NICE National Institute for Health and Care Excellence

Fast Track Appraisal

Aflibercept for treating myopic choroidal neovascularisation [ID952]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

FAST TRACK APPRAISAL

Aflibercept for treating myopic choroidal neovascularisation [ID952]

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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Technical briefing

Aflibercept for treating myopic choroidal neovascularisation

This slide set is the technical briefing for this appraisal. It has been prepared by the technical team and it is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

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

It highlights key issues for discussion at the appraisal committee meeting and is expected reading for committee members. The submissions made by the company, consultees and nominated experts as well as the ERG report are available for committee members, and are optional reading.

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The technologies

	Aflibercept (intervention)	Ranibizumab (comparator)
Mechanism of action	Vascular endothelial growth factor inhibitor	Vascular endothelial growth factor inhibitor
Marketing authorisation	Visual impairment due to myopic choroidal neovascularisation	Visual impairment due to choroidal neovascularisation
Administration and dose	• Single, 2 mg intravitreal injection • Additional injections if monitoring reveals disease activity or reduced visual acuity	• Single, 0.5 mg intravitreal injection • Additional injections if monitoring reveals disease activity or reduced visual acuity
Monitoring	• The schedule for monitoring should be determined by the treating physician	• The schedule for monitoring should be determined by the treating physician

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Key drivers of the cost-effectiveness of the comparator – ranibizumab (TA298)

Clinical outcomes	• Mean change best-corrected visual acuity (BCVA) and proportions gaining or losing 5, 10 and 15 ETDRS letters • Adverse effects of treatment • Health related quality of life
Key clinical drivers	• Treatment effectiveness: BCVA and ETDRS letter outcomes
Clinical uncertainties	• Uncertainty about long-term effectiveness of ranibizumab, as outcomes measured at 3 months • Treatment benefit assumed to continue indefinitely
Resource use assumptions	• Number of injections: 3.5 in year 1 and 1 in year 2
Resource use uncertainties	• 1 injection in year 2 may be too low – ERG scenario 1.7 • Cost of blindness may have been too high • Administration costs may have been too low
Cost-effectiveness estimate	• Ranibizumab dominated vPDT • Not sensitive to alternative clinical or resource use scenarios

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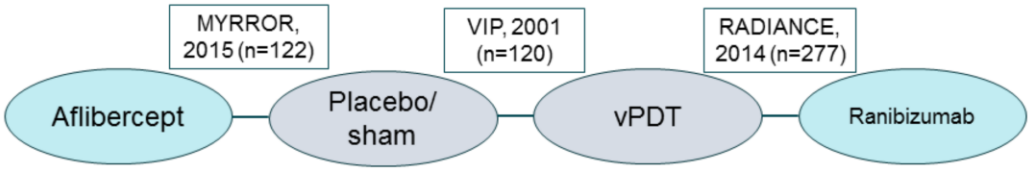
Clinical effectiveness evidence

Indirect treatment comparison

- Indirect treatment comparison for mean change in BCVA at 3 months - this is the only common measurement time point



- RADIANCE (ranibizumab) and VIP (vPDT) used in TA298
- Retreatment criteria differ
  - MYRROR (aflibercept): loss of visual acuity or disease progression
  - RADIANCE ranibizumab arm A: loss of visual acuity, ranibizumab arm B: disease activity
- Difference in baseline characteristics:
  - VIP: 91% Caucasian, RADIANCE: 57% Caucasian, MYRROR: 100% east Asian

ERG review

Clinical effectiveness evidence

- ERG clinical adviser has no concerns about generalisability of the results of aflibercept trials to the NHS
  - no evidence that the effect of aflibercept differs by ethnicity
- Proportion of people gaining or losing 5,10 or 15 ETDRS letters could not be included in the indirect comparison (limited data in VIP), but important model driver in TA298
  - provided by company at clarification, ERG concluded proportions similar

ETDRS letter gain and loss at 3 months		Aflibercept	Ranibizumab - visual acuity	Ranibizumab - disease activity
Proportion (%)	≥15 letters gain	38.9	38.1	43.1
	≥10 letters gain	63.3	61.9	65.5
	≥10 letters loss	0	1.9	0.9
	≥15 letters loss	0	1.9	0

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Source: Table 5, ERG report

Similarity of health benefits and safety

Company conclusion

Indirect treatment comparison results	Mean 3-month gain in BCVA
Aflibercept vs. ranibizumab (arm A: vision) (95% CI)	1.34 (-5.35 to 8.00)
Aflibercept vs. ranibizumab (arm B: disease) (95% CI)	0.94 (-5.67 to 7.56)

- Point estimates favours aflibercept, but confidence intervals overlap
- Not possible to include adverse events in indirect treatment comparison
  - EPAR: no new safety concerns identified in MYRROR compared with the existing indications for aflibercept
  - rate of adverse events in head-to-head trial of aflibercept vs. ranibizumab for wet age-related macular degeneration are similar
  - rate of adverse events in MYRROR and RADIANCE seem similar
- Aflibercept and ranibizumab are from same therapeutic class, therefore similarity in health benefits biologically plausible

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Source: table 23, company submission

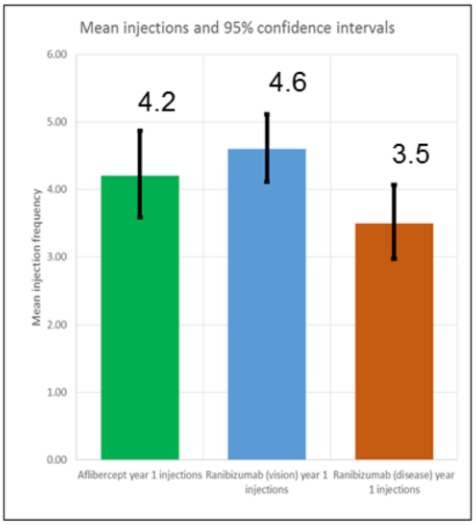
Similarity of health benefits and safety

ERG conclusion

- ERG conclude aflibercept and ranibizumab are similarly effective in treating myopic choroidal neovascularisation, based on:
  - difference in mean gain in best corrected visual acuity from indirect comparison
  - comparison of proportion of people gaining and losing 5, 10 and 15 EDTRS letters
- ERG conclude that safety profile of aflibercept and ranibizumab are similar, based on:
  - adverse events reported in MYRROR similar to adverse events seen with aflibercept in other eye indications
  - adverse events of aflibercept similar to those with ranibizumab in head to head trials for wet AMD

Resource use assumptions

Company submission (1)



- Injection frequencies assumed to be the same, as confidence intervals for year 1 injections overlap:
  - 4.2 in year 1, based on aflibercept trial
  - 1 in year 2, based on TA298
- Rationale: market research study of ophthalmologists shows that the MYRROR retreatment protocol reflects clinical practice in England
- Market research also suggests that clinicians expect to administer less than half the number of aflibercept injections than ranibizumab injections
  - equal injection frequency assumption may overestimate number of aflibercept injections used in clinical practice

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Source: figure 10, company submission

Resource use assumptions

Company submission (2)

- Fellow-eye involvement assumed equal: [redacted]
  - patients have same treatment in fellow-eye as in study-eye
- Probability of recurrence assumed equal: [redacted]
  - same number of injections as year 1 (4.2)
- No costs in model for:
  - administration; no additional resources required as injection frequency equal
  - monitoring; number of visits assumed equal as injection frequency equal
  - blindness – visual outcomes assumed to be the same
  - adverse events – assumed to be equal

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Resource use assumptions

ERG review

- Equal injection frequency assumption drives cost comparison
- ERG believes that the re-treatment criteria in aflibercept trial more closely reflect ranibizumab retreatment criteria based on disease activity
- ERG scenario analysis uses year 1 injection frequency from RADIANCE arm with retreatment based on disease activity for ranibizumab (3.5) and 4.2 for aflibercept from MYRROR
- Using these assumptions, total costs of aflibercept are higher than for ranibizumab - although confidence intervals around injection frequency overlap
- However, ERG's clinical adviser agrees with company assumption that injection frequency is unlikely to differ

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Patient, professional organisation and expert submissions

RNIB

- The disease develops at a younger age than other eye conditions and can be a serious threat to vision for people of working age
- Clinicians consider aflibercept to be more potent than ranibizumab, meaning that people may need fewer injections to stabilise the condition

Royal College of Ophthalmologists

- Increasingly aflibercept replacing ranibizumab for other eye conditions as biological studies and clinical trials have found it is more potent
- As aflibercept may be more effective than ranibizumab it would be beneficial to have as a possible first-line option
- No additional resources required - fewer injections may be needed

Clinical experts

- Expect a similar number of injections to ranibizumab, but could be fewer in small subset of patients needing more injections to stabilise disease

Technical team recommendation and rationale

Criteria for cost comparison case are met

- Company's indirect treatment comparison shows no statistically significant difference in mean gain in best corrected visual acuity
- ERG agrees that data for other clinical outcomes and adverse events are similar
- Main driver of cost comparison is injection frequency - company assumes that this would be the same for aflibercept and ranibizumab as confidence intervals from trials overlap
- Clinical experts, patient and professional organisations and the ERG's clinical adviser agree that injection frequency likely to be similar or lower compared with ranibizumab
- Total costs of aflibercept including all discounts are similar or lower than total costs of ranibizumab (see confidential appendix)
- Risk associated with decision low: even if aflibercept injection frequency is higher, indirect comparison suggests aflibercept slightly more effective

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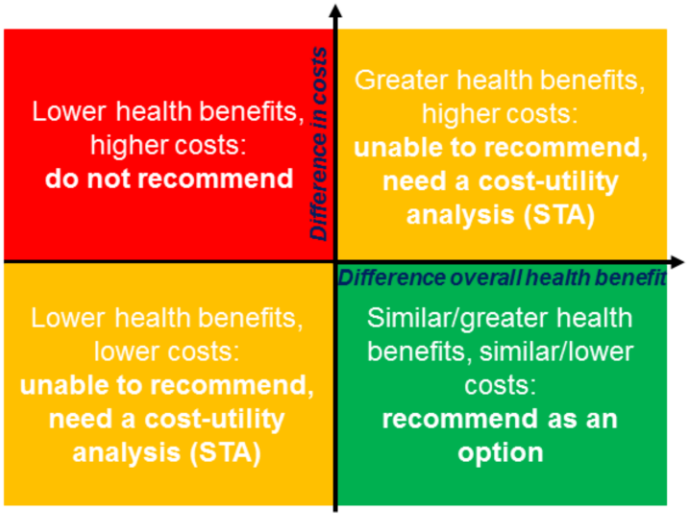
Potential recommendations: cost comparison



Key issues

- Is it appropriate to assume the same number of aflibercept and ranibizumab injections?

Confidential Appendix

There are confidential patient access schemes for both aflibercept and ranibizumab, so the results of the cost comparison taking these discounts into account are confidential.

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Fast track appraisal: cost-comparison case

Aflibercept for treating myopic choroidal neovascularisation [ID952]

Document B

Company evidence submission

May 2017

File name	Version	Contains confidential information	Date
		Yes/no	

Contents

Tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication(1) i.e. visual impairment due to myopic choroidal neovascularisation (myopic CNV). Myopic choroidal neovascularisation (myopic CNV) is a frequent cause of vision loss in adults with pathological myopia.

The submission covers the full population for the comparator, ranibizumab, as recommended by NICE(2) i.e. for treating visual impairment due to choroidal neovascularisation secondary to pathological myopia.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with visual impairment due to myopic choroidal neovascularisation	Adults with visual impairment due to myopic choroidal neovascularisation	N/A
Intervention	Aflibercept	Aflibercept	N/A
Comparator(s)	• Ranibizumab • Verteporfin photodynamic therapy	Ranibizumab	Bayer considers that the most appropriate comparator is ranibizumab (Lucentis). Ranibizumab (an alternative anti-VEGF therapy) has been appraised by NICE in this indication (Technology Appraisal 298)(2). Verteporfin photodynamic therapy (vPDT) is not an appropriate comparator as it is not standard treatment within the NHS for mCNV. It was acknowledged by the Evidence Review Group (ERG) during appraisal of ranibizumab in this indication, that vPDT was rarely used in clinical practice.
Outcomes	The outcome measures to be considered include: • best corrected visual acuity (the affected eye) • best corrected visual acuity (both eyes) • contrast sensitivity • adverse effects of treatment	The outcome measures to be considered include: • best corrected visual acuity (the affected eye) • adverse effects of treatment • health-related quality of life In addition to the outcomes proposed in the scope, Bayer will	Bayer will not be presenting data on contrast sensitivity, as listed in the pre-invitation scope, as this was not collected in the pivotal study. Bayer will also not be presenting data on best corrected visual acuity (both eyes) as in the pivotal study, only one eye was designated as the study eye and BCVA (both eyes) was not assessed.

	• health-related quality of life.	present on: • Proportion of patients gaining ≥ 15 ETDRS letters at week 24 from baseline • Mean change from baseline in BCVA score at each visit and at week 48. • Proportion of patients gaining or losing ≥15, ≥10 or ≥5 ETDRS letters at week 48 from baseline • Ad-hoc analysis of exposure	Further outcome data are presented to further report on the efficacy of aflibercept. Exposure is presented as it is relevant to the indirect comparison with ranibizumab.

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 will be taken into account. Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.	In light of the consultation on the ATA process for appraisal, Bayer considers that the most appropriate economic evaluation should be based on a cost-comparison analysis compared to standard of care ranibizumab.	As discussed at the decision problem meeting.

B.1.2 Description of the technology being appraised

Appendix C includes the summary of product characteristics and the European public assessment report.

Table 2Technology being appraised

UK approved name and brand name	Aflibercept (Eylea®) 40 mg/ml solution for injection in a vial.
Mechanism of action	Aflibercept (Eylea®) is a potent specific inhibitor of VEGF and is a fully human fusion protein, consisting of soluble VEGF receptors 1 and 2. Aflibercept binds to all known VEGF-A isoforms and also Placental Growth Factor (PlGF) with higher affinity than their natural receptors, and has substantially increased binding affinity to VEGF-A when compared to that of ranibizumab(3;4), and thereby can inhibit the binding and activation of these cognate VEGF receptors. Patients with active mCNV have elevated levels of VEGF in the aqueous humour of affected eye(s). Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases; VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergise with VEGF-A in these processes, and is also known to promote leucocyte infiltration and vascular inflammation.
Marketing authorisation/CE mark status	A UK marketing authorisation for the indication being appraised was issued on the 28th October 2015.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Eylea® is indicated for adults for the treatment of(1) • neovascular (wet) age-related macular degeneration (AMD), • visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), • visual impairment due to diabetic macular oedema (DME), • visual impairment due to myopic choroidal

	neovascularisation (myopic CNV). Contraindications to the use of aflibercept are: • Hypersensitivity to the active substance aflibercept or to any of the excipients. • Active or suspected ocular or periocular infection. • Active severe intraocular inflammation. See Appendix C for Summary of Product Characteristics (SmPC) and European public assessment report (EPAR).
Method of administration and dosage	Eylea® is for intravitreal injection only(1). *Myopic choroidal neovascularisation* • The recommended dose for Eylea® is a single intravitreal injection of 2 mg aflibercept equivalent to 50 microlitres. • Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease. • The schedule for monitoring should be determined by the treating physician. • The interval between two doses should not be shorter than one month.
Additional tests or investigations	There are no additional tests or investigations required for selection or monitoring of patients appropriate for aflibercept, over and above the current routine assessments in mCNV. Ranibizumab, another anti-VEGF, is already recommended by NICE and used within the NHS, for the treatment of mCNV(2).
List price and average cost of a course of treatment	NHS List price £816 per vial The cost of a course of treatment depends on patient response. The SPC states that 'The recommended dose for Eylea is a single intravitreal injection of 2 mg aflibercept equivalent to 50 microlitres. Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists.(1)'
Patient access scheme (if applicable)	A confidential simple patient access scheme is available. The cost after application of the simple discount is [redacted] per vial. The PAS scheme has been previously approved by the Department of Health and the scheme covers all the indications for aflibercept.

B.1.3 Health condition and position of the technology in the treatment pathway

Disease overview

Pathological or high myopia (PM) is the most severe form of myopia (short-sightedness). It is a chronic condition, defined as refractive error ≥ -6 diopters (D) associated with degenerative changes at the back of the eye. Such pathologic tissue alterations include retinal pigment epithelial thinning and defects, lacquer cracks and Bruch's membrane ruptures, choroidal neovascularisation (CNV), subretinal haemorrhage, and choroidal thinning and atrophy. A recent systematic review suggests the prevalence of PM is 1–3% in adults(5), occurring more frequently in those from Asian than White ethnic groups(6). The prevalence in an older population (≥49 years) has been estimated at 1.2%(7)

Myopic CNV – the indication of focus in this submission - is one of the most important vision-threatening complications of myopia, occurring in 5-11% of patients with PM(8). Choroidal neovascularisation (CNV) occurs when new blood vessels develop from the choroid layer underneath the retina and grow up through 'lacquer cracks' or areas of atrophy, and onto the retina. These new blood vessels can bleed very easily as they are very weak and fragile, causing damage and swelling to the retina, and eventual scarring, which can permanently affect vision. At the macula, this scarring is called a Foster Fuchs spot, which is a circular area of pigment which develops after the neovascularisation and bleeding has gone. The pathogenesis of myopic CNV remains poorly understood(8). Hypoxia in the outer retina due to choroidal stretching and thinning is considered part of the pathological pathway and has been suggested to stimulate VEGF secretion. The development of mCNV is subfoveal in approximately 58% of cases and juxtafoveal in 32%.

Typically, mCNV affects adults aged 40-50 years and has a poor prognosis, especially if left untreated, resulting in progressive and irreversible loss of visual acuity, particularly central vision, and leading to blindness(9).

As highlighted in the manufacturer submission for ranibizumab appraisal in CNV, '*if patients with CNV secondary to PM do not receive treatment, their vision will deteriorate over time and they are at risk of going blind. Eleven studies have reported on the visual outcome in untreated patients with CNV secondary to PM; all reported deterioration in vision over time(7;9-19). Eight studies reported best corrected visual acuity (BCVA) at baseline and at study end, and all but two of these reported either an increase of at least 20% in the proportion of individuals who were legally blind (BCVA ≤ 20/200), or a statistically significant*

decrease in mean BCVA, over a mean follow-up ranging from 3 months to 11 years(9;10;12-14;16;18;19). The two studies that did not report deterioration in BCVA had a high proportion of legally blind patients at baseline (45% and 60%)(10;12). Seven studies reported the rates of legal blindness (BCVA ≤ 20/200) at follow-up; 53 to 96% of patients were legally blind after a mean follow-up ranging from 1 to 11 years(9;10;13;14;18;19)'.

A Japanese study reported the incidence of CNV in patients with PM over an 11 year period to be 10.2% (0.98% per year)(20). Thus, in England, with an estimated 326,770 people with myopia (1.2% of population aged 40 years or over), incident population of myopic CNV is 3200 (NICE ranibizumab in mcNV costing statement).

Standard tests for diagnosing myopic CNV are fundus biomicroscopy, fluorescein angiography (FA) and optical coherence tomography (OCT). Primary symptoms of mCNV are loss of visual acuity, scotomas, and metamorphopsia. Most eyes progress to 20/200[1] or worse within 5 to 10 years after onset. Factors generally associated with poor visual prognosis include subfoveal (rather than juxtafoveal or extrafoveal location), age >40years at onset, and size of CNV lesion(8). Among myopic patients with pre-existing CNV, more than 30% will develop CNV in the fellow eye within 8 years(6).

1.3.1 Current management pathway

There is currently no cure for mCNV, and the key management strategy is to maintain visual capability for the daily activities such as driving, working, reading and writing. Prompt diagnosis and treatment is particularly important due to pathological myopia affecting younger patients of working age (over 50% of patients are < 50 years of age).

Patients with active mCNV have elevated levels of VEGF in the aqueous humour of affected eye(s). In England, ranibizumab (an anti-VEGF therapy) is the standard of care (Bayer market research, data on file), and was approved for use by NICE in November 2013 (TA298)(2) for the treatment of visual impairment due to CNV secondary to PM in adults. In October 2016, after consultation, TA298 was transferred to the static list by NICE.

Treatment with ranibizumab, according to its SmPC is initiated with one injection per month until maximum visual acuity is achieved and/or there are no sign of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued

[1] 20/200 - refers to a level of visual acuity measured using the Snellen chart (US equivalent), where a person needs to approach to a distance of 20 ft (6 metres) to read letters that a person with normal acuity could read at 200 ft (60 metres). The largest letter on an eye chart often represents an acuity of 6/60 (20/200), the value that is considered "legally blind".

treatment. The treatment of visual impairment due to CNV should be determined individually per patient based on disease activity. Some patients may only need one injection during the first 12 months; others may need more frequent treatment, including a monthly injection. For CNV secondary to pathologic myopia (PM), many patients may only need one or two injections during the first year.

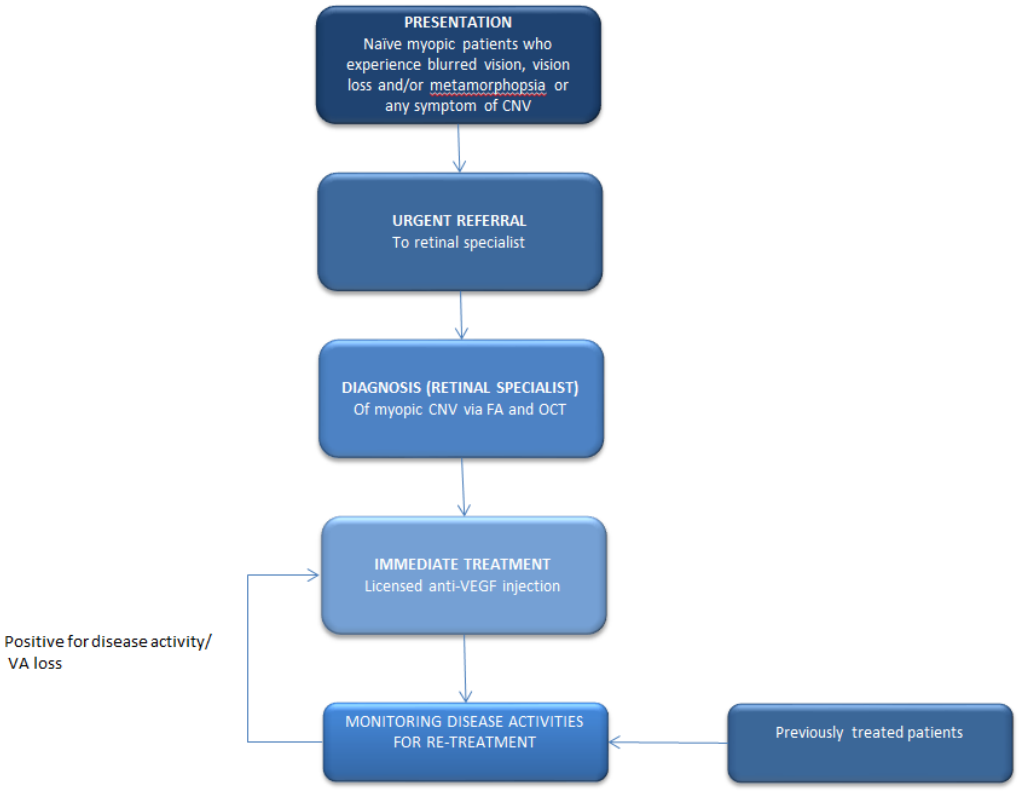
The introduction of aflibercept provides an effective alternative treatment option to ranibizumab for patients with mCNV. NICE has published an evidence summary on the use of aflibercept in the treatment of visual impairment due to myopic choroidal neovascularisation (14th June 2016; http://www.nice.org.uk/guidance/esnm76).

In Scotland, the Scottish Medicines Consortium (SMC) accepted aflibercept (10 October 2016; 1186/16(21)) for adults for the treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV). In 2013, the SMC accepted ranibizumab for use within NHS Scotland for the treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia in adults (November 2013; 907/13(22)). Also, the All Wales Medicines Strategy Group (AWMSG) recently recommended aflibercept (14th March 2017; 0117)(23) as an option for use within NHS Wales for the treatment of adult patients with visual impairment due to myopic choroidal neovascularisation. Ranibizumab was already available in Wales due to the prior NICE guidance on mCNV.

At the time of scoping of the NICE appraisal for ranibizumab in mCNV, other, now rarely used, options for treatment were considered as part of clinical practice including laser photocoagulation, verteporfin photodynamic therapy (vPDT), bevacizumab, surgical excision and macular translocation. The final scope for ranibizumab in mCNV included vPDT and bevacizumab.

The regulatory approval of ranibizumab, approved by NICE in November 2013 (TA298)(22), has changed the standard of care for mCNV and these treatments have now been mostly superseded by ranibizumab (Bayer market research, data on file). In addition, bevacizumab is not licensed for use in the treatment of any eye conditions. Verteporfin PDT (photodynamic therapy) was an established treatment for subfoveal myopic CNV for many years(24), but this treatment does not restore visual acuity and is associated with long-term chorioretinal atrophy(8).

Figure 1 Adapted from Wong TY, et al.Br J Ophthalmol 2015;99:289–296.(8)



Monitoring for disease activity may include clinical examination, OCT or FA. If monitoring reveals signs of disease activity (reduced VA, blurred vision, metamorphopsia and/or lesion activity), further treatment is recommended. Market research indicates that around 75% of retreatments are guided by a combination of disease activity and VA (Bayer plc, data on file).

B.1.4 Equality considerations

mCNV affects the working age population (people aged 40-60) and predominates in those of an Asian descent. Thus, it is important to ensure these groups are considered.

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

The main comparator for aflibercept in mCNV in this economic appraisal and highlighted in the final scope of this appraisal is ranibizumab. Ranibizumab has been evaluated in the NICE Technology Appraisal (TA298) published in 2013. Verteporfin Photodynamic Therapy (vPDT) has also been listed as a comparator, however, vPDT has not been evaluated in this submission (see Table 1).

The pivotal clinical trial for ranibizumab considered in TA298 was RADIANCE(25). RADIANCE was a Phase III, randomised, double-masked, multicentre, active-controlled study in patients with visual impairment due to myopic CNV. Patients were randomised to three groups: (1) ranibizumab and re-treatment guided by visual acuity stabilisation criteria (2) ranibiumab and re-treatment guided by disease activity criteria and (3) vPDT with disease activity treated with ranibizumab or vPDT at investigators' discretion from month 3.

The primary outcome measure was the mean average best-corrected visual acuity (BCVA) change from baseline to month 1 through months 3. Further details of the study can be found in Appendix D.

Table 3 sets out the clinical outcomes and measures appraised in the published NICE guidance for ranibizumab.

It is important to note that as 72% of the patients in the vPDT group received ranibizumab after 3 months, the manufacturer did not compare the results of the vPDT group with the results of the ranibizumab groups after the initial 3-month period.

Table 3 Clinical outcomes and measures appraised in published NICE guidance for the comparator(s).

	Outcome	Source	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties
NICE TA298(2)	Best corrected visual acuity (BCVA) in the study eye for ranibizumab and vPDT for the first 3 months	RADIANCE	Mean average change in BCVA between baseline and months 1–3 on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart	Yes	NR	NR	The Committee noted that the primary end point of RADIANCE was the mean average change in BCVA between baseline and months 1–3. The Committee heard from a clinical specialist that 3 months was not a long time period to assess the longer term benefits of ranibizumab. The Committee concluded that, because the clinical effectiveness of ranibizumab was not compared with vPDT after 3 months,there is uncertainty about the long-term efficacy of ranibizumab for choroidal neovascularisation associated with pathological myopia.
	BCVA in the study eye for ranibizumab during months 4 to 12	RADIANCE	Mean average change in BCVA between baseline and months 4–12 on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart	Yes	N/R	NR	NR
	BCVA in the study eye for vPDT during months 4 to 12	VIP(26)	Mean average change in BCVA between baseline and months 4–12 on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart	Yes	N/R	NR	NR

	Outcome	Source	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties
	BCVA in the study eye after 1 year	Yoshida et al. 2002(19)	BCVA (Snellen - for the purpose of analysis, Snellen VA data were transformed into equivalent logarithms of the minimum angle of resolution (LogMAR) values)	Yes	N/R	The manufacturer assumption was that the average BCVA gain of ranibizumab treatment at the end of year 1 would continue indefinitely. The Committee heard from the clinical specialist that data collected at the 3 time points in RADIANCE showed that the benefit of ranibizumab was maintained for at least 12 months. Besides that, the ERG's sensitivity analyses included different durations of treatment benefit, which showed that ranibizumab dominated vPDT even when the duration of treatment benefit was reduced to 1 year. The Committee concluded that the duration of treatment benefit was likely to be less than the manufacturer's assumption of an indefinite duration, but that ranibizumab dominated vPDT also when the duration of effect was reduced.	The assumption about the long-term benefit of ranibizumab treatment
	Adverse effects of treatment Ranibizumab	Bandello et al 2013(27)	NA	Yes	NR	NR	NR

	Outcome	Source	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties
	Adverse effects of treatment vPDT	VIP	NA	Yes	NR	NR	NR
	Health related quality of life (HRQoL)	RADIANCE	By means of the National Eye Institute Visual Functioning Questionnaire 25 item (NEI VFQ-25)	No	NR	NA	NA
	Health related quality of life (HRQoL)	RADIANCE	By means of EQ-5D	No	NR	See below in relation to Czoski-Murray et al	See below in relation to Czoski-Murray et al
	Health related quality of life (HRQoL)	RADIANCE	By means of WPAI-GH	No	NR	See below in relation to Czoski-Murray et al	See below in relation to Czoski-Murray et al

	Outcome	Source	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties
	Health related quality of life (HRQoL)	Czoski-Murray et al. (2009)(28)	Taken from the experimental lenses study of Czoski-Murray et al. (2009). This study included the UK general population and simulated BCVA health states with contact lenses that created the effects of age-related macular degeneration.	Yes	HRQoL values of Czoski-Murray et al. 2009 results in slightly lower total QALYs and ICER compared to the values of Brown et al.(29)	The Committee was aware that EQ-5D data were also collected in RADIANCE, but these data were not used in the model. It heard from the manufacturer that the EQ-5D data from RADIANCE were not included because the EQ-5D is widely recognised as not being sensitive in studies of eye conditions. The Committee heard from the ERG that using the EQ-5D data collected in RADIANCE did not have a large effect on the model, although the effect for the worse-seeing eye was not clear. The Committee concluded that using the EQ-5D data from RADIANCE was unlikely to change the overall results of the base-case analysis.	The use of Czoski-Murray et al. (2009) as a source of utility values, rather than the EQ-5D data collected in RADIANCE

The manufacturer developed a cost–utility Markov model that evaluated the cost effectiveness of ranibizumab compared with vPDT in people with choroidal neovascularisation associated with pathological myopia. There were 8 health states in the model, defined by the BCVA in the treated eye in addition to the absorbing health state of death. The health states were defined by a 10-letter range in BCVA. The transition probabilities for the first cycle of the model (baseline to month 3) for both ranibizumab and vPDT were based on treatment efficacy as measured in RADIANCE(25). For the next 3 cycles (months 4 to 12), the transition probabilities between health states were derived from RADIANCE for ranibizumab and from the Verteporfin in Photodynamic Therapy (VIP)(26) trial for vPDT.

Although EQ-5D quality of life data was collected in RADIANCE, base-case utility values for the better-seeing eye were taken from the experimental lenses study of Czoski-Murray et al. This study included the UK general population and simulated BCVA health states with contact lenses that created the effects of age-related macular degeneration (Czoski-Murray et al. 2009)(28).

The key drivers of the ranibizumab cost-effectiveness analysis, as described in TA298(2), included the unit cost of ranibizumab and vPDT, the number of ranibizumab injections in the first and second year, the starting age of the patient group, the discount rate for benefits and the maximum utility gain in the worse-seeing eye. The Committee concluded that the uncertainties associated with the key drivers in the model were unlikely to have an effect on the overall cost-effectiveness results.

This appraisal for aflibercept is based on a cost-comparison analysis, based on the assumption that the health benefits between aflibercept and ranibizumab are similar at similar or lower costs (see section B.3.9, B.3.11.2, B.4.2). One of the consequences of this assumption is that the key drivers in the ranibizumab model are not relevant to this framework. In our model, the starting age of the cohort influences total treatment costs over the model time horizon, but does not have any significant direct impact on incremental results themselves.

Discount rates of benefits and the maximum utility gain in the worse-seeing eye were key drivers in the ranibizumab model as they directly influenced the magnitude of incremental utility gains. However, as efficacy and safety are assumed equal in this framework, there is no incremental utility gain which can be magnified by manipulating these parameters.

The drivers of interest (unit costs and number of injections) are addressed in the next section.

In terms of health benefits, the analysis focuses on a comparison that assumes similar efficacy (mean BCVA gain at 3 months) and safety. In the indirect treatment comparison (ITC) performed for this appraisal, it was not possible to compare other efficacy measures such as central retinal thickness (CRT), or the Quality of Life (QoL) results of the RADIANCE trial(25) with the aflibercept

MYRROR trial(30), as there was no bridge in the evidence network. Due to this limitation, other efficacy measures and QoL outcomes were not included in the ITC (as addressed in more detail in Appendix D).

B.2.2 Resource use assumptions

The resources and associated costs included in the technology appraisal of ranibizumab (TA298)(2) were divided into treatment costs, recurrence costs, adverse event costs and blindness costs.

Treatment cost was composed of the unit cost of the drug, a cost for treatment administration and a cost for monitoring. The estimated number of administration visits per patient for ranibizumab were 3.5 for year 1 and 1.0 for year 2. The estimated number of administration visits per patient for vPDT were 3.4 and 1.7 for the years 1 and 2, respectively. Additionally patients treated by ranibizumab had 8.5 monitoring visits in year 1 and 4 in year 2. Patients treated by vPDT had 4 monitoring visits in both years. A 2 year treatment course was assumed for both treatments.

For both ranibizumab and vPDT, visits are needed to monitor disease status. In many cases, such monitoring visits can be combined with a treatment visit and would not incur any additional costs. However, there are occasions when monitoring visits are done without treatment. The health economic model for ranibizumab assumed that monitoring visits were separate from treatment visits.

Administration and monitoring costs were based on NHS reference costs (2011-2012). Administration costs for ranibizumab were based on the cost for vitreous retinal procedures – category 1 (BZ23Z) and the cost of optical coherence tomography (OCT) using code RA23Z. Administration costs for vPDT were based on the cost of OCT and a consultation with an ophthalmologist (consultant led multi-professional face-to-face follow-up visit for ophthalmology). Monitoring costs for both treatments were based on the cost for an outpatient attendance visit with an ophthalmologist and OCT.

Costs for recurrence were assumed to be equal to the first year of treatment. For patients with bilateral disease, the treatment cost per patient (including drug costs, administration costs and monitoring costs) is doubled, since the same treatment would be needed for the second eye as for the first eye. This was considered a conservative approach as some patients with bilateral disease would be able to receive treatment in both eyes at the same visit. Furthermore the costs of OCT should be applied only once for both eyes.

The unit costs for the adverse events were drawn from literature. A set price per event was defined. The cost of blindness was separated into costs related to the first year of blindness (£17,326) and costs related to blindness in each year after (£17,245).

2.2.1 Committee's preferred assumptions

The Committee accepted the model structure for the ranibizumab submission, but was concerned by some of the uncertainties about the assumptions used by the manufacturer. In particular, the Committee queried the following assumptions related to resource use and costs:

- The low number of ranibizumab injections needed in year 2 of treatment. The Committee heard from the clinical specialist that, on average, patients only need ranibizumab injections in the first 3 months of their first year of treatment. For example patients in the REPAIR trial(31) had well preserved eyesight after 18 months and did not need further treatment. Based on the study by Franqueira et al. (2012)(32), the ERG felt it would be a more reasonable assumption to administer 1.7 ranibizumab injections in the second year of treatment, while the clinical specialist felt that this number could be too high. The Committee concluded that the number of injections included in the manufacturer's base case could be an underestimate and that even if the number of injections was increased, the base-case analysis would not be affected.

- The high estimated costs of blindness. This was driven by the differences in calculating the costs of residential care by the ERG and the manufacturer. The Committee noted that the manufacturer's sensitivity analysis showed that the model was not sensitive to changes in the costs of blindness. The Committee concluded that the ERG's assumptions about the costs of blindness were likely to be more realistic than those used by the manufacturer, and that any changes were unlikely to have a large impact on the base-case analysis.

- The low estimated costs of ranibizumab and vPDT administration compared to the true costs incurred in the NHS. The Committee recognised that the manufacturer's sensitivity analysis showed that the model was not sensitive to changes in the administration costs. The Committee concluded that the NHS costs were uncertain, but the uncertainty was not great enough to affect the base-case analysis.

As stated earlier, the key drivers of the ranibizumab cost-effectiveness analysis, included the unit cost of ranibizumab and vPDT, the number of ranibizumab injections in the first and second year, the starting age of the patient group, the discount rate for benefits and the maximum utility gain in the worse-seeing eye.

This appraisal for aflibercept is based on a cost-comparison analysis, based on the assumption that the health benefits between aflibercept and ranibizumab are similar at similar or lower costs

(see section B.3.9, B.3.11.2, B.4.2). One of the consequences of this assumption is that the key drivers in the ranibizumab model are not relevant to this framework. In our model, the starting age of the cohort influences total treatment costs over the model time horizon, but does not have any significant direct impact on incremental results themselves.

Discount rates of benefits and the maximum utility gain in the worse-seeing eye were key drivers in the ranibizumab model as they directly influenced the magnitude of incremental utility gains. However, as efficacy and safety are assumed equal in this framework, there is no incremental utility gain which can be magnified by manipulating these parameters.

The only cost category included in this submission is drug acquisition cost (see section B.4.2.3 for more detail). In this appraisal for aflibercept, key drivers of the results are the unit cost of the treatments and the number of injections in the first and second year (and indirectly the rate of recurrence). The results are described in more detail in section B.4.3.

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

The identification and selection of the relevant clinical studies have been described in Appendix D. This appendix also presents the studies included in the indirect treatment comparison (ITC) and the methodology of the ITC.

B.3.2 List of relevant clinical effectiveness evidence

Table 4 Clinical effectiveness evidence

Study	The MYRROR Study (Ikuno 2015)(30)
Study design	Phase 3, multicentre, randomised, double-masked, sham-controlled study
Population	Patients with choroidal neovascularisation secondary to pathologic myopia (mCNV)
Intervention(s)	Aflibercept [n=91]: • Day 1 to week 20: aflibercept 2mg by intravitreal (IVT) injection at baseline followed by PRN dosing every 4 weeks of aflibercept or sham injection in accordance with specific re-treatment criteria (see Table 7) • Week 24 to week 44: PRN dosing of aflibercept 2mg or sham injection in accordance with specific re-treatment criteria (see Table 7)
Comparator(s)	Control group [n=31]: • Day 1 to week 20: one sham injection at baseline followed by repeated sham injections every 4 weeks through Week 20. • Week 24 to week 44: aflibercept 2mg by IVT injection followed by monthly PRN dosing of 2 mg aflibercept *or* sham injection in accordance with specific re-treatment criteria (see Table 7) from Week 28 through Week 44.
Indicate if trial supports application for marketing authorisation (yes/no)	Yes
Reported outcomes specified in the decision problem	• Mean change from baseline in BCVA score at week 24 (Primary endpoint) • Change from baseline in the EQ-5D at week 24 and week 48 (general health-related quality of life)

Study	The MYRROR Study (Ikuno 2015)(30)
	• Change from baseline in the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25) total score at week 24 and week 48 (vision-related quality of life) • Safety – ocular and non-ocular adverse events (AEs) and serious AEs, vital signs, laboratory measures.
All other reported outcomes	• Proportion of patients gaining ≥ 15 ETDRS letters at week 24 from baseline • Mean change from baseline in BCVA score at each visit and at week 48. • *Change from baseline in central retinal thickness (CRT) at week 24 and 48)*.* • *Absolute change in CNV lesion size from baseline to week 24 and 48.** • Proportion of patients gaining or losing ≥15, ≥10 or ≥5 ETDRS letters at week 48 from baseline • *Change in leakage from CNV from baseline to week 24 and week 48** • *Proportion of patients who withdrew from study drug by week 24 and week 48** • Ad hoc analysis of exposure ** These outcomes are not reported in this submission as they are supplementary to the decision problem, however, are available on request.*

AE=adverse events; BCVA=best corrected visual acuity; CNV=choroidal neovascularisation; CRT=central retinal thickness; EQ-5D=EuroQol 5-dimension; ETDRS=Early Treatment Diabetic Retinopathy Study; IVT=intravitreal; NEI-VFQ-25=National Eye Institute Visual Function Questionnaire 25; PRN=pro re nata [as needed];

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

A phase 3, multicentre, randomised, double-masked, sham-controlled study of the efficacy, safety, and tolerability of intravitreal VEGF Trap-Eye in subjects with choroidal neovascularisation secondary to pathologic myopia (mCNV) [The MYRROR Study; BAY 86-5321 / 15170; NCT01249664)(30;33-36)

The MYRROR study has been fully published(30), including the European Public Assessment Report(36) (See Appendix C). This submission also draws from unpublished

data from clinical study protocol(33), clinical study report (CSR)(34) and module 2.5 of the European regulatory submission dossier(35).

3.3.1 Trial design and methodology

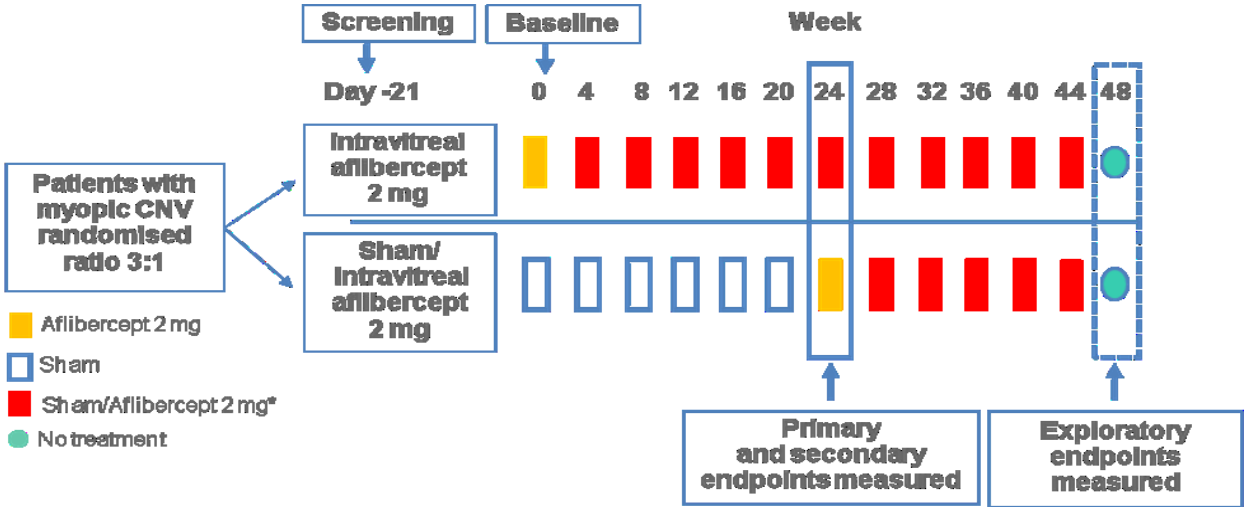
MYRROR was an international, phase 3, multicentre, randomised, double-masked, sham-controlled study.

Settings and locations where the data were collected: The study took place across 20 study centres in Asia (Hong Kong, Japan, Republic of Korea, Singapore, and Taiwan), evaluating the efficacy and safety of intravitreal (IVT) aflibercept 2mg compared with sham treatment in patients with myopic CNV. The study took place within secondary care, and patients were treated as 'outpatients'.

Study enrolment started in November 2010 and was completed in August 2013, during which time a total of 122 patients were randomised (aflibercept: n=91; sham treatment: n=31).

The study consisted of two phases of treatment, over a total of 44 weeks (see Figure 2). A follow-up safety visit was performed at week 48.

Figure 2 MYRROR study design. Adapted from Ikuno 2015(30)



At the time of study design and initiation, there was no recognised standard of care for patients with visual impairment due to mCNV, hence the use of a sham only control group. No anti-VEGF therapy had been approved in this indication anywhere in the world and although photodynamic therapy with verteporfin (vPDT) received approval in the EU in March 2001 and in the US in August 2001 for the treatment of mCNV, its limited efficacy

meant that its widespread utilisation for mCNV in Asia and Europe was never adopted. In Japan, one of the countries in the MYRROR trial, vPDT has never been approved.

Only one eye was designated as the study eye. However, safety of the fellow eye was monitored also, and all systemic adverse events (AEs) were collected. For patients meeting eligibility criteria in both eyes, the eye with the worst VA was selected as the study eye.

Efficacy (visual acuity, central retinal thickness [by optical coherence tomography (OCT)]) and safety [redacted] assessments were performed at regular scheduled clinic visits i.e. day 1, week 4 and every 4 weeks thereafter to the end of the study. Fundus photography (FP), fluorescein angiography (FA), [redacted] and assessment of vision-related quality of life (NEI VFQ-25) were performed at baseline and weeks 12, 24, 36 and 48. Quality of life was also assessed by completion of the EuroQol 5-Dimension (EQ-5D) questionnaire at baseline, week 24 and week 48. [redacted].

