	0.0351	0.0208	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA5	0.0000	0.0000	0.0002	[redacted]	[redacted]	0.0351	0.0208	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA6	0.0000	0.0000	0.0000	0.0002	[redacted]	[redacted]	0.0351	0.0208	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA7	0.0000	0.0000	0.0000	0.0000	0.0002	[redacted]	[redacted]	0.0351	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002	[redacted]	[redacted]	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA1	0.0058	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9913	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA2	0.0000	0.0058	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA3	0.0000	0.0000	0.0058	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA4	0.0000	0.0000	0.0000	0.0058	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000	0.0000	0.0000
VA5	0.0000	0.0000	0.0000	0.0000	0.0058	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000	0.0000
VA6	0.0000	0.0000	0.0000	0.0000	0.0000	0.0058	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000
VA7	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0058	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9910	0.0000	0.0000
VA8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0058	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9982	0.0000
D	0.0014	0.0014	0.0014	0.0014	0.0014	0.0014	0.0018	0.0018	0.0014	0.0014	0.0014	0.0014	0.0014	0.0014	0.0018	0.0018	1.0000

Table 74. Transition matrices during the efficacy phase for ranibizumab

	On treatment								Off treatment								
	VA1	VA2	VA3	VA4	VA5	VA6	VA7	VA8	VA1	VA2	VA3	VA4	VA5	VA6	VA7	VA8	D
VA1	0.9815	0.0295	0.0148	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA2	0.0047	0.9520	0.0295	0.0148	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA3	0.0015	0.0047	0.9372	0.0295	0.0148	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA4	0.0000	0.0015	0.0047	0.9372	0.0295	0.0148	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA5	0.0000	0.0000	0.0015	0.0047	0.9372	0.0295	0.0148	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA6	0.0000	0.0000	0.0000	0.0015	0.0047	0.9372	0.0295	0.0148	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA7	0.0000	0.0000	0.0000	0.0000	0.0015	0.0047	0.9384	0.0295	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0015	0.0047	0.9431	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA1	0.0108	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9913	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA2	0.0000	0.0108	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA3	0.0000	0.0000	0.0108	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA4	0.0000	0.0000	0.0000	0.0108	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000	0.0000	0.0000
VA5	0.0000	0.0000	0.0000	0.0000	0.0108	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000	0.0000
VA6	0.0000	0.0000	0.0000	0.0000	0.0000	0.0108	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000
VA7	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0108	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9910	0.0000	0.0000
VA8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0108	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9982	0.0000
D	0.0014	0.0014	0.0014	0.0014	0.0014	0.0014	0.0018	0.0018	0.0014	0.0014	0.0014	0.0014	0.0014	0.0014	0.0018	0.0018	1.0000

Table 75. Transition matrices during the efficacy phase for laser treatment

	On treatment								Off treatment								
	VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA6**	**VA7**	**VA8**	**VA1**	**VA2**	**VA3**	**VA4**	**VA5**	**VA6**	**VA7**	**VA8**	**D**
VA1	[redacted]	0.0170	0.0067	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA2	[redacted]	[redacted]	0.0170	0.0067	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA3	0.0078	[redacted]	[redacted]	0.0170	0.0067	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA4	0.0000	0.0078	[redacted]	[redacted]	0.0170	0.0067	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA5	0.0000	0.0000	0.0078	[redacted]	[redacted]	0.0170	0.0067	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA6	0.0000	0.0000	0.0000	0.0078	[redacted]	[redacted]	0.0170	0.0067	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA7	0.0000	0.0000	0.0000	0.0000	0.0078	[redacted]	[redacted]	0.0170	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0078	[redacted]	[redacted]	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA1	0.0125	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.9913	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA2	0.0000	0.0125	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA3	0.0000	0.0000	0.0125	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
VA4	0.0000	0.0000	0.0000	0.0125	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000	0.0000	0.0000
VA5	0.0000	0.0000	0.0000	0.0000	0.0125	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000	0.0000
VA6	0.0000	0.0000	0.0000	0.0000	0.0000	0.0125	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9913	0.0000	0.0000	0.0000
VA7	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0125	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9910	0.0000	0.0000
VA8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0125	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0073	0.9982	0.0000
D	0.0014	0.0014	0.0014	0.0014	0.0014	0.0014	0.0018	0.0018	0.0014	0.0014	0.0014	0.0014	0.0014	0.0014	0.0018	0.0018	1.0000

Maintenance phase

During the maintenance phase, all living patients who remain on treatment maintain vision. However, patients may discontinue treatment or die. Blind patients are not treated during this phase.

If patients are off treatment during the maintenance phase, they may remain in the same health state, lose at least 10 letters of vision (one health state) or die.

Rest of life phase

It is assumed that patients receive no treatment during the rest of life phase. Patients may remain in the same health state, lose at least 10 letters of vision (one health state) or die.

Any eye that is affected by DMO and is not on treatment will lose vision at a monthly rate in line with natural progression. Given the absence of relevant studies identified in the literature review, a rate estimated from the ranibizumab NICE appraisal for DMO was used(1). This appraisal reported a 3 month probability of 3.5% of losing 10 letters during the decline phase. This value was obtained by calibrating results from two different studies: The Early Treatment Diabetic Retinopathy Study (ETDRS) group (73) and the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) study(74). To calculate the monthly probability of losing 10 letters in the current model, the probability was normalised to 1 month (1.15%).

Consideration of the fellow eye

All fellow eyes are either at risk of DMO or already affected by DMO when they enter the model. An annual incidence rate is used to estimate the proportion of fellow eyes becoming affected with DMO between model entry and year 4. The annual incidence is based on an assumption, as no suitable data were available in the literature for annual rates in the medium term.

A proportion of eyes that are affected with DMO may be treated. Treated fellow eyes follow the efficacy, maintenance and rest of life phases. Beyond year 4 the model does not consider newly incident DMO cases in the study or fellow eyes. The impact of not including incident fellow eye DMO beyond five years is equivalent between arms.

Unaffected fellow eyes may maintain or lose vision. Vision loss in unaffected eyes is slower than in affected eyes.

In the model, to minimise complexity, the BCVA in one eye evolves independently of the other. We consulted experts (Appendix 16) and one UK ophthalmologist highlighted that it may be reasonable for eyes to be modelled independently because each eye may have different problems.

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.

Data from the VIVID/VISTA clinical programme suggest that treatment with anti-VEGF therapy leads to an initial increase in mean BCVA across a cohort followed by a plateau. This is supported by data shown in (section 6.5). The three phase approach of the model is used to represent this change.

A scenario analysis using patient data is also presented to demonstrate whether the rate of change in BCVA changes during the efficacy period.

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?

No intermediate outcomes were used to link treatment to BCVA.

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

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

A validation meeting was held with four experts: two economists and two consultant ophthalmologists from the north of England and west midlands. The meeting format was a face to face interview where all participants were given the opportunity to answer all questions. Questions were asked about the face validity of the clinical and economic assumptions made in the model. Full details are presented in Appendix 16: Model validation meeting summary.

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.

Table 76. Summary of variables applied in the economic model

[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.

Variable	Value	CI (distribution)	Reference to section in submission
Age	63 years	63.39-64.62	7.3.1
Proportion female, %	42.1	38.8-45.4	7.3.1
Fellow eye involvement, %	46.5	37.2-55.8	7.3.1
Efficacy parameters			
Monthly transition probabilities for gain or loss of letters with laser treatment			
Gain 10 letters	0.016971		7.3.2
Lose 10 letters	0.012760		7.3.2
Gain 15 letters	0.006738		7.3.2
Lose 15 letters	0.007814		7.3.2
RR vs laser treatment of gaining or losing letters of vision			
Aflibercept: ≥10 letter gain	2.07	1.68-2.48	7.3.2
Aflibercept: ≥10 letter loss	[redacted]	[redacted]	7.3.2
Aflibercept: ≥15 letter gain	3.09	2.20-4.21	7.3.2
Aflibercept: ≥15 letter loss	0.03	0.00-0.16	7.3.2
Ranibizumab: ≥10 letter gain	1.74	1.36-2.17	7.3.2
Ranibizumab: ≥10 letter loss	0.37	0.13-0.92	7.3.2
Ranibizumab: ≥15 letter gain	2.19	1.47-3.13	7.3.2
Ranibizumab: ≥15 letter loss	0.19	0.03-0.63	7.3.2
Long-term decline in vision			
Monthly probability of losing 10 letters (study eye)	1.15%		7.3.2
Monthly probability of losing ≥10 letters per year (unaffected eye)	0.17%		7.3.2
Mortality rates			
Background mortality	Various	NA	7.3.1
RR of mortality (diabetes)	1.95	1.64-2.33	7.3.1
RR of mortality (one eye blind)	1.23	1.16-1.31	7.3.1
Monthly treatment discontinuation rates			
Aflibercept	0.00678		7.3.1
Ranibizumab	0.00502		7.3.1
Laser treatment	0.00847		7.3.1
Adverse event rates, % per month			
Aflibercept			
Cataract	0.41		7.3.1
Endophthalmitis	0.00		7.3.1
Retinal detachment	0.03		7.3.1
Vitreous haemorrhage	0.11		7.3.1
Ocular hypertension	0.26		7.3.1
Glaucoma	0.29		7.3.1

Ranibizumab			
Cataract	0.11		7.3.1
Endophthalmitis	0.03		7.3.1
Retinal detachment	0.00		7.3.1
Vitreous haemorrhage	0.00		7.3.1
Ocular hypertension	0.31		7.3.1
Glaucoma	0.00		7.3.1
Laser treatment			
Cataract	0.43		7.3.1
Endophthalmitis	0.03		7.3.1
Retinal detachment	0.03		7.3.1
Vitreous haemorrhage	0.31		7.3.1
Ocular hypertension	0.29		7.3.1
Glaucoma	0.12		7.3.1
Mean number of injections/treatment			
Aflibercept			
Year 1	8		7.5.5
Year 2	4		7.5.5
Year 3	2.3		7.5.5
Year 4	1.2		7.5.5
Year 5	1		7.5.5
Ranibizumab			
Year 1	7.93		7.5.5
Year 2	4		7.5.5
Year 3	2.3		7.5.5
Year 4	1.2		7.5.5
Year 5	1		7.5.5
Laser			
Year 1	2.4		7.5.5
Year 2	1.4		7.5.5
Year 3	0.8		7.5.5
Year 4	0.4		7.5.5
Year 5	0.3		7.5.5
Mean number of monitoring visits			
Aflibercept			
Year 1	8		7.5.5
Year 2	6		7.5.5
Year 3	4		7.5.5
Year 4	4		7.5.5
Year 5	2		7.5.5

Ranibizumab			
Year 1	12		7.5.5
Year 2	6		7.5.5
Year 3	4		7.5.5
Year 4	4		7.5.5
Year 5	2		7.5.5
Laser			
Year 1	4		7.5.5
Year 2	4		7.5.5
Year 3	2.6		7.5.5
Year 4	2.2		7.5.5
Year 5	1.9		7.5.5
Utility values (due to the number of health states utilities are presented in section 7.4.9			
CI, confidence interval; RR, relative risk			

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.

The VIVID trial provides data for treatment up to 1 year and the VISTA trial for up to 2 years. As stated in section 7.2.3, the maintenance phase was extended up to the 5-year time point because data from a UK physician survey showed that physicians would continue to treat patients for up to 5 years with the aim of stabilising vision (see Appendix 15: Physician survey). This approach to maintaining vision in the medium term has been accepted in previous HTA submissions (1;10). The rest of life phase is based on the assumption that patients' vision declines at a steady rate over the remainder of their life, as described in section 7.3.2.

Post treatment, the only cost applied is the cost of blindness which is a function of BCVA.

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

Table 77. Assumptions in the economic model

Parameter	Assumptions	Justification
Time horizon and treatment duration	The efficacy phase lasts for 1 year (does not necessarily equal the length of treatment, only the duration over which vision gains are made). Model time horizon is patient's lifetime.	VIVID provides comparative efficacy data for up to 1 year and VISTA for up to 2 years. Lifetime horizon is selected to reflect the chronic nature of the condition.
Baseline distribution	Distribution as in VIVID and VISTA trials.	Baseline health state distribution of the population should reflect those of the key trials used in the model.
Health states	Defined by 10 or 15 letters increments (one or two health states, respectively).	10-letter categories were the most granular binary endpoint in the VIVID/VISTA studies. 15-letter categories were used in the ranibizumab trials, which limited the endpoints that could be used in the NMA. A 15-letter change was deemed an adequate representation of two health states because it is equivalent to a 1.5 health state transition which could be reasonably round to two health states.
Treatment efficacy	Efficacy of aflibercept has been established in VIVID and VISTA. During the maintenance phase, patient vision is assumed to remain stable for 4 years. During the rest of life phase, a long-term decline of vision occurs.	Transition probabilities were derived from the VIVID/VISTA analysis. Data from a UK survey show that physicians would continue to treat patients for up to 5 years with the aim of stabilising vision. Vision in patients not receiving treatment is expected to decline over the long term.
Mortality	Excess mortality for diabetes and blindness was applied.	The Framingham Heart Study demonstrates excess mortality in patients with diabetes (relative risk 1.95) (Preis et al., 2009). A higher mortality rate associated with poor vision has also been shown (relative risk 1.23) (Christ et al., 2008).
Discontinuation	Estimated treatment discontinuation rates have been included in the model.	Discontinuation rates have been estimated from the NMA, VIVID/VISTA and RESTORE trials.
Adverse events		
Resource use		

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.

DMO is associated with a rapid decline in vision and therefore affects patients' ability to perform everyday tasks, primarily driving and reading. Studies by Brown 1999 & 2000 and Czoski Murray(75;76) show that decline in vision is associated with reduced quality of life.

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

If DMO causes a patient's vision to decline, all other things being equal, the patient's HRQoL will fall. The reverse is also true.

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. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.

Results with confidence intervals.

Exploratory EQ-5D data were collected at baseline, week 24 and week 52 of the VIVID and VISTA clinical trials. Utilities were estimated using the UK valuation tariff by Dolan et al. A regression analysis was performed to estimate the relationship between BCVA (in both eyes) and quality of life. The EQ-5D questionnaires were completed by patients but quality of life estimates were based on a general population tariff meaning that the estimates were consistent with the NICE reference case.

OLS, GLM and GEE models were estimated. All produced similar results in terms of the magnitude and direction of the coefficients. The selected model structure was:

$$y_i = \boldsymbol{\alpha} + \boldsymbol{\beta_1}\ (\text{log of BCVA of BSE}) + \boldsymbol{\beta_2}\ (\text{log of BCVA of WSE}) + \boldsymbol{\beta_3}\ (\text{age}) + \boldsymbol{\beta_4}\ (\text{baseline BMI}) + u_i$$

Given the similarity between estimators, the OLS was selected. The results of the OLS model are given in Table 78.

Table 78: Results of the OLS regression model estimating the relationship between EQ-5D and BCVA

	Coefficients	SE	P-values
log(BCVA of BSE)	[redacted]	0.0372	0.049
log (BCVA of WSE)	[redacted]	0.0221	0.038
Age	[redacted]	0.0005	0.038
Baseline BMI	[redacted]	0.0008	0.000
Constant	[redacted]	0.134	0.000

The regression model shown was used to estimate the utilities shown in Table 79.

Table 79: Utilities as a function of BSE and WSE health states derived from OLS regression

BSE	WSE							
	>85	85-76	75-66	65-56	55-46	45-36	35-26	<26
>85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
85-76	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
75-66	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
65-56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
55-46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45-36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
35-26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

These values were estimated to correspond directly with the health states used in the economic model.

Mapping

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

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.

Details of validation of the mapping technique.

No mapping studies were performed.

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.

A systematic literature review was conducted to answer the following research questions: (1) How does DMO affect HRQoL?; (2) What utilities are attached to different levels of VA?; (3) How does treatment affect the HRQoL of patients with DMO?; (4) What disutilities are associated with treatment-related adverse events?

The search was conducted in literature databases, the websites of UK-based HTA agencies, and conference proceedings (Table 80). The searches were conducted on 6 February 2014. Publication dates were set from 1999 until the date of the search for the literature databases, for the last 10 years for HTA websites, and for the last 3 years for conference proceedings. The search was conducted using English language search terms and only articles published in English were included.

Table 80. Databases searched

Literature	HTA agencies	Conference proceedings
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) (https://ovidsp.ovid.com/autologin.cg)	SCOTLAND: Scottish Medicines Consortium (SMC) (www.scottishmedicines.org.uk/Home)	International Society For Pharmacoeconomics and Outcomes Research (ISPOR) (www.ispor.org/)
Ovid Embase (https://ovidsp.ovid.com/autologin.cg)	ENGLAND AND WALES: National Institute of Health and Care Excellence (NICE) (www.nice.org.uk/)	The Association for Research in Vision and Ophthalmology (ARVO) (www.arvo.org/; www.iovs.org/)
National Health Service Economic Evaluation Database (NHS EED) (www.crd.york.ac.uk/crdweb/)	WALES: All Wales Medicines Strategy Group (AWMSG); (www.awmsg.org/)	American Academy of Ophthalmology (AAO) (www.aao.org/)
EconLit (http://ovidsp.tx.ovid.com/)		Retina Congress (EURETINA) (www.euretina.org/default.asp)
		World Ophthalmology Congress (WOC) (www.woc2014.org/; www.icoph.org/)

The searches considered the following treatment options: aflibercept, bevacuzimab, ranibizumab, fluocinolone implant, dexamethasone implant and laser treatment. The search terms applied to the utility review concentrated on HRQoL terms, disease-related terms for DMO, vision and vision loss terms, as well as terms designed to capture studies describing adverse events and their impact on HRQoL. The search covered populations with DMO, diabetic retinopathy, visual impairment or blindness. The utility search strategies for Medline and Embase were adapted from Papaioannou and colleagues (Papaioannou et al., 2012, Papaioannou et al., 2011). In addition, the search strategy to identify common treatment-related adverse events was based on the principles of Golder and colleagues (Golder et al., 2006, Golder and Loke, 2012). Relevant MESH terms were included within the search strategies for the Medline database and their equivalent Emtree terms were used within the Embase search strategies.

Search terms for each database are shown in Appendix 10.12.

After removal of duplicates, the titles and abstracts of all references identified from the search were reviewed by two researchers during phase 1 of the study selection process. The suitability of the articles for inclusion in phase 2 was evaluated against the eligibility criteria shown in Table 81. In phase 2, full texts of the studies selected at phase 1 were reviewed and the same eligibility criteria applied. In the event of disagreement between the two reviewers during phases 1 and 2, a third reviewer was consulted. All papers included after the full text review were retained for data extraction. One reviewer carried out the data extraction and a second reviewer was consulted in case of uncertainty.

Table 81. Eligibility criteria for the utilities review

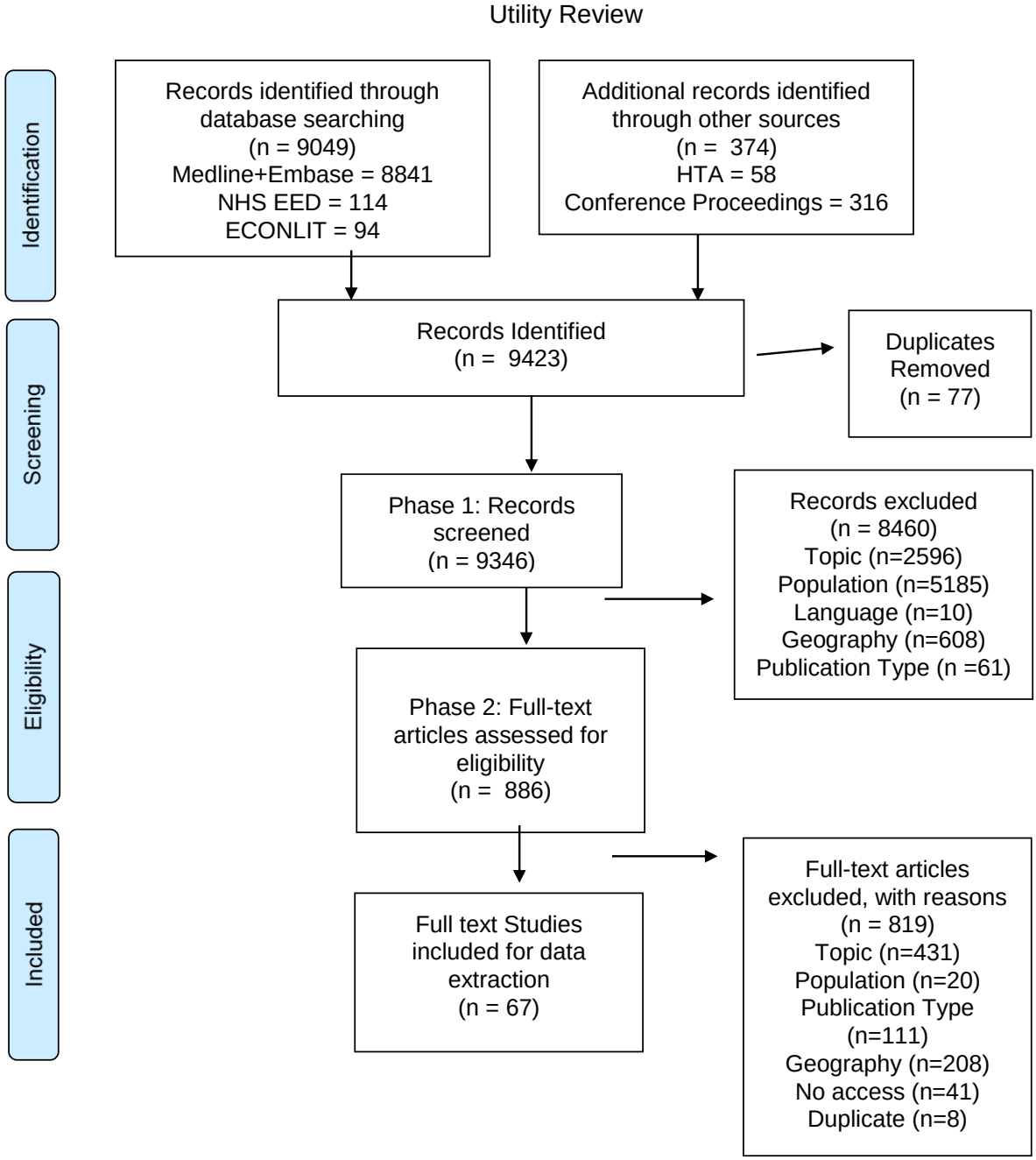
Topic	Inclusion criteria	Exclusion criteria
Population	• Vision-related illnesses • Visually impaired/blind patients • Visually impaired patients with treatment-related adverse events for Eylea, Lucentis, Rhufab, Ozurdex, Avastin, Iluvien. • Humans • Adults (≥ 18 years)	• Patient population not specific to vision-related disorders • Adverse events not related to treatments of interest (ie: Eylea, Lucentis, Rhufab, Ozurdex, Avastin, Iluvien.) or population of interest (i.e. vision-related diseases) • Not humans • Not adults (≤18 years)
Outcomes	Disutility and utility measures: 1. Health State Utility values elicited using direct methods: Time Trade Off and Standard Gamble 2. Preference-based methods: EQ-5D, HUI3, SF-6D, SF-36 Summary scores 3.Economic evaluations reporting outcomes based on Points 1 and 2 4. Disutility values relating to adverse events (e.g: endophthalmitis, cataract, vitreous haemorrhage, ocular hypertension, intraocular pressure, retinal detachment) reporting outcomes based on Points 1 and 2	• Outcomes not related to change in utility/disutility due to change in visual acuity • Vision related questionnaires (e.g: VF-14 or NEI-VFQ-25) without utility estimates (either 1 or 2) • Design of vision related questionnaires without results of relevant study population and country of interest
Study type	• Phase (II, III, IV) clinical trials • Economic evaluations • Cross sectional studies • Longitudinal studies • Registry studies • Observational studies	• Phase 1 clinical trials • Individual case reports • Systematic reviews • Non-systematic reviews • Genetic/biochemical studies
Geography[5]	Scope is within UK, Canada, Australia and Latin America	Scope is outside UK, Canada, Australia and Latin America
Publication Date	• ≥ 1999 – 2014 for peer-reviewed publications • ≥ 2010-2013 for conference proceedings • (local) guidelines: only most recent version of similar guidelines	• < 1999 for peer-reviewed publications • <2010 for conference proceedings • (local) guidelines: older versions of similar guidelines
Publication Type	• In English language • Full texts • Conference proceedings • Paper abstracts if full texts not available	• Not in English • Reviews (systematic/non-systematic; used to check references, but not extracted) • Editorials • Errata • Letters (to editor) • Notes • Comments/Commentary

A total of 9049 hits (including duplicates) were obtained from the search (Medline and Embase = 8841; NHS EED = 114; Econ Lit = 94; HTAs = 58; conference abstracts = 316). In total, 77 duplicates were removed before

[5] The scope of the search covered Australia, Canada and Colombia as well as the UK. Only studies relevant to the UK were used to derive model parameters. However, during the study selection phase, the country of study was recorded in order to allow articles from alternative countries to be consulted in case no relevant information was identified for the UK.

phase 1 review. Following the phase 1 review of titles and abstracts, 886 sources were selected for full text review. The key reasons for exclusion in phase 1 were topic (n = 2696) and population (n = 5185). Phase 2 review of the full text articles resulted in 67 articles proceeding to data extraction (NHS EED = 4, Medline and Embase = 57, HTAs = 6). The key reasons for exclusion at phase 2 were topic (n = 431) and geography (n = 208). Out of the 77 conference abstracts reviewed in phase 2, none was deemed suitable for extraction. The PRISMA flow diagram describes the final results of the utility review (Figure 69).

Figure 69. PRISMA flow diagram for utility review



A total of 67 articles went forward to data extraction, 61 full text articles from literature databases and 6 from HTA websites. Out of the 67 articles that went forward for data extraction, 67 were potentially relevant to inform the UK model.

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.

- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

Appropriateness of the study for cost-effectiveness analysis.

A summary of the full text articles reviewed is given in the Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects).

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 estimated utilities showed that the EQ-5D was not sensitive to changes in BCVA. The insensitivity of the EQ-5D to changes in BCVA has been highlighted previously(77-81). The estimates found in the literature search (Appendix 12) seemed more sensitive. Given this, utility estimates based on direct valuation techniques were preferred for the base case analysis.

Adverse events

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

Based on the review, utility decrements were applied when patients experienced adverse events. These decrements are shown in Table 82.

Table 82: Utility decrements due to adverse events

	Disutility	Source
Cataract disutility (normalised)	0.14	Brown et al, 2007
Endophthalmitis disutility (normalised)	0.00	Assumption
Retinal detachment disutility (normalised)	0.13	Busbee et al, 2002
Vitreous haemorrhage disutility (normalised)	0.02	Brandle et al, 2007
Ocular hypertension (IOP) disutility (normalised)	0.00	Assumption

Interviews with two UK ophthalmologists (Appendix 16) suggested that there may be a long term impact on quality of life of treating patients with laser such as the potential for damage to the eye where laser goes beyond the affected area. This impact could not be incorporated into the model due to the lack of data and the model structure but should be borne in mind when comparing laser to anti-VEGF therapies.

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.

QALYs are derived by multiplying the time spent in a particular model health state by a utility value associated with that health state.

The model health states are defined by vision in both eyes and therefore health state utilities (and hence QALYs) account for which is the better-seeing and worse-seeing eye. This approach requires a total of 36 utility values to account for every possible combination of best-seeing eye and worse-seeing eye.

For the base case analysis, quality of life estimates are taken from a study in AMD using the TTO value elicitation method(76). This study has been referenced and accepted in a previous NICE HTA (NICE, 2012). Three AMD vision states were produced by simulating the visual impairment associated with AMD through the use of custom-made contact lenses. Participants were randomly recruited from the healthy UK population. The TTO was anchored at

full health and immediate death. After the insertion of each lens, participants undertook five activities of daily living and completed five VF-14 items, HUI3, and TTO of the new simulated vision state. The values used are shown in Table 83.

Within the following transformation was applied to obtain utilities as a function of both eyes. The formula below was used to estimate the impact of a change in BCVA in the worse seeing eye on the patient's overall utility.

$$\Delta WSE = \Delta Both\ eyes * \left(\frac{1}{1 + \left(\frac{1}{x\%}\right)} \right)$$

Where *x* is the % impact on utility of a change in the WSE, compared to the BSE.

Table 83. Vision state utility values derived from Czoski-Murray et al (2009)

		Better-seeing eye							
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA6**	**VA7**	**VA8**
Worse-seeing eye	**VA1**	0.86							
	VA2	0.83	0.76						
	VA3	0.82	0.75	0.69					
	VA4	0.8	0.73	0.67	0.62				
	VA5	0.78	0.71	0.66	0.6	0.54			
	VA6	0.77	0.7	0.64	0.58	0.53	0.47		
	VA7	0.75	0.68	0.62	0.57	0.51	0.45	0.4	
	VA8	0.72	0.65	0.59	0.54	0.48	0.42	0.37	0.26

In addition, the model incorporates the calculation of adverse event disutilities which reflect the negative impact of adverse events on quality of life. Disutilities are subtracted from utility total QALYs, lowering the amount of QALYs a patient accrues. These decrements were presented in Table 82.

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

N/A

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 BCVA category in both eyes. Patients are assumed to have a constant HRQoL during their time in a health state, as such HRQoL is only affected by changes in BCVA 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?

N/A

[6] 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.

7.4.13 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?

The baseline HRQL was defined according to the baseline distribution of BCVA across the model cohort.

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 the ageing of the population. HRQL was only dependent on the model health state a patient is in, and changes in HRQL were driven by changes in visual acuity, not ageing. This assumption seemed reasonable as it allowed all patients to have the same HRQL gain from improved vision, regardless of age.

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.

A two eye adjustment was applied. This is described in 7.4.9.

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.

All costs associated with management of DMO are stated in section 7.5.5 (intervention and comparator), section 7.5.6 (specific to health states) and section 7.5.7 (adverse events). Costs were taken from the British National Formulary (version 66), previous ophthalmology submissions to NICE (NICE,

2014), and 2012-2013 NHS reference costs (NHS, 2013), in line with standard HTA methods.

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) were preferred to PbR in the base-case and the scenario analyses, as they provide relevant costs and volume that reflect the pattern of care delivered in the NHS. 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. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis

technology costs.

Meads and Hyde, as used in previous NICE appraisals of back-of-the-eye appraisals, estimated the costs to the NHS of blindness associated with AMD in elderly people using published and unpublished sources (Meads and Hyde, 2003). The probability of an elderly person with poor vision incurring these costs was also estimated from published sources. Costs and probabilities were estimated for outcomes such as low vision clinic assessment and

rehabilitation, acute admission for broken hip, residential or community care, tax and social security benefits and treatment of depression. The potential costs and probabilities of occurrence were multiplied and the totals summed to give an estimate of the cost of blindness in the first and subsequent years. Estimates of the cost and probabilities for each outcome are shown in Table 84. This estimated cost was updated for inflation in the ranibizumab NICE submission for DMO. The updated value (£6,066) has been used in this analysis.

Table 84. Estimated costs and probabilities of outcomes associated with blindness

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

[1]First year of blindness only; [2]~30% of residents pay for themselves. Estimated from Meads and Hyde, Br J Ophthalmol 2003;87:1201-1204 doi:10.1136/bjo.87.10.1201

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[7]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought

[7] 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.

- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

A physician survey was developed with the primary objective of understanding how often patients with clinically significant DMO who are being treated with laser and/or ranibizumab require treatment and monitoring. As secondary objectives, the survey included questions related to treatment discontinuation, treatment for adverse events, and frequency of hospital-provided transport to attend DMO appointments. The survey was developed jointly by IMS Health and Bayer, with input from an ophthalmologist employed by Bayer to ensure clinical relevance.

A full description of the analysis is provided in section 10.15 appendix 15.

An in-depth face-to-face meeting was also held with 2 consultant ophthalmologists from the north of England and West Midlands.

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.

The cost of treatment encompassed the cost of administering the intervention and the cost of monitoring. The cost of administering the intervention included the unit cost of the intervention (aflibercept, ranibizumab, dexamethasone, fluocinolone or laser treatment) plus the cost of administration. The individual

cost of each treatment and monitoring visit were multiplied by a rate reflecting the frequency of administration to estimate the expected cost of treatment and monitoring.

Resource use

Treatment: The estimated number of treatments given per year for each treatment featured in the model is shown in Table 85. The number of laser treatments are taken from the VIVID/VISTA study in year 1. The number of aflibercept injections represents the fixed dose regimen stated in the SmPC in year 1 and are assumed to be equal to ranibizumab in years 2 to 5. The SmPC for aflibercept states that treatment intervals may be extended (from bi-monthly) beyond 12 months. However, real-life data are not yet available for aflibercept.

In year 1, the number of ranibizumab injections is derived from a weighted average based on reported data on the number of injections from the studies included in the NMA, the relative risks of which are used in the model (section 6.7) The number of ranibizumab injections in years 2 to 5 is based on a survey of 30 UK ophthalmologists (see section 10.15 appendix 15)

Table 85. Number of treatments per year

No. of treatments	Year 1	Year 2	Year 3	Year 4	Year 5	Beyond (annual)	Source (year 1 only)	Source (years 2-5)
Laser treatment	2.4	1	0.8	0.4	0.3	0	VIVID/VISTA	Physician survey
Aflibercept	8	4	2.3	1.2	1	0	SmPC	Assume same as ranibizumab
Ranibizumab	7.93	4	2.3	1.2	1	0	NMA	Physician survey

Hospital visits: It is assumed that each monitoring visit will include an eye test and an OCT. Fluorescein angiographs are assumed to occur only once, at baseline, for all treatments (as a diagnostic procedure).

The number of monitoring visits for laser treatment was estimated from the VIVID/VISTA study (year 1) and the physician survey (years 2 to 5). Monitoring visits for aflibercept and ranibizumab are estimated based on their SmPCs in year 1. The SmPC for aflibercept states that monitoring is not required in the first year, given the fixed dose regimen. Until recently (EMA, September 2014), the SmPC for ranibizumab mandated monthly monitoring of visual acuity. This has recently changed but does not state the monitoring between injections is not required between injections in the first year, as is the case with aflibercept. However, it is unlikely that well established clinical practice will suddenly change. The mechanism of action and fixed dosing regimen for aflibercept indicate that less monitoring will be required in the first year compared with ranibizumab. Conservatively, the two treatments are assumed to require the same frequency of monitoring in years 2 to 5. The physician survey indicates that monthly monitoring for ranibizumab cannot be sustained in clinical practice in the long term. Similarly, the SmPC for aflibercept allows flexibility for monitoring between injections beyond 12 months, although monitoring visits are not required for the bi-monthly regimen in the first year. The estimated number of hospital visits for treatment and monitoring is shown in Table 86.

Table 86. Number of hospital visits for treatment and monitoring per year

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

The model uses a one stop strategy for all pharmaceutical treatments. A two stop strategy is.used for laser. For patients with bilateral DMO, resource use shared between eyes during a monitoring visit depends upon the treatment received (Table 87).

Table 87. Shared resource use for patients with bilateral DMO

Treatment	Resource use shared between eyes during monitoring visit	Source
Anti-VEGF/dexamethasone	87.7%	Physician survey
Laser	91.4%	Physician survey

Costs

The costs of each treatment are shown in Table 88. The costs associated with hospital visits for treatment and monitoring are shown in Table 89. The cost of an injection visit is £193.76 which assumes that the patient has an injection in addition to their standard monitoring visit (£139.22). The cost of a standard monitoring visit was made up of one non admitted consultant visit (£122) plus one ulrasound scan (<20 minutes) (£18).

