Common Drug Review
Clinical Review Report

August 2015

Drug	Aflibercept (Eylea) (40 mg/mL Solution for Intravitreal Injection available as a 2 mg single-use vial)
Indication	Treatment of neovascular (wet) age-related macular degeneration (wAMD)
Listing request	As per indication
Manufacturer	Bayer Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in specializing in the treatment of retinal disease (ophthalmologist) who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AE	adverse event
AMD	age-related macular degeneration
BCVA	best corrected visual acuity
CI	confidence interval
CNV	choroidal neovascularization
CRT	central retinal thickness
EQ-5D	EuroQol 5-Dimensions Questionnaire
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	full analysis set
IVT	intravitreal
NEI VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
OCT	optical coherence tomography
PDT	photodynamic therapy
PPS	per-protocol analysis set
QoL	quality of life
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SAF	safety analysis set
TEAE	treatment-emergent adverse event
VA	visual acuity
VEGF	vascular endothelial growth factor
wAMD	neovascular (wet) age-related macular degeneration
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Age-related macular degeneration (AMD) is a degenerative disease of the macula. In Canada, about one million people currently have early AMD and approximately 250,000 have the advanced form of AMD.[1,2] AMD is the leading cause of registered visual impairment in Canada.[3] The prevalence of blindness due to AMD in Canada has been estimated at more than 100,000.[4,5] There are two types of AMD: dry AMD and neovascular (wet) AMD (wAMD). While wAMD develops in only 10% to 20% of people with dry AMD, it accounts for more than 90% of those who have advanced vision loss.[4] The hallmark of wAMD is choroidal neovascularization, which is an abnormal angiogenic process modulated by growth factors including vascular endothelial growth factor (VEGF).[6]

Currently, there is no cure for wAMD. The goal of treatment is to minimize vision loss and disability in order to maintain independence.[7] The first line of pharmacological therapy for wAMD in Canada is 0.5 mg ranibizumab, a monoclonal antibody that inhibits VEGF and that is administered monthly by intravitreal (IVT) injection.[8] Pegaptanib and photodynamic therapy (PDT) using verteporfin are also indicated for the treatment of wAMD in Canada, but as these treatments are limited to stabilization of the disease and produce little to no improvement in vision, they are generally used as a second-line therapy in clinical practice. For instance, PDT is usually reserved for patients with wAMD for whom IVT injection is not suitable. Bevacizumab is a much larger antibody fragment derived from the same parent antibody as ranibizumab. It is not approved for treatment of wAMD in Canada, although it is used off-label for treating wAMD in patients who are ineligible for ranibizumab treatment coverage.

Aflibercept (Eylea) is a novel VEGF inhibitor that is indicated in Canada for the treatment of patients with wAMD. Aflibercept is supplied as a solution for IVT injection (40 mg/mL) at a dose of 2 mg every eight weeks after three initial monthly injections.[9] The objective of this report was to review the beneficial and harmful effects of aflibercept at the dosing regimen recommended by Health Canada for the treatment of wAMD.

Results and Interpretation

Included studies

Two similarly designed, double-blind, multi-centre, active-controlled, randomized controlled trials (RCTs) (VIEW 1[10] and VIEW 2[11]) met the inclusion criteria for the review. Both studies assessed whether aflibercept was non-inferior to ranibizumab for preventing moderate vision loss (≥ 15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) in treatment-naive patients with wAMD.[12] The VIEW 1 and VIEW 2 studies comprised a 52-week-long, fixed-dose phase (which is the focus of the report) and a subsequent flexible-dose phase through 96 weeks (which is summarized in Appendix 6).

Efficacy

More than 94% of patients achieved the primary end point of maintained vision, losing fewer than 15 letters on the ETDRS letter score at 52 weeks in both treatment groups in VIEW 1 and VIEW 2. The between-treatment differences (aflibercept versus ranibizumab) in the proportion of patients with vision maintained at week 52 were –0.7% (95% confidence interval [CI], –4.5% to 3.1%) and –1.13% (95% CI, –4.81% to 2.55%) in VIEW 1 and VIEW 2, respectively. These differences met the predefined criteria for non-inferiority.

An improvement of eight to nine ETDRS letters from baseline was observed in both studies, irrespective of treatment. There was improvement in VA (≥ 15 ETDRS letters gained) in 31% to 34% of patients treated with ranibizumab and in 31% of patients treated with aflibercept, in both studies. There was improvement in VA (≥ 30 ETDRS letters gained) in 6% of patients treated with ranibizumab and 5% to 7% of patients treated with aflibercept, in both studies. [redacted] and 3% of patients experienced a moderate or severe reduction in VA (≥ 15 or ≥ 30 ETDRS letters lost, respectively) in both treatment groups in both studies. None of the changes in VA between treatment groups in either study were statistically significant.

[redacted]

Quality of life (QoL), as measured by the National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) score, improved by at least four points by week 52 in both treatment groups in both studies. This improvement exceeded the minimal clinically important difference (4 points). The magnitude of the changes in the NEI VFQ-25 score observed in the ranibizumab group was similar to that seen in previously published studies,[13-15] and there were no statistically significant differences between treatments in the change in NEI VFQ-25 scores in either study.

At week 52, the central retinal thickness (CRT) had decreased by [redacted] in both treatment groups in VIEW 1, and by 138 µm to 149 µm in VIEW 2, but there were no statistically significant differences between treatments in the change in central retinal thickness in either study.

The aforementioned results are consistent with the conclusion that aflibercept is non-inferior to ranibizumab in maintaining vision in treatment-naive patients with wAMD.

Harms

The overall safety profile appears to be similar between ranibizumab and aflibercept at the recommended dosing regimen. The incidence of treatment-emergent adverse events (TEAEs) was similar between ranibizumab and aflibercept (85% to 95% versus 90% to 95% for ranibizumab versus aflibercept, respectively), as was the incidence of ocular TEAEs in the study eye (64% to 81% versus 65% to [redacted] for ranibizumab versus aflibercept, respectively) and non-ocular TEAEs (62% to 77% versus 69% to 74% for ranibizumab versus aflibercept, respectively). The most frequently reported ocular adverse events (AEs) were conjunctival hemorrhage, vitreous floaters, eye pain, vitreous detachment, [redacted] and increased intraocular pressure.

The incidence of serious TEAEs was similar for ranibizumab and aflibercept (15.6% to 18.5% for ranibizumab and 12.5% to 22%, for aflibercept), and most TEAEs were attributable to the injection procedure or the progression of the disease. The incidence of ocular serious adverse events (SAEs) in the study eye was numerically higher in the ranibizumab group than in the aflibercept group (3.3% versus 1.0% in VIEW 1, and 3.1% versus 2.9% in VIEW 2). The reported ocular SAEs in the study eye were mainly endophthalmitis, VA reduction, retinal hemorrhage, and [redacted]. Non-ocular SAEs were similar in both treatment groups (8.9% to 18.8% and 12.4% to 16.8% for ranibizumab and aflibercept, respectively). The incidence of AEs leading to withdrawal from the study during the 52 weeks was low (< 3%) and was similar between treatment groups in both studies. [redacted]

Notable AEs identified by the clinical expert consulted by the CADTH Common Drug Review (CDR) were infrequent. Five (1.6%) patients treated with ranibizumab and [redacted] patients treated with aflibercept experienced an arterial thrombotic event in VIEW 1, while [redacted] was reported in VIEW 2. Endophthalmitis occurred in three (1%) patients in the ranibizumab group and in none of the aflibercept-treated patients in VIEW 1; no endophthalmitis was reported for the VIEW 2 study. The incidence of retinal detachment was 5.2% for ranibizumab and 3.9% for aflibercept in the VIEW 2 study. No retinal detachment was reported for the VIEW 1 study.

Overall, the rates of ocular and non-ocular TEAEs reported during the first year of study were similar between treatment groups in both studies, and are in line with rates reported previously.[14,15] The safety profiles of ranibizumab and aflibercept appeared to remain similar after the 96-week extension phase (Appendix 6).

Finally, few deaths were reported in either the ranibizumab or aflibercept groups in either study, and no deaths were related to the study drug.

Other Considerations

The clinical expert consulted by CDR indicated that there is a potential for off-label use of aflibercept if it is administered more frequently than every eight weeks, such as every six to eight weeks. Both the clinical expert and the patient groups who provided input to CDR (see Appendix 1) noted that the apparently similar efficacy and safety of aflibercept and ranibizumab suggest that aflibercept potentially would be the more desirable treatment option due to the need for fewer injections compared with ranibizumab.

Although bevacizumab is not approved in Canada for the treatment of wAMD and was not considered to be a valid comparator for this review, bevacizumab is reimbursed for wAMD treatment in some jurisdictions that participate in the CDR process and is used off-label for the treatment of wAMD in patients in jurisdictions in which ranibizumab is not reimbursed or in patients who are ineligible for coverage.

Pharmacoeconomic Summary

Summary of economic analysis

The manufacturer conducted a cost-minimization analysis based on the results of the VIEW 1 and VIEW 2 clinical trials. The expected drug costs of aflibercept and ranibizumab were calculated by multiplying the price per dose and the associated physician fee by the number of doses per patient expected over a 10-year analysis horizon. The dose frequency of aflibercept was based on the frequencies observed in the VIEW trials, and the dose frequency of ranibizumab was based on Canadian consensus guidelines.

Results of the manufacturer's analysis

In the manufacturer's base case, the manufacturer reported that aflibercept was cost saving compared with ranibizumab, with a savings of $23,127 over 10 years.

Interpretations and key limitations

The main limitation of the cost-minimization analysis was the uncertainty regarding the dose frequency of ranibizumab. The clinical expert felt it was unlikely that ranibizumab would be administered as frequently as was assumed for the base-case analysis, particularly in year 1. Therefore, the base case

may have overestimated the expected cost of ranibizumab and the relative cost savings associated with aflibercept.

Results of the CADTH Common Drug Review analysis

Considering alternative dosing schedules, as ranibizumab is rarely administered monthly in clinical practice in year 1, CDR tested the impact of individualizing ranibizumab in the first year, resulting in an estimated cost savings of $15,019 over 10 years for aflibercept. Various CDR analyses resulted in cost-savings estimates of approximately $7,000 to $15,000 over 10 years for aflibercept.

At the submitted price of $1,418 per vial, aflibercept is less costly than ranibizumab. The extent of the cost savings is highly dependent on the dose frequency used for each comparator.

Conclusions

The results of the two double-blind, multinational, active-controlled RCTs (VIEW 1 and VIEW 2) suggest that aflibercept is non-inferior to ranibizumab for maintaining vision in treatment-naive patients with wAMD. At least 94% of patients maintained their vision after 52 weeks of treatment, irrespective of whether they were treated with aflibercept or ranibizumab. There were no statistically significant differences between treatment groups in either study with respect to other outcomes, including changes in VA, the proportion of patients with legal blindness, and changes in QoL. Aflibercept and ranibizumab have similar safety profiles, as the incidences of TEAEs, SAEs, and withdrawals due to adverse event (WDAEs) were similar for both treatment groups in both studies. The results of the extension phase of VIEW 1 and VIEW 2 suggest that the similar efficacy and safety profile of aflibercept and ranibizumab observed at 52 weeks appears to persist through 96 weeks of treatment.

TABLE 1: SUMMARY OF RESULTS

Outcome	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304	N = 303	N = 304	N = 303
Patients With Maintained[a] Vision at Week 52 (PPS)				
n/N (%)	254/269 (94.4)	252/265 (95%)	254/269 (94.4)	258/270 (95.6)
Between-group difference in proportion (%) (95% CI)	–0.7 (–4.5 to 3.1)		–1.13 (–4.8 to 2.6)	
RR (95% CI)	0.99 (0.95 to 1.0)		0.99 (0.95 to 1.0)	
NNT	100		100	
Change From Baseline to Week 52 in ETDRS Letter Score in the Study Eye (FAS, LOCF)				
Baseline, mean (SD)	54.0 (13.4)	55.7 (12.8)	53.8 (13.5)	51.6 (13.9)
At 52 weeks, mean (SD)	62.1 (17.7)	63.6 (16.9)	63.1 (16.6)	60.5 (17.5)
Mean change from baseline (SD)	8.1 (15.3)	7.9 (15.0)	9.4 (13.5)	8.9 (14.4)
LSM difference[b] (95% CI) between groups	0.26 (–1.97 to 2.5)		–0.90 (–3.1 to 1.3)	
P value	0.82		0.41	
Patients Lost ≥ 15 Letters in the ETDRS Letter Score in the Study Eye at Week 52 (FAS, LOCF)				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group difference in proportion (%) (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

Outcome	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304	N = 303	N = 304	N = 303
RR (95% CI)	[redacted]		[redacted]	
NNT	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Legal blindness				
Baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
At week 52, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group difference in proportion (%) (95% CI) at 52 weeks	[redacted]		[redacted]	
[redacted]				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
SAEs				
n/N (%)	71/304 (23.4)	58/303 (19.1)	36/291 (12.4)	50/307 (16.3)
RR (95% CI)	1.22 (0.90 to 1.66)		0.76 (0.51 to 1.13)	
NNH	25		25	
WDAEs				
n/N (%)	4/306 (1.3)	6/303 (2.0)	3/303 (1.0)	10/313 (3.3)
RR (95% CI)	0.66 (0.19 to 2.32)		0.31 (0.09 to 1.12)	
NNH	100		50	
Notable harm(s)				
Injection-related ocular TEAE				
n/N (%)	183/304 (60.2)	164/303 (54.1)	94/291 (32.3)	92/307 (30.0)
RR (95% CI)	1.11 (0.97 to 1.28)		1.08 (0.85 to 1.37)	
NNH	17		50	

AE = adverse event; AFL = aflibercept; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; FAS = full analysis set; LOCF = last observation carried forward; LSM = least squares mean; NC = not calculated; NNH = number needed to harm; NNT = number needed to treat; PPS = per-protocol analysis set; RAN = ranibizumab; RR = relative risk; SAE = serious adverse event; SD = standard deviation; TEAE = treatment-emergent adverse event; VA = visual acuity; WDAE = withdrawal due to adverse event.