[redacted].

Method of randomisation: Patients were randomised into two groups (aflibercept : sham injection) on a 3:1 basis according to a predetermined central randomisation scheme provided by an interactive voice/web response system (IV/WRS). Randomisation was stratified by country.

Masking(33;36):

[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 rescue treatment (see Table 5). Masked and unmasked roles were assumed for the entire study and switching from an unmasked to a masked role after the first patient was randomised at a site was not permitted. [redacted] and optical coherence tomography, fundus and fluorescein angiographic images were sent to an independent reading centre and read by masked readers.

To maintain masking in the study, sham injections were performed throughout the duration of the study. [redacted]

[redacted]

Table 5 Responsibilities of the Masked and Unmasked Personnel(33;36)

Masked personnel	
– Study site principal investigator – [redacted] Assesses for re-treatment or alternative treatment (physician only) – Assesses all AEs, including severity and relationship – Assesses efficacy – Performs ophthalmic examinations at all study visits (except post injection examinations immediately after treatment)	– [redacted] Test visual acuity and perform any other non-ophthalmic assessments – Acquire OCT, FP, and FA images and ensure archiving and/or transfer of images to reading centres, where required – Evaluate OCT images [redacted]
Unmasked personnel	
– [redacted]	– xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxx

AEs=adverse events; EQ-5D=EuroQoL 5 Dimensions; FA= fluorescein angiography; FP= Fundus photography; IVRS/IWRS=interactive voice/web response system; NEI VFQ-25= National Eye Institute Visual Functioning Questionnaire-25; OCT=optical coherence tomography
[a] Either masked or unmasked site personnel may call the IVRS/access IWRS to have the patient randomised

Eligibility criteria(30;33;36):

Table 6 Eligibility criteria

Inclusion criteria	Exclusion criteria
All of the following criteria had to be met: [redacted] 3. **Age ≥ 18 years of age.** 4. **Myopia of less than or equal to -6 D OR axial length of greater than or equal to 26.5 mm.** 5. **Active subfoveal or juxtafoveal (within 1 to 199 µm of the centre of the fovea) CNV secondary to pathologic myopia as defined by leakage on FA.** [redacted] 6. **Best-corrected visual acuity of 73 to 35 letters (ETDRS equivalent of 20/40 to 20/200) in the study eye at 4 metres.** 7. Decrease in vision in the study eye determined by the investigator, using his/her medical judgment, to be primarily the result of the current active mCNV. [redacted]	**Ophthalmic** 1. **Only one functional eye**. 2. Ocular media of insufficient quality to obtain fundus and OCT images in the study eye 3. Greatest linear dimension (GLD) of the lesion in the study eye > than 12 disc areas 4. **Recurrent mCNV in the study eye.** 5. **Aphakia in the study eye** 6. **History or presence of CNV with an origin other than pathologic myopia in the study eye**. Particular attention should be made to exclude subjects with an origin of diabetic macular oedema or diabetic retinopathy, AMD, or polypoidal choroidal vasculopathy. 7. **Ocular inflammation (including trace or above) or external ocular inflammation in the study eye.** 8. Concurrent disease in the study eye that would compromise BCVA or require medical or surgical intervention during the study period. 9. Any ocular disorder in the study eye that, in the opinion of the investigator, may confound interpretation of the study results. 10. Significant scarring or atrophy in the fovea that indicates substantial irreversible vision loss in the study eye. 11. History of idiopathic or autoimmune-associated uveitis in either eye. 12. Evidence at examination of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye or current treatment for serious systemic infection. 13. Vitreomacular traction or traction retinal detachment, epiretinal membrane in either eye as evident biomicroscopically or on OCT that is considered by the investigator to affect significantly central vision. 14. **Any iris neovascularisation and/or vitreous haemorrhage in either eye** 15. **Uncontrolled glaucoma**, defined as intraocular pressure (IOP) ≥ 25 mm Hg on optimal medical regimen, or **previous filtration surgery in either eye**. **Prior and concomitant treatments** 16. In the **study eye**: - Any prior or concomitant treatment with another investigational agent for mCNV. - Any previous panretinal photocoagulation or subfoveal thermal laser therapy. - Any prior treatment with PDT. - Cataract surgery within 3 months prior to Day 1. - Yttrium-aluminum-garnet laser capsulotomy within 2 months prior to Day 1. - Any other intraocular surgery within 3 months prior to Day 1. - History of vitreoretinal surgery and/or scleral buckle surgery.

Inclusion criteria	Exclusion criteria
	17. Any prior treatment with anti-VEGF agents in **either eye**, or systemic use of an anti-VEGF product at any time. 18. Previous use of intraocular or periocular corticosteroids in **either eye** within 3 months prior to Day 1. **Other criteria** 19. Previous assignment to treatment during this study 20. Uncontrolled hypertension defined as a single measurement of systolic blood pressure > 180 mm Hg, two consecutive measurements of systolic blood pressure > 160 mm Hg, or diastolic blood pressure > 100 mm Hg on optimal medical regimen. 21. History of cerebrovascular disease or myocardial infarction within 6 months prior to Baseline/Day 1. 22. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, may affect interpretation of the results of the study, or renders the subject at high risk from treatment complications [redacted] 24. Renal failure requiring dialysis or renal transplant. [redacted] 26. Known serious allergy to the fluorescein sodium for injection in angiography 27. Inability to obtain fundus photographs or fluorescein angiograms of sufficient quality.

Interventions: Patients were randomised to one of two treatment groups. In the first phase of the study (weeks 0 to 24), eligible patients were randomised in a 3:1 ratio to receive either:

- one 2mg aflibercept IVT injection at baseline followed by PRN dosing (*pro re nata*; as needed) at a maximum frequency of once every 4 weeks of aflibercept or sham injection in accordance with specific re-treatment criteria in the event of CNV persisting or recurring (see Table 7) OR

- one sham injection at baseline followed by repeated sham injections every 4 weeks through Week 20.

At week 24:

- The aflibercept group continued the PRN dosing of aflibercept (2mg) or sham injection in accordance with specific re-treatment criteria (see Table 7) through to week 44.

- Following assessment of the primary efficacy endpoint, patients in the control group, who had received sham injections weeks 0 to 20, received one 2mg aflibercept IVT injection followed by monthly PRN dosing of 2 mg of aflibercept or sham injection in accordance with the specific re-treatment criteria (see Table 7) from Week 28 through Week 44.

[redacted]

The rationale for the choice of dose for aflibercept was based primarily upon the favourable safety and efficacy profile achieved using the 2mg dose in the pivotal phase 3 studies for wet age-related macular degeneration (wet AMD) (VIEW 1 and VIEW 2)(37), diabetic macular oedema(38), as well as the pivotal phase 3 studies for branch (BRVO)(VIBRANT) and central retinal vein occlusion (CRVO)(COPERNICUS and GALILEO)(39-42). Based on this experience, the 2mg dose of aflibercept as one single intravitreal injection followed by PRN dosing every 4 weeks was selected.

Re-treatment criteria:

Table 7 MYRROR study re-treatment criteria

Re-treatment criteria
Re-treatment was allowed in patients who met 1 or more of the following criteria: 1. reduction in VA by ≥5 letters from the previous Early Treatment Diabetic Retinopathy Study examination; 2. increase in central retinal thickness (CRT) >50µm from the time of the previous examination, new or persistent cystic retinal changes, subretinal fluid, or pigment epithelial detachment, and new or persistent CNV or bleeding; or 3. deemed necessary by the investigator based on his/her clinical impression or diagnostics performed in the context of standard medical care.

Treatment compliance:

[redacted]

[redacted].

Treatment compliance was calculated based on the number of actual treatments (active or sham) in relation to the number of planned injections (i.e. a denominator of 12 injections for the Week 48 analyses).

During the 24 weeks of the study, in the Full Analysis Set (FAS), the mean of compliance value was 97.41% and 88.71%, in the aflibercept group and the sham group, respectively. A total of 95.6% of patients in the aflibercept group and 83.9% in the sham group received 80% to 100% of all scheduled treatments(36).

The compliance to Week 48 was good in both treatment groups. In the FAS, 75 patients (83.3%) in the aflibercept group and 24 patients (77.4%) in the sham plus aflibercept group had received the complete set of 12 injections (sham or aflibercept).

Mean compliance for the entire study period of 48 weeks in the aflibercept group was 92.8% (median: 100%) and in the Sham + aflibercept group 83.9% (median: 100%). During the entire 48 weeks of the study, 104 of the 121 patients (86.0%) in the FAS received 80% to 100% of all scheduled treatments.

From baseline to Week 20, 73.3% of patients in the aflibercept group needed ≤ 3 active injections. Patients in the aflibercept group received a mean (median) of 2.9 ± 1.6 [median 3.0] active (i.e. aflibercept) injections from baseline to week 20, and 1.3 ± 1.8 [median: 1.0] injections between week 24 and week 44.

Patients in the control group (sham + aflibercept) received 3.0 ± 2.2 [median: 3.0] in the first active treatment period for that group (i.e. week 24 to week 44).

Permitted and disallowed concomitant medications(36): Patients who had received another investigational agent to treat mCNV or any other condition were excluded from the study.

No other treatments could be given for mCNV in the study eye once enrolled in the study and until study completion.

See Table 6 Eligibility criteria for a complete list of permitted and disallowed medications.

The fellow eye could receive approved treatment for mCNV except anti-VEGF therapies or steroids.

Efficacy outcome measures: Table 8 summarises MYRROR study endpoints, and when / how each were measured. All endpoints described were pre-specified in the analyses. The primary efficacy endpoint was the mean change in BCVA from baseline to week 24, using an ETDRS chart, generally accepted as the gold standard for visual acuity measurements in clinical trials and used in clinical practice(43). All other efficacy and safety variables and the methods to measure them are standard variables and methods in clinical studies, and in ophthalmic practice. They are widely used and generally recognised as reliable, accurate, and relevant.

Table 8 MYRROR trial – primary and key secondary endpoints(30;33;36)

Endpoint	Measure – definition & assessment	
Primary Endpoint		
Mean change from baseline in BCVA score at week 24.	Assessments performed at day 0, week 4 and every 4 weeks thereafter.	The ETDRS 4m protocol(44)
Confirmatory Secondary Endpoint		
Proportion of patients gaining ≥ 15 ETDRS letters at week 24 from baseline	Assessments performed at day 0, week 4 and every 4 weeks thereafter.	The ETDRS 4m protocol
Exploratory endpoints		
Mean change from baseline in BCVA score at each visit and at week 48.	Assessments performed every 4 weeks.	The ETDRS 4m protocol. VA examiners were certified to ensure consistent measurement of BCVA and remained masked to treatment assignment.
Change from baseline in central retinal thickness (CRT) at week 24 and 48.	Assessments performed on the study eye at all visits (baseline and every 4 weeks) and in addition on the fellow eye at screening, week 24, and week 48.	Assessed by optical coherence tomography (OCT) scans. OCT images were evaluated by study-site personnel specifically trained and certified to do so. These were also sent to an independent central reading centre.
Absolute change in CNV lesion size from baseline to week 24 and 48.	Assessments performed at screening, weeks 12, week 24, week 36 and week 48.	Assessed by fluorescein angiography [redacted]. Fundus and angiographic images sent to an independent reading centre and read by masked readers.
Proportion of patients gaining or losing ≥ 15, ≥ 10 , or ≥ 5 ETDRS letters at week 48 from baseline	Assessments performed every 4 weeks.	The ETDRS 4m protocol.
Change in Leakage from CNV from baseline to week 24 and week 48	Assessments performed at screening, weeks 12, week 24, week 36 and week 48.	Assessed by fluorescein angiography. FA images sent to an independent reading centre and read by masked readers.

Endpoint	Measure – definition & assessment	
Quality of life (QoL), general health: Change from baseline in the EQ-5D at week 24 and week 48;	EQ-5D was administered at baseline, week 24, and week 48.	Both questionnaires assessed by masked interviewer [redacted] The EQ-5D consists of five dimensions: Mobility, self-care, usual activities, Pain/discomfort, and anxiety/depression. Each dimension has three levels, reflecting "no health problems," "moderate health problems," and "extreme health problems". A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. The possible range for the EQ-5D total score, based on the five dimensions, ranges between -0.6 (worst possible state) and 1.0 (best possible state). NEI VFQ-25 total score ranges from 0 (worse possible state) to 100 (best possible state).
Vision-related quality of life (QoL): Change from baseline in the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25) total score at week 24 and week 48.	NEI VFQ-25 was administered at baseline, week 12, week 24, week 36 and week 48.	[redacted]
Safety: Ocular and non-ocular adverse events (AEs), and serious adverse events (SAEs), vital signs, laboratory measures.	AEs, [redacted] were recorded at each visit. A physical examination was performed at screening and weeks 24 and 48, [redacted]	Adverse events were summarised using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0
Proportion of patients who withdrew from study drug by week 24 and week 48		
Ad hoc analysis of exposure	Number of injections administered in total and per quarter of treatment period (i.e. within weeks 0 to 8, weeks 12 to 20, weeks 24 to 32 and weeks 36 to 44).	

Pre-planned subgroups(34;36):

- Country (Japan, Other)
- Sex (Male, Female)
- Age group (< 45, 45 - < 55, 55 - < 65, 65 - < 75, ≥ 75)
- Baseline BCVA (> 20/200 [letters read ≥ 35], ≤ 20/200 [letters read ≤ 34])
- Duration of disease (< 2 months, ≥ 2 months)
- Renal impairment, classified by creatinine clearance (CrCl) at baseline. CrCl was calculated according to the Cockcroft-Gault formula. (Normal: CrCl > 80 mL/min; Mild: 50 < CrCl ≤ 80 mL/min; Moderate: 30 < CrCl ≤ 50 mL/min; Severe: CrCl ≤ 30 mL/min or requiring dialysis)
- Hepatic impairment (Yes, No)
- In the aflibercept group, the descriptive summary of efficacy variables was also calculated by number of active injections.

Additional subgroups for safety analyses included a [redacted]

3.3.2 Baseline characteristics(30;34;36)

Overall, baseline demographics, clinical and disease characteristics were well balanced between the 2 treatment groups (Table 9) [redacted].

Table 9 Patient baseline demographic and disease characteristics – MYRROR study (FAS)(30;34;36)

	Aflibercept n=90	Sham n=31
Mean age, years ± SD (min-max)	58.5 ± 13.7 (27-83)	57.5 ±12.1 (27-82)
Sex, n (%)		
Male	25 (27.8)	4 (12.9)
Female	65 (72.2)	27 (87.1)
Race, n (%)		
Asian	90 (100)	31 (100)
Country, n (%)		
Japan	67 (74.4)	23 (74.2)
Korea	9 (10.0)	3 (9.7)
Singapore	2 (2.2)	0 (0.0)
Taiwan	7 (7.8)	3 (9.7)
Hong Kong	5 (5.6)	2 (6.5)
BCVA		
Mean, letters ± SD (min-max)	56.4 ± 9.8 (28-76)	56.6 ± 8.9 (37-70)
>20/200 (35-73 letters), n (%)	87 (96.7)	31 (100.0)
<20/200 (24-34 letters), n (%)	3 (3.3)	0
Mean central retinal thickness, µm ± SD (min-max)	349.7 ± 91.3 (147-777)	354.2 ± 107.2 (125-674)
Mean intraocular pressure (IOP), mmHg ± SD (min-max)	15.2 ± 2.7 (8-22)	15.8 ± 2.8 (11-24)
Mean axial length, mm ± SD (min-max)	28.8 ± 1.5 (24.5-33.8)	28.6 ± 1.7 (25.3-31.9)
Duration if disease, n (%)		
<2 months, n (%)	73 (81.1)	24 (77.4)
≥2 months, n (%)	17 (18.9)	7 (22.6)
CNV location, n (%)		
Centre (subfoveal)	54 (60.0)	20 (64.5)
Juxtafoveal, ≤ 200µm	35 (38.9)	11 (35.5)
Extrafoveal, > 200µm*	1 (1.1)	0
Mean CNV size, DA ± SD (min-max)	0.4086 ± 0.5028 (0.008-2.758)	0.3334 ± 0.3413 (0.018-1.851)
Type of CNV lesion at screening, n (%)		
Classic CNV	90 (100.0)	29 (93.5)
Classic and occult	0	1 (3.2)
Occult	0	1 (3.2)
NEI VFQ-25 score, mean ± SD (min-max)		
Total	[redacted]	[redacted]
Near activities		
Distance activities		
Vision dependency		
Baseline EQ-5D score, mean ± SD (min-max)	[redacted]	

* Extrafoveal location of CNV was categorised as a major protocol deviation. BCVA = best corrected visual acuity; CNV = choroid neovascularisation; DA = disc area; EQ-5D = EuroQol 5-Dimension; NEI VFQ = National Eye Institute Visual Function Questionnaire; SD = standard deviation;

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence(30;36)

3.4.1 Analysis sets

The primary analysis population comprised the full analysis set (FAS).

Table 10 Definition of all data analysis sets in MYRROR

Analysis set	Definition	Number of valid patients in treatment group	
		Aflibercept	Laser
Full analysis set (FAS)	All randomised patients who received ≥1 study injection (intravitreal aflibercept or sham) and had baseline and ≥1 post-baseline BCVA assessment. Analysed as randomised.	90 (98.9%)*	31 (100%)
Per protocol set (PPS)	All patients in the FAS who attended at least two scheduled visits during the first 24 weeks of the study, except for those excluded because of major protocol violations. Analysed as treated.	86 (94.5%)	29 (93.5%)
Safety analysis set (SAF)	All randomised patients who had received any study medication. Analysed as treated.	91 (100%)	31 (100%)

* 1 patient received one injection but had no post-baseline BCVA measurement

3.4.2 Overview of statistical analyses(30;36)

Table 11 Summary of statistical analyses in MYRROR

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
MYRROR	Null hypothesis: $\mu_A = \mu_c$ versus Alternative hypothesis: $\mu_A > \mu_c$ where μ_A is the true mean change of the aflibercept and μ_c is that of the control sham injection. The trial was designed as a superiority trial.	**Primary efficacy analysis (conducted on the FAS):** The primary efficacy endpoint was the mean change in BCVA from baseline to week 24 in patients with myopic CNV receiving intravitreal aflibercept 2.0 mg or sham treatment. The difference in the changes between treatment groups (intravitreal aflibercept minus sham injection) and a 2-sided 95% confidence interval was estimated using an analysis of covariance (ANCOVA) model, including treatment groups and country/region as fixed effects and baseline BCVA as a covariate. To confirm the superiority of intravitreal aflibercept injection over control sham injection, the lower limit of the 95% confidence interval must have exceeded 0. **Sensitivity analysis of primary endpoint:** To assess the robustness of the results of the primary analysis, a per protocol analysis was also carried out using the above ANCOVA model, fixed effects and covariate. No per-protocol analyses were performed on study data obtained beyond Week 24. See also Data management, patient withdrawals column for additional analyses. **Secondary efficacy analyses:** With the establishment of superiority on the primary endpoint, the confirmatory secondary efficacy endpoint - the proportion of patients who gained ≥15 letters - was tested at a 2-sided alpha level of 0.05 by the Cochran-Mantel-Haenszel method weight-adjusted for country/region. **Tertiary efficacy analyses:**	By assuming • a treatment difference of 10 BCVA letters and • a standard deviation of 14 letters, • under a randomisation schedule of 3:1 and • using a *t* test with 1-sided alpha level of 0.025, a sample size of 112 patients was estimated to provide 90% power to show a statistical significance with respect to the primary end point. By considering a 5% dropout rate, 120 patients (90 intravitreal aflibercept and 30 sham) were planned to be randomised.	**Handling of missing data:** A last observation carried forward (LOCF) approach for the primary analysis and an observed case analysis (OC) for both the FAS and the PPS as sensitivity analyses were initially selected. Data were not imputed for the safety analysis. **Further sensitivity analyses** To further explore the robustness of the pre-specified primary analysis and assess the impact of missing data on the efficacy evaluation of study drug more comprehensively, further sensitivity analyses (mixed model for repeated measurements, multiple imputation, worst case imputation) were added before database lock and unmasking of the study data. These analyses are based on the Committee for Medicinal Products for Human Use (CHMP) guideline on missing data (dated 2 July 2010).

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		All exploratory efficacy variables were summarised descriptively at each visit prior to the last visit and at the last visit (as observed and LOCF) for the FAS population. The last visit is defined as Week 24 for the analysis of Week-24 data, and Week 48 for the analysis of Week-48 data. The difference between treatment groups and a corresponding two-sided 95% confidence interval were estimated - the continuous variables (i.e., change in central retinal thickness, absolute change in CNV lesion size, change in EQ-5D score, and change in NEI VFQ-25 total score) using an ANCOVA model, including treatment groups and country as fixed effects and baseline measurement as a covariate; and the binary variables (the difference in proportions of patients) using the Cochran-Mantel-Haenszel method weight-adjusted for country. All results (except CRT) are based on the last observation carried forward approach (least squares [LS] mean difference); observed data (mean difference) are used for CRT.		
ANCOVA=analysis of covariance; BCVA=Best Corrected Visual Acuity; CNV=choroidal neovascularisation; CRT=central retinal thickness; EQ-5D=EuroQol-5 Dimension; FAS=Full analysis set; LOCF=Last observation carried forward; LS=least squares; NEI VFQ-25=National Eye Institute Visual Function Questionnaire; OC=observed case; PPS=per protocol set;				

Participant flow in the MYRROR study

See Appendix D.

B.3.5 Quality assessment of the relevant clinical effectiveness evidence

See Appendix D.

B.3.6 Clinical effectiveness results of the relevant trials(30;34;36)

3.6.1 Clinical outcomes

Table 12 summarises the outcomes reported in the MYRROR study, those listed in the final scope and outcomes used in the NICE appraisal of ranibizumab in mCNV (TA298). The cost-effectiveness analysis of ranibizumab in mCNV uses results of outcomes relating to best corrected visual acuity (BCVA), health-related quality of life (HRQoL), and adverse effects of ranibizumab and vPDT. In addition, the number of injections required over a given timepoint is a model input.

Thus, the clinical effectiveness results presented here for aflibercept in the treatment of mCNV will focus on similar outcomes as those used in the appraisal of ranibizumab (i.e. mean changes in BCVA, and proportions of patients with ≥ 10 letter and ≥ 15 letter gains from baseline to various timepoints, HRQoL, adverse effects, and injection frequency).

Other outcomes such as change from baseline in central retinal thickness (CRT), absolute change in CNV lesion size, change in leakage from CNV and proportion of patients who withdrew from study drug are not reported in this submission as they are supplementary to the decision problem, however, are available on request.

Table 12 Summary of outcomes considered in the submission (shaded in grey)

Pre-specified outcomes assessed in MYRROR	Outcomes specified in decision problem	Outcomes presented by manufacturer and appraised in published guidance for ranibizumab (TA298)	Outcomes that model sensitive to in prior NICE appraisal in mCNV
Mean change from baseline in BCVA score at week 24 **(Primary endpoint)**	Best corrected visual acuity (affected eye)	Mean change in BCVA between baseline and months 1–3 **(primary endpoint)**	✓
Proportion of patients gaining ≥ 15 ETDRS letters at week 24 from baseline		The proportion of patients gaining 10 or more or 15 or more letters from baseline. Loss of ≥10 or ≥15 letters was also assessed in the phase III study but results not presented in the submission (provided in response to ERG questions)	
Mean change from baseline in BCVA score at each visit and at week 48		Mean change in BCVA from baseline	
Proportion of patients gaining or losing ≥15, ≥10 or ≥5 ETDRS letters at week 48 from baseline			
Change from baseline in the EQ-5D at week 24 and week 48 (general health-related quality of life)	Health-related quality of life	Mean change in the EQ-5D questionnaire from baseline to 3, 6 and 12 months	
Change from baseline in the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25) total score at week 24 and week 48 (vision-related quality of life)		Mean change in National Eye Institute Visual Functioning Questionnaire 25 item (NEI VFQ-25) composite score from baseline to 3, 6 and 12 months	
Safety – ocular and non-ocular adverse events (AEs) and serious AEs, vital signs, laboratory measures	Adverse effects of treatment	Safety – ocular and non-ocular adverse events (AEs) and serious AEs	
Change from baseline in central retinal thickness (CRT) at week 24 and 48)		Changes in central retinal thickness from baseline	
Absolute change in CNV lesion size from baseline to week 24 and 48			
Change in leakage from CNV from baseline to week 24 and week 48		Proportion of patients with presence of active leakage over time up to month 12	
Proportion of patients who withdrew from study drug by week 24 and week 48			
Ad hoc analysis of exposure Number of injections Analysis of injection frequency		Mean number of injections received over 3, 6 and 12 months.	✓
	Best corrected visual acuity (both eyes)		
	Contrast sensitivity		

MYRROR study - Summary of efficacy of aflibercept in mCNV

The efficacy, safety and tolerability of aflibercept in the treatment of visual impairment due to mCNV was demonstrated in the phase 3, multicentre, randomised, double-masked, sham-controlled MYRROR study.

Patients were randomised 3:1 to intravitreal aflibercept (n=91) or sham (n=31). In the aflibercept arm, patients received one injection at baseline and then additional injections upon persistence or recurrence of the CNV based on pre-defined re-treatment criteria at monthly visits through week 44. If re-treatment was not indicated, patients received sham treatment to maintain masking. In the sham arm, patients received sham injections through week 20. At week 24, after assessment of the primary efficacy endpoint, sham patients received a mandatory aflibercept injection followed by aflibercept (if disease persisted/recurred) or sham injection every 4 weeks.

All efficacy results (i.e. primary, confirmatory secondary, and exploratory) showed robust benefits and confirmed the superiority of aflibercept for improving visual and anatomic outcomes over sham treatment in myopic CNV. Significant improvements compared to sham (with nominal p-values <0.05) were observed in all functional (BCVA) and morphological (CRT, CNV lesion size, leakage area) variables as well as in the NEI VFQ-25 total score. In 73% aflibercept patients, the disease was well controlled with 1-3 injections during this period of 24 weeks. In contrast, the baseline disease conditions in the untreated sham group on average continued to persist, or even had deteriorated by week 24. Further treatment (as needed) in the aflibercept group until week 48 maintained and even slightly increased the efficacy results observed at Week 24. Although patients in the Sham+aflibercept arm experienced improvements in all assessments from Week 24 to Week 48, they did not reach the efficacy results observed for patients who had received active treatment from the beginning of the study.

The primary outcome measure was ‘mean change in BCVA from baseline to week 24’. At week 24, patients in the aflibercept and sham groups gained 12.1 and lost 2 letters, respectively (P < 0.0001). By week 48, patients in the aflibercept group, maintained and even slightly increased their letter score gain from baseline (13.5 letters) and sham+aflibercept group gained 3.9 letters (p<0.0001). Notably, this improvement in the sham + aflibercept group was less pronounced than in the aflibercept group at Week 24 compared to baseline, suggesting that patients benefit from early treatment, while if mCNV is left untreated irreversible damage may occur. This is in line with previous findings for anti-VEGF agents and current mCNV treatment recommendations.

The proportion of patients gaining ≥ 15 letters in BCVA at week 24 (confirmatory secondary efficacy variable) confirmed the clinically and statistically significant superiority of aflibercept (38.9%) over sham treatment (9.7%) (p=0.0001). This treatment difference was reduced by week 48 as these percentages increased to 50.0% in the aflibercept group and to 29.0% in the sham+aflibercept group (after aflibercept treatment from week 24) (p=0.0308). In all other categories of vision gain, more patients in the aflibercept group experienced gains from baseline than did patients in the Sham+ aflibercept group. In all categories of vision loss, more patients in the Sham+ aflibercept group experienced losses than did patients in the aflibercept group. Additional exploratory efficacy analyses supported the findings for BCVA changes from baseline. These efficacy analyses included changes from baseline in central retinal thickness (CRT), changes in CNV lesion size and mean area of leakage, as well as quality of life.

Sensitivity analyses (i.e. per protocol set (PPS), and those using only observed values) generally confirmed the results on the FAS, LOCF. Overall, the subgroup analyses were consistent with the results observed in the total study population.

Aflibercept was generally well tolerated and demonstrated a similar safety profile in myopic CNV as seen in previous indications.

3.6.2 Primary efficacy endpoint: Mean change in BCVA from baseline to week 24

Patients in the intravitreal aflibercept group had a mean change in BCVA of +12.1 letters compared with a letter loss of 2.0 in the sham group (P < 0.0001).

Using the ANCOVA model, after adjusting country effect and baseline BCVA measurement, the difference between treatment groups in Least Square (LS) mean changes from baseline to Week 24 was 14.1 ETDRS letters, with a 95% CI of 10.8-17.4 and a p-value < 0.0001.

Results, consistent with the primary analysis, were observed in the PPS and sensitivity analyses (OC, Mixed Model for Repeated Measurements and Multiple Imputation).

Figure 3 Mean change from baseline in BCVA (ETDRS letter score) to week 24 (and 48) (FAS; LOCF)

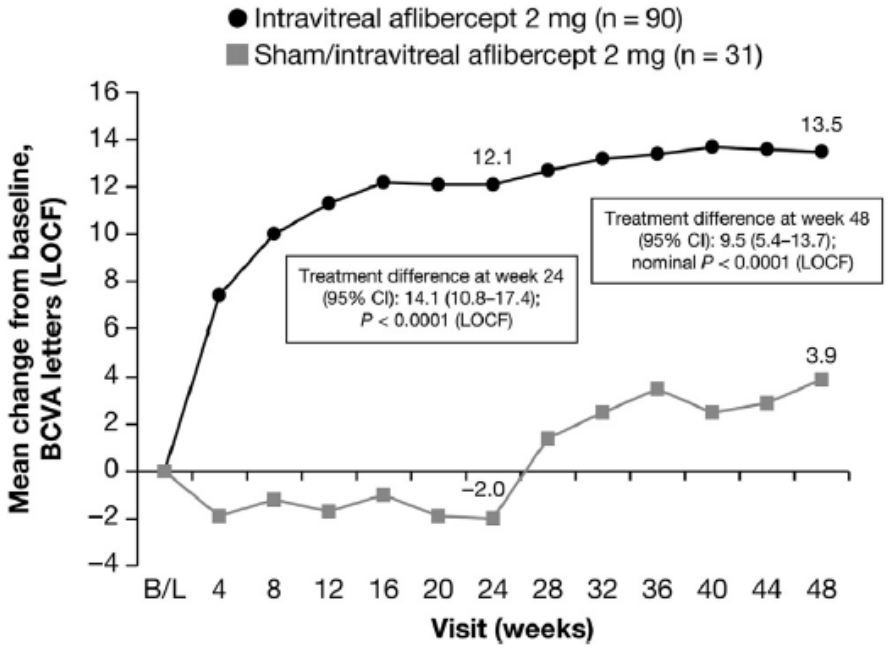


Table 13 Mean change in BCVA from baseline to week 24, ANCOVA (FAS, LOCF)(36)

	Aflibercept [a] N=90	**Sham N=31**
Mean BCVA (SD) at baseline	56.4 (9.8)	56.6 (8.9)
Mean BCVA (SD) at Week 24	68.5 (10.8)	54.6 (9.8)
Mean change from baseline to week 24	12.1	-2.0
LS mean change	13.2	-0.9
Difference in LS mean changes [b] 95% Confidence Interval [b] p-value [b]	14.1 [10.8; 17.4] <0.0001	

BCVA = best corrected visual acuity; LS=least squares; SD=standard deviation
[a] Aflibercept administered at baseline and potentially every 4 weeks in the event of disease recurrence
[b] Point estimate, 95% CI and p-value are based on treatment difference (aflibercept minus sham) in LS mean changes, using an analysis of covariance (ANCOVA) model with treatment group and country (country designations) as fixed effects. Baseline value of BCVA was included in the model.

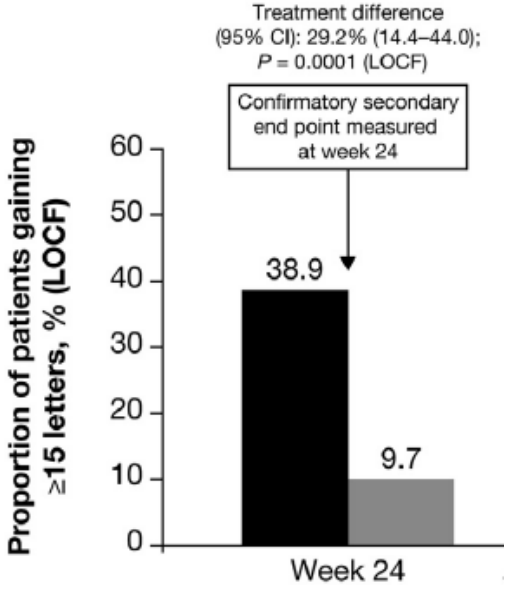
3.6.3 Confirmatory Secondary endpoint - Proportion of patients who gained ≥ 15 letters from baseline until week 24(30;35;36)

A letter gain by at least 15 letters at Week 24 in the FAS (LOCF) was the confirmatory secondary efficacy criterion in this study, and the corresponding test was found to be statistically significant. A greater proportion of intravitreal aflibercept-treated patients gained ≥ 15 letters compared with sham-treated patients (38.9% [n=35] vs. 9.7% [n=3]; P = 0.0001). After weight-adjusting by country using the two- sided Cochran-Mantel-Haenszel method, the difference between treatment groups was 29.2% in favour of aflibercept (95% CI:14.4%-

44.0%; p-value = 0.0001). The superiority of aflibercept over sham treatment, demonstrated in the primary efficacy analysis, was thus confirmed in analysis of the secondary endpoint.

Sensitivity analyses (OC, worst case imputation) were consistent with the FAS, LOCF analysis and supportive of the conclusion drawn from the primary analysis.

Figure 4 Proportion of patients gaining ≥ 15 letters from baseline to week 24(30)



3.6.4 Mean change in BCVA from baseline to week 48 and over time(30;36)

By Week 48, the mean letter score remained mainly stable in the aflibercept group (69.9 ± 11.1 letters; mean change from baseline by 13.5 ± 8.8 letters) compared to Week 24, while improvement was now also visible in the sham+aflibercept group, in which active treatment was initiated from Week 24 onwards (mean letter score at Week 48 was 60.5 ± 14.4 letters; mean change from the original baseline: 3.9 ± 14.3 letters) (see Table 14). Due to the improvement in the sham+aflibercept group from Week 24 onwards, the treatment difference in the LS mean change in BCVA letter score from baseline at Week 48 was not as marked as at Week 24 (9.5 vs. 14.1 letters), but still nominally significant ($p < 0.0001$).

The improvement in the sham+aflibercept group in the first 24 weeks of active treatment (i.e. Weeks 24 to 48) was not as marked as previously observed in the aflibercept group from baseline to Week 24 (12.1 ± 8.3 letters in the FAS with LOCF).

With regards to changes in BCVA over time, in the aflibercept group, the mean change in BCVA from baseline increased as early as Week 4 (+ 7.4 letters) compared to a mean change of -1.9 letters in the sham group.

Sensitivity analyses using observed instead of LOCF-imputed data showed a similar trend as FAS, LOCF.

Table 14 Mean change in BCVA from baseline to week 48, ANCOVA (FAS, LOCF)(30;36)

	Aflibercept [a] N=90	**Sham N=31**
Mean BCVA (SD) at baseline	56.4 (9.8)	56.6 (8.9)
Mean BCVA (SD) at Week 48	69.9 (11.1)	60.5 (14.4)
Mean change from baseline to week 48	13.5	3.9
LS mean change	14.3	4.8
Difference in LS mean changes [a] 95% Confidence Interval [a] p-value [a]	9.5 [5.4; 13.7] <0.0001	

BCVA = best corrected visual acuity; LS=least squares; SD=standard deviation
[a] Point estimate, 95% CI and p-value are based on treatment difference (aflibercept minus sham) in LS mean changes, using an analysis of covariance (ANCOVA) model with treatment group and country (country designations) as fixed effects. Baseline value of BCVA was included in the model. P-values are nominal.

3.6.5 *Post hoc* analyses of Mean change in BCVA from baseline to week 48 and over time

There was a slight inverse correlation between the mean improvement in BCVA and the categorised number of active injections in the aflibercept group (1-3 active injections: 15.2 ± 8.0 letters, 4-6 active injections: 13.8 ± 8.8 letters, 7-9 active injections: 10.3 ± 10.9 letters, and 10-12 active injections: 4.9 ± 5.8 letters). Patients with an initially good and sustained response to IVT aflibercept presumably did not meet the re-treatment criteria. In contrast, patients with myopic CNV less responsive to treatment required more repeat aflibercept injections.

3.6.6 Proportions of patients gaining or losing pre-specified numbers of letters from baseline through Week 48(34;36)

A summary of vision gains and losses (i.e., at least 5, 10, or 15 letters compared to baseline) at week 12, 24, 36 and 48 is provided in Table 15.

Vision gains

During the first 24 weeks, a rapid increase in the percentage of patients gaining ≥15 letters in BCVA was observed in the aflibercept group as early as Week 4 and Week 8 (see Figure 5). Thereafter, the percentage of letter gains progressed slowly (from 32.2% at Week 12, to 38.9% at Week 24). A similar tendency was also observed for the gains of at least 10 or 5 letters.

Table 15 Overview of proportions of patients gaining ≥5, ≥10, or ≥15 letters over time through week 48 (FAS; LOCF)(30;34-36)

Letter gain	Time point	Aflibercept N=90 n (%)	Sham N=31 n (%)	Difference (%)	Adjusted Difference (%) [a]	95% CI [a]	p-value [b]
	Week 12	29 (32.2)	1 (3.2)				
≥15 letters*	**Week 24**	**35 (38.9)**	**3 (9.7)**	**29.2**	**29.2**	**[14.4, 44.0]**	**0.0001**
	Week 36	[redacted]	[redacted]				
	Week 48	**45 (50.0)**	**9 (29.0)**	**21.0**	**21.0**	**[1.9, 40.1]**	**0.0308**
	Week 12	58 (64.4)	4 (12.9)				
≥10 letters	**Week 24**	**57 (63.3)**	**4 (12.9)**			[redacted]	**<0.0001**
	Week 36	[redacted]	[redacted]				
	Week 48	**62 (68.9)**	**13 (41.9)**	**27.0**	**27.0**	**[7.2, 46.8]**	**0.0075**
	Week 12	77 (85.6)	9 (29.0)				
≥5 letters	**Week 24**	**75 (83.3)**	**6 (19.4)**			[redacted]	**<0.0001**
	Week 36	[redacted]	[redacted]				
	Week 48	**79 (87.8)**	**14 (45.2)**	**42.6**	**42.7**	**[23.7, 61.6]**	**<0.0001**
Letter loss	**Time point**	**Aflibercept N=90 n (%)**	**Sham N=31 n (%)**	**Difference (%)**	**Adjusted Difference (%) [a]**	**95% CI [a]**	**p-value [b]**
	Week 12	3 (3.3)	11 (35.5)				
≥5 letters	**Week 24**	**3 (3.3)**	**11 (35.5)**				
	Week 36	[redacted]	[redacted]				
	Week 48	[redacted]	[redacted]		[redacted]	[redacted]	**0.0012**
	Week 12	1 (1.1)	5 (16.1)				
≥10 letters	**Week 24**	**0**	**8 (25.8)**				
	Week 36	[redacted]	[redacted]				
	Week 48	[redacted]	[redacted]		[redacted]	[redacted]	**0.035**
	Week 12	0	4 (12.9)				
≥15 letters	**Week 24**	**0**	**2 (6.5)**				
	Week 36	[redacted]	[redacted]				
	Week 48	[redacted]	[redacted]		[redacted]	[redacted]	**0.2446**

* the proportion of patients gaining ≥15 letters at week 24 was the study confirmatory secondary endpoint

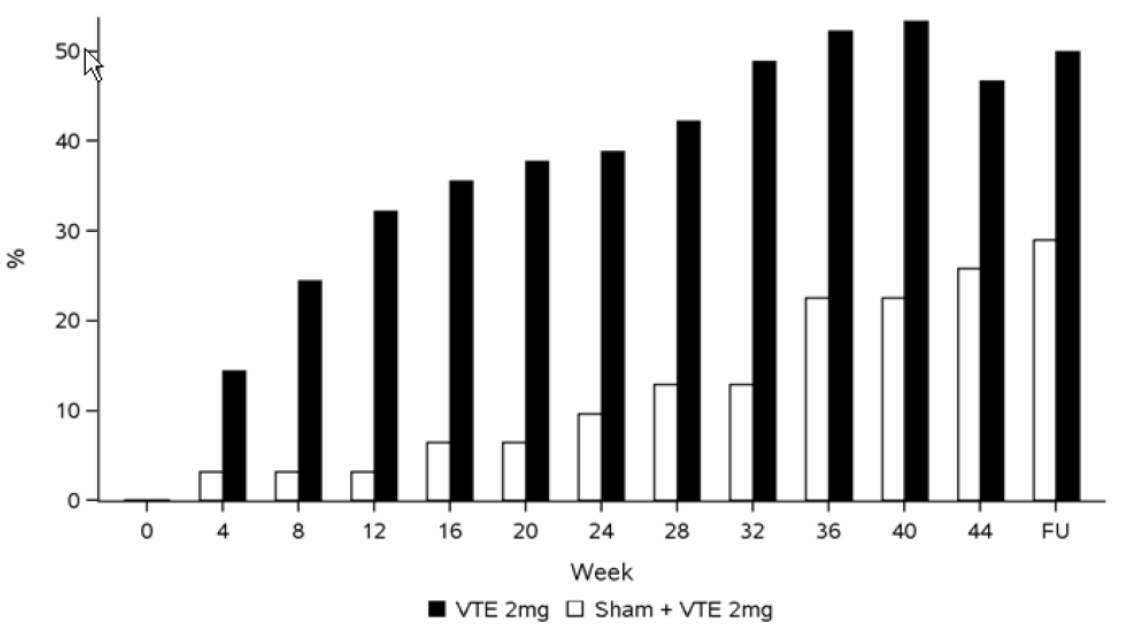
[a] Estimate (aflibercept group minus Sham+aflibercept group) and confidence interval are calculated using Cochran-Mantel-Haenszel (CMH) weights, adjusted for country (country designations).

[b] P-value is calculated using 2-sided CMH-test adjusted by country (country designations). P-values are nominal except week 24, ≥15 letter gains.

Proportions of patients gaining ≥15 letters from baseline through Week 48(30;36)

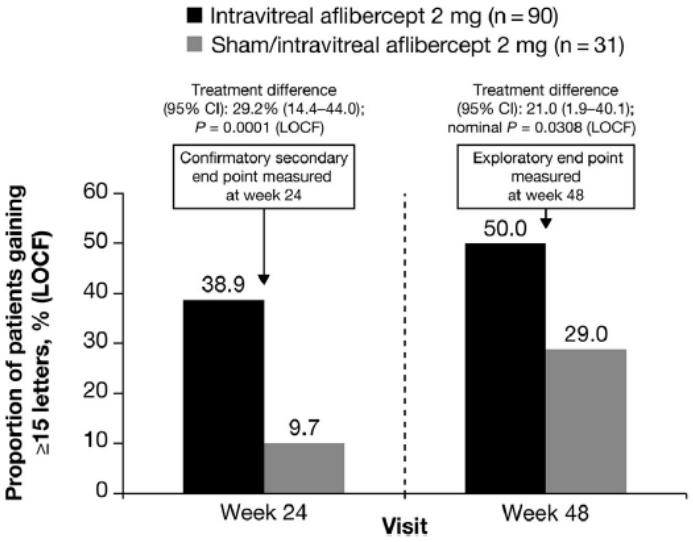
At week 48, the differences in the proportion of patients who gained ≥15 letters still favoured aflibercept (50%; n=45) over Sham+aflibercept (29%; n=9), with a CMH-adjusted difference of 21.0%; 95% CI [1.9; 40.1] (p=0.0308). The treatment difference had slightly diminished because of the improvement in the sham+ aflibercept group from Week 24 onwards.

Figure 5 Proportion of patients gaining ≥15 Letters in BCVA by Study Visit through Week 48 (FAS, LOCF)(36)



VTE=aflibercept

Figure 6 Proportion of patients gaining ≥ 15 letters from baseline to week 48(30)



Sensitivity analyses of Proportions of patients gaining ≥15 letters from baseline through Week 48

In the FAS, OC analysis, the difference was not so marked; difference of 50% in the aflibercept group versus 37.5% in the Sham+aflibercept group, with a CMH-adjusted difference of 13.1%; 95% CI [-9.4; 35.6], (p=0.2541). These results again reflect the improvement of the Sham+aflibercept group from Week 24 with the initiation of the aflibercept active treatment.

Similar results at Week 48 were obtained for the proportion of patients who gained either ≥10 or ≥5 letters.

Vision losses

Vision losses were very limited in the aflibercept group compared to the sham group. At week 24, deterioration by ≥5, ≥10 or ≥15 letters occurred only sporadically in the aflibercept group (0-3% patients; see Table 15), while such events were consistently more frequent in the sham group (6.5-35.5%) with a trend to decrease after Week 24, once these patients started to receive aflibercept.

3.6.7 NEI VFQ-25 Questionnaire

Change in total NEI VFQ-25 score from baseline at weeks 24 and 48(34;36)

NEI VFQ-25 total score assessed bilateral functional vision. The total NEI-VFQ-25 mean score showed a slight increase from baseline at week 24 in the aflibercept group (3.14 [redacted]) and a slight decrease in the sham group (-2.[redacted]). There was a difference between treatment groups of 5.21 points (ANCOVA: FAS, LOCF), favouring aflibercept, p=0.0104 (95% CI: 1.25; 9.18).