Table 88. Unit costs of treatment

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

Table 89. Costs associated with hospital visits for treatment or monitoring

Treatment or monitoring visit	Cost	Source
Injection or laser visit (includes a cost for standard monitoring + injection)	£193.76	2012-13 NHS reference costs(82). Based on Aberdeen Evidence Review Group estimates for appraisal of aflibercept for CRVO (TA305) updated to 2013
Monitoring visit (outpatient cost), includes eye test, OCT, fundus photography	£139.22	2012-13 NHS reference costs. Based on Aberdeen Evidence Review Group estimates as above (TA305)
Fluorescein angiography	£117.00	BZ23Z (2012-13 NHS reference costs) as featured in the aflibercept CRVO submission (TA305) as above

There are no published sources providing detailed estimates of the cost of laser treatment per unit. Expert opinion indicates that a laser visit may take twice as long as an injection visit, doubling the resource and clinic time required. Therefore, the model considers the cost of administering laser

treatment to be equivalent to a minor vitreous retinal procedure (reference BZ23Z). Two consultant ophthalmologists (Appendix 16) were asked about the cost of administering laser. They stated that it is a costly procedure in their respective practices and would like to see a code for it included in the NHS reference costs. They cited a number of components of the cost of laser:

- Ophthalmic lasers may be purchased outright or leased on hire purchase schemes. If the laser is purchased outright, then depreciation becomes a factor. Modern types of lasers may cost up to £85,000 or more.
- Ophthalmic lasers require servicing by trained professionals: servicing contracts may be bundled with the purchase or lease of the machine or they may also be provided by contractors. According to expert opinion, contracts may be several thousands of pounds per year.
- Servicing may or may not include the cost of replacing consumables.
- Ophthalmic lasers have a life span of approximately 5-10 years.
- Senior ophthalmologists' time is required to train junior staff on the use of the lasers.

The cost used may therefore underestimate the cost of administering laser therapy and future work should consider the addition of a reference cost for this procedure or a microcosting study. An additional cost for monitoring has been included.

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.

Blindness is the only health state in the model (VA7 or VA8) associated with additional costs and resource use. The annual costs of blindness are shown in Table 84. This is described in section 7.5.5.

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.

Costs of treatment-related adverse events are shown in Table 90.

Table 90. Costs of adverse events associated with treatment

Adverse event	Cost (per patient)	Source (NHS Reference Costs, 2013)(82)
Cataract	£1,146.87	BZ02Z DC cataract extraction (£882.00) 3 outpatient consultant-led visits (3 * £88.29 = £264.87)
Endophthalmitis	£1,541.74	BZ23Z non-elective long stay 6 outpatient consultant-led visits (6 * £88.29 = £529.74)
Retinal detachment	£1,843.16	BZ22Z non-elective short stay 4 outpatient consultant-led visits (4 * £88.29 = £353.16)
Vitreous haemorrhage	£1,666.58	BZ22Z non-elective short stay 2 outpatient consultant-led visits (2 * £88.29 = £176.58)
Ocular hypertension	£3.57	Aflibercept CRVO NICE submission
Glaucoma	£1,151.00	TA301 ERG fluocinolone NICE submission (83)

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.

Travel costs for patients visiting hospital are not included in the model as, even when reimbursed, there is not a good source for these costs. There are no additional costs considered in the model.

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 following scenario analyses were conducted:

- Comparison of aflibercept and laser based on observed efficacy data from the VIVID/VISTA trials
- Utility estimates – Brown (1999), Brown (2000), EQ5D estimates from VIVID/VISTA
- Same number of monitoring visits between aflibercept and ranibizumab
- Equivalent efficacy between aflibercept and ranibizumab
- The ERG's suggested relative risk of mortality
- Comparison with dexamethasone
- Comparison with fluocinolone

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.

A one-way sensitivity analysis was conducted to examine the effect of a range of parameter values on the incremental costs, incremental outcomes and incremental cost-effectiveness ratio (Table 91).

Table 91. Variables included in the one-way sensitivity analysis

Parameter	Base case value	Lower value	Upper value	Reference
Starting age of cohort	63	58	68	±5 years
% of bilateral involvement at baseline	0.647	0.37	0.56	± 20% of the mean value
Annual incidence of FEI	0.1	0.08	0.12	± 20% of the mean value
Proportion of FE treated	0.5	0.40	0.60	± 20% of the mean value
% of shared visit between eyes (VEG-F)	0.877	0.70	1.05	± 20% of the mean value
% of shared visit between eyes (laser)	0.914	0.73	1.10	± 20% of the mean value
% of shared injection/monitoring visits (VEG-F)	0.5	0.40	0.60	± 20% of the mean value
% of shared injection/monitoring visits (laser)	0	0.00	0.00	± 20% of the mean value
Discounting				
Discounting of costs	0.035	0.02	0.06	± 20% of the mean value
Discounting of outcomes	0.035	0.02	0.06	± 20% of the mean value
Mortality				
RR of mortality for diabetic patients	1.95	1.64	2.33	(Preis et al., 2009)(68)
RR of mortality with one eye blind	1.23	1.16	1.31	(Christ et al., 2008)(12)
Costs				
Cost of aflibercept	816	652.80	979.20	± 20% of the mean value
Cost of ranibizumab	742.17	593.74	890.60	± 20% of the mean value
Cost of laser	117	93.60	140.40	± 20% of the mean value
Monitoring visit costs	139.22	111.38	167.06	± 20% of the mean value
Cataract cost	1146.87	917.50	1376.24	± 20% of the mean value
Endophthalmitis cost	1541.74	1233.39	1850.09	± 20% of the mean value
Retinal detachment cost	1843.16	1474.53	2211.79	± 20% of the mean value
Vitreous haemorrhage cost	1666.58	1333.26	1999.90	± 20% of the mean value
Glaucoma cost	1151.00	920.80	1381.20	± 20% of the mean value

Efficacy aflibercept				
Probability of gaining ≥15 letters	0.0208	0.0148	0.0284	VIVID/VISTA
Probability of gaining ≥10 letters	0.0351	0.0285	0.0421	VIVID/VISTA
Probability of losing ≥10 letters	[redacted]	[redacted]	[redacted]	VIVID/VISTA
Probability of losing ≥15 letters	0.0002	0.0000	0.0013	VIVID/VISTA
Efficacy ranibizumab				
Probability of gaining ≥15 letters	0.0148	0.0099	0.0211	RESTORE
Probability of gaining ≥10 letters	0.0295	0.0231	0.0368	RESTORE
Probability of losing ≥10 letters	0.0047	0.0017	0.0117	RESTORE
Probability of losing ≥15 letters	0.0015	0.0002	0.0049	RESTORE
Efficacy laser				
Probability of gaining ≥15 letters	0.0067	0.0042	0.0092	VIVID/VISTA
Probability of gaining ≥10 letters	0.0170	0.0136	0.0203	VIVID/VISTA
Probability of losing ≥10 letters	0.0128	0.0096	0.0158	VIVID/VISTA
Probability of losing ≥15 letters	0.0078	0.0051	0.0104	VIVID/VISTA
Off treatment decline				
Unaffected eye decline rate	0.0017	0.0013	0.0020	± 20% of the mean value
DMO eye decline rate	0.0115	0.0092	0.0138	± 20% of the mean value
Discontinuation				
Aflibercept	0.0064	0.0051	0.0076	± 20% of the mean value
Ranibizumab	0.0096	0.0076	0.0115	± 20% of the mean value
Laser	0.0085	0.0068	0.0102	± 20% of the mean value

Frequency of visits				
Aflibercept Injection year 1	8.00	6.40	9.60	± 20% of the mean value
Aflibercept Injection year 2	4.00	3.92	5.88	± 20% of the mean value
Ranibizumab Injection year 1	7.77	5.92	8.88	± 20% of the mean value
Ranibizumab Injection year 2	4.00	3.20	4.80	± 20% of the mean value
Laser year 1	2.40	1.92	2.88	± 20% of the mean value
Laser year 2	1.00	0.80	1.20	± 20% of the mean value
Aflibercept monitoring year 1	8.00	7.20	10.80	± 20% of the mean value
Aflibercept monitoring year 2	6.00	4.80	7.20	± 20% of the mean value
Aflibercept monitoring year 3	4.00	3.92	5.88	± 20% of the mean value
Aflibercept monitoring year 4	4.00	2.88	4.32	± 20% of the mean value
Aflibercept monitoring year 5	2.00	2.32	3.48	± 20% of the mean value
Ranibizumab monitoring year 1	12.00	9.60	14.40	± 20% of the mean value
Ranibizumab monitoring year 2	6.30	5.04	7.56	± 20% of the mean value
Ranibizumab monitoring year 3	4.00	3.92	5.88	± 20% of the mean value
Ranibizumab monitoring year 4	4.00	2.88	4.32	± 20% of the mean value
Ranibizumab monitoring year 5	2.00	2.32	3.48	± 20% of the mean value
Laser monitoring year 1	4.00	3.20	4.80	± 20% of the mean value
Laser monitoring year 2	4.00	3.20	4.80	± 20% of the mean value
Laser monitoring year 3	2.60	2.08	3.12	± 20% of the mean value
Laser monitoring year 4	2.20	1.76	2.64	± 20% of the mean value
Laser monitoring year 5	1.90	1.52	2.28	± 20% of the mean value

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).

Probabilistic sensitivity analysis 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 equal to 20% of the mean (point estimate) were 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 1,000 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 in Table 92.

The utilities are also included in the PSA and are varied using normal distributions and variance covariance matrices around the regression parameters.

Table 92. Variables included in the probabilistic sensitivity analysis

Input	Mean	Distribution type
% of bilateral involvement at baseline	0.465	Beta
Annual incidence of FEI	0.100	Beta
Proportion of FE treated	0.500	Beta
% of shared visit between eyes (VEG-F)	0.877	Beta
% of shared visit between eyes (laser)	0.914	Beta
% of shared injection/monitoring visits (VEG-F)	0.500	Beta
% of shared injection/monitoring visits (Laser)	0.000	Beta
Mortality		
RR of mortality for diabetic patients	1.950	Normal
RR of mortality with one eye blind	1.230	Normal
Costs		
Cost of aflibercept	816.00	Gamma
Cost of ranibizumab	742.17	Gamma
Cost of laser	117.00	Gamma
Monitoring visit costs	222.00	Gamma
Cataract cost	1146.87	Gamma
Endophthalmitis cost	1541.74	Gamma

Retinal detachment cost	1843.16	Gamma
Vitreous haemorrhage cost	1666.58	Gamma
Efficacy aflibercept		
Probability of gaining ≥15 letters	0.02081	Beta
Probability of gaining ≥10 letters	0.03512	Beta
Probability of losing ≥10 letters	[redacted]	Beta
Probability of losing ≥15 letters	0.00023	Beta
Efficacy ranibizumab		
Probability of gaining ≥15 letters	0.01475	Beta
Probability of gaining ≥10 letters	0.02952	Beta
Probability of losing ≥10 letters	0.00472	Beta
Probability of losing ≥15 letters	0.00148	Beta
Efficacy laser		
Probability of gaining ≥15 letters	0.00673	Beta
Probability of gaining ≥10 letters	0.01697	Beta
Probability of losing ≥10 letters	0.01275	Beta
Probability of losing ≥15 letters	0.00781	Beta
Off-treatment decline		
Study eye decline rate	0.00166	Beta
Unaffected eye decline rate	0.01153	Beta
Discontinuation		
Aflibercept	0.00635	Beta
Ranibizumab	0.00956	Beta
Laser	0.00851	Beta

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 mean change in BCVA at 12 months observed in VIVID/VISTA was compared with the estimated change in mean BCVA in the first year of the model. The average BCVA in the model population is estimated as the

weighted average of the midpoints of BCVA ranges which define health states. It should be noted that in the model patients' distribution at baseline is the same between arms while in the clinical trials it is different between arms. Comparison of the model and trial results indicates that the model underestimates the impact of aflibercept and laser on mean change in BCVA (Table 93).

Table 93: Summary of model results compared with clinical data

Treatment	Source	Trial results	Model results	Difference
		Mean change of BCVA from baseline after month 12, letters		
Aflibercept	VIVID/VISTA	[redacted]	[redacted]	2.3 letters
Ranibizumab	RESTORE	5.9	5.9	0 letters
Laser	VIVID/VISTA	[redacted]	[redacted]	0.5 letters

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 94: Markov trace: aflibercept arm

Study eye	Fellow eye	Year 1	Year 2	Year 3	Year 4	Year 5
1	**1**	0.0697	0.1772	0.1711	0.1629	0.1531
1	**2**	0.1919	0.4245	0.3953	0.3649	0.3344
1	**3**	0.1615	0.3604	0.3445	0.3262	0.3062
1	**4**	0.0874	0.2012	0.1996	0.1963	0.1914
1	**5**	0.0442	0.1026	0.1034	0.1039	0.1039
1	**6**	0.0168	0.0405	0.0423	0.0442	0.0459
1	**7**	0.0083	0.0197	0.0203	0.0210	0.0218
1	**8**	0.0107	0.0244	0.0243	0.0244	0.0246
2	**1**	0.1271	0.2591	0.2521	0.2428	0.2316
2	**2**	0.3553	0.6207	0.5825	0.5441	0.5058
2	**3**	0.2994	0.5270	0.5076	0.4863	0.4633
2	**4**	0.1618	0.2942	0.2942	0.2927	0.2896
2	**5**	0.0818	0.1500	0.1524	0.1549	0.1572
2	**6**	0.0310	0.0592	0.0624	0.0658	0.0694
2	**7**	0.0154	0.0289	0.0299	0.0313	0.0330
2	**8**	0.0198	0.0356	0.0359	0.0364	0.0372
3	**1**	0.4307	0.4455	0.4313	0.4137	0.3934
3	**2**	1.2892	1.0673	0.9965	0.9269	0.8591
3	**3**	1.0925	0.9061	0.8685	0.8285	0.7869

3	**4**	0.5873	0.5059	0.5032	0.4986	0.4919
3	**5**	0.2967	0.2579	0.2608	0.2639	0.2670
3	**6**	0.1113	0.1018	0.1068	0.1122	0.1179
3	**7**	0.0555	0.0496	0.0512	0.0534	0.0560
3	**8**	0.0725	0.0613	0.0614	0.0620	0.0631
4	**1**	0.3820	0.3601	0.3531	0.3439	0.3329
4	**2**	1.1515	0.8625	0.8156	0.7705	0.7269
4	**3**	0.9763	0.7322	0.7109	0.6888	0.6657
4	**4**	0.5246	0.4089	0.4119	0.4146	0.4162
4	**5**	0.2650	0.2085	0.2135	0.2194	0.2260
4	**6**	0.0993	0.0823	0.0874	0.0933	0.0998
4	**7**	0.0495	0.0401	0.0419	0.0444	0.0474
4	**8**	0.0648	0.0495	0.0502	0.0515	0.0534
5	**1**	0.1801	0.1726	0.1728	0.1729	0.1727
5	**2**	0.5426	0.4135	0.3992	0.3874	0.3770
5	**3**	0.4601	0.3511	0.3480	0.3463	0.3454
5	**4**	0.2472	0.1960	0.2017	0.2085	0.2159
5	**5**	0.1249	0.1000	0.1045	0.1103	0.1172
5	**6**	0.0468	0.0394	0.0428	0.0469	0.0518
5	**7**	0.0233	0.0192	0.0205	0.0223	0.0246
5	**8**	0.0305	0.0237	0.0246	0.0259	0.0277
6	**1**	0.0792	0.0756	0.0764	0.0777	0.0793
6	**2**	0.2388	0.1810	0.1765	0.1741	0.1732
6	**3**	0.2025	0.1537	0.1538	0.1556	0.1586
6	**4**	0.1088	0.0858	0.0892	0.0937	0.0992
6	**5**	0.0550	0.0438	0.0462	0.0496	0.0539
6	**6**	0.0206	0.0173	0.0189	0.0211	0.0238
6	**7**	0.0103	0.0084	0.0091	0.0100	0.0113
6	**8**	0.0134	0.0104	0.0109	0.0116	0.0127
7	**1**	0.0368	0.0324	0.0327	0.0333	0.0342
7	**2**	0.1115	0.0775	0.0754	0.0745	0.0747
7	**3**	0.0946	0.0658	0.0657	0.0666	0.0684
7	**4**	0.0508	0.0368	0.0381	0.0401	0.0428
7	**5**	0.0257	0.0187	0.0197	0.0212	0.0232
7	**6**	0.0096	0.0074	0.0081	0.0090	0.0103
7	**7**	0.0048	0.0036	0.0039	0.0043	0.0049
7	**8**	0.0063	0.0044	0.0046	0.0050	0.0055
8	**1**	0.0054	0.0054	0.0061	0.0073	0.0088
8	**2**	0.0164	0.0128	0.0142	0.0163	0.0192
8	**3**	0.0139	0.0109	0.0124	0.0146	0.0176
8	**4**	0.0075	0.0061	0.0072	0.0088	0.0110
8	**5**	0.0038	0.0031	0.0037	0.0046	0.0060
8	**6**	0.0014	0.0012	0.0015	0.0020	0.0026
8	**7**	0.0007	0.0006	0.0007	0.0009	0.0013
8	**8**	0.0009	0.0007	0.0009	0.0011	0.0014
DEATH		0.0173	0.0402	0.0625	0.0844	1.1057

Table 95: Markov trace: ranibizumab arm

Study eye	Fellow eye	Year 1	Year 2	Year 3	Year 4	Year 5
1	**1**	0.0457	0.1128	0.1086	0.1035	0.0977
1	**2**	0.1331	0.2930	0.2736	0.2538	0.2339
1	**3**	0.1139	0.2546	0.2446	0.2329	0.2203
1	**4**	0.0620	0.1434	0.1429	0.1413	0.1387
1	**5**	0.0315	0.0734	0.0743	0.0751	0.0755
1	**6**	0.0120	0.0291	0.0305	0.0319	0.0333
1	**7**	0.0060	0.0142	0.0147	0.0153	0.0159
1	**8**	0.0076	0.0174	0.0175	0.0176	0.0179
2	**1**	0.0980	0.1970	0.1906	0.1829	0.1743
2	**2**	0.2889	0.5118	0.4802	0.4486	0.4174
2	**3**	0.2472	0.4447	0.4292	0.4118	0.3930
2	**4**	0.1345	0.2504	0.2507	0.2498	0.2475
2	**5**	0.0682	0.1282	0.1304	0.1327	0.1348
2	**6**	0.0259	0.0508	0.0535	0.0565	0.0595
2	**7**	0.0129	0.0248	0.0258	0.0270	0.0284
2	**8**	0.0165	0.0304	0.0307	0.0312	0.0319
3	**1**	0.4135	0.4171	0.4020	0.3844	0.3652
3	**2**	1.2884	1.0838	1.0128	0.9429	0.8747
3	**3**	1.1046	0.9418	0.9053	0.8656	0.8236
3	**4**	0.5967	0.5302	0.5288	0.5250	0.5187
3	**5**	0.3022	0.2715	0.2751	0.2789	0.2824
3	**6**	0.1135	0.1075	0.1129	0.1187	0.1247
3	**7**	0.0566	0.0526	0.0544	0.0567	0.0595
3	**8**	0.0738	0.0644	0.0648	0.0655	0.0668
4	**1**	0.3802	0.3599	0.3503	0.3391	0.3266
4	**2**	1.1892	0.9352	0.8826	0.8317	0.7823
4	**3**	1.0197	0.8127	0.7889	0.7635	0.7366
4	**4**	0.5505	0.4576	0.4609	0.4631	0.4639
4	**5**	0.2788	0.2343	0.2398	0.2460	0.2526
4	**6**	0.1047	0.0928	0.0984	0.1047	0.1115
4	**7**	0.0522	0.0454	0.0474	0.0500	0.0532
4	**8**	0.0682	0.0556	0.0564	0.0578	0.0597
5	**1**	0.1851	0.1835	0.1812	0.1788	0.1762
5	**2**	0.5777	0.4768	0.4565	0.4385	0.4220
5	**3**	0.4953	0.4143	0.4080	0.4026	0.3974
5	**4**	0.2675	0.2333	0.2384	0.2442	0.2503
5	**5**	0.1355	0.1194	0.1240	0.1297	0.1363
5	**6**	0.0509	0.0473	0.0509	0.0552	0.0602
5	**7**	0.0254	0.0231	0.0245	0.0264	0.0287
5	**8**	0.0331	0.0283	0.0292	0.0305	0.0322
6	**1**	0.0834	0.0842	0.0837	0.0836	0.0837
6	**2**	0.2599	0.2188	0.2109	0.2050	0.2005
6	**3**	0.2228	0.1901	0.1886	0.1882	0.1888
6	**4**	0.1203	0.1071	0.1102	0.1142	0.1189

6	**5**	0.0609	0.0548	0.0573	0.0607	0.0648
6	**6**	0.0229	0.0217	0.0235	0.0258	0.0286
6	**7**	0.0114	0.0106	0.0113	0.0123	0.0137
6	**8**	0.0149	0.0130	0.0135	0.0142	0.0153
7	**1**	0.0394	0.0376	0.0373	0.0372	0.0374
7	**2**	0.1231	0.0978	0.0939	0.0912	0.0896
7	**3**	0.1055	0.0849	0.0840	0.0838	0.0844
7	**4**	0.0570	0.0478	0.0491	0.0508	0.0531
7	**5**	0.0289	0.0245	0.0255	0.0270	0.0289
7	**6**	0.0108	0.0097	0.0105	0.0115	0.0128
7	**7**	0.0054	0.0047	0.0050	0.0055	0.0061
7	**8**	0.0071	0.0058	0.0060	0.0063	0.0068
8	**1**	0.0067	0.0079	0.0084	0.0091	0.0103
8	**2**	0.0208	0.0205	0.0211	0.0224	0.0246
8	**3**	0.0179	0.0178	0.0188	0.0206	0.0231
8	**4**	0.0097	0.0100	0.0110	0.0125	0.0146
8	**5**	0.0049	0.0051	0.0057	0.0066	0.0079
8	**6**	0.0018	0.0020	0.0023	0.0028	0.0035
8	**7**	0.0009	0.0010	0.0011	0.0014	0.0017
8	**8**	0.0012	0.0012	0.0013	0.0016	0.0019
DEATH		0.0173	0.0402	0.0626	0.0845	1.1059

Table 96: Markov trace: laser arm

Study eye	Fellow eye	Year 1	Year 2	Year 3	Year 4	Year 5
1	**1**	0.0157	0.0361	0.0337	0.0311	0.0283
1	**2**	0.0514	0.1113	0.1026	0.0935	0.0845
1	**3**	0.0455	0.1019	0.0974	0.0919	0.0858
1	**4**	0.0254	0.0597	0.0593	0.0583	0.0567
1	**5**	0.0131	0.0315	0.0319	0.0320	0.0320
1	**6**	0.0051	0.0129	0.0135	0.0141	0.0146
1	**7**	0.0026	0.0064	0.0066	0.0069	0.0071
1	**8**	0.0032	0.0075	0.0076	0.0076	0.0077
2	**1**	0.0468	0.0890	0.0835	0.0776	0.0714
2	**2**	0.1543	0.2741	0.2541	0.2337	0.2133
2	**3**	0.1363	0.2511	0.2413	0.2296	0.2167
2	**4**	0.0759	0.1470	0.1470	0.1457	0.1432
2	**5**	0.0392	0.0776	0.0790	0.0801	0.0808
2	**6**	0.0152	0.0318	0.0336	0.0353	0.0369
2	**7**	0.0076	0.0158	0.0165	0.0172	0.0180
2	**8**	0.0095	0.0185	0.0187	0.0190	0.0194
3	**1**	0.3612	0.3118	0.2903	0.2676	0.2445
3	**2**	1.2230	0.9600	0.8830	0.8060	0.7308
3	**3**	1.0734	0.8792	0.8383	0.7921	0.7425
3	**4**	0.5903	0.5148	0.5108	0.5027	0.4907
3	**5**	0.3029	0.2716	0.2744	0.2761	0.2767

3	**6**	0.1155	0.1114	0.1166	0.1216	0.1264
3	**7**	0.0577	0.0554	0.0572	0.0593	0.0616
3	**8**	0.0740	0.0648	0.0651	0.0657	0.0666
4	**1**	0.3609	0.3200	0.3028	0.2848	0.2660
4	**2**	1.2215	0.9851	0.9212	0.8576	0.7949
4	**3**	1.0722	0.9021	0.8745	0.8429	0.8076
4	**4**	0.5898	0.5282	0.5329	0.5350	0.5338
4	**5**	0.3027	0.2787	0.2863	0.2939	0.3010
4	**6**	0.1154	0.1143	0.1217	0.1294	0.1375
4	**7**	0.0577	0.0568	0.0597	0.0631	0.0670
4	**8**	0.0739	0.0665	0.0680	0.0699	0.0724
5	**1**	0.1946	0.2017	0.1943	0.1870	0.1796
5	**2**	0.6562	0.6209	0.5911	0.5633	0.5366
5	**3**	0.5765	0.5686	0.5612	0.5537	0.5452
5	**4**	0.3177	0.3330	0.3420	0.3514	0.3604
5	**5**	0.1632	0.1757	0.1837	0.1931	0.2032
5	**6**	0.0623	0.0721	0.0781	0.0850	0.0928
5	**7**	0.0312	0.0358	0.0383	0.0415	0.0453
5	**8**	0.0398	0.0419	0.0436	0.0459	0.0489
6	**1**	0.0954	0.1099	0.1067	0.1042	0.1019
6	**2**	0.3208	0.3382	0.3246	0.3137	0.3045
6	**3**	0.2820	0.3098	0.3082	0.3083	0.3094
6	**4**	0.1556	0.1814	0.1879	0.1957	0.2045
6	**5**	0.0800	0.0957	0.1009	0.1075	0.1154
6	**6**	0.0306	0.0393	0.0429	0.0474	0.0527
6	**7**	0.0153	0.0195	0.0211	0.0231	0.0257
6	**8**	0.0195	0.0228	0.0240	0.0256	0.0278
7	**1**	0.0480	0.0574	0.0555	0.0542	0.0533
7	**2**	0.1613	0.1766	0.1689	0.1633	0.1592
7	**3**	0.1418	0.1617	0.1604	0.1605	0.1618
7	**4**	0.0782	0.0947	0.0977	0.1019	0.1070
7	**5**	0.0402	0.0500	0.0525	0.0560	0.0603
7	**6**	0.0154	0.0205	0.0223	0.0247	0.0276
7	**7**	0.0077	0.0102	0.0110	0.0120	0.0134
7	**8**	0.0098	0.0119	0.0125	0.0133	0.0145
8	**1**	0.0118	0.0202	0.0205	0.0214	0.0229
8	**2**	0.0391	0.0621	0.0623	0.0645	0.0683
8	**3**	0.0345	0.0569	0.0592	0.0634	0.0694
8	**4**	0.0191	0.0333	0.0361	0.0403	0.0459
8	**5**	0.0098	0.0176	0.0194	0.0221	0.0259
8	**6**	0.0038	0.0072	0.0082	0.0098	0.0118
8	**7**	0.0019	0.0036	0.0040	0.0048	0.0058
8	**8**	0.0024	0.0042	0.0046	0.0053	0.0062
DEATH		0.0173	0.0400	0.0625	0.0846	0.1062

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.

The three tables below (Table 97,Table 98,Table 99) show the cumulative discounted QALYs for the two treatment arms under base-case assumptions. A similar presentation format as above is provided, where cumulative QALYs are shown for annual cycle from year 1 to year 5.

Table 97: QALYs accrued over time – aflibercept arm

		Undiscounted					Discounted				
Study eye	**Fellow eye**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
1	**1**	0.060	0.152	0.147	0.140	0.132	0.059	0.144	0.134	0.123	0.112
1	**2**	0.159	0.352	0.328	0.303	0.278	0.156	0.334	0.300	0.267	0.236
1	**3**	0.132	0.296	0.283	0.267	0.251	0.129	0.280	0.258	0.236	0.214
1	**4**	0.070	0.161	0.160	0.157	0.153	0.068	0.152	0.146	0.138	0.130
1	**5**	0.034	0.080	0.081	0.081	0.081	0.034	0.076	0.074	0.071	0.069
1	**6**	0.013	0.031	0.033	0.034	0.035	0.013	0.030	0.030	0.030	0.030
1	**7**	0.006	0.015	0.015	0.016	0.016	0.006	0.014	0.014	0.014	0.014
1	**8**	0.008	0.018	0.018	0.018	0.018	0.008	0.017	0.016	0.015	0.015
2	**1**	0.105	0.215	0.209	0.202	0.192	0.103	0.204	0.191	0.178	0.164
2	**2**	0.270	0.472	0.443	0.413	0.384	0.264	0.447	0.404	0.365	0.327
2	**3**	0.225	0.395	0.381	0.365	0.347	0.220	0.374	0.348	0.322	0.296
2	**4**	0.118	0.215	0.215	0.214	0.211	0.116	0.203	0.196	0.188	0.180
2	**5**	0.058	0.107	0.108	0.110	0.112	0.057	0.101	0.099	0.097	0.095
2	**6**	0.022	0.041	0.044	0.046	0.049	0.021	0.039	0.040	0.041	0.041
2	**7**	0.010	0.020	0.020	0.021	0.022	0.010	0.019	0.019	0.019	0.019
2	**8**	0.013	0.023	0.023	0.024	0.024	0.013	0.022	0.021	0.021	0.021
3	**1**	0.353	0.365	0.354	0.339	0.323	0.347	0.346	0.323	0.299	0.274
3	**2**	0.967	0.800	0.747	0.695	0.644	0.952	0.758	0.683	0.613	0.548
3	**3**	0.754	0.625	0.599	0.572	0.543	0.742	0.592	0.547	0.504	0.462
3	**4**	0.393	0.339	0.337	0.334	0.330	0.387	0.321	0.308	0.295	0.280
3	**5**	0.196	0.170	0.172	0.174	0.176	0.193	0.161	0.157	0.154	0.150
3	**6**	0.071	0.065	0.068	0.072	0.075	0.070	0.062	0.062	0.063	0.064
3	**7**	0.034	0.031	0.032	0.033	0.035	0.034	0.029	0.029	0.029	0.030
3	**8**	0.043	0.036	0.036	0.037	0.037	0.042	0.034	0.033	0.032	0.032
4	**1**	0.306	0.288	0.282	0.275	0.266	0.301	0.273	0.258	0.243	0.227
4	**2**	0.841	0.630	0.595	0.562	0.531	0.828	0.596	0.544	0.496	0.451
4	**3**	0.654	0.491	0.476	0.461	0.446	0.645	0.464	0.435	0.407	0.379
4	**4**	0.325	0.253	0.255	0.257	0.258	0.320	0.240	0.233	0.227	0.220
4	**5**	0.159	0.125	0.128	0.132	0.136	0.157	0.118	0.117	0.116	0.115
4	**6**	0.058	0.048	0.051	0.054	0.058	0.057	0.045	0.046	0.048	0.049
4	**7**	0.028	0.023	0.024	0.025	0.027	0.028	0.022	0.022	0.022	0.023
4	**8**	0.035	0.027	0.027	0.028	0.029	0.034	0.025	0.025	0.025	0.025

5	**1**	0.140	0.135	0.135	0.135	0.135	0.138	0.127	0.123	0.119	0.115
5	**2**	0.385	0.294	0.283	0.275	0.268	0.380	0.278	0.259	0.242	0.228
5	**3**	0.304	0.232	0.230	0.229	0.228	0.299	0.219	0.210	0.201	0.194
5	**4**	0.148	0.118	0.121	0.125	0.130	0.146	0.111	0.111	0.110	0.110
5	**5**	0.067	0.054	0.056	0.060	0.063	0.066	0.051	0.052	0.053	0.054
5	**6**	0.025	0.021	0.023	0.025	0.027	0.024	0.020	0.021	0.022	0.023
5	**7**	0.012	0.010	0.010	0.011	0.013	0.012	0.009	0.010	0.010	0.011
5	**8**	0.015	0.011	0.012	0.012	0.013	0.014	0.011	0.011	0.011	0.011
6	**1**	0.061	0.058	0.059	0.060	0.061	0.060	0.055	0.054	0.053	0.052
6	**2**	0.167	0.127	0.124	0.122	0.121	0.165	0.120	0.113	0.107	0.103
6	**3**	0.130	0.098	0.098	0.100	0.102	0.128	0.093	0.090	0.088	0.086
6	**4**	0.063	0.050	0.052	0.054	0.058	0.062	0.047	0.047	0.048	0.049
6	**5**	0.029	0.023	0.024	0.026	0.029	0.029	0.022	0.022	0.023	0.024
6	**6**	0.010	0.008	0.009	0.010	0.011	0.010	0.008	0.008	0.009	0.010
6	**7**	0.005	0.004	0.004	0.005	0.005	0.005	0.004	0.004	0.004	0.004
6	**8**	0.006	0.004	0.005	0.005	0.005	0.006	0.004	0.004	0.004	0.005
7	**1**	0.028	0.024	0.024	0.025	0.026	0.027	0.023	0.022	0.022	0.022
7	**2**	0.076	0.053	0.051	0.051	0.051	0.075	0.050	0.047	0.045	0.043
7	**3**	0.059	0.041	0.041	0.041	0.042	0.058	0.039	0.037	0.036	0.036
7	**4**	0.029	0.021	0.022	0.023	0.024	0.029	0.020	0.020	0.020	0.021
7	**5**	0.013	0.010	0.010	0.011	0.012	0.013	0.009	0.009	0.010	0.010
7	**6**	0.004	0.003	0.004	0.004	0.005	0.004	0.003	0.003	0.004	0.004
7	**7**	0.002	0.001	0.002	0.002	0.002	0.002	0.001	0.001	0.002	0.002
7	**8**	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
8	**1**	0.004	0.004	0.004	0.005	0.006	0.004	0.004	0.004	0.005	0.005
8	**2**	0.011	0.008	0.009	0.011	0.012	0.010	0.008	0.008	0.009	0.011
8	**3**	0.008	0.006	0.007	0.009	0.010	0.008	0.006	0.007	0.008	0.009
8	**4**	0.004	0.003	0.004	0.005	0.006	0.004	0.003	0.004	0.004	0.005
8	**5**	0.002	0.001	0.002	0.002	0.003	0.002	0.001	0.002	0.002	0.002
8	**6**	0.001	0.001	0.001	0.001	0.001	0.001	0.000	0.001	0.001	0.001
8	**7**	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
8	**8**	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Table 98: QALYs accrued over time – ranibizumab arm

		Undiscounted					**Discounted**				
Study eye	**Fellow eye**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
1	**1**	0.039	0.097	0.093	0.089	0.084	0.038	0.092	0.085	0.078	0.071
1	**2**	0.110	0.243	0.227	0.211	0.194	0.108	0.230	0.207	0.186	0.165
1	**3**	0.093	0.209	0.201	0.191	0.181	0.091	0.198	0.183	0.168	0.154
1	**4**	0.050	0.115	0.114	0.113	0.111	0.048	0.109	0.104	0.100	0.094
1	**5**	0.025	0.057	0.058	0.059	0.059	0.024	0.054	0.053	0.052	0.050
1	**6**	0.009	0.022	0.023	0.025	0.026	0.009	0.021	0.021	0.022	0.022
1	**7**	0.004	0.011	0.011	0.011	0.012	0.004	0.010	0.010	0.010	0.010
1	**8**	0.005	0.013	0.013	0.013	0.013	0.005	0.012	0.012	0.011	0.011
2	**1**	0.081	0.163	0.158	0.152	0.145	0.080	0.155	0.145	0.134	0.123