[a] Maintained vision defined as VA loss < 15 letters in ETDRS.

[b] Difference is ranibizumab minus aflibercept; CI was calculated using a normal approximation. LSM differences were calculated using analysis of covariance (ANCOVA) main-effect model with baseline measure as a covariate. LSM was reported and adjusted (ANCOVA) with various important baseline assessments such as VA for all efficacy outcomes analysis (such as the between-treatment group difference in proportion or the between-group difference of changes from baseline).

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Age-related macular degeneration (AMD) is a degenerative disease of the macula, the part of the retina responsible for detailed vision. In Canada, about one million people currently have early AMD and approximately 250,000 have an advanced form of AMD.[1,2] Given the aging population, the number of persons aged 85 years and older and, subsequently, those affected by AMD, is expected to double over the next 25 years.[8] In the United States, AMD is expected to affect 7.5 million people by 2020.[16] AMD is the leading cause of vision loss in people older than 50 years in North America,[17,18] and the leading cause of registered visual impairment in Canada, according to Canadian National Institute for the Blind statistics.[3] The prevalence of blindness from AMD in Canada has been estimated at more than 100,000.[4,5] Given the effect of blindness on activities of daily living, in particular self-care and mental health, AMD will become an even more important health issue as Canada's population ages.[19]

There are two types of AMD: dry AMD and neovascular (wet) AMD (wAMD). In the early stages of AMD, the dry form predominates, accounting for 90% of the disease burden. While wAMD develops in only 10% to 20% of people with dry AMD, it accounts for more than 90% of those who have advanced vision loss.[4]

The hallmark of wAMD is choroidal neovascularization, which is an abnormal angiogenic process modulated by growth factors, including vascular endothelial growth factor (VEGF).[6] It is characterized by the growth of abnormal new blood vessels arising from the choroid, leading to subretinal fluid, blood, and lipid exudation, culminating in the destruction of macular vision through the formation of disciform, fibrovascular scarring. Blocking the VEGF signal that contributes to the progression of choroidal neovascularization may allow for stabilization or regression of the disease process without adversely affecting the overlying retina. wAMD was originally classified by the proximity of the leading edge of the lesion to the centre of the macula (fovea): extrafoveal, juxtafoveal, and subfoveal. wAMD may also be subdivided angiographically into predominantly classic, minimally classic, and pure occult forms. About 40% of wAMD is of the classic subtypes, while about 60% is of the occult subtype.[4]

1.2 Standards of Therapy

Currently, there is no cure for wAMD. The goal of treatment is to minimize vision loss and disability in order to maintain independence.[7] Recent practice guidelines (June 2012),[8] based on a national consensus from Canadian retina specialists for the management of wAMD, state that intravitreal (IVT) antivascular endothelial growth factor (anti-VEGF) drugs significantly improve vision outcomes in patients with wAMD by preventing and, in some cases, reversing the damage caused by wAMD.[8] The standard pharmacological therapy is 0.5 mg ranibizumab IVT, administered monthly.[8] When monthly dosing is not feasible, an individualized ranibizumab regimen with close monitoring by optical coherence tomography (OCT) is an option. Treatment should be maintained in the presence of disease activity unless the physician believes there is sufficient permanent structural damage that continued treatment would provide no visual benefit.[8]

Pegaptanib (Macugen), an anti-VEGF aptamer that binds VEGF 165, and photodynamic therapy (PDT) using verteporfin (Visudyne), are also indicated for the treatment of wAMD in Canada. The CADTH Common Drug Review (CDR) clinical expert involved in this review, however, indicated that pegaptanib has rarely been used in clinical practice since ranibizumab was approved in Canada. PDT is occasionally used for patients with wAMD who are not suitable for IVT therapy. Bevacizumab (Avastin), a VEGF

antibody that is approved for the treatment of cancers such as lung cancer, has been used off-label as monotherapy or in combination (with PDT) as an IVT treatment for wAMD in some patients in some Canadian jurisdictions where ranibizumab is not reimbursed or in patients who are ineligible for coverage.

1.3 Drug

Aflibercept (Eylea), a solution for IVT injection (40 mg/mL) 2 mg every eight weeks after the first initial three monthly injections, is indicated in the treatment of patients with wAMD. Health Canada granted a Notice of Compliance for aflibercept for this indication in November 2013,[9] based on the strength and consistency of the results from two phase 3 randomized clinical trials.[12] Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and formulated as an iso-osmotic solution for IVT administration. Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and placental growth factor (PlGF) with higher affinity than their natural receptors, and can thereby inhibit the binding and activation of these cognate VEGF receptors.[9]

Indication under review
Treatment of neovascular (wet) age-related macular degeneration (wAMD)
Listing criteria requested by sponsor
As per indication

TABLE 2: KEY CHARACTERISTICS OF AFLIBERCEPT AND RANIBIZUMAB

	Aflibercept	Ranibizumab
Mechanism of Action	Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and can thereby inhibit the binding and activation of these cognate VEGF receptors.[9]	Ranibizumab is a humanized recombinant monoclonal antibody fragment targeted against human VEGF-A. It binds with high affinity to all active VEGF-A isoforms, thereby preventing neovascularization and vascular leakage that contribute to the progression of AMD and macular edema causing visual impairment.[20]
Indication[a]	Treatment of wAMD	
Route of Administration	Intravitreal injection	
Recommended Dose	2 mg, every 8 weeks after initial 3 monthly injections	0.5 mg, once a month
Serious Side Effects/ Safety Issues	• SAE: endophthalmitis, traumatic cataract, increased intraocular pressure, and vitreous detachment • Contraindications: patients who are hypersensitive to this drug, who have ocular or periocular infection, and who have active intraocular inflammation	• SAE: endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract, intraocular inflammation, and increased IOP • Contraindications: patients who are hypersensitive to this drug, who have active or suspected ocular or periocular infections, and who have active intraocular inflammation

IOP = intraocular pressure; PIGF = placental growth factor; SAE = serious adverse event; VEGF = vascular endothelial growth factor; wAMD = neovascular (wet) age-related macular degeneration.
[a] Health Canada indication.
Source: Product monographs for aflibercept[9] and ranibizumab.[20]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a review of the beneficial and harmful effects of aflibercept, a 40 mg/mL solution for IVT injection at the Health Canada–recommended dose and regimen for the treatment of wAMD.

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies supporting the Health Canada indication provided in the manufacturer's submission to CDR, as well as those meeting the inclusion criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with wAMD Subgroup: baseline VA
Intervention	Aflibercept (40 mg/mL solution for IVT injection), 2 mg, IVT injection every 8 weeks after 3 initial monthly injections.
Comparators	Ranibizumab[a]
Outcomes	**Efficacy outcomes:** • Change from baseline in VA[b] • QoL/vision function (assessed by validated measures, such as NEI VFQ-25) • Legal blindness • Change in CRT **Harms outcomes:** • AE • SAEs (ocular or non-ocular) • WDAE • Mortality • Notable AEs: endophthalmitis, retinal detachment, ATE
Study Design	Published and unpublished DB RCTs

AE = adverse event; ATE = arterial thrombotic event; CRT = central retina thickness; DB = double-blind; IVT = intravitreal injection; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; NEI VFQ-25 = National Eye Institute 25-Item Visual Function Questionnaire; VA = visual acuity; wAMD = neovascular (wet) age-related macular degeneration; WDAE = withdrawal due to adverse event.

[a] Standard pharmacotherapy available in Canada. Other approved drugs include verteporfin photodynamic therapy and pegaptanib. Bevacizumab has been used off-label in Canada.

[b] VA change from baseline comprised absolute change, percentage of patients maintaining vision (defined as VA worsening from baseline of ≤ 15 letters), percentage of patients maintaining vision (defined as VA worsening from baseline of ≥ 15 letters or ≥ 30 letters visual acuity).

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid, Embase (1974–) through Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Eylea (aflibercept) and macular degeneration.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on May 23, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on Sept 17, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug regulatory approvals, advisories and warnings, drug class reviews, and databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and by contacting appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

2.2.1 Supplemental issues

1. Validity of Outcome Measures: Early Treatment Diabetic Retinopathy Study (ETDRS), Snellen chart, National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25)
2. Summary of findings from extension studies at 96 weeks.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in Appendix 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

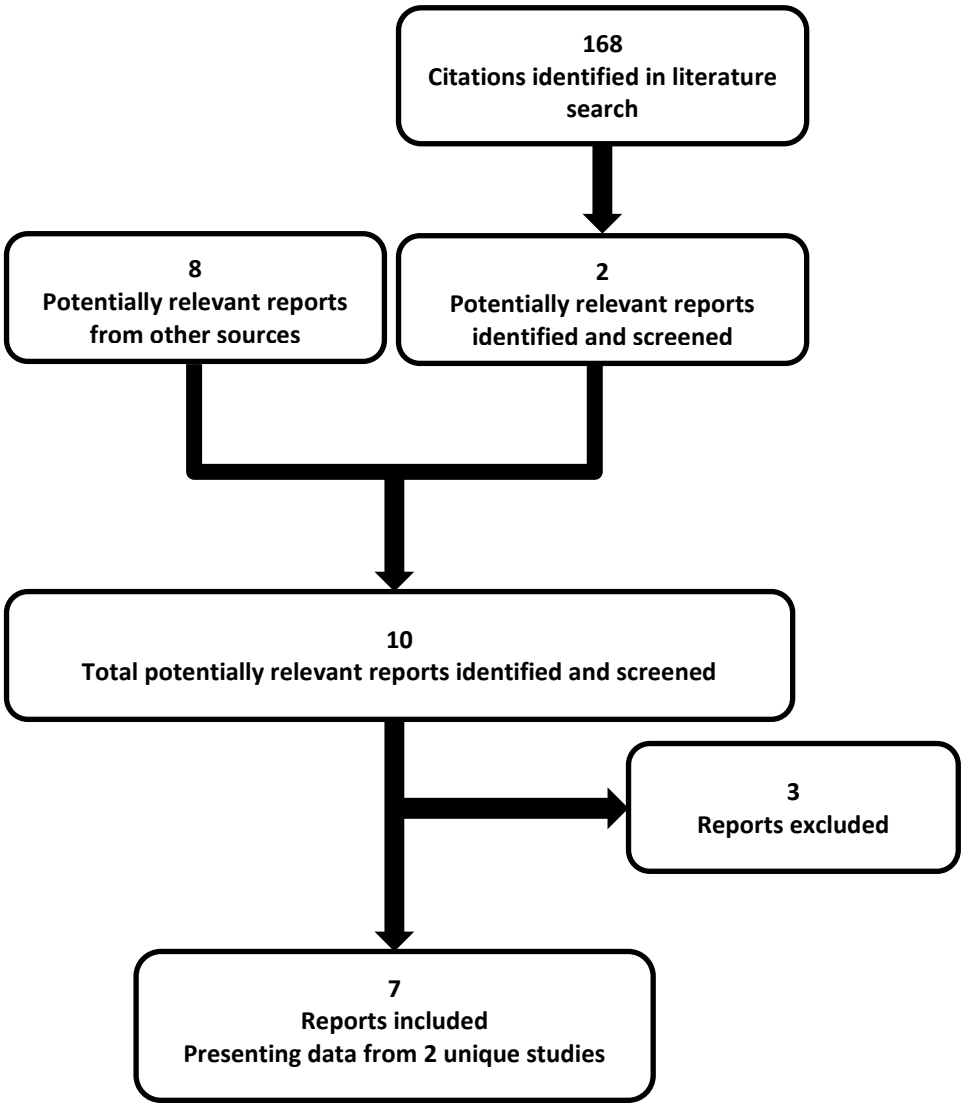

TABLE 4: DETAILS OF INCLUDED STUDIES

		VIEW 1	VIEW 2
DESIGNS & POPULATIONS	**Study Design**	Phase 3, DB, multinational, active-controlled, non-inferiority design RCT	
	Locations	154 sites in the United States and Canada	172 sites in Asia, Europe, and Australia[12]
	Randomized (N)[a]	609 (in ranibizumab and aflibercept [2 mg every 8 weeks]) (1,217 in all 4 groups in total)	616 (in ranibizumab and aflibercept [2 mg every 8 weeks]) (1,240 in all 4 groups in total)
	Inclusion Criteria	● Age ≥ 50 years with active subfoveal CNV lesions (any subtype) secondary to AMD; juxtafoveal lesions with leakage affecting the fovea were also allowed ● CNV comprising at least 50% of total lesion size ● BCVA between 73 and 25 ETDRS letter score (20/40 to 20/320 Snellen equivalent)[12]	
	Exclusion Criteria	●Patients with prior treatment for AMD (including an investigational drug or anti-VEGF therapy) in the study eye were excluded[b12]	
DRUGS	**Intervention**	2 mg aflibercept every 8 weeks (2q8), IVT injection after 3 initial monthly injections	
	Comparator(s)	0.5 mg ranibizumab (Rq4) IVT injection every 4 weeks	
DURATION	**Phase**		
	Screen phase	21 days (day –21 to day 0)	
	Run-in	None	
	DB	52 weeks	
	Extension phase	44 weeks (from week 52 to week 96)	40 weeks (from week 52 to week 96)
	Follow-up	None	
OUTCOMES	**Primary End Point**	The primary end point analysis was the non-inferiority of the IVT aflibercept regimens to the IVT ranibizumab regimen in the proportion of patients maintaining vision at week 52 (losing < 15 ETDRS letters; per-protocol data set) in each study.	
	Other End Points	Pre-specified secondary efficacy variables compared baseline data and data at week 52 regarding mean change in BCVA, gain or loss ≥ 15 letters, change in total NEI VFQ-25 score, and change in CNV area on fluorescein angiography. Anatomic measures included CRT and persistent fluid as assessed by OCT.[12] Adverse events.	
NOTES	**Publications**	Heier et al. (2012)[12]	