[redacted]

Overall, these data suggested a clinically meaningful outcome (i.e. a difference of ≥4 points)(45) in the aflibercept group compared to the sham + aflibercept group at Week 48.

Table 16 ANCOVA for mean change in total NEI VFQ-25 score from baseline to week 24 and week 48 (FAS, LOCF)(34;36)

Week 24	**Aflibercept N=89**	**Sham N=31**
Mean total NEI VFQ-25 score at baseline [DA]	70.72	72.73
Mean total NEI VFQ-25 score (SD) at Week 24	73.86 [redacted]	70.14 ([redacted]
Mean change (SD) from baseline to week 24	3.14 ([redacted]	-2.58 ([redacted]
LS mean change	3.45	-1.76
Difference in LS mean changes 95% Confidence Interval [a] p-value [a]	5.21 [1.25; 9.18] 0.0104	
Week 48	**Aflibercept [a] N=89**	**Sham N=31**
Mean total NEI VFQ-25 score at baseline [DA]	70.72	72.73
Mean total NEI VFQ-25 score (SD) at Week 48	[redacted]	[redacted]
Mean change from baseline to week 48	[redacted]	[redacted]
LS mean change	[redacted]	[redacted]
Difference in LS mean changes	[redacted]	

Note: Point estimate, 95%-CI and p-value are based on treatment difference (aflibercept group minus sham+aflibercept group) in LS mean changes, using an analysis of covariance (ANCOVA) model with treatment group and country (country designations) as fixed effects. Baseline value of BCVA was included in the model. P-values are nominal.

Sensitivity analysis of Change in total NEI VFQ-25 score from baseline at weeks 24 and 48

[redacted]

Table 17 ANCOVA for mean change in total NEI VFQ-25 score from baseline to week 24 and week 48 (FAS, Observed Case)(34;36)

Week 24	**Aflibercept N=84**	**Sham N=25**
Mean total NEI VFQ-25 score at baseline [DA]	[redacted]	[redacted]
Mean total NEI VFQ-25 score at Week 24	[redacted]	[redacted]
Mean change from baseline to week 24	[redacted]	[redacted]
LS mean change	[redacted]	[redacted]
Difference in LS mean changes	[redacted]	
95% Confidence Interval [a]	[redacted]	
p-value [a]	[redacted]	
Week 48	**Aflibercept [a] N=78**	**Sham N=24**
Mean total NEI VFQ-25 score at baseline [DA]	[redacted]	[redacted]
Mean total NEI VFQ-25 score (SD) at Week 48	[redacted]	[redacted]
Mean change from baseline to week 48	[redacted]	[redacted]
LS mean change	[redacted]	[redacted]
Difference in LS mean changes	[redacted]	

Note: Point estimate, 95%-CI and p-value are based on treatment difference (aflibercept group minus sham+aflibercept group) in LS mean changes, using an analysis of covariance (ANCOVA) model with treatment group and country (country designations) as fixed effects. Baseline value of BCVA was included in the model. P-values are nominal.

Brief overview of ANCOVA outcomes for treatment group difference in LS mean changes from baseline at Week 48 separated by NEI VFQ-25 subscales

Table 16 summarises the treatment group differences in LS mean changes from baseline at week 48 in the FAS seen within each of the 12 subscales of the NEI VFQ-25. [redacted] This was consistent with most of the functional and morphological variables and with the NEI VFQ-25 total score (LOCF).

Table 18 Overview of ANCOVA results for difference in changes in NEI VFQ-25 subscale scores from baseline at week 48 (FAS)(34)

Subscale	LOCF				Data as observed		
	Difference	95% CI	p-value		Difference	95% CI	p-value
GH	[redacted]						
GV							
OP							
NV							
DV							
SF							
MH							
RL							
DP							
DR							
CV							
PV							

GH=general health; GV=general vision; OP=ocular pain; NV=difficulty with near-vision activities; DV=difficulty with distance-vision activities; SF=limitation of social functioning due to vision; MH=mental health problems due to vision; RL=role limitations due to vision; DP=dependency on others due to vision; DR=driving difficulties; CV=difficulties with colour vision; PV=difficulty with peripheral vision.
Note: Point estimate, 95%-CI and p-value are based on treatment difference (aflibercept group minus sham+aflibercept group) in LS mean changes, using an analysis of covariance (ANCOVA) model with treatment group and country (country designations) as fixed effects. Baseline value of BCVA was included in the model. P-values are nominal.

3.6.8 EQ-5D questionnaire

Change in total EQ-5D score from baseline at weeks 24 and 48(30;36)

Changes in total EQ-5D score from baseline at week 24 were small in both treatment groups (aflibercept: 0.0187; sham: 0.0341) and the ANCOVA (LOCF) did not point to a nominally significant difference either in the LOCF or OC analysis. In the LOCF, there was an LS mean change of 0.0107 in the aflibercept group vs. 0.0152 in the sham group (treatment difference of -0.0045, 95%-CI: [-0.0579; 0.0490], p=0.8690). In the observed case analysis, the difference between groups was -0.0020 (95% CI: -0.0607; 0.0566), p=0.9451.

At Week 48, the mean change from baseline was 0.0154 score points in the aflibercept group and -0.0252 in the sham + aflibercept group. The adjusted treatment difference between groups was 0.0517 score points (95% CI: [0.0022; 0.1011], p=0.0408 in the LOCF analysis and 0.0583 score points (95%-CI: [0.0025; 0.11142], p=0.0409 in the OC analysis, showing in contrast to Week 24, a significant difference between treatment groups.

3.6.9 Analysis of injection frequency

Notably, 14% of patients in the aflibercept group only required 1 injection in the 48-week study period, and nearly 60% required no more than 3 injections. The most common reasons for re-treatment were new or persistent CNV or bleeding, and investigator's discretion, however the data suggests that retreatment decisions are based on a number of factors which might be different on each retreatment occasion (see Table 19). Only in a minority of cases is the decision to re-treat based on visual acuity change OR disease activity alone.

The number of injections over the study duration is reported in Table 20.Overall, the mean number of active injections needed in the aflibercept arm over the total period of study was low with 4.2 injections. An increased number of injections over the 24 or 48 weeks did not seem to result in higher improvements in VA, but quite the opposite with more limited gains in VA. These data showed that in some patients the disease may be controlled with a single injection. Therefore, the recommended dosing regimen of an initial injection followed by additional doses as needed, based on visual and/or anatomic outcomes, at intervals of no less than 4 weeks, was agreed by the CHMP.

Data were also analysed by quarters of the treatment length (i.e. baseline to week 8, weeks 12 to 20, weeks 24 to 32, and weeks 36 to 44) (Table 21). According to this analysis, most of the injections were administered in the first quarter of the study, with less frequent re-injections over the subsequent 3 quarters.

Table 19 Summary of reasons for re-treatment injections during MYRROR (Bayer, data on file)

Reason for retreatment			Week 0-20			Week 24-44			Week 0-44	
			Aflibercept group	Sham + aflibercept group		Aflibercept group	Sham + aflibercept group		Aflibercept group	Sham + aflibercept group
Visual Acuity	ONLY for 'Reduction in visual acuity by ≥5 letters from the previous ETDRS examination'	Number of active injections	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
		Number of patients receiving active injections	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
	Reduced Visual acuity +/- other reasons for retreatment	Number of active injections	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
		Number of patients receiving active injections	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
Disease worsening	ONLY for CRT increased thickness, new or persistent retinal changes, subretinal fluid, pigment epithelial detachment, CNV or bleeding	Number of active injections	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
		Number of patients receiving active injections	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
	CRT increased thickness, new or persistent retinal changes, subretinal fluid, pigment epithelial detachment, CNV or bleeding +/- other reasons for retreatment	Number of active injections	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
		Number of patients receiving active injections	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
Investigator decision	ONLY because deemed necessary by investigator	Number of active injections	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
		Number of patients receiving active injections	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
	Deemed necessary by investigator +/- other reasons for retreatment	Number of active injections	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
		Number of patients receiving active injections	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]

Table 20 Number of active injections and study period through week 48(36)

	Aflibercept (N=90) n (%)	Sham + aflibercept (N=31) n (%)	Total (N=121) n (%)
Number of active injections from baseline to week 20 [a]			
1	19 (21.1)	0 (0.0)	19 (15.7)
2	25 (27.8)	0 (0.0)	25 (20.7)
3	22 (24.4)	0 (0.0)	22 (18.2)
4	7 (7.8)	0 (0.0)	7 (5.8)
5	4 (4.4)	0 (0.0)	4 (3.3)
6	13 (14.4)	0 (0.0)	13 (10.7)
Number of active injections from week 24 to week 44 [b]			
Missing (none)	40 (44.4)	6 (19.4)	46 (38.0)
1	22 (24.4)	2 (6.5)	24 (19.8)
2	14 (15.6)	6 (19.4)	20 (16.5)
3	3 (3.3)	6 (19.4)	9 (7.4)
4	2 (2.2)	2 (6.5)	4 (3.3)
5	3 (3.3)	0 (0.0)	3 (2.5)
6	6 (6.7)	9 (29.0)	15 (2.4)
Total number of active injections from baseline to week 44			
Missing (none)	0 (0.0)	6 (19.4)	6 (5.0)
1	13 (14.4)	2 (6.5)	15 (12.4)
2	14 (15.6)	6 (19.4)	20 (16.5)
3	26 (28.9)	6 (19.4)	32 (26.4)
4	11 (12.2)	2 (6.5)	13 (10.7)
5	3 (3.3)	0 (0.0)	3 (2.5)
6	5 (5.6)	9 (29.0)	14 (11.6)
7	3 (3.3)	0 (0.0)	3 (2.5)
8	5 (5.6)	0 (0.0)	5 (4.1)
9	3 (3.3)	0 (0.0)	3 (2.5)
11	1 (1.1)	0 (0.0)	1 (0.8)
12	6 (6.7)	0 (0.0)	6 (5.0)
All active injections by category			
Missing (none)	0 (0.0)	6 (19.4)	6 (5.0)
>3	37 (41.1)	11 (35.5)	48 (39.7)
1 to 3	53 (58.9)	14 (45.2)	67 (55.4)
4 to 6	19 (21.1)	11 (35.5)	30 (24.8)
7 to 9	11 (12.2)	0 (0.0)	11(9.1)
10 to 12	7 (7.8)	0 (0.0)	7 (5.8)

[a] Excluding the active injections at week 24

[b] Including the active injections administered at week 24. Six patients in the sham + aflibercept group discontinued study treatment before week 24 and thus were not exposed to any active injections.

Table 21 Number of active injections by quarters of study duration (aflibercept group) (FAS)

	Number of injections	Week 0-8	Week 12-20	Week 24-32	Week 36-44
Aflibercept group	Median (Mean)	[redacted]	[redacted]	[redacted]	[redacted]
		3 (2.9) (week 0-20)		1 (1.3) (week 24-44)	
		3 (4.2)			
Sham + aflibercept group	Median (Mean)	0	0	[redacted]	[redacted]
		0		3 (3.0)	
		3 (3.0)			

B.3.7 Subgroup analysis

Subgroup analyses were consistent with the results observed in the total study population. These have not been presented in this submission because subgroup analyses results are only required if the technology does not provide similar or greater health benefits at a similar or lower cost to the comparator in the full population.

B.3.8 Meta-analysis

In a traditional meta-analysis, all included studies compare the same intervention with the same comparator in a direct head-to-head comparison. For this appraisal, a meta-analysis was not conducted as none of the clinical publications identified in the SLR compared aflibercept directly in a head-to-head study with the comparator of interest (ranibizumab). The only way to compare aflibercept against ranibizumab is via an indirect treatment comparison (ITC), as described in the next section. In this ITC a closed evidence network of three clinical studies could be created. None of the remaining clinical RCTs identified in the SLR contributed to this evidence network.

B.3.9 Indirect and mixed treatment comparisons

See appendix D for full details of the methodology for the indirect comparison.

3.9.1 Summary of the trials included in the indirect comparison

With the three key RCTs identified in the clinical SLR (MYRROR, RADIANCE and VIP), a closed evidence network could be created. These three selected RCTs are the best publicly available evidence for efficacy data for each treatment and all studies were double blinded RCTs. As such, we believe the RADIANCE, VIP and MYRROR studies are the best sources for efficacy data for the England and Wales population of this submission.

The network provides appropriate mean BCVA gain efficacy data for all treatments of interest. Table 22 presents a summary of these studies.

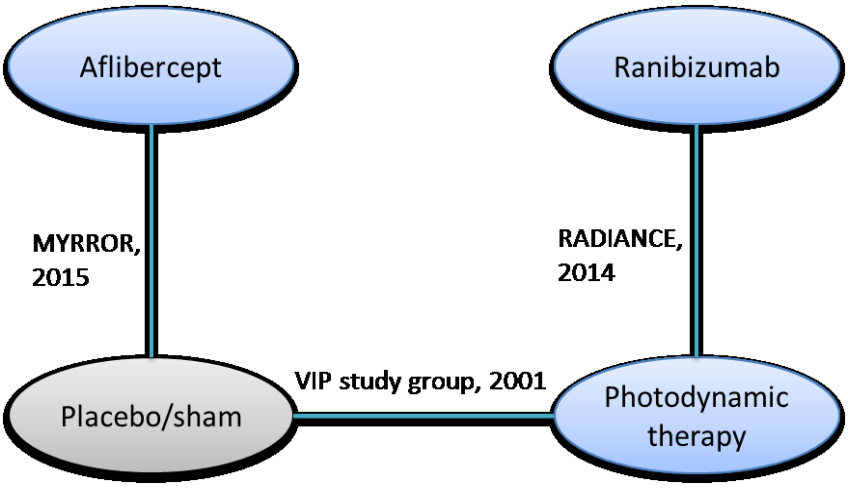
Note that the RADIANCE trial was the key study in the ranibizumab NICE submission (TA298)(2).

Table 22 Summary of RCTs included in the evidence network

Author	Year	Trial name	Treatment 1	Treatment 2	Mean BCVA gain available
Ikuno et al. 2015(30)	2015	MYRROR	Aflibercept	Placebo	Through to **week 24**, at which point the placebo arm is given the option of aflibercept
Wolf et al. 2014(25) ***[data included in NICE TA for ranibizumab]***	2014	RADIANCE	Ranibizumab	vPDT	Through to **3 months**, at which point the vPDT arm is given the option of ranibizumab
VIP study group, 2001(26) ***[included in NICE TA for ranibizumab]***	2001	VIP	vPDT	Placebo	Through to **12 months**
BCVA, Best Corrected Visual Acuity; vPDT, verteporfin photodynamic therapy					

Figure 7 presents a diagram of the evidence network using the studies in Table 22.

Figure 7 Evidence network



The RADIANCE trial compared IVT ranibizumab to vPDT in patients with mCNV. In the trial, two ranibizumab arms were included (ranibizumab VA and ranibizumab disease) and one vPDT arm. In the ranibizumab VA arm, patients were treated by 0.5 mg IVT injections on day 1 and month 1. Retreatment was based on VA stabilization criteria. Patients in the ranibizumab disease arm received 0.5 mg IVT injection on day 1. Starting from month 1, retreatment was based on disease activity criteria. The disease guided protocol dictated that treatment is discontinued when no disease activity is observed. Disease activity in this regard was defined as visual impairment attributable to intraretinal or subretinal fluid or active leakage secondary to mCNV. In this ITC both

ranibizumab arms have been compared separately with the other treatment options. Patients who were randomized to vPDT, were allowed to be treated with ranibizumab after the evaluation of the primary end point at 3 months.

The VIP trial compared vPDT to placebo in patients with subfoveal choroidal neovascularisation in pathologic myopia.

The MYRROR trial compared IVT aflibercept to placebo (sham) in patients with mCNV. In the intravitreal aflibercept group, patients were given 1 injection of intravitreal aflibercept 2.0 mg at baseline. Thereafter, intravitreal aflibercept 2.0 mg injections could be administered in case CNV persisted or recurred (based on the assessment of predefined criteria for retreatment) at a maximum frequency of once every 4 weeks through week 44. Re-treatment was allowed in patients who met 1 or more of the following criteria: (1) reduction in VA by ≥5 letters from the previous Early Treatment Diabetic Retinopathy Study examination; (2) increase in central retinal thickness (CRT) >50 mm from the time of the previous examination, new or persistent cystic retinal changes, subretinal fluid, or pigment epithelial detachment, and new or persistent CNV or bleeding; or (3) deemed necessary by the investigator based on his/her clinical impression or diagnostics performed in the context of standard medical care. In case the assessment of retreatment criteria was negative, patients received sham injections only for masking purposes. In the control group, patients were given 1 sham injection followed by repeated sham injections every 4 weeks through week 20 regardless of whether re-treatment criteria were fulfilled or not. At week 24, after assessment of the primary efficacy end point, control patients received the first mandatory intravitreal aflibercept 2.0 mg injection. Thereafter, as in the intravitreal aflibercept group, additional intravitreal aflibercept treatment could be administered from week 28 to week 44 (at a maximum frequency of once every 4 weeks) if CNV persisted or recurred.

More details on the studies included in the ITC and methodology of the ITC can be found in Appendix D.

Due to treatment switching in RADIANCE and MYRROR at fixed time points, the only common time period for which BCVA gain is available between the studies is at 3 months (13 weeks). Therefore, the main ITC output is mean BCVA gain over 3 months. Please see the section (B.3.9.3) on ‘Uncertainties in the indirect and mixed treatment comparisons’ for further discussion on this point.

3.9.2 Results of the indirect comparison

Table 23 presents the ITC results of the 3-month mean BCVA change in all treatments versus placebo and versus aflibercept, as well as the SD of the mean.

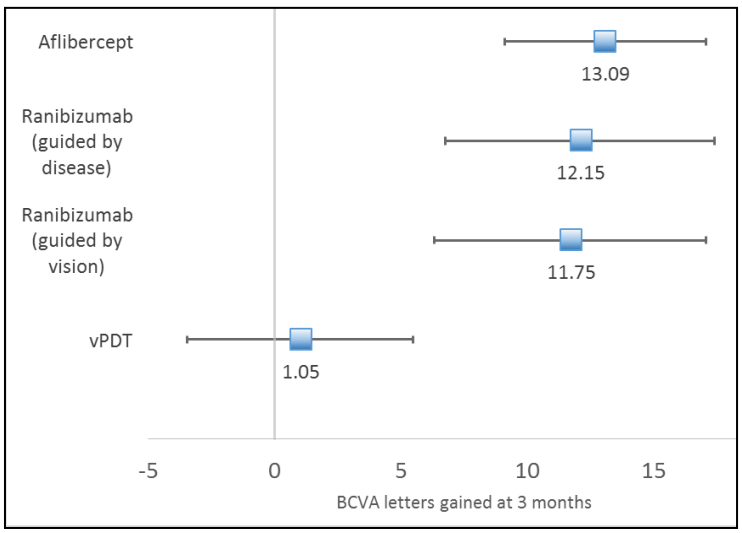
Figure 8 illustrates the results in the form of a forest plot. As illustrated by the results, aflibercept and both ranibizumab arms have similar efficacy. Aflibercept has the higher point estimate, but the uncertainty margins are overlapping with both ranibizumab arms, meaning this result is statistically insignificant.

Table 23 ITC results for mean 3-month gain in BCVA

	Mean	SD	95% low	95% high
vPDT vs placebo	1.05	2.29	-3.47	5.50
Ranibizumab (vision) vs placebo	11.75	2.75	6.31	17.09
Ranibizumab (disease) vs placebo	12.15	2.72	6.76	17.43
Aflibercept vs placebo	13.09	2.04	9.10	17.08
Aflibercept vs vPDT	12.04	3.05	6.10	18.00
Aflibercept vs ranibizumab (vision)	1.34	3.40	-5.35	8.00
Aflibercept vs ranibizumab (disease)	0.94	3.38	-5.67	7.56

BCVA, Best Corrected Visual Acuity; ITC, indirect treatment comparison; SD, standard deviation; vPDT, verteporfin photodynamic therapy.

Figure 8 ITC results for mean 3-month gain in BCVA



3.9.3 Uncertainties in the indirect and mixed treatment comparisons

A fundamental assumption in the ITC framework is that the included studies are quite similar, at least in terms of parameters which may act as relative treatment effect modifiers.

Although the inclusion of all three trials is essential to form the evidence network, it is important that heterogeneity between studies is acknowledged and investigated, to try and understand the potential bias that may be present in relative treatment effect estimates.

All three trials are multicentre, double-masked and randomised trials. Across most patient demographics, all three trials are reasonably balanced. Age and sex distributions compare reasonably well (see Appendix D), as well as the distribution of CNV location (majority subfoveal). Mean baseline BCVA compares well between MYRROR and RADIANCE. Only median baseline BCVA is presented in the VIP study, which is slightly higher than the mean baseline BCVAs in MYRROR and RADIANCE. However, this may just be a reflection of a slightly left skewed distribution.

The biggest area of heterogeneity in terms of the patient population is found with the ethnic distribution. Of the patients included in the VIP study 91% are caucasian. This is assumed to be a valid representation of the England and Wales population. However, this contrasts with the RADIANCE study, whereby 56.6% of patients were caucasian. The MYRROR study was conducted in an East Asian population exclusively (Japan, Hong Kong, Singapore, South Korea and Taiwan).

To support the regulatory submissions, Bayer conducted an evaluation of the ethnical insensitivity of aflibercept in Asians and Whites including intrinsic factors and extrinsic factors in line with International Conference on Harmonization (ICH E5) guidance, in order to justify extrapolation of efficacy data from MYRROR to other ethnicities and geographic regions, in particular European patients.

For the main analysis of ethnical insensitivity, clinical trials conducted with aflibercept in other approved indications were considered. Statistical evaluation of comparisons included descriptive statistics and regression analyses. The main efficacy results used for comparison were based on the assessment of BCVA and central retinal thickness (CRT) improvements.

The data pooling included 1,104 subjects. Among them, the majority were Caucasian (884, i.e. 80%) including 536 AMD, 156 central retinal vein occlusion (CRVO) and 385 diabetic macular oedema (DMO) patients.

Absolute treatment differences between Asians and Whites showed generally similar efficacy trends between treatment groups. This was confirmed by consistent overlaps of the corresponding 95% confidence intervals for all comparisons. Any observed differences were not statistically significant and were not clinically meaningful differences.

Overall, no evidence supporting a difference in the efficacy profiles in Asian and non-Asian patients were found in the evaluation. From these data, there was no basis to assume that intrinsic or extrinsic factors would cause differences in efficacy between ethnic subgroups. Thus, the CHMP agreed that the results of the MYRROR study could be extrapolated to the EU population.

Therefore, it is accepted by the European Medicines Agency (EMA) that the efficacy results of MYRROR are representative for mCNV patient populations in Europe, regardless of ethnicity.

Furthermore, a possible point of heterogeneity might be expected in the study design between the ranibizumab arms (ranibizumab retreatment based on VA and ranibizumab retreatment based on disease activity) of the RADIANCE study. However, no significant difference is expected as this stratification was part of the trial protocol and hence randomisation is maintained. Moreover, it is not expected that the population of the ranibizumab arms will be different from the population treated with aflibercept in the MYRROR study. Table in Appendix D shows that the mean age, gender ratio and mean BVCA at baseline are comparable. The only difference can be found in the ethnicity ratio, which has been discussed above.

Besides the population and the RADIANCE study design, there is also a degree of heterogeneity in the reported outcomes.

In the ITC the 3-month BCVA gain was used as the main result and anchor point, as it was the only common endpoint available to pool the evidence successfully. This is because patients in the vPDT arm of RADIANCE were administered ranibizumab after 3 months, which made comparisons during subsequent time periods impossible without bias. The implication of this approach is that not all potential vision gain has necessarily occurred by this time point. As illustrated in both the MYRROR trial and the RADIANCE study, vision improvements over time do not seem to completely plateau until around month 6. However, the majority of anti-VEGF BCVA gain has already occurred by month 3 and as this approach was taken for all treatments, it is not expected to introduce any considerable bias.

As each active treatment is only featured once in the evidence network, it was not possible to analyse the heterogeneity between treatment protocols across different trials. This also removes the possibility of a random effects model, or any quantitative assessment of heterogeneity, such as a chi-squared test.

B.3.10 Adverse reactions

3.10.1 Introduction to adverse event data

No studies directly compare aflibercept, as a single agent, with alternative active treatments i.e. ranibizumab, in mCNV. Data on the safety and tolerability profile of aflibercept in the treatment of mCNV is drawn from the safety analyses and adverse event (AE) reporting from the pivotal phase III study MYRROR. Safety and tolerability of repeated intravitreal administration of aflibercept, when compared with sham injections as a control arm, for a period of 24 weeks, and ongoing

safety of aflibercept treatment for up to 48 weeks was included as a secondary objective in MYRROR. The safety analysis population (SAF) included all patients who had received any study treatment: aflibercept group n=91; sham + aflibercept group n=31.

Mean exposure to aflibercept in the aflibercept group (SAF) was 5.8mg (standard deviation, SD=3.3), over a mean duration of 163 days (SD=24.8) for the first 24 weeks of the study; and 8.4±6.1mg over a mean duration of 44±10 weeks for the entire study. Patient exposure by number of active injections is summarised in Table 20 for the FAS. During the first 24 weeks of the MYRROR study, 22% (20/91) of patients in the aflibercept group (safety analysis set; SAF) received only 1 active injection (at baseline), and 74% of aflibercept patients (SAF) received 3 or fewer active injections. Over the whole duration of the study, 59% (54/91) of aflibercept patients received 1-3 active injections, while this number was 45% (14/31) for the Sham+aflibercept group, where active treatment only started at Week 24.

Safety was monitored by recording ocular (study and fellow eye) and non-ocular AEs at each study visit i.e. every 4 weeks. The term AE refers here to treatment-emergent AEs, (TEAEs) i.e. AEs which occurred or worsened after the first administration of study drug and within 30 days after the last study injection (active or sham). Adverse events were summarised using the Medical Dictionary for Regulatory activities (MedDRA) (version 16.0) and also assessed for seriousness, intensity, pattern, causal relationship to study drug and injection procedure. Laboratory values, vital signs, and intraocular pressure (IOP) were also measured.

3.10.2 Summary of treatment-related adverse events

A total of 67 patients in MYRROR experienced at least one TEAE during the first 24 weeks of the study period (aflibercept: n= [redacted] sham: n= [redacted]) and 82 (67.2%) patients during the entire 48 weeks (aflibercept: n= 64 [70.3%]; sham: n= 18 [58.1%]) (Table 24). The difference between treatment groups was mainly driven by non-ocular TEAEs. However, some baseline imbalances in terms of medical history findings to the disadvantage of the aflibercept group, such as hypertension, and the relatively small size of the Sham+aflibercept group must be considered in the safety assessment and interpretation of AE frequencies. No deaths were reported during the study.

Table 24 Overall adverse event profile through week 24 and week 48 (SAF)(30;34;36)

	Through week 24		Through week 48	
	Aflibercept (N=91) n (%)	**Sham (N=31) n (%)**	**Aflibercept (n=91) n (%)**	**Sham +aflibercept (N=31) n (%)**
Any TEAE	[redacted]	[redacted]	**64 (70.3)**	**18 (58.1)**
Non-ocular (systemic)	40 (44.0)	10 (32.3)	53 (58.2)	12 (38.7)
Ocular (study eye)	21 (23.1)	6 (19.4)	29 (31.9)	11 (35.5)
Any study drug-related TEAE	[redacted]	[redacted]	**9 (9.9)**	**2 (6.5)**
Ocular drug-related (study eye)	[redacted]	[redacted]	6 (6.6)	1 (3.2)
Non-ocular drug-related	[redacted]	[redacted]	3 (3.3)	1 (3.2)
Any injection-related TEAE	**15 (16.5)**	**4 (12.9)**	**18 (19.8)**	**4 (12.9)**
Injection-related ocular TEAE in study eye	[redacted]	[redacted]	18 (19.8)	4 (12.9)
Any procedure-related TEAE	[redacted]	**0**	**12 (13.2)**	**0**
Procedure-related ocular TEAE in study eye	5 (5.5)	0	6 (6.6)	0
Any serious AE	[redacted]	[redacted]	**7 (7.7)**	**1 (3.2)**
Non-ocular (systemic)	[redacted]	[redacted]	4 (4.4)	0
Ocular (study eye)	0	0	1 (1.1)	0
Any serious TEAE	[redacted]	**0**	**7 (7.7)**	**0**
Drug-related serious TEAE	**0**	**0**	**1 (1.1) (ocular)**	**0**
Any injection-related serious TEAE (study eye)	**0**	**0**	**1 (1.1)**	**0**
Any procedure-related serious TEAE	**0**	**0**	**1 (1.1)**	**0**
Any AEs leading to discontinuation of study drug	[redacted]	[redacted]	[redacted]	[redacted]
Any death	**0**	**0**	**0**	**0**
Any ATE events	[redacted]	**0**	**1 (1.1)**	**0**

AE=adverse event; ATE=arterial thromboembolic event; TEAE=treatment-emergent adverse event

Ocular TEAEs and Serious Adverse Events (SAEs)

An overview of ocular TAEs in the study eye at Week 24 and 48 is provided in Table 25. Most of the reported ocular TEAEs in the intravitreal aflibercept and sham+ aflibercept groups were considered to be of mild intensity, resolved within the study period, and did not lead to the interruption or permanent discontinuation of study treatment.

The most frequently reported (≥5%) ocular TEAEs in the study eye were conjunctival haemorrhage (11.0%), eye pain (7.7%), and punctate keratitis (6.6%) in the intravitreal aflibercept group and punctate keratitis (12.9%), dry eye (6.5%), and posterior capsule opacification (6.5%) in the sham+ aflibercept group.

Injection related TEAEs were reported slightly more frequently in the aflibercept group than in the sham+aflibercept group, and procedure related TEAEs occurred exclusively in the aflibercept group. Similar observations were made at Week 24 and 48.

As judged by the investigator, ocular TEAEs in the study eye were considered to be related to study drug in 6.6% of patients in the aflibercept group compared with 3.2% of patients in the sham+aflibercept group.

Overall, 7 patients (5.7%) (all in the aflibercept group) experienced a serious TEAE [4 (4.4%) non-ocular and 3 (3.3%) ocular]. Of these, only 1 ocular serious AE (a macular hole) occurred in a study eye (between week 24 and week 48). This was the only SAE assessed as related to study drug, to the procedure, as well as to the injection. During licensing, the CHMP acknowledged that high myopia is a risk factor for macular hole, which could also have caused the event. However, a causal relationship to the use of aflibercept could not be entirely excluded as the event occurred one month after aflibercept injection. Based on this single report of macular hole, however, no firm conclusions could be drawn and the AE should be further analysed in the next PSUR.

The other 2 ocular SAEs (macular hole and CNV) occurred in the fellow eye, between week 24 and week 48.

In the sham+aflibercept group, the only SAE reported was ‘visual acuity reduced’ in one patient, which occurred in the study eye and was considered unrelated to treatment or injection.

There were no cases of endophthalmitis in either treatment group.

Table 25 Ocular TEAEs in the study eye reported in any treatment group through Week 48 (SAF)(30;36)

MedDRA preferred term	Through week 24		Through week 48	
	Aflibercept (N=91) n (%)	Sham (N=31) n (%)	Aflibercept (N=91) n (%)	Sham +aflibercept (N=31) n (%)
Any ocular TEAE (study eye)	**21 (23.1)**	**6 (19.4)**	**29 (31.9)**	**11 (35.5)**
Anterior chamber cell	1 (1.1)	0	1 (1.1)	0
Blepharitis	1 (1.1)	0	1 (1.1)	0
Cataract subcapsular	0	0	1 (1.1)	0
Chorioretinal atrophy	0	0	0	1 (3.2)
Conjunctival haemorrhage	7 (7.7)	1 (3.2)	10 (11.0)	1 (3.2)
Conjunctivitis	1 (1.1)	0	1 (1.1)	0
Conjunctivitis allergic	1 (1.1)	0	1 (1.1)	0
Corneal deposits	1 (1.1)	0	1 (1.1)	0
Corneal erosion	2 (2.2)	1 (3.2)	2 (2.2)	1 (3.2)
Dry eye	1 (1.1)	1 (3.2)	2 (2.2)	2 (6.5)
Eye allergy	0	1 (3.2)	0	1 (3.2)
Eye pain	6 (6.6)	1 (3.2)	7 (7.7)	1 (3.2)
Intraocular pressure increased	0	0	0	1 (3.2)
Keratitis	0	0	1 (1.1)	0
Macular degeneration	0	0	1 (1.1)	0
Macular hole	0	0	1 (1.1)	0
Ocular discomfort	0	0	1 (1.1)	0
Ocular hyperaemia	2 (2.2)	1 (3.2)	2 (2.2)	1 (3.2)
Photophobia	1 (1.1)	0	1 (1.1)	0
Posterior capsule opacification	0	0	0	2 (6.5)
Punctate keratitis	4 (4.4)	3 (9.7)	6 (6.6)	4 (12.9)
Retinal degeneration	0	0	1 (1.1)	0
Retinal detachment	0	1 (3.2)	0	1 (3.2)
Retinal haemorrhage	1 (1.1)	0	1 (1.1)	0
Retinal tear	1 (1.1)	0	1 (1.1)	0
Retinoschisis	1 (1.1)	0	2 (2.2)	0
Vitreous floaters	0	0	1 (1.1)	0
Vitreous haemorrhage	0	0	1 (1.1)	0

Note: A patient is counted only once within each preferred term of any primary system organ class (SOC)

Fellow eye: The incidence of ocular TEAEs was higher in the study eye than the fellow eye for both treatment groups. A low number of ocular TEAEs were reported in the fellow eye at week 48 (20.9% aflibercept vs. 16.1% sham+aflibercept), none of which were reported to be drug-related, or procedure-related. There was one report of an injection-related TEAE in the fellow eye in the aflibercept group.

Non-ocular TEAEs and SAEs

The incidence of non-ocular TEAEs at Week 24 was 44.0% in the aflibercept group and 32.3% in the Sham+aflibercept group. The proportion of patients experiencing at least one non-ocular TEAE by Week 48 was still higher in the aflibercept group with 58.2% versus 38.7% in the Sham+aflibercept group.

The most commonly reported non-ocular TEAEs occurring in ≥5% of all patients were nasopharyngitis (18.7% aflibercept; 9.7% Sham+aflibercept group), headache (6.6% aflibercept 2 mg; 3.2% Sham+aflibercept group), and nausea (7.7% aflibercept 2 mg; 0.0% Sham+aflibercept group).

Four patients experienced a non-ocular TEAE considered to be related to the study drug (aflibercept: n=3; sham+aflibercept: n=1). No non-ocular TEAEs were considered to be related to the injection. Eight aflibercept patients experienced a 'procedure-related' non-ocular TEAE.

Overall, 4 patients (all in the aflibercept group) (4.4%) experienced a serious non-ocular TEAE. Three events were reported during the first 24 weeks of the study, but not considered related to study treatment. These were idiopathic thrombocytopenic purpura, cerebral haemorrhage and depression. The case of severe cerebral haemorrhage occurred 3 weeks after the third injection of aflibercept. The patient was a 58-year old woman without relevant medical history, who at the same time developed hypertension of moderate intensity. Both events were not considered as related to study drug. The idiopathic thrombocytopenic purpura of moderate intensity occurred in a patient with history of Sjogren's syndrome and required prolonged hospitalisation. The case of mild depression required prolonged hospitalisation and recovered after 10 days. A case of Moraxella-positive pneumonia occurred between week 24 and 48, the patient recovering within 4 weeks.

Table 26 Non-ocular TEAEs reported in ≥2% of patients in any treatment group through Week 48 by Primary System Organ Class and Preferred Term in the MYRROR study(30;36)

System organ class MedDRA preferred term	**Through week 24**		**Through week 48**	
	Aflibercept (N=91) n (%)	**Sham (N=31) n (%)**	**Aflibercept (N=91) n (%)**	**Sham +aflibercept (N=31) n (%)**
Any non-ocular TEAE	40 (44.0)	10 (32.3)	53 (58.2)	12 (38.7)
Nasopharyngitis	9 (9.9)	2 (6.5)	17 (18.7)	3 (9.7)
Nausea	5 (5.5)	0	7 (7.7)	0
Headache	6 (6.6)	1 (3.2)	6 (6.6)	1 (3.2)
Dizziness	[redacted]	0	5 (5.5)	0
Hypertension	4 (4.4)	0[a]	4 (4.4)	0[a]
Upper respiratory tract infection	3 (3.3)	0	3 (3.3)	0
Back pain	[redacted]	0	3 (3.3)	0
Diarrhoea	[redacted]	[redacted]	2 (2.2)	1 (3.2)

[a] one person in the sham+aflibercept group was reported to have had 'blood pressure increased'

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

Arterial thromboembolic events (ATEs) have been reported, on rare occasions, after intravitreal administration of VEGF inhibitors, including with intravitreal aflibercept injection and may potentially

be related to systemic VEGF inhibition. ATEs, as defined by APTC criteria, include non-fatal myocardial infarction (MI), non-fatal ischaemic or haemorrhagic stroke, or vascular death (including deaths of unknown cause). These events are the most clinically important arterial thromboembolic events because they can represent irreversible morbidity or mortality(46).

In MYRROR, there were was 1 (1.1%) arterial thromboembolic event (cerebral haemorrhage; as defined by APTC). This event occurred in the aflibercept-treated group in a patient diagnosed with hypertension. It was not considered by the investigator to be related to study drug, injection, or study procedures.

Other investigations

No clinically meaningful change in laboratory values or vital signs was seen in either treatment group in the MYRROR study. Laboratory abnormalities and other general safety parameters were determined to be consistent with the patients' underlying disease and medical history.

Aflibercept injections are accompanied by small IOP increases in the study eye, which did not result in any sustained IOP increases over time.

No treatment-emergent formation of antibodies to aflibercept was detected in either treatment group.

Adverse events leading to withdrawal

A total of 3 patients (3%) discontinued study drug treatment due to TEAEs before Week 24. Of these, 2 patients were aflibercept group (idiopathic thrombocytopenic purpura and cerebral haemorrhage) and 1 patient from the sham group (impetigo contagiosa). By Week 48, two further patients had discontinued treatment because of TEAEs (aflibercept: one case each of mild CNV in the fellow eye, and one of mild abnormal hepatic function).

3.10.3 Overview of the safety of the technology in relation to the decision problem

Aflibercept has been licenced and marketed in Europe since October 2015 for treatment of visual impairment due to mCNV. Prior to this, aflibercept was approved in 2012 for neovascular (wet) age-related macular degeneration (AMD); in 2013 for the treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO); in 2014 for treatment of visual impairment due to diabetic macular oedema (DMO) and in 2015 the treatment of visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO). Thus, within UK clinical practice, aflibercept is an established ophthalmological treatment with a known and manageable safety profile.

Review of the MYRROR safety data shows intravitreal injections of aflibercept 2mg to be well tolerated, and that the safety profile of aflibercept in mCNV patients(30;34;36) was generally consistent with the known safety profile in these other licensed populations (e.g. wet AMD, RVO, DMO)(37-39;41;42). In MYRROR, the incidence of ocular adverse events was similar in both groups through week 48 (to week 24: aflibercept 23.1% vs sham 19.4%; to week 48: 31.9% vs. 35.5%); most were assessed by investigators as mild. There were no reports of endophthalmitis. No deaths occurred. The results of the subgroup analyses appeared broadly consistent with the results in the entire study population, however, the sample sizes were relatively small to allow robust conclusions.

The MYRROR study generated data in the East-Asian populations only. However, based on the available evidence, including the results of a systematic review of ethnic (in-) sensitivity of aflibercept treatment in Asian versus non-Asian patients, there was no basis to assume that intrinsic or extrinsic factors would cause differences in safety between ethnic subgroups. Thus, during licensing review, the CHMP was of the view that the safety data from MYRROR could be extrapolated to European patients(47).

Overall, the safety data from the MYRROR study did not give rise for new safety concerns with aflibercept in the treatment of mCNV compared to the existing indications. In terms of exposure, mCNV patients would be expected to receive fewer injections of aflibercept compared to other target populations.

Based on the above safety evidence, it is anticipated that aflibercept will provide a suitable alternative option to ranibizumab for the treatment of visual impairment due to mCNV in England.

B.3.11 Conclusions about comparable health benefits and safety

3.11.1 Principal findings from aflibercept clinical evidence: clinical benefits and harms

In this submission, aflibercept's effectiveness in the treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV; mCNV) is reviewed. With no cure, the key management strategy for mCNV is to maintain visual capability for the daily activities such as driving, working, reading and writing. The current standard of care for mCNV is ranibizumab, also an anti-VEGF factor (recommended by SMC and NICE for use in clinical practice for this indication(2;22). Another treatment option is verteporfin photodynamic therapy(PDT) however this treatment does not restore visual acuity and is associated with long-term chorioretinal atrophy(8), and its use has been superseded by ranibizumab.

Clinical evidence to support the use of aflibercept for the treatment of visual impairment due to CNV secondary to pathological myopia is provided by results from MYRROR, a prospective, phase 3, multicentre, randomised, double-masked, sham-controlled, study. In this study, 122 patients with active subfoveal or juxtafoveal CNV secondary to pathologic myopia, were randomised to receive aflibercept or sham treatment. The primary endpoint was 'mean change in BCVA from baseline to week 24'. The confirmatory secondary endpoint was the proportion of patients gaining ≥ 15 letters in BCVA at week 24. Other endpoints included degree of vision gain, vision loss, changes from baseline in central retinal thickness (CRT), changes in CNV lesion size and mean area of leakage, as well as quality of life.

MYRROR met its primary efficacy objective. Aflibercept treatment resulted in a significantly greater mean change in BCVA from baseline to week 24 compared with sham treatment (+12.1 and -2 letters, respectively; P < 0.0001). By week 48, patients in the aflibercept group, maintained and even slightly increased their letter score gain from baseline (13.5 letters) and sham+aflibercept group gained 3.9 letters (p<0.0001). Notably, this improvement in the sham + aflibercept group was less pronounced than in the aflibercept group at Week 24 compared to baseline, suggesting that patients benefit from early treatment. This is in line with previous findings for anti-VEGF agents and current mCNV treatment recommendations, while if mCNV is left untreated, progressive and irreversible loss of visual acuity, particularly central vision can occur(9).

Analysis of the confirmatory secondary endpoint (the proportion of patients gaining ≥ 15 letters in BCVA at week 24) further confirmed the clinically and statistically significant superiority of aflibercept (38.9%) over sham treatment (9.7%) (p=0.0001). This treatment difference was reduced by week 48 (50.0% in the aflibercept group and 29.0% in the sham+aflibercept group; p=0.0308) as patients in the sham group received aflibercept from week 24.

In all other categories of vision gain (≥10 or ≥5 letters) more patients in the aflibercept group experienced gains from baseline than did patients in the Sham+ aflibercept group. In all categories of vision loss, more patients in the Sham+ aflibercept group experienced losses than did patients in the aflibercept group.

Additional exploratory efficacy analyses supported the beneficial BCVA changes from baseline with aflibercept. At week 24, aflibercept-treated patients had a substantially larger mean decrease in central retinal thickness (CRT) than sham patients, mean CNV lesion size decreased (whereas CNV size increased in the sham-treated group) and mean change in area of CNV leakage was significantly reduced for aflibercept-treated patients (small increase in sham treated patients). By week 48, patients in the aflibercept group maintained their improvements. Sham patients, who had switched to intravitreal aflibercept at week 24, also experienced an improvement in CRT, a

decrease in CNV size and a reduced area of CNV leakage, although the difference was less pronounced than observed in the aflibercept group.

Sensitivity analyses (i.e. per protocol set (PPS), and those using only observed values) generally confirmed the results on the FAS, LOCF. Overall, the subgroup analyses were consistent with the results observed in the total study population, indicating the robustness of the results in a broad spectrum of patients.

Thus, all efficacy results (i.e. primary, confirmatory secondary, and exploratory) showed robust benefits and confirmed the superiority of aflibercept for improving visual and anatomic outcomes over sham treatment in myopic CNV. Significant improvements compared to sham (with nominal p-values <0.05) were observed in all functional (BCVA) and morphological (CRT, CNV lesion size, leakage area) variables. In most aflibercept patients (>70%), the disease was well controlled with 1-3 injections during this period.

The beneficial clinical profile of aflibercept was accompanied by an acceptable safety profile, both locally and systemically, when compared with sham treatment in patients with mCNV. The most frequently reported (≥5%) ocular TEAEs in the study eye in the intravitreal aflibercept group were conjunctival haemorrhage, eye pain, and punctate keratitis, - TEAEs consistent with the injection procedure. Most reported ocular TEAEs were assessed by investigators as mild, resolved within the study period, and did not lead to the interruption or permanent discontinuation of study treatment. There were no reports of endophthalmitis. No deaths occurred. The most common non-ocular TEAEs were nasopharyngitis, headache, and nausea. One (1.1%) arterial thromboembolic event (cerebral haemorrhage; as defined by APTC) was reported. This event occurred in the aflibercept-treated group in a patient diagnosed with hypertension. It was not considered by the investigator to be related to study drug, injection, or study procedures. Results of the subgroup analyses of safety parameters appeared broadly consistent with the results in the entire study population, however, the sample sizes were mostly too small to allow robust conclusions.