2	**2**	0.220	0.389	0.365	0.341	0.317	0.215	0.368	0.333	0.301	0.270
2	**3**	0.185	0.334	0.322	0.309	0.295	0.181	0.316	0.294	0.272	0.251
2	**4**	0.098	0.183	0.183	0.182	0.181	0.096	0.173	0.167	0.161	0.154
2	**5**	0.048	0.091	0.093	0.094	0.096	0.047	0.086	0.085	0.083	0.081
2	**6**	0.018	0.036	0.037	0.040	0.042	0.018	0.034	0.034	0.035	0.035
2	**7**	0.009	0.017	0.018	0.018	0.019	0.009	0.016	0.016	0.016	0.016
2	**8**	0.011	0.020	0.020	0.020	0.021	0.011	0.019	0.018	0.018	0.018
3	**1**	0.339	0.342	0.330	0.315	0.299	0.334	0.324	0.301	0.278	0.255
3	**2**	0.966	0.813	0.760	0.707	0.656	0.951	0.770	0.694	0.624	0.558
3	**3**	0.762	0.650	0.625	0.597	0.568	0.750	0.615	0.571	0.527	0.484
3	**4**	0.400	0.355	0.354	0.352	0.348	0.394	0.336	0.324	0.310	0.296
3	**5**	0.199	0.179	0.182	0.184	0.186	0.196	0.170	0.166	0.162	0.159
3	**6**	0.073	0.069	0.072	0.076	0.080	0.072	0.065	0.066	0.067	0.068
3	**7**	0.035	0.033	0.034	0.035	0.037	0.035	0.031	0.031	0.031	0.031
3	**8**	0.044	0.038	0.038	0.039	0.039	0.043	0.036	0.035	0.034	0.034
4	**1**	0.304	0.288	0.280	0.271	0.261	0.299	0.273	0.256	0.239	0.222
4	**2**	0.868	0.683	0.644	0.607	0.571	0.855	0.646	0.589	0.535	0.486
4	**3**	0.683	0.544	0.529	0.512	0.494	0.673	0.515	0.483	0.451	0.420
4	**4**	0.341	0.284	0.286	0.287	0.288	0.336	0.269	0.261	0.253	0.245
4	**5**	0.167	0.141	0.144	0.148	0.152	0.165	0.133	0.131	0.130	0.129
4	**6**	0.061	0.054	0.057	0.061	0.065	0.060	0.051	0.052	0.054	0.055
4	**7**	0.030	0.026	0.027	0.029	0.030	0.029	0.024	0.025	0.025	0.026
4	**8**	0.037	0.030	0.030	0.031	0.032	0.036	0.028	0.028	0.028	0.027
5	**1**	0.144	0.143	0.141	0.139	0.137	0.142	0.135	0.129	0.123	0.117
5	**2**	0.410	0.339	0.324	0.311	0.300	0.404	0.320	0.296	0.274	0.255
5	**3**	0.327	0.273	0.269	0.266	0.262	0.322	0.259	0.246	0.234	0.223
5	**4**	0.161	0.140	0.143	0.147	0.150	0.158	0.132	0.131	0.129	0.128
5	**5**	0.073	0.064	0.067	0.070	0.074	0.072	0.061	0.061	0.062	0.063
5	**6**	0.027	0.025	0.027	0.029	0.032	0.027	0.024	0.025	0.026	0.027
5	**7**	0.013	0.012	0.013	0.013	0.015	0.013	0.011	0.011	0.012	0.012
5	**8**	0.016	0.014	0.014	0.015	0.015	0.016	0.013	0.013	0.013	0.013
6	**1**	0.064	0.065	0.064	0.064	0.064	0.063	0.061	0.059	0.057	0.055
6	**2**	0.182	0.153	0.148	0.143	0.140	0.179	0.145	0.135	0.126	0.119
6	**3**	0.143	0.122	0.121	0.120	0.121	0.140	0.115	0.110	0.106	0.103
6	**4**	0.070	0.062	0.064	0.066	0.069	0.069	0.059	0.058	0.058	0.059
6	**5**	0.032	0.029	0.030	0.032	0.034	0.032	0.027	0.028	0.028	0.029
6	**6**	0.011	0.010	0.011	0.012	0.013	0.011	0.010	0.010	0.011	0.011
6	**7**	0.005	0.005	0.005	0.006	0.006	0.005	0.005	0.005	0.005	0.005
6	**8**	0.006	0.005	0.006	0.006	0.006	0.006	0.005	0.005	0.005	0.005
7	**1**	0.030	0.028	0.028	0.028	0.028	0.029	0.027	0.026	0.025	0.024
7	**2**	0.084	0.066	0.064	0.062	0.061	0.082	0.063	0.058	0.055	0.052
7	**3**	0.065	0.053	0.052	0.052	0.052	0.064	0.050	0.048	0.046	0.044
7	**4**	0.032	0.027	0.028	0.029	0.030	0.032	0.026	0.026	0.026	0.026
7	**5**	0.015	0.012	0.013	0.014	0.015	0.014	0.012	0.012	0.012	0.013
7	**6**	0.005	0.004	0.005	0.005	0.006	0.005	0.004	0.004	0.005	0.005
7	**7**	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
7	**8**	0.003	0.002	0.002	0.002	0.003	0.003	0.002	0.002	0.002	0.002
8	**1**	0.005	0.006	0.006	0.007	0.007	0.005	0.005	0.005	0.006	0.006

8	**2**	0.014	0.013	0.014	0.015	0.016	0.013	0.013	0.012	0.013	0.014
8	**3**	0.011	0.010	0.011	0.012	0.014	0.010	0.010	0.010	0.011	0.012
8	**4**	0.005	0.005	0.006	0.007	0.008	0.005	0.005	0.005	0.006	0.007
8	**5**	0.002	0.002	0.003	0.003	0.004	0.002	0.002	0.003	0.003	0.003
8	**6**	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
8	**7**	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.000	0.001
8	**8**	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Table 99: QALYs accrued over time – laser arm

		Undiscounted					**Discounted**				
Study eye	**Fellow eye**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
1	**1**	0.013	0.031	0.029	0.027	0.024	0.013	0.029	0.027	0.024	0.021
1	**2**	0.043	0.092	0.085	0.078	0.070	0.042	0.087	0.078	0.068	0.060
1	**3**	0.037	0.084	0.080	0.075	0.070	0.036	0.079	0.073	0.066	0.060
1	**4**	0.020	0.048	0.047	0.047	0.045	0.020	0.045	0.043	0.041	0.039
1	**5**	0.010	0.025	0.025	0.025	0.025	0.010	0.023	0.023	0.022	0.021
1	**6**	0.004	0.010	0.010	0.011	0.011	0.004	0.009	0.010	0.010	0.010
1	**7**	0.002	0.005	0.005	0.005	0.005	0.002	0.005	0.005	0.005	0.005
1	**8**	0.002	0.005	0.005	0.005	0.006	0.002	0.005	0.005	0.005	0.005
2	**1**	0.039	0.074	0.069	0.064	0.059	0.038	0.070	0.063	0.057	0.050
2	**2**	0.117	0.208	0.193	0.178	0.162	0.115	0.197	0.176	0.157	0.138
2	**3**	0.102	0.188	0.181	0.172	0.163	0.100	0.178	0.165	0.152	0.138
2	**4**	0.055	0.107	0.107	0.106	0.105	0.054	0.102	0.098	0.094	0.089
2	**5**	0.028	0.055	0.056	0.057	0.057	0.027	0.052	0.051	0.050	0.049
2	**6**	0.011	0.022	0.023	0.025	0.026	0.010	0.021	0.021	0.022	0.022
2	**7**	0.005	0.011	0.011	0.012	0.012	0.005	0.010	0.010	0.010	0.010
2	**8**	0.006	0.012	0.012	0.012	0.013	0.006	0.011	0.011	0.011	0.011
3	**1**	0.296	0.256	0.238	0.219	0.201	0.292	0.242	0.218	0.193	0.171
3	**2**	0.917	0.720	0.662	0.605	0.548	0.903	0.682	0.605	0.533	0.466
3	**3**	0.741	0.607	0.578	0.547	0.512	0.729	0.574	0.528	0.482	0.436
3	**4**	0.396	0.345	0.342	0.337	0.329	0.389	0.326	0.313	0.297	0.280
3	**5**	0.200	0.179	0.181	0.182	0.183	0.197	0.170	0.165	0.161	0.155
3	**6**	0.074	0.071	0.075	0.078	0.081	0.073	0.067	0.068	0.069	0.069
3	**7**	0.036	0.034	0.035	0.037	0.038	0.035	0.033	0.032	0.032	0.032
3	**8**	0.044	0.038	0.038	0.039	0.039	0.043	0.036	0.035	0.034	0.033
4	**1**	0.289	0.256	0.242	0.228	0.213	0.284	0.242	0.221	0.201	0.181
4	**2**	0.892	0.719	0.672	0.626	0.580	0.878	0.681	0.614	0.552	0.494
4	**3**	0.718	0.604	0.586	0.565	0.541	0.707	0.572	0.535	0.498	0.460
4	**4**	0.366	0.327	0.330	0.332	0.331	0.360	0.310	0.302	0.292	0.282
4	**5**	0.182	0.167	0.172	0.176	0.181	0.179	0.158	0.157	0.155	0.154
4	**6**	0.067	0.066	0.071	0.075	0.080	0.066	0.063	0.064	0.066	0.068
4	**7**	0.033	0.032	0.034	0.036	0.038	0.032	0.031	0.031	0.032	0.033
4	**8**	0.040	0.036	0.037	0.038	0.039	0.039	0.034	0.034	0.033	0.033
5	**1**	0.152	0.157	0.152	0.146	0.140	0.149	0.149	0.138	0.129	0.119
5	**2**	0.466	0.441	0.420	0.400	0.381	0.458	0.417	0.383	0.353	0.324

5	**3**	0.381	0.375	0.370	0.365	0.360	0.374	0.355	0.338	0.322	0.306
5	**4**	0.191	0.200	0.205	0.211	0.216	0.187	0.189	0.187	0.186	0.184
5	**5**	0.088	0.095	0.099	0.104	0.110	0.087	0.090	0.091	0.092	0.093
5	**6**	0.033	0.038	0.041	0.045	0.049	0.032	0.036	0.038	0.040	0.042
5	**7**	0.016	0.018	0.020	0.021	0.023	0.016	0.017	0.018	0.019	0.020
5	**8**	0.019	0.020	0.021	0.022	0.023	0.019	0.019	0.019	0.019	0.020
6	**1**	0.073	0.085	0.082	0.080	0.078	0.072	0.080	0.075	0.071	0.067
6	**2**	0.225	0.237	0.227	0.220	0.213	0.221	0.224	0.208	0.194	0.181
6	**3**	0.181	0.198	0.197	0.197	0.198	0.177	0.188	0.180	0.174	0.168
6	**4**	0.090	0.105	0.109	0.114	0.119	0.089	0.100	0.100	0.100	0.101
6	**5**	0.042	0.051	0.053	0.057	0.061	0.042	0.048	0.049	0.050	0.052
6	**6**	0.014	0.018	0.020	0.022	0.025	0.014	0.017	0.018	0.020	0.021
6	**7**	0.007	0.009	0.009	0.010	0.012	0.007	0.008	0.009	0.009	0.010
6	**8**	0.008	0.010	0.010	0.011	0.012	0.008	0.009	0.009	0.009	0.010
7	**1**	0.036	0.043	0.042	0.041	0.040	0.035	0.041	0.038	0.036	0.034
7	**2**	0.110	0.120	0.115	0.111	0.108	0.108	0.114	0.105	0.098	0.092
7	**3**	0.088	0.100	0.099	0.099	0.100	0.086	0.095	0.091	0.088	0.085
7	**4**	0.045	0.054	0.056	0.058	0.061	0.044	0.051	0.051	0.051	0.052
7	**5**	0.021	0.025	0.027	0.029	0.031	0.020	0.024	0.024	0.025	0.026
7	**6**	0.007	0.009	0.010	0.011	0.012	0.007	0.009	0.009	0.010	0.011
7	**7**	0.003	0.004	0.004	0.005	0.005	0.003	0.004	0.004	0.004	0.005
7	**8**	0.004	0.004	0.005	0.005	0.005	0.004	0.004	0.004	0.004	0.005
8	**1**	0.008	0.015	0.015	0.015	0.016	0.008	0.014	0.013	0.014	0.014
8	**2**	0.025	0.040	0.041	0.042	0.044	0.025	0.038	0.037	0.037	0.038
8	**3**	0.020	0.034	0.035	0.037	0.041	0.020	0.032	0.032	0.033	0.035
8	**4**	0.010	0.018	0.019	0.022	0.025	0.010	0.017	0.018	0.019	0.021
8	**5**	0.005	0.008	0.009	0.011	0.012	0.005	0.008	0.008	0.009	0.011
8	**6**	0.002	0.003	0.003	0.004	0.005	0.002	0.003	0.003	0.004	0.004
8	**7**	0.001	0.001	0.001	0.002	0.002	0.001	0.001	0.001	0.002	0.002
8	**8**	0.001	0.001	0.001	0.001	0.002	0.001	0.001	0.001	0.001	0.001

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:

Tables below report discounted life years (LY) and discounted QALYs accrued for each model HS for the treatment (aflibercept) and the comparators (ranibizumab, laser). Costs were not presented in the tables below because the model structure does not disaggregate costs by health state.

Table 100: Model output (discounted) by clinical outcomes: Aflibercept

	LYs	QALYs
1,1	1.085	0.933
1,2	2.613	2.169
1,3	2.473	2.028
1,4	1.602	1.282
1,5	0.920	0.718
1,6	0.440	0.339
1,7	0.223	0.167
1,8	0.255	0.184
2,1	1.822	1.512
2,2	4.484	3.408
2,3	4.353	3.265
2,4	2.910	2.124
2,5	1.725	1.225
2,6	0.863	0.604
2,7	0.449	0.305
2,8	0.517	0.336
3,1	3.355	2.751
3,2	8.452	6.339
3,3	8.168	5.636
3,4	5.421	3.632
3,5	3.212	2.120
3,6	1.607	1.029
3,7	0.842	0.522
3,8	0.982	0.580
4,1	3.131	2.504
4,2	8.046	5.873
4,3	7.984	5.349
4,4	5.475	3.395
4,5	3.349	2.009
4,6	1.750	1.015
4,7	0.941	0.536
4,8	1.109	0.599
5,1	1.899	1.482
5,2	5.038	3.577
5,3	5.241	3.459
5,4	3.798	2.279
5,5	2.443	1.319
5,6	1.361	0.722
5,7	0.760	0.388
5,8	0.915	0.439
6,1	1.028	0.791
6,2	2.826	1.978
6,3	3.068	1.964
6,4	2.332	1.352
6,5	1.568	0.831
6,6	0.922	0.433
6,7	0.533	0.240

6,8	0.661	0.277
7,1	0.507	0.380
7,2	1.434	0.975
7,3	1.600	0.992
7,4	1.252	0.714
7,5	0.866	0.442
7,6	0.526	0.237
7,7	0.311	0.124
7,8	0.392	0.145
8,1	0.277	0.199
8,2	0.867	0.563
8,3	1.069	0.631
8,4	0.921	0.497
8,5	0.689	0.331
8,6	0.456	0.191
8,7	0.285	0.105
8,8	0.379	0.098

Table 101: Model output (discounted) by clinical outcomes: Ranibizumab

	LYs	QALYs
1,1	0.695	0.598
1,2	1.815	1.506
1,3	1.762	1.445
1,4	1.152	0.922
1,5	0.665	0.519
1,6	0.319	0.246
1,7	0.162	0.122
1,8	0.185	0.133
2,1	1.363	1.131
2,2	3.618	2.750
2,3	3.585	2.689
2,4	2.409	1.759
2,5	1.430	1.015
2,6	0.714	0.500
2,7	0.371	0.252
2,8	0.427	0.278
3,1	3.081	2.526
3,2	8.326	6.244
3,3	8.182	5.645
3,4	5.439	3.644
3,5	3.216	2.122
3,6	1.597	1.022
3,7	0.834	0.517
3,8	0.970	0.572
4,1	3.048	2.439

4,2	8.379	6.117
4,3	8.457	5.667
4,4	5.817	3.607
4,5	3.556	2.133
4,6	1.848	1.072
4,7	0.991	0.565
4,8	1.164	0.629
5,1	1.921	1.498
5,2	5.424	3.851
5,3	5.729	3.781
5,4	4.163	2.498
5,5	2.677	1.446
5,6	1.485	0.787
5,7	0.828	0.422
5,8	0.993	0.477
6,1	1.069	0.823
6,2	3.113	2.179
6,3	3.425	2.192
6,4	2.610	1.514
6,5	1.755	0.930
6,6	1.029	0.484
6,7	0.594	0.267
6,8	0.734	0.308
7,1	0.541	0.406
7,2	1.615	1.098
7,3	1.824	1.131
7,4	1.430	0.815
7,5	0.989	0.505
7,6	0.599	0.270
7,7	0.354	0.142
7,8	0.446	0.165
8,1	0.305	0.219
8,2	0.993	0.646
8,3	1.236	0.729
8,4	1.068	0.576
8,5	0.802	0.385
8,6	0.530	0.223
8,7	0.332	0.123
8,8	0.441	0.115

Table 102: Model output (discounted) by clinical outcomes: Laser

	LYs	**QALYs**
1,1	0.210	0.181
1,2	0.661	0.549
1,3	0.682	0.559
1,4	0.465	0.372
1,5	0.277	0.216

1,6	0.137	0.106
1,7	0.071	0.054
1,8	0.080	0.058
2,1	0.569	0.472
2,2	1.804	1.371
2,3	1.886	1.414
2,4	1.310	0.957
2,5	0.798	0.567
2,6	0.407	0.285
2,7	0.215	0.146
2,8	0.245	0.159
3,1	2.143	1.758
3,2	6.851	5.139
3,3	7.030	4.851
3,4	4.784	3.205
3,5	2.877	1.899
3,6	1.443	0.923
3,7	0.762	0.472
3,8	0.874	0.515
4,1	2.497	1.997
4,2	8.067	5.889
4,3	8.508	5.701
4,4	6.002	3.721
4,5	3.736	2.242
4,6	1.965	1.139
4,7	1.065	0.607
4,8	1.240	0.670
5,1	1.852	1.445
5,2	6.083	4.319
5,3	6.673	4.404
5,4	4.943	2.966
5,5	3.222	1.740
5,6	1.800	0.954
5,7	1.011	0.516
5,8	1.208	0.580
6,1	1.180	0.909
6,2	3.948	2.764
6,3	4.482	2.868
6,4	3.463	2.008
6,5	2.352	1.246
6,6	1.382	0.650
6,7	0.804	0.362
6,8	0.991	0.416
7,1	0.677	0.508
7,2	2.296	1.562
7,3	2.662	1.650
7,4	2.109	1.202
7,5	1.469	0.749

7,6	0.890	0.400
7,7	0.528	0.211
7,8	0.664	0.246
8,1	0.469	0.338
8,2	1.681	1.093
8,3	2.111	1.246
8,4	1.826	0.986
8,5	1.377	0.661
8,6	0.911	0.383
8,7	0.574	0.212
8,8	0.767	0.200

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 discounted incremental clinical and economic outcomes are reported by health states for each comparison in the tables below.

Table 103: Summary of QALY gain by health state: aflibercept vs. ranibizumab

Health state	QALY intervention (Aflibercept)	QALY comparator (Ranibizumab)	Increment	Absolute increment	% absolute increment
1,1	0.933	0.598	0.335	0.335	365%
1,2	2.169	1.506	0.662	0.662	720%
1,3	2.028	1.445	0.583	0.583	635%
1,4	1.282	0.922	0.360	0.360	392%
1,5	0.718	0.519	0.199	0.199	216%
1,6	0.339	0.246	0.093	0.093	101%
1,7	0.167	0.122	0.045	0.045	49%
1,8	0.184	0.133	0.050	0.050	55%
2,1	1.512	1.131	0.381	0.381	414%
2,2	3.408	2.750	0.658	0.658	716%
2,3	3.265	2.689	0.576	0.576	626%
2,4	2.124	1.759	0.365	0.365	398%
2,5	1.225	1.015	0.209	0.209	228%
2,6	0.604	0.500	0.104	0.104	114%
2,7	0.305	0.252	0.053	0.053	57%
2,8	0.336	0.278	0.059	0.059	64%
3,1	2.751	2.526	0.225	0.225	245%
3,2	6.339	6.244	0.095	0.095	103%
3,3	5.636	5.645	-0.010	0.010	11%
3,4	3.632	3.644	-0.012	0.012	13%
3,5	2.120	2.122	-0.002	0.002	3%
3,6	1.029	1.022	0.007	0.007	7%
3,7	0.522	0.517	0.005	0.005	5%
3,8	0.580	0.572	0.008	0.008	8%
4,1	2.504	2.439	0.066	0.066	72%
4,2	5.873	6.117	-0.243	0.243	265%
4,3	5.349	5.667	-0.317	0.317	345%
4,4	3.395	3.607	-0.212	0.212	231%
4,5	2.009	2.133	-0.124	0.124	135%
4,6	1.015	1.072	-0.057	0.057	62%
4,7	0.536	0.565	-0.029	0.029	31%
4,8	0.599	0.629	-0.030	0.030	32%
5,1	1.482	1.498	-0.016	0.016	18%
5,2	3.577	3.851	-0.274	0.274	298%
5,3	3.459	3.781	-0.322	0.322	350%
5,4	2.279	2.498	-0.219	0.219	238%
5,5	1.319	1.446	-0.126	0.126	137%
5,6	0.722	0.787	-0.066	0.066	72%
5,7	0.388	0.422	-0.034	0.034	37%
5,8	0.439	0.477	-0.037	0.037	41%
6,1	0.791	0.823	-0.032	0.032	35%
6,2	1.978	2.179	-0.201	0.201	219%
6,3	1.964	2.192	-0.229	0.229	249%
6,4	1.352	1.514	-0.161	0.161	176%

6,5	0.831	0.930	-0.099	0.099	108%
6,6	0.433	0.484	-0.050	0.050	55%
6,7	0.240	0.267	-0.027	0.027	30%
6,8	0.277	0.308	-0.031	0.031	34%
7,1	0.380	0.406	-0.026	0.026	28%
7,2	0.975	1.098	-0.123	0.123	134%
7,3	0.992	1.131	-0.138	0.138	151%
7,4	0.714	0.815	-0.101	0.101	110%
7,5	0.442	0.505	-0.063	0.063	68%
7,6	0.237	0.270	-0.033	0.033	36%
7,7	0.124	0.142	-0.017	0.017	19%
7,8	0.145	0.165	-0.020	0.020	21%
8,1	0.199	0.219	-0.020	0.020	22%
8,2	0.563	0.646	-0.082	0.082	90%
8,3	0.631	0.729	-0.098	0.098	107%
8,4	0.497	0.576	-0.079	0.079	86%
8,5	0.331	0.385	-0.054	0.054	59%
8,6	0.191	0.223	-0.031	0.031	34%
8,7	0.105	0.123	-0.017	0.017	19%
8,8	0.098	0.115	-0.016	0.016	18%

QALY, quality-adjusted life year

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 104: Summary of QALY gain by health state: aflibercept vs. laser

Health state	QALY intervention (Aflibercept)	QALY comparator (Laser)	Increment	Absolute increment	% absolute increment
1,1	0.933	0.215	0.718	0.718	184%
1,2	2.169	0.657	1.511	1.511	388%
1,3	2.028	0.681	1.347	1.347	345%
1,4	1.282	0.463	0.818	0.818	210%
1,5	0.718	0.275	0.442	0.442	113%
1,6	0.339	0.139	0.200	0.200	51%
1,7	0.167	0.072	0.096	0.096	25%
1,8	0.184	0.078	0.106	0.106	27%
2,1	1.512	0.570	0.942	0.942	242%
2,2	3.408	1.670	1.738	1.738	446%
2,3	3.265	1.759	1.506	1.506	386%
2,4	2.124	1.222	0.902	0.902	231%
2,5	1.225	0.743	0.482	0.482	124%
2,6	0.604	0.387	0.217	0.217	56%
2,7	0.305	0.204	0.102	0.102	26%
2,8	0.336	0.225	0.111	0.111	29%
3,1	2.751	2.085	0.666	0.666	171%
3,2	6.339	6.140	0.199	0.199	51%
3,3	5.636	5.925	-0.289	0.289	74%
3,4	3.632	4.029	-0.397	0.397	102%
3,5	2.120	2.453	-0.333	0.333	85%
3,6	1.029	1.240	-0.212	0.212	54%
3,7	0.522	0.649	-0.127	0.127	32%
3,8	0.580	0.718	-0.139	0.139	36%
4,1	2.504	2.440	0.065	0.065	17%
4,2	5.873	7.274	-1.401	1.401	359%
4,3	5.349	7.231	-1.882	1.882	483%
4,4	3.395	4.882	-1.488	1.488	382%
4,5	2.009	3.039	-1.029	1.029	264%
4,6	1.015	1.614	-0.599	0.599	154%
4,7	0.536	0.884	-0.348	0.348	89%
4,8	0.599	0.996	-0.397	0.397	102%
5,1	1.482	1.844	-0.362	0.362	93%
5,2	3.577	5.604	-2.027	2.027	520%
5,3	3.459	5.896	-2.436	2.436	625%
5,4	2.279	4.124	-1.845	1.845	473%
5,5	1.319	2.510	-1.191	1.191	305%
5,6	0.722	1.441	-0.720	0.720	185%
5,7	0.388	0.804	-0.416	0.416	107%
5,8	0.439	0.931	-0.492	0.492	126%
6,1	0.791	1.210	-0.418	0.418	107%
6,2	1.978	3.758	-1.780	1.780	457%
6,3	1.964	4.037	-2.073	2.073	532%
6,4	1.352	2.943	-1.591	1.591	408%

6,5	0.831	1.900	-1.068	1.068	274%
6,6	0.433	1.038	-0.605	0.605	155%
6,7	0.240	0.597	-0.357	0.357	92%
6,8	0.277	0.713	-0.435	0.435	112%
7,1	0.380	0.695	-0.315	0.315	81%
7,2	0.975	2.189	-1.213	1.213	311%
7,3	0.992	2.397	-1.405	1.405	360%
7,4	0.714	1.820	-1.106	1.106	284%
7,5	0.442	1.180	-0.738	0.738	189%
7,6	0.237	0.661	-0.424	0.424	109%
7,7	0.124	0.360	-0.236	0.236	61%
7,8	0.145	0.435	-0.290	0.290	74%
8,1	0.199	0.518	-0.319	0.319	82%
8,2	0.563	1.722	-1.158	1.158	297%
8,3	0.631	2.024	-1.393	1.393	357%
8,4	0.497	1.657	-1.160	1.160	298%
8,5	0.331	1.149	-0.818	0.818	210%
8,6	0.191	0.691	-0.500	0.500	128%
8,7	0.105	0.395	-0.290	0.290	74%
8,8	0.098	0.386	-0.287	0.287	74%
QALY, quality-adjusted life year					

Table 105: Summary of predicted resource use by category of cost: aflibercept vs. ranibizumab

Item	Cost intervention (aflibercept)	Cost comparator (ranibizumab)	Increment	Absolute increment	% absolute increment
Technology cost	[redacted]	[redacted]	-6,038	6,038	67.8%
Administration and monitoring costs	[redacted]	[redacted]	-568	568	6.4%
Adverse events costs	[redacted]	[redacted]	477	477	5.4%
Blindness costs	[redacted]	[redacted]	-2,798	2,798	31.4%
Total	[redacted]	[redacted]	-8,911	8,911	100%
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 106: Summary of predicted resource use by category of cost: aflibercept vs. laser

Item	Cost intervention (aflibercept)	Cost comparator (laser)	Increment	Absolute increment	% absolute increment
Technology cost	[redacted]	[redacted]	10,914	10,914	447.7%
Administration and monitoring costs	[redacted]	[redacted]	-213	213	8.7%
Adverse events costs	[redacted]	[redacted]	-93	93	3.8%
Blindness costs	[redacted]	[redacted]	-13,046	13,046	535.1%
Total	[redacted]	[redacted]	-2,438	2,438	100%
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					

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.

In the base-case analyses aflibercept is compared to ranibizumab and laser. Results are reported in terms of incremental cost, incremental QALY, incremental LY and incremental cost per QALY. Base-case results are reported using aflibercept PAS price ([redacted]). The results of the base-case

analyses showed that compared with ranibizumab aflibercept was associated with marginal gains in LYs (incremental LYs: 0.0144), QALYs (incremental QALYs: 0.0919). However, there are savings associated with monitoring and the cost of blindness resulting in cost-savings for the aflibercept arm (Incremental costs: £-8,737). When compared to laser, aflibercept leads to a significant improvement in QALYs gained (incremental QALYs: 0.3889) and cost savings (incremental costs: £-2,438) mainly associated with a reduction in costs associated with blindness.

Table 107: Base-case results

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

Table 108 shows that when the PAS price for aflibercept is used, it remains cost effective up to a ranibizumab price discount of 80% and cost saving up to 60%.

Table 108: Incremental cost utility ratios comparing aflibercept (PAS price) with ranibizumab at various price discount levels

Discount %	Discounted ranibizumab price	ΔCosts	ΔQALYs	ICER
0%	742.2	-8,911	0.0919	-96,997
5%	705.1	-8,181	0.0919	-89,057
10%	668.0	-7,452	0.0919	-81,117
15%	630.8	-6,723	0.0919	-73,177
20%	593.7	-5,993	0.0919	-65,237
25%	556.6	-5,264	0.0919	-57,297
30%	519.5	-4,534	0.0919	-49,357
35%	482.4	-3,805	0.0919	-41,417
40%	445.3	-3,075	0.0919	-33,477
45%	408.2	-2,346	0.0919	-25,537
50%	371.1	-1,617	0.0919	-17,597
55%	334.0	-887	0.0919	-9,657
60%	296.9	-158	0.0919	-1,717
65%	259.8	572	0.0919	6,223
70%	222.7	1,301	0.0919	14,163
75%	185.5	2,030	0.0919	22,103

80%	148.4	2,760	0.0919	30,043
85%	111.3	3,489	0.0919	37,983
90%	74.2	4,219	0.0919	45,923
95%	37.1	4,948	0.0919	53,863
100%	0.0	5,678	0.0919	61,803

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Deterministic sensitivity analysis was performed by means of one-way and multivariate sensitivity analysis.

Overall, there were 116 sensitivity analysis conducted for the base-case analysis plus nine scenario analyses. A tornado plot for the top 25 most sensitive parameters based on the net monetary benefit (NMB) measure at a willingness to pay of £30,000 per QALY was use to illustrate the results of the analyses. Note the tornado diagram reports both the OWSA and the scenario analysis; this is why for several parameters only one bar, showing either the results of “low” or the “high” variation, can be seen.

The tornado diagram (Figure 70) shows variation in the NMB from the base-case of £11,631, when aflibercept is compared to ranibizumab. Aflibercept is not the cost effective alternative only when a time horizon of 5 years is applied. The key drivers of this comparison were the time horizon, the relative efficacy for both aflibercept and ranibizumab, the cohort starting age and the number of ranibizumab injection at year 1.

The tornado diagram (Figure 71) shows variation in the NMB from the base case of £14,026 when aflibercept is compared to laser. The key drivers of this comparison were a shorter time horizon of 5 and 10 years, the starting age of the cohort and the rate at which a DMO eye visual acuity declines.

Figure 70: One-way sensitivity analysis – tornado diagram (aflibercept vs. ranibizumab)

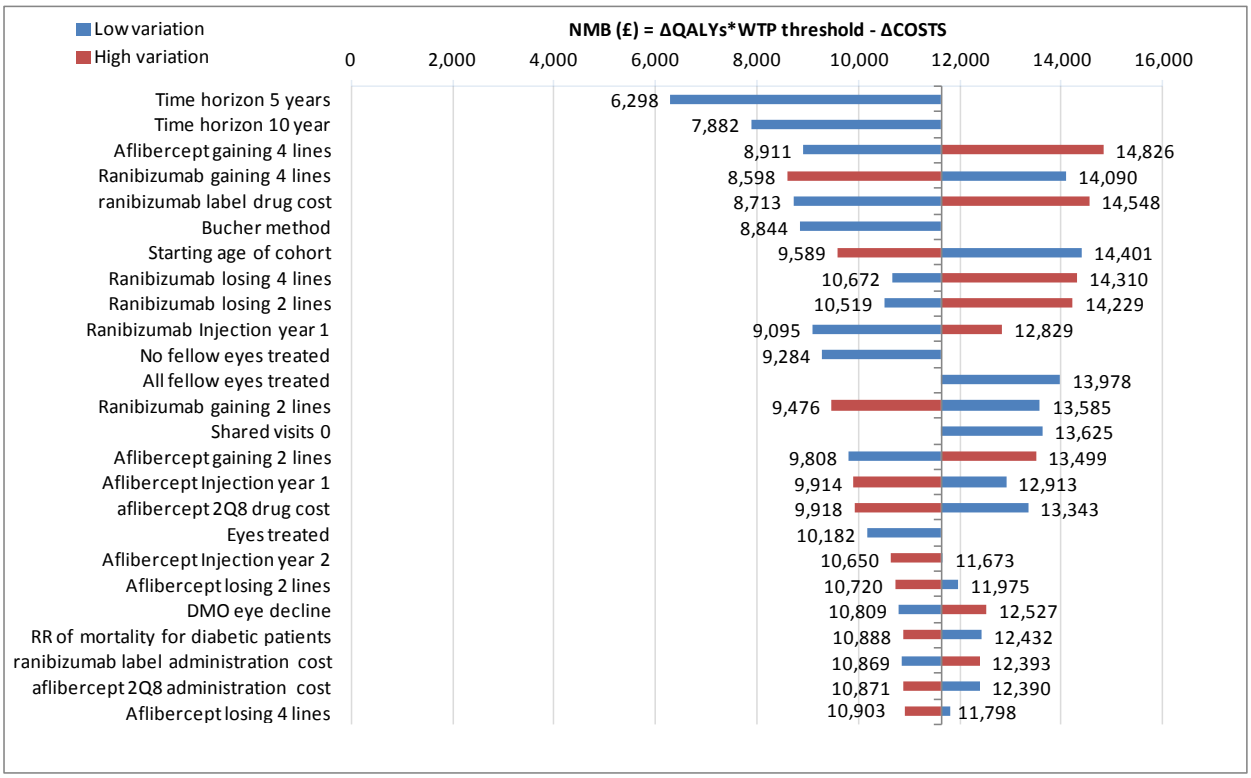
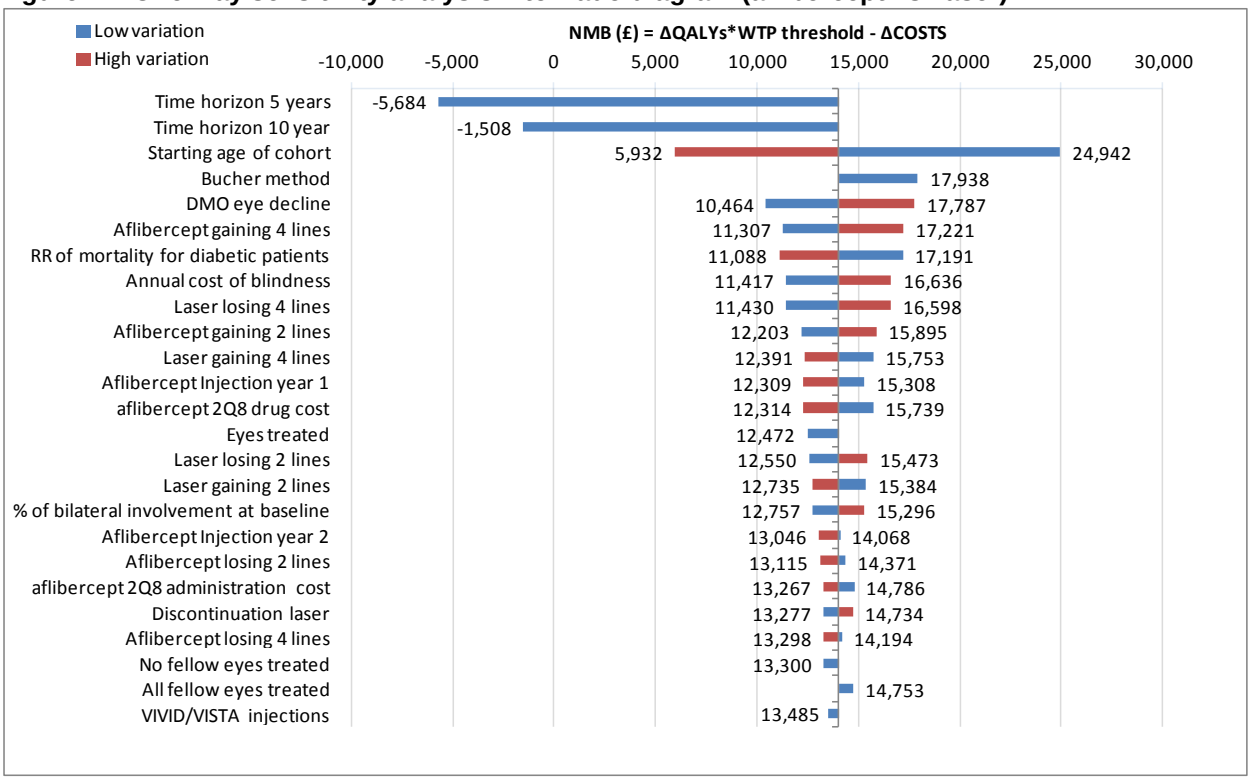


Figure 71: One-way sensitivity analysis – tornado diagram (aflibercept vs. laser)



7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The probabilistic sensitivity analysis (PSA) was run with 1,000 simulations. PSA outputs are represented graphically by i) plotting incremental cost and QALY pairs on the cost effectiveness plane (CE scatter plot) ii) presenting the likelihood of aflibercept being cost-effective at a range of willingness-to-pay (WTP) thresholds. The results of the PSA for the comparison with ranibizumab and laser are presented in the figures below. Table 109 shows the probability of ranibizumab being cost-effective, it should be noted that this is based on the PAS price. The probability that aflibercept is cost effective when compared to ranibizumab is 0.996 at a WTP threshold of £20,000 and 0.996 at a WTP threshold of £30,000. This is because over 99% of observations were dominant (less costly and more effective) due to the use of the PAS price (as requested by NICE). For the comparison with laser the aflibercept probability of being cost-effective is lower (0.971 and 0.993 at a WTP threshold of £20,000 and £30,000 respectively). Again more than 50% of observations were dominant.