2q4 = 2 mg aflibercept every four weeks; 2q8 = 2 mg aflibercept every eight weeks; AFL = aflibercept; AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CNV = choroidal neovascularization; CRT = central retinal thickness; DB = double-blind; ETDRS = Early Treatment Diabetic Retinopathy Study; IVT = intravitreal; NEI VFQ-25 = National Eye Institute 25-Item Visual Function Questionnaire; OCT = optical coherence tomography; RCT = randomized controlled trial; Rq4 = 0.5 ranibizumab every four weeks; VEGF = vascular endothelial growth factor.

[a] Patients were randomized in a 1:1:1:1 ratio to the following regimens: 0.5 mg aflibercept every four weeks (0.5q4); 2 mg aflibercept every four weeks (2q4); 2 mg aflibercept every eight weeks (2q8) after three injections at weeks 0, 4, and 8 (to maintain masking, sham injections were given at the interim four-week visits after week 8); or 0.5 mg ranibizumab every four weeks (Rq4). Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation, managed by an interactive voice response system.[12] In this review, only 2q4, 2q8, and Rq4 were reported.

[b] Prior treatment with an approved anti-VEGF therapy in the fellow eye was allowed.

Note: In addition to the one published article, six additional reports and documents were included: one submission package,[21] two Clinical Study Reports,[10,11] two FDA review reports,[22,23] and one Health Canada review report.[24]

Source: Heier et al. (2012).[12]

3.2 Included Studies

3.2.1 Description of studies

Two studies (VIEW 1[10] and VIEW 2[11]) that met the inclusion criteria for the review were identified. Both studies were non-inferiority designed, double-blind, randomized controlled trials (RCTs) that examined the efficacy and safety of aflibercept versus ranibizumab in the treatment of patients with wAMD. VIEW 1 was conducted at 154 sites in the US and Canada (N = 1,217) and VIEW 2 was conducted at 172 sites in Asia, Europe, and Australia (N = 1,240).[10-12] Sample sizes in the ranibizumab (Rq4) and aflibercept (2q8) groups ranged from 606 to 616. The entire trial duration was 96 weeks, including a first year (52-week), fixed-dose interval phase and a second year (up to 96 weeks), flexible-dose interval phase.

The primary objective of the two studies was to assess the efficacy of IVT aflibercept compared with ranibizumab in preventing moderate vision loss (i.e., loss of < 15 ETDRS letters) at week 52.[12] In the included two trials, there were four treatment groups: 0.5 mg aflibercept every four weeks (0.5q4); 2 mg aflibercept every four weeks (2q4); 2 mg aflibercept every eight weeks (2q8) after three injections at weeks 0, 4, and 8 (to maintain masking, sham injections were given at the interim four-week visits after week 8); or 0.5 mg ranibizumab every four weeks (Rq4). This report focuses primarily on the comparative efficacy and safety profile of aflibercept (2 mg aflibercept every eight weeks [2q8] after three monthly injections with ranibizumab (0.5 mg ranibizumab every four weeks [Rq4]) at week 52. The results observed at week 96 are briefly summarized in Supplemental Issues (Appendix 6).

3.2.2 Populations

a) Inclusion and exclusion criteria

The key inclusion criteria included patients aged 50 years or older with active subfoveal choroidal neovascularization (CNV) lesions (any subtype) secondary to AMD, including juxtafoveal lesions that had affected the fovea as evidenced by fluorescein angiography in the study eye; CNV comprising at least 50% of total lesion size; and ETDRS best corrected visual acuity (BCVA) between 73 and 25 letters (20/40 to 20/320 Snellen equivalent). Patients with prior treatment for AMD (including an investigational drug or anti-VEGF therapy) in the study eye were excluded. Inclusion and exclusion criteria were designed to maintain constancy with the pivotal trials for ranibizumab (the reference drug, the comparator) and were consistent with regulatory guidelines for non-inferiority studies.[12]

b) Baseline characteristics

Overall, the demographic and baseline characteristics of the patients included in the studies were balanced between treatment groups in both studies (Table 5). The mean age of the randomized patients was 73 to 78 years old (range from 49 to 99 years old). More female patients (57% to 59%) were included in both trials. Patients were predominantly Caucasian (95% to 97% in VIEW 1, and 71% to 73% in VIEW 2). The mean baseline BCVA letter scores ranged from 52 to 58 and were similar between the two treatment groups (see Table 5). The proportions of patients with 20/40 BCVA ranged from 4% to 6%. The most commonly represented lesion type was occult (38% to 39% in VIEW 1, and 36% to 40% in VIEW 2). The mean central retinal thickness (CRT) ranged from 315 µm to 343 µm. The mean CNV area ranged from 6.89 mm^2 to 6.99 mm^2 in VIEW 1, and from 8.01 mm^2 to 8.22 mm^2 in VIEW 2. Mean baseline NEI VFQ-25 total scores ranged from 69 to 73 out of a total of 100 possible points (see Table 5). More detailed information on baseline characteristics is presented in Appendix 4, Table 9.

TABLE 5: SUMMARY OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS (FULL ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304	N = 301	N = 291	N = 306
Age (years)				
Mean (SD)	78.2 (7.6)	77.9 (8.4)	73.0 (9.0)	73.8 (8.6)
Sex, n (%)				
Female	172 (56.6)	178 (59.1)	169 (58.1)	175 (57.2)
Male	132 (43.4)	123 (40.9)	122 (41.9)	131 (42.8)
Baseline ETDRS BCVA, mean (SD)	54.0 (13.4)	55.7 (12.8)	53.8 (13.5)	51.6 (13.9)
[redacted]				
[redacted]				
[redacted]				
Lesion subtype, n (%)				
Predominantly classic	82 (27.0)	71 (23.6)	70 (24.1)	88 (28.8)
Minimally classic	101 (33.2)	110 (36.5)	104 (35.7)	106 (34.6)
Occult	115 (37.8)	118 (39.2)	116 (39.9)	110 (35.9)
Juxtafoveal lesions	15 (4.9)	17 (5.6)	20 (6.9)	14 (4.6)

AFL = aflibercept; BCVA = best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; RAN = ranibizumab; SD = standard deviation.
Source: Clinical Study Reports: VIEW 1[25] (T12, p. 80), VIEW 2[11] (T13, p. 87), and Heier et al. (2012)[12] (T1, p. 2,541).

3.2.3 Interventions

In both trials, there were four treatment groups. Only the Health Canada–recommended dosage and regimen are discussed in this report: 0.5 mg ranibizumab every four weeks (Rq4) and 2 mg aflibercept every eight weeks (2q8) after three initial monthly injections (to maintain masking, sham injections were given at the interim four-week visits after week 8 for the aflibercept group; sham injections using a mock procedure, including pressure on the eye exerted by a syringe without a needle, were performed without intraocular penetration and thus without the injection of any substance). Patients were assigned to treatment groups on the basis of a predetermined, central randomization scheme with balanced allocation, managed by an interactive voice response system.[12] For each individual patient, one eye was designated as the study eye; i.e., the eye to receive the study treatment. The non-study eye was designated as the fellow eye. If a patient's fellow eye required treatment for AMD at study entry or during the study, the fellow eye could receive any FDA or Health Canada–approved treatment for wAMD in the VIEW 1 study, or any European Medicines Agency or regionally approved treatment in accordance with the treating physician's decision in the VIEW 2 study, but systemic treatments (standard or investigational drugs) for AMD of the fellow eye were not permitted. The fellow eye was not considered an additional study eye.

3.2.4 Outcomes

Outcomes were assessed at four-week intervals for safety and efficacy throughout the 52 weeks. BCVA was evaluated using the 4 m ETDRS protocol. QoL was measured using the NEI VFQ-25. Retinal thickness was evaluated using OCT on the study eye. OCT examinations were performed at screening, on day 1,

and at weeks 4, 12, 24, 36, and 52. Safety was monitored through the collection of data on ocular and non-ocular adverse events (AEs) and concomitant medications.

a) Primary outcome

The primary outcome was maintained vision, which was defined as a VA loss of < 15 ETDRS letters compared with baseline at week 52. Usually, a loss of < 15 letters on the ETDRS chart was considered a mild VA loss. A loss of ≥ 15 letters was considered a moderate vision loss. A loss of ≥ 30 letters was considered to be a severe VA loss. Therefore, the primary outcome, maintained vision, was also interpreted as the prevention of moderate VA loss.

b) Secondary outcomes

Visual acuity measured with early treatment diabetic retinopathy study letters

The secondary outcome was the change from baseline in BCVA as measured by ETDRS letter score at week 52. ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between the letters and rows. There are a total of 14 lines (i.e., 70 letters). Reading more lines (i.e., more letters) indicates better VA. The FDA recommends a mean change of ≥ 15 letters on an ETDRS chart, or a statistically significant difference in the proportion of patients with a ≥ 15 letter change in VA, as clinically relevant outcome measures in trials of interventions for macular edema.[22]

With regard to the proportion of subjects who gained or lost ≥ 15 letters of vision (or ≥ 30) from baseline to week 52, a loss or gain of three lines (15 letters) is usually considered a moderate degree of change and is commonly used as an outcome in clinical trials.[26] A gain of ≥ 30 ETDRS letters is considered a significant improvement, and loss of ≥ 30 is considered severe loss in VA.[26]

Visual acuity measured with the Snellen eye chart

The Snellen eye chart is a commonly employed, well-recognized test of VA in clinical practice. A patient with a BCVA of 20/200 or worse at week 52 (equivalent to < 35 ETDRS letters) is considered legally blind.[11,25]

Quality of life/vision function

Quality of life (QoL) and vision function were evaluated using the NEI VFQ-25 in both VIEW 1 and VIEW 2. The VFQ-25 includes 25 items relevant to 11 vision-related constructs, in addition to a single-item general health component.[27] The possible range of the NEI VFQ-25 total score is between 0 (worst possible) and 100 (best possible). A four-point improvement from baseline was considered to be a minimal clinically important difference (MCID).[27] The change in total NEI VFQ-25 score from baseline to week 52 was measured. QoL, measured using the EuroQol 5-Dimensions Questionnaire (EQ-5D), was also reported in VIEW 2. EQ-5D is a generic QoL instrument that has been applied to a wide range of health conditions.[28,29]

Change in central retinal thickness

Change in CRT was evaluated using OCT on the study eye.

Safety outcomes

Mortality, ocular and non-ocular SAEs, overall AEs, potential AEs with special clinical interest, and injection-related AEs were also reported.

3.2.5 Statistical analysis

a) Primary outcome analysis

The primary outcome analysis was non-inferiority of IVT aflibercept to ranibizumab in the proportion of patients maintaining vision (i.e., a loss of < 15 letters) at week 52 (per-protocol analysis set [PPS]) in both studies. The non-inferiority margin was set as < 10% of the 95% confidence interval (CI) of the difference between ranibizumab and aflibercept in the proportion of patients who maintained vision at week 52 compared with baseline. A non-inferiority margin of 10% in the individual studies was chosen to preserve approximately two-thirds of the ranibizumab effect for the prevention of moderate vision loss (loss of < 15 letters) demonstrated in the pivotal ranibizumab studies[14,15] using the two-sided CI approach. For last observation carried forward (LOCF), baseline values were not carried forward. The difference was expressed as ranibizumab minus aflibercept; 95% CI was calculated using a normal approximation.