Overall, the safety data from the MYRROR study did not give rise for new safety concerns with aflibercept in the treatment of mCNV compared to the existing indications (e.g. wet AMD, DMO, branched and central RVO). Also, in terms of exposure, mCNV patients would be expected to receive fewer injections of aflibercept compared to other target populations.

In line with the clinical improvements in most of the functional and morphological variables and a manageable safety profile demonstrated with the use of aflibercept in mCNV, there was indication of a clinically meaningful outcome in the aflibercept group compared to the sham + aflibercept group for vision-related quality of life using the NEI VFQ-25 Questionnaire. A 4- to 6-point improvement in the mean composite NEI VFQ-25 scores is considered to represent a clinically meaningful change, corresponding to at least a 15-letter change in BCVA. The total NEI-VFQ-25

mean score showed a slight increase from baseline at week 24 in the aflibercept group (3.14) and a slight decrease in the sham group (-2.[redacted]), a difference between treatment groups of 5.21 points (ANCOVA: FAS, LOCF), favouring aflibercept, p=0.0104 (95% CI: 1.25; 9.18), a benefit still observed at week 48.

[redacted]

On the basis of the evidence presented above, the benefits of aflibercept in the treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV) outweigh any treatment related risks.

3.11.2 Comparative evidence – Aflibercept vs. ranibizumab

Both the ranibizumab NICE appraisal and this aflibercept NICE submission recognise the main impact of CNV secondary to pathological myopia as the rapid loss or change in vision, and the key outcome measures being based around assessment of treatment effects on vision and the ability of the technology to halt, slow or reverse disease progression.

Pivotal RCTs for both ranibizumab and aflibercept in mCNV (Ranibizumab vs. vPDT: RADIANCE; Aflibercept vs. sham: MYRROR) demonstrate both technologies to significantly improve visual function, based on the primary endpoint of 'mean change in BCVA from baseline to a specified timepoint (ranibizumab: 3 months; aflibercept: 6 months). Secondary endpoints of 'proportions of patients gaining' at least 10 letters or at least 15 letters from baseline at 3 months (ranibizumab) and 6 months (aflibercept) were also statistically significantly greater than each study's comparator arm. In both studies, gains in BCVA were accompanied by improvements in vision-related functioning, as assessed using the 25-item National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25).

There is no head to head data available for aflibercept and ranibizumab. The MYRROR study was 'sham-controlled' and there was no 'active' comparator because, at the time of the study design, no therapy was considered to be the standard of care in all participating countries. No anti-VEGF therapy had been approved in this indication anywhere in the world and although photodynamic therapy with verteporfin (vPDT) received approval in the EU in March 2001 and in the US in August 2001 for the treatment of mCNV, its limited efficacy meant that its widespread utilisation for mCNV in Asia and Europe was never adopted. In Japan, one of the countries in the MYRROR trial, vPDT has never been approved.

An indirect comparison has been conducted and is used as the basis for this submission (see section B.3.9 and Appendix D). In summary, the ITC reported that aflibercept and both ranibizumab arms from RADIANCE have similar efficacy. The ITC suggested that differences in vision between

both ranibizumab arms and aflibercept were both very small and statistically insignificant. At 3 months, aflibercept has the higher point estimate and was estimated to improve vision by 0.94 and 1.34 letters against the RADIANCE disease-guided retreatment and vision-guided retreatment arms, respectively. Evidence of a study conducted in patients with diabetic retinopathy, which examined the link between visual acuity and HRQoL, suggests that at least a 10 letter change in vision must occur before significant functional changes in HRQoL are observed(48). There is no reason to expect a change in vision to be any more or less significant in patients with mCNV. Therefore we consider these treatment differences clinically insignificant as well as statistically insignificant. Regarding HRQoL, it was not possible to compare the QoL measures of the included studies in the ITC. As the VIP trial did not report on QoL measures, there was no bridge in the evidence network.

With respect to safety, the numbers of adverse events and the evidence network for adverse events in the ITC was too small to make a comparative evidence synthesis between the trials possible. More specifically: the VIP trial did not report/encounter the same adverse events as MYRROR/RADIANCE so there was no bridge in the evidence network. Due to this limitation, safety outcomes were not included in the ITC. However, safety results are available from two randomised controlled trials in a different eye condition (wet AMD - VIEW 1 and VIEW 2 studies), where aflibercept and ranibizumab were directly compared. The VIEW studies demonstrated aflibercept to be well tolerated, with a comparable safety profile to ranibizumab in relation to ocular and non-ocular adverse events (see Table 27 and

Table 28). VIEW 1 and VIEW 2 involved participants receiving aflibercept or ranibizumab for two years, therefore providing a robust, long-term comparison. On this basis, and alongside the consistency of the safety profile of aflibercept in MYRROR compared to that observed in studies in existing ophthalmological indications, it is anticipated that aflibercept will also have a comparable safety profile to ranibizumab in the treatment of mCNV.

Table 27 Frequency of ocular and non-ocular TEAEs during the entire study period for the VIEW 1 and VIEW 2 studies in wet age-related macular degeneration(49;50)

	Ranibizumab			Aflibercept		
	0.5mg Q4			2mg Q4		
	VIEW 1	VIEW 2	Pooled	VIEW 1	VIEW 2	Pooled
	N=304 n (%)	N=291 n (%)	N=595 n (%)	N=304 n (%)	N=309 n (%)	N=613 n (%)
Any TEAE	**297 (97.7)**	**270 (92.8)**	**567 (95.3)**	**296 (97.4)**	**291 (94.2)**	**587 (95.8)**
Non-ocular (systemic)	271 (89.1)	223 (76.6)	494 (83.0)	265 (87.2)	257 (83.2)	522 (85.2)
Ocular (study eye)	284 (86.8)	222 (76.3)	486 (81.7)	247 (81.3)	228 (73.8)	475 (77.5)

Table 28 Integrated analysis of VIEW 1 and VIEW 2 studies: Ocular TEAEs in the study eye occurring in ≥5.0% of patients at preferred term level in any treatment group during entire study period (Baseline to Week 96)(SAF)(49)

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

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

3.11.3 Clinical or biological plausibility of similarities in health benefits between the technology and the comparator(s)

Both ranibizumab and aflibercept are from the therapeutic class 'vascular endothelial growth factor (VEGF) inhibitors'. Therefore, based on their biological similarity, similarities in health benefits between the two technologies are clinically and biologically plausible. The results of the indirect comparison support the conclusion of similarity.

However, compared with ranibizumab, aflibercept has an innovative design, being the only fusion protein licensed for use in the eye(1). It binds tightly to all isoforms of VEGF-A, and also to other cytokines implicated in pathological angiogenesis: Placental growth factor (PlGF), VEGF-B and Galectin-1(1;4;51;52).

Aflibercept has been shown to bind more tightly to VEGF-A than native receptors (3) and in addition, Stewart et al.(53) demonstrated that 79 days after a single aflibercept (1.15 mg) injection, the intravitreal VEGF-binding activity would be comparable to ranibizumab at 30 days.

Suppression of anterior chamber VEGF has been reported for patients with neovascular age-related macular degeneration (AMD) and with visual impairment due to diabetic macular oedema (DMO):

• A mean of 34–37 days (5–6 weeks) and less than 2 months in most patients with ranibizumab(54;55)

• A mean of >69 days (10 weeks) with aflibercept in most patients(56;57)

3.11.4 The committee's preferred clinical assumptions from the NICE technology appraisal of ranibizumab

There were no preferred clinical assumptions that were key drivers of the cost-effectiveness results.The key drivers of the cost-effectiveness results in the ranibizumab NICE Technology Appraisal (TA298)(2) included the unit cost of ranibizumab and vPDT, the number of ranibizumab injections in the first and second year, the starting age of the patient group, the discount rate for benefits and the maximum utility gain in the worse-seeing eye. The Committee concluded that the uncertainties associated with the key drivers in the model were unlikely to have an effect on the overall cost-effectiveness results.

3.11.5 Describe and explain any uncertainties in the evidence informing your conclusions.

The development program for aflibercept in mCNV was based on one pivotal trial (MYRROR) that, owing to the high prevalence of mCNV in patients of Asian race, was conducted exclusively in East-Asian countries (Japan, Hong Kong, Republic of Korea, Singapore, and Taiwan). A limitation to the evidence from MYRROR is the lack of data in Caucasians and Europeans, and thus there could be uncertainty as to the applicability of MYRROR to mCNV patients in routine clinical practice in England.

To support the claim of ethnical insensitivity of aflibercept and thus extrapolation of the results of MYRROR from the Asian population recruited to European mCNV patients, a systematic review of efficacy, safety and pharmacokinetic results from previous clinical trials in existing indications (AMD, CRVO and DMO) was performed in line with International Conference on Harmonisation ICH E5 guidance. Details of the data selection, method of analysis of intrinsic and extrinsic factors and full results can be found within the referenced report(58). Statistical evaluation of comparisons included descriptive statistics and regression analyses. The main efficacy results used for

comparison were based on the assessment of BCVA and CRT improvements. The data pooling for the report included 1104 patients. Among them, the majority were Caucasian (884, i.e. 80%) including 536 AMD, 156 CRVO and 385 DMO patients.

Within the analyses, absolute treatment differences between Asians and Whites showed generally similar efficacy trends between treatment groups. This was confirmed by consistent overlaps of the corresponding 95% confidence intervals for all comparisons. A tendency to numerically slightly more variable results of differences was seen for the Asian subgroups. The analyses of extrinsic factors included the intravitreal administration of aflibercept in retinal diseases in East Asia as compared to Europe (North America and Australia) and the medical practice of the diagnosis and treatment of mCNV in East Asia as compared to Europe, North America and Australia. These analyses did not identify any extrinsic factors that would indicate the potential for ethnical sensitivity of aflibercept in East Asia as compared to Europe (or other geographic regions with a mainly White population including North America and Australia). Also, exploratory subgroup analyses did not reveal any relevant influence of age, sex, BMI, renal function, medical history of hepatic impairment, or geographic region (Europe/Japan, Japan/non-Japan) on the plasma concentrations of free or bound aflibercept.

Overall, no evidence supporting a difference in the efficacy and safety profiles in Asian and non-Asian patients was found during systematic review. From these data, there was no basis to assume that intrinsic or extrinsic factors would cause differences in efficacy and safety between ethnic subgroups. Thus, the CHMP agreed that the available clinical and safety data were sufficient to support the licensing of aflibercept in the treatment of adult patients with visual impairment due to mCNV and that the data could be extrapolated to European patients(36).

Aside from ethnicity, demographic and baseline characteristics of patients in MYRROR are broadly representative of a UK population of patients with mCNV. For example, typically, mCNV affects adults aged 40-50 years. In MYRROR, the total population ranged in age from 27 to 83 years with a mean age 58.2 years. Also, the development of mCNV is subfoveal in approximately 58% of cases and juxtafoveal in 32%. In MYRROR, approximately 62% patients had a diagnosis of subfoveal CNV and 38% of patients juxtafoveal CNV.

Results of subgroup analyses in all efficacy endpoints and safety parameters were generally consistent with those of the overall population and indicate no apparent influences on the efficacy of aflibercept of age, sex, and baseline disease characteristics such as baseline BCVA score, duration of target disease, renal impairment, hepatic impairment.

Results of the MYRROR study are therefore considered applicable to the population in England and Wales, as defined in the scope.

The limited sample size and lack of long-term data in mCNV patients, may also bring in some uncertainty to the data, which may have precluded the detection of rare adverse events. It is not anticipated that this will be the case, on the basis that aflibercept has been used extensively worldwide in other eye conditions and also aflibercept exposure in mCNV patients is much less compared with administration for these other indications. Nevertheless, additional data are being generated by inclusion of mCNV patients in an ongoing post-authorisation safety study (PASS) programme.

Also, the MYRROR study did not include patients with extrafoveal lesions, nor those who had previously undergone treatment with verteporfin photo-dynamic therapy (vPDT) and had recurrent mCNV, situations which may arise in clinical practice.

B.3.12 Ongoing studies

No ongoing studies or updated analyses are anticipated within the next 12 months.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Introduction of this technology for the treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV) does not require additional infrastructure to be put in place. The submission considers aflibercept as an alternative treatment option to ranibizumab in adult patients with visual impairment due to myopic choroidal neovascularisation (mCNV).

Aflibercept, in the same way as ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections in an appropriate facility. The injection procedure would be similar to that of ranibizumab, meaning that there will be no change in resource use.

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. 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 should be available (see aflibercept SmPC Appendix C). 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 mCNV in the NHS. Also, as with current practice, monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography). The monitoring and treatment schedule is determined by the treating physician based on the individual patient's response.

B.4.2 Cost-comparison analysis inputs and assumptions

4.2.1 Features of the cost-comparison analysis

A cost-comparison analysis model was developed for the economic evaluation of aflibercept in accordance with its marketing authorisation in mCNV in England and Wales. The model was developed to capture the lifetime costs related to mCNV treatment.

An indirect comparison with ranibizumab demonstrated that both the anti-VEGF treatments have similar efficacy. Aflibercept has the higher point estimate, but the uncertainty margins are overlapping with both ranibizumab arms, meaning this result is statistically insignificant. In addition, the injection frequencies for aflibercept and ranibizumab have wide and overlapping uncertainty

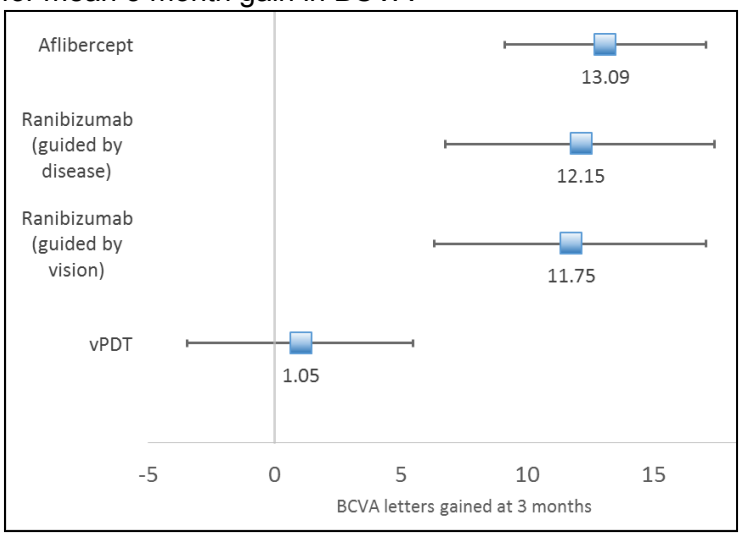
margins, showing no statistically significant difference. Furthermore, medical opinion and comparative data in other indications suggests that adverse event rates would be expected to be the same between the two treatments. As such, a cost comparison whereby treatment efficacy, treatment safety and treatment injection frequencies are all set equal was deemed appropriate and the preferred model framework.

As mentioned previously, the RADIANCE trial included two separate ranibizumab arms, one in which the retreatment protocol was guided by visual acuity (VA) and one where retreatment was guided by disease activity. In contrast, the treatment protocol for the MYRROR trial involved consideration for both disease activity and VA outcomes or due to the clinician`s judgement.

A market research study was conducted in January 2016 among 52 UK ophthalmologists with experience treating mCNV and other eye diseases (Bayer plc, data on file). All clinicians interviewed had prescribed ranibizumab for mCNV, with 58% having prescribed aflibercept for mCNV and all clinicians had at least 2 years of experience working in a district general hospital or academic hospital. The aim of the research was to obtain data and metrics about treatment usage, patient monitoring, costing and patient population estimates (e.g. bilateral mCNV). The clinicians queried in the market research suggested that around 75% of retreatments are guided by a combination of disease activity and VA (Bayer plc, data on file). Therefore, the MYRROR protocol may be broadly reflective of clinical practice with regards to retreatment criteria, whilst the RADIANCE protocol investigates different retreatment criteria in different arms. Both arms were therefore considered in the indirect comparison.

As shown in Figure 9, the ITC suggested that differences in vision between both ranibizumab arms and aflibercept were both very small and statistically insignificant. At 3 months, aflibercept was estimated to improve vision by 0.94 and 1.34 letters against the RADIANCE disease-guided retreatment and vision-guided retreatment arms, respectively. Evidence of a study conducted in patients with diabetic retinopathy, which examined the link between visual acuity and HRQoL, suggests that at least a 10 letter change in vision must occur before significant functional changes in HRQoL are observed(48). In conducting the analysis to establish the clinically significant letter change between ranibizumab and aflibercept, baseline demographics and clinical characteristics were balanced by controlling for age, gender and baseline visual acuity in the regression model. This isolates the analysis to considering only the relationship between visual acuity and HRQoL, with other potential disease relevant factors controlled for. There is no reason to expect a change in vision to be any more or less significant in patients with mCNV. Therefore we consider these treatment differences clinically insignificant as well as statistically insignificant.

Figure 9 ITC results for mean 3 month gain in BCVA

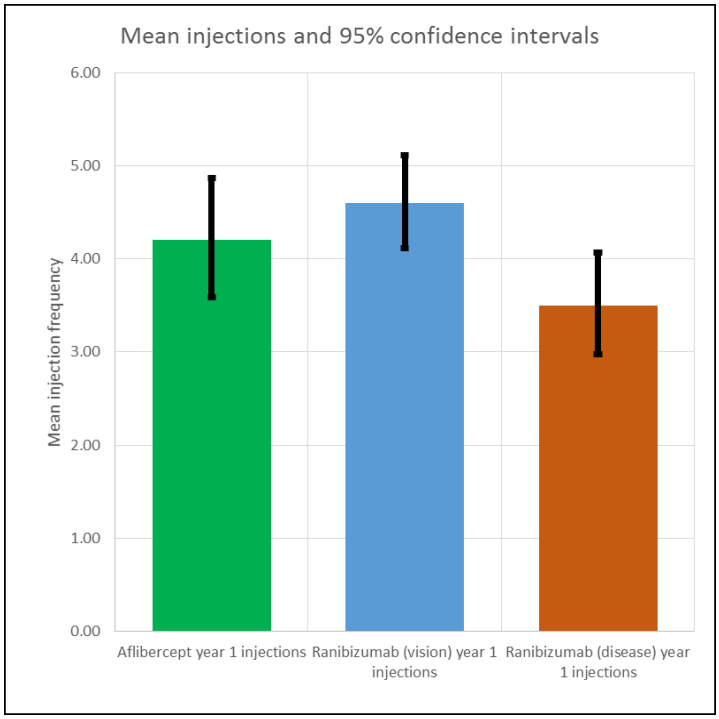


In addition, medical opinion suggests that adverse event rates would be expected to be the same between the two treatments (based on other ophthalmology indications), and data availability was too limited for inclusion in the ITC evidence network. Results from head-to-head trials between aflibercept and ranibizumab in other eye indications support the assumption of an equivalent safety profile (section B.3.11.2).

Furthermore, no differences in survival are expected, and due to the similarity of each drug's administration and safety profile, no differences in patient preference or adherence are expected either. This covers all relevant domains of HRQoL which might differ between the drugs.

For these reasons, as stated, the economic evaluation takes the form of a cost-comparison model, whereby treatment efficacy and safety are equalised. In addition, treatment injection frequencies have been equalised, due to the injection frequencies for aflibercept and ranibizumab in MYRROR and RADIANCE having wide and overlapping uncertainty margins, showing no statistically significant difference (see Figure 10). Equalising these parameters avoids any unfair comparisons being drawn which might be a product of sampling variance as opposed to true differences in treatment efficacy or drug posology. It also restricts the analysis to one which is driven completely by differences in drug acquisition costs.

Figure 10 Mean injection frequencies and associated uncertainty



Additionally, development of a full cost-utility model which attempts to claim differences across the aforementioned HRQoL domains is fraught with additional assumptions and uncertainty:

- Assumptions surrounding how to define health states, and how to robustly estimate unbiased and consistent transition probabilities for aflibercept and ranibizumab, and how to validate these assumptions given the limited evidence base.
- There is no data to help guide assumptions around the duration of relative treatment effect between aflibercept and ranibizumab. Aflibercept has a point estimate advantage in vision gains at 3 months, but the duration upon which these potential benefits may last is unclear.
- Assumptions surrounding the long term visual outcomes for patients, and how to model the gradual decline in vision with age.
- Uncertainty surrounding which ranibizumab arm from RADIANCE is the most relevant comparator. Both have re-treatment protocols which differ from the aflibercept protocol in MYRROR, which will affect resource use and efficacy outcomes to an unknown degree.

Given the large degree of uncertainty associated with these dynamics, combined with the clinically and statistically insignificant point estimate differences in efficacy and resource use in the trials, indicates that resulting cost-utility results are likely a reflection of model design/assumptions and

statistical noise, as opposed to true underlying differences in treatment effectiveness. We therefore believe a simplified cost-comparison framework will provide greater clarity from a decision making perspective.

To strengthen the justification, we suggest that if this approach introduces any bias, it is likely to bias against aflibercept. Evidence suggests that the equalisation assumptions surrounding efficacy and injection frequencies are conservative for aflibercept. In terms of efficacy, the point estimates of the ITC suggest better treatment efficacy for aflibercept versus ranibizumab. In terms of injection frequency, the ITC shows wide and overlapping uncertainty margins, which supports the use of an equal number of injections. In the absence of a definitive answer from the ITC, physicians in the market research questionnaire 2016 were queried. The results suggest that clinicians expect to administer less than half the number of aflibercept injections than ranibizumab injections in clinical practice in any given year (Bayer plc, data on file).

Population and model characteristics

The overall patient population considered in the analysis reflects the indication for aflibercept for myopic choroidal neovascularisation evaluated in the relevant phase 3 study, MYRROR(30).

The inclusion criteria for this study was:

- aged >18 years
- with visual impairment due to mCNV
- with a VA of between 73-35 letters (inclusive)

This population is in line with the population defined in the scope and decision problem for the NICE technology appraisal, which is adults with visual impairment due to myopic choroidal neovascularisation.

In the health economic model the same patient population is modelled for both aflibercept and ranibizumab treatments.

The cohort included in the model has a baseline age and gender distribution in line with what was observed in the MYRROR trial (Table 29). The baseline age and gender distribution will determine the population life expectancy based on background mortality rates. Age and gender-specific background mortality rates have been taken from England and Wales life tables published by the Office for National Statistics based on 2013-2015 mortality data (59) and incorporated in the model.

Table 29 General model settings: Population inputs

Parameter	Value	Source
Baseline age (years)	58	MYRROR (30) (rounded to the nearest year)
Proportion female	76.00%	MYRROR

Although the model results are only directly driven by drug acquisition costs, the extent to which drug costs impact incremental costs is modulated by other parameters. Two of those parameters are age and sex: these parameters influence survival time, and hence the number of future recurrences.

Additional key model characteristics used in the cost-comparison model structure are: an annual cycle length and a lifetime time horizon (till the maximum age of 110 years). As mCNV is a chronic condition, a lifetime time horizon, where all patients are followed until death, is considered appropriate to capture all important differences in costs between the two treatments.

4.2.2 Intervention and comparators' acquisition costs

The drug acquisition list price for ranibizumab is based on the British National Formulary (BNF, March 2017). The confidential aflibercept Patient Access Scheme (PAS) price has been agreed with the Department of Health (see Table 30).

Table 30 Acquisition costs of the intervention and comparator technologies

	Aflibercept	**Ranibizumab**
Pharmaceutical formulation	Eylea 40 mg/ml solution for injection in a vial. 1 ml solution for injection contains 40 mg aflibercept. Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. This provides a usable amount to deliver a single dose of 50 microlitres containing 2 mg aflibercept.	Lucentis® 10 mg/ml solution for injection. One ml contains 10 mg ranibizumab. Each vial contains 2.3 mg of ranibizumab in 0.23 ml solution. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab. Lucentis® 10 mg/ml solution for injection in pre-filled syringe. One ml contains 10 mg ranibizumab. One pre-filled syringe contains 0.165 ml, equivalent to 1.65 mg ranibizumab. The extractable volume of one pre-filled syringe is 0.1 ml. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab.
(Anticipated) care setting	Treatment in adult patients with visual impairment due to mCNV in an outpatient setting	Treatment in adult patients with visual impairment due to mCNV in an outpatient setting.
Acquisition cost (excluding VAT) *	£[redacted] (PAS)	£551.00 (NHS list price)
Method of administration	Intravitreal injection	Intravitreal injection
Doses	A single intravitreal injection of 2 mg aflibercept is equivalent to 50 microliters	0.5 mg ranibizumab given as a single intravitreal injection of 0.05 ml.
Dosing frequency	4.2 injections in year 1, 1 injection in year 2	4.2 injections in year 1, 1 injection in year 2
Dose adjustments	NA	NA
Average length of a course of treatment	2-years	2-years
Average cost of a course of treatment (acquisition costs only)	£[redacted]	£2,865.20
(Anticipated) average interval between courses of treatment	The interval between two doses should not be shorter than one month.	The interval between two doses injected into the same eye should be at least four weeks.
(Anticipated) number of repeat courses of treatment	The annual probability of recurrence is [redacted] for which a treatment course similar to first year of initial treatment is assumed.	The annual probability of recurrence is [redacted] for which a treatment course similar to first year of initial treatment is assumed.

4.2.3 Intervention and comparators' healthcare resource use and associated costs

Appendix G describes how relevant cost and healthcare resource data for England were identified.

Table 31 presents the estimated number of treatments given per year for each therapy featured in the model. A 2 year treatment duration has been assumed, which is in line with the number of treatment years included in the ranibizumab NICE submission (TA298)(2). First year data for aflibercept is estimated from MYRROR(30) as there is no UK specific injection frequencies from clinical practice available. The number of injections for ranibizumab in the first year has been equalised to the number of injections for aflibercept (see B.4.2.1). It is assumed that only a single injection will be given in year 2, which is in line with the assumed number of injections given in year 2 in the ranibizumab NICE submission (TA298). The ERG questioned the number of injections in year 2 in the ranibizumab NICE submission (TA298) and felt it would be a more reasonable assumption to administer 1.7 ranibizumab injections in the second year of treatment. In a scenario analysis, the number of injections will be increased to 1.7 for both ranibizumab and aflibercept. The SLR on cost and resource use did not provide any additional sources for number of injections for both treatments (see Appendix G).

Table 31 Resource costs of the intervention and comparator technologies

	Aflibercept	**Ranibizumab**
Treatment		
Unit cost		
Cost (£), price year	£[redacted] (PAS, 2017)	£551.00 (NHS list price, 2017)
Source reference	Bayer	BNF, March 2017
Rationale for source	NA	NA
Units per course of treatment		
Number of units	4.2 injections in year 1, 1 injection in year 2	4.2 injections in year 1, 1 injection in year 2
Source reference	Year 1: MYRROR(30) Year 2: Assumption, in line with TA298(2)	Year 1: Assumed same as aflibercept Year 2: Assumption, in line with TA298
Rationale for source	a single injection in year 2 , which is in line with the assumed number of injections given in year 2 in the ranibizumab NICE submission (TA298)(2).	a single injection in year 2 , which is in line with the assumed number of injections given in year 2 in the ranibizumab NICE submission (TA298).
Total cost of treatment		
Per course of treatment	£[redacted]	£2,865.20
Over the full time horizon	Over 2 years	Over 2 years
Recurrence		
Unit cost		
Cost (£), price year	£[redacted] (PAS, 2017)	£551.00 (NHS list price, 2017)
Source reference	Bayer	BNF, March 2017
Rationale for source	NA	NA
Units per course of treatment		
Number of units	4.2 injections	4.2 injections
Source reference	It is assumed that the cost of recurrence is equal to the cost of the first year of initial treatment.	It is assumed that the cost of recurrence is equal to the cost of the first year of initial treatment.
Rationale for source	This approach is consistent with the modelling approach utilised in the mCNV ranibizumab economic model submitted to NICE (TA298).	This approach is consistent with the modelling approach utilised in the mCNV ranibizumab economic model submitted to NICE (TA298).

Total cost of recurrence		
Per course of treatment	£[redacted]	£2,314.20
Over the full time horizon	Over 1 year	Over 1 year
Fellow-eye involvement		
Unit cost		
Cost (£), price year	£[redacted] (PAS, 2017)	£551.00 (NHS list price, 2017)
Source reference	Bayer	BNF, March 2017
Rationale for source	NA	NA
Units per course of treatment		
Number of units	4.2 injections in year 1, 1 injection in year 2	4.2 injections in year 1, 1 injection in year 2
Source reference	The fellow eye of patients with FEI is assumed to 'follow' the same treatment course and cost profile as the first study eye at the same points in time.	The fellow eye of patients with FEI is assumed to 'follow' the same treatment course and cost profile as the first study eye at the same points in time.
Rationale for source	This approach is consistent with the modelling approach utilised in the mCNV ranibizumab economic model submitted to NICE (TA298).	This approach is consistent with the modelling approach utilised in the mCNV ranibizumab economic model submitted to NICE (TA298).
Total cost of fellow-eye involvement		
Per course of treatment	£[redacted]	£2,865.20
Over the full time horizon	Over 2 years	Over 2 years

Based on clinical opinion from the market research 2016 (n=52), using the injection frequency from MYRROR for year one for both treatment options is expected to be a conservative approach for aflibercept as physician responses suggest that clinicians expect to administer fewer aflibercept injections than ranibizumab injections in any given year (Bayer plc, data on file).

Although the model results are only directly driven by drug acquisition costs, the extent to which drug costs impact incremental costs is modulated by other parameters which affect drug resource use (although set the same for both treatments). Fellow eye involvement and recurrence rates influence the total number of drug administrations over the model time horizon, and hence magnify the impact associated with differences in drug acquisition costs.

The following cost categories are included in the model:

- Drug acquisition costs for initial treatment in the first eye,
- Drug acquisition costs for initial treatment in the fellow eye,
- Drug acquisition costs for recurrence treatment in the first eye,
- Drug acquisition costs for recurrence treatment in the fellow eye.

Although pertinent to the disease and treatment pathway, the following cost categories are not included as we expect them not to influence incremental costs:

- Vision related costs, i.e. blindness: visual outcomes are assumed the same, so no incremental impact is expected,
- Monitoring costs: no incremental impact is expected as the number of visits are assumed the same and costs are not treatment-specific,
- Adverse event costs: no incremental impact is expected as rates are set equal, and adverse event costs are assumed to be treatment-independent,
- Administration costs: no incremental impact is expected as injection frequencies are assumed equal, and we do not expect treatment-specific administration costs.

These cost categories have all been included in the ranibizumab NICE submission (TA298)(2), as a cost-utility model has been used to show the economic impact of ranibizumab as treatment for mCNV.

The only clinical parameters which have been taken into account in the model, like in the ranibizumab NICE submission (TA298), are bilateral mCNV presentation/ fellow-eye involvement at baseline and future annual disease recurrence.

Fellow-eye involvement

Patients with mCNV may develop fellow-eye involvement (FEI) at some point in the future(5). Modelling the costs associated with fellow-eye treatment is an important consideration within the cost-comparison framework.

In line with the ranibizumab NICE submission (TA298), FEI is modelled to be present or absent at baseline only. The fellow eye of patients with FEI is assumed to 'follow' the same treatment course and cost profile as the first study eye at the same points in time. This approach is consistent with the modelling approach utilised in the mCNV ranibizumab economic model submitted to NICE (TA298).

The responses to the market research questionnaire 2016 suggested that approximately [redacted] of the patients will present with FEI at the start of treatment. This percentage is assumed treatment-independent. In the ranibizumab NICE submission (TA298), a baseline rate of FEI of 15% was considered, which was derived from 2 published studies (Cohen 1996; Hampton 1983)(13). Besides that, the costing statement(60) reports a FEI rate of 5.5%, also based on Hampton et al. In scenario analyses, the impact of both FEI rates will be presented.

Fellow eye involvement is handled in the model in the same way for both aflibercept and ranibizumab.

Recurrence

mCNV may recur(61-66), therefore this dynamic has been included within the model structure. The average number of injections administered in case of a recurrence, as suggested in the market research questionnaire 2016 (Bayer plc, data on file), did not differ significantly from the number of injections considered for the first year of initial treatment. Therefore, it is assumed that the cost of recurrence is equal to the cost of the first year of initial treatment. This approach is consistent with the modelling approach utilised in the mCNV ranibizumab economic model submitted to NICE (TA298).

Based on clinical opinion from the market research 2016 (n=52), it has been assumed that the annual probability of recurrence is [redacted] (Bayer plc, data on file). This annual risk of recurrence is assumed treatment-independent, which will be applied after patients completed their initial 2 year treatment course (post treatment). There is no (long-term) clinical evidence available assuming that the annual risk of recurrence is different for aflibercept versus ranibizumab. In the ranibizumab NICE submission (TA298), disease recurrence after treatment is assumed to be 6% per year regardless of which treatment is received. In a scenario analysis, the impact of this recurrence rate will be presented.

Recurrence is handled in the model in the same way for both aflibercept and ranibizumab.

In the analysis costs are discounted at a rate of 3.5% annually beyond year 1, in accordance the NICE reference case 2013. In scenario analyses the discount rate will be varied between 0% and 6%.

Although the model results are only directly driven by drug acquisition costs, the extent to which drug costs impact incremental costs is modulated by other parameters. One of those parameters is the discount rate of costs: this influences the cost impact of future recurrences, which is treatment-specific.

4.2.4 Adverse reaction unit costs and resource use

As there is no difference expected in adverse event rates between the two treatments, adverse events have not been included in the cost-comparison model.

4.2.5 Miscellaneous unit costs and resource use

No other cost categories have been included in the model.

4.2.6 Clinical expert validation

A clinician was interviewed by telephone and asked for expert opinion on the following aspects of the submission:

- Similarity of efficacy between aflibercept and ranibizumab
- Similarity of safety profile between aflibercept and ranibizumab
- Similarity of resource use between aflibercept and ranibizumab
- Similarity of rates of bilateral disease/fellow eye involvement as well as recurrence between aflibercept or ranibizumab
- Assumptions around how recurrences and fellow eye involvement are managed

The clinician found the assumptions to be acceptable, particularly the assumptions about similarity between aflibercept and ranibizumab and was supportive of them. A full record of the validation and responses is available on request. One suggestion however, was for the number of injections for recurrence for both treatments to be reduced to a single injection. This has been tested in sensitivity analysis (see B.4.4).

The clinical expert is a consultant ophthalmologist and vitreoretinal surgeon practicing in the UK. The clinician was selected due to their long term involvment in clinical research, being principal investigator for numerous international and national trials of novel treatments and therapies. The clinical expert has also in the past performed the role of specialist clinical expert advisor to NICE.

4.2.7 Uncertainties in the inputs and assumptions

By equalising the treatment efficacy, adverse event rate and treatment frequency, we believe to avoid any unfair comparisons being drawn which might be a product of sampling variance as opposed to true differences in treatment efficacy or drug posology. It also restricts the analysis to one which is driven completely by differences in drug acquisition costs. Even the impact of FEI rate and the recurrence rate are related to the difference in drug acquisition cost between the two treatments.

We expect that if any bias is introduced by our choice of modelling methods, it is likely to bias against aflibercept. Evidence suggests that the equalisation assumptions surrounding efficacy and injection frequencies are conservative for aflibercept. In terms of efficacy, the point estimates of the ITC suggest better treatment efficacy for aflibercept vs ranibizumab. In terms of injection frequency, the physician responses to the market research questionnaire

2016 (n=52) suggest that clinicians expect to administer less than half the number of aflibercept injections than ranibizumab injections in any given year.

Assumptions:

- It is assumed that the baseline patient population characteristics are the same in both the aflibercept and ranibizumab arms of the model.
- It is assumed that patients follow a 2-year treatment course, based on the number of treatment years included in the ranibizumab NICE submission. The only exception is if a patient experiences a recurrence.
- It is assumed that the efficacy and safety of aflibercept and ranibizumab are the same.
- It is assumed that the resource use associated with the aflibercept and ranibizumab treatment courses are the same.
- It is assumed that in case of a recurrence, patients will receive additional treatment, which is equal to the number of injections for the first year of treatment (based on market research 2016).
- It is assumed that bilateral disease/fellow eye involvement as well as recurrence rates are the same in both the aflibercept and ranibizumab arms.
- It is assumed that the only difference between aflibercept and ranibizumab is the drug acquisition cost.
- It is assumed that all patients with FEI will receive the same treatment/resource usage in their fellow-eye as their first study-eye.

Summary of economic model inputs

The input values included in the economic analyses are presented in

Table 32. The input variables are separated into different categories for ease of reading.

Table 32 Summary of input variables applied in the economic model

Parameter	Deterministic value
General model characteristics	
Discount rate of costs	3.50%
Starting age of cohort	58 years
% of females	76.0%
% of bilateral involvement at baseline	[redacted]
Recurrence 12 month probability	[redacted]
Treatment	
Number of treatments in Year 1	4.2
Number of treatments in Year 2	1.0
Drug costs	
Ranibizumab NHS List price	£ 551.00
Aflibercept PAS price	£ [redacted]

B.4.3 Base-case results

Aflibercept PAS vs ranibizumab list

Table 33 presents the discounted costs accrued for aflibercept (PAS) and ranibizumab (list) over a lifetime time horizon and for respectively 2, 5, 10, 15 and 20 years. The costs are separated into total cost per treatment course and further differentiated into initial treatment and recurrence treatment costs for the first eye and the fellow-eye. The total costs for the aflibercept (PAS) and ranibizumab (list) treatment courses in adult patients with visual impairment due to mCNV for a lifetime horizon is estimated at £[redacted] and £12,448, respectively. The recurrence treatment costs do not contribute to the total cost in the first two years. However, after 10 years and more, the recurrence treatment cost is the biggest contributor to the total cost for both treatment courses.

Table 33 Discounted costs over time for aflibercept (PAS) and ranibizumab (list)

Discounted costs	Aflibercept PAS					Ranibizumab LIST				
	First eye		Second eye		Total cost	First eye		Second eye		Total cost
Time horizon	Initial treatment	Recurrence treatment	Initial treatment	Recurrence treatment		Initial treatment	Recurrence treatment	Initial treatment	Recurrence treatment	
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,830	£0	£354	£0	£3,184
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,830	£1,496	£354	£187	£4,866
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,830	£3,593	£354	£449	£7,225
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,830	£5,247	£354	£656	£9,087
20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,830	£6,499	£354	£812	£10,495
Lifetime	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,830	£8,235	£354	£1,029	£12,448

Table 34 presents the discounted incremental costs between the aflibercept (PAS) and ranibizumab (list) treatment courses over a lifetime time horizon and for respectively 2, 5, 10, 15 and 20 years. The incremental costs are differentiated into initial treatment and recurrence treatment costs for the first eye and the fellow-eye. The total incremental cost between the aflibercept (PAS) and ranibizumab (list) treatment courses

over a lifetime time horizon is estimated at £[redacted] cost savings for aflibercept (PAS). As can be seen in the table the recurrence treatment cost is the biggest contributor to the incremental cost after 10 years and more.

Table 34 Discounted incremental costs over time for aflibercept (PAS) and ranibizumab (list)

Discounted Incremental costs	Aflibercept PAS vs Ranibizumab LIST				
	First eye		Second eye		Total incremental cost
Time horizon	Initial treatment	Recurrence treatment	Initial treatment	Recurrence treatment	
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lifetime	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The model provided an estimated mean life expectancy of 25.84 years for the patients with mCNV in this economic analysis.

Both aflibercept and ranibizumab are available with a confidential patient access scheme. Bayer does not, and does not wish to know the ranibizumab PAS price, however, the cost of aflibercept and ranibizumab achieve parity when ranibizumab is available at a discount of [redacted] to its list price. Discounts greater than this would make ranibizumab cost saving vs aflibercept. Discounts smaller than this would make ranibizumab more expensive than aflibercept.

B.4.4 Sensitivity and scenario analyses

In this appraisal for aflibercept as an effective treatment option for mCNV, a couple of alternative inputs values have been described, which will be investigated in additional scenario analyses.

The following scenarios have been investigated:

- A baseline rate of FEI of 15%, which was derived from 2 published studies (Cohen 1996; Hampton 1983(13) as used in the ranibizumab NICE submission (TA298).
- A baseline rate of FEI of 5.5%, also based on Hampton et al., as used in the costing template of the ranibizumab NICE submission (TA298).
- A disease recurrence after treatment of 6% per year as used in the mCNV ranibizumab economic model submitted to NICE (TA298).
- An annual discount rate of 0%, in accordance the NICE reference case 2013.
- An annual discount rate of 6%, in accordance the NICE reference case 2013.
- The number of injections for both treatments in the second year of treatment increased to 1.7, compared to 1.0 in the base case scenario, as assumed more reasonable by the ERG for the ranibizumab NICE submission (TA298).
- The number of injections for recurrence for both treatments is reduced to a single injection, as suggested by the clinical expert (section B.4.2.6).

Table 35 Incremental total costs over time for different scenarios comparing aflibercept (PAS) and ranibizumab (list)

Scenarios	Lifetime	2 years	5 years	10 years	15 years	20 years
Base case scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEI = 15%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEI = 5.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence rate = 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate = 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate = 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second year number of injections = 1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of injections for recurrence = 1.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 35 shows that for all scenarios the total incremental cost between the aflibercept (PAS) and ranibizumab (list) treatment courses over a lifetime time horizon results in cost savings for aflibercept (PAS). By increasing the FEI rate, the savings increase. By reducing

the FEI rate or the recurrence rate, the savings decrease. Without discount of costs over time, the cost savings are higher. The higher the discount rate of cost over time, the lower the savings of costs. In the scenario where the number of injections in the second year increases, the cost savings for aflibercept increase and when the number of injections for a recurrence decrease to a single injection, the cost savings for aflibercept decrease. So there is no change in the direction of the results, just in the magnitude of the results.

B.4.5 Subgroup analysis

No subgroups have been explored in this submission.

B.4.6 Interpretation and conclusions of economic evidence

The economic evaluation considers aflibercept as an effective alternative treatment option to ranibizumab in all licensed adult patients with visual impairment due to myopic choroidal neovascularisation.

Bayer believes that the results are generalisable to clinical practice in England and Wales as the analysis has considered first year treatment frequency and aflibercept efficacy from the MYRROR study, which the CHMP agreed could be extrapolated to the EU population. Besides that, second year treatment frequency is based on the ranibizumab NICE submission (TA298). Other relevant model inputs (like recurrence rate and FEI) have been based on market research of a large sample of UK ophthalmologists, alongside the use of UK drug acquisition costs.

To avoid any unfair comparisons being drawn which might be a product of sampling variance as opposed to true differences in treatment efficacy/safety and/or drug posology, a cost-comparison model was developed which estimated total and incremental costs associated with each treatment. The model equalised treatment efficacy, safety and injection frequency, and model results were driven by drug acquisition costs, number of injections and indirectly by survival, FEI and recurrence.

Evidence suggests that the equalisation assumptions surrounding efficacy and injection frequencies are conservative for aflibercept. In terms of efficacy, the point estimates of the ITC suggest superior treatment efficacy for aflibercept vs ranibizumab. In terms of injection

frequency, the physician responses to the market research study suggest that clinicians expect to administer less than half the number of aflibercept injections than ranibizumab injections in any given year (Bayer plc, data on file).

The analyses show that aflibercept (PAS) is expected to be related to incremental cost savings of £[redacted] over a lifetime horizon compared to ranibizumab (NHS list price). The cost of aflibercept and ranibizumab achieve parity when ranibizumab is available at a discount of [redacted] to its list price. If the ranibizumab PAS price is lower than this, we would expect it to be cost saving vs aflibercept. If the ranibizumab PAS price is higher than this, we would expect aflibercept to be the cost saving treatment.

Scenario analyses did not show any change in the direction of the results; the analyses showed cost savings. Only the magnitude of the cost savings changes.

Bayer concludes that aflibercept provides similar or greater benefits at a similar or lower overall cost than ranibizumab.

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B.6 Appendices

Appendix C: Summary of product characteristics and European public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence (see section 3.1)

Appendix E: Sungroup analysis (see section 3.7)

Appendix F: Adverse reactions (see section 3.10)

Appendix G: Cost and healthcare resource identification, measurement and valuation (see section 4.2)

Appendix H: Checklist of confidential information

Appendix I: Resource implications

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Fast track appraisal: cost-comparison case

Aflibercept for treating myopic choroidal neovascularisation [ID952]

Dear [redacted]

The Evidence Review Group, Aberdeen HTA Group, and the technical team at NICE have looked at the submission received on 10 May 2017 from Bayer. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Thursday 15 June 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Ross Dent, Technical Lead (ross.dent@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (Stephanie.yates@nice.org.uk).

Yours sincerely

Dr Sally Doss
Technical Adviser – Appraisals

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. Please provide the central retinal thickness outcome data from the MYRROR trial referred to in section 3.6.1 of the submission.

A2. In Table 10: 'Definition of all data analysis sets in MYRROR': the heading of the second column is 'Laser'. Please clarify whether this should be 'Sham'.

A3. In Table 15: 'Overview of proportions of people gaining ≥5 letters, ≥10 letters or ≥15 letters', the difference estimate and the adjusted difference for some of the 24-week assessments are missing and the confidence intervals also do not seem to be correct. Please confirm these results.

A4. In Table 18 'Overview of ANCOVA results', please provide the number of patients in each group for both the last observation carried forward analysis and observed data.