Table 109: Probability of being cost-effective

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

Figure 72: cost effectiveness scatterplot - aflibercept vs. ranibizumab

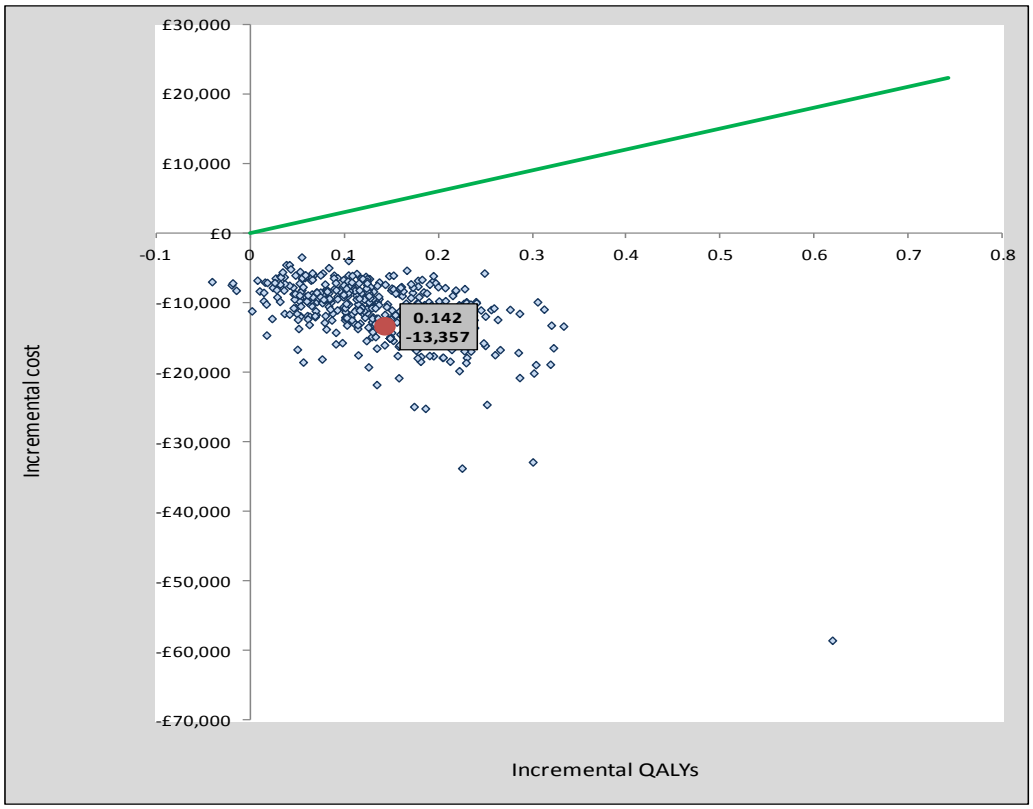


Figure 73: Cost effectiveness acceptability curve - aflibercept vs. ranibizumab

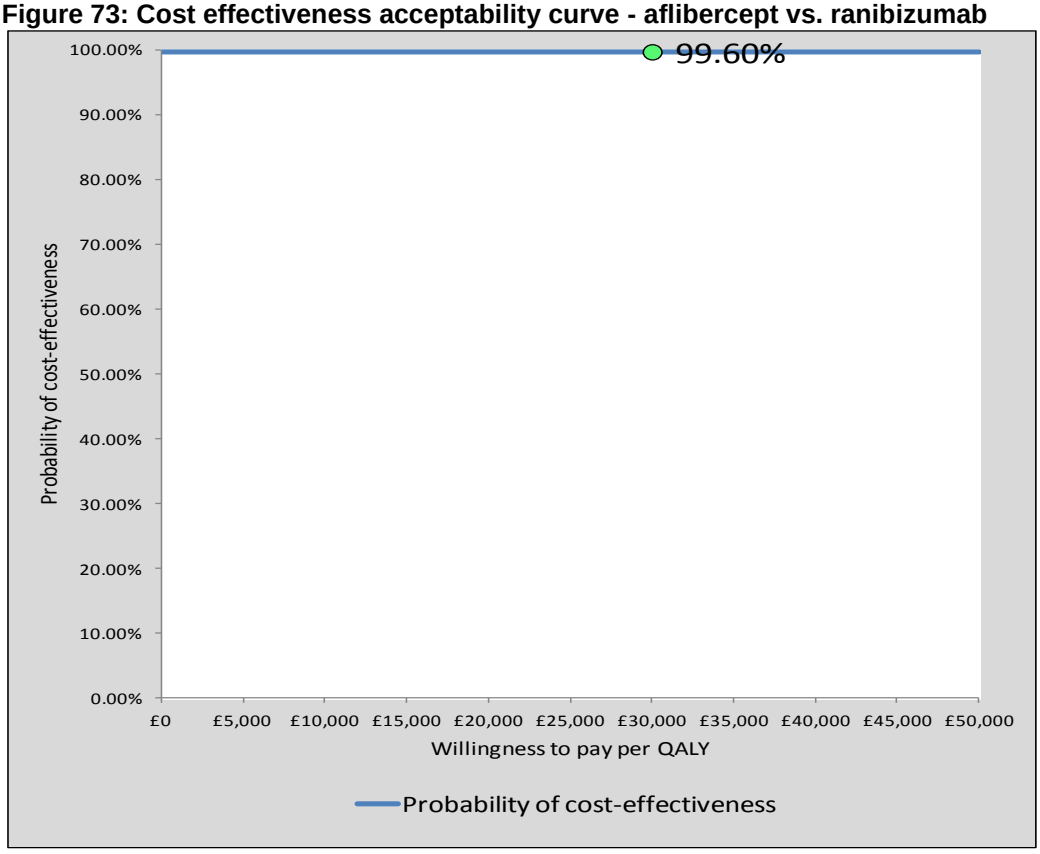


Figure 74: cost effectiveness scatterplot - aflibercept vs. laser

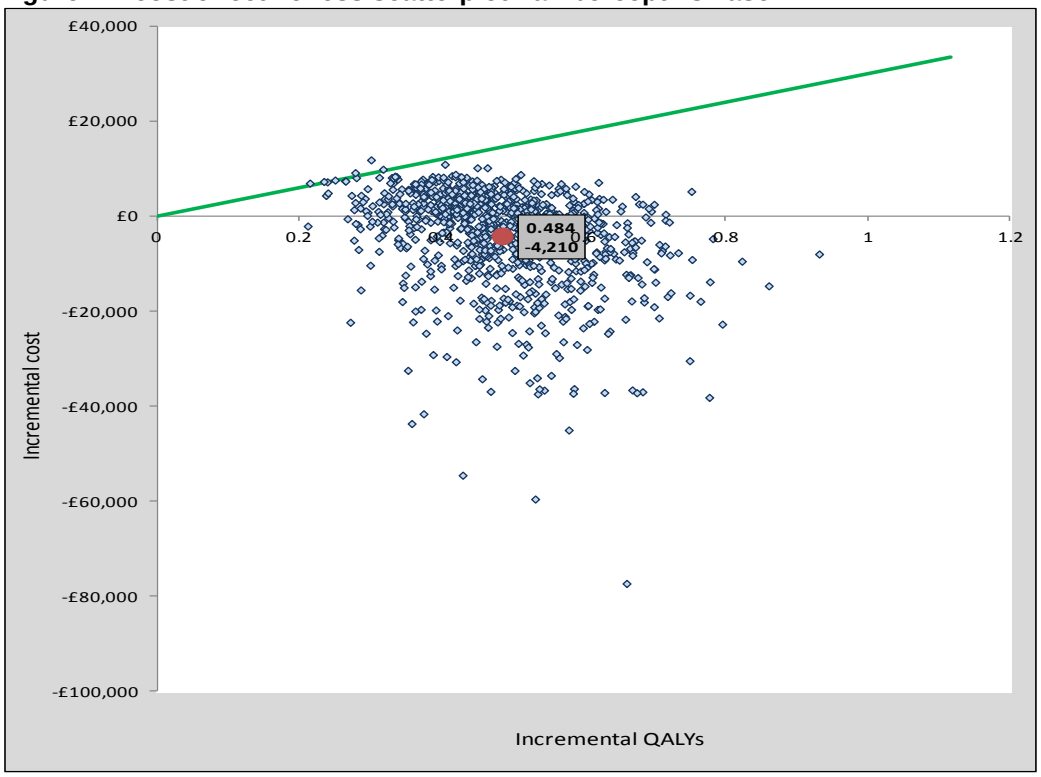
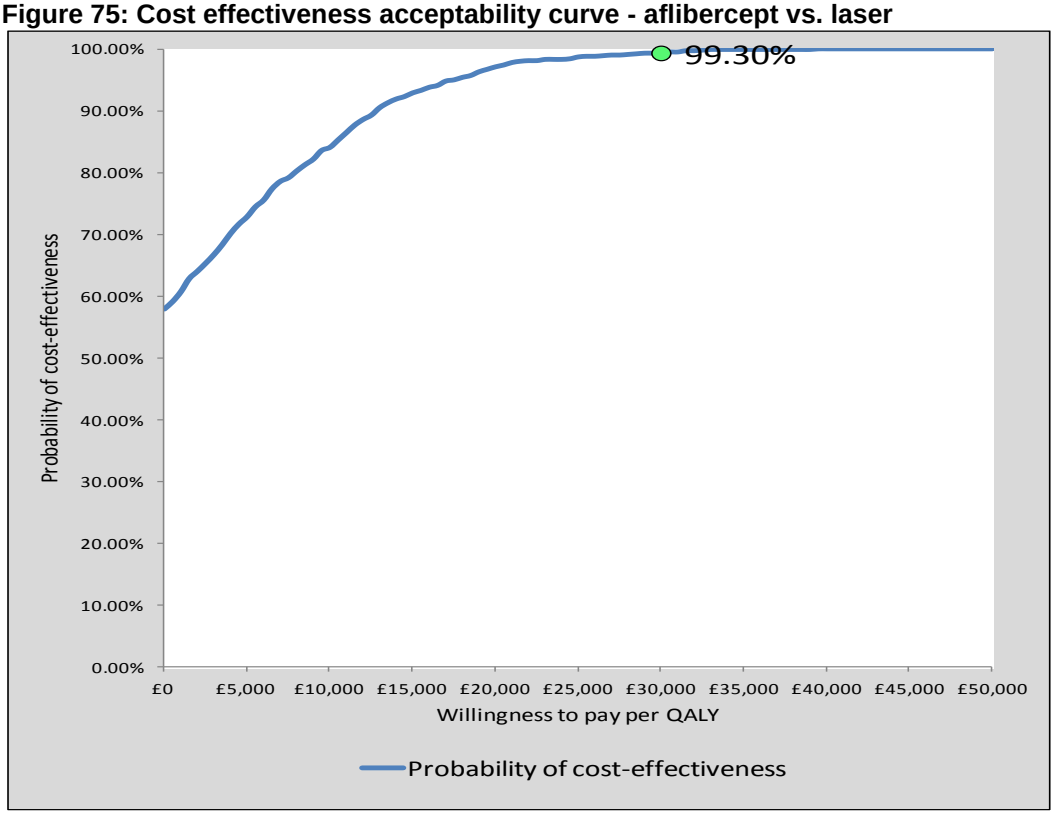


Figure 75: Cost effectiveness acceptability curve - aflibercept vs. laser



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

The results of the scenario analyses described in 7.6.1 are presented below:

Comparison of aflibercept and laser based on observed efficacy data from the VIVID/VISTA trials

Efficacy data based on the direct comparison between aflibercept and laser were obtained from the VIVID/VISTA trials. Different probabilities of gaining or losing letters were applied at each cycle during the first year. The results of this scenario analysis showed that compared to laser, aflibercept was associated with higher LYs (incremental LYs: 0.0699), QALYs (incremental QALYs: 0.4100) and lower costs (incremental costs: -£5,937). Compared to laser, aflibercept was deemed cost-effective in the treatment of DMO (ICER:£ -£14,481).

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]	11.329	7.606				
Laser	[redacted]	11.259	7.196	-5,937	0.0699	0.4100	Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Utility values from different sources

i) VIVID/VISTA utility values

This scenario was performed using the utility values from the integrated VIVID/VISTA trial analysis which were derived using the EQ-5D. Regression analyses were used to estimate mean utility values for health states. Full details on how utility values were obtained are reported in Appendix 14: EQ-5D based utilities from VIVID/VISTA. Utility values elicited through TTO methods have reported a large range between best and worst utility values, suggesting that EQ-5D may not be responsive to disease severity in this condition.

Utility values used in this scenario are reported in Table 110.

Table 110: Utilities from the VIVID/VISTA trial based on the EQ-5D

		Better seeing eye							
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA6**	**VA7**	**VA8**
Worse seeing eye	**VA1**	[redacted]							
	VA2	[redacted]	[redacted]						
	VA3	[redacted]	[redacted]	[redacted]					
	VA4	[redacted]	[redacted]	[redacted]	[redacted]				
	VA5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
	VA6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	VA7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	VA8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The results of this scenario where utility values are derived from the integrated VIVID/VISTA trial analysis, are presented in Table 111.

Table 111: Results of the scenario analysis using EQ-5D utilities from VIVID/VISTA

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**
Aflibercept	[redacted]	11.398	9.052				
Ranibizumab	[redacted]	11.386	9.035	-8,911	0.014	0.0168	Dominant
Laser	[redacted]	11.339	8.901	-2,438	0.059	0.1504	Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

ii) Brown 1999 utilities

In this scenario utility values derived from Brown 1999 (75) were applied. Utilities derived from Brown et al present a small range between the best and the worse utility values. Utility values used in this scenario are reported in Table 112.

Table 112: Utilities based on Brown 1999

		Better seeing eye							
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA6**	**VA7**	**VA8**
Worse seeing	**VA1**	0.84							
	VA2	0.84	0.84						
	VA3	0.83	0.83	0.78					

eye	**VA4**	0.83	0.83	0.78	0.78				
	VA5	0.81	0.81	0.77	0.77	0.73			
	VA6	0.80	0.80	0.76	0.76	0.72	0.68		
	VA7	0.79	0.79	0.75	0.75	0.71	0.67	0.63	
	VA8	0.78	0.78	0.74	0.74	0.70	0.66	0.62	0.58

As expected, replacing the utility values used in the base case impacted incremental QALYs only.

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**
Aflibercept	[redacted]	[redacted]	[redacted]				
Ranibizumab	[redacted]	[redacted]	[redacted]	-8,911	0.014	0.0306	Dominant
Laser	[redacted]	[redacted]	[redacted]	-2,438	0.059	0.1960	Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

iii) Brown 2000 utilities

Utilities derived from Brown 2000 (84) were used in this scenario analysis. As for Brown 1999(75), utilities values are concentrated in a smaller range between best and worst utility values when compared to Czosky-Murray (76) (Table 83).

		Better seeing eye							
		VA1	**VA2**	**VA3**	**VA4**	**VA5**	**VA6**	**VA7**	**VA8**
Worse seeing eye	**VA1**	0.89							
	VA2	0.89	0.89						
	VA3	0.87	0.87	0.81					
	VA4	0.84	0.84	0.78	0.69				
	VA5	0.81	0.81	0.75	0.66	0.56			
	VA6	0.81	0.81	0.75	0.66	0.56	0.55		
	VA7	0.80	0.80	0.74	0.65	0.55	0.54	0.52	
	VA8	0.79	0.79	0.73	0.64	0.54	0.53	0.51	0.46

Aflibercept is still dominant when compared to both ranibizumab and laser since change in the utilities source only has an impact on the final QALYs. Results of this scenario are presented in Table 113 below.

Table 113: Results of the scenario analysis using Brown 1999 utilities

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]	[redacted]	8.738				
Ranibizumab	[redacted]	[redacted]	8.648	-8,911	0.014	0.0892	Dominant
Laser	[redacted]	[redacted]	8.346	-2,438	0.059	0.3919	Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

No difference in the number of monitoring visits between aflibercept and ranibizumab

In this scenario the impact on results assuming same number of monitoring visit for aflibercept and ranibizumab was investigated. When benefits derived from a lower number of monitoring visits associated with aflibercept are not modelled, aflibercept is still dominant when compared to ranibizumab. Results are presented in Table 114 below.

Table 114: Results of the scenario assuming ranibizumab and aflibercept require equivalent monitoring

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]	11.398	7.690				
Ranibizumab	[redacted]	11.386	7.598	-8,365	0.014	0.0919	Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Equivalent efficacy and safety (aflibercept and ranibizumab)

In the base case different efficacy and safety values were applied to aflibercept and ranibizumab, they were derived from an MTC. In this scenario the same efficacy and safety were applied to aflibercept and ranibizumab. The

same number of injections was also assumed. Efficacy and resource use applied in this scenario are reported below.

Table 115: Efficacy values used in the scenario assuming equivalent efficacy between ranibizumab and aflibercept

		Base-case value	Scenario value
Efficacy input			
Year 1	Aflibercept	Gain ≥15 letters:0.021 Gain ≥10 letters:0.035 Lose ≥10 letters:[redacted] Lose ≥15 letters:0.000	Aflibercept efficacy applied to both treatments
	Ranibizumab	Gain ≥15 letters:0.015 Gain ≥10 letters:0.030 Lose ≥10 letters:0.005 Lose ≥15 letters:0.001	
Safety input			
Year 1 to 5	Aflibercept	Discontinuation: 0.0068 Cataract: 0.0041 Endophthalmitis: 0.0000 Retinal detachment:0.0003 Vitreous haemorrhage: 0.0029 Glaucoma: [redacted] IOP: 0.0026	Aflibercept safety applied to both treatments
	Ranibizumab	Discontinuation: 0.0063 Cataract: 0.0011 Endophthalmitis: 0.0003 Retinal detachment: 0.0000 Vitreous haemorrhage: 0.0000 Glaucoma: 0.0000 IOP: 0.0031	
Number of injection/treatment			
Year 1	Aflibercept	8	8
	Ranibizumab	7.93	8

Results of this cost minimisation analysis are reported below.

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) incremental (QALYs)**
Aflibercept	[redacted]	11.398	7.690				
Ranibizumab	[redacted]	11.398	7.690	-6,524	0.000	0.000	Cost saving
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

ERG's suggested relative risk of mortality

A scenario analysis was also considered using a recommendation from the ERG following a review of the decision problem. A relative risk of 1.27 from the ranibizumab submission was applied to the risk of mortality of patients with diabetes to represent the increased likelihood of death in a patient with DMO. A relative risk of 2.45 was applied to the whole population considered in the model independently on the level of visual acuity. Results of this scenario are reported in Table 116.

Table 116: Results of the scenario analysis where the ERG's suggested relative risk of mortality was used

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]	[redacted]	7.199				
Ranibizumab	[redacted]	[redacted]	7.122	-8,626	0.000	0.0768	Dominant
Laser	[redacted]	[redacted]	6.870	-1,505	-0.006	0.330	Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Comparisons with intravitreal corticosteroids

For reasons described in Section A, and the limitations of any evidence to inform a robust indirect comparison of efficacy and safety in the appropriate population, as described in Section 6.7 and 7.9, these scenarios should be considered as exploratory.

Comparing aflibercept vs. dexamethasone

This scenario analysis was included for completeness but note that as per decision problem rationale (see section 2.7), dexamethasone is not considered to be a direct comparator aflibercept in the treatment of DMO. Administration of dexamethasone to both eyes concurrently is not recommended, hence, only results derived from the one eye model are presented.

Table 117: Inputs and assumptions for the comparison of aflibercept and dexamethasone

	Aflibercept	Dexamethasone	Justification for dexamethasone input	Source (dexamethasone input)
Efficacy				
Gaining ≥15 letters	0.0208	0.0067	Equivalent to laser from VIVID/VISTA	VIVID/VISTA
Gaining ≥10 letters	0.0351	0.0200	Indirect comparison	PLACID, indirect comparison
Losing ≥10 letters	[redacted]	0.0128	Assumed equivalent to laser from VIVID/VISTA as no other available evidence	VIVID/VISTA
Losing ≥15 letters	0.0002	0.0078		VIVID/VISTA
Safety				
Discontinuation	0.0068	0.0059	Indirect comparison	PLACID, indirect comparison
Cataract	0.0041	0.0094	Indirect comparison	PLACID, indirect comparison
Endophthalmitis	0.0000	0.0003	Indirect comparison	PLACID, indirect comparison
Retinal detachment	0.0003	0.0003	Indirect comparison	PLACID, indirect comparison
Vitreous haemorrhage	0.0011	0.0000	Indirect comparison	PLACID, indirect comparison
Glaucoma	[redacted]		Indirect comparison	PLACID, indirect comparison
IOP	0.0026	0.0018	Indirect comparison	PLACID, indirect comparison
Number of treatments				
Year 1	8	3 DEX + 2.25 Laser	The dexamethasone+laser arm from the PLACID study was used in the indirect comparison	PLACID/indirect comparison
Year 2	4	2 DEX + 2.25 Laser	The dexamethasone+laser arm from the PLACID study was used in the indirect comparison	PLACID/indirect comparison

Year 3	2.3	2 DEX + 2.25 Laser	The dexamethasone+laser arm from the PLACID study was used in the indirect comparison	PLACID/indirect comparison
Year 4	1.2	0	SmPC states that dexamethasone is unproven in >7 treatments	Assumption
Year 5	1	0	SmPC states that dexamethasone is unproven in >7 treatments	Assumption
Number of monitoring visits				
Year 1	8	5	In the absence of other information, given that dexamethasone is not part of current NHS practice for DMO and has not yet been assessed by NICE, it is assumed that dexamethasone monitoring will reflect that assumed for dexamethasone in the manufacturer submission for the NICE appraisal for aflibercept for central retinal vein occlusion (TA305)	
Year 2	6.3	4		
Year 3	4	4		
Year 4	4	4		
Year 5	2	4		
Technology cost	[redacted]	£870		BNF 2014

Table 118 shows the results of the scenario analysis comparing aflibercept with dexamethasone.

Table 118: Results of the scenario analysis comparing aflibercept with dexamethasone

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]	11.398	7.552				
Dexamethasone	[redacted]	11.346	7.232	-9,888	0.052	0.320	Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 119 shows the incremental cost utility ratio at various dexamethasone price discounts.

Table 119: Incremental cost utility ratios comparing aflibercept (PAS price) with dexamethasone at various price discount levels

Discount %	Discounted price	ΔCosts	ΔQALYs	ICER
0%	870.0	-9,888	0.3197	-30,929
5%	826.5	-9,627	0.3197	-30,112
10%	783.0	-9,366	0.3197	-29,295
15%	739.5	-9,105	0.3197	-28,478
20%	696.0	-8,844	0.3197	-27,661
25%	652.5	-8,582	0.3197	-26,844
30%	609.0	-8,321	0.3197	-26,027
35%	565.5	-8,060	0.3197	-25,210
40%	522.0	-7,799	0.3197	-24,393
45%	478.5	-7,538	0.3197	-23,576
50%	435.0	-7,276	0.3197	-22,759
55%	391.5	-7,015	0.3197	-21,943
60%	348.0	-6,754	0.3197	-21,126
65%	304.5	-6,493	0.3197	-20,309
70%	261.0	-6,232	0.3197	-19,492
75%	217.5	-5,970	0.3197	-18,675
80%	174.0	-5,709	0.3197	-17,858
85%	130.5	-5,448	0.3197	-17,041
90%	87.0	-5,187	0.3197	-16,224
95%	43.5	-4,926	0.3197	-15,407
100%	0.0	-4,664	0.3197	-14,590

Comparing aflibercept vs. fluocinolone

This scenario analysis was included for completeness but note that as per the decision problem rationale (see section 2.7); fluocinolone is not considered to be a direct comparator aflibercept in the treatment of DMO. The treatment of

only the study eye is considered for this comparison since concurrent treatment of both eyes is not recommended. It should be noted that In FAME, a considerable number of participants received more one treatment during 36 months and also received off protocol treatments and additional laser treatment. The following parameters and relative values were used in this analysis (Table 120).

Table 120: Efficacy data used in the scenario comparing aflibercept with fluocinolone

	Aflibercept	Fluocinolone	Justification for fluocinolone input
Efficacy			
Gaining ≥15 letters	0.0235	0.0162	Taken from the FAME study (Campochiaro et al, 2012)
Gaining ≥10 letters	0.0377	0.0170	Equivalent to laser from VIVID/VISTA as no other data available
Losing ≥10 letters	[redacted]	0.0128	Equivalent to laser from VIVID/VISTA as no other data available
Losing ≥15 letters	0.0003	0.0078	Equivalent to laser from VIVID/VISTA as no other data available
Safety			
Discontinuation	0.0069	0.0076	Data taken from the FAME study (Campochiaro et al, 2012)
Cataract	0.0040	0.0099	
Endophthalmitis	0.0000	0.0001	
Retinal detachment	0.0012	0.0003	
Vitreous haemorrhage	0.0012	0.0000	
Glaucoma	[redacted]	0.0002	
IOP	0.0034	0.0110	
Number of treatments		0.0363	
Year 1	8	1	Assumes one injection every 2 years as, although the FAME study was 36 months duration, between 18.7-24.8% of participants in the fluocinolone arm received 2 treatments during the 36 month study. A small number received more than 2 treatments and others received off-protocol treatments. Maximum of two implants modelled.
Year 2	4	0	
Year 3	2.3	1	
Year 4	1.2	0	
Year 5	1	0	
Number of monitoring visits			
Year 1	8	4	Taken from NICE TA301 fluocinolone for chronic DMO manufacturer submission (based on 3 years)
Year 2	6.3	4	
Year 3	4	4	
Year 4	4	4	
Year 5	2	4	
Technology cost	[redacted]	£5,500	BNF 68

Results of this comparison are summarised in the table below (Table 121)

Table 121: Results of the exploratory analysis comparing aflibercept with fluocinolone

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]	11.399	7.566				
Fluocinolone	[redacted]	11.345	7.295	-12,414	0.054	0.271	Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

7.7.10 What were the main findings of each of the sensitivity analyses?

- Time horizon: When comparing aflibercept with ranibizumab and laser the incremental costs are higher in scenarios with a time horizon of 1o years or less. Over a longer time horizon incremental treatment costs incurred early in the model are offset by cost savings from severe vision loss avoided.

- The deterministic sensitivity analysis has shown that results in both comparisons were most sensitive to a shorter time horizon (explained above), the RR of gaining and losing letter for each intervention. When compared to ranibizumab one of the main drivers was the cost of ranibizumab injection, whilst in the comparator with laser was the starting age of the cohort. The OWSA also demonstrated the aflibercept remains cost effective when compared with ranibizumab and laser when varying the values of several parameters, while it was not cost effective on one occasion only, when a time horizon of 5 or 10 years is considered (aflibercept vs. laser).

- Results from the probabilistic sensitivity analysis showed that aflibercept is 99.6% and 99.3% likely to be cost effective when compared to ranibizumab and laser respectively at a willingness-to-pay of £30,000 per QALY.

- Scenario analyses were performed to test how key model assumptions impacted the base case results. Inputs tested in the scenarios included using different sources of utilities values, no difference in number of monitoring visits and no difference in efficacy and safety between aflibercept and ranibizumab, using

efficacy data from the VIVID/VISTA trials for the comparison with laser. Results have shown that aflibercept remains dominant in all the scenarios tested.

In summary, the base-case results demonstrated that compared with ranibizumab and laser, aflibercept is cost effective in the treatment of patients with DMO. The robustness of these results was confirmed by the outputs of both the OWSA and the PSA

7.7.11 What are the key drivers of the cost-effectiveness results?

Aside from differences in efficacy and safety the model is driven by factors which affect the cost of managing blind patients. All other things being equal, patients have less capacity to benefit from treatment if they amount of time they can spend blind is reduced. This leads to a smaller incremental QALY gain for aflibercept (the more effective treatment). Similarly, if the cost of managing a blind patient is reduced, the cost offset from preventing blindness is also reduced. This increases the incremental cost of treatment with aflibercept.

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.

Two clinicians and two economists were consulted during model development to ensure key assumptions (e.g. around model structure and disease progression) underlying the model were robust. Furthermore, a Physician survey was conducted to estimate values for resource use inputs. Unit costs' values were aligned with those used in previous HTA submissions in ophthalmic indications.

In addition, a check of internal validity was performed to ensure that outputs were 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 in which extreme value scenarios were tested to cross check that the model behaved logically.

The model was additionally validated against the underlying trial data as shown in 7.7.1.

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.

As reported in Section 6.5, mainly *post hoc* analyses of VIVID and VISTA were conducted in order to address the subgroups stated in the final scope. The selection of subgroups was mainly driven by the precedence of other NICE appraisals rather than any priori expectation or biological expectations. As per the total population, compared with laser, aflibercept was clinically effective across all the selected subgroups.

It was not feasible to conduct indirect comparisons between subgroups in the VIVID and VISTA study with subgroups in other studies included in the network meta-analysis, as reported in Section 6.7. In the systematic review of the literature, data was extracted for the subgroups of interest. Subgroup data were reported by LRT for DME for PRP (3m data), LRT for DME (12m data), RISE and RIDE (24m data), IVT (24 m data), VIVID VISTA (12 m data) and RESTORE (12m data). No subgroup analyses was performed for 2Q8 AFB versus 0.5mg PRN RBZ since although there was 12m data available for baseline visual acuity for VIVID/VISTA and LRT for DME the same data was not available for RESTORE (there were no standard deviations). To impute data for standard deviations data from another trial with exactly the same treatment arms was not available. No subgroup analysis was performed for 2Q8 AFB versus 2Q8 AFB versus dexamethasone implants since PLACID did not report subgroup data for prior DMO therapy or prior cataract surgery. As previously stated, the pivotal MEAD and FAME studies for intravitreal steroids could not be included in the network meta-analysis as there was no common control arm with which to indirectly compare with the VISTA/VIVID studies.

This paucity of comparative data considerably limits any consideration of clinical and cost effectiveness among subgroups versus comparators other than laser.

Figure 76: **Comparison of the visual acuity subgroups in RESTORE, VIVID and VISTA**

[FIGURE DELETED – ACADEMIC IN CONFIDENCE]

[FIGURE DELETED - ACADEMIC IN CONFIDENCE]

Versus laser and ranibizumab, the main subgroup of interest is that of baseline retinal thickness < and ≥ 400 µm. For the 2Q8 aflibercept group, outcomes were

similar (see Table 22). Mean change in BCVA from baseline at 52 weeks was [redacted] in the thinner retina group [redacted] in the thicker retina group [redacted] in the total population. For laser, in the subgroup of patients with thinner retinas, the mean change in BCVA from baseline was [redacted] for thicker retinas, [redacted] for the total population.

Table 122: Mean average change in best-corrected visual acuity letter score from baseline to week 52 – subgroup analysis (FAS, LOCF)

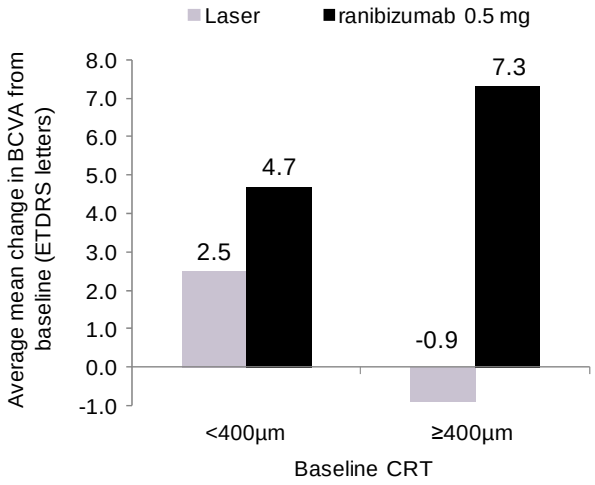
VISTA and VIVID (data on file)

Population	Treatment group	Number of patients	Mean change (SD)
Baseline CRT <400µm	VTE 2Q4	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]
	Laser	[redacted]	[redacted]
Baseline CRT ≥400µm	VTE 2Q4	[redacted]	[redacted]
	VTE 2Q8	[redacted]	[redacted]
	Laser	[redacted]	[redacted]

RESTORE (Mitchell 2011(31)):

	Ranibizumab	Ranibizumab 0.5mg +Laser	Laser
CRT (µm) <300	3.0 (N=19)	3.0 (N=20)	1.7 (N=21)
CRT (µm) 300-400	5.7 (N=32)	6.6 (N=37)	3.0 (N=34)
CRT (µm) >400	7.3 (N=62)	6.1 (N=59)	-0.9 (N=53)

NICE TA274 manufacturer's submission:
Average mean change in BCVA from baseline to M1-12, by CRT at baseline



	n	55	52	54	62
Mean BCVA at baseline (ETDRS letters)		66	69	59	61

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Patients in the subgroups considered were those with a central retinal thickness of equal or more than 400 micrometres. No other characteristics were used to select patients for this group.