A CI approach was used for the non-inferiority analysis. The statistical objective was to demonstrate that the 95% CI of the difference between ranibizumab and aflibercept in the proportion of patients who maintained vision at week 52 compared with baseline lay entirely below 10%, the non-inferiority margin. Because both included studies were designed as a four-group study, two-group pairwise comparisons were of interest, and the primary outcome was assessed by a pre-specified, hierarchical testing sequence of non-inferiority of aflibercept to ranibizumab, with the sequence to control the 5% overall type I error while maintaining a 5% significance level for each individual comparison.

The sample size calculation was computed using the following assumption: test of equivalence for proportions from the commercial software nQuery Advisor 6.0. Assuming that 90% of patients treated with ranibizumab would maintain vision, and assuming that 90% of patients treated with aflibercept (2q8) would also maintain vision, and defining the non-inferiority margin at 10%, 191 patients per group would provide 90% power to demonstrate non-inferiority, assuming an alpha level = 0.049. This included an adjustment of 0.001 for the independent data monitoring committee safety assessments, 0.0001 for each of the 10 assessments, thereby preserving an overall alpha of 0.05 for the study. Assuming a dropout rate of approximately 30%, an enrolment of 300 patients per group was determined to provide adequate power for this study to achieve its objectives under the stated assumptions.

b) Secondary outcome analyses

Secondary outcome analyses were tested for the superiority of aflibercept (2q8) over ranibizumab. If all aflibercept groups demonstrated non-inferiority to ranibizumab for the primary end point, additional comparisons with ranibizumab were pre-specified regarding the secondary end points, also using a hierarchical testing sequence in which each secondary end point was tested for the superiority of aflibercept over ranibizumab.

Analyses of continuous outcomes used analysis of covariance (ANCOVA) with a main-effects model, with baseline measure as a covariate and treatment as a fixed factor. The pairwise comparisons of aflibercept and ranibizumab were carried out in these models by corresponding CONTRAST statements and a point estimate, and two-sided 95% CIs for the treatment difference of aflibercept minus ranibizumab were calculated. The effects of investigator site differences were examined as a supportive analysis. Sites were described separately with calculations of CIs and other appropriate descriptive statistics. Assessment of treatment-by-site interaction was performed using ANCOVA for continuous variables and the Pearson chi-square test for proportion.

c) Sensitivity analyses

To assess the robustness of the main analysis results, additional methods (worst observation carried forward, all dropouts counted as non-responders, or treatment failures counted as non-responders) were used to impute missing values for the purpose of sensitivity analyses. Sensitivity analyses using worst-case scenarios were performed in both the PPS and full analysis set (FAS) populations (Table 13 and Table 14).

d) Subgroup analyses

The following subgroup analyses were performed on primary outcomes and key secondary outcomes: baseline VA (better than 20/100 [≥ 50 letters]), 20/100 to 20/200 VA [≥ 35 to < 50 letters], and worse than 20/200 VA [< 35 letters]); age (< 65 years, ≥ 65 to < 75 years, ≥ 75 years); gender; race (e.g., Caucasian, black or African-American); lesion size (> 10.16 mm^2 to ≤ 10.16 mm^2); and lesion type (predominantly classic, minimally classic, and occult) (Appendix 4, Table 30, Table 31 and Table 32).

e) Analysis populations

All efficacy analyses were conducted with patients as randomized. The following three analysis sets were used for all statistical analyses: FAS, PPS, and the safety analysis set (SAF). The FAS included all randomized patients who had received any study medication and who had a baseline assessment and at least one post-baseline BCVA assessment. The FAS was used for all hypothesis tests of superiority (for all secondary outcomes) (Table 6). The PPS included all patients in the FAS who had received at least nine doses of the study drug (sham injections were counted as doses administered) and who had attended at least nine scheduled visits during the first year, except for those who were excluded because of major protocol deviations. The PPS was used for the primary analysis (statistical evaluation of non-inferiority) (Table 6). The SAF included all patients who had received any study medication (Table 6).

3.3 Patient Disposition

Information on patient disposition in the VIEW 1 and VIEW 2 studies is summarized in Table 6. The discontinuation rate from the study was similar between the aflibercept (2q8) and ranibizumab groups in both studies (8.9% to 9.3% in VIEW 1, and 7.2% to 8.9% in VIEW 2, respectively). The most common reason for discontinuation in the aflibercept (2q8) and ranibizumab groups was withdrawal by patients with no further detailed reason reported (3.3% to 3.6% in VIEW 1, and 2.6% to 3.5% in VIEW 2, respectively). Completion of the first year was not necessarily associated with completion of the study drug during this period; i.e., patients who discontinued the study drug were allowed to remain in the study and undergo the planned evaluations. More detailed information on patient disposition is presented in Appendix 4, Table 10.

TABLE 6: PATIENT DISPOSITION

	VIEW 1		VIEW 2	
Disposition or Reason	**RAN**	**AFL**	**RAN**	**AFL**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Screened[a]	2,063		2,031	
Randomized	306 (100)	303 (100)	303	313
Completed at 52 weeks	284 (92.8)	276 (91.1)	276 (91.1)	284 (90.7)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FAS[b]	304 (99.3)	301 (99.3)	291 (96)	306 (97.8)
PPS[b]	269 (87.9)	265 (87.5)	269 (88.8)	270 (86.3)
Safety	304 (99.3)	303 (100)	291 (96)	307 (98.1)

AFL = aflibercept; FAS = full analysis set; PPS = per-protocol analysis set; RAN = ranibizumab.
[a] Total screened number of patients.
[b] The number could vary with different outcomes.
Source: VIEW 1: T7, p. 73; and VIEW 2: T7, p. 83.

3.4 Exposure to Study Treatments

Detailed information on medication exposure and compliance is presented in Appendix 4 (Table 11 and Table 12). The median numbers of aflibercept and ranibizumab injections were 8 and 13, respectively. The median amount of aflibercept and ranibizumab was 16 mg and 6.5 mg, respectively. Compliance with aflibercept and ranibizumab was high and also similar (97% to 98% for both treatment groups).[12] During the study, patients were not permitted to receive any other treatment for AMD in the study eye. Other commonly concomitant medications, including antiseptics and disinfectants, ophthalmologicals, and dermatologicals, were used in a similar manner in both treatment groups.

3.5 Critical Appraisal

3.5.1 Internal validity

The included studies were double-masked, multi-centre, randomized, active-controlled, non-inferiority trials. The randomization process, including allocation concealment and masking method, were well described and performed. Overall, the important baseline characteristics were similar between the two treatment groups.

Up to 14% of patients dropped out of the PPS analysis. Protocol deviation would likely bias the study findings toward non-inferiority, which includes loss to follow-up (7% to 9%) and non-adherence to the assigned therapy. The non-inferiority analysis was based on the PPS, which is more conservative than an analysis based on the FAS. Confidence regarding non-inferiority could be enhanced if there is consistency between both analyses.

In both trials, the efficacy of aflibercept and ranibizumab as compared with "placebo" is not confirmed directly. The non-inferiority findings may mean that both interventions are not significantly more effective than placebo. Under the constancy assumption, the non-inferiority trial should have a design similar to previous trials, which demonstrated the efficacy of ranibizumab versus placebo. It seems likely that this assumption was satisfied, as the absolute change in BCVA from baseline to 52 weeks was similar to previous pivotal studies on ranibizumab.[14,15]

The methodological approach to assessing non-inferiority was to calculate the 95% CI using a normal approximation of the difference between the proportions of patients with maintained vision at week 52 for each group. While it is unknown whether the assumption of a normal approximation is valid, this does not substantially affect the construction of the 95% CI.

Multiplicity for the primary analysis was performed to control the type I error. In the VIEW 2 study, which was conducted in Asia, Australia, and Europe, the primary analysis was also adjusted by study region. The robustness of the primary analysis results was confirmed by various sensitivity analyses, including using worst-case scenarios and worst-observation-carried-forward analysis.

While the studies were considered to be well designed overall, the methodological quality could potentially have been limited because randomization was not stratified by investigation site, and the main analyses were adjusted by region only in VIEW 2, not VIEW 1. However, because VIEW 1 was conducted in the US and Canada, where the management of wAMD is highly consistent, significant treatment response variation between regions is unlikely. The randomization was not stratified based on the baseline VA, although the subgroup analysis showed that the results are consistent with the main primary analysis. The primary analysis was adjusted by baseline VA due to the relatively small sample size. It is unknown whether the absence of statistically significant differences between the two treatments in the various subgroups reflects actual differences or is due to a lack of power. Sample size was calculated based on the non-inferiority design for the primary outcome. Therefore, it remains unknown whether the observed statistically non-significant difference between ranibizumab and aflibercept (2q8) in terms of secondary outcomes is due to lack of power or because there is truly no difference.

The assessment of any improvements in QoL as an effect of the treatments in study eyes may have been compromised by the treatments received by the fellow eyes at study entry or during the course of the study.

3.5.2 External validity

Patients were excluded if they had had any prior or concomitant therapy, surgery, or photodynamic therapy (PDT) for wAMD. Therefore, the non-inferiority of the study drug to a standard therapy was demonstrated only in a treatment-naive population based on the two included studies for this review. Patients previously treated with anti-VEGF drugs were excluded in both studies. Only one eye per patient was treated with aflibercept; therefore, further study is needed on the efficacy and safety of aflibercept in patients with wAMD who failed previous treatment or who had aflibercept therapy administered to both eyes concurrently or consecutively.

Moreover, patients with eye disease or comorbidities other than wAMD — such as a history of any vitreous hemorrhage, vitrectomy, severe subretinal hemorrhages, or large lesion size (> 12 disc areas) — were excluded from the study. Therefore, the safety profiles as demonstrated in the studies may not reflect real-world clinical practice. In other words, the comparability of efficacy and safety between aflibercept and ranibizumab was assessed based on a highly selected patient population.

The non-inferiority of aflibercept to ranibizumab in the treatment of wAMD was assessed at 52 weeks. Therefore, the sustainability of the comparative efficacy and safety of aflibercept (2q8) versus ranibizumab beyond one year remains uncertain.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See Appendix 4: DETAILED OUTCOME DATA for detailed efficacy data. This report focuses primarily on the comparative efficacy and safety profile of aflibercept with ranibizumab at week 52. The results observed at week 96 are briefly summarized in Supplemental Issues (Appendix 6).

3.6.1 Patients with vision maintained at week 52

At week 52, based on the per-protocol analysis, the proportion of patients who achieved maintained vision was 94% in the ranibizumab groups and 95% in the aflibercept (2q8) groups in both studies. It was shown that aflibercept (2q8) was non-inferior to ranibizumab, as demonstrated by the upper bound of the 95% CI (≤ 3.1%), which was well below the pre-specified, non-inferiority margin of 10%. The difference in vision maintenance between the ranibizumab and aflibercept (2q8) groups was –0.7% (95% CI, – 4.5% to 3.1%; *P* = 0.73) and –1.13 (95% CI, –4.81 to 2.55; *P* = 0.55) in VIEW 1 and VIEW 2, respectively (Table 7). Furthermore, the observed upper bound of 95% CI of difference (4.5% to 4.8%) also met the threshold for clinical equivalence based on a pre-specified margin of 5%. In addition, the observed upper bound of the 95% CI of difference (4.5% to 4.8%) also met the threshold for clinical equivalence based on a pre-specified margin of 5%.

The results from various sensitivity analyses using FAS were consistent with the PPS result (Appendix 4, Table 13 and Table 14). The subgroup analyses based on baseline VA showed that treatment group differences in terms of maintained vision were all similar to those in the [redacted]).

The relative risk (95% CI) (ranibizumab versus aflibercept, calculated by CDR) is 0.99 (0.95 to 1.03) for both VIEW 1 and VIEW 2 (Table 7).

3.6.2 Change from baseline to week 52 in ETDRS letter score

Baseline BCVA was similar between treatment groups in FAS. A BCVA improvement of eight to nine letters was observed in both the ranibizumab and aflibercept groups in both studies. The least squares mean treatment group difference of BCVA improvement from baseline (aflibercept minus ranibizumab, mean [95% CI]) was 0.26 (–1.97 to 2.49) in VIEW 1 and –0.90 (–3.06 to 1.26) in VIEW 2, respectively. No statistically significant difference between the two treatment groups was observed (Table 7). Repetition of the ANCOVA with region adjustment yielded nearly identical results; i.e., [redacted]. No region adjustment was performed in VIEW 1. The subgroup analyses based on baseline VA showed that treatment group differences in terms of change from baseline to week 52 in ETDRS letter score were all similar to those in the overall study population among different baseline VA levels (Appendix 4, Table 31).

3.6.3 Proportion of patients with 20/40 vision or better

The proportion of patients with 20/40 vision or better was similar among treatment groups at baseline in both studies. [redacted].