A5. Please provide the numerical values for the mean and 95% confidence interval data presented in Figure 10: 'Mean Injection Frequencies and Associated Uncertainty'. Please explain how these values were calculated and confirm the period of time they relate to in terms of the number of weeks since baseline, with full referencing.

A6. In Appendix D, Table 25, please explain why the Pece et al. (2015) and the Rinaldi et al. (2016) studies are included. The comparator in the first study is bevacizumab, which is not specified as an eligible comparator in Table 24, and the second study involves two arms with vPDT/ranibizumab combination therapy, which is not specified as an eligible intervention or comparator (Table 24).

A7. Appendix D, section 1.1 states "*Later in the study selection stage more targeted inclusion and exclusion criteria were applied to align the results with the decision problem outlined in the decision scope*". Please provide these targeted criteria.

A8. In Appendix D, Table 26, please clarify the meaning of "no," in column 2.

A9. In Appendix D, Table 27, a number of studies do not appear to meet the eligibility criteria for study selection set out in Table 24:

- 3 studies have "No treatment as intervention"

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- neither the population nor the outcomes of the Ohno-Matsui et al. (2003) study appear to meet the eligibility criteria
- the outcomes of the Zaour et al. (2013) study do not appear to meet the eligibility criteria.

Please clarify if the eligibility criteria for non-randomised studies differs from that set out in Table 24, and if not, the reasons for including the above studies.

A10. Please clarify the nature and results of any narrative or quantitative analyses conducted on the non-RCTs listed in Table 27 of Appendix D. Please also clarify whether quality assessment was carried out on the included non-RCTs and provide the results if it was.

A11. Table 34 in Appendix D provides a detailed quality assessment of MYRROR. Please provide equivalent quality assessments for the VIP and RADIANCE studies.

A12. Please clarify whether transitivity and inconsistency assumptions across the indirect treatment comparison evidence network have been evaluated.

A13. In Appendix D, it is stated that for MYRROR a weighted average of the 12-week and 16-week data has been used to estimate the outcomes at 13-weeks in order to compare with VIP and RADIANCE in the network-meta-analysis. It is unclear why the 12-week data from MYRROR, which are only one week short of the 13-week time point, have not been used. Please provide results of the network meta-analysis using the 12-week data from MYRROR.

A14. In Appendix D, Table 33 indicates the mean BCVA gain for placebo is -1 and for vPDT is 0 for the VIP trial, but Table 30 suggests these values correspond to the mean BVCA (approximated from median) rather than the change in BCVA. Table 30 suggests the correct values to be included in the network meta-analysis are 0.2 for vPDT and -1.6 for placebo. Please clarify which values are correct, and if necessary, provide the results of the updated network meta-analysis.

A15. The network meta-analysis only considers 3-month best-corrected visual acuity data. If available, please provide any of the relative risks of gaining 15, 10 and 5 letters and losing 15, 10 and 5 letters from the network meta-analysis. Please note that estimates for ranibizumab (proportion of people gaining or losing 10 and 15 letters) are present in the literature.

A16. In terms of the retreatment criteria, it is unclear which of the ranibizumab arms in RADIANCE that Bayer views as most similar to the aflibercept arm of MYRROR. Please clarify this.

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A17. In Appendix D, Figure 9, the MYRROR participant flow diagram, numbers are missing from some of the boxes. Please provide a complete flow diagram for MYRROR. Please also provide for each arm, the number of patients remaining in the study at each of the 4-week follow up points and the number of injections at baseline and at each follow up point. For the sham arm please report the numbers of sham injections and those of aflibercept injections separately.

Section B: Clarification on cost-effectiveness data

None

Section C: Textual clarifications and additional points

C1. Please provide the clinical study report for the MYRROR trial.

C2. Please provide the clinical study reports for VIEW1 and VIEW2, which are important for demonstrating safety considerations.

C3. Please provide the following Bayer data on file:

a. Market share data

b. Market research survey of 52 ophthalmologists

Bayer response to ERG and NICE technical team questions

Fast track appraisal: cost-comparison case

Aflibercept for treating myopic choroidal neovascularisation [ID952]

June 2017

Dear Dr Sally Doss

Thank you for your letter seeking clarification on the clinical and cost effectiveness data for aflibercept for treating myopic choroidal neovascularisation [ID952]. Please find below the response from Bayer plc.

Section A: Clarification on effectiveness data

A1. Please provide the central retinal thickness outcome data from the MYRROR trial referred to in section 3.6.1 of the submission.

This information is provided below.

Mean change in central retinal thickness (CRT) from baseline to week 24 and to week 48(1;2).

At week 24, aflibercept-treated patients had a substantially larger mean decrease in CRT than sham patients (-80.7 vs. -13.9; LS mean treatment difference [95% confidence interval]: -67.7µm [-94.3 to -41.1]; observed cases, P < 0.0001). A rapid reduction in CRT was seen, beginning at week 4 and 8, which stabilised through week 24.

By week 48, patients in the aflibercept group maintained their improvement, whereas, sham patients, who had switched to intravitreal aflibercept at week 24, experienced an improvement in CRT. The difference in the decrease in CRT between the aflibercept-treated patients and sham + aflibercept patients at week 48 was therefore small and not statistically significant (-86.2 vs. -74.0; LS mean treatment difference [95% confidence interval]: -11.2µm [-37.2 to 14.8]; observed cases, P = 0.39).

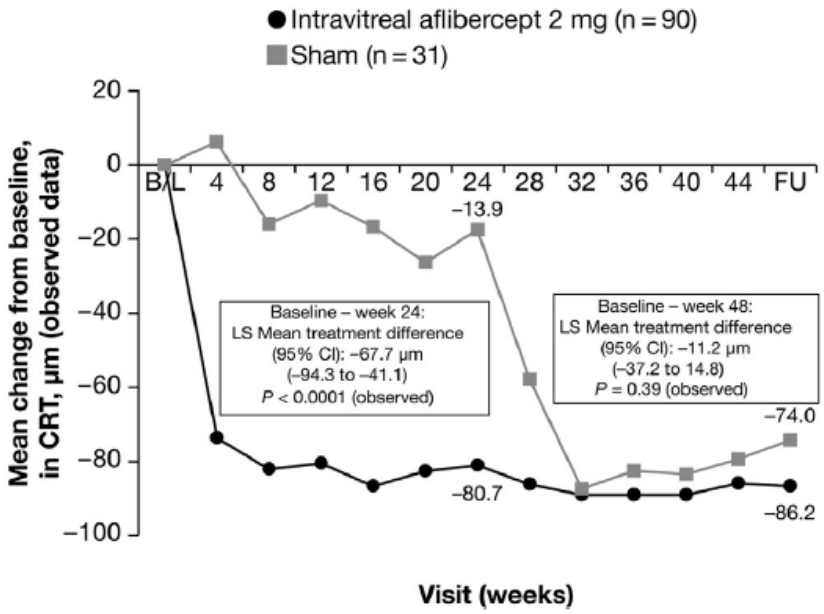
Table 1: ANCOVA for mean change in CRT from baseline to week 24 and week 48 (FAS, OC)

Week 24	**Aflibercept [a] N=84**	**Sham N=25**
Mean CRT at baseline	[redacted]	[redacted]
Mean CRT at Week 24	[redacted]	[redacted]
Mean change from baseline to week 24	-80.7	-13.9
LS mean change	[redacted]	[redacted]
Difference in LS mean changes [a] 95% Confidence Interval [a] p-value [a]	-67.7 [-94.3; -41.1] <0.0001	
Week 48	**Aflibercept [a] N=78**	**Sham N=24**
Mean CRT at baseline	[redacted]	[redacted]
Mean CRT (SD) at Week 48	[redacted]	[redacted]
Mean change from baseline to week 48	-86.2	-74.0
LS mean change	[redacted]	[redacted]
Difference in LS mean changes [a]	-11.2 [-37.2; 14.8] 0.39	

CRT = central retinal thickness; LS=least squares; SD=standard deviation

[a] Point estimate, 95% CI and p-value are based on treatment difference (aflibercept minus sham + aflibercept) in LS mean changes, using an analysis of covariance (ANCOVA) model with treatment group and country (country designations) as fixed effects. Baseline value of BCVA was included in the model. P-values are nominal.

Figure 1: Mean change in CRT from baseline to week 24 and to week 48 (FAS, observed cases)



CI=confidence interval; CRT=central retinal thickness; FU=follow-up; LS=least squares

Sensitivity analyses of mean change in central retinal thickness (CRT) from baseline to week 24 and to week 48

Using LOCF analysis, the difference in CRT reduction between the aflibercept and sham groups at Week 24 favoured active treatment (p<0.0001). At Week 48, aflibercept patients maintained their improvement in CRT [redacted] whereas in the Sham+aflibercept group, with the initiation at Week 24 of aflibercept active treatment, an improvement in CRT was observed, mainly perceptible between Week 24 and Week 32 ([redacted] from baseline). The between-group difference at Week 48 was -29.3 µm (p=0.0650, LOCF).

Table 2: ANCOVA for mean change in CRT from baseline to week 24 and week 48 (FAS, LOCF)(1;3)

Week 24	**Aflibercept [a] N=90**	**Sham N=31**
Mean CRT (SD) at baseline	349.7 (91.3)	354.2 (107.2)
Mean CRT at Week 24	270.6 [redacted]	350.0 [redacted]
Mean change from baseline to week 24	-79.1 [redacted]	-4.2 [redacted]
LS mean change	-85.7	-7.8
Difference in LS mean changes [a] 95% Confidence Interval [a] p-value [a]	-77.9 [-108.9; -46.9] <0.0001	
Week 48	**Aflibercept [a] N=90**	**Sham N=31**
Mean CRT at baseline	349.7 (91.3)	354.2 (107.2)
Mean CRT (SD) at Week 48	[redacted]	[redacted]
Mean change from baseline to week 48	[redacted]	[redacted]
LS mean change	[redacted]	[redacted]
Difference in LS mean changes [a]	-29.3 [-60.4; 1.8] 0.0650	

CRT = central retinal thickness; LOCF=last observation carried forward; LS=least squares; SD=standard deviation
[a] Point estimate, 95% CI and p-value are based on treatment difference (aflibercept minus sham + aflibercept) in LS mean changes, using an analysis of covariance (ANCOVA) model with treatment group and country (country designations) as fixed effects. Baseline value of BCVA was included in the model. P-values are nominal.

A2. In Table 10: 'Definition of all data analysis sets in MYRROR': the heading of the second column is 'Laser'. Please clarify whether this should be 'Sham'.

Our apologies for this oversight; the heading of the second treatment column should read 'Sham'. A corrected version of the table is included below:

Table 3: *[Table 10 of original submission]* Definition of all data analysis sets in MYRROR

Analysis set	**Definition**	**Number of valid patients in treatment group**	
		Aflibercept	**Sham**
Full analysis set (FAS)	All randomised patients who received ≥1 study injection (intravitreal aflibercept or sham) and had baseline and ≥1 post-baseline BCVA assessment. Analysed as randomised.	90 (98.9%)*	31 (100%)
Per protocol set (PPS)	All patients in the FAS who attended at least two scheduled visits during the first 24 weeks of the study, except for those excluded because of major protocol violations. Analysed as treated.	86 (94.5%)	29 (93.5%)
Safety analysis set (SAF)	All randomised patients who had received any study medication. Analysed as treated.	91 (100%)	31 (100%)

* 1 patient received one injection but had no post-baseline BCVA measurement

A3. In Table 15: 'Overview of proportions of people gaining ≥5 letters, ≥10 letters or ≥15 letters', the difference estimate and the adjusted difference for some of the 24-week assessments are missing and the confidence intervals also do not seem to be correct. Please confirm these results.

Bayer can verify the confidence intervals. Missing data values for difference estimate / adjusted difference have been added to the table below – apologies for the omission.

Table 4: *[Table 15 amended original]* Overview of proportions of patients gaining ≥5, ≥10, or ≥15 letters over time through week 48 (FAS; LOCF)(1-4)

Letter gain	Time point	Aflibercept N=90 n (%)	Sham N=31 n (%)	Difference (%)	Adjusted Difference (%) [a]	95% CI [a]	p-value [b]
≥15 letters*	Week 12	29 (32.2)	1 (3.2)				
	Week 24	**35 (38.9)**	**3 (9.7)**	**29.2**	**29.2**	**[14.4, 44.0]**	**0.0001**
	Week 36	[redacted]	[redacted]				
	Week 48	**45 (50.0)**	**9 (29.0)**	**21.0**	**21.0**	**[1.9, 40.1]**	**0.0308**
≥10 letters	Week 12	58 (64.4)	4 (12.9)				
	Week 24	**57 (63.3)**	**4 (12.9)**	[redacted]	[redacted]	[redacted]	**<0.0001**
	Week 36	[redacted]	[redacted]				
	Week 48	**62 (68.9)**	**13 (41.9)**	**27.0**	**27.0**	**[7.2, 46.8]**	**0.0075**
≥5 letters	Week 12	77 (85.6)	9 (29.0)				
	Week 24	**75 (83.3)**	**6 (19.4)**	[redacted]	[redacted]	[redacted]	**<0.0001**
	Week 36	[redacted]	[redacted]				
	Week 48	**79 (87.8)**	**14 (45.2)**	**42.6**	**42.7**	**[23.7, 61.6]**	**<0.0001**
Letter loss	**Time point**	**Aflibercept N=90 n (%)**	**Sham N=31 n (%)**	**Difference (%)**	**Adjusted Difference (%) [a]**	**95% CI [a]**	**p-value [b]**
≥5 letters	Week 12	3 (3.3)	11 (35.5)				
	Week 24	**3 (3.3)**	**11 (35.5)**	**-32.2**	[redacted]	[redacted]	[redacted]
	Week 36	[redacted]	[redacted]				
	Week 48	[redacted]	[redacted]	**-25.7**	[redacted]	[redacted]	**0.0012**
≥10 letters	Week 12	1 (1.1)	5 (16.1)				
	Week 24	**0**	**8 (25.8)**	**-25.8**	[redacted]	[redacted]	[redacted]
	Week 36	[redacted]	[redacted]				
	Week 48	[redacted]	[redacted]	**-21.5**	[redacted]	[redacted]	**0.035**
≥15 letters	Week 12	0	4 (12.9)				
	Week 24	**0**	**2 (6.5)**	**-6.5**	[redacted]	[redacted]	[redacted]
	Week 36	[redacted]	[redacted]				
	Week 48	[redacted]	[redacted]	**-5.4**	[redacted]	[redacted]	**0.2446**

* the proportion of patients gaining ≥15 letters at week 24 was the study confirmatory secondary endpoint

[a] Estimate (aflibercept group minus Sham+aflibercept group) and confidence interval are calculated using Cochran-Mantel-Haenszel (CMH) weights, adjusted for country (country designations).

[b] P-value is calculated using 2-sided CMH-test adjusted by country (country designations). P-values are nominal except week 24, ≥15 letter gains.

A4. In Table 18 'Overview of ANCOVA results', please provide the number of patients in each group for both the last observation carried forward analysis and observed data.

This information is provided in the amended table below.

Table 5: *[Table 18 amended original]* Overview of ANCOVA results for difference in changes in NEI VFQ-25 subscale scores from baseline at week 48 (FAS)(1)

Subscale	LOCF						Data as observed				
	AFL (n)	Sham (n)	Diff	95% CI	p-value		AFL (n)	Sham (n)	Diff	95% CI	p-value
GH											
GV											
OP											
NV											
DV											
SF											
MH											
RL											
DP											
DR											
CV											
PV											

AFL=aflibercept; Diff=difference; GH=general health; GV=general vision; OP=ocular pain; NV=difficulty with near-vision activities; DV=difficulty with distance-vision activities; SF=limitation of social functioning due to vision; MH=mental health problems due to vision; RL=role limitations due to vision; DP=dependency on others due to vision; DR=driving difficulties; CV=difficulties with colour vision; PV=difficulty with peripheral vision.
Note: Point estimate, 95%-CI and p-value are based on treatment difference (aflibercept group minus sham+aflibercept group) in LS mean changes, using an analysis of covariance (ANCOVA) model with treatment group and country (country designations) as fixed effects. Baseline value of BCVA was included in the model. P-values are nominal.

A5. Please provide the numerical values for the mean and 95% confidence interval data presented in Figure 10: 'Mean Injection Frequencies and Associated Uncertainty'. Please explain how these values were calculated and confirm the period of time they relate to in terms of the number of weeks since baseline, with full referencing.

The mean number of injections as presented in Figure 10 of the submission were taken from the trial publications, MYRROR(2) for the aflibercept arm and RADIANCE(5) for the two ranibizumab arms. The mean number of injections for ranibizumab was measured from day 1 until prior to month 12. For aflibercept the mean number of injections was measured over the study period of 48 weeks.

As both publications did not report the 95% confidence interval (95% CI) around the mean number of injections, the 95% CI was defined by using the standard error.

For the ranibizumab arms, the SE was based on the number of patients per arm and the standard deviation (SD) of the mean number of injections, as reported in the RADIANCE trial publication. The number of patients in the ranibizumab (vision) and ranibizumab (disease) arms were 105 and 116, respectively. The SD of the mean number of injections in the ranibizumab (vision) and ranibizumab (disease) arms were 2.6 and 3.0 respectively.

For aflibercept the number of patients on aflibercept was 90, which was taken from the MYRROR trial publication. The SD of the mean number of injections for aflibercept was [redacted], and was taken from the trial CSR (it is not reported in the publication).

The values of the mean number of injections and their associated 95% CI for the aflibercept arm and the two ranibizumab arms are presented in Table 6.

Table 6: Mean injection frequencies and associated uncertainty

No. of treatments	Year 1	95% Confidence Interval	Source
Aflibercept	4.20	3.56-4.84	MYRROR
Ranibizumab (vision)	4.60	4.10-5.10	RADIANCE
Ranibizumab (disease)	3.50	2.95-4.05	RADIANCE

A6. In Appendix D, Table 25, please explain why the Pece et al. (2015) and the Rinaldi et al. (2016) studies are included. The comparator in the first study is bevacizumab, which is not specified as an eligible comparator in Table 24, and the second study involves two arms with vPDT/ranibizumab combination therapy, which is not specified as an eligible intervention or comparator (Table 24).

Bayer apologises for not making it clearer in the submission. As we expected that there would be little evidence available comparing aflibercept versus the comparator of interest (ranibizumab), we included RCTs in which one of these interventions was included. The treatment arm of interest in these publications would have been used as a single arm in an matching adjusted indirect comparison (MAIC), in case no head-to-head trial comparing aflibercept versus ranibizumab was identified nor a closed network to compare aflibercept versus ranibizumab with the identified RCTs could be created. A MAIC is not a preferred technique for indirect treatment comparison, as there is no direct network, however in the absence of a direct network, it is a commonly used technique for generating comparative evidence. The advantage of using one arm of RCTs instead of using single arm studies is that randomisation for receiving treatment has taken place, which decreases the risk of bias.

Subsequently, there was no need for a MAIC, as a closed network could be created using the MYRROR, RADIANCE and VIP(6) trials.

We accept that we might have created confusion by presenting the publications of Pece et al. (2015) and the Rinaldi et al. (2016) in table 25 of the submission, without providing additional explanation.

A7. Appendix D, section 1.1 states "*Later in the study selection stage more targeted inclusion and exclusion criteria were applied to align the results with the decision problem outlined in the decision scope*". Please provide these targeted criteria.

The sentence you are highlighting in question A7 is referring to Table 24 in Appendix D of the submission. Table 24 presents the eligibility criteria used for study selection in the systematic literature review.

A copy of table 24 is reproduced below for your convenience.

Table 7: *[Table 24 in original submission]* Eligibility criteria used for study selection

	Inclusion criteria	**Exclusion criteria**
Population	• Patients with the indication; mCNV of 18 years and older, including patients with concomitant eye diseases.	• Non humans. • Healthy subjects.
Intervention	• Treatments are: o Aflibercept (Eylea), o Ranibizumab (Lucentis), o vPDT, o Thermal laser photocoagulation therapy.	• Treatments other than; o Aflibercept (Eylea), o Ranibizumab (Lucentis), o vPDT, o Thermal laser photocoagulation therapy. • Interventions; Avastin (bevacizumab) and/or surgery are excluded.
Comparators	• Comparator arm: o Standard of Care (SoC), o Placebo, o Best supportive care (BSC). • Active comparator: o Aflibercept (Eylea), o Ranibizumab (Lucentis), o vPDT, o Thermal laser photocoagulation therapy.	• Studies not investigating placebo, BSC or relevant active comparator in the comparator arm.

Outcomes	• Best Corrected Visual Acuity (BCVA) (affected eye).
	• BCVA (both eyes).
	• Proportion of patients that gained or lost sight by predefined values (lines or letters).
	• Recurrence.
	• Central foveal, macular or retinal thickness.
	• Choroidal neovascularisation (CNV) or lesion size.
	• CNV leakage or progression.
	• Contrast or macular sensitivity.
	• Adverse effects of treatment:
	  ○ Conjunctival haemorrhage,
	  ○ Punctate keratitis,
	  ○ Dry eye,
	  ○ Eye pain,
	  ○ Cataract,
	  ○ Myopic foveoschisis,
	  ○ Injection site haemorrhage,
	  ○ Raised intraocular pressure (IOP),
	  ○ Posterior capsule opacification.
	• Health Related Quality of Life (HRQoL).
	• Disease Progression.
	• Number of injections administered in total treatment period.
	• Withdrawal rates.
	• Fellow Eye Involvement (FEI).
	• Mortality.
		• Publications without at least one of the relevant endpoints.

Study design	• Double-blind, single-blind and open-label RCTs* reporting efficacy and/or safety results. • Systematic reviews including references to relevant RCTs*. • Indirect treatment comparisons including references to relevant RCTs*.	• Non-randomised clinical trials, case reports. • Systematic reviews discussing only other trial designs besides RCTs or not discussing relevant outcomes. • Posters which report no new/different study outcomes than the full publication reporting on the same trial.
Other	• Publications in all languages are included without restriction to date or study duration.	• Publications are not restricted to any language.

BCVA, Best Corrected Visual Acuity; BSC, Best Supportive Care; CNV, choroidal neovascularisation; FEI, Fellow Eye Involvement; HRQoL, Health Related Quality of Life; IOP, Intraocular Pressure; mCNV, myopic choroidal neovascularisation; RCT, Randomised Controlled Trial; SoC, Standard of Care; vPDT, Verteporfin Photodynamic Therapy.

* RCT data will only be extracted from publications which report primary results. Systematic reviews and indirect treatment comparisons will be screened for references to relevant RCTs, but data will not be extracted from this source.

A8. In Appendix D, Table 26, please clarify the meaning of “no,” in column 2.

In Table 26 in Appendix D of the submission, “no” was the response to the question if the publication should be included in phase II of the clinical SLR. Behind the “no” was the reason for exclusion.

Apologies - we concede that we didn`t used a consistent format throughout table 26. An update of the table has been provided for your convenience below.

Table 8: *[Table 26 in original submission, amended]* Reference and reason for exclusion of studies excluded in phase II of clinical SLR

Study Reference	**Reason for Exclusion**
El Matri L, Chebil A, Kort F. Current and emerging treatment options for myopic choroidal neovascularization. Clinical Ophthalmology, 2015:9; 733-744.	Review
Teo KYC, Ng WY, Lee SY, Cheung CMG. Management of myopic choroidal neovascularization: focus on anti-VEGF therapy. Drugs, 2016:76; 1119-1133.	Review
Munk MR, Ruckert R, Zinkernagel M, Ebneter A, Wolf S. The role of anti-VEGF agents in myopic choroidal nevascularisation: current standards and future outlook. Expert Opinion on Biological Therapy, 2016:4; 477-487.	Review
Willis JR, Vitale S, Morse L, Parke DW, Rich WIL, et al. The prevalence of myopic choroidal neovascularization in the United States. Ophthalmology, 2016:123; 1771-1782.	Outcomes
Ceklic L, Munk MR, Wolf-Schnurrbusch U, Gekkieva M, Wolf S. Visual acuity outcomes of ranibizumab treatment in pathologic myopic eyes with macular retinoschisis and choroidal neovascularization. Retina, 2016:0; 1-7.	Population
Chan N, Teo K, Cheung C. Epidemiology and diagnosis of myopic choroidal neovascularization in Asia. Eye & Contact Lens, 2016:42; 48-55.	Study design
Lai T, Cheung C. Myopic choroidal neovascularization: diagnosis and treatment. Retina, 2016:36; 1614-1621.	Review
Wecker T, Ehlken C, Buhler A, Lange C, Agostini H, et al. Five-year visual acuity outcomes and injection patterns in patients with pro-re-nata treatments for AMD, DME, RVO and myopic CNV. British Journal of Ophthalmology, 2016:0; 1-7.	Intervention
Hykin P, Lai T, Lanzetta P, Desset-Brethes S, Staines H, Liew S. Efficacy and safety of ranibizumab 0.5mg in adult patients with visual impairment due to choroidal neovascularization associated with rare diseases: 12-month results of the MINERVA study. Ophthalmologica, 2016:236 (Suppl 1); 1-67.	Population
Weber M, Heier J. Choroidal neovascularization secondary to myopia, infection and inflammation. Developments in Ophthalmology, 2016:55; 167-175.	Review
Parmeggiani F, Costagliola C, Semeraro F, Romano M, Rinaldi M, et al. Effect of factor XIII-A G185T polymorphism on visual prognosis after photodynamic therapy for neovascular macular degeneration. International Journal of Molecular Sciences, 2015:16; 19796-19811.	Study design
Lee J, Lee S, Kim S, Koh H, Kim S, et al. Choroidal thickness and chorioretinal atrophy in myopic choroidal neovascularization with anti-vascular endothelial growth factor therapy. Retina, 2016; 0: 1-7.	Outcomes
Bruyere E, Caillaux V, Cohen Y, Martiano D, Ores R, et al. Spectral-domain optical coherence tomography of subretinal hyperreflective exudation in myopic choroidal neovascularization. American Journal of Ophthalmology, 2015;160(4): 749-758.	Outcomes
Pakzad-Vaezi K, Mehta H, Mammo Z, Tufail A. Vascular endothelial growth factor inhibitor use and treatment approach for choroidal neovascularization secondary to pathologic myopia. Expert Opinion on Biological Therapy, 2016:16 (7); 873-881.	Review
Ahn S, Park K, Woo S. Subfoveal choroidal thickness changes following anti-vascular endothelial growth factor therapy in myopic choroidal neovascularization. Investigative Ophthalmology and Visual Science, 2015:56; 5794-5800.	Outcomes

Ahn S, Park K, Woo S. Subretinal fibrosis after antivascular endothelial growth factor therapy in eyes with myopic choroidal neovascularization. Retina, 2016: 36; 2140-2149.	Outcomes
Wang J, Huang T, Su P, Chang P. Approved pharmacotherapy for myopic choroidal neovascularization: A review of randomized controlled trials in ranibizumab and aflibercept. Journal of Eye Science, 2016; 1: 14	Review
Zhang Y, Han Q, Ru Y, Bo Q, Wei R. Anti-VEGF treatment for myopic choroid neovascularization: from molecular characterization to update on clinical application. Drug Design, Development and Therapy, 2015: 9; 3413-3421.	Study design
Filho R, Zacharias L, Monteiro T, Preti R, Pimentel S. Prevalence of outer retinal tubulation in eyes with choroidal neovascularization. International Journal of Retina and Vitreous, 2016: 2; 6.	Study design
Giocanti-Auregan A, Tadayoni R, Grenet T, Fajnkuchen F, Ngheim-Buffet S, et al. Estimation of the need for bilateral intravitreal anti-VEGF injections in clinical practice. BMC Ophthalmology, 2016; 16: 142.	Outcomes
Ziemssen F, Lagreze W, Voykov B. Secondary diseases in high myopia. Der Ophthalmologe, 2016.	Outcomes
Cho B, Shin J, Gon H. Complications of pathologic myopia. Eye & Contact Lens, 2016; 42: 9-15.	Study design
Smith A, Kaiser P. Therapeutic monoclonal antibodies and fragments: ranibizumab. Developments in Ophthalmology, 2016; 55: 246-251.	Population
Ranibizumab (Lucentis®) in high myopia with neovascularization. Rev Prescrire, 2015; 35 (376): 90-91.	Outcomes
Stuart A, Ford J, Duckworth S, Jones C, Pereira A. Anti-VEGF therapies in the treatment of choroidal neovascularization secondary to non-age-related macular degeneration: a systematic review. BMJ Open, 2015; 5: e007746.	Review
Adatia F, Luong M, Munro M, Tufail A. The other CNVM: A review of myopic choroidal neovascularization treatment in the age of anti-vascular endothelial growth factor agents. Survey of Ophthalmology, 2015; 60: 204-215.	Review
Loutfi M, Siddiqui M, Dhedhi A, Kamal A. A systematic review and meta-analysis comparing intravitreal ranibizumab with bevacizumab for the treatment of myopic choroidal neovascularisation. Saudi Journal of Ophthalmology, 2015; 29: 147-155.	Outcomes
National Institute for Health and Care Excellence. Visual impairment due to myopic choroidal neovascularization: aflibercept (ESNM76). June, 2016. Accessed via: https://www.nice.org.uk/guidance/esnm76/resources/visual-impairment-due-to-myopic-choroidal-neovascularisation-aflibercept-1502681169047749	Review
Scottish Medicines Consortium, NHS Scotland. Aflibercept (Eylea). September, 2016. Accessed via: http://www.scottishmedicines.org.uk/files/advice/aflibercept_Eylea_FINAL_Sept_2016_for_website.pdf	Review
Iacono P, Parodi MB, Papayannis A, La Spina C, Varano M, Bandello F. A new treatment algorithm for the management of myopic choroidal neovascularisation using intravitreal ranibizumab. Acta Ophthalmologica, 2015; e519-520.	Study design
National Institute for Health Research. Aflibercept solution (Eylea) for visual impairment due to choroidal neovascularization secondary to pathological myopia. October, 2015. Accessed via: http://www.hsric.nihr.ac.uk/topics/aflibercept-solution-eylea-for-visual-impairment-due-to-choroidal-neovascularisation-secondary-to-pathological-myopia/	Study design
Ruiz-Moreno JM, Roura M. Cost of myopic patients with and without myopic choroidal neovascularisation. Archivos de la Sociedad Española de Oftalmología. 2016; 91(6): 265-272.	Study design
Iacono P, Parodi MB, Papayannis A, La Spina C, Varano M, Bandello F. A new treatment algorithm for the management of myopic choroidal neovascularisation using intravitreal ranibizumab. Acta Ophthalmologica, 2015; e519-520.	Study design
Amoaku W, Gale R, Lotery A, Menon G, Sivaprasad S, et al. Treatment satisfaction and well-being in patients with myopic choroidal neovascularization treated with ranibizumab in the REPAIR study. PLoS ONE, 2015; 10(6): e0129403.	Study design
Ruiz-Moreno JM, Roura M. Cost of myopic patients with and without myopic choroidal neovascularisation. Archivos de la Sociedad Española de Oftalmología. 2016; 91(6): 265-272.	Study design
Brue C, Pazzaglia A, Mariotti C, Reibaldi M, Giovanni A. Aflibercept as primary treatment for myopic choroidal neovascularisation: a retrospective study. Eye. 2016;30:139-145	Study design
Ji L, Lv W, Xiao Y, Xu Z, Zhang X, Zhang W. Therapeutic effect of intravitreal injections of ranibizumab for the treatment of macular choroidal neovascularisation caused by pathological myopia. Experimental and Therapeutic Medicine. 2015;10: 1121-1126.	Study design

Yuan JS, Wu Y, Wang YW. Changes of subfoveal choroidal thickness after treated by Ranibizumab for choroidal neovascularization secondary to pathologic myopia. Guoji Yanke Zazhi(Int Eye Sci) 2016;16(5):905-908	Study design
Parodi MB, Iacono P, Sacconi R, Iuliano L, Bandello F. Fundus Autofluorescence changes after ranibizumab treatment for dubfoveal choroidal neovascularisation secondary to pathological myopia. Am J Ophthalmol. 2015;160(2):322-327	Study design
Holz FG, Tufail A, Leveziel N, Lai TY, Lanzetta P, et al; on behalf of the RADIANCE Study Group. Ranibizumab in Myopic Choroidal Neovascularization: A Subgroup Analysis by Ethnicity, Age, and Ocular Characteristics in RADIANCE. Ophthalmologica (2016);236:19–28.	Study design
Pece A, Milani M. Intravitreal aflibercept for myopic choroidal neovascularisation. Graefe's Archive for Clinical and Experimental Ophthalmology. 2016;254:2327-2332	Study design
Rishi P, Rishi E, Bhende M, Agarwal V, Vyas CH, et al. Comparison of photodynamic therapy, ranibizumab/nevacizumab or combination in the treatment of myopic choroidal neovascularisation: a 9 year study from a single centre. British Journal of Ophthalmology. 2016; 100: 1337-1340	Study design
Korol AR, Zadorozhnyy OS, Naumenko VO, Kustryn TB, Pasyechnikova NV. Intravitreal aflibercept for the treatment of choroidal neovascularization associated with pathologic myopia: a pilot study. Clinical Ophthalmology (2016):10 2223–2229.	Study design
Ruiz-Moreno JM, Montero JA, Ariaz J, Arias L, Garcia-Layana A, et al. Intravitreal anti-vascular endothelial growth factor therapy for choroidal neovascularisation secondary to pathologic myopia: Six years outcome. Retina, 2015; 35: 2450-2456.	Study design
Hamilton RD. Ranibizumab in patients with myopic choroidal neovascularization: latest results from the third interim analysis of the LUMINOUS™ study. Investigative Ophthalmology & Visual Science (2016). 57;12: 2140	Study design
Pascual-Camps I, Hernandez-Martinez P, Monje-Fernandez L, Andreu-Fenoll M, Dolz-Marco R, Gallego-Pinazo R. Prognostic value of the tomographic phenotypic characterisation of myopic choroidal neovascularisation. Investigative Ophthalmology & Visual Science (2016). 57; 12: 2131	Study design
Macfadden W, Skelly A. Long-term outcomes of anti-vascular endothelial growth factor treatment in East-Asian patients with myopic choroidal neovascularization. Investigative Ophthalmology & Visual Science (2016). 57; 12: 2142	Study design
Kang EC, Kim M, Lee KH, Koh HJ. Long-term clinical outcomes after intravitreal bevacizumab injections or photodynamic therapy for myopic choroidal neovascularization: 7 years follow-up. Investigative Ophthalmology & Visual Science (2016). 57; 12; 4444	Study design
Nassaralla JJ, Nassaralla BA, Nasssaralla AA. Aflibercept Intravitreal Injection for Myopic Choroidal Neovascularization. Investigative Ophthalmology & Visual Science (2016). 56; 7: 4622	Study design
Abadia B, Calvo P, Ferraras A, Torron C, Leciaena J, et al. Myopic choroidal neovascularisation: long-term outcomes of intravitreal ranibizumab. EURETINA (2016).	Study design
Balaskas K, Patel R, Chaturverdi R, de la Mata G, Aslam T, Mahmood S. Morphological predictors of treatment response to anti-VEGF in myopic choroidal neovascularisation on Optical Coherence Tomography. EURETINA (2016).	Study design
Wang J, Hsu Y, Chen Y, Chen F. Comparison of intravitreal aflibercept and bevacizumab for myopic choroidal neovascularisation. EURETINA (2016).	Study design
Tan, N. Long-term outcomes of anti-VEGF treatment in East-Asian patients with myopic choroidal neovascularization. APAO (2016). P63	Study design
Sar C, Oksuz E, Malhan S, Eldem B, Unlu N, et al. Burden of visual impairment due to myopic choroidal neovascularisation in Turkey. IPSOR (2016)	Study design
Battaglia Parodi M, Iacono P, Bandello F. Antivascular endothelial growth factor for choroidal neovascularization in pathologic myopia. Developments in ophthalmology, 2010:46; 73-83.	Study design
Ng DS, Kwok AKH, Chan CW. Anti-vascular endothelial growth factor for myopic choroidal neovascularization. Clinical and Experimental Ophthalmology, 2012:40(1); e98-e110.	Study design
Kwong TQ, Mohamed M. Anti-vascular endothelial growth factor therapies in ophthalmology: current use, controversies and the future. British journal of clinical pharmacology, 2014:78(4); 699-706.	Study design
Cohen SY. Anti-VEGF drugs as the 2009 first-line therapy for choroidal neovascularization in pathologic myopia. Retina, 2009:29(8); 1062-1066.	Review
Chan WM, Ohji M, Lai TYY, Liu DTL, Tano Y, Lam DSC. Choroidal neovascularisation in pathological myopia: An update in management. British Journal of Ophthalmology, 2005:89(11); 1522-1528.	Review

Schargus M, Pauleikoff D, Haeusser-Fruh G, Maier MM. Choroidal neovascularisation in pathological myopia : Epidemiological data from a health services research study conducted in Germany. Klinische Monatsblatter fur Augenheilkunde, 2013:230(7); 707-714.	Population
Dave V, Narayanan R. Choroidal neovascularization in pathologic myopia. American Journal of Ophthalmology, 2010:150(5); 752.	Study design
Soubrane G. Choroidal Neovascularization in Pathologic Myopia: Recent Developments in Diagnosis and Treatment. Survey of Ophthalmology, 2008:53(2); 121-138.	Review
Neelam K, Cheung CMG, Ohno-Matsui K, Lai TY, Wong TY. Choroidal neovascularization in pathological myopia. Progress in Retinal and Eye Research, 2012:31(5); 495-525.	Review
Cheung CMG, Loh BK, Li X, Mathur R, Wong E, et al. Choroidal thickness and risk characteristics of eyes with myopic choroidal neovascularization. Acta Ophthalmologica, 2013:91(7); e580-e581.	Study design
Brancato R, Menchini U, Pece A, Avanza P, Radrizzani E, Capoferri C. Dye laser photocoagulation of macular subretinal neovascularization in pathological myopia . A randomized study of three different wavelengths. International Ophthalmology, 1988:11(4); 235-238.	Comparator
Tufail A, Patel PJ, Sivaprasad S, Amoaku W, Browning AC, et al. Erratum: Ranibizumab for the treatment of choroidal neovascularisation secondary to pathological myopia: Interim analysis of the REPAIR study. Eye, 2013:27(6); 786.	Outcomes
Costagliola C, Campa C, Incorvaia C, Parmeggiani F, Menzione M, et al. Erratum in: Verteporfin photodynamic therapy for subfoveal choroidal neovascularization in pathologic myopia : A 12-month retrospective review. European Journal of Ophthalmology, 2009:19(2); 329.	Outcomes
Carvalho B, Freitas-Costa P, Pinheiro-Costa J, Falcão M, Carneiro Â, Falcão-Reis F. Evaluation of antiangiogenic treatment results in choroidal neovascularization related to pathological myopia. Acta médica portuguesa, 2014:27(1); 49-58.	Outcomes
Wang E, Chen Y. Intravitreal anti-vascular endothelial growth factor for choroidal neovascularization secondary to pathologic myopia : Systematic review and meta-analysis. Retina, 2013:33(7); 1375-1392.	Review
Rajendram R, Costa-Gomes N, Horgan SE. Intravitreal ranibizumab for choroidal neovascularisation secondary to pathologic myopia: 12 month results. Eye, 2010:24(8); 1420.	Study design
Virgili G, Menchini F. Laser photocoagulation for choroidal neovascularisation in pathologic myopia. The Cochrane database of systematic reviews, 2005.	Review
Lai TYY, Luk FOJ, Lee GKY, Lam DSC. Long-term outcome of intravitreal anti-vascular endothelial growth factor therapy with bevacizumab or ranibizumab as primary treatment for subfoveal myopic choroidal neovascularization. Eye, 2012:26(7); 1004-1011.	Intervention
Gopal KS. Low-fluence PDT better than anti-vascular endothelial growth factor. Indian journal of ophthalmology, 2013:61(11); 691.	Study design
Pece A, Isola V, Vitale L. Management of choroidal neovascularization in myopic macular degeneration. Expert Review of Ophthalmology, 2008:3(3); 311-323.	Study design
Zhou L, Xing YQ, Li T, Li Y, Song XS, Li JZ. Meta-analysis of best corrected visual acuity after treatment for myopic choroidal neovascularisation. International journal of ophthalmology, 2014:7(4); 720-5.	Review
Helbig H, Joussen A. Myopie. Klinische Monatsblätter für Augenheilkunde, 2011:228(9); 753.	Study design
Wong TY, Ohno-Matsui K, Leveziel N, Holz FG, Lai TY, et al. Myopic choroidal neovascularisation : Current concepts and update on clinical management. British Journal of Ophthalmology, 2015:99; 289-296.	Outcomes
Hassenstein A. Myopic choroidal neovascularization. Der Ophthalmologe, 2012:109(8); 737.	Outcomes
Ruiz-Moreno JM, López-Gálvez MI, Donate J, Gomez-Ulla F, García-Arumí J, et al. Myopic choroidal neovascularization. Ophthalmology, 2011:118(12); 2521-2523.	Study design
Voykov B, Ziemssen F. Myope CNV. Klinische Monatsblätter für Augenheilkunde, 2011:228(9); 762-770.	Study design
Rejdak R, Szkaradek M, Taslaq W, Kałuzny JJ, Grieb P, Jünemann AG. New drug VEGF Trap-Eye- -Eylea- -and its use in the treatment of age-related macular degeneration, central retinal vein occlusion, diabetic macular edema, and choroidal neovascularization secondary to pathologic myopia. Klinika oczna, 2012:114(4); 308-310.	Population
New indication in complications of high myopia: No sustained benefit. Prescrire International, 2003:12(63); 5-8.	Outcomes

Mennel S, Barbazetto I, Meyer CH, Peter S, Stur M. Ocular photodynamic therapy - Standard applications and new indications (part 1): Review of the literature and personal experience. Ophthalmologica, 2007:221(4); 216-226.	Outcomes
Tano Y. Pathologic myopia: where are we now? American journal of ophthalmology, 2002:134(5); 645-60.	Population
Dahlmann C. Photodynamic therapy (PDT) for non-subfoveal choroidal neovascularization in pathological myopia is effective. Klinische Monatsblatter fur Augenheilkunde, 2007:224; 451.	Outcomes
Lim JI. Photodynamic therapy for choroidal neovascular disease: Photosensitizers and clinical trials. Ophthalmology Clinics of North America, 2002:15(4); 473-478.	Study design
Schachat AP. Photodynamic therapy for choroidal neovascularization. Ophthalmologica, 2001:215(2); 27-36.	Population
Woodburn KW, Engelman CJ, Blumenkranz MS. Photodynamic therapy for choroidal neovascularization: a review. Retina, 2002:22(4); 391-405.	Review
Chan WM, Lam DSC, Liu DTL, Wong TH, Yuen KSC. Photodynamic therapy for recurrent myopic choroidal neovascularisation after limited macular translocation surgery. The British journal of ophthalmology, 2003:87(9); 1188-9.	Study design
Tasman WS. Photodynamic therapy of subfoveal choroidal neovascularization in high myopia in a clinical setting: Visual outcome in relation to age at treatment. Evidence-Based Ophthalmology, 2005:6(3); 151-152.	Study design
Brown GC, Landy J. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. Evidence-Based Eye Care, 2001:2(4); 206-207.	Study design
Kaiser PK. Photodynamic therapy with verteporfin for choroidal neovascularization. Today's Therapeutic Trends, 2000:18(4); 313-326.	Review
Gibson J. Photodynamic therapy with verteporfin for juxtafoveal choroidal neovascularisation secondary to pathological myopia. Eye, 2005:19(8); 829-30.	Study design
Medvedev IB, Belikova EI, Siamichev MP. Photodynamic visudyne therapy in the treatment of choroidal neovascularization in complicated myopia. Vestnik oftalmologii, 2007:123(6); 23.	Outcomes
Heier JS, Brown D, Ciulla T, Abraham P, Bankert JM, et al. Ranibizumab for choroidal neovascularization secondary to causes other than age-related macular degeneration: A phase i clinical trial. Ophthalmology, 2011:118(1); 111-118.	Population
Deeks ED. Ranibizumab: a review of its use in myopic choroidal neovascularization. BioDrugs, 2014:28(4); 403-10.	Study design
Keam SJ, Scott LJ, Curran MP. Spotlight on verteporfin in subfoveal choroidal neovascularisation. Drugs & aging, 2004:21(3); 203-209.	Review
Flaxel CJ. The use of systemic steroids and photodynamic treatment for choroidal neovascularisation in young patients. British Journal of Ophthalmology, 2007:91(5); 564-565.	Study design
Voykov B, Ziemssen F, Bartz-Schmidt KU. Therapy of myopic choroidal neovascularization. Der Ophthalmologe, 2012:109(8); 766-9.	Study design
Ruiz-Moreno JM, Montero JA, Arias L, Araiz J, Gomez-Ulla F, et al. Three versus one intravitreal bevacizumab injections as initial protocol to treat myopic choroidal neovascularization. Acta Ophthalmologica, 2012:90(1); e82-e83.	Intervention
Nabawi KS, Shaarawi AS. Transpupillary thermotherapy of subfoveal choroidal neovascularization secondary to pathologic myopia. Ophthalmic surgery, lasers & imaging: the official journal of the International Society for Imaging in the Eye, 2010:41(1); 12-7.	Intervention
Lang GE. Treatment of Choroidal Neovascularisations with Photodynamic Therapy. Klinische Monatsblätter für Augenheilkunde, 2003:220(10); 653.	Outcomes
Montero JA, Ruiz-Moreno JM. Treatment of choroidal neovascularization in high myopia. Current drug targets, 2010:11(5); 630-644.	Review
Jampol LM, Scott L. Treatment of juxtafoveal and extrafoveal choroidal neovascularization in the era of photodynamic therapy with verteporfin. American Journal of Ophthalmology, 2002:134(1); 99-101.	Study design
Chew M, Tan CS. Treatment options for myopic CNV - Is photodynamic therapy still relevant? Indian journal of ophthalmology, 2014:62(7); 834-5.	Study design
Costa RA, Williams GA. Twofold illumination photodynamic therapy scheme for subfoveal choroidal neovascularization in pathologic myopia: Results from a randomized pilot study. Retina, 2006:26(7); 757-764.	Comparator