7.9.3 Please describe how the statistical analysis was undertaken.

A post hoc analysis of the change in BCVA over 12 months was performed using patients baseline CRT status in the VISTA/VIVID study. The proportions of patients gaining and losing ten and fifteen letters was calculated using the same method as the main patient population.

The only change to the economic model in the subgroup analysis was a change in the probability of gaining or losing lines for patients treated with laser. The relative risks from the MTC were still used meaning that the relative efficacy of aflibercept and ranibizumab when compared to laser remained unchanged. However, the probabilities of gaining and losing letters for the anti-VEGF treatments used in the model were affected indirectly via the change in laser efficacy.

The efficacy of the aflibercept, laser and ranibizumab in the subgroup analysis is shown below:

Table 123: Efficacy data used in the sub-group analysis

Efficacy	Aflibercept	Ranibizumab	Laser
Gaining≥15 letters	[redacted]	0.018426	0.008414
Gaining≥10 letters	[redacted]	0.005210	0.014081
Losing≥10 letters	[redacted]	0.018426	0.008414
Losing≥15 letters	[redacted]	0.001737	0.009141

Aflibercept vs. fluocinolone in pseudophakes subgroup

In this comparison probabilities of gaining 10 and 15 letters were obtained from the pseudophakes subgroup in the VIVD/VISTA trial and from the FAME trial (gaining≥15 letters for fluocinolone). In terms of probabilities of losing 10 or 15 letters, they were obtained from the VIVID/VISTA overall population. This approach has been undertaken because a small number of patients (aflibercept arm n=[redacted], laser arm n=[redacted]) lost at least 10 letters in the overall population and subgroup number would have been too small to perform a meaningful comparison

Table 125: Efficacy data used in the scenario comparing aflibercept with fluocinolone in pseudophakes.

	Aflibercept	**Fluocinolone**	**Source for fluocinolone input**
Efficacy			
Gaining ≥15 letters	0.0275	0.0162	FAME trial
Gaining ≥10 letters	0.0374	0.0131	Due to lack of available information, assumed equivalent to laser from VIVID/VISTA pseudophakes subgroup
Losing ≥10 letters	[redacted]	0.0128	
Losing ≥15 letters	0.0003	0.0131	

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).

The results shown in Table 124 and **Error! Reference source not found.** are based on the subgroup data described in Table 123. There were insufficient data available from the ranibizumab clinical programme to perform a network meta-analysis or indirect comparison meaning that the relative risks for the overall patient population were used for both aflibercept and ranibizumab to ensure consistency.

Table 124: Subgroup analysis results (CRT≥400), aflibercept vs ranibizumab

	Aflibercept	Ranibizumab	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Total LYS	11.417	11.400	0.0167
Incremental cost utility ratio			Dominant

Table 125: Subgroup analysis results (CRT≥400), aflibercept vs laser

	Aflibercept	Laser	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Total LYs	11.417	11.352	0.0646

Incremental cost utility ratio			Dominant

Results also show that when aflibercept is compared to fluocinolone in pseudophakes, aflibercept is associated with lower costs and higher QALYs.

Table 126: Results of the explanatory analysis comparing aflibercept with fluocinolone in pseudophakes

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Aflibercept	[redacted]	11.402	7.596				
Fluocinolone	[redacted]	11.342	7.278	-13,662	0.060	0.318	Dominant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 127: Incremental cost utility ratios comparing aflibercept (PAS price) with fluocinolone at various price discount levels: pseudophakes subgroup

Discount %	Discounted price	ΔCosts	ΔQALYs	ICER
0%	5,500	-13,662	0.3182	-42,935
5%	5,225	-13,213	0.3182	-41,525
10%	4,950	-12,765	0.3182	-40,114
15%	4,675	-12,316	0.3182	-38,704
20%	4,400	-11,867	0.3182	-37,294
25%	4,125	-11,418	0.3182	-35,884
30%	3,850	-10,969	0.3182	-34,473
35%	3,575	-10,521	0.3182	-33,063
40%	3,300	-10,072	0.3182	-31,653
45%	3,025	-9,623	0.3182	-30,242
50%	2,750	-9,174	0.3182	-28,832
55%	2,475	-8,726	0.3182	-27,422
60%	2,200	-8,277	0.3182	-26,011
65%	1,925	-7,828	0.3182	-24,601
70%	1,650	-7,379	0.3182	-23,191
75%	1,375	-6,931	0.3182	-21,781
80%	1,100	-6,482	0.3182	-20,370
85%	825	-6,033	0.3182	-18,960
90%	550	-5,584	0.3182	-17,550
95%	275	-5,136	0.3182	-16,139
100%	0	-4,687	0.3182	-14,729

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.

The NICE scope requested the following subgroups:

- baseline visual acuity
- baseline central retinal thickness
- Treatment history (including people who have received no prior treatment, and those who have received and/or whose disease is refractory to laser photocoagulation, ranibizumab or bevacizumab)
- presence of pseudophakic lens

The subgroups described above were considered in the clinical effectiveness section as post hoc subgroup analyses were conducted for VIVID and VISTA. Similarly the possibility of indirect comparisons with other treatmetns in these subgroups were considered in the network meta-analysis section. Results from VISTA and VIVID showed that aflibercept was clinically effective in all the subgroups. Consultation with clinicians confirmed that these parameters would are unlikely to affect the relative efficacy of the main treatments considered (laser and ranibizumab). Morevover, robust comparisons were not possible due to the paucity of reported subgroup data in DMO clinical trials to enable indirect comparisons to use in the economic model. To address the issue that NICE recommends ranibizumab and fluocinolone in specific subgroups, we have conducted exploratory analyses in the subgroups available (central retinal thickness and pseudophakes). However, there is insufficient information to conduct robust analyses in the appropriate subgrups.

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?

There are currently no other studies investigating the cost effectiveness of aflibercept in patient with DMO in the UK. Analyses have been peformed in the UK comparing ranibizumab and laser, the two most relevant comparators in this indication.

Mitchell et al found that ranibizumab generated a QALY gain of 0.17 over laser over a 15 year time horizon. Using a similar time horizon the analysis presented above shows that ranibizumab generates a gain of 0.249 QALYs. This may be justified given than the current analysis considers the impact of DMO occurrence and treatment in both eyes. From a cost perspective, the results cannot be compared as Mitchell does not report a detailed breakdown of costs. The incremental cost per QALY for similar settings in the current model cannot be compared due to the difference in costing assumptions

The de novo model presented should be given additional credence because the treatment patterns to develop resource use and subsequent cost estimates are based on an up to date real world study of practising ophthamologists. The committee may note that the incremental QALY estimates are similar between the models when similar settings are compared.

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 DMO. The economic evaluation is relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 0. The NMA used

to derive RR applied in the economic evaluation (see Section 6.7) included studies of DMO only.

The cohort modelled is the patient population from the VIVID/VISTA clinical trial programme. These patients all had DMO in one or both eyes and were eligible for treatment with anti-VEGF treatments.

The modelled cohort is less compatible with the patient population eligible for steroids treatment as these treatments are restricted to second line use.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strength of the model is the inclusion of outcomes based on both eyes. A review of previous submissions to NICE in ophthalmic conditions has shown that this is an area that has been extensively critcised. This model, has been developed, following consultation with experts, to consider all possible permutations of BVCA in both the better and worse seeing eyes removing the need to make assumptions about which eye (better or worse seeing) is treated and how the other performs.

The second strength is that the resource use estimates are based on a large, UK based physician survey designed specifically to capture inputs relevant for the de novo model presented.

The main weakness of the analysis is lack of data on the impact of treatment beyond two years meaning that assumptions were required to model the impact of treatment on BCVA beyond this point.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Three analyses could further enhance the robustness and completeness of results.

Firstly, a long term observational study of aflibercept and ranibizumab in DMO should be performed to understand how long patients remain on treatment and how BCVA responds to long term anti-VEGF treatment.

Secondly, a long term observational study should be performed to understand the progression of the disease without treatment focussing on the incidence of second eye involvement and the rate of decline in BCVA post treatment.

Finally, a costing study should be performed to understand the true cost of administering laser treatment to a DMO patient.

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.

The population eligible for treatment comprises DMO patients suffering from vision impairment and meeting criteria for active treatment.

In order to estimate a projected eligible DMO population from year 2014 to 2018, the following parameters have been considered:

- Total projected England and Wales population > 18 years of age from 2014 to 2018. This was estimated on the basis of population projections (2010-based) for 2014 and a fixed annual growth rate index of 0.6% for subsequent years, calculated using projections data from the ONS(67).

- Incidence of DMO as a whole. The annual incidence rate of DMO was derived from the ranibizumab NICE submission (85) To our knowledge, no study was conducted this date to estimate the incidence of DMO in the UK. The prevalence of DMO in diabetic population was obtained from the draft scope(86).

- Eligible patients are defined as patients with DMOVI. Visual impairment (VI) is defined as BCVA between 36 and 75 letters in one or both eyes. Thus, patients with BCVA greater than 75 letters and lower than 36 letters are not eligible to start treatment. No adjustment was made for eligible DMOVI patients who may be contraindicated or unsuitable for intervention or comparator technologies, or who may decline treatment.

- The number of prevalent cases estimated in the first year is constant over time (without adjustment for mortality). The eligible population increases over time, based on the number of incident cases.

- It is assumed that 46.5% of patients are eligible for treatment of two eyes every year within a five year time horizon. The budget impact will therefore include treatment of more than one eye per patient.

The input parameters and estimated eligible patients are shown in Table 128 and Table 129.

Table 128: Parameters for estimation of eligible patients

Parameter	Estimated value	Reference
General population (+45)	44,438,964	ONS (67)
Prevalence of diabetes	6.00%	NICE draft scope for aflibercept (86)
Prevalence of DMO (Amongst the diabetic population)	7.00%	NICE draft scope for aflibercept(86)
Incidence of DMO (Amongst the diabetic population)	0.25%	Ranibizumab NICE submission(85)
Proportion of patients with fellow eye involvement at presentation	46.50%	Physician survey

Table 129: Forecast of number of eligible cases

	2014	2015	2016	2017	2018
Incident cases (eyes)	9,889	9,948	10,008	10,068	10,129
Cumulative incident cases (eyes)	9,889	19,837	29,845	39,913	50,042

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

It assumed that current treatment options are restricted to ranibizumab, as this is the only active treatment recommended for patients with DMO in the UK. The number of injections patients received is based on the data reported in section 7.5 for both aflibercept and ranibizumab.

8.3 What assumption(s) were made about market share (when relevant)?

It is assumed that the uptake of aflibercept will displace a portion of ranibizumab share every year. The assumed market share projections in the world with aflibercept are shown in Table 130 below.

Table 130: Projected market shares: world with aflibercept

	2014	**2015**	**2016**	**2017**	**2018**
Aflibercept uptake	17%	44%	56%	62%	67%
Ranibizumab	83%	56%	44%	38%	33%

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).

In addition to technology costs, the following additional costs were modelled in the cost-effectiveness analysis (see section 7.5) and were therefore also incorporated into the budget impact analysis:

- Cost of treatment administration,
- Cost of follow-up monitoring visits.

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?

Unit costs are the same as in the cost-effectiveness analysis (Section 7.5). The costs of treatment (technology and administration costs) and monitoring costs were combined with rates of occurrence reported in section 7.5. Rates used in the budget impact analysis cover the treatment and maintenance duration in the base case cost-effectiveness analysis (5 years).

8.6 Were there any estimates of resource savings? If so, what were they?

Resource savings were predicted in terms of avoidance of ophthalmologist visits, as ranibizumab was anticipated to be associated with more monitoring visits than aflibercept. To put this in perspective, for the cohort considered, over 5 year period, a total of 4 monitoring visits were avoided in the aflibercept arm relative to the ranibizumab arm.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

As shown in Table 131, the base case analysis yielded a total £[redacted] net budget impact of aflibercept over the time period 2014-2018

Table 131: Budget impact results: aflibercept vs. ranibizumab

Budget impact in world without aflibercept (£)					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Drug Costs	58,199,329	87,906,031	105,314,942	114,755,550	122,785,132
Admin and Monitoring Costs	20,797,447	31,753,193	38,691,554	45,078,395	48,642,374
Total Costs	**78,996,777**	**119,659,224**	**144,006,496**	**159,833,945**	**171,427,506**
Budget impact in world with aflibercept (£)					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Drug Costs	[redacted]				
Admin and Monitoring Costs					
Total Costs					
Net budget impact (£)					

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug Costs	[redacted]				
% change					
Admin and Monitoring Costs					
% change					
Total Costs	**150,507**	**888,351**	**2,079,920**	**3,106,239**	**3,914,695**
Total %	*0.19%*	*0.74%*	*1.44%*	*1.94%*	*2.28%*

As expected, a negative net budget impact was observed in all years following the launch of aflibercept given the lower total costs associated with aflibercept.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

N/A

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10 Appendices

10.1 Appendix 1

10.1.1 SmPC available at:
http://www.medicines.org.uk/emc/medicine/27224

10.1.2 EPAR available at: http://www.ema.europa.eu/ema/

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- *Medline*
- *Embase*
- *Medline (R) In-Process*

The Cochrane Library.

The following databases were searched from inception:

- Medline (OvidSP): 1946-2014/7/wk 5
- Medline In-Process Citations & Daily Update (OvidSP): up to 2014/8/6
- Embase (OvidSP): 1974-2014/8/7
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 7: 2014

10.2.2 The date on which the search was conducted.

See section 10.2.1

10.2.3 The date span of the search.

See section 10.2.1

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline (OvidSP): 1946-2013/10/wk 1
Searched 23.10.13

1 exp Diabetes Mellitus/ (317892)
2 Diabet$.ti,ab,ot,hw. (445731)
3 (T1dm or t1-DM or IDDM or DMI or DM1 or DM-1 or DM-I or TIDM).ti,ab,ot. (12670)
4 (T2dm or DM2 or DM-2 or T2-DM or MODY or DM2 or NIDDM or IIDM or TIIDM).ti,ab,ot. (14233)
5 ((juvenile$ or child$ or labil$ or brittle$ or ((earl$ or sudden) adj onset)) adj4 DM).ti,ab,ot. (405)
6 ((adult$ onset or matur$ or late$ or slow or stable) adj4 DM).ti,ab,ot. (303)
7 ((insulin-dependen$ or non-insulin dependen$ or noninsulin dependen$) adj4 DM).ti,ab,ot. (149)
8 ((typ$ 2 or typ$ ii or typ$ two or type2 or typeii) adj3 DM).ti,ot,ab. (2597)
9 ((keto$ or nonketo$ or autoimmun$ or auto-immun$) adj4 DM).ti,ab,ot. (121)
10 ((obes$ or non-obes$ or nonobes$) adj4 DM).ti,ab,ot. (271)
11 exp Insulin Resistance/ (55441)
12 (Insulin$ resist$ adj4 DM).ti,ab,ot. (141)
13 or/1-12 (480373)
14 Macular degeneration/ (12148)
15 Macular Oedema/ (4542)
16 Retinal Hemorrhage/ (4433)
17 ((parafovea$ or fovea$ or retina$ or macul$ or eye or eyes) adj2 (oedema$ or oedema$ or degenerat$ or swell$ or h?emorrhag$ or microaneur?sm$ or micro-aneur?sm$ or (dilat$ adj2 capillar$))).ti,ot,ab. (27644)
18 (CSME or CSMO or CME or CMO).ti,ab,ot. (4060)
19 or/14-18 (38010)
20 13 and 19 (5744)
21 diabetic retinopathy/ or ((diabet$ adj2 maculop$) or (diabet$ adj2 macul$ adj2 oedema$) or (diabet$ adj2 macul$ oedema$)).ti,ot,ab. (19288)
22 (DME or DMO).ti,ot,ab. (1657)
23 2 and 22 (596)
24 21 or 23 (19304)
25 20 or 24 (21174)
26 randomized controlled trial.pt. (387734)
27 controlled clinical trial.pt. (89736)
28 randomized.ab. (285393)
29 placebo.ab. (156181)
30 drug therapy.fs. (1760424)
31 randomly.ab. (198338)
32 trial.ab. (300539)
33 groups.ab. (1270218)
34 or/26-33 (3284645)
35 animals/ not (animals/ and humans/) (3957888)
36 34 not 35 (2797245)
37 25 and 36 (5922)

Based on Trials filter:
Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S

(editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Update – August 2014
Medline (OvidSP): 1946-2014/7/wk 5
Searched 7.8.14

Date limit applied - (201310$ or 201311$ or 201312$ or 2014$).ed,dc. or "2014".yr. (685106)

264 records retrieved

Medline In-Process Citations (OvidSP): up to 2013/10/22
Medline Daily Update (OvidSP): up to 2013/10/22
Searched 23.10.13

1 exp Diabetes Mellitus/ (424)
2 Diabet$.ti,ab,ot,hw. (26510)
3 (T1dm or t1-DM or IDDM or DMI or DM1 or DM-1 or DM-I or TIDM).ti,ab,ot. (622)
4 (T2dm or DM2 or DM-2 or T2-DM or MODY or DM2 or NIDDM or IIDM or TIIDM).ti,ab,ot. (1382)
5 ((juvenile$ or child$ or labil$ or brittle$ or ((earl$ or sudden) adj onset)) adj4 DM).ti,ab,ot. (26)
6 ((adult$ onset or matur$ or late$ or slow or stable) adj4 DM).ti,ab,ot. (22)
7 ((insulin-dependen$ or non-insulin dependen$ or noninsulin dependen$) adj4 DM).ti,ab,ot. (9)
8 ((typ$ 2 or typ$ ii or typ$ two or type2 or typeii) adj3 DM).ti,ot,ab. (279)
9 ((keto$ or nonketo$ or autoimmun$ or auto-immun$) adj4 DM).ti,ab,ot. (9)
10 ((obes$ or non-obes$ or nonobes$) adj4 DM).ti,ab,ot. (40)
11 exp Insulin Resistance/ (123)
12 (Insulin$ resist$ adj4 DM).ti,ab,ot. (13)
13 or/1-12 (26937)
14 Macular degeneration/ (17)
15 Macular Oedema/ (4)
16 Retinal Hemorrhage/ (3)
17 ((parafovea$ or fovea$ or retina$ or macul$ or eye or eyes) adj2 (oedema$ or oedema$ or degenerat$ or swell$ or h?emorrhag$ or microaneur?sm$ or micro-aneur?sm$ or (dilat$ adj2 capillar$))).ti,ot,ab. (1746)
18 (CSME or CSMO or CME or CMO).ti,ab,ot. (774)
19 or/14-18 (2463)
20 13 and 19 (368)
21 diabetic retinopathy/ or ((diabet$ adj2 maculop$) or (diabet$ adj2 macul$ adj2 oedema$) or (diabet$ adj2 macul$ oedema$)).ti,ot,ab. (185)
22 (DME or DMO).ti,ot,ab. (428)
23 2 and 22 (75)
24 21 or 23 (188)
25 20 or 24 (396)
26 randomized controlled trial.pt. (1142)
27 controlled clinical trial.pt. (66)
28 randomized.ab. (19690)
29 placebo.ab. (7425)
30 drug therapy.fs. (1717)
31 randomly.ab. (17409)
32 trial.ab. (20509)
33 groups.ab. (100905)
34 or/26-33 (135439)
35 animals/ not (animals/ and humans/) (2837)
36 34 not 35 (134847)
37 25 and 36 (89)

Based on Trials filter:
Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Update – August 2014
Medline In-Process Citations (OvidSP): up to 2014/07/6
Medline Daily Update (OvidSP): up to 2014/07/6
Searched 7.8.14

Date limit applied - (201310$ or 201311$ or 201312$ or 2014$).ed,dc. or "2014".yr.

66 records retrieved

Embase (OvidSP): 1974-2013/10/23
Searched 24.10.13

1 exp diabetes mellitus/ (579114)
2 Diabet$.ti,ab,ot,hw. (681896)
3 (T1dm or t1-DM or IDDM or DMI or DM1 or DM-1 or DM-I or TIDM).ti,ab,ot. (16400)
4 (T2dm or DM2 or DM-2 or T2-DM or MODY or DM2 or NIDDM or IIDM or TIIDM).ti,ab,ot. (21738)
5 ((juvenile$ or child$ or labil$ or brittle$ or ((earl$ or sudden) adj onset)) adj4 DM).ti,ab,ot. (591)
6 ((adult$ onset or matur$ or late$ or slow or stable) adj4 DM).ti,ab,ot. (433)
7 ((insulin-dependen$ or non-insulin dependen$ or noninsulin dependen$) adj4 DM).ti,ab,ot. (218)
8 ((typ$ 2 or typ$ ii or typ$ two or type2 or typeii) adj3 DM).ti,ot,ab. (4579)
9 ((keto$ or nonketo$ or autoimmun$ or auto-immun$) adj4 DM).ti,ab,ot. (179)
10 ((obes$ or non-obes$ or nonobes$) adj4 DM).ti,ab,ot. (633)
11 Insulin resistance/ (73984)
12 (Insulin$ resist$ adj4 DM).ti,ab,ot. (214)
13 or/1-12 (721677)
14 exp Retina maculopathy/ (35532)
15 exp Retina macula oedema/ (9946)
16 eye oedema/ (447)
17 retina macula hemorrhage/ (630)
18 ((parafovea$ or fovea$ or retina$ or macul$ or eye or eyes) adj2 (oedema$ or oedema$ or degenerat$ or swell$ or h?emorrhag$ or microaneur?sm$ or micro-aneur?sm$ or (dilat$ adj2 capillar$))).ti,ot,ab. (32853)
19 (CSME or CSMO or CME or CMO).ti,ab,ot. (7336)
20 or/14-19 (56272)
21 13 and 20 (9453)
22 exp diabetic retinopathy/ or ((diabet$ adj2 maculop$) or (diabet$ adj2 macul$ adj2 oedema$) or (diabet$ adj2 macul$ oedema$)).ti,ot,ab. (28832)
23 (DME or DMO).ti,ot,ab. (2289)
24 2 and 23 (683)
25 22 or 24 (28857)
26 21 or 25 (31846)
27 Random$.tw. or clinical trial$.mp. or exp health care quality/ (3217214)
28 animal/ (1891296)
29 animal experiment/ (1723174)

30 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5832413)
31 or/28-30 (5832413)
32 exp human/ (15046117)
33 human experiment/ (317572)
34 or/32-33 (15047558)
35 31 not (31 and 34) (4647208)
36 27 not 35 (3063570)
37 26 and 36 (7487)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE (best sens). J Med Libr Assoc 2006;94(1):41-7.

Update – August 2014
Embase (OvidSP): 1974-2014/8/8
Searched 8.8.14

Date limit applied - (2014$ or 2015$).em. or (201310$ or 201311$ or 201312$ or 2014$).dd.

575 records retrieved

Cochrane Central Register of Controlled Trials (Central) (Wiley). Issue 9:2013
http://www.thecochranelibrary.com
Searched 15.10.13

#1 MeSH descriptor: [Diabetes Mellitus] explode all trees 14750
#2 Diabet*:ti,ab,kw 26235
#3 (T1dm or t1-DM or IDDM or DMI or DM1 or DM-1 or DM-I or TIDM):ti,ab,kw 725
#4 (T2dm or DM2 or DM-2 or T2-DM or MODY or NIDDM or IIDM or TIIDM):ti,ab,kw 1472
#5 ((juvenile* or child* or labil* or brittle* or ((earl* or sudden) near/1 onset)) near/4 DM):ti,ab,kw 26
#6 (((adult* near/2 onset) or matur* or late* or slow or stable) near/4 DM):ti,ab,kw 15
#7 (((insulin near/2 dependen*) or (non-insulin near/2 dependen*) or (noninsulin near/2 dependen*)) near/4 DM):ti,ab,kw 33
#8 (("typ* 2" or "typ* ii" or "typ* two" or type2 or typeii) near/3 DM):ti,ab,kw 251
#9 ((keto* or nonketo* or autoimmun* or auto-immun*) near/4 DM):ti,ab,kw 1
#10 ((obes* or "non obes*" or nonobes*) near/4 DM):ti,ab,kw 21
#11 MeSH descriptor: [Insulin Resistance] explode all trees 2581
#12 ((Insulin* near/2 resist*) near/4 DM):ti,ab,kw 5
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 27972
#14 MeSH descriptor: [Macular Degeneration] this term only 607
#15 MeSH descriptor: [Macular Oedema] explode all trees 401
#16 MeSH descriptor: [Retinal Hemorrhage] this term only 45
#17 ((parafovea* or fovea* or retina* or macul* or eye or eyes) near/2 (oedema* or oedema* or degenerat* or swell* or h*emorrhag* or microaneur?sm* or micro-aneur?sm* or (dilat* near/2 capillar*))):ti,ab,kw 2248
#18 (CSME or CSMO or CME or CMO):ti,ab,kw 281
#19 #14 or #15 or #16 or #17 or #18 2363
#20 #13 and #19 663
#21 MeSH descriptor: [Diabetic Retinopathy] this term only 854
#22 ((diabet* near/2 maculop*) or (diabet* near/2 macul* near/2 oedema*) or (diabet* near/2 macul* oedema*)):ti,ab,kw 404
#23 (DME or DMO):ti,ab,kw 143
#24 #2 and #23 134

#25 #21 or #22 or #24 1051
#26 #20 or #25 1233

CENTRAL search retrieved 1129 references.

Update – August 2014
Cochrane Central Register of Controlled Trials (Central) (Wiley). Issue 7: 2014/7
Searched 8.8.14

CENTRAL search retrieved 1287 references (158 new records). No date limit applied, search strategy was just re-run.

Update – August 2014

Pubmed top up search

PubMed (https://www.ncbi.nlm.nih.gov/pubmed): up to 12.8.2014
Searched 12.8.14

#23 #21 AND #22 60

#22 ("2013/10/23"[Date - Publication] : "3000"[Date - Publication]) 921421

#21 #19 AND #20 486 05:52:53

#20 (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]) 1807638

#19 #14 OR #18 20789

#18 #16 OR #17 20043

#17 (DME OR DMO[Title/Abstract]) 2132

#16 "Diabetic Retinopathy"[Mesh] 18390

#14 #12 AND #13 3348

#13 #7 OR #9 OR #11 19712

#12 #3 OR #4 472015

#11 "Retinal Hemorrhage"[Mesh] 4370

#9 "Macular Edema"[Mesh] 4180

#7 "Macular Degeneration"[Mesh] 15701

#4 diabet*[Title/Abstract] 419760

#3 "Diabetes Mellitus"[Mesh] 311138

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Supplementary searches were carried out to identify grey literature, completed and ongoing trials:

- NIH ClinicalTrials.gov (Internet): up to 2014/8/7 http://www.clinicaltrials.gov
- metaRegister of Current Controlled Trials (mRCT) (Internet): up to 2014/8/7 http://www.controlled-trials.com

- WHO International Clinical Trials Registry Platform (ICTRP) (Internet): up to 2014/8/7 http://www.who.int/ictrp/en

Key conference proceedings were also screened for the last six years, in order to identify recent studies:

- Association for Research in Vision and Ophthalmology (ARVO) http://www.iovs.org/search?arvomtgsearch=true
- American Diabetes Association (ADA) http://professional.diabetes.org
- European Association for the Study of Diabetes (EASD) http://www.easd.org/index.php?option=com_content&view=article&id=69&Itemid=509
- European Society of Retina Specialists (EURETINA) http://www.euretina.org/abstracts.asp
- American Academy of Ophthalmology (AAO) https://secure.aao.org/apps/MeetingArchive/tabid/433/Default.aspx
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) http://www.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp
- World Ophthalmology Conference (WOC) – 2012 only http://www.woc2012.org/files/abstract_book_woc2012.pdf
- European Society of Ophthalmology (ESO) – 2013 only http://www.abstractserver.com/soe2013/ebook/index.html

NIH Clinicaltrials.gov (Internet): up to 2013/10/24
http://www.clinicaltrials.gov/ct2/search/advanced
Searched 24.10.13

Terms searched	Hits
DME OR DMO OR CSME OR CSMO	145
Diabetic macular oedema	289
Diabetic macula oedema	44
Diabetic retinopathy	574
Diabetic maculopathy	21
Clinically significant macular oedema	41
Diabetic retina maculopathy	20

Diabetic retina macular oedema	285
Diabetic retina macula oedema	44
Diabetic eye oedema	291
Diabetic macula hemorrhage	4
Diabetic macular haemorrhage	26
Total (prior to deduplication)	**1784**
Total (after deduplication)	**587**

Update – August 2014
NIH Clinicaltrials.gov (Internet): up to 2014/8/7
http://www.clinicaltrials.gov/ct2/search/advanced
Searched 7.8.14

1998 records retrieved (666 after deduplication)

No date limits were applied to the update search due to the unreliable date limit function in this resource, the searches were just rerun and endnote used to deduplicate results from the original search results.

metaRegister of Controlled Trials (mRCT) (Internet): up to 2013/10/24
http://www.controlled-trials.com/mrct/
Searched 24.10.13

Terms searched	Hits
DME OR DMO OR CSME OR CSMO	78
(Diabetic OR diabetes) AND oedema	5*
(Diabetic OR diabetes) AND oedema	17*
(Diabetic OR diabetes) AND retinopathy	47*
(Diabetic OR diabetes) AND maculopathy	4*
Clinically significant macular oedema	3*
Clinically significant macular oedema	2*
(Diabetic OR diabetes) AND maculopathies	0*
(Diabetic OR diabetes) AND retinopathies	0*
(Diabetic OR diabetes) AND macular	30*
(Diabetic OR diabetes) AND (eye or eyes) AND oedema	3*
(Diabetic OR diabetes) AND (eye or eyes) AND oedema	12*
(Diabetic OR diabetes) AND retina	5*
(Diabetic OR diabetes) AND macular AND (haemorrhage or hemorrhage)	1*
Total	**207**

*NIH Clinicaltrials.gov was excluded from this search.

Update – August 2014
metaRegister of Controlled Trials (mRCT) (Internet): up to 2014/8/7
http://www.controlled-trials.com/mrct/
Searched 7.8.14

61 records retrieved

WHO International Clinical Trials Registry Platform (ICTRP) (Internet): up to 2013/10/24
http://www.who.int/ictrp/en/
Searched 24.10.13

Condition	Hits
DME OR DMO OR CSME OR CSMO	37
Diabet* AND oedema*	378
Diabet* AND oedema*	45
Diabet* AND retinopath*	368

Diabet* AND maculopath*	10
Diabet* AND macula*	413
Clinically significant macular oedema*	8
Clinically significant macular oedema*	1
Diabet* AND eye* AND oedema*	413
Diabet* AND eye* AND oedema*	1
Diabet* AND retina* AND (haemorrhage* or hemorrhag*)	0
Diabet* AND macul* AND (haemorrhage* or hemorrhag*)	0
Total	**1374**

Update – August 2014

WHO International Clinical Trials Registry Platform (ICTRP) (Internet): up to 2013/10/24
http://www.who.int/ictrp/en/
Searched 7.8.14

Searched date of registration between 24.10.13 and 7.8.14
237 records retrieved

Association for Research in Vision and Ophthalmology (ARVO) (Internet 2009-2013)
http://www.arvo.org/
Searched 22.10.13
ARVO meeting abstracts (title and abstract)
http://www.iovs.org/search?arvomtgsearch=true

Terms	Words: any/all/phrase	Hits
DME DMO	any(in clinical trial)	9
DME DMO	Any (in clinical and epidemiologic research)	4
DME DMO	any (in new developments)	0
DME DMO	any (in retina)	13
Diabetic macular oedema	Phrase (in all)	426
Diabetic macular edemas	Phrase (in all)	0
Diabetic macula oedema	Phrase (in all)	19
Diabetic macula oedemas	Phrase (in all)	0
Diabetic retinopathy	Phrase (in clinical trial)	8
Diabetic retinopathy	Phrase (in clinical and epidemiologic research)	23
Diabetic retinopathy	Phrase (in new developments)	0
Diabetic retinopathy	Phrase (in retina)	90
Diabetic maculopathy	Phrase (in all)	31
CSME CSMO CME CMO	Any (in all)	197
Clinically significant macular oedema	Phrase (in all)	52
Clinically significant macula oedema	Phrase (in all)	4
Total		***876***

Update – August 2014

Association for Research in Vision and Ophthalmology (ARVO) (Internet Oct 2013-2014)
http://www.arvo.org/
Searched 7.8.14
ARVO meeting abstracts (title and abstract)
http://www.iovs.org/search?arvomtgsearch=true

220 records retrieved

American Diabetes Association Conference (Internet 2009-2013)
http://professional.diabetes.org/

Searched 22.10.13
Searched using keywords in posters and meeting abstracts: all years, all meetings and all topics.