3.6.4 Proportion of patients who gained ≥ 15 letters (or ≥ 30 letters) in the ETDRS letter score

At week 52, the proportions of patients who made a gain in vision of ≥ 15 letters in the aflibercept (2q8) group and in the ranibizumab group were similar (31% in both the aflibercept and ranibizumab groups in VIEW 1, and 31% in aflibercept and 34% in the ranibizumab group in VIEW 2). The treatment group differences in percentage improvement between aflibercept and ranibizumab were –0.4 (95% CI, –7.7 to 7) in VIEW 1 and –2.65 (95% CI, –10.18 to 4.88) in VIEW 2, respectively. [redacted]

3.6.5 Proportion of patients who lost ≥ 15 letters (or ≥ 30 letters) in the ETDRS letter score

Overall, the proportion of patients who lost ≥ 15 letters in the aflibercept group was similar to the proportion in the ranibizumab group in both VIEW 1 (6%) and VIEW 2 (5%) at week 52 (Table 7). [redacted]

3.6.6 Quality of life/vision function

The baseline mean NEI VFQ-25 total score was similar in both treatment groups in both studies (70 to 73, out of a total score of 100). At week 52, the NEI VFQ-25 total score improved by about five points in both the ranibizumab and aflibercept (2q8) groups in both studies. The mean difference between treatment groups in the changes from baseline (ANCOVA), with or without region adjustment, was not statistically significant (Table 7). No noticeable improvement in the EQ-5D score was observed in either of the treatment groups in VIEW 2 (Table 20).

3.6.7 Legal blindness

Legal blindness refers to a BCVA of 20/200 or worse. The proportion of patients with a BCVA of 20/200 or worse at baseline was [redacted]. At week 52, [redacted] in ranibizumab and aflibercept, respectively. There was no statistically significant difference between treatment groups at week 52 (Table 7).

3.6.8 Change from baseline to week 52 in central retinal thickness

Baseline CRT was similar between treatment groups in both studies, although the central retina was thicker in VIEW 2 than in VIEW 1 in the FAS (326 µm to 342 µm in VIEW 2 and 267 µm to 269 µm in VIEW 1, respectively). At week 52, in VIEW 1, [redacted]. In VIEW 2, [redacted].

TABLE 7: KEY EFFICACY OUTCOMES

	VIEW 1		VIEW 2	
	RAN N = 304	AFL N = 301	RAN N = 291	AFL N = 306
Patients with vision maintained at week 52 (PPS)[a, b]				
n/N (%)	254/269 (94.4)	252/265 (95)	254/269 (94.4)	258/270 (95.6)
Non-inferiority test difference in proportion (RAN – AFL), (%) (95% CI)	–0.7 (–4.5 to 3.1)		–1.13 (–4.81 to 2.6)	
RR (95% CI)	0.99 (0.95 to 1.0)		0.99 (0.95 to 1.0)	
NNT	100		100	
P value[c]	0.73		0.55	
Change from baseline to week 52 in ETDRS letter score in the study eye (FAS, LOCF): Mean (SD)				
Baseline	54.0 (13.4)	55.7 (12.8)	53.8 (13.5)	51.6 (13.9)
At 52 weeks	62.1 (17.7)	63.6 (16.9)	63.1 (16.6)	60.5 (17.5)
Change from baseline	8.1 (15.3)	7.9 (15.0)	9.4 (13.5)	8.9 (14.4)
LSM difference (AFL – RAN), (95% CI)	0.26 (–1.97 to 2.5)		–0.90 (–3.1 to 1.3)	
P value	0.82		0.42	
Patients gained ≥ 15 letters in the ETDRS letter score in the study eye at week 52 (FAS, LOCF)[b]				
n/N (%)	94/304 (30.9)	92/301 (30.6)	99/291 (34.2)	96/306 (31.4)
LSM difference in proportion (AFL – RAN), (%) 95% CI	–0.4 (–7.7 to 7.0)		–2.65 (–10.2 to 4.9)	
P value	0.93		0.49	
RR (CI)	1.01 (0.8 to 1.3)		1.08 (0.9 to 1.4)	
NNT	NE		34	
P value	0.92		0.49	
[redacted]				

	VIEW 1		VIEW 2	
	RAN N = 304	AFL N = 301	RAN N = 291	AFL N = 306
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Between-group difference in proportion (%) (95% CI) at 52 weeks	0.1 (–4.5 to 4.7)		3.22 (–1.39 to 7.84)	
P value	< 1		0.173	
Change from baseline to week 52 in NEI VFQ-25 (total score) (FAS, LOCF)				
Baseline				
n	303	293	291	306
Mean (SD)	71.8 (17.2)	69.6 (16.8)	72.9 (19.1)	71.3 (19.1)
At 52 weeks				
n	300	299	287	299
Mean (SD)	76.8 (16.1)	74.6 (17.7)	79.5 (16.7)	76.4 (19.3)
Change from baseline at week 52	4.9 (14.1)	5.1 (14.7)	6.3 (14.8)	4.9 (14.7)
LSM between-group difference in changes from baseline, % (95% CI) (AFL – RAN)	–0.60 (–2.6 to 1.4)		–1.95 (–4.1 to 0.2)	
P value	-	0.56	-	0.072
Change from baseline to week 52 in CRT (FAS, LOCF)				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
LSM between-group difference in changes from baseline, (95% CI) (AFL – RAN)	–0.05 (–9.7 to 9.6)		3.6 (–6.99 to 14.2)	
P value		0.99	-	0.51

AFL = aflibercept; CDR = CADTH Common Drug Review; CI = confidence interval; CRT = central retinal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; FAS = full analysis set; LOCF = last observation carried forward; LSM = least squares mean; NEI VFQ-25 = National Eye Institute 25-Item Visual Function Questionnaire; NNT = number needed to treat; PPS = per-protocol analysis set; RAN = ranibizumab; RR = relative risk; SD = standard deviation; VA = visual acuity.

[a] "Maintained vision" is defined as VA loss < 15 letters in ETDRS. Difference is ranibizumab minus aflibercept; CI was calculated using a normal approximation. LSM difference was calculated using an analysis of covariance (ANCOVA) main-effect model with baseline measure as a covariate.

[b] All RR, absolute risk reduction, NNT, and NNH for proportion outcome were calculated by CDR.

[c] "Legal blindness" is defined as a patient with VA of 20/200 or worse.

Source: VIEW 1: T18, p.88, and VIEW 2: T19, p. 97; VIEW 1: T28, p. 108, p. 930–931, and VIEW 2: T30, p. 124; VIEW 1: T23, p. 97, and VIEW 2: T25, p. 111; VIEW 1: T24, p. 100, and VIEW 2: T26, p. 114; VIEW 1: T30, p. 111, and VIEW 2: T32, p. 130.

3.7 Harms

Only those harms identified in the review protocol are reported below (see Section 2.2.1 – Protocol, and Appendix 4: DETAILED OUTCOME DATA for detailed harms data). All AEs occurring during this study were classified as either ocular AEs or non-ocular AEs. Harms data from the included studies are reported as treatment-emergent adverse events (TEAEs). In addition, SAEs, mortality, and WDAEs, injection-related TEAEs, and notable AEs identified for the review following discussion with the clinical expert involved in the review, such as an arterial thrombotic event (ATE), are reported.

3.7.1 Adverse events

Overall, 95% of patients in VIEW 1 and 85% to 90% in VIEW 2 reported TEAEs during the first year of the study (Table 8). The incidences of overall TEAEs, ocular TEAEs in the study (Table 21, Table 22), and non-ocular TEAEs (Table 23) were similar between the treatment groups. Injection-related TEAEs were reported to be 60% in the ranibizumab group versus 54% in the aflibercept group in VIEW 1, and 32% and 29% in the ranibizumab and aflibercept groups, respectively, in VIEW 2 (Table 24). The most commonly reported ocular AEs were conjunctival hemorrhage, vitreous floaters, eye pain, vitreous detachment, reduced VA, retinal pigment epitheliopathy, macular degeneration, and increased intraocular pressure (Table 22).

3.7.2 Serious adverse events

In VIEW 1, the incidence of treatment-emergent SAEs was numerically higher in the ranibizumab group (22.4%) than in the aflibercept group (18.5%), while in VIEW 2, the incidence of treatment-emergent SAEs was numerically higher in the aflibercept group (15.6%) than in the ranibizumab group (12.0%) (Table 8).

a) Ocular serious adverse events in the study eye

A serious ocular AE was defined as an AE causing a decrease in VA of more than 30 letters lasting more than one hour post-injection, and an AE requiring surgical intervention to prevent permanent loss of vision. The incidence of ocular SAEs in the study eye was numerically higher in the ranibizumab group than in the aflibercept group (3.3% versus 1.0% in VIEW 1 and 3.1% versus 2.9% in VIEW 2, respectively). Most of them were attributable to the injection procedure or the progression of the disease. The reported ocular SAEs in the study eye were mainly endophthalmitis, retinal hemorrhage, reduction in VA, and posterior capsule opacification. Details on ocular SAEs in the study eye are presented in Table 25.

b) Ocular serious adverse events in the fellow eye

The incidence of ocular SAEs in the fellow eye was low and was similar between treatment groups in both studies (1.0% versus 0.7% in VIEW 1 and 1% versus 1% in VIEW 2, respectively). Details on ocular SAEs in the fellow eye are presented in Table 26.

c) Non-ocular serious adverse events

The overall incidence of non-ocular SAEs was similar in both treatment groups (18.8% versus 16.8% in the ranibizumab and aflibercept groups, respectively, in VIEW 1; and 8.9% versus 12.4% in the ranibizumab and aflibercept groups, respectively, in VIEW 2) (Table 27). The reported non-ocular SAEs included pneumonia (ranibizumab versus aflibercept: 2.3% versus 1.7%, in VIEW 1, and 0% versus 0.7% in VIEW 2, respectively) and falls (ranibizumab versus aflibercept: 1.6% versus 2.0% in VIEW 1, and 0.7% versus 0% in VIEW 2, respectively). Details on non-ocular SAEs are presented in Table 27.

d) Ocular injection-related serious adverse events in the study eye

In the ranibizumab groups in both studies, 1.3% of patients experienced ocular injection-related SAEs in the study eye. No ocular injection-related SAEs were reported by patients in the aflibercept group in VIEW 1, but 0.3% reported ocular injection-related SAEs in the study eye in both treatment groups in VIEW 2 (Table 28).

3.7.3 Withdrawals due to adverse events

a) Withdrawal from the study due to adverse event

The incidence of AEs leading to withdrawal from the study during the 52 weeks was low in both studies. It was similar in both treatment groups (ranibizumab versus aflibercept: 1.3% versus 1.3% in VIEW 1); however, it was numerically higher in the aflibercept (2.9%) than in the ranibizumab (0.7%) group in VIEW 2 (Table 6). The most common AEs leading to withdrawal were eye disorders including retinal hemorrhage, reduced VA, and retinal detachment (Table 29).

b) Discontinuation of the study drug due to adverse event

The incidence of TEAEs leading to discontinuation of the study drug was also low. It was similar in both treatment groups in VIEW 1 (ranibizumab versus aflibercept: 1.6% versus 1.0%). However, it was numerically higher in the aflibercept group (3.3%) than in the ranibizumab group (1.4%) in VIEW 2. The most common AE leading to discontinuation of the study drug was retinal hemorrhage (0.3% in both the ranibizumab and aflibercept groups in VIEW 1, and 0% in both groups in VIEW 2). Detailed data on TEAEs are presented in Table 29.

3.7.4 Mortality

In VIEW 1, five deaths (1.6%) in the ranibizumab group and eight deaths (2.6%) in the aflibercept group were reported during the first year, while in VIEW 2, two deaths (0.7% in both ranibizumab and aflibercept) were reported in each group (Table 6 and Table 8). None of the deaths was considered to be related to the study drug.

3.7.5 Notable harms

After consulting with the clinical expert involved in the review, the following notable harms (i.e., AEs with special interest clinically) were identified: endophthalmitis, retinal detachment, and ATEs.

In VIEW 1, endophthalmitis occurred in three patients (1%) in the ranibizumab group, but did not occur in the aflibercept (2q8) group. No endophthalmitis was reported in VIEW 2. The incidence of retinal detachment was 5.2% in the ranibizumab group and 3.9% in the aflibercept (2q8) group in VIEW 2. No retinal detachments were reported in the ranibizumab and aflibercept (2q8) groups in VIEW 1. ATEs are adverse events potentially related to systemic VEGF inhibition. There is a potential risk of ATEs following IVT use of VEGF inhibitors, including aflibercept.[21] ATEs, as defined by the Antiplatelet Trialists' Collaboration criteria, include nonfatal myocardial infarction, nonfatal stroke, or vascular death (including deaths of unknown cause).[21] During the first year [redacted] in the ranibizumab group and [redacted] in the aflibercept (2q8) group in VIEW 1 reported an ATE; none were reported in VIEW 2 in the ranibizumab and aflibercept (2q8) groups (Table 8).