Miyake M, Yamashiro K, Akagi-Kurashige Y, Kumagai K, Nakata I, et al. Vascular endothelial growth factor gene and the response to anti-vascular endothelial growth factor treatment for choroidal neovascularization in high myopia. Ophthalmology, 2014:121(1); 225-233.	Intervention
Keam SJ, Scott LJ, Curran MP. Verteporfin: a review of its use in the management of subfoveal choroidal neovascularisation. Drugs, 2003:63(22); 2521-54.	Study design
Bakri SJ, Kaiser PK. Verteporfin ocular photodynamic therapy. Expert Opinion on Pharmacotherapy, 2004:5(1); 195-203.	Study design
Verteporfin: new indication. New indication in complications of high myopia: no sustained benefit. Prescrire international, 2003:12(63); 5-8.	Outcomes
Ceklic L, Wolf-Schnurrbusch U, Gekkieva M, Wolf S. Visual acuity outcome in RADIANCE study patients with dome-shaped macular features. Ophthalmology, 2014:121(11); 2288-9.	Population
Slakter J, VIP Research Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin: study design and baseline characteristics in the vip randomized clinical trial. Invest Ophthalmol Vis Sci., 1999:40; S401. ARVO Abstract nr 2114.	Outcomes
Costa RA, Calucci D, Melo LA, Cardillo JA, Jorge R. Two-Fold Illumination PDT Scheme for Subfoveal CNV in Pathologic Myopia: Six-Month Efficacy and Safety Results of a Randomized, Double-Masked, Active-Controlled Clinical Trial. Investigative Ophthalmology & Visual Science, 2005:46(13); 299. ARVO abstract.	Study design
Barbazetto I, Schmidt-Erfurth U, Laqua H. [Photodynamic treatment of occult and myopic choroidal neovascularisation: Status of the VIP-study]. Ophthalmologe, 1999:96(1); S144.	Outcomes
Tittl M, Stur M. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration and pathologic myopia - two year results of the VIP trial. 2001:15; 63.	Outcomes
Cummins E, Fielding S, Cruickshank M, Fraser C, Lois N, Brazzelli M. Ranibizumab for the treatment of choroidal neovascularisation associated with pathological myopia. Aberdeen HTA Group, Institute of Applied Health Sciences, University of Aberdeen, 2013.	Review
NICE. Ranibizumab for treating choroidal neovascularisation associated with pathological myopia (TA298). Technology appraisal, 2013.	Review
SMC. Ranibizumab (Lucentis). Advice, 2013.	Review
National Horizon Scanning Centre. Ranibizumab (Lucentis) for visual impairment due to choroidal neovascularisation (CNV) secondary to pathological myopia - first line. Birmingham: National Horizon Scanning Centre (NHSC), 2011.	Review
Ying Z, Ting Z, Gezhi X, Lijun P. Anti-vascular endothelial growth factor for choroidal neovascularisation in people with pathologic myopia. Cochrane Database of Systematic Reviews: Reviews, 2014:(6).	Study design
EMEA. SCIENTIFIC DISCUSSION - This module reflects the initial scientific discussion for the approval of Visudyne. 2004; 1-36.	Outcomes
Committee for Medicinal Products for Human Use (CHMP). Assessment report: Lucentis - International non-proprietary name: RANIBIZUMAB. EMA/716504/2012, 2013; 1-60.	Review
Novartis Pharmaceuticals| Novartis. Efficacy and Safety of Ranibizumab 0.5 vs Veteporfin PDT in Patients With Visual Impairment Due to Choroidal Neovascularization Secondary to Pathologic Myopia. NCT01922102.	Outcomes
Second University of Naples. Reduced-fluence Verteporfin Photodynamic Therapy Plus Ranibizumab for Choroidal Neovascularization in Pathologic Myopia. NCT01968486.	Outcomes
Novartis Pharma Services AG. A 12 month, phase III, randomized, double-masked, multi-center, active-controlled study to evaluate the efficacy and safety of two different dosing regimens of 0.5 mg ranibizumab vs. verteporfin PD... CRFB002F2301.	Outcomes
Wong TY, Ishibashi T, Ohno-Matsui K, Ikuno Y, Korobelnik J, et al. Efficacy and Safety of Intravitreal Aflibercept for Choroidal Neovascularization Secondary to Pathological Myopia: 48-week Results of MYRROR Study. Retina, ARVO 2014.	Study design
Ohno-Matsui K, Tan N, Wong TY, Ishibashi T, Petrillo J, et al. Impact of Ranibizumab on Patient-Reported Visual Functioning in Myopic Choroidal Neovascularization: 3- and 6-Month Results. Retina - Sessions, ARVO 2013.	Study design
Bandello F. Twelve-month efficacy and safety of ranibizumab 0.5 mg(RBZ) versus verteporfin photodynamic therapy(vPDT) in the treatment of visual impairment(VI) due to choroidal neovascularization(CNV) secondary to pathologic myopia(PM). Retina - Sessions, ARVO 2013.	Study design
Silva R, Wong TY, Asmus F. Prognostic factors in myopic choroidal neovascularisation. EVER 2014.	Study design
Korobelnik J, Ikuno Y, Asmus F. Visual outcomes following intravitreal aflibercept in patients with myopic choroidal neovascularisation. EVER 2014.	Study design

Bandello F. Evaluating the Use of Intravitreal Aflibercept in Patients with Choroidal Neovascularisation Secondary to Pathological Myopia (mCNV): The MYRROR Study. RCOphth, Annual Congress Final Programme & Abstracts, Birmingham 2014.	Study design
Yang Y, The REPAIR Study Group. Ranibizumab for the treatment of choroidal neovascularisation (CNV) due to pathological myopia (PM). The REPAIR Study 12 month analyses. RCOphth, Annual Congress Final Programme & Abstracts, Liverpool 2013.	Study design
Freitas-da-Costa Portugal P, Carvalho B, Pinheiro-Costa J, Falcao M, Carneiro A, FalcAo-Reis F. Myopic choroidal neovascularization treatment: drug of choice. RETINA Congress (European Society of Retina Specialists) congress 2013.	Study design

A9. In Appendix D, Table 27, a number of studies do not appear to meet the eligibility criteria for study selection set out in Table 24:

- 3 studies have “No treatment as intervention”
- neither the population nor the outcomes of the Ohno-Matsui et al. (2003) study appear to meet the eligibility criteria
- the outcomes of the Zaour et al. (2013) study do not appear to meet the eligibility criteria.

Please clarify if the eligibility criteria for non-randomised studies differs from that set out in Table 24, and if not, the reasons for including the above studies.

We do agree that the heading “No treatment as intervention” in Table 27 is misleading. A more appropriate heading would be “No specified intervention/SoC”. Besides that, we apologise that the study by Ohno-Matsui et al. (2003) slipped through our selection procedure. Ohno-Matsui et al. (2003) should have been excluded in the clinical SLR, as the outcomes do not meet the eligibility criteria.

The Zaour et al. (2013) study identifies the real world standard of care.

The publication by McFadden is a post-RADIANCE, non-interventional, observational, retrospective multicentre chart review, which we decided to include as RADIANCE is one of the key publications for this submission.

The eligibility criteria used for non-randomised studies did not differ from the eligibility criteria set out in Table 24 in Appendix D of the submission.

A10. Please clarify the nature and results of any narrative or quantitative analyses conducted on the non-RCTs listed in Table 27 of Appendix D. Please also clarify whether quality assessment was carried out on the included non-RCTs and provide the results if it was.

We apologise that we didn`t make it clear in the submission, but as we expected that there would be little evidence available comparing aflibercept versus the comparator of interest (ranibizumab) in direct head-to-head trials or publications which could contribute to an evidence network for comparing aflibercept versus ranibizumab, we also searched for non-RCTs which could provide useful evidence.

As a closed network could be created of the MYRROR, RADIANCE and VIP trials, there was no need for non-RCT`s to support the evidence network. Because of that, no further analyses on the non-RCTS were conducted. Also, no quality assessment was carried out on the included non-RCTs.

A11. Table 34 in Appendix D provides a detailed quality assessment of MYRROR. Please provide equivalent quality assessments for the VIP and RADIANCE studies.

Please find below the quality assessment tables created for the VIP and RADIANCE studies. Please note that we only have access to the study publications, which limits the quality assessment.

	VIP(6)	
Study question	**How is the question addressed in the study?**	**Grade (yes/ no/ not clear/ N/A)**
Was randomisation carried out appropriately?	Vision testing, color photographs, stereoscopic fluorescein angiographs, medical histories, and ocular examinations were completed within 7 days before patients were randomly assigned to treatment in the trial. The protocol stipulated that VIP Trial patients with pathologic myopia were to be randomized and analyzed separately from VIP Trial patients enrolled with CNV lesions from AMD. After reviewing and signing a written informed consent form accompanied by an oral consent process with a certified investigator (ophthalmologist), patients who were judged by a VIP-certified enrolling ophthalmologist to satisfy all eligibility criteria were assigned randomly to placebo or verteporfin infusion. Random assignments were prepared by Statprobe (Ann Arbor, MI). Statprobe also prepared sealed envelopes with random assignments and distributed them to the clinical centers. Patients were randomized in a ratio of 2:1 to verteporfin treatment or placebo (to gather more safety data on patients receiving verteporfin), with only one eye of a patient to be randomized. For cases in which an enrolling ophthalmologist believed that both eyes of a patient were eligible, the patient and ophthalmologist chose which eye would be enrolled in the study. Randomization was stratified by clinical center. Separate groups of color-coded envelopes were used to distinguish patients participating in the VIP Trial with pathologic myopia from those with AMD. A study coordinator was instructed to open the sealed envelope only after a patient was judged to meet all of the eligibility criteria and only after the enrolling ophthalmologist and the patient agreed to the patient's participation in the trial. The randomization code was not broken for any patient through the month 12 examination.	Yes
Was the concealment of treatment allocation adequate?	Random assignments were prepared by Statprobe (Ann Arbor, MI). Statprobe also prepared sealed envelopes with random assignments and distributed them to the clinical centers. Patients were randomized in a ratio of 2:1 to verteporfin treatment or placebo (to gather more safety data on patients receiving verteporfin), with only one eye of a patient to be randomized. For cases in which an enrolling ophthalmologist believed that both eyes of a patient were eligible, the patient and ophthalmologist chose which eye would be enrolled in the study. Randomization was stratified by clinical center. Separate groups of color-coded envelopes were used to distinguish patients participating in the VIP Trial with pathologic myopia from those with AMD. A study coordinator was instructed to open the sealed envelope only after a patient was judged to meet all of the eligibility criteria and only after the enrolling ophthalmologist and the patient agreed to the patient's participation in the trial.	Yes

Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The baseline characteristics for the patients were well balanced between the 2 treatment groups with the following exceptions: more women were assigned to verteporfin therapy, more patients assigned to placebo had blood as a lesion component in the study eye, and the median age of patients assigned to verteporfin was older. Sixty-nine of the 81 eyes (85%) in the verteporfin-treated group and 31 of the 39 eyes (79%) in the placebo-treated group had a predominantly classic lesion with evidence of classic CNV that was at least 50% of the entire lesion. Only 12 eyes (15%) of the verteporfin-treated group and 5 eyes (13%) of the placebo-treated group had evidence of any occult CNV at the baseline examination. Only four CNV lesions (5%) in the verteporfin-treated group and 4 (10%) in the placebo group were more than three disc areas in size at baseline. The median greatest linear dimension of the lesion was 1900 μm in the verteporfin-treated group and 1840 mm in the placebo-treated group (P = 0.65).	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)?	The allocation of verteporfin therapy or placebo was recorded on a randomisation log that was stored in a locked cabinet with both opened and unopened randomisation envelopes at each clinical centre. The study coordinator aware of the treatment assignment and anyone else who might assist in the set up of verteporfin or placebo solutions were trained to make every reasonable attempt to maintain masking of the ophthalmologist, patient, vision examiner and Photograph Reading Centre personnel. The verteporfin and placebo solutions were different colours (green vs colourless). All verteporfin and placebo solutions as well as the intravenous tubing were covered entirely with foil so that the patient and treating ophthalmologist were masked during the infusion. The ophthalmologist remained masked whilst administering the light since the fundus appearance during treatment does not change in any way to indicate verteporfin or placebo treatment. On the materials submitted to them, the Photograph Reading Centre graders did not have any information to indicate that verteporfin or placebo had been administered. The marked hypofluorescence within a treated area noted within 1 week after verteporfin therapy in Phase 1 and 2 studies is not readily apparent 3 months after treatment. Therefore this hypofluorescence was not judged to be a likely source of potential unmasking of the graders evaluating photographs obtained at least 3 months after verteporfin therapy. Clinic monitors also had no access to information that would indicate treatment assignment. All patients were to remain masked until all of them had completed the month 24 examination and the data collection and entry was completed.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Seventy-nine of the 81 patients (98%) in the verteporfin-treated group compared with 36 of the 39 patients (92%) in the placebo-treated group completed the month 12 examination. Reason for drop-out was not reported.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The VIP Trial design included patients with pathologic myopia for this report, as well as a study (not part of this report but submitted for publication separately) of patients with subfoveal CNV caused by AMD with criteria that were not included in the TAP Investigation. The protocol stipulated that VIP Trial patients with pathologic myopia were to be randomized and analyzed separately from VIP Trial patients enrolled with CNV lesions from AMD.	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?	The primary efficacy analyses were based on a strict intent-to-treat analysis; patients were analyzed within the group to which they were randomized. All 120 randomized patients were included in the primary efficacy analyses. Demographic and baseline characteristics were summarized and tested for treatment group comparability using a Fisher's exact test for categorical variables and a Wilcoxon rank-sum test for continuous variables. The proportions of eyes that lost fewer than 8 or 15 letters from baseline to 1 year were analyzed using a Pearson chi-square test. The distributions of changes in visual acuity from baseline, visual acuity categories, and changes in contrast sensitivity from baseline were compared between groups using a Wilcoxon rank-sum test. Assessments of fluorescein leakage were compared between groups using a Pearson chi-square test. The intent-to-treat analysis included all patients who were randomized; missing values were imputed using the method of last observation carried forward.	Yes Yes

	RADIANCE(5)	
Study question	**How is the question addressed in the study?**	**Grade (yes/ no/ not clear/ N/A)**
Was randomisation carried out appropriately?	A randomization list was produced by Novartis Drug Supply Management using a validated system that automates the random assignment of treatment groups to randomization numbers in the specified ratio. At enrollment, patients received the lowest available randomization number that then assigned them in a 2:2:1 ratio to 1 of the 3 treatment groups. For all patients, 1 eye was selected and treated as the study eye. If both eyes were eligible, then the eye with the worse VA (assessed at visit 1) was selected for the study treatment. However, if medical reasons and local ethical requirements dictated, the investigator could select the eye with the better VA as the study eye. If needed, the fellow eye was treated as per the investigator's discretion. The randomized set consisted of all randomized patients. Patients were considered randomized when they had been given a randomization number. The full analysis set (FAS) consisted of all randomized patients who received at least 1 application of the study treatment (ranibizumab [sham] or vPDT [sham]) and had at least 1 post-baseline record of study eye VA data.	Yes
Was the concealment of treatment allocation adequate?	To ensure masking, 2 investigators were involved at each study center. All study assessments were made by the evaluating investigator, VA assessor, or other site personnel who were masked to the treatment assignment. The treating investigator was unmasked and administered the randomized study medication per the protocol; however, they were not involved in any other aspects of the study and could not communicate details of the treatment.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Overall, baseline patient demographics and ocular and disease characteristics were comparable across the 3 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)?	RADIANCE was a 12-month, phase III, multicenter, randomized, double-masked, active-controlled study. To ensure masking, 2 investigators were involved at each study center. All study assessments were made by the evaluating investigator, VA assessor, or other site personnel who were masked to the treatment assignment. The treating investigator was unmasked and administered the randomized study medication per the protocol; however, they were not involved in any other aspects of the study and could not communicate details of the treatment.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The majority of the patients across the 3 treatment groups completed the 12- month study period (group I: 94.3%; group II: 96.6%; group III:100%). No patients discontinued due to AEs. The reasons for treatment discontinuation in the ranibizumab (VA) arm were: unsatisfactory therapeutic effect (n=1), subject withdrew consent (n=1), lost to follow-up (n=3), protocol deviation (n=1). The reasons for treatment discontinuation in the ranibizumab (disease activity) arm were: subject withdrew consent (n=2), lost to follow-up (n=1), protocol deviation (n=1). None of the patients in the vPDT arm discontinued the study.	No

Is there any evidence to suggest that the authors measured more outcomes than they reported?	Nothing to suggest this in the publication.	Not clear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary analysis was performed on the full analysis set (FAS) with a modified last observation carried forward (LOCF) approach, wherein the missing values occurring between the observed values were computed from the mean of the observed values before and after the missing time point. The full analysis set (FAS) consisted of all randomised patients who received at least 1 application of the study treatment (ranibizumab [sham] or vPDT [sham]) and had at least 1 post-baseline record of study eye VA data	Not clear

A12. Please clarify whether transitivity and inconsistency assumptions across the indirect treatment comparison evidence network have been evaluated.

Transitivity/similarity

The transitivity/similarity assumption is briefly discussed qualitatively in section 3.9.3 of the submission. No quantitative analysis was performed on potential anti-VEGF treatment effect modifiers in MYRROR as the patient characteristics were well balanced with RADIANCE across all observed covariates, aside from the race distribution. Race distribution could not be investigated quantitatively, as no counterfactuals exist within the MYRROR trial (all patients were East Asian), however our expected implications of this (or lack of) are discussed in section 3.9.3. In addition, the structure of MYRROR and RADIANCE in terms of the trial design and endpoints collected, had a large degree of agreement.

There is less agreement with the VIP trial. The trial itself is much older (2001) and there are some noticeable differences in methodology (particularly in how results are presented). The patients in vPDT are younger in age than the patients in both MYRROR and RADIANCE, and CNV location is described differently between the trials. As previously mentioned there are also large differences in the ethnicity of patients. If any of these differences in patient characteristics are treatment effect modifiers, it will lead to bias in the ITC estimates.

In addition, the nature of the placebo arm is fundamentally different in VIP vs MYRROR. In MYRROR, the placebo is intravitreal (i.e. injected in eye), whereas the placebo protocol in VIP involved an intravenous injection. Also, the MYRROR trial involved 1 sham injection followed by repeated sham injections every 4 weeks through week 20 regardless of whether re-treatment criteria were fulfilled or not (i.e. at least 6 injections throughout the observed trial period), whereas placebo is administered once at baseline in VIP. It is unclear if these two different protocols could lead to differences in BCVA outcomes, especially given one is injected into the eye. However, placebo outcomes in MYRROR and VIP are broadly similar which supports their comparability for linking together the evidence network.

Furthermore, the VIP study presents medians instead of means. Even if the underlying BCVA change data is normally distributed, with only 39 patients it is plausible that the observed

median could be quite different from the observed mean. Any skewness in the distribution will add to this discrepancy.

It is important to weigh up these issues next to the claims of the ITC. Due to lack of statistically significant differences between aflibercept and ranibizumab, we are claiming sufficient clinical similarity to justify a cost-comparison modelling approach. For this claim to be violated (i.e. for the ITC to produce a statistically significant result), the treatment effects estimated would have to vary by a considerable amount.

In addition, given how well balanced the observed characteristics and trial design are between MYRROR and RADIANCE, and the transitivity concerns surrounding VIP, an argument could be made that a naïve comparison of ranibizumab and aflibercept across RADIANCE and MYRROR would be more reliable than the ITC results presented here (the outcomes of a naive comparison would also support an assumption of clinical similarity).

Consistency

Given the limitations of the evidence network (in particular, its linearity), it is not possible to evaluate the consistency assumption (i.e. a comparison between direct and indirect evidence). This is because there are no indirect comparisons which match a given direct comparison. For example, vPDT can be compared directly with ranibizumab and placebo, but it cannot be indirectly compared with either, as any 'indirect' comparison would need to 'pass through' the direct comparison. More data (i.e. a trial of aflibercept vs ranibizumab, or aflibercept vs vPDT) would be needed to provide an alternative indirect path which doesn't rely on the direct comparisons. The table below shows that for any given treatment/placebo, there is no match between direct comparisons and indirect comparisons.

Table 9: Direct and indirect comparisons

Treatment	Can be directly compared to:	Can be indirectly compared to:
Aflibercept	Placebo	vPDT, Ranibizumab
vPDT	Placebo, Ranibizumab	Aflibercept
Ranibizumab	vPDT	Placebo, Aflibercept
Placebo	Aflibercept, vPDT	Ranibizumab

A13. In Appendix D, it is stated that for MYRROR a weighted average of the 12-week and 16-week data has been used to estimate the outcomes at 13-weeks in order to compare with VIP and RADIANCE in the network-meta-analysis. It is unclear why the 12-week data from MYRROR, which are only one week short of the 13-week time point, have not been used. Please provide results of the network meta-analysis using the 12-week data from MYRROR.

Bayer's thinking was that for a BCVA-over-time function which is increasing, imputing 13-week outcomes using linear interpolation from two observed values either side would provide a more reliable estimate than 12-week outcomes (and if anything we would expect this to be

conservative due to the BCVA-over-time function increasing at a decreasing rate). However, we acknowledge the merit in using observed values over imputation.

Figure 2 presents the ITC results using 12-week MYRROR outcomes. The relative treatment benefit of aflibercept vs placebo is almost the same at 12 weeks as the imputed 13-week values, so the overall results do not change significantly.

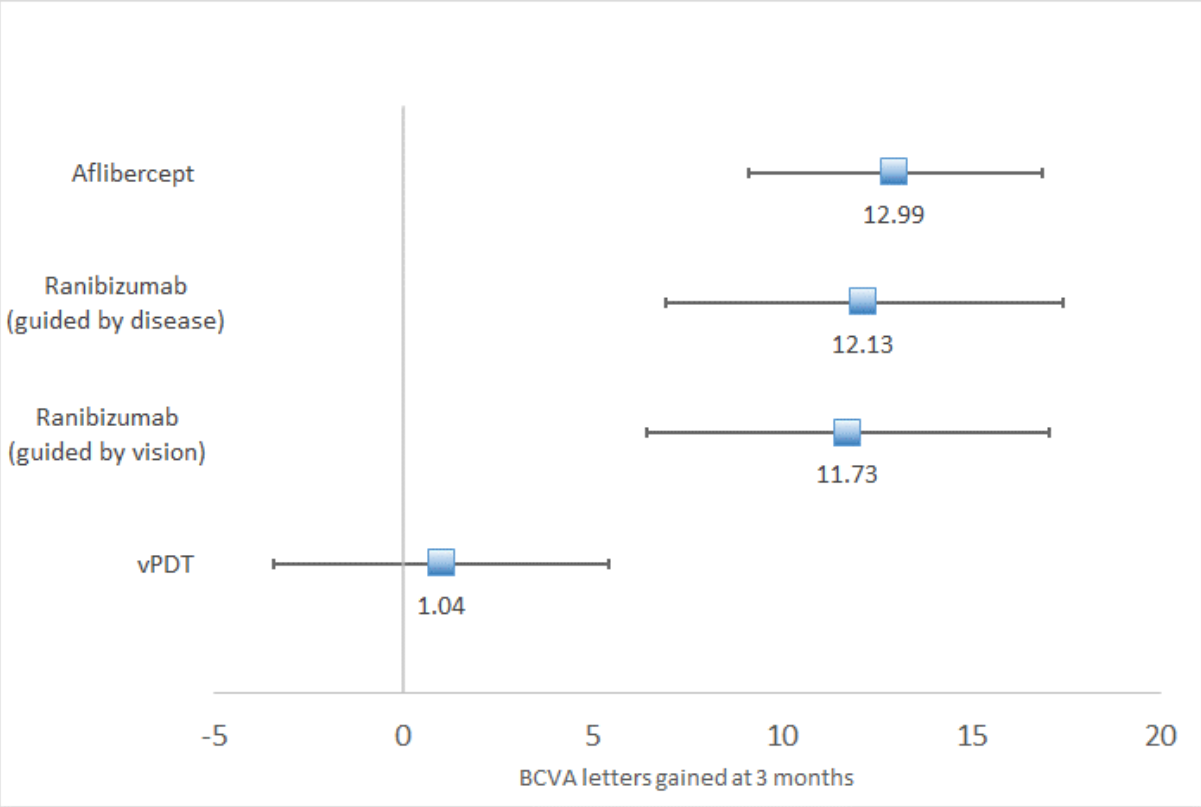


Figure 2 - Results using 12-week data from MYRROR

A14. In Appendix D, Table 33 indicates the mean BCVA gain for placebo is -1 and for vPDT is 0 for the VIP trial, but Table 30 suggests these values correspond to the mean BVCA (approximated from median) rather than the change in BCVA. Table 30 suggests the correct values to be included in the network meta-analysis are 0.2 for vPDT and -1.6 for placebo. Please clarify which values are correct, and if necessary, provide the results of the updated network meta-analysis.

Apologies, the mean BCVA presented in Table 30 is incorrect and instead refers to the change, as opposed to the absolute BCVA. Please see updated Table 30 below (Table 10). The change of 0.2 and -1.8 that are presented are in reference to the 12-month change from the paper, whereas we use the 3-month change in the ITC (i.e. 0 and -1).

The values presented in Table 33 (and those used in the analysis) are the 3-month BCVA change.

Table 10 *[Table 30 amended original]* Mean or mean change in (best-corrected) visual acuity

Study	Mean BCVA			Change in BCVA		
VIP VIP study group, 2001[1];	NR	NR		Median change in lines (letters) vPDT: 3-months: 0.0 12-months: 0.2 (1.0) 24-months: 0.2 (1.0)	Median change in lines (letters) placebo: 3-months: -1.0 12-months: -1.8 (-9.0) 24-months: -1.6 (-8.0)	
MYRROR Ikuno et al. 2015;	Baseline mean BCVA, letters ± SD (min-max) aflibercept: 56.4 ± 9.8 (28-76) placebo: 56.6 ± 8.9 (37-70)			Mean change in letters: aflibercept: Week 4: 7.56 Week 8: 14 Week 12: 11.44 Week 16: 12.38 Week 20: 12.23 Week 24: 12.19 Week 28: 12.81 Week 32: 13.39 Week 36: 13.50 Week 40:13.92 Week 44: 13.78 Week 48: 13.68	Mean change in letters: placebo: Week 4: -1.98 Week 8: -1.04 Week 12: -1.70 Week 16: -1.03 Week 20: -1.89 Week 24: -1.94 Week 28: 1.42 Week 32: 2.57 Week 36: 3.55 Week 40: 2.53 Week 44: 3.00 Week 48: 3.99	
RADIANCE Wolf et al. 2014;	Mean (SE) in ETDRS letters: ranibizumab (I): Week 13: 66 (12.98) Week 26: 69.2 (12.44) Week 52: 68.3 (12.61)	Mean (SE) in ETDRS letters: ranibizumab (II): Week 13: 66.4 (12.28) Week 26: 68.4 (13.56) Week 52: 68.3 (12.45)	Mean (SE) in ETDRS letters: vPDT: Week 13: 56.9 (14.49) Week 26: 62.7 (14.65) Week 52: 61.1 (14.86)	Mean change from baseline in ETDRS: ranibizumab (I): Week 13: 12.1 Week 52: 13.8	Mean change from baseline in ETDRS: ranibizumab (II): Week 13: 12.5 Week 52: 14.4	Mean change from baseline in ETDRS: vPDT: Week 13: 1.4 Week 52: 9.3

BCVA, Best Corrected Visual Acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation; SE, standard error; vPDT, verteporfin photodynamic therapy.

[1] Additional VIP publication: Blinder et al. 2003

A15. The network meta-analysis only considers 3-month best-corrected visual acuity data. If available, please provide any of the relative risks of gaining 15, 10 and 5 letters and losing 15, 10 and 5 letters from the network meta-analysis. Please note that estimates for ranibizumab (proportion of people gaining or losing 10 and 15 letters) are present in the literature.

These analyses were explored early into the project; however, they were unfeasible.

VIP did not present any gain/loss in >10 letters, but it did present gain/loss of >15 (alongside MYRROR and RADIANCE), so we did explore conducting an indirect comparison of the relative risk of gaining/losing >15 letters.

Unfortunately, due to the presence of zero events (combined with quite a limited network) it was not possible to reliably conduct this comparison. For the gain in >15 letters, there were zero events in the placebo arm of VIP, and for a loss of >15 letters there were zero events in the ranibizumab arm in RADIANCE.

The Bayesian model can incorporate zero events naturally without any change in specification, but due to the small network we didn't achieve convergence to the posterior distribution, despite trying numerous different initial values and prior distribution specifications.

We also tried a Bucher analysis, where the typical solution to the zero-event problem is to apply a continuity correction (as suggested in the Cochrane Handbook), by adding 0.5 to number of responses and N for both the placebo and vPDT arms. This is an imperfect solution, with the value of the continuity correction being quite arbitrary, and has been demonstrated to introduce bias(7). This approach did produce a point estimate, however just changing the continuity correction by 0.01 (to 0.49 or 0.51) significantly changed the results, so we abandoned this approach due to its volatility/instability.

A16. In terms of the retreatment criteria, it is unclear which of the ranibizumab arms in RADIANCE that Bayer views as most similar to the aflibercept arm of MYRROR. Please clarify this.

Neither of the ranibizumab arms in the RADIANCE trial are considered particularly similar to the aflibercept arm of MYRROR in terms of retreatment criteria.

In the ranibizumab (guided by vision) arm, retreatment was based on VA stabilisation criteria. Patients in the ranibizumab (guided by disease) arm, retreatment was based on disease activity criteria. In contrast, the retreatment protocol for the MYRROR trial involved consideration for both disease activity and VA outcomes or due to the clinician`s judgement.

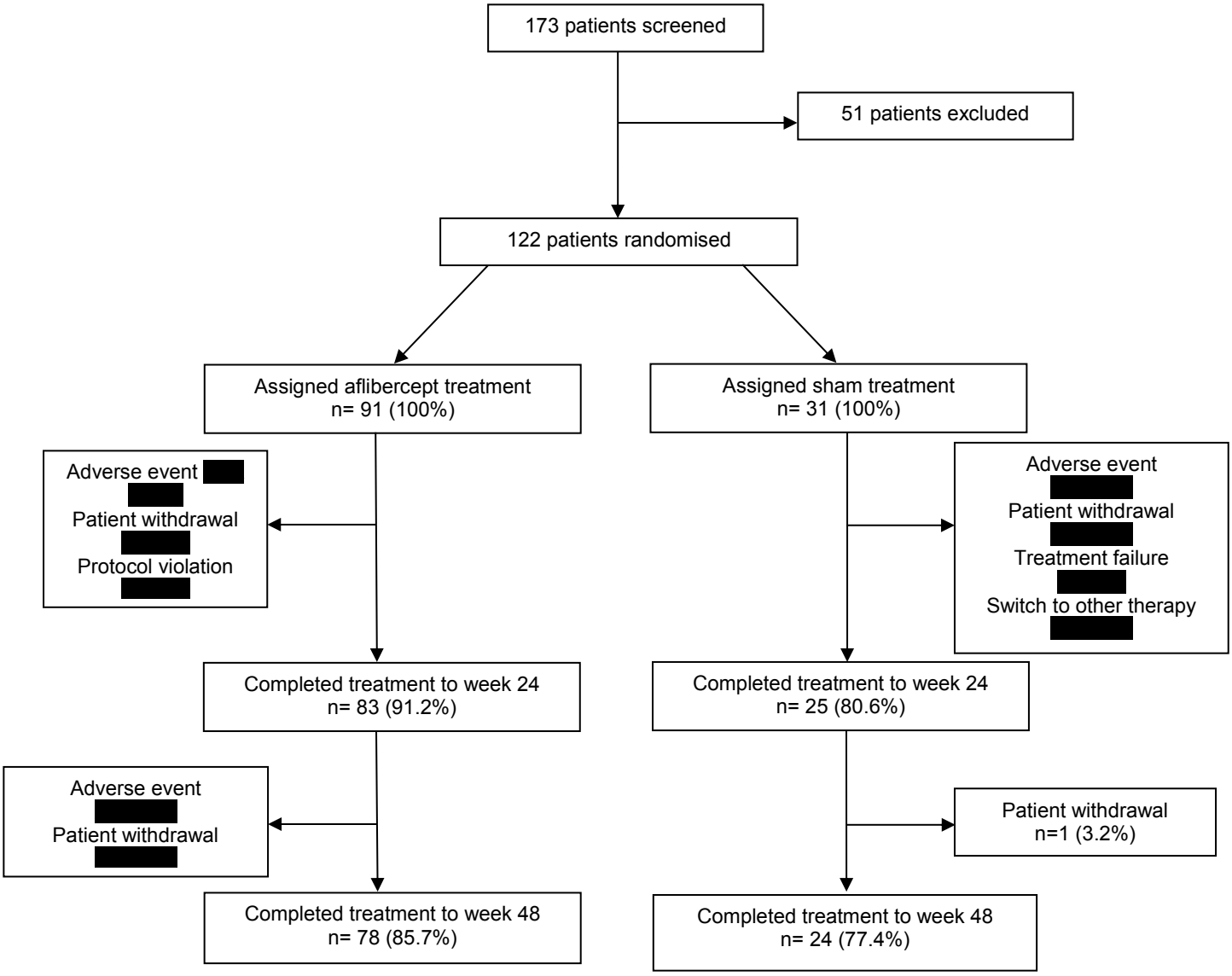
The data from MYRROR suggests that retreatment decisions are based on a number of factors which might be different on each retreatment occasion (see Table 19 of submission). Only in a minority of cases is the decision to re-treat based on visual acuity change OR disease activity alone.

Furthermore, the clinicians interviewed in the market research suggested that around 75% of retreatments are guided by a combination of disease activity and VA (Bayer plc, data on file). Therefore, the MYRROR protocol may be broadly reflective of clinical practice with regards to retreatment criteria, whilst the RADIANCE protocol investigates different retreatment criteria in the two ranibizumab arms.

A17. In Appendix D, Figure 9, the MYRROR participant flow diagram, numbers are missing from some of the boxes. Please provide a complete flow diagram for MYRROR. Please also provide for each arm, the number of patients remaining in the study at each of the 4-week follow up points and the number of injections at baseline and at each follow up point. For the sham arm please report the numbers of sham injections and those of aflibercept injections separately.

Apologies for this omission due to formatting across draft versions of the document.

Figure 3: Patient Disposition in MYRROR



For each arm, the number of patients remaining in the study at each of the 4-week follow up points and the number of injections at baseline and at each follow up point are presented in the table below. This information is reported for the Full Analysis set (FAS)(1).

Table 10: Patients remaining in study and number of injections at different time points

Follow-up point	Aflibercept		Sham + VTE		
	No of patients remaining in study	Number of injections	No of patients remaining in study	Number of injections	
				Sham injection	Aflibercept injections
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]		[redacted]		

Section B: Clarification on cost-effectiveness data

None

Section C: Textual clarifications and additional points

C1. Please provide the clinical study report for the MYRROR trial.

Please find uploaded the 24 week and 48 week CSRs for the MYRROR study.

C2. Please provide the clinical study reports for VIEW1 and VIEW2, which are important for demonstrating safety considerations.

Please find uploaded the study population and safety data from the CSR of the combined studies VIEW1 and VIEW2.

C3. Please provide the following Bayer data on file:

a. Market share data

Bayer presumes you are referring to the figures in Appendix I. These market share figures are assumptions and do not have a reference source.

b. Market research survey of 52 ophthalmologists

Please find the results of this research uploaded as requested.

Reference List

(1) Bayer Healthcare. Clinical Study Report (CSR) (48 weeks): A Phase-3, Multi-center, Randomized, Double-masked, Sham-controlled Study of the Efficacy, Safety, and Tolerability of Intravitreal VEGF Trap-Eye in Subjects with Choroidal Neovascularization Secondary to Pathologic Myopia. 2014 Feb 17. Report No.: PH-37599.

(2) Ikuno Y, Ohno-Matsui K, Wong T-Y, Korobelnik J-F, Vitti R, Li T, et al. Intravitreal aflibercept injection in patients with myopic choroidal neovascularization: The MYRROR study. Ophthalmology 2015;122(6):1220-7.

(3) European Medicines Agency (Committee for Medicinal Products for Human Use [CHMP]. EPAR (European Public Assessment Report) for Eylea in the treatment of mCNV. 2015 Sep 24. Report No.: EMA/758988/2015.

(4) Bayer Healthcare. 2.5 Clinical Overview: : Eylea myopic CNV 48 weeks (European dossier submission). 2015.

(5) Wolf S, Balciuniene VJ, Laganovska G, Menchini U, Ohno-Matsui K, Sharma T, et al. RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia. Ophthalmology 2014;121:682-92.

(6) Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial-VIP report no. 1. Ophthalmology 2001;108:841-52.

(7) Spittal et al. Meta-analysis of incidence rate data in the presence of zero events. BMC Medical Research Methodology 2015;DOI 10.1186/s12874-015-0031-0.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Aflibercept for treating myopic choroidal neovascularisation [ID952]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

N**ame of your organisation:** Royal National Institute of Blind People

Your position in the organisation: Policy and Campaigns Officer (Eye Health)

Brief description of the organisation: RNIB is the UK's leading charity helping people with sight loss lead independent and fulfilling lives. An increasing focus of our work is on sight loss prevention and access to treatments. As part of this work we aim to ensure that patients are treated with new, clinically proven treatments as quickly as possible.

This form has been completed in Ariel 14, the minimum standard for accessibility, as per RNIB's guidelines.

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Myopia is caused by excessively long growth of the eyeball. Myopic choroidal neovascularisation (mCNV) occurs when new blood vessels grow from the blood supply underneath the retina (from the choroid layer), through lacquer cracks or areas of atrophy and onto the retina. These new blood vessels can bleed very easily as they are very weak and fragile, causing damage and swelling to the retina.

Myopic macular degeneration or myopic maculopathy occurs when new blood vessels develop at the macula (the central part of the

retina). Subsequent changes to central vision can make it difficult for people to read and see people's faces. Colour vision is also affected and straight lines look bent or distorted. Damage to the retina caused by the new blood vessels results in scarring. This eye condition develops rapidly, and without treatment can lead to permanent sight loss.
The condition affects people of working age, often in their forties or fifties. Loss of vision at this age can leave people at risk of losing employment, early retirement and dependence on family and carers. Loss of reliable income can lead to dependence on state benefits. Additionally this age group often have a number of caring responsibilities for dependents or older relatives.

People living with the condition, at risk of sight loss, face increases in the cost of living including the cost of visual aids. The loss of central vision can stop people from driving resulting in increased transport costs to retain independence. A loss of independent mobility can lead to social isolation.

The need for domestic help may incur further costs as people with sight loss find it more difficult to cook safely, read food labels and maintain a healthy diet. Individuals may also find it difficult to keep up with medical regimes un-related to their sight loss such as self-administration of drugs or attending hospital appointments.

Sight loss can often lead to increased risk of falls and accidents requiring further NHS treatment. People also report the impact of not being able to recognise the faces of loved ones. Further to this, the loss of sight leads to loss of confidence, lower self-esteem and in some cases clinical depression.

In addition to being at risk of sight loss and the associated impacts, patients with mCNV face expensive prescriptions for glasses and additional comorbidities as they are at higher risk of developing cataracts and retinal detachment.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Being diagnosed with a condition that can lead to sight loss is a sudden and terrible shock. The financial, emotional and social implications cannot be underestimated. Patients with mCNV want

to retain as much sight as possible to avoid these implications; this is therefore the most important treatment outcome.

Patients currently treated with ranibizumab, a NICE approved biosimilar to aflibercept, reported improved vision. In the long term this helped to prevent anxiety and depression as a treatment option was available. Additionally patients were able to continue to live independent lives; they could cook, work and drive. Given the evidence of the MYRROR clinical trial, we would expect to see the same outcomes for patients treated with aflibercept.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

VPT

Vertporfin Photodynamic Therapy is licenced for the treatment for mCNV. However this is very rarely considered or used as a treatment option as it causes scarring and can lead to visual loss.

Ranibizumab

Ranibizumab, an anti-VEGF, is the standard treatment for mCNV. Ranibizumab is given by an injection into the eye and works by reducing the growth of new blood vessels and the oedema (swelling) they may cause. Doing this can reduce the risk of scarring and damage to the retina caused by these new vessels, which in turn can help to avoid sight loss. The treatment is both safe and effective with NICE approval [TA298]. Patients express anxiety about having injections in their eyes, however they also report that the procedure doesn't hurt and although unpleasant it is worth undergoing in order to retain sight.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)

- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

- Data from the MYRROR study has shown aflibercept to be a safe and effective treatment for mCNV offering patients a treatment to stabilise a serious sight condition and prevent sight loss.

- As a biosimilar to the current NICE approved anti-VEGF ranibizumab, aflibercept offers patients a further treatment choice if they do not respond to ranibizumab.

- Aflibercept is considered by clinicians as more potent than ranibizumab, meaning that a patient may need fewer injections to stabilise the condition, lowering the frequency of hospital visits.
- The method of delivery is tried and tested. Intravitreal injections are widely used for a range of eye conditions and patients and clinicians can be confident that this is a safe practice.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Aflibercept is a biosimilar of ranibizumab, an additional safe and effective treatment choice is advantageous for patients who may not respond to ranibizumab.

As Vertporfin Photdynamic Therapy is rarely used due to its negative side effects (scarring and visual loss) aflibercept provides the only safe and effective alternative to ranibizumab.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Patients express concerns about having injections in their eyes, however are willing to deal with an unpleasant procedure in order to retain sight.

Prior to the NICE approval of ranibizumab, PDT was rarely offered to patients and remains an uncommon treatment option. This means that there is currently only one viable treatment option for mCNV. If a patient is unresponsive to ranibizumab they are left without a treatment option and faced with potential permanent visual loss.

Please list any concerns patients or carers have about the treatment being appraised.

Patients express concerns about having injections in their eyes, however as mentioned, they are willing to undergo an unpleasant procedure to retain sight.

Endophthalmitis, an inflammation of the internal eye tissue caused by infection can result from intravitreal injections. Sight can be reduced as a result of this infection and inflammation and treatment must be started quickly. The likelihood of the

endophthalmitis occurring is reduced by a limited injection regime as patients would experience with aflibercept.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes X No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes X No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

MCNV is common in people Asian (far East) descent. Additionally the indication affects people of working age (people aged 40-60). NICE should consider how its decision affects these groups of individuals.

Not approving the treatment will increase health inequalities as some patients will be able to pay for private treatment (with aflibercept) while others will not (and will be left to lose their sight if they do not respond to the current NICE approved treatment, ranibizumab). Aflibercept for treating mCNV is available in Wales and Scotland, leaving English patients at a disadvantage in the UK.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such

impacts.

Patients with a fear of injections may find this technology difficult. However patients tell us that they will do anything to save their sight, including injections and undertaking difficult journeys to get the treatment they need.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☒ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Aflibercept is a safe and effective treatment for myopic choroidal neovascularisation
- As a biosimilar to ranibizumab, aflibercept offers patients an additional treatment choice should they not respond to ranibizumab
- Aflibercept is considered to be more potent than ranibizumab potentially requiring fewer injections, reducing the impact on patients in terms of invasive procedure and number of hospital visits.
- The minimal number of injections and small patient population will not require large NHS resources in comparison to other retinal conditions such as wet AMD.
- RNIB call on NICE to approve aflibercept for the treatment of myopic choroidal neovascularisation.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Aflibercept for treating myopic choroidal neovascularisation [ID952]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: The Royal College of Ophthalmologists
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? yes
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Aflibercept for treating myopic choroidal neovascularisation [ID952]

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Response:Myopic choroidal neovascularisation is currently treated by ranibizumab intravitreal injections which are provided in secondary care. Another possible treatment is photodynamic therapy with visudyne, however this is rarely used now for this indication as it can lead to atrophy, or damage to the retinal tissue. Ranibizumab and aflibercept injections are widely used in the NHS for treatment of choroidal neovascularisation due to age-related macular degeneration, as well as diabetic macular oedema and macular oedema due to retinal vein occlusions, following positive NICE guidance. The use of aflibercept for myopic choroidal neovascularisation would just be a small extension of its current use. Increasingly the use of ranibizumab is being replaced by aflibercept as it is a more potent anti-VEGF as demonstrated by biological studies and clinical trials. In the VIEW studies, which lead to the licensing and NICE approval of aflibercept for AMD, the visual outcome of 8 weekly aflibercept was just as good as 4 weekly ranibizumab. In the DRCR.net protocol T study at one year aflibercept produced better visual acuity improvement compared to ranibizumab and bevacizumab for diabetic macular oedema. There has not been a direct comparison of ranibizumab and aflibercept for myopic choroidal neovascularisation and both have been shown to be effective in clinical trials but in view of the evidence that aflibercept maybe more effective it would be good to have this as a possible first line choice for myopic choroidal neovascularisation.
Myopic choroidal neovascularisation can develop at a younger age than age-related macular degeneration and so can be a serious threat to vision for working age patients and high myopia is more common in Asians. Ideally we should be able to give the most effective treatment as soon as possible if this condition arises to give the best chance of a good outcome.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for

example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Response: The implementation of using aflibercept for myopic choroidal neovascularisation is straight forward as this condition is already treated with injections so it only a matter of a choice of anti-VEGF injections. As aflibercept is a more potent anti-VEGF it would seem a good option. In the Myrror study comparing aflibercept to sham for this condition the results were good and on average only 1 to 2 injections were needed. The use of aflibercept in terms of starting and stopping would be the same as are currently used for ranibizumab. Essentially active choroidal neovascularisation is identified with a combination of OCT and fluorescein angiography in a symptomatic patient and retreatment is based on reviewing the visual acuity, symptoms and the same imaging modalities.