Terms	Resources	Hits
DME	Meeting Abstracts Posters	16 4
DMO	Meeting Abstracts Posters	0 0
Diabetic macular oedema	Meeting Abstracts Posters	44 8
Diabetic macula oedema	Meeting Abstracts Posters	0 1
Diabetic retinopathy*	Meeting Abstracts Posters	252 24
Diabetic maculopathy	Meeting Abstracts Posters	13 1
CSME	Meeting Abstracts Posters	5 2
CSMO	Meeting Abstracts Posters	0 0
CME	Meeting Abstracts Posters	7 2
CMO	Meeting Abstracts Posters	1 0
Clinically significant macular oedema	Meeting Abstracts Posters	13 3
Clinically significant macula oedema	Meeting Abstracts Posters	0 0
Total		***396***

*Category: In Complications – Ocular

Update – August 2014

American Diabetes Association Conference

http://diabetes.diabetesjournals.org/content/63/Supplement_1.toc

Searched 11.8.14

Searched in Diabetes Issue 63 (Supplement 1) – searched subject index for terms below and located abstracts

Terms	Hits
DME	0
DMO	0
Diabetic macular edema	6
Diabetic macula oedema	0
Diabetic retinopathy	16
Diabetic maculopathy	0
CSME	0
CSMO	0
CME	0
CMO	0
Clinically significant macular edema	0

Clinically significant macula oedema	0
Total	***22***

European Association for the Study of Diabetes (Internet 2009-2013)
http://www.easd.org
Searched: 22.10.13
Searched using the given term as the presentation titles and using key word limit of 'retinopathy'

Terms	**Hits**
DME DMO	0
Diabetic macular oedema	2013 = 14 2012=11 2011=12 2010=15 2009=0
Diabetic macula oedema	Gave same results as above. Therefore not included
Diabetic retinopathy	2013 = 16 2012=14 2011=13 2010=19 2009=0
Diabetic maculopathy	2013 = 13 2012=11 2011=12 2010=15 2009=0
CSME CSMO CME CMO	0
Clinically significant macular oedema	2013 = 3 2012=1 2011=3 2010=2 2009=0
Clinically significant macula oedema	Gave same results as above, therefore not included
Total	***174***

Update – August 2014
Conference not yet taken place in 2014

European Society of Retina Specialists (Internet 2009-2013)
http://www.euretina.org/
Searched: http://www.euretina.org/abstracts.asp

years	**Topic**	**Presentation type**	**Hits**
2013	vascular diseases and diabetic retinopathy	Poster	92
	New drug technology	Free paper	12
2012	vascular diseases and diabetic retinopathy	Free paper	14
	None given – no posters	poster	0
2011 (not all abstracts available to down load in	vascular diseases and diabetic retinopathy	Free paper	36

this year)			
	vascular diseases and diabetic retinopathy 2	Free paper	17
	vascular diseases and diabetic retinopathy 3	Free paper	12
	vascular diseases and diabetic retinopathy	poster	66
2010	vascular diseases and diabetic retinopathy	Free paper	***39***
	vascular diseases and diabetic retinopathy	poster	***83***
2009	vascular diseases and diabetic retinopathy	Free paper	***0***
	vascular diseases and diabetic retinopathy	poster	***58***
Total			***429***

Update – August 2014
Conference not yet taken place in 2014

American Association of Ophthamology (Internet 2009-2013)
Searched 22.10.13
Searched using keyword: all years, all meetings, all topics, scientific posters original papers and special interests
https://secure.aao.org/apps/MeetingArchive/tabid/433/Default.aspx

Terms	**Words: any/all/phrase**	**Hits**
DME DMO	any	2013 = 0 2012=18 2011=13 2010=10 2009=7
Diabetic macular oedema	phrase	2013 = 0 2012=26 2011=23 2010=20 2009=17
Diabetic macula oedema	phrase	0
Diabetic retinopathy	phrase	2013 = 0 2012=16 2011=13 2010=17 2009=11
Diabetic maculopathy	phrase	2013 = 0 2012=0 2011=0 2010=0 2009=0
CSME CSMO CME CMO	any	2013 = 1 2012=5 2011=0 2010=5 2009=8
Clinically significant macular oedema	phrase	2013 = 0 2012=1 2011=0

		2010=0 2009=1
Clinically significant macula oedema	phrase	0
Total		***212***

Update – August 2014
http://www.aao.org/
Searched 11.8.14 using term in the keyword search for 2013, all meetings, all topics, E-posters scientific posters, original papers, papers and all special interests
https://secure.aao.org/apps/MeetingArchive/tabid/433/Default.aspx

58 records retrieved

International Society For Pharmacoeconomics and Outcomes Research (Internet 2009-2013)
http://www.ispor.org/
Searched 22.10.13
Diabetes and Eye Disorders using keyword in abstract: all years, all meetings, all topics, scientific presentations.
http://www.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp

Terms	**Disease**	**Hits**
DME	Diabetes Eye Disorder	6 13
DMO	Diabetes Eye Disorder	0 0
Diabetic macular oedema	Diabetes Eye Disorder	3 13
Diabetic macula oedema	Diabetes Eye Disorder	0 0
Diabetic retinopathy	Diabetes Eye Disorder	37 20
Diabetic maculopathy	Diabetes Eye Disorder	0 0
CSME	Diabetes Eye Disorder	0 2
CSMO	Diabetes Eye Disorder	0 1
CME	Diabetes Eye Disorder	1 0
CMO	Diabetes Eye Disorder	1 0
Clinically significant macular oedema	Diabetes Eye Disorder	0 2
Clinically significant macula oedema	Diabetes Eye Disorder	0 0
Total		***99***

Update – August 2014
ISPOR
http://www.ispor.org/
ISPOR SCIENTIFIC PRESENTATIONS DATABASE (before formerly called the ISPOR Research Digest)

Searched 7.8.14

Diabetes and Eye Disorders highlighted in Disease/Disorder drop down menu; searched using Keyword Search/Abstract option; limited to specific meetings:

ISPOR 19th Annual International Meeting, May-June 2014, Montreal
ISPOR 6th Asia-Pacific Conference, 6-9 September, Beijing
ISPOR 16th Annual European Congress, November 2013, Dublin, Ireland

18 (10 after deduplication) records retrieved

World Ophthalmology Congress (Internet 2009-2013)Searched 23.10.13
Searched
for RCT abstracts using keyword in abstract book.
http://www.woc2012.org/files/abstract_book_woc2012.pdf

Terms	**2012**
Diabetic macular oedema	14
Diabetic macula oedema	0
Diabetic retinopathy	7
Diabetic maculopathy	0
Clinically significant macular oedema	2
Clinically significant macula oedema	0
Total	***23***

No abstracts were found for 2010.
The conference runs every 2 years so there are no results for 2009 & 2011.

Update – August 2014
WOC2014, April 2-6, Tokyo
http://www.woc2014.org/contents/program.html

Searched Program Online:
Find Presentations; Abstract Body
Poster/Video; Abstract Body
Searched 8.8.14

Terms	**Presentations**	**Poster/Video**
Diabetic macular edema	20	49
Diabetic macula oedema	3	6
Diabetic retinopathy	30	102
Diabetic maculopathy	2	1
Clinically significant macular edema	3	8
Clinically significant macula oedema	1	2
Total	***59*** ***After dedup 41***	***168*** ***After dedup 122***
Total combined	***163***	

European Society of Ophthmology (Internet 2009-2013)
Searched 23.10.13
Searched for RCT abstracts using keyword in abstract book.
http://www.abstractserver.com/soe2013/ebook/index.html

Terms	**2013**
Diabetic macular oedema	3
Diabetic macula oedema	2
Diabetic retinopathy	2
Diabetic maculopathy	0

Clinically significant macular oedema	0
Clinically significant macula oedema	0
Total	***7***

No abstracts were found for 2009 & 2011.
The conference runs every 2 years so there are no results for 2010 & 2012

Update – August 2014
Conference not taken place in 2014

10.2.6 The inclusion and exclusion criteria.

Please see Table 1 (section 6.2.1)

10.2.7 The data abstraction strategy.

Studies were included if they met at least one of each of the PICOS criteria in Table 1.

Identified references were downloaded into Endnote software for further assessment and handling. Rigorous records were maintained as part of the searching process. Individual records within the Endnote reference libraries were tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme or search question. This enabled the information specialist to track the origin of each individual database record, and its progress through the screening and review process. Two researchers independently screened each reference for relevance and any discrepancies between reviewers were resolved through discussion or the intervention of a third reviewer. Publications that appeared to be potentially relevant were ordered for a full review of the text to determine whether they met the criteria for inclusion in the review.

A flow diagram of the numbers of records included and excluded at each stage is provided in Figure 1.

The following data (where reported) were extracted from the selected publications:

- Study characteristics: Author, title, year, country, study design and phase, duration, other related publications, study group and funding, study aim, inclusion/exclusion criteria, use of ITT analysis
- Baseline characteristics of participants (age, gender, diagnosis, percentage diabetes type 1 or 2, diabetic retinopathy severity score, ethnicity, inclusion and exclusion criteria, HbA1c, blood glucose, comorbidities, previous and concomitant treatments, central macular thickness, ETDRS score, Snellen score: mean/SD or median/range, Previous treatment)
- Statistical analysis (ITT, per-protocol, last observation carried forward, other), Sample size or power calculation; Analysis sets and withdrawals (randomised, treated with intervention, used in analysis, cross-overs, withdrawals and reasons for withdrawal)
- Details of intervention and comparators: drugs used and treatment regimen, duration and intensity e.g. Fixed or PRN treatment, retreatment criteria. Concomitant therapies.
- Efficacy and safety outcomes, including HRQoL data; Outcomes assessed (e.g. definition of outcome, when assessed, who assessed, methods used to assess outcome(s), numbers used in analysis); Results per treatment or study arm; subgroup analyses of baseline VA, baseline CRT, baseline HbA1c.

plus any additional information to complete the quality assessments for each study

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

Table 132: Quality assessment of VISTA and VIVID studies

	VISTA		VIVID	
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/ N/A)**	**How is the question addressed in the study?**	**Grade (yes/no/not clear/ N/A)**
Was randomisation carried out appropriately?	Patients were randomised into the 3 treatment groups in a 1:1:1 ratio, [redacted]	Yes	Patients were randomised into the 3 treatment groups in a 1:1:1 ratio, [redacted]	Yes
Was the concealment of treatment allocation adequate?	[redacted] This was a double-masked study.	Yes	[redacted] This was a double-masked study.	[redacted]
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Demographic and baseline including disease characteristics were fairly well balanced among treatment groups..	Yes	Demographic and baseline including disease characteristics were fairly well balanced among treatment groups..	Yes
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)?	Patients and investigators were masked as to treatment assignment. All outcome assessors were masked including those assessing adverse events, efficacy and retreatment, visual acuity examiners, NEI VFQ-25 administrators, independent OCT scan reading centre. [redacted]	Yes	Patients and investigators were masked as to treatment assignment. All outcome assessors were masked including those assessing adverse events, efficacy and retreatment, visual acuity examiners, NEI VFQ-25 administrators, independent OCT scan reading centre. [redacted]	Yes

	VISTA		VIVID	
	[redacted] Sham injections were performed by pressing an empty, needleless syringe barrel to the conjunctival surface to simulate an injection. [redacted]		[redacted] Sham injections were performed by pressing an empty, needleless syringe barrel to the conjunctival surface to simulate an injection. [redacted]	

	VISTA		VIVID	
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. At Week 52, 20 (6.5%) patients had discontinued the study across the aflibercept arms and 11 (7.1%) patients in the laser photocoagulation group had discontinued from the study. By [redacted] patients had discontinued the study in the aflibercept arm and [redacted] patients in the sham control group had discontinued from the study.	No	No. At Week 52, 26 (9.6%) patients had discontinued the study across the aflibercept arms and 20 (14.8%) patients in the laser photocoagulation group had discontinued from the study. The laser group had a higher percentage of patients discontinuing study due to AEs, withdrawal of consent and physician decision; Sensitivity analyses demonstrated this had no major impact on the analysis of the primary endpoint. By [redacted] patients had discontinued the study in the aflibercept arm and [redacted] patients in the sham control group had discontinued from the study. Again, sensitivity analyses confirmed this had no impact on outcomes.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Results of all pre-specified outcomes have been reported in full.	No	Results of all pre-specified outcomes have been reported in full.	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?	Primary efficacy analyses were conducted using the 'Full analysis set' [redacted]	No.	Primary efficacy analyses were conducted using the 'Full analysis set' [redacted]	No.
	[redacted] Missing or censored values were imputed using the last non-censored value (last observation carried forward [LOCF]). Baseline values were not carried forward. Several sensitivity analyses were performed to address the impact of missing data due to drop-outs or receipt of additional treatment. [redacted] ○ [redacted] **Including data after additional treatment:** ○			
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination				

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

See appendix 10.2

10.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

Table 133: Detailed Cochrane Checklist for bias (see 10.3 for quality assessment of VISTA and VIVID)

RESTORE:

Domain	Judgement	Supporting text
Selection bias		
Random sequence generation	**Low risk of bias**	A randomisation list was produced by, or under the responsibility of, Novartis Drug Supply Management using a validated system that automated the random assignment of treatment arms to randomisation numbers in the specified ratio. ([76] Appendix 1)
Allocation concealment	**Unclear risk of bias**	A randomisation list was produced (see above) but no information is provided as to whether this list was concealed until the time of allocation.
Performance bias		
Blinding of participants and personnel.	**High risk of bias**	To fulfil the masking requirements of this study the following site personnel were required: • Best-corrected visual acuity (BCVA) assessor (Masked to the treatment assignment): to perform VA assessment and to provide the result to the evaluating investigator • Evaluating investigator (Masked to the treatment assignment): to receive VA result, to conduct or supervise all remaining assessments, and to provide the decision about the treatment to the treating investigator using formalised communication • Treating investigator (Unmasked to the treatment assignment): to perform the treatment – injection active/sham or laser active/sham ([76] Appendix 1) At least one member of personnel was unblinded at each study site therefore the treatment assignment could have been revealed
Detection bias		
Blinding of outcome assessment.	**High risk of bias**	See above - At least one member of personnel was unblinded at each study site therefore the treatment assignment could have been revealed. This may influence the outcome assessment.
Attrition bias		
Incomplete outcome data.	**Low risk of bias**	The analysis of the primary end point used the last observation carried forward approach for the imputation of missing data. ([76] p617).
Reporting bias		
Selective reporting.	**Low risk of bias**	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
Other bias		
Other	**Unclear**	The study was industry funded.

Domain	Judgement	Supporting text
sources of bias.	**risk of bias**	

REVEAL:

Domain	Judgement	Supporting text
Selection bias		
Random sequence generation	**Unclear risk of bias**	Only conference abstracts were available for this trial
Allocation concealment	**Unclear risk of bias**	Only conference abstracts were available for this trial
Performance bias		
Blinding of participants and personnel.	**Unclear risk of bias**	Only conference abstracts were available for this trial
Detection bias		
Blinding of outcome assessment.	**Unclear risk of bias**	Only conference abstracts were available for this trial
Attrition bias		
Incomplete outcome data.	**Unclear risk of bias**	Only conference abstracts were available for this trial
Reporting bias		
Selective reporting.	**Low risk of bias**	Outcomes listed in clinicaltrials.gov methods corresponds to outcome data reported on the results tab.
Other bias		
Other sources of bias.	**Unclear risk of bias**	Only conference abstracts were available for this trial. The study was industry funded.

RELATION:

Domain	Judgement	Supporting text
Selection bias		
Random sequence generation	**Unclear risk of bias**	Abstracts only. Not Reported
Allocation concealment	**Unclear risk of bias**	Abstracts only. Not Reported
Performance bias		
Blinding of participants and personnel.	**Unclear risk of bias**	Abstracts only. Not Reported
Detection bias		
Blinding of outcome assessment	**Unclear risk of bias**	Abstracts only. Not Reported
Attrition bias		
Incomplete outcome data.	**Low risk of bias**	Analysis by Last Observation Carried Forward
Reporting bias		
Selective reporting.	**Unclear risk of bias**	Clinicaltrials.gov record reports data at trial termination for the specified outcome
Other bias		
Other sources of bias.	**Unclear risk of bias**	Abstracts only. Not Reported The study was industry funded.

LRT for DME:

Domain	Judgement	Supporting text

Domain	Judgement	Supporting text
Selection bias		
Random sequence generation	**Unclear risk of bias**	"Study participants with 1 study eye were assigned randomly on the DCRC.net website. " "For study participants with 2 study eyes, the right eye was assigned randomly with equal probability to 1 of the 4 groups as indicated above. If the right eye was assigned to a treatment group other than the sham + prompt laser group, then the left eye was assigned to the sham + prompt laser group. If the right eye was assigned to the sham + prompt laser group, then the left eye was assigned randomly to 1 of the other 3 groups." [102] No further details were given.
Allocation concealment	**Unclear risk of bias**	"Study participants with 1 study eye were assigned randomly on the DCRC.net website. " "For study participants with 2 study eyes, the right eye was assigned randomly with equal probability to 1 of the 4 groups as indicated above. If the right eye was assigned to a treatment group other than the sham + prompt laser group, then the left eye was assigned to the sham + prompt laser group. If the right eye was assigned to the sham + prompt laser group, then the left eye was assigned randomly to 1 of the other 3 groups." [102] No further details were given.
Performance bias		
Blinding of participants and personnel.	**Unclear risk of bias**	Protocol: Visual acuity examiner and OCT technician will be masked to the treatment group assignment at the primary outcome visit (1 year). The subject will be masked during the first year to the treatment group assignment for groups A, B, and D but not for C.
Detection bias		
Blinding of outcome assessment.	**Low risk of bias**	Protocol: Visual acuity examiner and OCT technician will be masked to the treatment group assignment at the primary outcome visit (1 year).
Attrition bias		
Incomplete outcome data.	**Low risk of bias**	For main outcome, visual acuity at 12 months, ITT analyses was used. Number of drops-outs were low and balanced between studies although reasons were not reported. LOCF used to impute missing data.
Reporting bias		
Selective reporting.	**Low risk of bias**	The protocol is available and all outcomes in the protocol are reported.
Other bias		
Other sources of bias.	**High risk of bias**	Up to primary outcome assessment at 12 months no other sources of bias. After 12m sham + laser and IVTA + laser were allowed to crossover to RBZ + prompt laser, results for these study arms beyond 12m have a bias. In addition other treatments were allowed when treatment was unsuccessful, these could included BVZ, IVTA and vitrectomy, the eyes receiving sham injection + laser arm received alternative treatment in 14/293 eyes (year 1) 29/293 (year 1-2), therefore this unbalanced the groups. Mixed funders (industry and public).

LRT for DME for PRP:

Domain	Judgement	Supporting text
Selection bias		
Random sequence generation	**Unclear risk of bias**	"Study participants with 1 study eye were assigned randomly on the DCRC.net website. " "Study participants with 2 study eyes were randomised with equal probability to receive one of the three treatment scenarios: sham in the eye with a greater visual acuity score and ranibizumab or triamcinolone in the eye with a lower visual acuity score, or ranibizumab or triamcinolone acetonide in the eye with a greater visual acuity score and sham in the eye with a lower visual acuity score (if both eyes had the same visual acuity letter score, the right eye was considered the eye with the greater visual acuity score)." [106]. No further details were given.
Allocation concealment	**Unclear risk of bias**	"Study participants with 1 study eye were assigned randomly on the DCRC.net website. "

Domain	Judgement	Supporting text
		"Study participants with 2 study eyes were randomised with equal probability to receive one of the three treatment scenarios: sham in the eye with a greater visual acuity score and ranibizumab or triamcinolone in the eye with a lower visual acuity score, or ranibizumab or triamcinolone acetonide in the eye with a greater visual acuity score and sham in the eye with a lower visual acuity score (if both eyes had the same visual acuity letter score, the right eye was considered the eye with the greater visual acuity score)." [106]. No further details were given.
Performance bias		
Blinding of participants & personnel.	**Unclear risk of bias**	Study participants were masked to treatment assignments [106]. It's unclear who provided the injections, but this person cannot be blinded.
Detection bias		
Blinding of outcome assessment.	**Low risk of bias**	The visual acuity examiner and OCT technician at the primary outcome visit (14 weeks) were masked to the treatment groups [106]. AE: All adverse events were recorded irrespective of whether the event was considered treatment related. However, it is unclear who assessed these.
Attrition bias		
Incomplete outcome data.	**Unclear risk of bias**	The primary outcome was mean change in visual acuity from baseline to 14 weeks. The primary analysis followed the intent-to-treat principle and included all randomised eyes with the exception of 19 eyes randomised from one clinical site where 63% of eyes had baseline imputed central subfield thickness <250 µm. For eyes without 14-week data, LOCF method was used to impute data. For other outcomes, only data from completed visits were used with no imputation for missing data. Number of drops-outs were reasonable and balanced between studies although reasons were not reported.
Reporting bias		
Selective reporting.	**Low risk of bias**	The protocol is available and all outcomes in the protocol are reported.
Other bias		
Other sources of bias.	**High risk of bias**	A variety of additional treatments were given after 14 wks, Table 3 [106]. This included 9-14 patients per treatment arm who may receive BVZ, therefore large crossover of treatments after week 14. Mixed funders (industry and public).

LUCIDATE:

Domain	Judgement	Supporting text
Selection bias		
Random sequence generation	**Unclear risk of bias**	Abstract only
Allocation concealment	**Unclear risk of bias**	Abstract only
Performance bias		
Blinding of participants & personnel.	**Unclear risk of bias**	Abstract only
Detection bias		
Blinding of outcome assessment.	**Unclear risk of bias**	Abstract only
Attrition bias		
Incomplete outcome data.	**Unclear risk of bias**	Abstract only
Reporting bias		
Selective reporting.	**Unclear risk of bias**	Abstract only
Other bias		

Domain	Judgement	Supporting text
Other sources of bias.	**Unclear risk of bias**	Abstract only. Mixed funding sources (public and industry).

PLACID:

Domain	Judgement	Supporting text
Selection bias		
Random sequence generation	**Low risk of bias**	Randomisation schedule was computer generated and stored in a locked cabinet until the study ended.
Allocation concealment	**Low risk of bias**	Patients were randomised and received first study treatment at the baseline visit.
Performance bias		
Blinding of participants and personnel	**Low risk of bias**	Both the patients and the study personnel who collected BCVA, OCT and FA data were masked to the patient study assignment.
Detection bias		
Blinding of outcome assessment.	**Low risk of bias**	Both the patients and the study personnel who collected BCVA, OCT and FA data were masked to the patient study assignment.
Attrition bias		
Incomplete outcome data.	**Low risk of bias**	Missing outcome data imputed by LOCF.
Reporting bias		
Selective reporting.	**Low risk of bias**	All outcomes described in the methods are reported.
Other bias		
Other sources of bias.	**Unclear risk of bias**	Industry funded.

IBETA:

Domain	Judgement	Supporting text
Selection bias		
Random sequence generation	**Unclear risk of bias**	Insufficient information reported. Pts were “randomly assigned”.
Allocation concealment	**Unclear risk of bias**	No information on allocation concealment reported
Performance bias		
Blinding of participants and personnel.	**High risk of bias**	Open label trial. No information whether this influenced any behaviours or outcomes of the trial.
Detection bias		
Blinding of outcome assessment.	**Unclear risk of bias**	No clear information on whether assessment of outcomes was blinded.
Attrition bias		
Incomplete outcome data.	**High risk of bias**	Data only appear to be reported for eyes completing trial but this is unclear. No description of statistical analysis. Reasons for loss to follow-up not reported.
Reporting bias		
Selective reporting.	**High risk of bias**	Method of reporting outcomes and statistical analysis not pre-specified. Only selected outcomes reported.
Other bias		
Other sources of bias.	**High risk of bias**	Trial is reported in three separate abstracts with different authors and different numbers of eyes reported in each. No pt baseline characteristics reported. No full paper appears to have been published for the study.

Maia 2009/NCT00443521:

Domain	Judgement	Supporting text
Selection bias		
Random sequence generation	**Unclear risk of bias**	"After completion of the bilateral PRP session at week 3, one eye (per patient) was randomly assigned to receive …."
Allocation concealment	**Unclear risk of bias**	"After completion of the bilateral PRP session at week 3, one eye (per patient) was randomly assigned to receive …."
Performance bias		
Blinding of participants and personnel	**High risk of bias**	Patients were not blinded as no sham injections were given. "A single retinal specialist performed all laser and injection treatment procedures."
Detection bias		
Blinding of outcome assessment	**Low risk of bias**	Measurement of best-corrected ETDRS visual acuity (BCVA) was performed by a single certified examiner prior to any other study procedure. Optical coherence tomography (OCT) was performed by a single experienced certified ophthalmic technician. Both examiners were masked throughout the study period. It's unclear who assessed the adverse events. If this was the retinal specialist the risk of bias is high. If this were the outcome assessors, the risk of bias is low.
Attrition bias		
Incomplete outcome data	**High risk of bias**	Three eyes were excluded from the main analyses due to AE. These AE were exclusion criteria so the eyes were excluded.
Reporting bias		
Selective reporting.	**Unclear risk of bias**	Protocol is not available.
Other bias		
Other sources of bias.	**Low risk of bias**	No other sources of bias were identified.

10.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

No non-RCTs included in the submission of clinical evidence.

10.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

Not applicable.

10.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

See appendix 10.2

10.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

See appendix 10.3 for quality assessment of the VISTA and VIVID trials which provided evidence of the safety of aflibercept in the treatment of DMO.

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

10.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT

NHS EED.

The search was conducted in literature databases and conference proceedings.

Literature databases: The following literature databases were searched from inception:

- Medline (OvidSP): 1946 to week 5, July 2014
- Medline In-Process Citations & Daily Update (OvidSP): up to 8 August 2014

- Embase (OvidSP): 1974 to 8 August 2014
- NHS Economic Evaluations Database (NHS EED) (Wiley): Issue 3. July 2014
- Health Economic Evaluation Database (HEED) (Wiley): up to 11 August 2014
- Econlit (EBSCO): 1886 to 1 July 2014

An additional companion PubMed search was undertaken in tandem with Medline via OvidSP to detect the latest 'ahead of print' and 'online first' electronic content.

Conference abstracts: The following conference proceedings were screened for the past 5 years in October 2013:

- Association for Research in Vision and Ophthalmology (ARVO) http://www.iovs.org/search?arvomtgsearch=true
- American Diabetes Association (ADA) http://professional.diabetes.org
- European Association for the Study of Diabetes (EASD) http://www.easd.org/index.php?option=com_content&view=article&id=69&Itemid=509
- European Society of Retina Specialists (EURETINA) http://www.euretina.org/abstracts.asp
- American Academy of Ophthalmology (AAO) https://secure.aao.org/apps/MeetingArchive/tabid/433/Default.aspx
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) http://www.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp
- World Ophthalmology Conference (WOC) – 2012 only http://www.woc2012.org/files/abstract_book_woc2012.pdf
- European Society of Ophthalmology (ESO) – 2013 only

http://www.abstractserver.com/soe2013/ebook/index.html

An update performed in August 2014 screened the following proceedings (EASD, EURETINA and ESO proceedings were not rescreened, as the conferences had not yet taken place):

- Association for Research in Vision and Ophthalmology (ARVO) http://www.iovs.org/search?arvomtgsearch=true
- American Diabetes Association (ADA) http://diabetes.diabetesjournals.org/content/63/Supplement_1.toc
- American Academy of Ophthalmology (AAO) https://secure.aao.org/apps/MeetingArchive/tabid/433/Default.aspx
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) http://www.ispor.org/RESEARCH_STUDY_DIGEST/index.asp
- World Ophthalmology Conference (WOC) http://www.woc2014.org/contents/program.html

10.10.2 The date on which the search was conducted.

October 2013 and August 2014 (refer to 10.10.4 for exact dates for each database).

10.10.3 The date span of the search.

Refer to 10.10.4 for exact dates for each database.

10.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Embase (OvidSP): 1974-2013/10/31
Searched 1.11.13

1 health-economics/ (33324)

2 exp economic-evaluation/ (206460)
3 exp health-care-cost/ (198141)
4 exp pharmacoeconomics/ (169971)
5 or/1-4 (473055)
6 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (592185)
7 (expenditure$ not energy).ti,ab. (23422)
8 (value adj2 money).ti,ab. (1327)
9 budget$.ti,ab. (23646)
10 or/6-9 (616025)
11 5 or 10 (888542)
12 letter.pt. (845746)
13 editorial.pt. (450329)
14 note.pt. (589404)
15 or/12-14 (1885479)
16 11 not 15 (801627)
17 (metabolic adj cost).ti,ab. (878)
18 ((energy or oxygen) adj cost).ti,ab. (3166)
19 ((energy or oxygen) adj expenditure).ti,ab. (20044)
20 or/17-19 (23275)
21 16 not 20 (796546)
22 exp animal/ (19426358)
23 exp animal-experiment/ (1728701)
24 nonhuman/ (4159519)
25 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (5022399)
26 or/22-25 (20775644)
27 exp human/ (15070342)
28 exp human-experiment/ (317838)
29 27 or 28 (15071783)
30 26 not (26 and 29) (5704830)
31 21 not 30 (736589)
32 exp diabetes mellitus/ (580436)
33 Diabet$.ti,ab,ot,hw. (683394)
34 (T1dm or t1-DM or IDDM or DMI or DM1 or DM-1 or DM-I or TIDM).ti,ab,ot. (16418)
35 (T2dm or DM2 or DM-2 or T2-DM or MODY or DM2 or NIDDM or IIDM or TIIDM).ti,ab,ot. (21781)
36 ((juvenile$ or child$ or labil$ or brittle$ or ((earl$ or sudden) adj onset)) adj4 DM).ti,ab,ot. (593)
37 ((adult$ onset or matur$ or late$ or slow or stable) adj4 DM).ti,ab,ot. (435)
38 ((insulin-dependen$ or non-insulin dependen$ or noninsulin dependen$) adj4 DM).ti,ab,ot. (218)
39 ((typ$ 2 or typ$ ii or typ$ two or type2 or typeii) adj3 DM).ti,ot,ab. (4589)
40 ((keto$ or nonketo$ or autoimmun$ or auto-immun$) adj4 DM).ti,ab,ot. (179)
41 ((obes$ or non-obes$ or nonobes$) adj4 DM).ti,ab,ot. (634)
42 Insulin resistance/ (74212)

43 (Insulin$ resist$ adj4 DM).ti,ab,ot. (214)
44 or/32-43 (723308)
45 exp Retina maculopathy/ (35596)
46 exp Retina macula oedema/ (9959)
47 eye oedema/ (449)
48 retina macula hemorrhage/ (630)
49 ((parafovea$ or fovea$ or retina$ or macul$ or eye or eyes) adj2 (oedema$ or oedema$ or degenerat$ or swell$ or h?emorrhag$ or microaneur?sm$ or micro-aneur?sm$ or (dilat$ adj2 capillar$))).ti,ot,ab. (32903)
50 (CSME or CSMO or CME or CMO).ti,ab,ot. (7355)
51 or/45-50 (56374)
52 44 and 51 (9472)
53 exp diabetic retinopathy/ or ((diabet$ adj2 maculop$) or (diabet$ adj2 macul$ adj2 oedema$) or (diabet$ adj2 macul$ oedema$)).ti,ot,ab. (28872)
54 (DME or DMO).ti,ot,ab. (2294)
55 33 and 54 (686)
56 53 or 55 (28897)
57 52 or 56 (31891)
58 31 and 57 (1294)

Costs filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Embase (Ovid) weekly search. York: Centre for Reviews and Dissemination; 2010.

Update – August 2014

Embase (OvidSP): 1974-2014/8/8

Searched 11.8.13

Date limit applied - (2014$ or 2015$).em. or (201310$ or 201311$ or 201312$ or 2014$).dd.

152 records retrieved

Medline (OvidSP): 1946-2013/10/wk 4

Searched 1.11.13

1 economics/ (27117)
2 exp "costs and cost analysis"/ (182817)
3 economics, dental/ (1866)
4 exp "economics, hospital"/ (19436)
5 economics, medical/ (8580)
6 economics, nursing/ (3880)
7 economics, pharmaceutical/ (2607)
8 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (428332)
9 (expenditure$ not energy).ti,ab. (17575)

10 (value adj1 money).ti,ab. (22)
11 budget$.ti,ab. (17221)
12 or/1-11 (552792)
13 ((energy or oxygen) adj cost).ti,ab. (2756)
14 (metabolic adj cost).ti,ab. (800)
15 ((energy or oxygen) adj expenditure).ti,ab. (16687)
16 or/13-15 (19533)
17 12 not 16 (548438)
18 letter.pt. (804607)
19 editorial.pt. (335541)
20 historical article.pt. (299905)
21 or/18-20 (1425550)
22 17 not 21 (520378)
23 exp Diabetes Mellitus/ (318452)
24 Diabet$.ti,ab,ot,hw. (446557)
25 (T1dm or t1-DM or IDDM or DMI or DM1 or DM-1 or DM-I or TIDM).ti,ab,ot. (12677)
26 (T2dm or DM2 or DM-2 or T2-DM or MODY or DM2 or NIDDM or IIDM or TIIDM).ti,ab,ot. (14290)
27 ((juvenile$ or child$ or labil$ or brittle$ or ((earl$ or sudden) adj onset)) adj4 DM).ti,ab,ot. (405)
28 ((adult$ onset or matur$ or late$ or slow or stable) adj4 DM).ti,ab,ot. (303)
29 ((insulin-dependen$ or non-insulin dependen$ or noninsulin dependen$) adj4 DM).ti,ab,ot. (149)
30 ((typ$ 2 or typ$ ii or typ$ two or type2 or typeii) adj3 DM).ti,ot,ab. (2602)
31 ((keto$ or nonketo$ or autoimmun$ or auto-immun$) adj4 DM).ti,ab,ot. (121)
32 ((obes$ or non-obes$ or nonobes$) adj4 DM).ti,ab,ot. (273)
33 exp Insulin Resistance/ (55618)
34 (Insulin$ resist$ adj4 DM).ti,ab,ot. (141)
35 or/23-34 (481296)
36 Macular degeneration/ (12175)
37 Macular Oedema/ (4549)
38 Retinal Hemorrhage/ (4437)
39 ((parafovea$ or fovea$ or retina$ or macul$ or eye or eyes) adj2 (oedema$ or oedema$ or degenerat$ or swell$ or h?emorrhag$ or microaneur?sm$ or micro-aneur?sm$ or (dilat$ adj2 capillar$))).ti,ot,ab. (27702)
40 (CSME or CSMO or CME or CMO).ti,ab,ot. (4068)
41 or/36-40 (38080)
42 35 and 41 (5751)
43 diabetic retinopathy/ or ((diabet$ adj2 maculop$) or (diabet$ adj2 macul$ adj2 oedema$) or (diabet$ adj2 macul$ oedema$)).ti,ot,ab. (19309)
44 (DME or DMO).ti,ot,ab. (1657)
45 24 and 44 (596)
46 43 or 45 (19325)
47 42 or 46 (21197)
48 22 and 47 (484)

49 animals/ not (animals/ and humans/) (3962474)
50 48 not 49 (481)

Economics filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search. York: Centre for Reviews and Dissemination; 2010.

Update – August 2014

Medline (OvidSP): 1946-2014/7/wk 5

Searched 11.8.14

Date limit applied - (201310$ or 201311$ or 201312$ or 2014$).ed,dc. or "2014".yr.

32 records retrieved

Medline In-Process Citations (OvidSP): up to 2013/10/31

Medline Daily Update (OvidSP): up to 2013/10/31

Searched 1.11.13

1 economics/ (3)
2 exp "costs and cost analysis"/ (161)
3 economics, dental/ (0)
4 exp "economics, hospital"/ (18)
5 economics, medical/ (0)
6 economics, nursing/ (1)
7 economics, pharmaceutical/ (3)
8 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (40704)
9 (expenditure$ not energy).ti,ab. (1233)
10 (value adj1 money).ti,ab. (4)
11 budget$.ti,ab. (1879)
12 or/1-11 (42687)
13 ((energy or oxygen) adj cost).ti,ab. (231)
14 (metabolic adj cost).ti,ab. (69)
15 ((energy or oxygen) adj expenditure).ti,ab. (935)
16 or/13-15 (1194)
17 12 not 16 (42334)
18 letter.pt. (25676)
19 editorial.pt. (15258)
20 historical article.pt. (114)
21 or/18-20 (41037)
22 17 not 21 (41864)
23 exp Diabetes Mellitus/ (232)
24 Diabet$.ti,ab,ot,hw. (25377)

25 (T1dm or t1-DM or IDDM or DMI or DM1 or DM-1 or DM-I or TIDM).ti,ab,ot. (614)
26 (T2dm or DM2 or DM-2 or T2-DM or MODY or DM2 or NIDDM or IIDM or TIIDM).ti,ab,ot. (1300)
27 ((juvenile$ or child$ or labil$ or brittle$ or ((earl$ or sudden) adj onset)) adj4 DM).ti,ab,ot. (26)
28 ((adult$ onset or matur$ or late$ or slow or stable) adj4 DM).ti,ab,ot. (22)
29 ((insulin-dependen$ or non-insulin dependen$ or noninsulin dependen$) adj4 DM).ti,ab,ot. (10)
30 ((typ$ 2 or typ$ ii or typ$ two or type2 or typeii) adj3 DM).ti,ot,ab. (273)
31 ((keto$ or nonketo$ or autoimmun$ or auto-immun$) adj4 DM).ti,ab,ot. (9)
32 ((obes$ or non-obes$ or nonobes$) adj4 DM).ti,ab,ot. (36)
33 exp Insulin Resistance/ (86)
34 (Insulin$ resist$ adj4 DM).ti,ab,ot. (13)
35 or/23-34 (25785)
36 Macular degeneration/ (5)
37 Macular Oedema/ (11)
38 Retinal Hemorrhage/ (2)
39 ((parafovea$ or fovea$ or retina$ or macul$ or eye or eyes) adj2 (oedema$ or oedema$ or degenerat$ or swell$ or h?emorrhag$ or microaneur?sm$ or micro-aneur?sm$ or (dilat$ adj2 capillar$))).ti,ot,ab. (1664)
40 (CSME or CSMO or CME or CMO).ti,ab,ot. (762)
41 or/36-40 (2373)
42 35 and 41 (363)
43 diabetic retinopathy/ or ((diabet$ adj2 maculop$) or (diabet$ adj2 macul$ adj2 oedema$) or (diabet$ adj2 macul$ oedema$)).ti,ot,ab. (186)
44 (DME or DMO).ti,ot,ab. (431)
45 24 and 44 (76)
46 43 or 45 (189)
47 42 or 46 (391)
48 22 and 47 (14)
49 animals/ not (animals/ and humans/) (1801)
50 48 not 49 (14)

Economics filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search. York: Centre for Reviews and Dissemination; 2010.