TABLE 8: HARMS

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304	N = 303	N = 291	N = 307
	n (%)	n (%)	n (%)	n (%)
AE				
Patients with ≥ 1 TEAEs, N (%)	290 (95.4)	289 (95.4)	250 (85.9)	277 (90.2)
Any ocular TEAE	263 (86.5)	257 (84.8)	210 (72.2)	220 (71.7
Study eye	246 (80.9)	238 (78.5)	187 (64.3)	198 (64.5)
Fellow eye	150 (49.3)	143 (47.2)	124 (42.6)	123 (40.1)
SAE				
Patients with ≥ 1 serious TEAEs, N (%)	68 (22.4)	56 (18.5)	35 (12.0)	48 (15.6)
Most common ocular SAEs[a]				
Endophthalmitis	3 (1.0)	0	NR	NR
Reduced VA	2 (0.7)	0	1 (0.3)	5 (1.6)
Retinal hemorrhage	2 (0.7)	2 (0.7)	1 (0.3)	1 (0.3)
Most common injection-related ocular SAEs[a]				
Endophthalmitis	3 (1.0)	0	NR	NR
WDAE				
WDAEs, N (%) (discontinuation from study)	4 (1.3)	4 (1.3)	2 (0.7)	9 (2.9)
Most common reasons				
Retinal hemorrhage	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Endophthalmitis	1 (0.3)	0	NR	NR
Deaths				
Deaths, N (%)	5 (1.6)	8 (2.6)	2 (0.7)	2 (0.6)
Notable Harms				
Retinal detachment	NR	NR	15 (5.2)	12 (3.9)
ATE	5 (1.6)	12 (4.0)	0	0

AFL = aflibercept; ATE = arterial thrombotic event; NR = not reported; RAN = ranibizumab; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VA = visual acuity; WDAE = withdrawal due to adverse event.

[a] Frequency > 1%.

Source: VIEW 1: T37, p. 122 and VIEW 2: T36, p. 141; VIEW 1: T38, p. 124 and VIEW 2: T37, p. 144; VIEW 1: T39, p. 126–127 and VIEW 2: T38, p. 146–147; VIEW 1: T44, p. 137–138 and VIEW 2: T43, p. 157.

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was derived from two double-blind, randomized, active-controlled trials (VIEW 1 and VIEW 2) that compared aflibercept (2 mg every eight weeks following initial three monthly IVT injections [2q8 IVT]) with 0.5 mg IVT ranibizumab monthly for treating wAMD in treatment-naive patients. A total of 1,225 patients were treated with either aflibercept or ranibizumab. The aim of these studies was to determine whether aflibercept was non-inferior to ranibizumab in maintaining vision in wAMD patients over 52 weeks. The non-inferiority margin (< 10%) was set to preserve approximately two-thirds of the ranibizumab treatment effect for the prevention of moderate vision loss (loss of < 15 letters), based on several pivotal ranibizumab studies.[14,15] VA was measured with a valid ETDRS score. QoL was assessed using the NEI VFQ-25.

Overall baseline characteristics were similar in all treatment groups. Dropout rates were low (< 9%) and similar between treatment groups in both studies. As patients who were previously treated with anti-VEGF drugs were excluded from both studies, the available data cannot be used to determine the efficacy or safety of aflibercept in patients with wAMD who have failed previous treatment or in those patients who require treatment in both eyes concurrently or consecutively. No RCTs have been carried out to assess this population.

There were no serious violations of internal validity, but it is worth noting that no placebo group was included in the studies. The effect size for these active treatments must be seen in perspective versus the progression of vision deterioration in untreated patients. In addition, it is unclear whether the changes from baseline in VA were statistically significant, although the magnitude of changes in BCVA and NEI VFQ-25 were consistent with previous studies.[14,15] In addition, because the sample size was calculated to power the primary outcome, there may have been a lack of power for detecting differences between treatment groups for the secondary outcomes.

4.2 Interpretation of Results

4.2.1 Efficacy

More than 94% of patients in both treatment groups in both studies achieved maintained vision (losing < 15 letters on the ETDRS letter score) at 52 weeks. The between-group differences in the proportion of patients with vision maintained at week 52 compared with baseline were –0.7% (95% CI,–4.5 to 3.1%; *P* = 0.73) and –1.13 (95% CI, –4.81 to 2.55; *P* = 0.55) in VIEW 1 and in VIEW 2, respectively, which was well below the pre-specified upper bound of 10%. Therefore, aflibercept was non-inferior to ranibizumab for maintaining vision in treatment-naive wAMD patients over 52 weeks. In addition, aflibercept met the threshold for clinical equivalence to ranibizumab for the same outcome. The improvement of eight to nine ETDRS letters from baseline in either the ranibizumab or aflibercept (2q8) groups was also observed in both studies; this improvement is consistent with the finding reported previously,[14,15] although it was not reported whether this improvement from baseline was statistically significant. Note that the effect size for these active treatments must be seen in perspective versus the progression of vision deterioration in untreated patients: in trials in which the active treatments have been compared with placebo, vision was maintained in 60% of patients who were treated with placebo.[15]

In both studies, 30% to 34% of patients in the ranibizumab and aflibercept groups, respectively, experienced a moderate VA improvement (gained ≥ 15 ETDRS letters), and 5% to 7% of patients, respectively, experienced a significant VA improvement (gained ≥ 30 ETDRS letters). Patients

experiencing a moderate or severe VA reduction (lost ≥ 15 or ≥ 30 ETDRS letters) were ≤ 6% and ≤ 3%, respectively, in both treatments in both studies. The proportion of patients with legal blindness was lower at week 52 compared with baseline in both the ranibizumab and aflibercept groups. No statistical significance was reported for the proportion of patients with legal blindness at week 52 in either of the studies.

There was no statistically significant difference between the aflibercept (2q8) and ranibizumab groups in either study in terms of the above VA improvement or VA reduction, outcomes, or the proportion of patients with legal blindness. However, as these outcomes were secondary outcomes, it is not known whether the sample size provided was powered enough to detect treatment group difference. Therefore, the findings of the secondary outcomes should be interpreted with caution.

QoL and vision function were measured using the NEI VFQ-25 total score. The reported MCID for NEI VFQ-25 was 4 points,[27] which corresponds to a 15-letter gain in BCVA.[13] It was observed that the NEI VFQ-25 total score was improved (> 4 points) and was similar in both treatment groups in both studies at week 52. The between-treatment group difference in the changes from baseline was not statistically significant. The improvement in the mean NEI VFQ-25 score appears to be clinically relevant, and the magnitude of these changes was similar to that observed in published studies.[13] However, the assessment of any improvements in QoL as an effect of the treatments in study eyes may have been compromised by treatments that the fellow eyes may have received at study entry or during the course of the study.

At week 52, CRT decreased from baseline by 130 µm to 139 µm in the ranibizumab group and by 130 µm to 149 µm in the aflibercept (2q8) group, respectively. It was not reported whether these changes were statistically significant. In addition, the clinical significance of these changes is uncertain due to the lack of information regarding the MCID for this outcome. Nevertheless, no statistically significant differences were observed between treatments in either study.

In the extension phase of the VIEW trials, which evaluated patients using a flexible dosing regimen between weeks 52 and 96, visual and anatomical improvements appeared to have remained similar between treatment groups. However, the aflibercept treatment group received an average of five fewer injections over the 96-week study period.[30]

4.2.2 Harms

The overall safety profile appears to be similar for ranibizumab and aflibercept. Although the incidence of TEAEs was numerically lower in VIEW 2 than in VIEW 1, the overall TEAEs were similar between the ranibizumab and aflibercept groups (85% to 95% versus 90% to 95% in the ranibizumab and aflibercept groups, respectively). The incidences of ocular TEAEs in the study eye (ranibizumab versus aflibercept: 64% to 81% versus 65% to 89%), non-ocular TEAEs (ranibizumab versus aflibercept: 62% to 77% versus 69% to 74%) and the injection-related TEAEs (ranibizumab versus aflibercept: 32% to 60% versus 29% to 54%) were also similar between treatment groups.

The most commonly reported ocular AEs were conjunctival hemorrhage, vitreous floaters, eye pain, vitreous detachment, reduced VA, retinal pigment epitheliopathy, macular degeneration, and increased intraocular pressure. The incidence of serious TEAEs was similar in the ranibizumab and aflibercept groups (15.6% to 18.5% in ranibizumab and 12.5% to 22% in aflibercept). Most of them were attributable to the injection procedure or the progression of the disease. The incidence of ocular SAEs in

the study eye was numerically higher in the ranibizumab group than in the aflibercept group (3.3% versus 1.0% in VIEW 1 and 3.1% versus 2.9% in VIEW 2, respectively).

The reported ocular SAEs in the study eye were mainly endophthalmitis, VA reduction, retinal hemorrhage, and posterior capsule opacification. Non-ocular SAEs were similar in the ranibizumab and aflibercept groups (8.9% to 18.8% versus 12.4% to 16.8% in ranibizumab and aflibercept, respectively). The reported non-ocular SAEs included pneumonia and falls. The incidence of AEs leading to withdrawal from the study during the 52 weeks was low (< 3%) and was similar between treatment groups in both studies. The most common AEs leading to withdrawal were eye disorders, including retinal hemorrhage, reduced VA, and retinal detachment. [redacted] in the ranibizumab group and [redacted] in the aflibercept group experienced an ATE in VIEW 1, while none was reported in VIEW 2. Endophthalmitis occurred in three patients (1%) in the ranibizumab group and none occurred in the aflibercept group in VIEW 1; no endophthalmitis was reported in VIEW 2. The incidence of retinal detachment was 5.2% in the ranibizumab group and 3.9% in the aflibercept group in VIEW 2; none were reported in the ranibizumab and aflibercept groups in VIEW 1.

Overall, the rates of both ocular and non-ocular TEAEs reported during the first year of study were similar among the treatment groups. The TEAE pattern reported for the ranibizumab group in this study was generally consistent with the experience previously reported from the pivotal ranibizumab studies.[14,15] Very few deaths were reported in either the ranibizumab or aflibercept (2q8) groups in both studies, although numerically more deaths occurred in the aflibercept groups (aflibercept versus ranibizumab: 0.6% to 2.6% versus 0.7% to 1.6%, respectively). None of the deaths were considered related to the study drug.

In the extension phase of the VIEW trials, no new or unexpected safety issues were observed through week 96.[30]

4.3 Other Considerations

The clinical expert involved in this review indicated that there is a potential for the off-label use of aflibercept if it is administered more frequently than every eight weeks, such as every six to eight weeks. Both the clinical expert and patient groups cited the potential of having fewer injections to administer for aflibercept compared with ranibizumab as a desirable characteristic of the new drug. Moreover, they noted that the similar efficacy and safety profile of aflibercept and ranibizumab suggests that aflibercept would be the potentially more desirable treatment option because of the need for fewer injections. Indeed, the results of the extension phase (Appendix 6) revealed that aflibercept users required five fewer injections than did ranibizumab users over a period of approximately one year.

The included studies did not provide evidence related to the use of aflibercept in treatment-naive patients; there is a dearth of evidence related to the use of aflibercept patients who have been treated previously with another VEGF inhibitor. Indeed, only one low-quality study[31] was identified (an uncontrolled, retrospective chart review of a small number of patients) that suggested that aflibercept might be beneficial in a subset of patients with neovascular AMD who exhibit recurrent or resistant intraretinal or subretinal fluid following injections with bevacizumab or ranibizumab.

Bevacizumab (Avastin), a VEGF antibody that has been approved for the treatment of certain types of cancer, has not been approved in Canada for the treatment of wAMD and was not considered to be a valid comparator for the purpose of this review. However, bevacizumab is reimbursed for wAMD treatment in some of the jurisdictions that participate in the CDR process. In addition, according to the

clinical expert, bevacizumab is used off-label for the treatment of wAMD in patients living in jurisdictions in which ranibizumab is not reimbursed and in patients who are ineligible for coverage. It is noteworthy that recently, Italy decided to pay for bevacizumab to be used to treat AMD instead of ranibizumab, based on the lower cost of bevacizumab.[32] France is likely to do the same, despite bevacizumab's not being approved for AMD in the European Union.[32]

5. CONCLUSIONS

The results of the two double-blind, multinational, active-controlled, RCTs (VIEW 1 and VIEW 2) suggest that aflibercept is non-inferior to ranibizumab for maintaining vision in treatment-naive patients with wAMD. At least 94% patients in the trials maintained their vision after 52 weeks of treatment, irrespective of whether they were treated with aflibercept or ranibizumab. There were no statistically significant differences between treatments in either study with respect to other outcomes, including changes in VA, the proportion of patients with legal blindness, and changes in QoL. Aflibercept and ranibizumab have similar safety profiles, as the incidences of TEAEs, SAEs, and WDAEs were similar for both treatments in both studies. The results of the extension phase of VIEW 1 and VIEW 2 suggest that the similar efficacy and safety profiles of aflibercept and ranibizumab observed at 52 weeks appear to persist through 96 weeks of treatment.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups. While it has not been systematically reviewed, it has been reviewed by the submitting patient groups.

1. Brief Description of Patient Group(s) Supplying Input

The Canadian Council of the Blind (CCB), a registered charity, was founded in 1944 by blind war veterans and graduates from schools of the blind. All officers and directors are blind or visually impaired. The CCB has more than 65 chapters across Canada, and with more than 1,500 members, it is the largest membership-based organization for the blind in the country.

From 2011 to 2014, CCB received support from the following: VIA Rail, Cannondale, Community Foundation of Ottawa, Lions Club, Keith Communications Inc., Human Resources and Skills Development Canada, and the following pharmaceutical companies: Bayer, Merck Frosst, Novartis, and Pfizer. CCB declared no conflicts of interest in the preparation of this submission.