Visual acuity change is the main measure used to assess benefit and is the primary outcome of the trials. The Myrror study did seem to follow normal clinical practice in that a PRN approach was used rather than a series of injections in all. This was appropriate as in many patients only a few injections are needed.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Response: Not aware of this as ranibizumab is the main injection currently being used for myopic CNV.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Aflibercept for treating myopic choroidal neovascularisation [ID952]

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Response: As myopioc CNV is already being treated where necessary with an injection the approval of aflibercept would just give a choice of anti VEGF for this condition. As it is a potentially sight threatening problem this would be good thing. There should not be a need for any additional resources indeed slightly fewer injections may be found to be needed as it is a more potent anti VEGF than ranibizumab and there should be no reason that there would be a delay in implementing the guidelines as the cost of aflibercept is similar to ranibizumab.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. 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 tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Response: Myopic CNV is more common in Asians

NICE National Institute for Health and Care Excellence

Clinical expert statement

Aflibercept for treating myopic choroidal neovascularisation [ID952]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Stephen James Talks**
2. Name of organisation	**Newcastle Upon Tyne Hospitals NHS Foundation Trust**
3. Job title or position	**Consultant Ophthalmologist** On Scientific committee RCOphth

4. Are you (please tick all that apply):	**x**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? **x**☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x** yes, I agree with it
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve vision or at least stop it reducing. Reduce symptoms such as distortion which can make reading a problem.

8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Vision stabilisation, reduction in distortion. Trials will often report improvement in vision of,5,10 15 or more letters all of which can be very important but the overall benefit does depend where the vision starts. Pathological myopia can cause blindness gradually due to atrophy but the development of a CNV can make this much more rapid so both stabilisation and improvement are important.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Ranibizumab works well but aflibercept is a more potent anti-VEGF so may work a little better and less injections be required
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Ranibizumab intra vitreal injections
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes
• What impact would the technology have on the current pathway of care?	It wouldn't change but would give a choice. Whilst few ranibizumab are usually needed it may reduce that number further.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	Maybe stable quicker so can have fewer follow up visits or be more spaced out.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary eye care services
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	In AMD related CNV we find patient's macular are more likely to dry up when switched to aflibercept from ranibizumab although there might not be much vision change, but less injections can be given. In myopic CNV on average few injections are needed but some require more and it would be hoped that this would be less and the eye reach a stable situation quicker.
• Do you expect the technology to increase length of life more than current care?	N/A
• Do you expect the technology to increase health-related quality of life more than current care?	As myopic CNV can affect working age patients it may lead to quicker resolution of symptoms such as distortion and so enable a return to work quicker
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	CNV related to myopia normally occurs when there is some weakening of Bruch's membrane and the retinal pigment epithelium between the retina and the choroid. This may be described as a 'lacquer crack' or larger areas of atrophy. In pathological myopia atrophy can gradually develop which could limit benefit if it is central.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical	The same

requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The main tests used to start and monitor treatment are visual acuity, OCT and fundus fluorescein angiography (FFA). In some cases the presence of a myopic CNV can be hard to be certain from OCT alone and so an FFA is useful and the same maybe true with follow up. Treatment would be recommended early if a patient is symptomatic with distortion and or blurred vision due to a CNV. Haemorrhage maybe noted. If the vision is too poor with central damage then treatment maybe shouldn't be started or should be stopped, such as 6/96 as in the AMD CNV treatment guidelines.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Change in symptoms even if vision hasn't changed much may mean an earlier return to work.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Ranibizumab has been a significant improvement compared to PDT for myopic CNV, as the original comparator trials have shown. Whether aflibercept will be significantly better than ranibizumab is unlikely but it maybe better for some patients and would be appropriate to have as an option and both would be good to have as possibilities to switch to if the response is not as hoped.
• Is the technology a 'step-change' in the management of the condition?	Not compared to ranibizumab but yes compared to pre –anti VEGF days of PDT or laser.

• Does the use of the technology address any particular unmet need of the patient population?	No as long as ranibizumab is being offered. Maybe for a few who need many injections as this may lead to a more stable outcome, although most settle after a few injections but the condition can recur.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The risks are the same as for ranibizumab and that is mainly as the process of administration is an injection. So serious risks are retinal detachment and endophthalmitis but both have been found to be extremely rare in using injection therapy for myopia.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	In the Myrror study a baseline injection was given then patients reviewed monthly and were given repeat injections if need be through to week 44. The median number of injections was only 2 so it is likely if a patient was stable after the first few visits then monitoring intervals would be extended before week 44.
• If not, how could the results be extrapolated to the UK setting?	A review in The BJO in July 2014 by Tien et al. recommended one injection then 2 monthly reviews then if stable three month reviews unless the patient became symptomatic with distortion, using ranibizumab. This largely reflects UK practice although there might be one or two more visits at least initially.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Visual acuity was measured and good useful improvements of on average more than 10 letters have been shown. Reduction of symptoms such as distortion may not have been captured but are also important to patients.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA298]?	
22. How do data on real-world experience compare with the trial data?	The repair study done in the UK compared well with VA gains of mean 13.8 with 3.6 injections median 3 in 12 months. A Japanese study of long term outcomes Jap journal of Ophth 2015 S Gohen, found a good result but with some declining due to atrophy over time.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	More common in Asians
23b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions	
24. Are the clinical benefits of aflibercept similar to ranibizumab when they are used for the treatment of myopic choroidal neovascularisation?	Yes but no direct head to head comparison
25. Are the adverse events associated with aflibercept similar to those associated with ranibizumab when they are used for the treatment of myopic choroidal neovascularisation?	Yes
26. Are a similar number of injections required when using either aflibercept or ranibizumab for the treatment of myopic choroidal neovascularisation?	Probably as with ranibizumab on average it is low but could be even less, at least in the few who need more.
27. In clinical practice, is re-treatment of myopic choroidal neovascularisation mainly guided by visual acuity stabilisation criteria or by disease activity criteria, or by a combination of both?	Visual acuity, symptoms of distortion, OCT and sometimes FFA as it can be hard to tell on OCT alone and we would be concerned if a patient reports especially a change or increase in distortion.
28. If a patient with myopic choroidal neovascularisation did not respond to treatment with ranibizumab, would clinicians consider using aflibercept?	Yes
Key messages	

29. In up to 5 bullet points, please summarise the key messages of your statement.

- Trials have shown aflibercept is effective
- Biologically aflibercept is more potent than ranibizumab so may be more effective but no direct evidence for this
- Myopic CNV can affect working age patients so urgent effective treatment should be given
- The pathway and risks are the same
- Clinicians and patients would welcome a choice and option if response is not ideal with either.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Aflibercept for treating myopic choroidal neovascularisation [ID952]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Sobha Sivaprasad**
2. Name of organisation	**Moorfields Eye Hospital**
3. Job title or position	**Consultant Ophthalmologist**

4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Myopic choroidal neovascularisation (CNV) is a common vision-threatening complication of pathological (degenerative) myopia occurring in approximately 5–10% of people with this condition. Without treatment, the long-term prognosis of myopic CNV is poor; approximately 90% of patients will have a visual acuity of 20/200 or less after 5 years *(Wong TY et al 2015, Br J Ophth 2015;99:289).* The aim of treatment is to slow or stop progression of vision loss, and in addition, in a

	majority of patients can expect a clinically significant improvement in vision.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A visual acuity gain of 10 or more letters leads to an increase in the composite NEI-VFQ-25 scores by an amount judged to be clinically significant in diseases of the macula *(Bressler et al., Arch Ophthalmol 2009; Chang et al., Arch Ophthalmol 2007; Mangione et al. 2001)*
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is currently only one NICE-approved treatment for myopic CNV available (ranibizumab, TA298). It would be useful for both patients and clinicians to have a choice of treatments. Both treatments have similar efficacy in terms of mean visual acuity gains and proportions of patients gaining at least 15 letters. However, aflibercept and ranibizumab have different structures and modes of action, with aflibercept binding several growth factors in addition to VEGF-A; there is also some evidence from preclinical studies that aflibercept may offer greater durability of activity than ranibizumab, but this remains unproven for myopic CNV owing to lack of comparative clinical data.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Treatment is currently most often with ranibizumab according to NICE TA298. Photodynamic therapy with verteporfin is also a licensed option but rarely used since the advent of anti-vascular endothelial growth factor (VEGF) treatment. Surgical options (excision or macular translocation) are no longer used for this condition. Other VEGF inhibitors are not licensed for treating myopic CNV.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE has approved ranibizumab for treating choroidal neovascularisation associated with pathological myopia (TA298).
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is	The pathway of care for myopic CNV patients treated with anti-VEGF therapy is already well defined.

from outside England.)	
• What impact would the technology have on the current pathway of care?	The current pathway of care is intravitreal injection of anti-VEGF treatment (ranibizumab). The licensed posologies of both ranibizumab and aflibercept are similar for myopic CNV and the drugs have similar safety profiles; therefore there will be no negative impact on current pathway of care or increase in resource use. There are theoretical reasons why aflibercept may possibly offer a longer duration of action and tighter binding of VEGF-A compared to ranibizumab, related to its innovative structure (fusion protein) and mode of action through inhibition of multiple growth factors involved in neovascularisation (ranibizumab inhibits only VEGF-A), but at present there are no head-to-head clinical data to confirm or disprove this proposition.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes – please see above
• How does healthcare resource use differ between the technology and current care?	No difference in healthcare resource use to current care; theoretical possibility of increased durability compared to ranibizumab, related to different mode of action, but no comparative clinical evidence available (see above) and so injection frequencies are expected to be very similar in clinical practice
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics only, with experience of intravitreal injection
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment, as NHS facilities already set up for intravitreal injection
12. Do you expect the technology to provide clinically	See answers to Q9&10

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Not applicable to myopic CNV
• Do you expect the technology to increase health-related quality of life more than current care?	No evidence for this, as an effective treatment is available via TA298
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	None known
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Aflibercept has no additional practical requirements for administration over current standard NHS treatment with ranibizumab according to TA298. In terms of patients and healthcare professionals, it will therefore be no easier or more difficult to implement than current care.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing will be required over current standard NHS treatment with ranibizumab according to TA298
16. Do you consider that the use of the technology will result	It is recognised that the EQ-5D does not address all relevant aspects of health which may

in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	be improved by anti-VEGF treatment in myopic CNV *(Shah K et al. Important Aspects of Health Not Captured by EQ-5D: Views of the UK General Public. Office of Health Economics Research Paper 16/06. December 2016),* particularly related to sensory deprivation and resulting impact on mental health. If the QALY calculation relies on EQ-5D alone, these aspects may not be fully captured.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Aflibercept is innovative in that it is the only fusion protein licensed for use in retinal disease. Pre-clinical data have shown aflibercept binds VEGF many times more tightly than native receptors, and inhibits VEGF-A for twice as long as ranibizumab, but the clinical relevance of these data are uncertain *(Papadopoulos N et al.. Angiogenesis 2012; 15 (2): 171; Stewart MW, Rosenfeld PJ.. Br J Ophthalmol 2008 May;92(5):667).* In contrast to ranibizumab, aflibercept also binds several other growth factors in addition to VEGF-A (namely, placental growth factor, VEGF-B and Galectin-1). These additional growth factors are believed to be involved in pathological neovascularisation, although their specific role and the clinical benefits of their inhibition in myopic CNV remain undefined. Current evidence does not suggest a significant efficacy benefit for aflibercept over ranibizumab in myopic CNV but it is very useful for patients and clinicians to have a choice of treatments, especially where these treatments differ in mode of action.
• Is the technology a ‘step-change’ in the management of the condition?	See above
• Does the use of the technology address any particular unmet need of the patient population?	See above
18. How do any side effects or adverse effects of the	Clinical studies in myopic CNV show aflibercept to be well-tolerated with a safety profile

technology affect the management of the condition and the patient's quality of life?	similar to that seen in its other licensed indications, where extensive clinical trial and real world evidence has been published over several years of worldwide use. There is no evidence of a difference in safety profile between aflibercept and current standard of care, ranibizumab, in any indication.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	The pivotal trial Myrror *(Ikuno Y et al, Ophthalmology. 2015 Jun;122)* reflects the licensed posology for aflibercept in myopic CNV and hence likely usage within the NHS. Concerning study population, Myrror was conducted in a wholly East-Asian population which is not reflective of the UK population. However, the European Medicines Agency concluded, following a systematic review, that aflibercept treatment is not sensitive to Asian versus non-Asian race and so extrapolation of the data to a European population was appropriate (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002392/WC500198362.pdf)
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important clinical outcomes in myopic CNV are (1) improvement in visual acuity from baseline (2) number of aflibercept injections required to achieve this improvement and (3) the safety profile of aflibercept in myopic CNV. All these outcomes were measured in the pivotal study, Myrror *(Ikuno Y et al, Ophthalmology. 2015 Jun;122).* In this study 122 patients were randomized to intravitreal aflibercept (n = 91) or sham (n

	= 31). Baseline demographics were similar across groups. At week 24, patients in the intravitreal aflibercept and sham groups gained 12.1 and lost 2 letters, respectively (P < 0.0001). By week 48, patients in the intravitreal aflibercept and sham/intravitreal aflibercept groups gained 13.5 and 3.9 letters. Patients in the intravitreal aflibercept group received 2 injections (median) in the first study quarter (week 0-8). Median number of injections in quarters 2 to 4 was 0. Patients in the "sham/intravitreal aflibercept" group received 2 and 1 (median) intravitreal aflibercept injections in quarters 3 and 4. Central retinal thickness improved in parallel with visual gains. Incidence of ocular adverse events was similar in both groups through week 48 (37.4% vs. 38.7); most were assessed by investigators as mild. No deaths occurred.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA298]?	No
22. How do data on real-world experience compare with the	Other than the pivotal phase III licensing trial Myrror *(Ikuno Y et al, Ophthalmology. 2015 Jun;122(6))* there are limited published data on use of aflibercept in myopic CNV. Brue et

trial data?	al *(Eye (Lond). 2016 Jan; 30(1): 139*), is a single centre long term retrospective study in 38 patients followed for a minimum of 18 months. Overall, 55% (21/38) of the patients achieved resolution of their myopic CNV with a single aflibercept injection and vision gains were broadly in line with Myrror, with the best vision gains in younger patients (<50 years), who also required fewer injections than older patients (mean 1.8 vs 3.6). Korol et al *(Clin Ophthalmol. 2016; 10:2223)* is a prospective pilot study of 31 eyes, showing improvements over 12 month period with 2.6 injections (similar to Myrror which had median 3.0 injections over 48 weeks). Safety in both studies was in line with the Myrror pivotal study and other studies of aflibercept in retinal disease.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
24. Are the clinical benefits of aflibercept similar to ranibizumab when they are used for the treatment of myopic choroidal neovascularisation?	There are no head-to-head comparative data available, but based on qualitative comparison of the pivotal studies, aflibercept can be expected to offer very similar clinical benefits to ranibizumab, with a similar number of injections.

25. Are the adverse events associated with aflibercept similar to those associated with ranibizumab when they are used for the treatment of myopic choroidal neovascularisation?	Yes
26. Are a similar number of injections required when using either aflibercept or ranibizumab for the treatment of myopic choroidal neovascularisation?	Yes, injection numbers are likely to be similar. The RADIANCE study of ranibizumab in myopic CNV showed patients required a median of either 4 or 2 injections in year 1, depending on retreatment criteria *(Wolf S et al, Ophthalmology 2014;121:682);* in the Myrror study of aflibercept in myopic CNV, patients required a median of 3 injections in 48 weeks.
27. In clinical practice, is re-treatment of myopic choroidal neovascularisation mainly guided by visual acuity stabilisation criteria or by disease activity criteria, or by a combination of both?	Both will be taken into account.
28. If a patient with myopic choroidal neovascularisation did not respond to treatment with ranibizumab, would clinicians consider using aflibercept?	I am not aware of any published clinical data on switching between anti-VEGF therapies in myopic CNV, but if response to ranibizumab is suboptimal but continued treatment with an anti-VEGF is still indicated, it would be appropriate to offer a switch to aflibercept owing to aflibercept's different mode of action.
Key messages	

29. In up to 5 bullet points, please summarise the key messages of your statement.

- Although the overall UK prevalence of myopic CNV (mCNV) is low, amongst people with high (pathological) myopia, the prevalence of mCNV is relatively high (around 5-10%) in the high myopic population. Without anti-VEGF treatment, mCNV carries a very poor prognosis, with 90% of patients experiencing a reduction in visual acuity of 20/200 or less after 5 years. Many people with myopic CNV are of working age with dependent families.
- Aflibercept is a highly effective treatment for myopic CNV, providing clinically significant gains in vision (mean improvement in BCVA of 13.5 letters and 50% of patients achieving gains of 15 or more letters, with a median of only 3 injections at 48 weeks) and has a safety profile similar to current standard of care.
- An effective anti-VEGF agent (ranibizumab) is current standard of care for myopic CNV in the UK, in line with TA298. There are no other NICE-approved options for this condition. There are no head-to-head comparative data available, but based on qualitative comparison of pivotal studies, aflibercept can be expected to offer very similar clinical benefits to ranibizumab, with a similar number of injections.
- Aflibercept is an innovative molecule, the only fusion protein licensed in retinal disease. As well as a different structure, it has a different mode of action to ranibizumab in that it binds to a wider range of growth factors with a role in pathological neovascularisation. NHS use of aflibercept would not require more resources than current standard of care, and its approval by NICE would offer valuable choice to patients and clinicians.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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FAST TRACK APPRAISAL: COST COMPARISON CASE

Aflibercept for treating myopic choroidal neovascularisation

Produced by Aberdeen HTA Group

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AE	Adverse event
AMD	Age-related macular degeneration
ATA	Abbreviated technology appraisal
ATE	Arterial thromboembolic event
BCVA	Best corrected visual acuity
BRVO	Branch retinal vein occlusion
CI	Confidence interval
CHMP	Committee for Medicine Products for Human Use
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
CNV	Choroidal neovascularisation
D	Dioptres
DME	Diabetic macular edema
DMO	Diabetic macular oedema
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
EOT	End of trial
EQ5D	Euroqol 5 dimensions
ERG	Evidence review group
ETDRS	Early treatment diabetic retinopathy study
FA	Fluorescein angiography
FAD	Final appraisal determination
HRQoL	Health-related quality of life
IOP	Intra ocular pressure
ITC	Indirect treatment comparison
IVT	Intravitreal
LOCF	Last observation carried forward
LTFU	Long-term follow-up
mCNV	Myopic choroidal neovascularisation
MO	Macular oedema
NEI VFQ-25	National eye institute visual functioning questionnaire - 25

NHS	UK National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OCT	Ocular coherence tomography
PDT	Photodynamic therapy
PlGF	Placental growth factor
PM	Pathological myopia
PRN	Pro re nata
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RVO	Retinal vein occlusion
SD	Standard deviation
SmPC	Summary of product characteristics
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event
VA	Visual acuity
vPDT	Verteporfin photodynamic therapy
VEGF	Vascular endothelial growth factor

1 Evidence of comparable health benefits and safety

1.1 Is the technology pharmacologically similar to the comparator(s)?

Vascular endothelial growth factor (VEGF) is a potent, endothelial cell mitogen that stimulates proliferation, migration and tube formation, thus promoting angiogenic growth of new blood vessels.[1-3] VEGF has been shown to play an important role in the development and progression of neovascularization in the eye, including in eyes with myopic choroidal neovascularisation (mCNV).[4-6] Eyes with active mCNV have higher levels of VEGF in the aqueous humour than control eyes.[7] Aflibercept and ranibizumab are both anti-VEGF therapies.

Aflibercept (Eylea®, Bayer plc, Berkshire, UK) is a recombinant fusion protein formed by fusing portions of human VEGF receptor 1 and 2 extracellular domains and the Fc portion of human IgG1. It has a longer half-life in the eye than ranibizumab or bevacizumab and a higher binding affinity to VEGF-A, as well as other VEGF variants, including VEGF-B and placental growth factors (PlGF) 1 and 2.[8-12] Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF and, thus, can inhibit the binding and activation of these related VEGF receptors.[10, 12, 13] Aflibercept is the only available anti-VEGF drug that acts against PlGF.[12] Adverse events classified as very common (i.e. ≥1/10) associated with aflibercept include reduced visual acuity, conjunctival haemorrhage and eye pain. Common adverse events (i.e. ≥1/100 to < 1/10) include detachment of the retinal pigment epithelium, retinal degeneration, vitreous haemorrhage and cataract.

Ranibizumab (Lucentis®, Novartis Europharm Ltd, Camberley, UK) is a humanised monoclonal antibody fragment produced in Escherichia coli cells by recombinant DNA technology.[14] Ranibizumab is a high affinity recombinant antigen that neutralises all isoforms of VEGF-A. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the pathophysiology of mCNV. As ranibizumab binds with high affinity to the VEGF-A isoforms, it prevents binding of VEGF-A to its receptors.[15] Very common eye-related adverse reactions to ranibizumab include

vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters and conjunctival haemorrhage.

The Committee for TA298 considered that anti-VEGF treatments were a substantial improvement over previous treatments and that this improvement applied to the class of drugs.[16]

Verteporfin photodynamic therapy (vPDT) was specified in the NICE final scope as a comparator but was not included in the company's submission. Verteporfin (Visudyne®, Novartis Europharm Ltd, Camberley, UK) is not pharmacologically similar to aflibercept; it is a photosensitising drug which is injected intravenously and activated focally by illumination with light from a laser source at a wavelength corresponding to an absorption peak of the drug. This causes a photochemical reaction which results in direct cellular injury to vascular endothelial cells and subsequent vessel thrombosis, thereby inducing occlusion of the CNV.[17] Evidence from the VIP trial showed that vPDT stabilised visual acuity but did not improve it at the 24-month follow-up.[18, 19] Adverse events associated with vPDT include visual disturbance, injection site events, allergic reactions, photosensitivity reactions and chorioretinal atrophy.[18-21]

1.2 Does the technology have a marketing authorisation in the UK? And is the marketing authorisation the same as the NICE-recommended comparator(s)?

Aflibercept has UK marketing authorisation (since 28th October 2015) for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to macular oedema secondary to RVO (BRVO or CRVO), visual impairment due to diabetic macular oedema (DMO) and visual impairment due to myopic choroidal neovascularisation (CNV).

Ranibizumab has UK marketing authorisation for adults for the treatment of neovascular (wet) AMD, visual impairment due to DMO and visual impairment due to macular oedema secondary to retinal vein occlusion (BRVO or CRVO), visual impairment due to choroidal neovascularisation (CNV). Ranibizumab was approved by NICE for this indication on 27th November 2013 (TA298).[16]

The Eylea® summary of product characteristics (SmPC) specifies "myopic choroidal neovascularisation",[22] and the Lucentis® SmPC states "choroidal neovascularisation".[14]

Verteporfin photodynamic therapy has UK marketing authorisation for the treatment of adults with exudative (wet) age-related macular degeneration with predominantly classic subfoveal CNV or adults with subfoveal CNV secondary to pathological myopia.

The company's decision problem was not consistent with the comparators specified in the final scope issued by NICE, in that the company included ranibizumab as a comparator but did not include vPDT. The company's justification, that vPDT is not standard treatment in the NHS for mCNV, was previously noted by the ERG involved in TA298[16] and is further acknowledged by the ERG in this assessment (the same ERG in both cases). In addition, vPDT is indicated for subfoveal mCNV only and, therefore, suitable for only part of the population of adults with visual impairment due to mCNV which is specified in the scope (albeit the proportion of patients with subfoveal mCNV – as compared to juxtafoveal or extrafoveal mCNV – tends to be at least half of the overall population with mCNV.[23]

1.2.1 Is the company's decision problem consistent with the scope?

Table 1 presents a comparison of the NICE final scope and the decision problem addressed by the company.

Table 1 Comparison of NICE final scope and decision problem addressed by the company

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	Adults with visual impairment due to myopic choroidal neovascularisation	Adults with visual impairment due to myopic choroidal neovascularisation	None	None
Intervention	Aflibercept	Aflibercept	None	None
Comparators	• Ranibizumab • Verteporfin photodynamic therapy	• Ranibizumab	Bayer considers that the most appropriate comparator is ranibizumab (Lucentis). Ranibizumab (an alternative anti-VEGF therapy) has been appraised by NICE in this indication (TA 298)[16] Verteporfin photodynamic therapy (vPDT) is not an appropriate comparator as it is not standard treatment within the NHS for mCNV. It was acknowledged by the Evidence Review Group (ERG) during appraisal of ranibizumab in this indication, that vPDT was rarely used in clinical practice.	The ERG agrees that ranibizumab is the most appropriate comparator and that vPDT is not an appropriate comparator as it is rarely used in UK clinical practice for mCNV

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Outcomes	• Best corrected visual acuity (affected eye) • Best corrected visual acuity • (both eyes) • Contrast sensitivity • Adverse effects of treatment • Health-related quality of life	• Best corrected visual acuity (affected eye) • Adverse effects of treatment • Health-related quality of life In addition to the outcomes proposed in the scope, Bayer presented on: • Proportion of patients gaining ≥15 ETDRS letters at week 24 from baseline • Mean change from baseline in BCVA score at each visit and at week 48 • Proportion of patients gaining or losing ≥15, ≥10 or ≥5 ETDRS letters at week 48 from baseline • Ad-hoc analysis of exposure (as relevant to the indirect comparison with ranibizumab).	Bayer will not be presenting data on contrast sensitivity, as listed in the pre-invitation scope, as this was not collected in the pivotal study. Bayer will also not be presenting data on best corrected visual acuity (both eyes) as in the pivotal study, only one eye was designated as the study eye and BCVA (both eyes) was not assessed. Further outcome data are presented to further report on the efficacy of aflibercept. Exposure is presented as it is relevant to the indirect comparison with ranibizumab.	The ERG agrees with the company's justification for not presenting data on contrast sensitivity at it is not used in clinical practice to make decisions. In the case of BCVA (both eyes), the ERG considers that it would be useful to have scores for both eyes, but that the affected eye is sufficient information for the purposes of testing equivalence
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.	In light of the consultation on the ATA process for appraisal, Bayer considers that the most appropriate economic evaluation should be based on a cost-	As discussed at the decision problem meeting	The ERG considers the company's approach to be justified because of similar efficacy and safety.

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
	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 will be taken into account. Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.	comparison analysis compared to standard of care ranibizumab		

1.2.2 Does the company's decision problem cover all or only part of the technology's marketing authorisation for this indication?

The company's decision problem covers all of the marketing authorisation for this indication.

1.2.3 Does the company's decision problem cover all or only part of the population for whom the comparator has been recommended by NICE?

NICE TA298[16] states that "ranibizumab is recommended as an option for treating choroidal neovascularisation associated with pathological myopia when the manufacturer provides ranibizumab with the discount agreed in the patient access scheme". The Lucentis® summary of product characteristics states that it is indicated for adults and states that "The safety and efficacy of Lucentis in children and adolescents below 18 years of age have not been established".[14] However, it is worth noting that myopic choroidal neovascularization is extremely rare in children/young people under 18 years of age. Verteporfin PDT was specified in the NICE final scope as a comparator. Visudyne® is indicated for "adults with subfoveal choroidal neovascularisation secondary to pathological myopia". Thus, this comparator is only indicated for part of the population for whom aflibercept is indicated.

1.3 Has the company made a comparison to a relevant NICE-recommended comparator?

Yes. Ranibizumab was recommended by NICE on 27th November 2013 "as an option for treating visual impairment due to CNV secondary to pathological myopia when the manufacturer provides ranibizumab with the discount agreed in the patient access scheme"[16] Ranibizumab is the only anti-VEGF therapy currently approved by NICE for this indication. Bevacizumab is another anti-VEGF therapy that was used off-license in clinical practice prior to the approval of ranibizumab but is not licensed for any eye conditions. Its use has now all but ceased following the approval of ranibizumab for this indication. Verteporfin PDT is appropriately licensed for this condition (subfoveal CNV only) and was widely used in clinical practice in the past. However, it has now been superseded by anti-VEGF therapies which have showed superior gains in visual acuity[24] without the development of chorioretinal atrophy associated with vPDT.[20, 21]

1.4 Has the company positioned the technology as expected in the treatment pathway and is the population(s), and any subpopulation(s), defined as expected?

Yes. The company has positioned aflibercept as expected in the proposed treatment pathway. There are currently no definitive guidelines for treating mCNV. The company's submission reproduced a treatment algorithm for diagnosing and treating mCNV, proposed by Wong 2014,[23] and based on a summary of the current treatment options for mCNV (i.e. laser photocoagulation, vPDT, ranibizumab, bevacizumab, aflibercept). The ERG agrees that the treatment algorithm is an accurate reflection of current clinical practice in the NHS. The company's use of an immediate anti-VEGF injection as first-line therapy is consistent with the proposed algorithm and current UK practice; in the NHS, this can take place on the same day as the diagnosis or within a few weeks. **The ERG agrees with the company's follow-up monitoring strategy; the company's version of the algorithm does not specify time points for monitoring and the monitoring of disease activities strategy proposed by Wong et al states: monthly for months 1 and 2 and then at least three-monthly in the first year. The ERG clinical expert noted that the stage of disease at which patients present is not known in NHS clinical practice. It is, therefore, unclear if patients in the NHS are assessed at a similar stage as those recruited from different countries in the trials.**

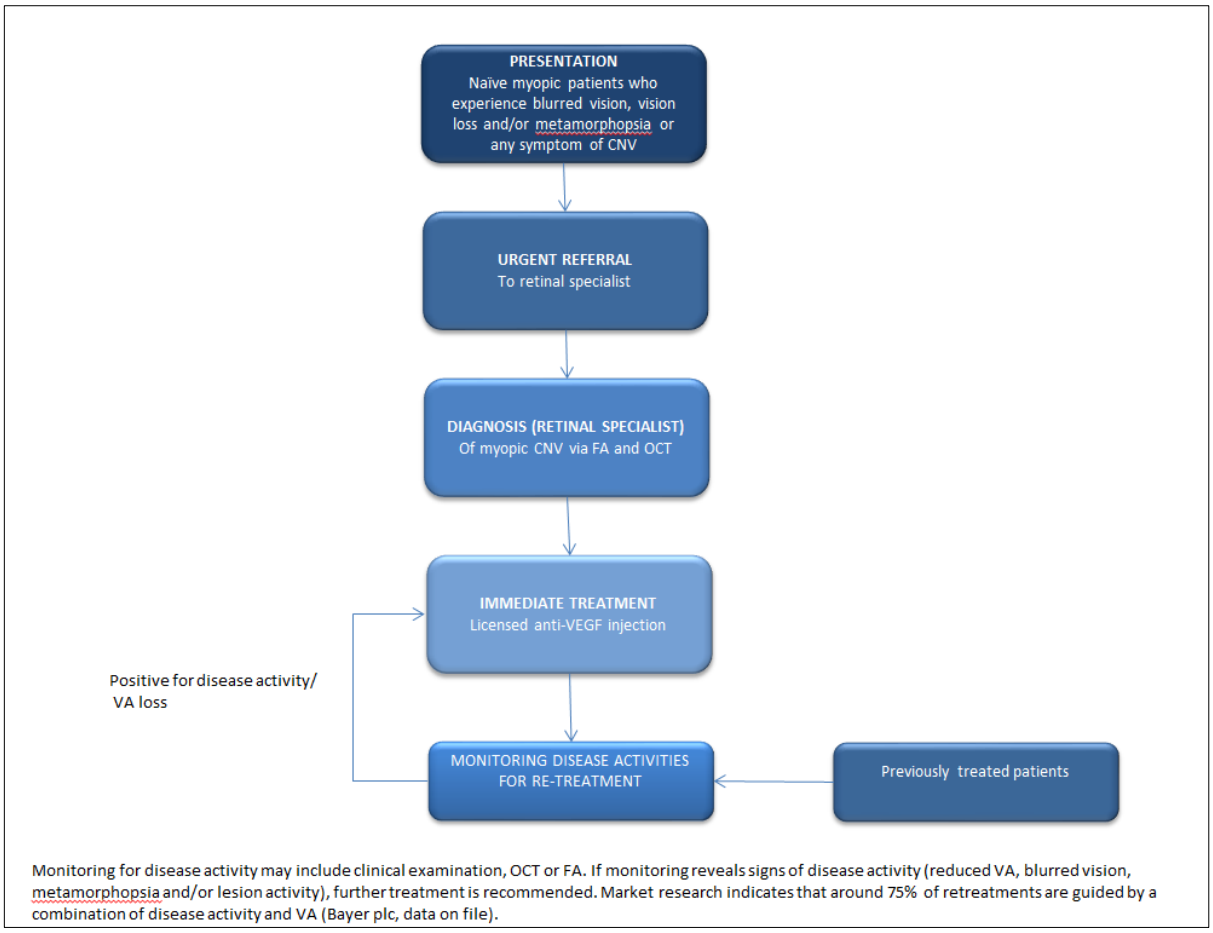

Figure 1 Company's proposed treatment pathway in mCNV, adapted from Wong et al 2015 (reproduced from Figure 1 of Document B of the company's submission)

The company's definition of the population is as would be reasonably expected, based on the marketing authorisation of aflibercept.

1.5 Is the claim for clinical similarity supported through the scoping consultation? (Refer back to the scope and decision problem pro-forma)

The company claimed clinical similarity during the decision problem phase. In their decision problem pro-forma they stated:

"Bayer considers that the appraisal of aflibercept for treating myopic choroidal neovascularisation could be conducted under the proposed Abbreviated Technology Appraisal (ATA) process. Whilst the process for conducting such an appraisal has not been finalised and published, Bayer would be happy to proceed on this basis, subject to NICE agreement. Aflibercept in this indication would appear to meet the criteria

for such an appraisal – 'We propose to use this process for new technologies that provide similar or greater health benefits, compared with existing NICE-recommended technologies at a similar or lower cost' https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/abbreviated-technology-appraisal-process-consultation".

1.6 Are the outcome measures and definitions of the trials for the treatment the same to those for the NICE-recommended comparator(s)? Or are they at least similar/comparable?

The outcomes specified in the NICE final scope and considered by the company were consistent with the outcomes considered in RADIANCE/TA298 (i.e. BCVA for the affected eye, adverse effects of treatment, HRQoL).[16, 25] In addition, the RADIANCE trial considered the proportion of participants with gain or loss of 5, 10 and 15 letters, which proved to be a major driver of the economic model. The company provided the relevant data to the ERG at clarification. The scopes for both the present appraisal and TA298 also specified BCVA (both eyes) and contrast sensitivity as outcomes but neither submission considered them. **The ERG agrees that it was appropriate for the company not to consider these outcomes, as (i) contrast sensitivity is not used in clinical practice to make decisions and (ii) whilst it would be clinically useful to have information about BCVA in both eyes, the affected eye is probably sufficient for the purposes of testing equivalence.**

RADIANCE has two ranibizumab arms, one with retreatment based on disease activity and one based on visual acuity stabilisation.[25] Details are presented in Table 2. The company stated in its clarification response that neither ranibizumab arm is particularly similar to the aflibercept arm of MYRROR in terms of retreatment criteria. **The ERG clinical expert is of the opinion that the disease activity arm in RADIANCE - where vision impairment is one of the criteria of disease activity - is most comparable with the aflibercept arm in MYRROR.[26]**

The company conducted risk of bias assessments of the MYRROR and RADIANCE [25, 26] trials based on the Cochrane risk of bias domains. **The ERG is satisfied that**

randomisation and masking were adequate in both trials and that they were, in general, at low risk of bias.

Table 2 Study characteristics of MYRROR and RADIANCE

	MYRROR[26]	**RADIANCE[25]**
Study design	Phase III, multicentre, randomised, double-masked, sham-controlled study	Phase III, multicentre, randomised, double-masked, active-controlled study
Location/no of centres	20 centres in Asia (Hong Kong, Japan, Republic of Korea, Singapore, Taiwan)	76 centres worldwide (Austria, Canada, France, Germany, Hong Kong, Hungary, India, Italy, Japan, Latvia, Lithuania, Poland, Portugal, Singapore, Slovakia, South Korea, Spain, Switzerland, Turkey, UK)
Intervention	**Intravitreal aflibercept 2.0mg** Day 1-week 20: IVT aflibercept at baseline, then PRN dosing every 4 weeks of IVT aflibercept 2mg or sham injection, subject to meeting at least one of the following re-treatment criteria: (i) Reduction in VA by ≥5 letters from the previous ETDRS examination; (ii) Increase in CRT >50μm from the time of the previous examination, new or persistent cystic retinal changes, subretinal fluid, or pigment epithelial detachment, and new or persistent CNV or bleeding; or	**Intravitreal ranibizumab 0.5mg (guided by disease activity criteria or VA stabilisation criteria)** Day 1: Both ranibizumab groups received IVT ranibizumab 0.5mg **Disease activity group**: from month 1 onwards, dosing was stopped if no disease activity was seen (i.e. vision impairment, attributable to intra or subretinal fluid or active leakage secondary to PM as assessed by OCT and/or FA). Treatment was resumed when the disease activity criterion was fulfilled and continued until no disease activity was seen

	MYRROR[26]	RADIANCE[25]
	(iii) Deemed necessary by the investigator based on their clinical impression or diagnostics performed in the context of standard medical care. Week 24-week 44: PRN dosing of IVT aflibercept 2mg or sham injection, subject to meeting at least one of the above retreatment criteria	**Stabilisation group**: IVT ranibizumab 0.5mg at month 1. For the following months, treatment was stopped if the stabilisation criterion for BCVA was fulfilled (i.e. no change in BCVA as compared with the two preceding monthly visits). Treatment was resumed with monthly injections when there was a loss of BCVA due to disease activity and was continued until stable BCVA was re-established for three consecutive monthly assessments
Comparator	**Sham injections** Day 1-week 20: sham injection at baseline, then sham injections every 4 weeks Week 24-week 44: mandatory IVT aflibercept 2mg, then PRN dosing every 4 weeks of IVT aflibercept 2mg or sham injection, subject to meeting at least one of the above retreatment criteria	**vPDT** Day 1: 6mg/m^2 intravenously followed by a standard fluence rate of 600 mW/cm^2 delivered for 83 seconds with a light dose of 50 J/cm^2 Months 3-11: patients with disease activity could receive ranibizumab 0.5mg, vPDT, or ranibizumab 0.5mg plus vPDT. Treatment was stopped if no disease activity was seen. Treatment was resumed when the above disease activity criterion was fulfilled and continued until no disease activity was seen

	MYRROR[26]	**RADIANCE[25]**
No of participants randomised	Aflibercept 2.0mg: n=91 Sham: n=31 Total: n=122	Ranibizumab 0.5mg (disease activity criteria): n=116 Ranibizumab 0.5mg (stabilisation criteria): n=106 vPDT: n=55 Total: n=277
Main inclusion criteria	≥18 years of age High myopia, defined as ≤-6.0 dioptres or axial length of ≥26.5mm Active (defined by leakage on fluorescein angiography) subfoveal or juxtafoveal (within 1-199μm from the centre of the fovea) myopic CNV BCVA of 73-35 letters (ETDRS equivalent of 20/40-20/200) at 4m	≥18 years of age Diagnosis of active CNV secondary to PM in the study eye using the following criteria: • Presence of myopia greater than −6 D of spherical equivalence • Ocular ultrasonography or biometry demonstrating anterio-posterior elongation measurement ≥ 26 mm • Presence of posterior changes compatible with the PM seen by fundus ophthalmoscopy and fundus photography • Presence of active leakage from CNV seen by FA • Presence of intra- or subretinal fluid seen or increase of CRT by OCT At least one of the following lesion types present in the study eye: • Subfoveal (presence of abnormal neovasculature in the avascular central fovea)

	MYRROR[26]	RADIANCE[25]
		• Juxtafoveal (presence of abnormal neovasculature not under the centre of the fovea but < 200 μm from the centre) with involvement of the central macular area • Extrafoveal (presence of abnormal neovasculature more than 200 μm from the centre of the fovea) with involvement of the central macular area • Margin of the optic disc (presence of abnormal neovasculature at peripapilar area) with involvement of the central macular area BCVA of ≥ 24 letters and ≤ 78 letters tested at 4 m starting distance using ETDRS-like BCVA chart Visual loss only due to the presence of any eligible types of CNV related to PM based on clinical ocular findings (described at inclusion criteria of the study eye), FA and OCT
Main exclusion criteria	Only 1 functional eye Recurrent myopic CNV or aphakia (including pseudophakic patients) in study eye	History of (a) stroke, (b) pan-retinal or focal/grid laser photocoagulation with involvement of the macular area in the study eye at any time, (c)

	MYRROR[26]	RADIANCE[25]
	CNV with an origin other than PM in study eye Any iris neovascularisation or vitreous haemorrhage in either eye Uncontrolled glaucoma, defined as intraocular pressure≥25mmHg on optimal medical regimen Previous filtration surgery in either eye Pregnant or nursing women	intraocular treatment with corticosteroids or intraocular surgery in past 3 months & anti-VEGF or vPDT treatment at any time in study eye, or (d) hypersensitivity to ranibizumab or verteporfin or drugs of a similar class Presence of CNV secondary to any cause other than PM Presence of active infectious disease or intraocular inflammation, active or suspected periocular infection, confirmed IOP≥25mmHg, or iris neovascularisation either eye at enrolment Pregnant or nursing women
Primary outcome	Mean change in BCVA from baseline to week 24	Mean average change in BCVA from baseline to month 1 through month 3 (defined as mean difference of BCVA versus baseline over all monthly post-baseline assessments from month 1 to month 3)
Other outcomes	Proportion of patients gaining ≥15 letters at week 24 Absolute change or mean change from baseline in CRT (as assessed by OCT at week 24 and week 48) Absolute change in CNV lesion size from baseline (as assessed by FA at week 24 and week 48)	Mean average change in BCVA from baseline to month 1 through month 6 Mean change in BCVA from baseline over time Proportion of patients gaining ≥10 and ≥15 ETDRS letters (or reaching 84 letters) at month 12

	MYRROR[26]	RADIANCE[25]
	Proportion of patients gaining ≥15 letters from baseline at week 48 Proportion of patients gaining ≥10 letters from baseline at week 24 and week 48 Leakage from CNV (as assessed by FA from baseline to week 24 and week 48) Change in EQ-5D score from baseline to week 24 and week 48 Change in 25-item NEIVFQ 25 total score from baseline to week 24 and week 48	Proportion of patients losing ≥10 and ≥15 ETDRS letters at month 12
Study duration	48 weeks	12 months
No of injections	**Aflibercept group:** Weeks 0-8: Median 2 (mean 2) Weeks 12-20: Median 0 (mean 0.9) Weeks 24-32: Median 0 (mean 0.8) Weeks 36-44: Median 0 (mean 0.5) Weeks 0-48: Median 3 (mean 4.2) **Sham group:** Weeks 0-48: Median 3 (mean 3) Weeks 24-32 (3rd quarter):Median 2 (mean 1.8) Weeks 36-44 (4th quarter): Median 1 (mean 1.2)	**Disease activity group:** Total 404 Mean (SD) 3.5 (3) Median 2 **VA stabilisation group:** Total 488 Mean (SD) 4.6 (2.6) Median 4 **vPDT group:** Total 131 Mean (SD) 2.4 (2.6) Median 2

1.7 Strength of the clinical evidence provided by the company for clinical similarity

1.7.1 Summary of evidence of aflibercept

The MYRROR study provides the only RCT evidence for use of aflibercept in treating mCNV in comparison to sham-controlled injections.[26] MYRROR randomised 122 patients (91 to aflibercept, 31 to sham) across 20 study centres in Asia. Baseline

characteristics were balanced across treatment groups. The primary outcome was mean change in BCVA from baseline to 24 weeks. Participants were followed until 48 weeks, to allow safety data to be collected alongside additional longer-term outcome data.

By 24 weeks, the aflibercept group showed an increase of 12.1 letters from baseline, while the sham group had lost two letters, resulting in a greater improvement in the aflibercept group of 14.1 ETDRS letters (95% CI 10.8, 17.4; p-value < 0.0001) adjusting for country and baseline BCVA. Aflibercept was significantly better in the proportion of patients with ≥5, ≥10 and ≥15 ETDRS letters, and had fewer participants with ≥5, ≥10, ≥15 ETDRS letter loss (Table 3).