Update – August 2014

Medline In-Process Citations (OvidSP): up to 2014/8/08

Medline Daily Update (OvidSP): up to 2014/8/08

Searched 11.8.14

Date limit applied - (201310$ or 201311$ or 201312$ or 2014$).ed,dc. or "2014".yr.

18 records retrieved

NHS Economic Evaluation Database (NHS EED) (Wiley). Issue 3: July/2013

Searched 15.10.13

#1 MeSH descriptor: [Diabetes Mellitus] explode all trees 14750
#2 Diabet*:ti,ab,kw 26235
#3 (T1dm or t1-DM or IDDM or DMI or DM1 or DM-1 or DM-I or TIDM):ti,ab,kw 725
#4 (T2dm or DM2 or DM-2 or T2-DM or MODY or NIDDM or IIDM or TIIDM):ti,ab,kw 1472
#5 ((juvenile* or child* or labil* or brittle* or ((earl* or sudden) near/1 onset)) near/4 DM):ti,ab,kw 26
#6 (((adult* near/2 onset) or matur* or late* or slow or stable) near/4 DM):ti,ab,kw 15
#7 (((insulin near/2 dependen*) or (non-insulin near/2 dependen*) or (noninsulin near/2 dependen*)) near/4 DM):ti,ab,kw 33
#8 (("typ* 2" or "typ* ii" or "typ* two" or type2 or typeii) near/3 DM):ti,ab,kw 251
#9 ((keto* or nonketo* or autoimmun* or auto-immun*) near/4 DM):ti,ab,kw 1
#10 ((obes* or "non obes*" or nonobes*) near/4 DM):ti,ab,kw 21
#11 MeSH descriptor: [Insulin Resistance] explode all trees 2581
#12 ((Insulin* near/2 resist*) near/4 DM):ti,ab,kw 5
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 27972
#14 MeSH descriptor: [Macular Degeneration] this term only 607
#15 MeSH descriptor: [Macular Oedema] explode all trees 401
#16 MeSH descriptor: [Retinal Hemorrhage] this term only 45
#17 ((parafovea* or fovea* or retina* or macul* or eye or eyes) near/2 (oedema* or oedema* or degenerat* or swell* or h*emorrhag* or microaneur?sm* or micro-aneur?sm* or (dilat* near/2 capillar*))):ti,ab,kw 2248
#18 (CSME or CSMO or CME or CMO):ti,ab,kw 281
#19 #14 or #15 or #16 or #17 or #18 2363
#20 #13 and #19 663
#21 MeSH descriptor: [Diabetic Retinopathy] this term only 854
#22 ((diabet* near/2 maculop*) or (diabet* near/2 macul* near/2 oedema*) or (diabet* near/2 macul* oedema*)):ti,ab,kw 404
#23 (DME or DMO):ti,ab,kw 143
#24 #2 and #23 134
#25 #21 or #22 or #24 1051
#26 #20 or #25 1233

NHS EED search retrieved 27 references.

Update – August 2014

NHS Economic Evaluation Database (NHS EED) (Wiley). Issue 3 2014/7

Searched 7.8.14

33 records retrieved (6 new records)

EconLIT (EBSCO): 1886-2013/09/01

Searched 4.11.13

S1 TX diabet* 321

S2 AB ((T1dm or t1-DM or IDDM or DMI or DM1 or DM-1 or DM-I or TIDM)) OR TI ((T1dm or t1-DM or IDDM or DMI or DM1 or DM-1 or DM-I or TIDM)) OR AB ((T2dm or DM2 or DM-2 or T2-DM or MODY or DM2 or NIDDM or IIDM or TIIDM)) OR TI ((T2dm or DM2 or DM-2 or T2-DM or MODY or DM2 or NIDDM or IIDM or TIIDM)) 41

S3 TX (((juvenile* or child* or labil* or brittle*) N3 DM)) OR TX (((earl* N3 onset N3 DM) OR (sudden N3 onset N3 DM)) OR TX (adult* N3 onset N3 DM) OR TX ((matur* or late* or slow or stable) N3 DM)) OR TX ((("insulin-dependen*" or "non-insulin dependent" or "noninsulin dependent") N3 DM)) 0

S4 TX ((("typ* 2" or "typ* ii" or "typ* two" or "type2" or "typeii") N3 DM)) OR TX (((keto* or nonketo* or autoimmun* or "auto-immun*") N3 DM)) OR TX (((obes* or "non-obes*" or nonobes*) N3 DM)) OR TX ((Insulin* N1 resist*) N3 DM) 0

S5 S1 OR S2 357

S6 TX (((parafovea* or fovea* or retina* or macul* or eye or eyes) AND (oedema* or oedema* or degenerat* or swell* or hemorrhag* or haemorrhag* or microaneur* or "micro-aneur*"))) OR TX (((parafovea* or fovea* or retina* or macul* or eye or eyes) AND ("dilat* capillar*"))) OR TX ((CSME or CSMO or CME or CMO)) 149

S7 TX S5 AND S6 1

S8 TX ((diabet* N3 maculop*) or (diabet* N3 macul* N3 oedema*) or (diabet* N3 macul* N3 oedema*) or (diabet* N3 retinopath*) 0

S9 TX Diabet* AND (DME or DMO) 0

S10 Diabet* AND (odema* or oedema* or retinopath* or macular* or maculopath*) 8

S11 TX DME or DMO 20

S12 TX S11 OR S10 OR S7 28

Update – August 2014

EconLIT (EBSCO): 1886-2014/07/01

Searched 11.8.14

30 records retrieved (2 new records)

Health Economic Evaluation Database (HEED) (Wiley): up to 2013/11/04

http://onlinelibrary.wiley.com/book/10.1002/9780470510933

Searched 4.11.13

Compound search, (all data)

All data	All data	Results
Diabet* OR T1dm OR t1-DM OR IDDM OR DMI OR DM1 OR DM-1 OR DM-I OR TIDM OR T2dm OR DM2 OR DM-2 OR T2-DM OR MODY OR DM2 OR NIDDM OR IIDM OR TIIDM	AND Retinopath*	141
Diabet* OR T1dm OR t1-DM OR IDDM OR DMI OR DM1 OR DM-1 OR DM-I OR TIDM OR T2dm OR DM2 OR DM-2 OR T2-DM OR MODY OR DM2 OR NIDDM OR IIDM OR TIIDM	AND Maculopath*	0
(Macul* AND oedema*)	OR (Macul* AND oedema*)	32
DME OR DMO OR CSME OR CSMO	-	7
Diabet* OR T1dm OR t1-DM OR IDDM OR DMI OR DM1 OR DM-1 OR DM-I OR TIDM OR T2dm OR DM2 OR DM-2 OR T2-DM OR MODY OR DM2 OR NIDDM OR IIDM OR TIIDM	AND eye AND oedema*	5
Diabet* OR T1dm OR t1-DM OR IDDM OR DMI OR DM1 OR DM-1 OR DM-I OR TIDM OR T2dm OR DM2 OR DM-2 OR T2-DM OR MODY OR DM2 OR NIDDM OR IIDM OR TIIDM	AND eye AND oedema*	7

Diabet* OR T1dm OR t1-DM OR IDDM OR DMI OR DM1 OR DM-1 OR DM-I OR TIDM OR T2dm OR DM2 OR DM-2 OR T2-DM OR MODY OR DM2 OR NIDDM OR IIDM OR TIIDM	AND Macula* OR maculo*	35
Total (prior to deduplication)		227
Total (after duplicate removal)		158

Update – August 2014

Health Economic Evaluation Database (HEED) (Wiley): up to 2014/08/11

http://onlinelibrary.wiley.com/book/10.1002/9780470510933

Searched 11.8.14

165 records retrieved

10.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not done

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

Table 134. Quality assessment of cost-effectiveness studies

	Stein	Smiddy	Smiddy	(Sharma et al., 2000b)	(Mitchell et al., 2012)	Dewan	(NICE, 2013)	(Haig et al., 2011a)	(Brennig et al., 2011b)	(Haig et al., 2013)
Year	2013	2012	2011	2000	2012	2012	2010	2011	2011	2013
YES	18	10	10	18	25	7	31	Not performed due to being available as abstract only.		
NO	12	21	22	7	3	11	0			
Unclear	3	1	0	6	4	13	0			
Not applicable	3	4	4	5	4	5	5			
Question 1 - Was a research question stated?	Yes	No	No	Yes	Yes	Yes	Yes			
Question 2 - Is the economic importance of the research question stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes			
Question 3 - Are the view points of the analysis clearly stated and justified	Unclear	No	No	Yes	Yes	Yes	Yes			
Question 4 - Is the rationale for choosing alternative programmes or interventions compared stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes			
Question 5 -Are the alternatives being compared clearly described?	Yes	Unclear	No	No	Yes	Yes	Yes			

	Stein	Smiddy	Smiddy	(Sharma et al., 2000b)	(Mitchell et al., 2012)	Dewan	(NICE, 2013)	(Haig et al., 2011a)	(Brennig et al., 2011b)	(Haig et al., 2013)
Question 6- Is the form of economic evaluation used stated?	Yes	No	No	Yes	Yes	Unclear	Yes			
Question 7 - Is the choice of economic evaluation justified in relation to the questions addressed?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes			
Question 8- Are the source(s) of effectiveness estimates used stated?	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes			
Question 9 - Are the details and design of the effectiveness study given (if based on a single study)	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable			
Question 10 -Are details of the methods of synthesis or meta-analysis of estimates given (if based on a number of synthesis of a number of effectiveness studies)	No	No	No	No	No	Not Applicable	Yes			
Question 11 - Is the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes			
Question 12 - Are the methods to value benefits stated?	No	No	No	Unclear	Yes	Unclear	Yes			
Question 13- Are the details of the subjects from whom valuations were obtained given?	No	No	No	Unclear	Yes	No	Not Applicable			
Question 14 - Are the productivity changes (if included) reported separately?	No	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable			
Question 15- Is the relevance of productivity changes to the study question discussed?	No	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Yes			
Question 16 - Are the quantities of resource use reported separately from their unit costs?	Yes	Yes	Yes	Yes	Yes	No	Yes			
Question 17 - Are the methods for estimation of quantities and unit costs described?	Yes	No	No	Yes	Yes	Unclear	Yes			

	Stein	Smiddy	Smiddy	(Sharma et al., 2000b)	(Mitchell et al., 2012)	Dewan	(NICE, 2013)	(Haig et al., 2011a)	(Brennig et al., 2011b)	(Haig et al., 2013)
Question 18- Are the currency and price data recorded?	Yes	Yes	Yes	Yes	Yes	Yes	Yes			
Question 19 - Are the details of price adjustments for inflation or currency conversion given?	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Yes	Not Applicable	Not Applicable			
Question 20- Are details of the model used given?	Yes	Yes	Yes	No	Yes	Unclear	Yes			
Question 21- Is the choice of the model used and the key parameters on which it is based justified?	Unclear	No	No	Unclear	Yes	No	Yes			
Question 22 - Is the time horizon of costs and benefits stated?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes			
Question 23- Is the discount rate(s) stated?	Yes	No	No	Yes	Yes	No	Yes			
Question 24 - Is the choice of discount rate (s) justified?	No	No	No	Unclear	Yes	No	Yes			
Question 25- Is an explanation given if costs and benefits are not discounted?	Not Applicable	No	No	Not Applicable	Not Applicable	No	Not Applicable			
Question 26 - Are details of statistical tests and confidence intervals given for stochastic data?	No	No	No	Yes	Yes	Yes	Yes			
Question 27 - Is the approach to sensitivity analysis given?	Yes	No	No	Yes	Yes	Unclear	Yes			
Question 28 - Are the choice of variables for sensitivity analysis justified?	No	No	No	Yes	Yes	No	Yes			
Question 29 -Are the ranges over which the variables are varied justified?	No	No	No	Yes	Unclear	No	Yes			

	Stein	Smiddy	Smiddy	(Sharma et al., 2000b)	(Mitchell et al., 2012)	Dewan	(NICE, 2013)	(Haig et al., 2011a)	(Brennig et al., 2011b)	(Haig et al., 2013)
Question 30 - Are the relevant alternatives compared? (as part of the incremental analysis)	Yes	No	No	Unclear	Unclear	Unclear	Yes			
Question 31 - Is the incremental analysis reported?	No	No	No	Yes	No	Unclear	Yes			
Question 32 - Are the major outcomes presented in a disaggregated as well as aggregated form?	No	Yes	Yes	No	Yes	Unclear	Yes			
Question 33 - Is the answer to the study question given?	Yes	No	No	Yes	Unclear	Unclear	Yes			
Question 34 - Do the conclusions follow from the data reported?	Yes	No	No	No	Unclear	No	Yes			
Question 35- Are the conclusions accompanied by the appropriate caveats?	Unclear	No	No	No	Yes	No	Yes			
Question 36- Are generalisability issues addressed	No	No	No	No	No	No	Yes			

10.12 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

The following information should be provided.

◊ The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Medline
Embase
Medline (R) In-Process
NHS Economic Evaluation Database (NHS EED)
EconLIT.

The search was conducted in literature databases, the websites of UK-based HTA agencies, and conference proceedings (Table 135).

Table 135. Databases searched

Literature	HTA agencies	Conference proceedings
vid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) (https://ovidsp.ovid.com/autologin.cg)	SCOTLAND: Scottish Medicines Consortium (SMC) (www.scottishmedicines.org.uk/Home)	International Society For Pharmacoeconomics and Outcomes Research (ISPOR) (www.ispor.org/)
vid Embase ttps://ovidsp.ovid.com/autologin.cg)	ENGLAND AND WALES: National Institute of Health and Care Excellence (NICE) (www.nice.org.uk/)	The Association for Research in Vision and Ophthalmology (ARVO) (www.arvo.org/; www.iovs.org/)
ational Health Service Economic Evaluation Database (NHS EED) (www.crd.york.ac.uk/crdweb/)	WALES: All Wales Medicines Strategy Group (AWMSG); (www.awmsg.org/)	American Academy of Ophthalmology (AAO) (www.aao.org/)
conLit ttp://ovidsp.tx.ovid.com/)		Retina Congress (EURETINA) (www.euretina.org/default.asp)
		World Ophthalmology Congress (WOC) (www.woc2014.org/; www.icoph.org/)

◊ The date on which the search was conducted.

6 February 2014.

◊ The date span of the search.

Publication dates were set from 2003 until the date of the search for the literature databases and the HTA agency websites, and for the last 3 years for conference proceedings.

◊ The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strategy for Embase is shown in Table 136, for Medline in Table 137, for NHS EED and EconLit in Table 138, for HTA websites in Table 139, and for conference proceedings in Table 140.

Table 136. Search strategy in Embase for the utilities review

Search Description	Search Number	Strategy	Results
Population			
	1	exp diabetes mellitus/	602,131
	2	Diabet$.ti,ab,ot,hw.	707,910
	3	(T1dm or t1-DM or IDDM or DMI or DM1 or DM-1 or DM-I or TIDM).ti,ab,ot.	16,950
	4	(T2dm or DM2 or DM-2 or T2-DM or MODY or DM2 or NIDDM or IIDM or TIIDM).ti,ab,ot.	23,203
	5	((juvenile$ or child$ or labil$ or brittle$ or ((earl$ or sudden) adj onset)) adj4 DM).ti,ab,ot.	621
	6	((adult$ onset or matur$ or late$ or slow or stable) adj4 DM).ti,ab,ot.	451
	7	((insulin-dependen$ or non-insulin dependen$ or noninsulin dependen$) adj4 DM).ti,ab,ot.	222
	8	((typ$ 2 or typ$ ii or typ$ two or type2 or typeii) adj3 DM).ti,ot,ab.	4,846
	9	((keto$ or nonketo$ or autoimmun$ or auto-immun$) adj4 DM).ti,ab,ot.	193
	10	((obes$ or non-obes$ or nonobes$) adj4 DM).ti,ab,ot.	672
	11	Insulin resistance/	77,319
	12	(Insulin$ resist$ adj4 DM).ti,ab,ot.	223
	13	OR/1-12	749,178
	14	exp Retina maculopathy/	36,627
	15	exp Retina macula edema/	10,318
	16	eye edema/	472
	17	retina macula hemorrhage/	645
	18	((parafovea$ or fovea$ or retina$ or macul$ or eye or eyes) adj2 (edema$ or oedema$ or degenerat$ or swell$ or h?emorrhag$ or microaneur?sm$ or micro-aneur?sm$ or (dilat$ adj2 capillar$))).ti,ot,ab.	33,749
	19	(CSME or CSMO or CME or CMO).ti,ab,ot.	7,529
	20	OR/14-19	57,864
	21	13 and 20	9,807
	22	exp diabetic retinopathy/ or ((diabet$ adj2 maculop$) or (diabet$ adj2 macul$ adj2 edema$) or (diabet$ adj2 macul$ oedema$)).ti,ot,ab.	29,559
	23	(DME or DMO).ti,ot,ab.	2,357

Search Description	Search Number	Strategy	Results
	24	2 and 23	729
	25	22 or 24	29,586
	26	21 or 25	32,685
Blindness[8]			
	27	exp low vision/	142
	28	exp blindness/ or blindness.af.	45,939
	29	(visual$ or vision or sight).mp. or exp visual acuity/	773,814
	30	(impair$ or defect$ or loss$ or disorder$ or reduc$ or diminish).mp.	5,731,661
	31	29 and 30	264,825
	32	27 or 28 or 31	296,085
Treatment Strategy			
	33	ranibizumab/	3,654
	34	fluocinolone acetonide/	2,384
	35	bevacizumab/	30,540
	36	dexamethasone/	110,364
	37	aflibercept/	1,400
	38	eylea.af.	108
	39	lucentis.af.	1,580
	40	rhufab.af.	18
	41	ozurdex.af.	242
	42	avastin.af.	7,505
	43	iluvien.af.	68
	44	OR/ 33-43	143,404
Laser Treatment			
	45	laser coagulation/	17,922
	46	photocoagulation.af.	10,236
	47	laser coagulation.af.	18,456
	48	45 or 46 or 47	20,681
Adverse Event			
	49	(safe or safety or side-effect$ or undesirable effect$ or treatment emergent or tolerability or toxicity or adrs).ti,ab.	1,136,520
	50	(adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.	345,960
	51	adverse drug reaction/	155,815
	52	side effect/	171,716
	53	49 or 50 or 51 or 52	1,519,028
Adverse Event DME			
	54	(vitreous haemorrhage or vitreous hemorrhage).af.	5,418
	55	(((eye$ or ocular).mp. or intraocular/) and (pressure$ or tension$).mp.) or ocular hypertension/ or intraocular pressure/	62,775
	56	retinal detachment/	24,421
	57	cataract/	40,730
	58	endophthalmitis/	8,858
	59	cataract.af.	73,358
	60	endophthalmitis.af.	10,317
Utility			

[8] [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Search Description	Search Number	Strategy	Results
	61	exp quality of life/ or quality of life.tw.	307,463
	62	QoL.tw.	31,914
	63	(hrqol or hrql or hql or hqol or h qol or hrqol or hr qol).tw.	14,716
	64	rosser.tw.	91
	65	(util$ and (value$ or weight$ or scor$ or index$ or assessment or evaluation)).mp.	244,948
	66	(health state utility or health utilit$).tw.	1,763
	67[9]	(health utility ind$ or hui or hui$ or hui2 or hui3).mp.	9,209
	68	(SG or standard gamble$).tw.	8,076
	69	(time trade-off or tto or time trade off or time tradeoff).tw.	1,561
	70	(euroqol or euro qol or eq5d or eq 5d or eq-5d).tw.	6,594
	71	(sf6 or sf 6 or sf-6d or sf 6d or sf6d or sf-36 or SF-36 or SF-36).tw.	21,668
	72	(short form 6 or shortform 6 or shortform 6D or sf sixD or sfsixD or shortform sixD or short form sixD or short form 6D or short-form 36 or short form 36 or short form thirtysix or short form thirty six).tw.	7,995
	73	(qaly$ or qald$ or qale$ or qtime$ or quality adjusted life).tw.	11,060
	74	(willingness to pay or wtp).tw.	3,587
	75	(quality of well being or qwb).tw.	412
	76	(disability adjusted life or daly$).tw.	2,064
	77	(hye or hyes).tw.	91
	78	disutilit$.tw.	357
	79	health$ year$ equivalent$.tw.	43
	80	health status indicators/	622
	81	preference based.tw.	896
	82	preference score.tw.	142
	83	preference measure.tw.	43
Treatment Type All	84	44 or 48	162,764
Adverse Event of All Treatment Types	85	53 and 84	31,546
Vision			
	86	exp monocular vision/	2,448
	87	exp binocular vision/	8,985
	88	vision/	67,526
	89	visual acuity/	76,705
	90	86 or 87 or 88 or 89	145,517
	91	animal/	1,906,909
	92	animal experiment/	1,748,225
	93	(rats or rat or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cat or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh.	5,449,703
	94	91 or 92 or 93	5,657,587
	95	exp human/	15,385,869
	96	human experiment/	321,454
	97	95 or 96	15,387,312
	98	94 not (94 and 97)	4,489,849
	99	letter.pt.	859,132
	100	editorial.pt.	459,199

[9] [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Search Description	Search Number	Strategy	Results
	101	comment.pt.	0
	102	erratum.pt.	119,960
	103	note.pt.	603,322
	104	99 or 100 or 101 or 102 or 103	2,041,613
Utility All	105	OR/61-83	566,780
DME and Utility	106	26 and 105	1,111
Blindness and Utility	107	32 and 105	13,862
Utiltiy related to Adverse Event of All Treatment Types	108	85 and 105	2,389
Vision related Utility	109	90 and 105	3,170
Adverse Event of DME	110	OR/ 54-60	154,745
Utility related to Adverse Event DME	111	105 and 110	3,327
Search All	112	106 or 107 or 108 or 109 or 111	19,683
Embase Exclusive articles	113	limit 112 to exclude medline journals	2,146
Date Limit	114	limit 113 to yr="1999 -Current"	2,103
Language limit	115	limit 114 to english	1,714
Human Filter	116	115 not 98	1,704
Publication Type Limit	117	116 not 104	1,618

Table 137. Search strategy in Medline for the utilities review

Search Description	Search Number	Strategy	Results
Population			
	1	exp diabetes mellitus/	303,098
	2	Diabet$.ti,ab,ot,hw.	449,065
	3	(T1dm or t1-DM or IDDM or DMI or DM1 or DM-1 or DM-I or TIDM).ti,ab,ot.	12,908
	4	(T2dm or DM2 or DM-2 or T2-DM or MODY or DM2 or NIDDM or IIDM or TIIDM).ti,ab,ot.	14,931
	5	((juvenile$ or child$ or labil$ or brittle$ or ((earl$ or sudden) adj onset)) adj4 DM).ti,ab,ot.	400
	6	((adult$ onset or matur$ or late$ or slow or stable) adj4 DM).ti,ab,ot.	324
	7	((insulin-dependen$ or non-insulin dependen$ or noninsulin dependen$) adj4 DM).ti,ab,ot.	153
	8	((typ$ 2 or typ$ ii or typ$ two or type2 or typeii) adj3 DM).ti,ot,ab.	2,767
	9	((keto$ or nonketo$ or autoimmun$ or auto-immun$) adj4 DM).ti,ab,ot.	124
	10	((obes$ or non-obes$ or nonobes$) adj4 DM).ti,ab,ot.	299
	11	exp Insulin Resistance/	51,331
	12	(Insulin$ resist$ adj4 DM).ti,ab,ot.	138
	13	OR/ 1-12	481,713
	14	Macular degeneration/	10,684
	15	Macular Edema/	4,001
	16	Retinal Hemorrhage/	4,317
	17	((parafovea$ or fovea$ or retina$ or macul$ or eye or eyes) adj2 (edema$ or oedema$ or degenerat$ or swell$ or h?emorrhag$ or microaneur?sm$ or micro-aneur?sm$ or (dilat$ adj2 capillar$))).ti,ot,ab.	26,384

Search Description	Search Number	Strategy	Results
	18	(CSME or CSMO or CME or CMO).ti,ab,ot.	4,558
	19	OR/ 14-18	36,886
	20	13 and 19	5,520
	21	diabetic retinopathy/ or ((diabet$ adj2 maculop$) or (diabet$ adj2 macul$ adj2 edema$) or (diabet$ adj2 macul$ oedema$)).ti,ot,ab.	18,467
	22	(DME or DMO).ti,ot,ab.	1,946
	23	2 and 22	568
	24	21 or 23	18,484
	25	20 or 24	20,335
Blindness			
	26	exp Blindness/	19,831
	27	visually impaired persons.af.	1,283
	28	blindness.af.	29,857
	29	exp vision,low/	2,144
	30	vision,low.af.	2,161
	31	exp visually impaired persons/	1,236
	32[10]	(visual$ or vision or sight).mp. or exp visual acuity/	527,584
	33	(impair$ or defect$ or loss$ or disorder$ or reduc$ or diminish).mp.	4,434,191
	34	32 and 33	168,026
	35	OR/ 26-31 or 34	191,832
Treatment Strategies			
	36	lucentis.af.	225
	37	rhufab.af.	4
	38	ranibizumab.af.	1,699
	39	ozurdex.af.	80
	40	dexamethasone intravitreal implant.af.	46
	41	avastin.af.	1,013
	42	bevacizumab.af.	8,670
	43	iluvien.af.	7
	44	eylea.af.	10
	45	aflibercept.af.	270
	46	fluocinolone acetonide.af.	1,336
	47	exp fluocinolone acetonide/	1,311
	48	OR/ 36-47	11,420
Laser Treatment			
	49	exp laser coagulation/	6,014
	50	laser coagulation.tw.	1,085
	51	exp light coagulation/	10,656
	52	light coagulation.tw.	216
	53	photocoagulation.af.	7,366
	54	OR/ 49-53	14,219
Adverse Event			
	55	(safe or safety or side-effect$ or undesirable effect$ or treatment emergent or tolerability or toxicity or adrs).ti,ab.	804,092
	56	(adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.	234,864

[10] [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Search Description	Search Number	Strategy	Results
	57	55 or 56	948,909
All treatments	58	48 or 54	25,188
Adverse Event of all treatments	59	57 and 58	4,470
Utility			
	60	exp quality of life/ or quality of life.tw.	183,421
	61	QoL.tw.	18,467
	62	(hrqol or hrql or hql or hqol or h qol or hrqol or hr qol).tw.	9,815
	63	rosser.tw.	72
	64	(hye or hyes).tw.	54
	65[11]	(utili$ and (value$ or weight$ or scor$ or index$ or assessment or evaluation)).mp.	164,442
	66	(health state utility or health utilit$).tw.	1,198
	67	(health utility ind$ or hui or hui$ or hui2 or hui3).mp.	5,171
	68	(SG or standard gamble$).tw.	5,965
	69	(time trade-off or time trade off or time tradeoff or tto).tw.	1,147
	70	(euroqol or euro qol or eq5d or eq 5d or eq-5d).tw.	3,817
	71	(sf6 or sf 6 or sf-6d or sf 6d or sf6d or sf-36 or SF-36 or SF-36).tw.	14,463
	72	(short form 6 or shortform 6 or sf six or short form six or shortform 6D or sf sixD or sfsixD or shortform sixD or short form sixD or short form 6D or short-form 36 or short form 36 or short form thirtysix or sf thirtysix or sf thirty six).tw.	6,135
	73	(disability adjusted life or daly$).tw.	1,522
	74	(qaly$ or qald$ or qale$ or qtime$ or quality adjusted life).tw.	6,945
	75	health$ year$ equivalent$.tw.	39
	76	(quality of well being or qwb).tw.	343
	77	(willingness to pay or wtp).tw.	2,389
	78	disutilit$.tw.	208
	79	health status indicators/	19,389
	80	preference score.tw.	102
	81	preference measure.tw.	43
Vision			
	82	exp visual acuity/ or visual acuity.af.	73,386
	83	exp vision,ocular/ or vision,ocular.af.	21,654
	84	exp vision, binocular/	5,536
	85	exp vision, monocular/	2,114
	86	vision.af.	144,027
	87	OR/ 82-86	189,270
DME related adverse event			
	88	exp cataract/ or cataract.af.	55,485
	89	exp endophthalmitis/ or endophthalmitis.af.	7,114
	90	(vitreous haemorrhage or vitreous hemorrhage).af.	2,891
	91	(((eye$ or ocular or intraocular) and (pressure$ or tension$)) or ocular hypertension).af. or exp ocular hypertension/ or exp intraocular pressure/ or intraocular pressure.af.	72,210
	92	retinal detachment/	15,709
	93	OR/ 88-92	137,087
	94	animals/ not (animals/ and humans/)	3,778,836
	95	letter.pt.	818,973

[11] [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Search Description	Search Number	Strategy	Results
	96	comment.pt.	564,767
	97	editorial.pt.	343,035
	98	published erratum.pt.	1,186
	99	OR/ 95-98	1,292,220
Utility All	100	OR/60-81	374,367
DME and utility	101	25 and 100	379
Utility of Adverse Event of all treatments	102	59 and 100	227
Blindness and utility	103	35 and 100	6,929
Vision and utility	104	87 and 100	3,967
Utility of DME related adverse event	105	93 and 100	1,868
Search All	106	101 or 102 or 103 or 104 or 105	9,770
Date Limit	107	limit 106 to yr="1999 -Current"	8,288
Language Limit	108	limit 107 to english	7,520
Human Limit	109	108 not 94	7,322
Publication Limit	110	109 not 99	7,208

Table 138. Search strategy for NHS EED and EconLit for the utilities review

Search description	Search number	Search strategy	Result
NHS EED			
Limit	1	FROM 2003 TO 2013	
Population	2	dme or dmo or csme or macular or cme or edema or oedema or diabetic macular edema or diabetic macular oedema or diabetic retinopathy AND #1	114
EconLit			
Limit	1	From 2003-2013	
Population	2	(dme or dmo or csme or macul$ or cme or $edema).tw. or diabetic macular edema.mp. or diabetic macular oedema.mp. or diabetic retinopathy.mp. or (macula$ adj2 (edema$1 or oedema$1)).mp.AND #1	98

Table 139. Search strategy for HTA websites for the utilities review

Search description	Search number	Search strategy	Result Hits
SMC			
Limit	1	Custom Date: (01/01/2003 – 31/12/2013)	
Population	2	(diabetic macular edema OR diabetic macular oedema) AND #1	MC Advice = 49 Forthcoming submissions = 2
Treatment Strategies	3	#2 AND (Lucentis OR rhufab OR ranibizumab OR Laser OR Ozurdex OR dexamethethosone intravitreal implant OR Iluvien OR eylea OR aflibercept OR Avastin OR bevacizumab) (Lucentis OR Laser OR Ozurdex OR Iluvien OR Avastin)	MC Advice = 21 Forthcoming submissions = 2
NICE			
Limit	1	Custom Date: (01/01/2003 – 31/12/2013)	
Population	2	diabetic macular oedema OR diabetic macular edema	47
Treatment Strategies	3	#2 AND (Lucentis OR rhufab OR ranibizumab OR Laser OR Ozurdex OR dexamethethosone intravitreal implant OR Iluvien OR eylea OR aflibercept OR Avastin OR bevacizumab)	31
AWMSG[12]			
Limit	1	Custom Date: (01/01/2003 – 31/12/2013)	
Population	2	(diabetic macular edema OR diabetic macular oedema) AND #1	30 (Appraisals = 10, Appraisal documents = 11, Medicines management = 2, AWMSG documents = 7)

Table 140. Search strategy for conference proceedings for the utilities review

Search description	Search number	Search strategy	Result Hits
POR			
mit		om January 2011 through November 2013)	
pulation		acular edema) OR (macular oedema) OR (Diabetic retinopathy) OR (Diabetic macular edema) OR (Diabetic macular oedema) AND #1	
arch		AND ((Cost OR Utility OR 'Resource Use' OR 'Economic Burden' OR 'Humanistic Burden')	
RVO[13]			
mit		om January 2011 through December 2013)	
arch		iabetic macular edema" AND ("cost" OR "utility") AND #1	
AO[14]			
mit		011 To 2013)	
arch		abetic macular edema OR diabetic macular oedema) AND (cost OR utility)	
OC[15]			
mit		om January 2011 through November 2013)	
arch		abetic macular edema OR diabetic macular oedema)	
		abetic macular edema OR diabetic macular oedema) AND (cost OR utility)	

[12] The Welsh Health Authority website does not allow 'OR/AND' search strategies, therefore only disease terms were searched.
[13] Investigative Ophthalmology and Visual Sciences search engine used (text/title/abstract).
[14] Meeting Archive search engine used.
[15] International Council of Ophthalmology search engine used.

◊ Details of any additional searches (for example, searches of company databases [include a description of each database]).

None done.

◊ The inclusion and exclusion criteria.

Inclusion and exclusion criteria are shown in Table 81.

Table 141. Eligibility criteria for the utilities review

Topic	Inclusion criteria	Exclusion criteria
Population	• Vision-related illnesses • Visually impaired/blind patients • Visually impaired patients with treatment-related adverse events for Eylea, Lucentis, Rhufab, Ozurdex, Avastin, Iluvien. • Humans • Adults (≥ 18 years)	• Patient population not specific to vision-related disorders • Adverse events not related to treatments of interest (ie: Eylea, Lucentis, Rhufab, Ozurdex, Avastin, Iluvien.) or population of interest (i.e. vision-related diseases) • Not humans • Not adults (≤18 years)
Outcomes	Disutility and utility measures: 1. Health State Utility values elicited using direct methods: Time Trade Off and Standard Gamble 2. Preference-based methods: EQ-5D, HUI3, SF-6D, SF-36 Summary scores 3.Economic evaluations reporting outcomes based on Points 1 and 2 4. Disutility values relating to adverse events (e.g: endophthalmitis, cataract, vitreous haemorrhage, ocular hypertension, intraocular pressure, retinal detachment) reporting outcomes based on Points 1 and 2	• Outcomes not related to change in utility/disutility due to change in visual acuity • Vision related questionnaires (e.g: VF-14 or NEI-VFQ-25) without utility estimates (either 1 or 2) • Design of vision related questionnaires without results of relevant study population and country of interest
Study type	• Phase (II, III, IV) clinical trials • Economic evaluations • Cross sectional studies • Longitudinal studies • Registry studies • Observational studies	• Phase 1 clinical trials • Individual case reports • Systematic reviews • Non-systematic reviews • Genetic/biochemical studies
Geography[16]	Scope is within UK, Canada, Australia and Latin America	Scope is outside UK, Canada, Australia and Latin America
Publication Date	• ≥ 1999 – 2014 for peer-reviewed publications • ≥ 2010-2013 for conference proceedings • (local) guidelines: only most recent version of similar guidelines	• < 1999 for peer-reviewed publications • <2010 for conference proceedings • (local) guidelines: older versions of similar guidelines
Publication Type	• In English language • Full texts • Conference proceedings • Paper abstracts if full texts not available	• Not in English • Reviews (systematic/non-systematic; used to check references, but not extracted) • Editorials • Errata • Letters (to editor) • Notes • Comments/Commentary

◊ The data abstraction strategy.

[16] The scope of the search covered Australia, Canada and Colombia as well as the UK. Only studies relevant to the UK were used to derive model parameters. However, during the study selection phase, the country of study was recorded in order to allow articles from alternative countries to be consulted in case no relevant information was identified for the UK.

The data extraction forms used for the utilities review contained information regarding study details, study setting, study design, population, sample size, baseline characteristics, type and duration of diabetes, mean BCVA, study duration, study outcomes, and disutility value per adverse event.