2. Condition- and Current Therapy–Related Information

CCB indicated that information provided in this section was obtained from printed information on current therapy from drug companies, online searches, one-to-one conversations with patients using current therapy, and focus groups.

Patients identified that the availability of coverage and the lack of choice of Health Canada–approved drugs for the treatment of eye diseases such as advanced macular degeneration (AMD), diabetic macular edema, and retinal vein occlusion (RVO) are important issues.

Impaired vision affects quality of life (QoL) and daily living. Because patients can no longer drive, they need to find alternative ways to attend medical appointments and social activities, and to go shopping. Assistance is required for simple tasks such as preparing meals, daily household chores, and reading (due to patients' inability to read regular-sized font). Vision loss can lead to falls and more frequent injuries. Patients often experience an economic impact due to loss of employment and the cost of treatment.

There is a social impact to AMD. Often, people visit patients with vision loss less frequently because they are unsure of how to deal with their friend's situation. Patients become isolated because they cannot move independently in their former environment. Depression may be experienced due to knowledge of the pending loss of independence, potential loss of employment, loss of driving privileges, and the uncertainty of QoL and of a life with no vision. Family dynamics often change as patients become more reliant on those around them.

Currently available therapies include laser therapy, oral therapies (Vitalux, ASA, Lutein) and injection therapies (ranibizumab [Lucentis] and bevacizumab [Avastin]). Many patients are using currently Health Canada–approved ranibizumab with good results, but ranibizumab may require more injections than Eylea. Some patients are receiving bevacizumab, which has not been tested or approved by Health Canada for this indication. Its long-term effects are not known and could lead to adverse results.

Some patients are restricted in their choice of treatment due to the costs incurred by travel to regional clinics; therefore, they feel they do not receive optimal treatment. Some provinces provide only a certain amount of funding for currently approved drug therapy.

The patients indicated that they need a choice of approved treatments, as only one is currently available. Physicians would benefit by having alternative treatments available should one not be available or not meet the current needs of their patients. Some patients may have an adverse reaction to an additive that may not be present in Eylea or experience irritation with the current treatment, which could possibly be avoided with a second choice of medication.

Patients expressed the desire to receive the best approved care for AMD, diabetic macular edema, and RVO wherever they live so that the cost of travel and out-of-pocket medication expenses do not prevent them from getting care.

Impact on caregivers

With a diagnosis of AMD or RVO in a loved one, caregivers have to deal with the emotional effects of vision loss in someone who had been previously independent; they must also deal with their own emotions. They may need to provide comfort and reassurance and a safe environment for the patient, may need to take time off work to transport the patient to medical appointments or do their shopping, and may need to do more household chores, especially if the patient lives alone.

Caregivers deal with an added financial burden due to both the patient and caregiver having to take time off from employment or arrange child care for other family members as they care for a loved one. Because of their lack of knowledge or understanding, they may not know how to deal with the personal feelings or depression in the patient.

3. Related Information About the Drug Being Reviewed

CCB indicated that information about Eylea was obtained through computer research, talking with physicians, and one-to-one conversations with patients.

Patients expect their lives will be improved with Eylea through decreased macular edema and therefore improved vision by arresting the progress of macular degeneration and possibly regaining vision.

If patients felt they were going to regain vision or prevent further vision loss, they would often be willing to experience some temporary adverse effects, e.g., mild, short-term irritation. Infection is not acceptable and may be reduced through the use of single-dose vials of Eylea. Regaining vision, controlling bleeding, requiring fewer hospital visits, returning to work, and regaining independence to a greater degree than before treatment would be considered adequate improvement and worth the risk of side effects. Patients indicated Eylea may meet an unmet need by offering a second option to patients who experience an adverse reaction to the currently available therapy. There may be a reduction in the number of eye drops needed in the future, thereby reducing adverse reactions or irritations.

Eylea may be administered every eight weeks, which is less frequently than current treatment and could result in fewer physician visits and caregivers missing less time from work.

None of the patients contacted by CCB had had experience with Eylea. However, based on material provided by the manufacturer (posted on the Internet), patients' expectations for Eylea include:

- a different treatment option
- five fewer injections
- no need for interim monitoring
- a predictable injections schedule.

4. Additional Information

CCB indicated that the questions they answered for this report were clear and easy to navigate. The council said it is important to have patient input when a new drug is being assessed for approval because patients are the ones who will benefit from the treatment. In addition, patients are the people most aware of the potential results if treatment is not available.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 23, 2014
Alerts:	Weekly search updates until Sept 17, 2014
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
Search Strategy:		
#	**Searches**	**Results**
1	(Eylea* or aflibercept* or "AVE 0005" or AVE0005 or Bay 86-5321 or Bay86-5321 or VEGF Trap or Zaltrap or Ziv-aflibercept or vasculotropin trap or vascular endothelial growth factor trap).ti,ab,rn,nm,sh,hw,ot.	2201
2	862111-32-8.rn,nm.	1370
3	1 or 2	2201
4	Macular degeneration/	18184
5	(macular degeneration* or Age-Related Maculopathies or macular Dystrophy or Macular Dystrophies or Age-Related Maculopathy or AMD or ARMD).ti,ab,sh,hw,ot.	36613
6	4 or 5	39587
7	3 and 6	351
8	7 use pmez	105
9	*aflibercept/	314
10	(Eylea* or aflibercept* or "AVE 0005" or AVE0005 or Bay 86-5321 or Bay86-5321 or VEGF Trap or Zaltrap or Ziv-aflibercept or vasculotropin trap or vascular endothelial growth factor trap).ti,ab.	1026
11	9 or 10	1064
12	exudative macular degeneration/ or retina macula age related degeneration/	12086
13	(macular degeneration* or Age-Related Maculopathies or macular Dystrophy or Macular Dystrophies or Age-Related Maculopathy or AMD or ARMD).ti,ab.	33602
14	12 or 13	36873
15	11 and 14	238
16	15 use oemezd	150
17	conference abstract.pt.	1452799
18	16 not 17	124
19	8 or 18	229
20	remove duplicates from 19	154

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey literature

Dates for Search:	May 2014
Keywords:	Drug name, Indication
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Clinical Study Report: VGFT-OD-0605 (VIEW 1 – Year 2)[25]	Not approved regimen
Clinical Study Report: A62515 (VIEW 2 – Year 2)[33]	Not approved regimen
Heier et al. (2013)[34]	Not approved regimen

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 9: SUMMARY OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS (FULL ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304	N = 301	N = 291	N = 306
Age (years)				
Mean (SD)	78.2 (7.6)	77.9 (8.4)	73.0 (9.0)	73.8 (8.6)
Median	79.0	79.0	74.0	75.0
Min to max	56 to 99	49[a] to 94	50 to 92	50 to 93
Sex (n [%])				
Female	172 (56.6)	178 (59.1)	169 (58.1)	175 (57.2)
Male	132 (43.4)	123 (40.9)	122 (41.9)	131 (42.8)
Race (n [%])				
White	296 (97.4)	287 (95.3)	213 (73.2)	217 (70.9)
Black	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.7)
Asian	0	4 (1.3)	60 (20.6)	69 (22.5)
Weight (kg)				
Mean (SD)	75.9 (17.8)	74.4 (17.7)	69.83 (15.0)	69.56 (14.4)
Median	74.8	72.6	68.0	68.0
Min to max	40 to 135	41 to 143	40.0 to 133.0	41.0 to 123.0
Body mass index (kg/m^2)				
Mean (SD)	27.3 (5.2)	27.2 (5.8)	26.3 (4.8)	26.2 (4.5)
Median	26.8	26.6	25.97	25.62
Min to max	15 to 45	17 to 71	15.8 to 57.6	17.1 to 39.2
Baseline ETDRS BCVA, mean (SD)	54.0 (13.4)	55.7 (12.8)	53.8 (13.5)	51.6 (13.9)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with 20/40 BCVA, n (%)	13 (4.3)	20 (6.6)	8 (2.7)	10 (3.3)
Lesion type, n (%)				
Predominantly classic	82 (27.0)	71 (23.6)	70 (24.1)	88 (28.8)
Minimally classic	101 (33.2)	110 (36.5)	104 (35.7)	106 (34.6)
Occult	115 (37.8)	118 (39.2)	116 (39.9)	110 (35.9)
Juxtafoveal lesions	15 (4.9)	17 (5.6)	20 (6.9)	14 (4.6)
CRT, µm, mean (SD)	315.3 (108.3)	324.4 (111.2)	325.9 (110.9)	342.6 (124.0)
NEI VFQ-25 mean (SD)	71.8 (17.2)	69.6 (16.8)	72.9 (19.1)	71.3 (19.1)

AFL = aflibercept; BCVA = best corrected visual acuity; CNV = choroidal neovascularization; CRT = central retina thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; FAS = full analysis set; max = maximum; min = minimum; NEI VFQ-25 = National Eye Institute 25-Item Visual Function Questionnaire; RAN = ranibizumab; SD = standard deviation.

[a] Although one of the inclusion criteria was ≥ 50 years of age, one patient who was 49 years old was admitted into the study as he was close to his 50th birthday and all other causes of CNV had been ruled out, rendering it highly likely that his CNV was age-related.

Source: Clinical Study Reports: VIEW 1,[25] T12, p. 80; VIEW 2,[11] T13, p. 87; and Heier et al. (2012),[12] T1, p. 2,541.

TABLE 10: PATIENT DISPOSITION (DETAILED)

Disposition/Reason	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	n (%)	n (%)	n (%)	n (%)
Screened[a]	2,063		2,031	
Randomized	306 (100)	303 (100)	303	313
Completed at 52 weeks	284 (92.8)	276 (91.1)	276 (91.1)	284 (90.7)
Discontinuation from study within 52 weeks	22 (7.2)	27 (8.9)	27 (8.9)	29 (9.3)
Adverse event	4 (1.3)	4 (1.3)	2 (0.7)	9 (2.9)
Death	5(1.6)	[redacted]	2 (0.7)	2 (0.6)
Withdrawal by patient	10 (3.3)	8 (2.6)	11 (3.6)	11 (3.5)
Protocol deviation	3 (1.0)	1 (0.3)	2 (0.7)	0 (0.0)
Lost to follow-up	1 (0.3)	4 (1.3)	4 (1.3)	2 (0.6)
Treatment failure[b]	0	2 (0.7)	0 (0.0)	1 (0.3)
Other[c]	1 (0.3)	1 (0.3)	7 (2.3)	5 (1.6)
Completed study medication[d]	[redacted]	[redacted]	[redacted]	[redacted]
Prematurely discontinued study medication	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Treatment failure [a]	[redacted]	[redacted]	[redacted]	[redacted]
Other[c]	[redacted]	[redacted]	[redacted]	[redacted]
FAS[e]	304 (99.3)	301 (99.3)	291 (96)	306 (97.8)
PPS[e]	269 (87.9)	265 (87.5)	269 (88.8)	270 (86.3)
Safety	304 (99.3)	303 (100)	291 (96)	307 (98.1)

AFL = aflibercept; FAS = full analysis set; PPS = per-protocol analysis set; RAN = ranibizumab.
[a] Total number of patients screened.
[b] Treatment failure was defined as a decrease from baseline in BCVA by ≥ 15 letters at 2 consecutive assessments, four weeks apart, during the first 52 weeks of the study.
[c] "Other" included patients who were discontinued from the study by the investigator for reasons such as no leakage, noncompliance, or health issues.
[d] Derived based on the number randomized and the number who prematurely discontinued study medication.
[e] The number could vary with different outcomes.
Source: VIEW 1: T7, p. 73 and VIEW 2: T7, p. 83.

TABLE 11: TREATMENT EXPOSURE DURING YEAR 1 (SAFETY ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304	N = 303	N = 291	N = 307
Number of all injections (including sham) during year 1, n (%)				
1 to 4	9 (3)	6 (2)	5 (1.7)	9 (2.9)
5 to 8	9 (3)	17 (6)	6 (2.1)	11 (3.6)
9 to 13	286 (94.1)	280 (92.4)	280 (96.2)	287 (93.5)
Mean (SD)	12.1 (2)	12.0 (2)	12.4 (1.8)	12.2 (2.2)
[redacted]				
[redacted]				
Number of active injections during the first year (excluding sham), n (%)				
[redacted]				
[redacted]				
[redacted]				
Mean (SD)	12.1 (2)	7.5 (1)	12.4 (1.8)	7.5 (1.3)
Median	13.0	8.0	13.0	8.0
[redacted]				
Total amount of study medication during the first year (mg)				
n	304	300	287	268
Mean (SD)	6.0 (1)	14.9 (2)	6.22 (0.90)	15.05 (2.88)
[redacted]				
Min to max	1.0 to 7.0	2.0 to 16.0	0.5 to 8.0	2.0 to 34.0
Treatment duration in year 1 (days)[a]				
n	304	303	291	307
Mean (SD)	350.1 (56)	347.3 (58)	353.3 (47.4)	347.6 (62.2)
[redacted]				
Min to max	28 to 378	28 to 379	28 to 378	28 to 385

AFL = aflibercept; min = minimum; max = maximum; RAN = ranibizumab; SD = standard deviation.
[a] Duration of study medication = last dose date – first dose date + 28.
Note: Sham injections were counted in the number of injections.
Source: VIEW 1: T35, p. 120 and T36, p. 121; and VIEW 2: T35, p. 139.