Table 3 Outcome estimates from MYRROR (full analysis set, LOCF)[26]

Week 24	Aflibercept (n =90)	Sham (n = 31)	Difference	95% CI	p-value
Mean change in BCVA baseline to 24 weeks	12.1	-2	14.1	(10.8, 17.4)	<0.0001
Proportion ≥15 letters gain (%)	38.9	9.7	29.2	(14.4, 44.0)	<0.001
Proportion ≥10 letters gain (%)	63.3	12.9	[redacted]	[redacted]	[redacted]
Proportion ≥5 letters gain (%)	83.3	19.4	[redacted]	[redacted]	[redacted]
Proportion ≥5 letters loss (%)	3.3	35.5	[redacted]	[redacted]	[redacted]
Proportion ≥10 letters loss (%)	0	25.8	[redacted]	[redacted]	[redacted]
Proportion ≥15 letters loss (%)	0	6.5	[redacted]	[redacted]	[redacted]
NEI VFQ-25 mean change baseline to 24 weeks	3.14([redacted])	-2.58 ([redacted])	5.21	(1.25, 9.18)	0.010
EQ5D mean change baseline to 24 weeks	0.0187	0.0341	-0.0045	(-0.058, 0.049)	0.8690

1.7.2 Critique of evidence for aflibercept

MYRROR was conducted on an entirely Asian population which may cause some concern regarding the applicability to a UK population.[26] **The ERG clinical opinion is that the effect would not differ between ethnic groups.** This view is shared by the CHMP, who agreed the results of MYRROR can be extrapolated to the European population, and the European Medicines Agency accepts the results of MYRROR as representative for mCNV patients in Europe, regardless of ethnicity. This issue is discussed further when describing the indirect treatment comparison.

Another issue with MYRROR is that efficacy data for aflibercept versus sham is only available up until 24 weeks, as after that time sham patients were switched to aflibercept. It would be better to have longer term outcome data; however, **the ERG opinion is that most of the effect will occur in the first few months.** Safety data are available up until 48 weeks.

1.7.3 Summary of evidence against its comparators using an indirect treatment comparison

There are no head to head trials of aflibercept against its comparator ranibizumab. The RADIANCE trial provides evidence of ranibizumab versus verteporfin photodynamic

therapy (vPDT).[25] The latter is not considered a relevant comparator in this appraisal as ranibizumab was approved by NICE and vPDT has been phased out of clinical practice. The VIP study [18, 19]compares vPDT with placebo and can be used as the link between MYRROR and RADIANCE in an indirect treatment comparison, even though we are not directly interested in the results of vPDT.

A network was established using the MYRROR, RADIANCE AND VIP trials.[18, 19, 25, 26] RADIANCE had two ranibizumab arms versus vPDT.[25] One group received ranibizumab injection on day 1 and month 1 with retreatment based on visual acuity stabilisation criteria. The second ranibizumab arm received injection on day 1 and, starting in month one, retreatment was based on disease activity criteria. These two arms are referred to ranibizumab visual acuity and ranibizumab disease activity, respectively. In the VIP trial, patients were randomised to either vPDT or placebo.[18, 19]

Table 4 ITC results for mean 3-month gain in BCVA

	Mean	**SD**	**95% low**	**95% high**
vPDT vs placebo	1.05	2.29	-3.47	5.50
Ranibizumab visual acuity vs placebo	11.75	2.75	6.31	17.09
Ranibizumab disease activity vs placebo	12.15	2.72	6.76	17.43
Aflibercept vs placebo	13.09	2.04	9.10	17.08
Aflibercept vs vPDT	12.04	3.05	6.10	18.00
Aflibercept vs ranibizumab visual acuity	1.34	3.40	-5.35	8.00
Aflibercept vs ranibizumab disease activity	0.94	3.38	-5.67	7.56
BCVA, Best Corrected Visual Acuity; ITC, indirect treatment comparison; SD, standard deviation; vPDT, verteporfin photodynamic therapy.				

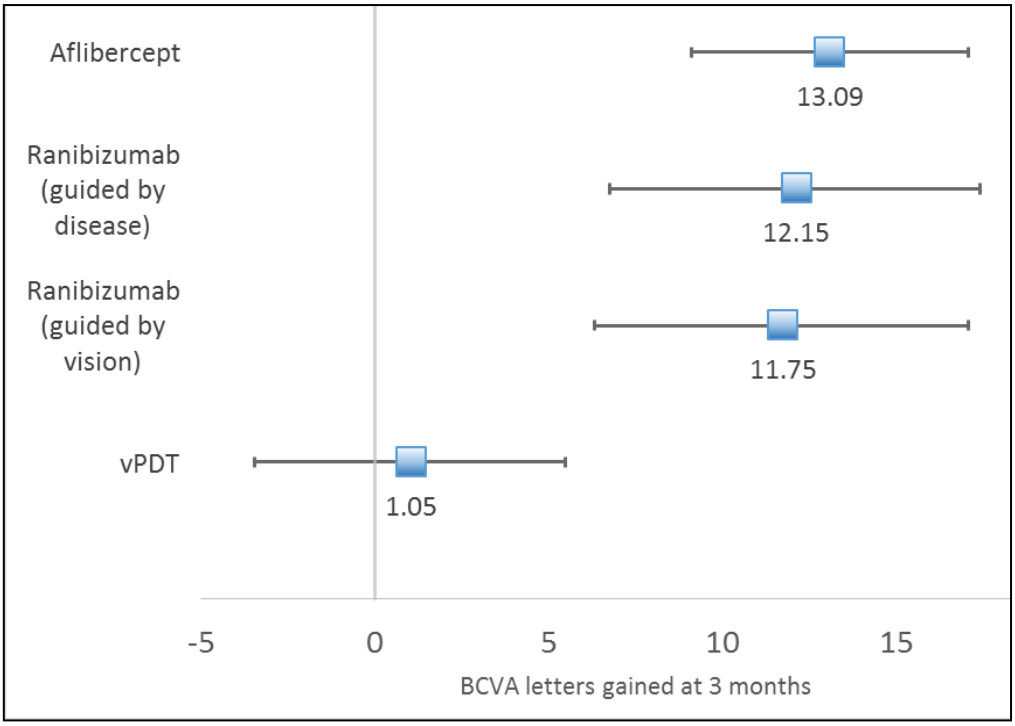

Figure 2 ITC results for mean 3-month gain in BCVA (reproduced from Figure 8 of Document B of the company's submission)

The network considered the 3-month mean BCVA change in all treatments versus placebo and versus aflibercept. Three months was used as, in RADIANCE,[25] the vPDT arm switched to ranibizumab after 3 months, so the only common endpoint that could be considered was at 3 months. Within MYRROR,[26] no 3-month end point data were collected, but data were collected at 12 and 16 weeks, so a weighted average was used (75% at 12 weeks and 25% of 16 week assessments). The results of the indirect treatment comparison are shown in Table 4 (source Table 23, Document B) and Figure 2 (for comparison with placebo). Both aflibercept and ranibizumab were found to be significantly better than placebo, but not significantly different from each other.

1.7.4 Critique of the indirect treatment comparison

The trials are similar in the majority of patient demographics but the biggest concern for heterogeneity is the ethnic distribution. Within VIP, 91% are Caucasian, while in RADIANCE it is 57% Caucasian.[25] The MYRROR study was conducted in an entirely Asian population (Japan, Hong Kong, Singapore, South Korea and Taiwan).[26] The company conducted their own analysis to test the sensitivity of effect in different ethnic groups. Trials using aflibercept for other approved conditions were considered.

Data on 1104 participants, 80% Caucasian, were obtained. The company reported that absolute treatment differences between Asian people and white people showed similar efficacy trends between groups, with overlapping confidence intervals (no actual data given). The European Medicines Agency (EMA) accepted that the efficacy results of MYRROR are representative for mCNV patient populations in Europe regardless of ethnicity. **The ERG clinical expert's opinion is that the efficacy of aflibercept is unlikely to be different in the various ethnic groups; thus, despite MYRROR being conducted in an Asian population, the results are considered transferrable to the UK population.** This view is shared by the EMA.

The indirect comparison makes use of the 3 month data only, because of treatment switching at this stage in the vPDT arm of RADIANCE.[25] Within MYRROR,[26] no 3 months end point data were collected, but data were collected at 12 and 16 weeks, so a weighted average was used (75% at 12 weeks and 25% of 16 week assessments). It could be argued that 12 weeks and 13 weeks (3 months) are not that different, so the 12 week data should have been included in the indirect treatment comparison, rather than the weighted average. The ERG requested this at clarification and the company provided an alternative ITC. The relative treatment benefit of aflibercept versus placebo was almost the same at 12 weeks as the imputed 13 week value, so the results of the ITC did not change significantly. **The ERG accept the results originally presented by the company (Table 4, Figure 2)**

The indirect treatment comparison was not undertaken for the proportion of patients who gained or lost 5, 10 and 15 ETDRS letters. The company indicated during the clarification process that they considered the possibility of conducting an indirect comparison for gaining and losing 15 ETDRS letters as VIP contained that information. However, due to zero events (no events in placebo arm of VIP and no events in ranibizumab arm of RADIANCE) and the limited network, this proves unfeasible. **The ERG agrees this indirect comparison is not possible and present the relevant information in Table 4.**

The proportions of patients gaining ≥ 15 letters and ≥ 10 letters and losing ≥ 15 letters and ≥ 10 letters are very similar in the aflibercept arm and the ranibizumab arm of the

respective trials. **The ERG is content that aflibercept and ranibizumab provide similar outcomes with regard to gaining and losing ETDRS letters.**

Table 5 Proportion of participants with letter gain and loss at 3 months in the three trials

			Proportion letter gain or loss			
			≥15 letters gain	**≥10 letters gain**	**≥10 letters loss**	**≥15 letters loss**
MYRROR[26]	Aflibercept	(n =90)	38.9	63.3	0	0
	Sham	(n = 31)	9.7	12.9	25.8	6.5
RADIANCE[25]	Ranibizumab visual acuity	(n =105)	38.1	61.9	1.9	1.9
	Ranibizumab disease activity	(n = 116)	43.1	65.5	0.9	0
	vPDT	(n=55)	14.5	27.3	16.4	7.4
VIP[18, 19]	vPDT	(n =81)	2	-	-	6
	placebo	(n = 39)	0	-	-	21

1.8 Is the claim for the toxicity/adverse event profile of the technology similar to the NICE-recommended comparators?

The ERG and the ERG clinical expert agree that there are unlikely to be major differences in the safety profile of aflibercept and its comparator ranibizumab. Further details are provided here.

1.8.1 Safety profile of aflibercept from MYRROR

The safety population included all patients who had received any study treatment. Safety was monitored by recording ocular and non-ocular adverse events (AEs) at each study visit (every 4 weeks). Treatment emergent AEs (TEAEs) were AEs which occurred or worsened after the first administration of study drug and within 30 days after the last study injection (active or sham). In total, across the 48 weeks, 64 (70.3%) aflibercept patients experienced at least one TEAE compared to 18 (58.1%) of those in the sham group. No deaths were reported during the study. Table 6 presents the overall adverse event profile.

Table 6 Overall adverse event profile through week 24 and week 48 (reproduced from Table 24 of Document B of the company's submission)

	Through week 24		Through week 48	
	Aflibercept (n=91) n (%)	**Sham (n=31) n (%)**	**Aflibercept (n=91) n (%)**	**Sham +aflibercept (n=31) n (%)**
Any TEAE	[redacted]	[redacted]	**64 (70.3)**	**18 (58.1)**
Non-ocular (systemic)	40 (44.0)	10 (32.3)	53 (58.2)	12 (38.7)
Ocular (study eye)	21 (23.1)	6 (19.4)	29 (31.9)	11 (35.5)
Any study drug-related TEAE	[redacted]	[redacted]	**9 (9.9)**	**2 (6.5)**
Ocular drug-related (study eye)	[redacted]	[redacted]	6 (6.6)	1 (3.2)
Non-ocular drug-related	[redacted]	[redacted]	3 (3.3)	1 (3.2)
Any injection-related TEAE	**15 (16.5)**	**4 (12.9)**	**18 (19.8)**	**4 (12.9)**
Injection-related ocular TEAE in study eye	[redacted]	[redacted]	18 (19.8)	4 (12.9)
Any procedure-related TEAE	[redacted]	**0**	**12 (13.2)**	**0**
Procedure-related ocular TEAE in study eye	5 (5.5)	0	6 (6.6)	0
Any serious AE	[redacted]	[redacted]	**7 (7.7)**	**1 (3.2)**
Non-ocular (systemic)	[redacted]	[redacted]	4 (4.4)	0
Ocular (study eye)	0	0	1 (1.1)	0
Any serious TEAE	[redacted]	**0**	**7 (7.7)**	**0**
Drug-related serious TEAE	**0**	**0**	**1 (1.1) (ocular)**	**0**
Any injection-related serious TEAE (study eye)	**0**	**0**	**1 (1.1)**	**0**
Any procedure-related serious TEAE	**0**	**0**	**1 (1.1)**	**0**
Any AEs leading to discontinuation of study drug	[redacted]	[redacted]	[redacted]	[redacted]
Any death	**0**	**0**	**0**	**0**
Any ATE events	[redacted]	**0**	**1 (1.1)**	**0**

AE=adverse event; ATE=arterial thromboembolic event; TEAE=treatment-emergent adverse event

Most reported ocular TEAEs were of mild intensity, resolved within the study period and did not lead to interruption or permanent discontinuation of treatment. The most frequently reported ocular TEAEs in the study eye were conjunctival haemorrhage (11%), eye pain (7.7%) and punctate keratitis (6.6%) in the aflibercept group. In the

sham group, the TEAEs were punctate keratitis (12.9%), dry eye (6.5%) and posterior capsule opacification (6.5%) [source: Company Submission Document B, Table 25]. Non-ocular TEAEs were reported in 44% of aflibercept patients and 32.3% sham patients ay 24 weeks, rising to 58.2% and 38.7%, respectively by 48 weeks. The most common non-ocular TEAEs reported by 48 weeks were nasopharyngitis (aflibercept 18.7%, sham+aflibercept 9.7%), headache (aflibercept 6.6%, sham+aflibercept 3.2%), and nausea (aflibercept 7.7%, sham+aflibercept, 0%).

The company report that aflibercept injections are well tolerated and the safety profile of aflibercept for mCNV was generally consistent with the known safety profile for the other conditions for which it is licensed (wet AMD, RVO, DMO). **The ERG and the ERG's clinical expert agree with the company that the safety profile is comparable to that observed in other eye conditions.**

1.8.2 Safety profile of aflibercept compared with ranibizumab

No head-to-head safety information is available for mCNV and the VIP trial did not collect relevant data to allow an indirect comparison. The company summarised the findings from VIEW 1 and VIEW 2, which compared aflibercept with ranibizumab for wet AMD. These studies demonstrated aflibercept to be well tolerated with comparable safety profile to ranibizumab in relation to ocular and non-ocular adverse events. Data in the VIEW trials were available for 2 years providing a longer term comparison. **This information provides evidence that aflibercept and ranibizumab are similar in their safety profile and we do not anticipate that to change across eye conditions.**

1.9 Is the treatment likely to offer similar or improved health benefits over the NICE recommended comparator(s), e.g. similar/fewer adverse events, similar/improved clinical outcomes?

The ERG's opinion is that aflibercept is likely to offer similar benefits to ranibizumab with a similar safety profile.

2 Evidence to support the cost-comparison case

2.1 Is the acquisition cost of the technology, for 1 course of treatment, similar to/lower than the comparator?

The list price of an aflibercept vial is £816. The list price of a ranibizumab pre-filled syringe and vial are both £551. If vials are used, needle and syringe costs will be minor. The aflibercept vial only contains enough for one administration. Both the ranibizumab pre-filled syringe and vial could theoretically be used for more than one administration which would result in significant cost savings, but ERG clinical expert opinion is that this does not occur in the NHS.

2.2 Are the healthcare resource costs associated with the technology likely to be similar to/lower than the respective costs in the NICE recommended comparator(s) appraisal?

The ranibizumab pre-filled syringe is more convenient to use than the aflibercept vial. ERG clinical expert opinion is that this does not affect the numbers of patients that can be seen in clinic. The administration cost per injection will be the same for aflibercept and ranibizumab as will the monitoring costs while patients are on treatment.

2.3 Has the company used the same data sources for resource costs as the NICE recommended comparator(s)? If so, do these reflect the most up-to-date information available from these sources?

The company has assumed that the same number of injections will be required whether aflibercept or ranibizumab is used. As a consequence, it does not need to consider administration and monitoring costs.

2.4 Are consequences of incorrect decision low?

Given the results of the company NMA the clinical consequences of an incorrect decision are minimal.

Under the company assumptions and applying list prices there is a net cost from aflibercept of £6,057 per patient due to £265 higher drug cost per administration. A 50% market share suggests an annual present value cost of £7.9mn.
Applying the mean numbers of injections from the trials for the 1st year of 4.2 injection for aflibercept and 3.5 for the ranibizumab disease activity arm and including a net cost of £55 per additional injection suggests a net cost of £8,257 per patient. A 50% market share suggests an annual present value cost of £10.7mn. If the statistically significant higher drop-out for aflibercept is adjusted for, the worst case scenario, this might suggest 4.5 aflibercept injections in the 1st year and a net cost of £9,612 per patient. A 50% market share suggests an annual present value cost of £12.5mn. These estimates are sensitive to the [redacted] recurrence rate. It also shows some sensitivity to the baseline [redacted] bilateralism rate, which is assumed to be constant.

Crude patient benefit calculations by the ERG, outlined in greater detail in the final summary section below, suggest that at central clinical and resource use estimates aflibercept is unlikely to be cost effective at list prices regardless of whether the better seeing eye is treated or only the worse seeing eye is treated.

2.5 Has the original literature search been updated?

A sensitive search was undertaken to identify relevant studies on any treatment for myopic choroidal neovascularisation. No date limits were applied to the main searches and date of last search was 22nd November 2016. The company did not rely on the literature searching that had been undertaken for the previous assessments.

3 ERG's summary of company's cost comparison case

3.1 Multiple treatments from a single vial or syringe

Aflibercept is only available as a 0.1ml 4mg vial. The dose per administration is 2mg. Given the need for some headroom, only one administration is possible with each aflibercept vial.

Ranibizumab is available as both a 0.23ml 2.3mg vial and as a 0.165ml 1.65mg prefilled syringe. The dose per administration is 0.5mg. The ERG clinical expert has indicated that both ranibizumab vials and syringes could, in theory, be used to treat more than a single eye. It might be possible to treat a patient bilaterally using a single vial, or even to treat more than one patient using a single vial. This could significantly reduce the costs of using ranibizumab compared to aflibercept.

The ERG clinical expert suggests that multiple injections of different patients from a single ranibizumab vial or syringe is not current NHS practice. The ERG clinical expert suggests that bilateral treatment of a single patient from a single ranibizumab vial or syringe is not current NHS practice.

3.2 Injection frequency

The company applies the same number of injections for aflibercept and ranibizumab. The company argues that since the mean numbers of injections are not statistically different between aflibercept and ranibizumab they should be equalised.

Table 7 Previous aflibercept submissions: 1st year dosing assumptions

	STA	Date	Aflibercept	Ranibizumab
Wet AMD	TA294[27]	May 2013	7.0	8.0
MO post CRVO	TA305[28]	Dec 2013	8.3	8.8
DMO	TA346[29]	May 2015	8.0	7.9
MO post BRVO*	TA409[30]	Aug 2016	4.4	4.4
*Last 6 months of 1st year after laser				

In previous STAs of aflibercept, the company has typically differentiated both the numbers of injections in the 1st year and the clinical effectiveness estimates between aflibercept and ranibizumab. Table 7 shows the base case dosing assumptions for these previous aflibercept submissions and they are summarized here:

- For TA294[27], the ERG subsequently equalised the numbers of injections.
- For TA305[28], the company estimated 1st year means of 8.3 aflibercept injections from GALILEO/COPERNICUS and 8.8 ranibizumab injections from the published trial. The ERG only equalised these in a scenario analysis.
- For TA346[29], the company estimated 1st year means of [redacted] aflibercept injections from VIVID/VISTA and 7.40 ranibizumab injections from RESTORE/REVEAL but applied 8.0 for aflibercept based upon the SmPC and 7.9 for ranibizumab based upon the mixed treatment comparison. The ERG suggested estimates of [redacted] injections for aflibercept and 7.4 for ranibizumab.
- Only for TA409[30] has the company equalised the 1st year injections between aflibercept and ranibizumab, with ranibizumab being assumed to require the same number of injections as aflibercept in the VIBRANT trial. The ERG noted that the VIBRANT trial involved 9 aflibercept injections in the 1st year for 1st line aflibercept compared to the BRAVO trial involving 8 ranibizumab injections in the 1st year for 1st line ranibizumab, and undertook a scenario analysis which reduced the number of 1st year 2nd line ranibizumab injections by 1.

The FADs have, at times, suggested that there is little evidence of any real difference in clinical effectiveness between aflibercept and ranibizumab.

The company surveyed 52 ophthalmologists all of whom treated a minimum of 2 mCNV cases annually. This survey estimated that there would be very much fewer aflibercept injections than ranibizumab injections.

Table 8 Company resource use survey: injection frequency medians

	Year 1	Year 2
Aflibercept	[redacted]	[redacted]
Ranibizumab	[redacted]	[redacted]

In the opinion of the ERG, given the trials' injection frequencies, the estimates in Table 8, while medians, are not credible.

In light of the company's previous approaches, it may be questionable for it to now switch to demanding a statistically significant difference in the numbers of injections in the 1st year for them to be differentiated.

Table 9 Company trial injection estimates, standard deviations and 95% CIs

	N	Mean Inj.	SD	95% CI
Aflibercept (AFLI)	91	4.2	[redacted]	(3.56, 4.84)
Ranibizumab visual acuity (RANI VA)	106	4.6	2.6	(4.10, 5.10)
Ranibizumab disease activity (RANI DA)	116	3.5	3.0	(2.95, 4.05)

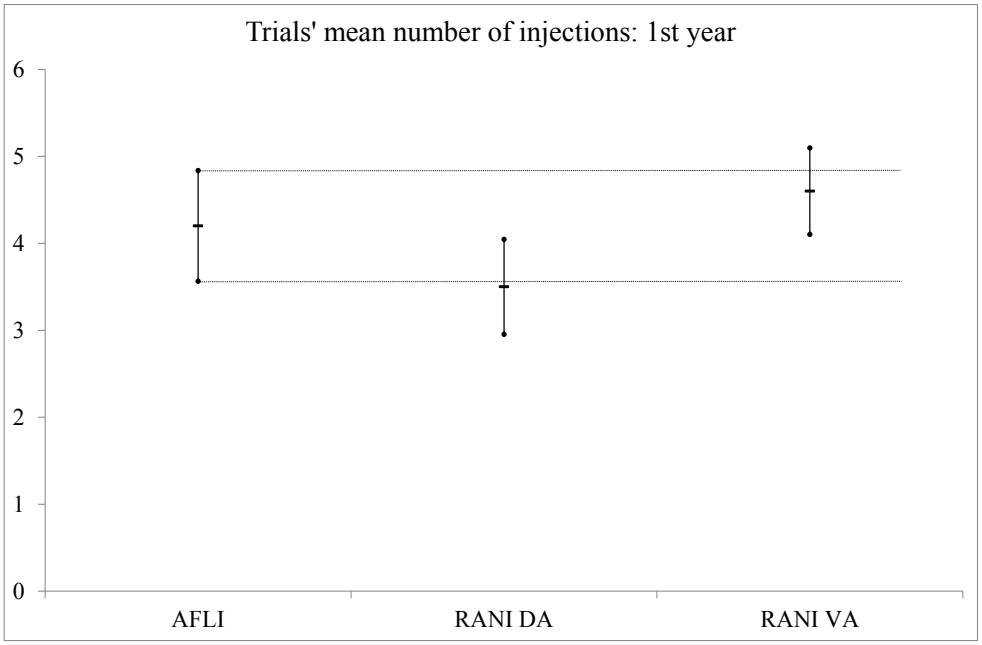

Figure 3 1st year mean numbers of injections

The ERG's clinical expert is of the opinion that the MYRROR[26] retreatment criteria are closer to the RADIANCE[25] disease activity retreatment arm than the RADIANCE visual acuity retreatment arm. Ranibizumab was also approved for mCNV based upon modelling of the disease activity retreatment arm.

ERG expert opinion is that the trials were relatively small, differed in terms of populations and sites and also in the protocols for the decision to retreat, and that, as a consequence, the number of aflibercept injections is unlikely to differ much from that of ranibizumab.

3.3 Injection frequency and patient drop outs

The patient flow within MYRROR and RADIANCE is presented below.

Table 10 MYRROR and RADIANCE patient flow

	MYRROR[26]		RADIANCE[25]		
	Aflibercept	**SHAM**	**Ranibizumab visual acuity**	**Ranibizumab disease activity**	**vPDT**
Baseline	91	31	106	116	55
Lack of efficacy	..	..	1	0	0
Adverse event	[redacted]	[redacted]	..	..	..
Patient withdrawal	[redacted]	[redacted]	1	2	0
Protocol violation	[redacted]	[redacted]	1	1	0
Other treatment	0	[redacted]	..	..	..
LTFU	0	0	3	1	0
EoT	78 (86%)	24 (77%)	100 (94%)	112 (97%)	55 (100%)

*Treatment failure

The 86% remaining in the MYRROR aflibercept arm at end of trial is reasonably different from the 97% remaining in the RADIANCE disease activity arm, and the difference is statistically significant (p=0.01).

Based upon figures 1 and 8 of the company submission to TA298[16] and an assumption that 1 month is 4 weeks, the ERG takes the period from day 1 until prior to month 12 during the RADIANCE trial to span the same amount of time as the MYRROR trial. Patient numbers and injections data supplied by the company at clarification are shown in Table 11. Note that the percentages for aflibercept injections are the number of injections divided by the baseline patient number and not the contemporaneous patient numbers remaining within the trial. The patient numbers and mean injections, as reported in Wolf et al[25], are also given for RADIANCE.

The mean number of injections for aflibercept is calculated as the total number of injections, 379, divided by the baseline number who received an injection, 90, to yield an estimate of an average of 4.2 aflibercept injections. Other things being equal, the total number of injections will fall as the number of patients remaining within the trial falls.

Table 11 MYRROR and RADIANCE dosing

MYRROR[26]			**RADIANCE[25]**		
Week	**Aflibercept**		**Month**	**Ranibizumab visual acuity**	**Ranibizumab disease activity**
	N	Injections		N	N
0	90	90 (100%)	0	106*	116
4	[redacted]	[redacted]	1	..	..
8	[redacted]	[redacted]	2	..	..
12	[redacted]	[redacted]	3	105	116
16	[redacted]	[redacted]	4	..	..
20	[redacted]	[redacted]	5	..	..
24	83	[redacted]	6	103	116
28	[redacted]	[redacted]	7	..	..
32	[redacted]	[redacted]	8	..	..
36	[redacted]	[redacted]	9	..	..
40	[redacted]	[redacted]	10	..	..
44	[redacted]	[redacted]	11	..	..
48	78		12	100	112
Mean inj	4.2			4.6	3.5
* 1 patient withdrew without any post baseline assessment so was excluded from the efficacy calculations					

Using a crude linear interpolation to infer the monthly RADIANCE patient numbers, the average duration of follow-up is around 5% higher in the ranibizumab visual acuity arm and around 7% higher in the ranibizumab disease activity arm than that of the MYRROR aflibercept arm. This might argue for increasing the mean number of aflibercept injections during the 1st year by a

similar amount, to between 4.4 and 4.5. None of this takes into account the possible effects of patient attrition during the MYRROR and RADIANCE trials upon clinical effectiveness estimates, and how the LOCF might be affected.

Wolf et al[25] also noted that, during the last 6 months of RADIANCE, only 37% of patients in the ranibizumab disease activity arm received any injections. Notably, Wolf et al,[25] which was supported by Novartis, do not supply the parallel 6 month dosing figure for the ranibizumab visual acuity arm. During the last 6 months of MYRROR, the percentage of patients receiving an injection each month was typically around [redacted]. This may suggest lower dosing during the last 6 months of the 1st year of treatment in the RADIANCE ranibizumab disease activity arm than in the MYRROR aflibercept arm. If so, any lower dosing for ranibizumab might flow into the 2nd year of treatment as well.

The ERG performed sensitivity analyses that apply the 1st year mean numbers of injections that were observed in the trials, increase the 1st year mean numbers of injections for aflibercept to 4.5 and a combination of these.

3.4 Administration costs

The ERG clinical expert has indicated that the ranibizumab prefilled syringe is more convenient but, compared to using a pre-filled vial, has little practical impact upon clinic time and the numbers of patients that can be treated. The additional costs of the needle and syringe required for each aflibercept administration compared to the prefilled ranibizumab syringe have typically not been included in previous assessments but are likely to be relatively minor.

As a consequence, administrations costs will only differ between aflibercept and ranibizumab if the numbers of administrations differ. The previous aflibercept STAs have made the following assumptions about administration and monitoring costs:

- TA294:[27] Wet AMD: Based upon a balance between one-stop administration and monitoring visits and two-stop administration and monitoring visits. This appears to have been largely superseded by the subsequent aflibercept STAs.

- TA305:[28] MO from CRVO: Administration costs based upon 52% as outpatient and 48% as day case to give an average of £233.24. Monitoring costs based upon BZ23Z plus the cost of a consultant-led outpatient appointment yielding a total of £197.00. A one-stop model is applied where administration visits double as monitoring visits suggesting a net cost for administration compared to monitoring of £36.24.
- TA346:[29] DMO: Administration costs based upon RD40Z 20 minute ultrasound cost of £54.54, which is additional to the £139.22 cost per monitoring visit.
- TA409:[30] MO from BRVO: Administration costs based upon RD407 20 minute ultrasound cost of £53.96, which is additional to the £150.07 cost per monitoring visit.

In the light of these precedents and the number of injections for mCNV in the 1st year probably being below the total number of patient visits, the ERG will apply a net administration cost of the 2015-16 reference costs for RD40Z of £55.14. Within the 2015-16 reference costs for outpatient procedures, the ERG cannot find BZ23Z, the closest alternative appearing to be BZ87A Minor vitreous procedures age 19+ at an average cost of £102. This will be applied as a sensitivity analysis. Based upon ERG clinical expert opinion, the ERG will assume that the total number of patient visits is the same for each treatment.

3.5 Monitoring frequency

The aflibercept SmPC states:[22]

> *The recommended dose for Eylea is a single intravitreal injection of 2 mg aflibercept equivalent to 50 microlitres. Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation of the disease. The schedule for monitoring should be determined by the treating physician. The interval between two doses should not be shorter than one month.*

The ranibizumab SmPC states:[14]

> *Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME and RVO, initially, three or more consecutive, monthly injections may be needed. Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.*

ERG clinical expert opinion indicates that, provided that there is broad clinical equivalence, there would be no difference in monitoring frequency between ranibizumab and aflibercept, with a probable average of around 6 visits during the 1st year of treatment.

3.6 Bilateralism and recurrence

Based upon a resource use survey of 52 ophthalmologists, the company models [redacted] bilateral involvement at baseline and so requiring treatment in both eyes. The company also estimates an annual recurrence rate of [redacted] from its resource use survey. Recurrence is assumed to require another year of treatment.

3.7 Cost comparison results

The company base case using list prices for both aflibercept and ranibizumab are shown in Table 12[a]. The per-patient based estimates are the discounted costs of the initial treatments of the first and second eye plus the discounted costs of the treatment of recurrence in the first and second eye.

[a] There is a minor error in the calculation of the discount factors, the company model applying $(1-r)^t$ rather than $1/(1+r)^t$. This has been corrected in what follows.

Table 12 Company model per patient: at ranibizumab and aflibercept list prices

	Drug	Admin	Total
Ranibizumab	£12,594	£1,260	£13,854
Aflibercept	£18,651	£1,260	£19,911
Net	£6,057	£0	£6,057

The quite substantial additional cost per patient of £6,057 from aflibercept is due to its list price being £265 more than the list price of ranibizumab.

The ERG revised base case adds £1,260 administration costs to both arms but does not affect the net amounts. The ERG sensitivity analyses are shown in table 13. The population based estimate is based upon the NICE estimate of an annual 2,917 incident eyes that will receive treatment which, when coupled with the company estimate of 12.5% bilateralism at baseline, suggests an annual number of new patients of 2,593. A 50% market share for aflibercept and a 50% market share for ranibizumab are also assumed. This may be less realistic for the scenarios where one drug requires more injections during the 1st year of treatment and recurrence than the other.

Table 13 ERG sensitivity analyses at ranibizumab and aflibercept list prices

	Drug	Admin	Total	Population
Base case	£6,057	£0	£6,057	£7.9mn
SA01: ranibizumab visual acuity dosing	£4,914	-£114	£4,800	£6.2mn
SA02: ranibizumab disease activity dosing	£8,057	£200	£8,257	£10.7mn
SA03: aflibercept 4.5 1st yr	£7,326	£86	£7,412	£9.6mn
SA04: SA01 + £102 admin	£4,914	-£212	£4,702	£6.1mn
SA05: SA02 + £102 admin	£8,057	£370	£8,427	£10.9mn
SA06: SA03 + £102 admin	£7,326	£159	£7,485	£9.7mn
SA07: No recurrence	£1,531	£0	£1,531	£2mn
SA08: No bilateral	£5,384	£0	£5,384	£7.9mn
SA09: SA07 + SA08	£1,361	£0	£1,361	£2.0mn
SA10: SA01 + SA09	£1,142	-£22	£1,120	£1.6mn
SA11: SA02 + SA09	£1,745	£38	£1,784	£2.6mn
SA12: SA03 + SA09	£1,605	£16	£1,621	£2.4mn
SA13: SA04 + SA09	£1,142	-£41	£1,101	£1.6mn
SA14: SA05 + SA09	£1,745	£71	£1,816	£2.6mn
SA15: SA06 + SA09	£1,605	£30	£1,635	£2.4mn
SA16: SA02 + SA03	£9,326	£286	£9,612	£12.5mn
SA17: SA16+ SA09	£1,989	£55	£2,044	£3.0mn
SA18: SA16 + SA09 + £102 admin	£1,989	£102	£2,090	£3.0mn
SA19: SA16 + SA07	£2,237	£62	£2,299	£3.0mn

As would be expected if the ranibizumab visual acuity dosing is applied [SA01], this increases costs in the ranibizumab arm and aflibercept results in a slightly smaller cost of £4,800 per patient. The annual incident population present value of the costs is estimated to be £6.2mn. However, if the ranibizumab disease activity dosing [SA02] is applied, aflibercept is still more costly by £8,257 per patient, which translates into an annual incident population present value cost of £10.7mn.

If aflibercept dosing in the 1st year should be adjusted for the statistically higher drop-out rate during MYRROR to 4.5 injections [SA03], it is more costly than

ranibizumab by £7,412 per patient. This still assumes the 4.2 1st year injections for ranibizumab. If these are reduced to the 3.5 of the ranibizumab disease activity arm [SA16], the increase in costs associated with aflibercept rises to £9,612 per patient and the annual incident population present value cost to £12.5mn.

Applying the 1st year injections frequencies of 4.5 for aflibercept and 3.5 for ranibizumab [SA16-SA19] can be seen as the worst case 1st year injections frequencies scenario for aflibercept given the trials' data. Differentiation by the number of 1st year injections might also argue for differentiating the numbers of subsequent injections.

If the 1st year numbers of injections are differentiated between aflibercept and ranibizumab, there are reasonable differences in total costs. The [redacted] recurrence and retreatment rate estimate is a key determinant of the total lifetime costs, and, by implication, the net lifetime patient costs if treatments are differentiated by the number of 1st year injections. The worst case 1st year injections frequencies scenario for aflibercept [SA16] estimated net cost of £9,612 falls to only £2,299 [SA19] if the rate of recurrence is set to 0%.

ERG clinical expert opinion views the [redacted] recurrence and retreatment as reasonable, certainly in the early years. The implied total number of anti-VEGF treatments over the patient lifetime exceeds that modelled by the company for other conditions: an initial 5.2 injections per eye followed by a further 24.6 injections for treatment of recurrence[b], suggesting a total lifetime number of injections of 29.7 per eye. The company has ignored the 1st and 2nd year injection frequency estimates of its expert survey.

Given the [redacted] recurrence and retreatment assumptions, the model will also show some sensitivity to both the baseline age and the proportion of female patients since this will determine survival which rolls through to the costs of recurrence. Given that the MYRROR trial was in an Asian population, there might be some questions about its generalisability, but the baseline age and

[b] These injections may also to some degree cover further bilateral incidence further to the baseline [redacted] prevalence estimate.

proportion of women of 58 years and 76%, respectively, are similar to the 56 years and 75% of RADIANCE.

3.8 Differentiating aflibercept from ranibizumab in a cost utility analysis

This section is highly speculative. It is intended to highlight the possible approaches to differentiating aflibercept from ranibizumab through the cost utility modelling that would be required for an STA, and the approaches the company might explore. It does not provide formal estimates of the cost effectiveness of aflibercept compared to ranibizumab.

The costing considerations outlined above do not address any effects upon patient gains. The company indirect treatment comparison suggests that aflibercept is better, though not statistically significantly better, than both ranibizumab visual acuity retreatment and ranibizumab disease activity retreatment.

Table 14 Company indirect treatment comparison - mean letters gain in BCVA treated eye at 3 months

	Mean	SD	95% CI
Aflibercept vs ranibizumab visual acuity	1.34	3.40	(-5.35, 8.00)
Aflibercept vs ranibizumab disease activity	0.94	3.38	(-5.67, 7.56)

Due to the VIP trial not reporting the proportions gaining and losing 10 letters and 15 letters it is not possible to undertake an indirect treatment comparison for these variables. Any modelling of the cost effectiveness of aflibercept versus ranibizumab that adopted the modelling framework of the ranibizumab assessment[16] would have to infer the relative risks of gaining and losing letters from the mean letters change and some mapping from this to the proportions of patients gaining and losing letters. This would introduce a reasonable amount of uncertainty to any cost effectiveness modelling that adopted the modelling framework of the ranibizumab assessment.[16]

The alternative would seem to be to develop a new model based upon the mean letters change in BCVA at 3 months. It seems likely that this would immediately suggest that aflibercept dominates the ranibizumab visual acuity dosing arm. However, it should be borne in mind that ranibizumab was approved for mCNV based upon modelling of the ranibizumab disease activity dosing arm.

Previous assessments have often used the Czoski-Murray mapping from changes in the patients' overall BCVA to quality of life.[31] The mean gain of 0.94 letters for aflibercept versus the ranibizumab disease activity arm would translate to a quality of life gain of 0.007. The gains in visual acuity with the anti-VEGFs are relatively rapid and then tend to plateau and, assuming that the gain at three months would apply for the remainder of the year, may be reasonable. The [redacted] recurrence and retreatment rate might justify an assumption of the gain being maintained for the remainder of the patient lifetime. While this might be optimistic, it appears that it would suggest a total patient gain of 0.114 QALYs from aflibercept compared to ranibizumab if the gain was in the patient's bilateral BCVA. A willingness to pay of £30k/QALY would justify an additional expense of £3,420. If the gain was in the worse seeing eye, previous assessments have suggested it might be only 30% of this, and so only warrant an additional expense of £1,026. These amounts can be compared with the estimates of the net additional costs and savings per patient associated with aflibercept under the various scenarios outlined above.

Aflibercept would dominate ranibizumab visual acuity retreatment at central estimates. Whether aflibercept is cost effective compared to ranibizumab disease activity retreatment at central estimates is less clear. It may depend upon the proportion that has their better seeing eye treated, and so upon the baseline [redacted] bilateralism rate and whether further bilateralism develops post baseline.

Any move to an STA and the associated cost-utility modelling could result in the company revising or limiting the duration of its [redacted] recurrence rate estimate. ERG clinical expert opinion suggests that the [redacted] estimate is reasonable, at least in the short term. Limiting its duration might have a limited impact upon cost effectiveness

estimates since there would probably have to be a parallel limitation on patient benefits.

Any move to an STA could result in the company modelling an incidence of bilateralism post baseline. This would increase the proportion of patients being treated in their better seeing eye. Net costs would increase, unless there were significant cost offsets from reduced blindness which seems unlikely to the ERG. But the net benefits would increase more due to the better seeing eye being treated and the cost effectiveness of aflibercept would improve.

Given the uncertainty about the clinical effectiveness estimates, the uncertainty about the mean numbers of injections in the 1st year, the overlapping confidence intervals and that indirect treatment comparison estimates of the proportions gaining and losing letters are not possible any cost utility modelling would have a high degree of uncertainty around it.

4 ERG's overall view of the company's cost comparison case

The ERG opinion is that aflibercept is likely to offer similar benefits to ranibizumab with a similar safety profile. A cost comparison was thus possible. The cost comparison findings are sensitive to the number of injections, recurrence and retreatment rates.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Aflibercept for treating myopic choroidal neovascularization [ID952]

You are asked to check the ERG report from Aberdeen HTA to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Thursday 3 August** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Comparison of marketing authorisation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
A reference is made to the difference in wording of the Eylea and Lucentis SmPCs regarding myopic choroidal neovascularisation. *'The Eylea® summary of product characteristics (SmPC) specifies "myopic choroidal neovascularisation", whereas the Lucentis® SmPC states merely "choroidal neovascularisation".'* Not a factual inaccuracy but could be considered misleading. Page 3.	Whilst not factually inaccurate, it should be noted that the NICE Technology Appraisal TA 298 was titled 'Ranibizumab for treating choroidal neovascularisation associated with pathological myopia'. Further, the RADIANCE trial was conducted in patients with visual impairment due to myopic CNV.	The current text implies that there may be differences between Eylea and Lucentis with respect to the indicated patient population.	Not a factual error. Sentence has been changed to: The Eylea® summary of product characteristics (SmPC) specifies "myopic choroidal neovascularisation"[22] and the Lucentis® SmPC states "choroidal neovascularisation".[14]

Issue 2 Decision problem - outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Text from the Company comments has been omitted.	Please add, as per company comments: *'Further outcome data are presented to further report on the efficacy of aflibercept. Exposure is presented as it is relevant to the indirect*	For completeness.	Not a factual error. We have clarified that e*xposure is presented as it is relevant to the indirect comparison with*

Page 5	*comparison with ranibizumab'*		*ranibizumab.*

Issue 3 Duplication

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The 'other outcomes row of Table 2 has been duplicated' Page 16	Please delete the duplicate row.	The duplicate row is unnecessary.	Proposed revision accepted.

Issue 4 AIC data (also see Issues 7-9 below)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Two numbers have been marked as AIC that do not need to be. Page 18	Regarding the NEI VFQ-25 mean change baseline to 4 weeks, the value '3.14' and the p-value of 0.010 do not need to be marked as AIC.	Appropriate marking of AIC data.	Proposed revision accepted.

Issue 5 Cross referencing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 5 is cross-referenced incorrectly on three occasions.	On page 20, the text should be changed from '*The results of the indirect treatment comparison are shown in Table 5 (source Table 23, Document B) and Figure 2 (for comparison*	Correct cross-referencing of data.	Proposed revision accepted.

Pages 20 and 21	*with placebo).'* To *'The results of the indirect treatment comparison are shown in Table 4 (source Table 23, Document B) and Figure 2 (for comparison with placebo).'* On page 21, the text should be changed from '***The ERG accept the results originally presented by the company (Table 5, Figure 2)'*** To ***'The ERG accept the results originally presented by the company (Table 4, Figure 2)'*** On page 21, the text should be changed from '***The ERG agrees this indirect comparison is not possible and present the relevant information in Table 5.'*** To ***'The ERG agrees this indirect comparison is not possible and present the relevant information in Table 4.'***		

Issue 6 Volume of ranibizumab vial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The volume of the ranibizumab vial is described incorrectly Page 27	The text should be changed from '*Ranibizumab is available as both a 2.3ml 2.3mg vial…'* To *'Ranibizumab is available as both a 0.23ml 2.3mg vial…'*	Appropriate description of vial size.	Proposed revision accepted.

Issue 7 AIC data (also see Issue 4 above and 8-9 below)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
A value from TA346 is not marked as AIC when it should be Page 28	The marking should be changed from '*For TA346, the company estimated 1st year means of 8.55 aflibercept injections…'* To *'For TA346, the company estimated 1st year means of [redacted] aflibercept injections …'*	Appropriate marking of AIC data.	Proposed revision accepted.

Issue 8 AIC data (also see Issues 4 and 7 above and 9 below)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
A value in Table 9 should be marked as AIC	The SD value for aflibercept should be marked as AIC i.e. [redacted]	Appropriate marking of AIC data.	Proposed revision accepted.

Page 29			

Issue 9 AIC data (also see Issues 4 and 7-8 above)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Several numbers in Table 10 should be marked as AIC Page 30	The following values for aflibercept should be marked as AIC: Adverse event [redacted] Patient withdrawal [redacted] Protocol violation [redacted] The following values for SHAM should be marked as AIC: Adverse event [redacted] Patient withdrawal [redacted] Other treatment [redacted] Further to this, the value of [redacted] for protocol violation should not be labelled as protocol violation, but instead 'treatment failure'	Appropriate marking of AIC data.	Proposed revision accepted.

Issue 10 Incorrect reference to previous TA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Third bullet point on page 33 refers to TA409 being an appraisal in the CRVO indication. This is incorrect.	TA409 is in the BRVO indication. Please update bullet point 3 accordingly.	Appropriate referencing.	Proposed revision accepted.