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

◊ The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Medline
Embase
Medline (R) In-Process
NHS EED
EconLIT.

The search was conducted in literature databases, the websites of UK-based HTA agencies, and conference proceedings (Table 135).

Table 142. Databases searched

Literature	HTA agencies	Conference proceedings
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) (https://ovidsp.ovid.com/autologin.cg)	SCOTLAND: Scottish Medicines Consortium (SMC) (www.scottishmedicines.org.uk/Home)	International Society For Pharmacoeconomics and Outcomes Research (ISPOR) (www.ispor.org/)
Ovid Embase (https://ovidsp.ovid.com/autologin.cg)	ENGLAND AND WALES: National Institute of Health and Care Excellence (NICE) (www.nice.org.uk/)	The Association for Research in Vision and Ophthalmology (ARVO) (www.arvo.org/; www.iovs.org/)
National Health Service Economic Evaluation Database (NHS EED) (www.crd.york.ac.uk/crdweb/)	WALES: All Wales Medicines Strategy Group (AWMSG); (www.awmsg.org/)	American Academy of Ophthalmology (AAO) (www.aao.org/)
EconLit (http://ovidsp.tx.ovid.com/)	AUSTRALIA: Department of Health and Ageing (http://www.health.gov.au/)	Retina Congress (EURETINA) (www.euretina.org/default.asp)
	COLOMBIA: Ministry of Health (http://www.minsalud.gov.co/Paginas/default.aspx)	World Ophthalmology Congress (WOC) (www.woc2014.org/; www.icoph.org/)
	CANADA: Canadian Agency for Drugs and Technologies in Health (CADTH) (http://www.cadth.ca/)	

◊ The date on which the search was conducted.

6 February 2014.

◊ The date span of the search.

Publication dates were set from 2003 until the date of the search for the literature databases and the HTA agency websites, and for the last 3 years for conference proceedings.

◊ The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strategy for Embase is shown in Table 143, for Medline in Table 144, for NHS EED and EconLit in Table 145, for HTA websites in Table 146, and for conference proceedings in Table 147.

Table 143. Search strategy in Embase for the cost and resource use review

Search Description	Search number	Strategy	Results
Population			
	1	exp diabetes mellitus/	602,131
	2	Diabet$.ti,ab,ot,hw.	707,910
	3	(T1dm or t1-DM or IDDM or DMI or DM1 or DM-1 or DM-I or TIDM).ti,ab,ot.	16,950
	4	(T2dm or DM2 or DM-2 or T2-DM or MODY or DM2 or NIDDM or IIDM or TIIDM).ti,ab,ot.	23,203
	5	((juvenile$ or child$ or labil$ or brittle$ or ((earl$ or sudden) adj onset)) adj4 DM).ti,ab,ot.	621
	6	((adult$ onset or matur$ or late$ or slow or stable) adj4 DM).ti,ab,ot.	451
	7	((insulin-dependen$ or non-insulin dependen$ or noninsulin dependen$) adj4 DM).ti,ab,ot.	222
	8	((typ$ 2 or typ$ ii or typ$ two or type2 or typeii) adj3 DM).ti,ot,ab.	4,846
	9	((keto$ or nonketo$ or autoimmun$ or auto-immun$) adj4 DM).ti,ab,ot.	193
	10	((obes$ or non-obes$ or nonobes$) adj4 DM).ti,ab,ot.	672
	11	Insulin resistance/	77,319
	12	(Insulin$ resist$ adj4 DM).ti,ab,ot.	223
	13	OR/1 -12	749,178
	14	exp Retina maculopathy/	36,627
	15	exp Retina macula edema/	10,318
	16	eye edema/	472
	17	retina macula hemorrhage/	645
	18	((parafovea$ or fovea$ or retina$ or macul$ or eye or eyes) adj2 (edema$ or oedema$ or degenerat$ or swell$ or h?emorrhag$ or microaneur?sm$ or micro-aneur?sm$ or (dilat$ adj2 capillar$))).ti,ot,ab.	33,749
	19	(CSME or CSMO or CME or CMO).ti,ab,ot.	7,529
	20	OR/14 -19	57,864
	21	13 and 20	9,807
	22	exp diabetic retinopathy/ or ((diabet$ adj2 maculop$) or (diabet$ adj2 macul$ adj2 edema$) or (diabet$ adj2 macul$ oedema$)).ti,ot,ab.	29,559
	23	(DME or DMO).ti,ot,ab.	2,357
	24	2 and 23	729
	25	22 or 24	29,586
	26	21 or 25	32,685
Resource Use			
	27	Socioeconomics/	113,455
	28	Cost benefit analysis/	67,469
	29	Cost effectiveness analysis/	94,569
	30	Cost of illness/	15,010
	31	Cost control/	48,018
	32	Economic aspect/	102,616
	33	Financial management/	102,659
	34	Health care cost/	127,969
	35	Health care financing/	11,318
	36	Health economics/	33,677

Search Description	Search number	Strategy	Results
	37	Hospital cost/	13,783
	38	(fiscal or financial or finance or funding).tw.	104,981
	39	Cost minimization analysis/	2,407
	40	(cost adj estimate$).mp.	1,991
	41	(cost adj variable$).mp.	156
	42	(unit adj cost$).mp.	2,444
Economic studies: SIGN Filter search	43	OR/27- 42	669,170
	44	indirect cost?.mp.	5,380
	45	exp medical leave/	3,533
	46	return to work/	620
	47	exp absenteeism/	13,128
	48	productivity/ and (lost/ or loss.mp.)	1,648
	49	work/ and hour.mp.	278
	50	(missed and paid).mp. and work/	6
	51	caregiver/ and burden.mp.	5,113
	52	'health care utili?ation'.mp.	40,603
	53	'health care util$'.mp.	40,638
	54	exp resource allocation/	15,205
	55	exp resource management/	28,001
	56	'resource utili?ation'.mp.	8,072
Blindness[17]			
	57	exp low vision/	142
	58	exp blindness/ or blindness.af.	45,939
	59	(visual$ or vision or sight).mp. or exp visual acuity/	773,814
	60	(impair$ or defect$ or loss$ or disorder$ or reduc$ or diminish).mp.	5,731,661
	61	59 and 60	264,825
	62	57 or 58 or 61	296,085
Treatment Strategy			
	63	ranibizumab/	3,654
	64	fluocinolone acetonide/	2,384
	65	bevacizumab/	30,540
	66	dexamethasone/	110,364
	67	aflibercept/	1,400
	68	eylea.af.	108
	69	lucentis.af.	1,580
	70	rhufab.af.	18
	71	ozurdex.af.	242
	72	avastin.af.	7,505
	73	iluvien.af.	68
	74	OR/ 63-73	143,404
Laser Treatment			
	75	laser coagulation/	17,922
	76	photocoagulation.af.	10,236

[17] [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Search Description	Search number	Strategy	Results
	77	laser coagulation.af.	18,456
	78	75 or 76 or 77	20,681
Adverse Event			
	79	(safe or safety or side-effect$ or undesirable effect$ or treatment emergent or tolerability or toxicity or adrs).ti,ab.	1,136,520
	80	(adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.	345,960
	81	adverse drug reaction/	155,815
	82	side effect/	171,716
	83	79 or 80 or 81 or 82	1,519,028
Adverse Event related to DME			
	84	(vitreous haemorrhage or vitreous hemorrhage).af.	5,418
	85[18]	(((eye$ or ocular).mp. or intraocular/) and (pressure$ or tension$).mp.) or ocular hypertension/ or intraocular pressure/ or increased intraocular pressure.mp	62,863
	86	retinal detachment/	24,421
	87	cataract/	40,730
	88	endophthalmitis/	8,858
	89	cataract.af.	73,358
	90	endophthalmitis.af.	10,317
	91	OR/ 44-56	98,238
Resource Use	92	43 or 91	731,452
Resource Use of DME	93	26 and 92	1,321
Resource Use of Blindness	94	62 and 92	6,986
Treatment Types All	95	74 or 78	162,764
Resource Use of treatments	96	92 and 95	3,360
Adverse Event of Treatments	97	83 and 95	31,546
Resource use of Adverse Event of Treatments	98	92 and 97	1,104
Adverse Event DME	99	OR/ 84-90	154,818
Resource Use of Adverse Event DME	100	92 and 99	3,697
Search All	101	93 or 94 or 96 or 98 or 100	12,963
	102	animal/	1,906,909

[18] . [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Search Description	Search number	Strategy	Results
	103	animal experiment/	1,748,225
	104	human/	15,233,887
	105	human experiment/	321,454
	106	(rats or rat or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cat or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh.	5,449,703
	107	102 or 103 or 106	5,657,587
	108	104 or 105	3,640,067
	109	107 not (107 and 108)	2,017,520
Human Filter	110	101 not 109	12,747
Date Filter	111	limit 110 to yr="2003 -Current"	10,017
Language Filter	112	limit 111 to english	9,609
Embase Exclusive Articles	113	limit 112 to exclude medline journals	1,091
	114	letter.pt.	859,132
	115	editorial.pt.	459,199
	116	note.pt.	603,322
	117	erratum.pt.	119,960
	118	114 or 115 or 116 or 117	2,041,613
Publication Type filter	119	113 not 118	1,048

Table 144. Search strategy in Medline for the cost and resource use review

Search Description	Search Number	Strategy	Results
Population			
	1	exp diabetes mellitus/	449,065
	2	Diabet$.ti,ab,ot,hw.	12,908
	3	(T1dm or t1-DM or IDDM or DMI or DM1 or DM-1 or DM-I or TIDM).ti,ab,ot.	14,931
	4	(T2dm or DM2 or DM-2 or T2-DM or MODY or DM2 or NIDDM or IIDM or TIIDM).ti,ab,ot.	400
	5	((juvenile$ or child$ or labil$ or brittle$ or ((earl$ or sudden) adj onset)) adj4 DM).ti,ab,ot.	324
	6	((adult$ onset or matur$ or late$ or slow or stable) adj4 DM).ti,ab,ot.	153
	7	((insulin-dependen$ or non-insulin dependen$ or noninsulin dependen$) adj4 DM).ti,ab,ot.	2,767
	8	((typ$ 2 or typ$ ii or typ$ two or type2 or typeii) adj3 DM).ti,ot,ab.	124
	9	((keto$ or nonketo$ or autoimmun$ or auto-immun$) adj4 DM).ti,ab,ot.	299
	10	((obes$ or non-obes$ or nonobes$) adj4 DM).ti,ab,ot.	51,331
	11	exp Insulin Resistance/	138
	12	(Insulin$ resist$ adj4 DM).ti,ab,ot.	481,713
	13	OR/1-12	10,684
	14	Macular degeneration/	4,001
	15	Macular Edema/	4,317
	16	Retinal Hemorrhage/	26,384
	17	((parafovea$ or fovea$ or retina$ or macul$ or eye or eyes) adj2 (edema$ or oedema$ or degenerat$ or swell$ or h?emorrhag$ or microaneur?sm$ or micro-aneur?sm$ or (dilat$ adj2 capillar$))).ti,ot,ab.	4,558

Search Description	Search Number	Strategy	Results
	18	(CSME or CSMO or CME or CMO).ti,ab,ot.	36,886
	19	OR/14-18	5,520
	20	13 and 19	18,467
	21	diabetic retinopathy/ or ((diabet$ adj2 maculop$) or (diabet$ adj2 macul$ adj2 edema$) or (diabet$ adj2 macul$ oedema$)).ti,ot,ab.	1,946
	22	(DME or DMO).ti,ot,ab.	568
	23	2 and 22	18,484
	24	21 or 23	20,335
	25	20 or 24	19,831
Resource Use			
	26	Economics/	26,421
	27	"costs and cost analysis"/	41,035
	28	Cost allocation/	1,933
	29	Cost-benefit analysis/	57,961
	30	Cost control/	19,929
	31	Cost savings/	8,436
	32	Cost of illness/	16,849
	33	Cost sharing/	1,888
	34	"deductibles and coinsurance"/	1,405
	35	Medical savings accounts/	478
	36	Health care costs/	25,944
	37	Direct service costs/	1,005
	38	Drug costs/	11,787
	39	Employer health costs/	1,058
	40	Hospital costs/	7,501
	41	Health expenditures/	13,280
	42	Capital expenditures/	1,932
	43	Value of life/	5,357
	44	exp economics, hospital/	19,064
	45	exp economics, medical/	13,395
	46	Economics, nursing/	3,881
	47	Economics, pharmaceutical/	2,478
	48	exp "fees and charges"/	26,504
	49	exp budgets/	11,910
	50	(low adj cost).mp.	23,701
	51	(high adj cost).mp.	7,846
	52	(health?care adj cost$).mp.	4,230
	53	(fiscal or funding or financial or finance).tw.	79,513
	54	(cost adj estimate$).mp.	1,387
	55	(cost adj variable).mp.	31
	56	(unit adj cost$).mp.	1,495
	57	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	170,592
Economic studies SIGN Filter.	58	OR/26-57	458,329
	59	"resource management".mp.	1,859
	60	resource allocation/	6,960
	61[19]	"resource use".mp.	4,400
	62	sick leave/	3,720
	63	health resources/	8,479

[19] [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Search Description	Search Number	Strategy	Results
	64	"health care util$".mp.	3,982
	65	"health resource utili?ation".mp.	222
	66	"indirect costs".mp.	3,277
	67	"caregivers burden".mp.	235
	68	"disability leave".mp.	29
	69	"sick days".mp.	275
	70	"resource utili?ation".mp.	4,880
	71	OR/ 59-70	35,022
	72	58 or 71	478,851
Resource Use of DME	73	25 and 72	428
Blindness			
	74	exp Blindness/	19,831
	75	visually impaired persons.af.	1,283
	76	blindness.af.	29,857
	77	exp vision,low/	2,144
	78	vision,low.af.	2,161
	79	exp visually impaired persons/	1,236
	80	(visual$ or vision or sight).mp. or exp visual acuity/	527,584
	81	(impair$ or defect$ or loss$ or disorder$ or reduc$ or diminish).mp.	4,434,191
	82	80 and 81	168,026
	83	OR/74-79 or 82	191,625
Resource Use of Blindness	84	72 and 83	3,356
Treatment Strategies			
	85	lucentis.af.	225
	86	rhufab.af.	4
	87	ranibizumab.af.	1,699
	88	ozurdex.af.	80
	89	dexamethasone intravitreal implant.af.	46
	90	avastin.af.	1,013
	91	bevacizumab.af.	8,670
	92	iluvien.af.	7
	93	eylea.af.	10
	94	aflibercept.af.	270
	95	fluocinolone acetonide.af.	1,336
	96	exp fluocinolone acetonide/	1,311
	97	OR/ 85-96	11,420
	98	72 and 97	402
Laser Treatment			
	99	exp laser coagulation/	6,014
	100	laser coagulation.tw.	1,085
	101	exp light coagulation/	10,656
	102	light coagulation.tw.	216
	103	photocoagulation.af.	7,366
	104	OR/ 99-103	14,219
	105	72 and 104	184
Resource use of All treatments	106	98 or 105	568
Adverse			

Search Description	Search Number	Strategy	Results
Event			
	107	(safe or safety or side-effect$ or undesirable effect$ or treatment emergent or tolerability or toxicity or adrs).ti,ab.	804,092
	108	(adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.	234,864
	109	107 or 108	947,670
All treatment	110	97 or 104	25,155
Adverse Event of All Treatment Types	111	109 and 110	4,463
Resource Use of adverse event of All treatments	112	72 and 111	169
Adverse event of DME			
	113	exp cataract/ or cataract.af.	55,485
	114	exp endophthalmitis/ or endophthalmitis.af.	7,114
	115	(vitreous haemorrhage or vitreous hemorrhage).af.	2,891
	116	(((eye$ or ocular or intraocular) and (pressure$ or tension$)) or ocular hypertension).af. or exp ocular hypertension/ or exp intraocular pressure/ or intraocular pressure.af.	72,210
	117	retinal detachment/	15,709
	118	OR/ 113-117	137,087
Resource use of DME related adverse events	119	72 and 118	2,155
Search All	120	73 or 84 or 106 or 112 or 119	5,501
Date Limit	121	limit 120 to yr="2003 -Current"	3,900
Language Limit	122	limit 121 to english	3,644
Human Limit	123	animals/ not (animals/ and humans/)	3,778,836
	124	122 not 123	3,551
	125	letter.pt.	818,973
	126	comment.pt.	564,767
	127	editorial.pt.	343,035
	128	published erratum.pt.	1,186
	129	125 or 126 or 127 or 128	1,292,220
Publication Limit	130	124 not 129	3,410

Table 145. Search strategy for NHS EED and EconLit for the cost and resource use review

Search description	Search number	Search strategy	Result
NHS EED			
Limit	1	FROM 2003 TO 2013	
Population	2	dme or dmo or csme or macular or cme or edema or oedema or diabetic macular edema or diabetic macular oedema or diabetic retinopathy AND #1	114
EconLit			
Limit	1	From 2003-2013	
Population	2	(dme or dmo or csme or macul$ or cme or $edema).tw. or diabetic macular edema.mp. or diabetic macular oedema.mp. or diabetic retinopathy.mp. or (macula$ adj2 (edema$1 or oedema$1)).mp.AND #1	98

Table 146. Search strategy for HTA websites for the cost and resource use review

Search description	Search number	Search strategy	Result Hits
SMC			
Limit	1	Custom Date: (01/01/2003 – 31/12/2013)	
Population	2	(diabetic macular edema OR diabetic macular oedema) AND #1	SMC Advice = 49 Forthcoming submissions = 2
Treatment Strategies	3	#2 AND (Lucentis OR rhufab OR ranibizumab OR Laser OR Ozurdex OR dexamethethosone intravitreal implant OR Iluvien OR eylea OR aflibercept OR Avastin OR bevacizumab) (Lucentis OR Laser OR Ozurdex OR Iluvien OR Avastin)	SMC Advice = 21 Forthcoming submissions = 2
NICE			
Limit	1	Custom Date: (01/01/2003 – 31/12/2013)	
Population	2	diabetic macular oedema OR diabetic macular edema	47
Treatment Strategies	3	#2 AND (Lucentis OR rhufab OR ranibizumab OR Laser OR Ozurdex OR dexamethethosone intravitreal implant OR Iluvien OR eylea OR aflibercept OR Avastin OR bevacizumab)	31
AWMSG[20]			
Limit	1	Custom Date: (01/01/2003 – 31/12/2013)	
Population	2	(diabetic macular edema OR diabetic macular oedema) AND #1	30 (Appraisals = 10, Appraisal documents = 11, Medicines management = 2, AWMSG documents = 7)
CADTH			
Limit	1	Custom Date: (01/01/2003 – 15/11/2013)	
Population	2	"macular edema" / "macular oedema" / "diabetic retinopathy"	5
Australian HA[21]			
Limit	1	2003-2013	
Population	2	"macular edema" OR "macular oedema" OR “diabetic retinopathy”	7

[20] The Welsh Health Authority website does not allow ‘OR/AND’ search strategies, therefore only disease terms were searched.
[21] The Australian Health Authority website does not allow ‘OR’/’AND’ search strategies, therefore, only disease terms were searched.

Colombian HA			
Limit	1	2003-2013	
Population	2	(diabetic macular edema OR diabetic macular oedema OR “diabetic retinopathy)	0

Table 147. Search strategy for conference proceedings for the cost and resource use review

Search description	Search number	Search strategy	Result Hits
ISPOR			
Limit	1	(from January 2011 through November 2013)	
Population	2	(macular edema) OR (macular oedema) OR (Diabetic retinopathy) OR (Diabetic macular edema) OR (Diabetic macular oedema) AND #1	27
Search	3	#2 AND ((Cost OR Utility OR 'Resource Use' OR 'Economic Burden' OR 'Humanistic Burden')	24
ARVO[22]			
Limit	1	(from January 2011 through December 2013)	
Search	2	“diabetic macular edema” AND (“cost” OR “utility”) AND #1	11
AAO[23]			
Limit	1	(2011 To 2013)	
Search	2	(diabetic macular edema OR diabetic macular oedema) AND (cost OR utility)	45
WOC[24]			
Limit	1	(from January 2011 through November 2013)	
Search	2	(diabetic macular edema OR diabetic macular oedema)	9
	3	(diabetic macular edema OR diabetic macular oedema) AND (cost OR utility)	7
EURETINA			
Limit	1	(from January 2011 through November 2013)	
Search	2	(diabetic macular edema OR diabetic macular oedema)	5

◊ Details of any additional searches (for example, searches of company databases [include a description of each database]).

None done.

◊ The inclusion and exclusion criteria.

Inclusion and exclusion criteria are shown in Table 148.

Table 148. Eligibility criteria for the cost and resource use review

Topic	Inclusion Criteria	Exclusion Criteria
Population	• Vision-related illnesses • Visually impaired patients with treatment related adverse events for Eylea, Lucentis,Rhufab,Ozurdex, Avastin, Iluvien, laser coagulation, photocoagulation	• Patient population not specificially studying vision-related disorders • Adverse event resource use not related to treatments or population of interest (vision related disease areas) • Not Humans

[22] Investigative Ophthalmology and Visual Sciences search engine used (text/title/abstract).
[23] Meeting Archive search engine used.
[24] International Council of Ophthalmology search engine used.

Topic	Inclusion Criteria	Exclusion Criteria
	• Humans • Adults (≥18 years)	• Not Adults (≤ 18 years)
Outcomes	Economic Evaluations of DME and other vision related disorders • Outpatient and inpatient resource use related to DME and other vision-related illnesses • Direct costs of inaptient and outpatient services related to DME and other vision-related illnesses • Indirect costs related to DME and other vision-related illnesses, (e.g. caregiver burden, production loss) Type and costs of adverse events related to DME and other vision-related illnesses	Resource use and cost outcomes not related to: • DME or any other vision-related illnesses
Study Type	• Economic evaluations • Chart reviews • Cost analyses • Comparative studies • Observational Studies	• Clinical Trials (Phase I/ II/ III/ IV) • Genetic studies • Duplicate of an article already identified
Geography[25]	• Scope is within UK, Canada, Australia, Latin America	• Scope of this study is outside UK, Canada, Australia and Latin America
Publication Date	• ≥ 2003 – 2014 for peer-reviewed publications • (local) guidelines: only the most recent version of similar guidelines • ≥ 2010-2013 conference proceedings	• < 2003 for peer-reviewed publications • (Local) guidelines: older versions of similar guidelines • <2010 for conference proceedings
Publication Type	• In English Language • Full texts Articles • Conference proceedings • Paper abstracts in case full texts are not available	• Not in English • Reviews (systematic/non-systematic; these will be used to check references, but will not be extracted)abstracts • Editorials • Erratums • Letters (to editor) • Notes • Comments/Commentary

◊ The data abstraction strategy.

The data extraction forms used for the utilities review contained information regarding study details, study design, population, sample size, baseline characteristics, type and duration of diabetes, mean BCVA, study duration, study outcomes, study conclusion and limitations.

[25] The scope of the search covered Australia, Canada and Colombia as well as the UK. Only studies relevant to the UK were used to derive model parameters. However, during the study selection phase, the country of study was recorded in order to allow articles from alternative countries to be consulted in case no relevant information was identified for the UK.

10.14 Appendix 14: EQ-5D based utilities from VIVID/VISTA

The objective of the analysis was to explore the relationship between patient reported utility and visual acuity in both eyes using EQ-5D utility data collected in the aflibercept clinical trial programme.

Methodology

Further, definitions of key concepts and variables used in the report are given below.

- Study eye (SE) is defined as the eye which receives initial treatment
- Fellow eye (FE) is defined as the non-study eye
- Worse seeing-eye (WSE) is defined as the eye with the lowest BCVA value of the two eyes
- Better seeing-eye (BSE) is defined as the eye with the highest BCVA value of the two eyes
- SE is WSE when BCVA of the SE is lower than BCVA of the FE
- SE is BSE when BCVA of the SE is higher than BCVA of the FE

The full analysis set (FAS) of the intention to treat (ITT) population was analysed. LOCF data were used for consistency with the primary endpoint. The VIVID and VISTA inclusion criteria for were:

- Adults ≥18 years with Type 1 or 2 diabetes
- Subjects with DME secondary to diabetes mellitus involving central subfield
- Decrease in vision determined to be primarily the result of DME in the study eye

- BCVA ETDRS letter score of 73 to 24 (equivalent to BCVA of 20/40 to 20/320) in the study eye

The VIVID and VISTA exclusion were:

- Uncontrolled diabetes mellitus
- No previous treatment for DME in last 3 months
- Previous use of intraocular or periocular corticosteroids in the study eye within 120 days of Day 1
- Active proliferative diabetic retinopathy (PDR) in the study eye, with the exception of inactive, regressed PDR
- Only 1 functional eye even if that eye is otherwise eligible for the study
- Intraocular pressure ≥ 25 mm Hg
- No previous vitreoretinal surgery
- History of CVA or MI within 6 months

Regression analysis

An OLS model was used to explore the relationship between patient reported utility and visual acuity in both eyes. EQ-5D utility score was the dependent variable. BCVA estimates from both BSE and WSE were used as the main explanatory variables.

Other variables were also considered as covariates and mainly included demographics, i.e. age, gender, geography and race. In addition, visit time was also included. In this analysis, the three time points at which utility data was collected (baseline, 24 weeks, 52 weeks) were considered to be independent observations.

Univariate analysis was performed to estimate relative strength of association between selected covariates and utility; subject-matter knowledge guided construction of a parsimonious model. Variables were also transformed to consider non-linear functional forms. Finally, a robust option was used for estimating the standard errors using the Huber-White sandwich estimator. This option can deal with any minor concerns about failure to meet OLS assumptions such as normality, heteroscedasticity, or some observations that exhibit large residuals, leverage or influence.

Diagnostics

For each regression, uncertainly was addressed using goodness-of-fit statistics including R-squared and root mean square error (RMSE). Variance covariance matrices were also produced for each regression model. These may be used in the economic model for coefficient sampling during probabilistic sensitivity analysis. All analysis was conducted using STATA/SE Version 11.0

Predicted utilities

Using the estimated coefficients of the analyses described above, predicted values for the utilities by HS were produced in order to smooth the data and remove inconsistencies. To estimate these utilities, the estimated regression coefficients were use. Utility values were estimated for each of the models described above. For age, we used 62.86311 years and 30.3038 kg/m2 for mean base BMI. For BCVA values, we used mid-points of each level with the exception of first and last levels of both 5 and 8-level BCVA grouping which were adjusted to ensure that mid-points were 15 letters apart at 5-level and 10 letters apart at 8-level BCVA grouping.

Results

Ordinary least squares regression

A complete case analysis approach resulted in regression model being made on 2321 observations. The regression equation was:

yi = α + β1 (log of BCVA of BSE) + β2 (log of BCVA of WSE) + β3 (age) + β4 (baseline BMI) + ui

The results indicated that there is a positive relationship between BCVA of the WSE and BSE and utilities. This multivariate analysis, in which both the BSE and WSE were considered simultaneously, suggests that BSE BCVA had higher impact on the utility than WSE. In terms of the covariates included in the model, age and baseline BMI had a negative impact on predicted utility. These values were small but statistically significant. Patient's visit time was found to be non-significant and so, not included in the model. Mean estimates of regression coefficients and uncertainty in these estimates are shown in below (Table 149).

Table 149: Ordinary least squares regression

	Coefficients	SE	P-values
log(BCVA of Table 150: Ordinary least squares regression BSE)	[redacted]	[redacted]	[redacted]
log (BCVA of WSE)	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]
Baseline BMI	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]

For this model, [redacted].The variance-covariance matrix is given below Table 151.

Table 151: Variance-covariance matrix for OLS regression

	log(BCVA of BSE)	log (BCVA of WSE)	Age	Baseline BMI	Constant
log(BCVA of BSE)	[redacted]				
log (BCVA of WSE)	[redacted]	[redacted]			
Age	[redacted]	[redacted]	[redacted]		
Baseline BMI	[redacted]	[redacted]	[redacted]	[redacted]	
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Predicted utilities

To estimate these utilities, we used the regression coefficients computed above using OLS.

These coefficients were substituted into the regression equation shown above. For age, we used [redacted] for mean base BMI. For BCVA values, we used mid-points of each level with the exception of first and last levels of the 8-level BCVA grouping which were adjusted to ensure that mid-points were 10 letters apart at 8-level BCVA grouping.

Utilities based on the eight level classification are reported in Table 152.

Table 152: Predicted utilities (8-level BCVA) from OLS regression model

BSE	**WSE**							
	>85	**85-76**	**75-66**	**65-56**	**55-46**	**45-36**	**35-26**	**<26**
>85	[redacted]							
85-76								
75-66								
65-56								
55-46								
45-36								
35-26								
<26								

10.15 Appendix 15: Physician survey

A physician survey was developed with the primary objective of understanding how often patients with clinically significant DMO who are being treated with laser and/or ranibizumab require treatment and monitoring. As secondary objectives, the survey included questions related to treatment discontinuation, treatment for adverse events, and frequency of hospital-provided transport to attend DMO appointments. The survey was developed jointly by IMS Health and Bayer, with input from an ophthalmologist employed by Bayer to ensure clinical relevance.

The survey was conducted with ophthalmologists in England and Scotland. As criteria for participation, individuals were required to: currently treat DMO patients, spend ≥50% of their time managing patients (as opposed to teaching, research, or administrative functions), and treat/manage ≥10 DMO patients per month. The administration of the survey complied with all UK laws protecting personal data, and the European Pharmaceutical Marketing Research Association and ESOMAR guidelines.

The survey was web-based, and participants were recruited via email or telephone. The survey was piloted with two ophthalmologists before going into the field. The purpose of the pilot was to ensure the survey was clear and clinically relevant, by gaining feedback from the two pilot ophthalmologists.

The survey was in the field from April 16 – May 14, 2014. 317 ophthalmologists were invited to participate. In total, 58 ophthalmologists agreed to participate, however 23 did not login to complete in the survey and 5 failed the screening criteria. 30 ophthalmologists completed the survey, including five from Scotland. The ophthalmologists completing the survey have been practicing ophthalmology for a mean of 18.9 years, 100% work in the public (NHS) setting, and they personally manage a mean of 411.3 DMO cases per year.

Results obtained and used in the economic model are summarized in Table 153Table 157 below.

Table 153: Proportion of DMO patients with bilateral DMO at baseline

Proportion of DMO patients with bilateral DMO at treatment initiation (%)	**46.5**

Table 154: Average number of treatments administrated per eye per year

		Therapy chosen			
		Laser	**Ranibizumab**	***Ranibizumab combined with laser***	
				Ranibizumab	**Laser**
Year 1	Mean	2.4	6*	5.6	2
	Median	2	6	6	2
	Min	1	3	0	1
	Max	4	9	10	6
Year 2	Mean	1.4	4.1	3.6	1.1
	Median	1	4	3	1
	Min	0	2	1	0
	Max	3	6	6	5
Year 3	Mean	0.8	2.3	2.1	0.6
	Median	1	3	2	0
	Min	0	0	0	0
	Max	2	6	6	4
Year 4	Mean	0.4	1.2	1.3	0.4
	Median	0.4	1.2	1.3	0.4
	Min	0.4	1.2	1.3	0.4
	Max	0.4	1.2	1.3	0.4
Year 5	Mean	0.3	1	1.1	0.4
	Median	0	0	0	0
	Min	0	0	0	0
	Max	1	6	6	4
Year 6+ (annual)	Mean	0.3	0.8	0.7	0.3
	Median	0	0	0	0
	Min	0	0	0	0
	Max	1	6	6	3

* This data was not used in the economic model as it is not known whether average dosing is capacity or clinically driven and the associated impact of less frequent dosing on the efficacy and safety results used in the mixed treatment comparison and model.

Table 155: Activities that typically take place at monitoring visit

Activity	% of yes
Eye exam (visual acuity)	100%
OCT	100%
Fundus photography	27%

Table 156: Average number of monitoring visits per eye, per patient, per year

		Therapy chosen		
		Laser	**Ranibizumab**	***Ranibizumab combined with laser***
Year 1	Mean	3.8	7.1	7.6
	Median	4	6.5	7.6
	Min	2	3	3
	Max	8	13	13
Year 2	Mean	3.2	6.3	6.3
	Median	3	5	5
	Min	1	3	3
	Max	7	12	12
Year 3	Mean	2.6	4.9	5
	Median	2	4	4
	Min	1	0	0
	Max	7	12	12
Year 4	Mean	2.2	3.6	3.8
	Median	2	2.5	3
	Min	0	0	0
	Max	7	12	12
Year 5	Mean	1.9	2.9	3.1
	Median	2	2	2
	Min	0	0	0
	Max	7	12	12
Year 6+ (annual)	Mean	1.6	2.7	2.9
	Median	1	1.5	2
	Min	0	0	0
	Max	6	12	12

Table 157: Shared resource use for patients with bilateral DMO

Therapy chosen	**Shared monitoring visit (%)**
Laser	91.4
Ranibizumab	87.7
Ranibizumab + laser	87.8

10.16 Appendix 16: Model validation meeting summary

Role of both eyes

A consensus that utility should be considered as a function of both eyes was found. KOLs agreed blind patients (BCVA <35 letters) have increased resource use including residential care, depression, hip replacement, low vision aids and rehabilitation, and community care. Economists stated costs such as community care should not be included in the ICER estimate. Clinicians were asked about any differences between groups VA7 (26-35 letters) and VA8 (<25 letters). Clinicians felt active treatment would not be conditional on BCVA, but patients with <350 Snellen will receive additional clinical support and welfare benefits.

Anti-VEGF

There is limited experience with anti-VEGF in the UK (less than 5 years); however, aggressive treatment is likely in the first year with lesser intensity in subsequent years. The group broadly agreed with the model structure comprising a treatment phase, a maintenance phase where BCVA was maintained and an off-treatment phase with declining BCVA. Clinicians felt it reasonable for treatment to continue for up to 5 years with the exception of non-responders.

Study eye treatment should not impact the decision on the fellow eye.

The group was asked about a standard monitoring visit. It usually includes an eye exam (usually done by healthcare assistant), OCT and Flourescien angiography (usually first visit only).

Laser

Clinicians were asked about the type, cost and adverse effects of laser treatment in the UK. DMO patients are treated with retinal lasers, which are mostly used for patients with proliferative disease rather than diabetic

patients. Multi-spot lasers are preferred to argon because they are associated with less pain. Lasers are purchased every 8-10 years and serviced once per year. In-house training incurs no additional costs. Scars due to argon laser spread over time and may expand into the macular area which can result in vision loss 20 years later. Clinicians report a marked reduction in quality of life after first treatment, with a larger impact for multiple treatments. Laser combined with anti-VEGF occurs only for a subgroup of patients. The laser is used to treated areas of the eye that are unreachable by anti-VEGF. It was agreed that laser combination is not a direct comparator for aflibercept.

Dexamethasone

Clinicians were asked about the role of Dexamethasone in the treatment pathway. Anti-VEGF treatments are favoured, with Dexamethasone used in second line unless the patient has had previous cataract surgery or they object to monthly injection visits.

Dexamethasone is administered similarly to anti-VEGF, except with a thicker needle and occasionally anaesthetic. A closer watch on patients' intra-ocular pressure is kept following administration. Patients typically receive injections every 3-4 months and it is reasonable to assume up to 5 years on-treatment. For resource use estimation, it was agreed that data from a previous submission for Dexamethasone in RVO is suitable.

Fluocinolone

Clinicians felt that fluocinolone was not a direct comparator for aflibercept and that around 80% of patients on fluocinolone require cataract surgery.

Subgroups

Of subgroups considered, the clinicians felt that baseline CRT was most likely to impact efficacy for each treatment arm.