TABLE 12: TREATMENT COMPLIANCE DURING YEAR 1 (FULL ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304	N = 301	N = 291	N = 306
Patients receiving all 3 injections within the first 12 weeks (n [%])	[redacted]	[redacted]	[redacted]	[redacted]
Patients with < 75 % compliance in the first year (n [%])[a]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 75 % compliance in the first year (n [%])[a]	[redacted]	[redacted]	[redacted]	[redacted]
Compliance in the first year (%)[a]				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to max	[redacted]	[redacted]	[redacted]	[redacted]

AFL = aflibercept; min = minimum; max = maximum; RAN = ranibizumab; SD = standard deviation.
[a] Treatment compliance in the first year was calculated as the (number of doses administered during period/number of planned doses) x 100. Period was defined as from day 1 to date of last visit. Planned doses included both aflibercept and sham injections.
Source: VIEW 1: T17, p. 87; and VIEW 2: T18, p. 97.

TABLE 13: SENSITIVITY ANALYSES OF THE PROPORTION OF PATIENTS WHO MAINTAINED VISION (PER-PROTOCOL ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 269	N = 265	N = 269	N = 270
Worst observation carried forward				
Patients who maintained vision at week 52, n (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (%) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
All dropouts counted as non-responders				
Patients who maintained vision at week 52, n (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (%) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
All treatment failures counted as non-responders				
Patients who maintained vision at week 52, n (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion difference, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

AFL = aflibercept; CI = confidence interval; RAN = ranibizumab; SD = standard deviation; VA = visual acuity.
[a] Maintenance of vision was defined as a loss of < 15 letters in the ETDRS letter score. Difference is ranibizumab minus aflibercept; CI calculated using a normal approximation.
Source: VIEW 1: T19, p. 90; VIEW 2: T22, p. 102.

TABLE 14: SENSITIVITY ANALYSES OF THE PROPORTION OF PATIENTS WHO MAINTAINED VISION (FULL ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304	N = 301	N = 291	N = 306
Last observation carried forward				
Patients who maintained vision at week 52 (%)[a]	285 (93.8)	284 (94.4)	276 (94.9)	292 (95.4)
Proportion difference (%) (95% CI)	–0.6 (–4.4 to 3.2)		–0.58 (–4.03 to 2.88)	
Worst observation carried forward				
Patients who maintained vision at week 52 (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion difference (%) (95% CI)	[redacted]		[redacted]	
All dropouts counted as non-responders				
Patients who maintained vision at week 52 (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion difference (%) (95% CI)	[redacted]		[redacted]	
All treatment failures counted as non-responders				
Patients who maintained vision at week 52, n (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion difference (%) (95% CI)	[redacted]		[redacted]	

AFL = aflibercept; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; RAN = ranibizumab; SD = standard deviation; VA = visual acuity.

[a] Maintenance of vision was defined as a loss of < 15 letters in the ETDRS letter score. Difference is ranibizumab minus aflibercept; CI was calculated using a normal approximation.

Source: VIEW 1: T20, p. 91; VIEW 2: T21, p. 102.

TABLE 15: CHANGE FROM BASELINE TO WEEK 52 IN ETDRS LETTER SCORE IN THE STUDY EYE (LAST OBSERVATION CARRIED FORWARD) (FULL ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
Baseline				
n	304	301	291	306
Mean (SD)	54.0 (13.41)	55.7 (12.77)	53.8 (13.5)	51.6 (13.9)
Median	56.0	56.0	56.0	52.0
Range	10.0 to 78.0	15.0 to 83.0	10.0 to 83.0	16.0 to 76.0
Week 52				
n	304	301	291	306
Mean (SD)	62.1 (17.71)	63.6 (16.85)	63.1 (16.6)	60.5 (17.5)
Median	67.0	68.0	67.0	64.0
Range	0.0 to 88.0	11.0 to 93.0	8.0 to 90.0	7.0 to 93.0
Week 52 (change from baseline)				
n	304	301	291	306
Mean (SD)	8.1 (15.25)	7.9 (15.00)	9.4 (13.5)	8.9 (14.4)
Median	9.0	9.0	10.0	9.0
Range	–75.0 to 56.0	–48.0 to 54.0	–47.0 to 56.0	–63.0 to 50.0
LSM difference[a] (95% CI)	0.26 (–1.97 to 2.49)		–0.90 (–3.06 to 1.26)	
P value	0.8179		0.413	

AFL = aflibercept; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study LSM = least squares mean; RAN = ranibizumab; SD = standard deviation.
[a] Difference is aflibercept minus ranibizumab. CI calculated using normal approximation. ANCOVA main-effect model.
Source: VIEW 1:T22, p. 94; VIEW 2: T24, p. 107.

TABLE 16: CHANGE FROM BASELINE TO WEEK 52 IN NEI VFQ-25 (FULL ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	4.9 (14.1)	5.1 (14.7)	6.3 (14.8)	4.9 (14.7)
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference[a] (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

AFL = aflibercept; CI = confidence interval; LSM = least squares mean; NEI VFQ-25 = National Eye Institute 25-Item Visual Function Questionnaire; RAN = ranibizumab; SD = standard deviation.
[a] Difference is aflibercept minus ranibizumab. CI calculated using normal approximation, ANCOVA, main-effect model.
Note on LOCF: The missing values were replaced by the last observed post-baseline values prior to the missing value.
Source: VIEW 1: T24, p. 100 and VIEW 2: T26, p. 114.

TABLE 17: PROPORTION OF PATIENTS WITH VISUAL ACUITY OF 20/40 OR BETTER

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	(N = 304) n (%)	(N = 301) n (%)	(N = 291) n (%)	(N = 306) n (%)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Proportion difference (%)[a] (95% CI) at week 52[b]	[redacted]		[redacted]	
***P* value[c]**	[redacted]		[redacted]	

AFL = aflibercept; CI = confidence interval; RAN = ranibizumab.
[a] Difference is aflibercept minus ranibizumab; CI was calculated using a normal approximation.
[b] Based on PPS; source: Clinical Study Report T14.2.6/31, p. 930. The statistics using FAS were not reported.
[c.] Chi-square test.
Source: VIEW 1: T28, p. 108, p. 930–931; VIEW 2: T30, p. 124.

TABLE 18: CHANGE FROM BASELINE TO WEEK 52 IN CENTRAL RETINAL THICKNESS (FULL ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD), µm	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD), µm	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 (change from baseline)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD), µm	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference[a] 95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

AFL = aflibercept; CI = confidence interval; LSM = least squares mean; RAN = ranibizumab; SD = standard deviation.
[a] Difference is aflibercept minus ranibizumab. CI calculated using normal approximation; ANCOVA, main-effect model.
Source: VIEW 1: T30, p. 111; VIEW 2:T32, p. 130.

TABLE 19: CHANGE FROM BASELINE TO WEEK 52 IN NEI VFQ-25 SUBSCALE (FULL ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
Near Activities				
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Change From baseline at week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference[a] (95% CI)	[redacted]		[redacted]	

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
P value	[redacted]		[redacted]	
Distance Activities				
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
Change From baseline at week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference[a] (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Vision Dependency				
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Change From baseline at week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
LSM difference[a] (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

AFL = aflibercept; CI = confidence interval; LSM = least squares mean; NEI VFQ-25 = National Eye Institute 25-Item Visual Function Questionnaire; RAN = ranibizumab; SD = standard deviation.

[a] Difference is aflibercept minus ranibizumab. CI calculated using normal approximation; ANCOVA, main-effect model.

Source: VIEW 1: T32, p. 116, T33, p. 117, T34, p. 118; VIEW 2: T33, p. 134–135.

TABLE 20: CHANGE FROM BASELINE TO WEEK 52 IN EUROQOL 5-DIMENSIONS QUESTIONNAIRE TOTAL SCORE (FULL ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Change From baseline at week 52				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]

AFL = aflibercept; RAN = ranibizumab; SD = standard deviation.
Source: VIEW 2: T34, p. 136 (VIEW 1: not reported).

TABLE 21: OVERALL ADVERSE EVENT PROFILE DURING YEAR 1 (SAFETY ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304	N = 303	N = 291	N = 307
	n (%)	n (%)	n (%)	n (%)
Patients with any AE	301 (99.0)	298 (98.3)	255 (87.6)	281 (91.5)
Any pre-treatment AE	224 (73.7)	226 (74.6)	63 (21.6)	69 (22.5)
Any TEAE	290 (95.4)	289 (95.4)	250 (85.9)	277 (90.2)
Any ocular TEAE	263 (86.5)	257 (84.8)	210 (72.2)	220 (71.7
Study eye	246 (80.9)	238 (78.5)	187 (64.3)	198 (64.5)
Fellow eye	150 (49.3)	143 (47.2)	124 (42.6)	123 (40.1)
Any treatment-related ocular TEAE	16 (5.3)	9 (3.0)	23 (7.9)	27 (8.8)
Study eye	16 (5.3)	8 (2.6)	23 (7.9)	25 (8.1)
Fellow eye	0	1 (0.3)	NR	NR
Any treatment-related TEAE	17 (5.6)	11 (3.6)	26 (8.9)	34 (11.1)
Any injection-related ocular TEAE	183 (60.2)	164 (54.1)	94 (32.3)	92 (30.0)
Study eye	182 (59.9)	163 (53.8)	93 (32.0)	89 (29.0)
Fellow eye	13 (4.3)	8 (2.6)	NR	NR
Maximum intensity for any ocular TEAE				
Mild	166 (54.6)	160 (52.8)	116 (39.9)	112 (36.5)
Moderate	78 (25.7)	92 (30.4)	83 (28.5)	91 (29.6)
Severe	19 (6.3)	5 (1.7)	11 (3.8)	17 (5.5)
Any non-ocular TEAE	234 (77.0)	223 (73.6)	181 (62.2)	213 (69.4)
Any treatment-related non-ocular TEAE	2 (0.7)	3 (1.0)	4 (1.4)	8 (2.6)
Maximum intensity for any non-ocular TEAE				
Mild	103 (33.9)	112 (37.0)	88 (30.2)	105 (34.2)
Moderate	96 (31.6)	83 (27.4)	78 (26.8)	81 (26.4)
Severe	35 (11.5)	28 (9.2)	15 (5.2)	27 (8.8)
Any death	5 (1.6)	7 (2.3%)	2 (0.7)	2 (0.7)
Any SAE	71 (23.4)	58 (19.1)	36 (12.4)	50 (16.3)
Any treatment-emergent SAE	68 (22.4)	56 (18.5)	35 (12.0)	48 (15.6)
Any AE leading to withdrawal from the study	4 (1.3)	6 (2.0)	3 (1.0)	10 (3.3)
Any AE leading to withdrawal from the study drug	5 (1.6)	4 (1.3)	4 (1.4)	10 (3.3)

AE = adverse event; AFL = aflibercept; NR = not reported; RAN = ranibizumab; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: VIEW 1: T37, p.122; VIEW 2: T36, p. 141.

TABLE 22: OCULAR TREATMENT-EMERGENT ADVERSE EVENTS IN THE STUDY EYE OCCURRING IN AT LEAST 5% OF PATIENTS (SAFETY ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304 n (%)	N = 303 n (%)	N = 291 n (%)	N = 307 n (%)
Number of patients with at least 1 ocular TEAE in study eye	246 (80.9)	238 (78.5)	187 (64.3)	198 (64.5)
Conjunctival hemorrhage	144 (47.4)	131 (43.2)	23 (7.9)	30 (9.8)
Vitreous floaters	33 (10.9)	21 (6.9%)	NR	NR
Eye pain	26 (8.6)	22 (7.3)	27 (9.3)	21 (6.8)
Vitreous detachment	24 (7.9)	19 (6.3)	9 (3.1)	15 (4.9)
Reduced VA	20 (6.6)	20 (6.6)	20 (6.9)	33 (10.7)
Retinal hemorrhage	19 (6.3)	23 (7.6)	29 (10.0)	27 (8.8)
Macular degeneration	16 (5.3)	10 (3.3)	23 (7.9)	30 (9.8)
Increased intraocular pressure	22 (7.2)	15 (5.0)	19 (6.5)	15 (4.9)
Eye irritation	16 (5.3)	12 (4.0)	NR	NR
Maculopathy	19 (6.3)	8 (2.6)	NR	NR
Sensation of foreign body in eyes	9 (3.0)	16 (5.3)	NR	NR
Detachment of retinal pigment epithelium	NR	NR	15 (5.2)	12 (3.9)
Cataract	NR	NR	15 (5.2)	12 (3.9)
Ocular hyperemia	NR	NR	18 (6.2)	9 (2.9)

AFL = aflibercept; NR = not reported; RAN = ranibizumab; TEAE = treatment-emergent adverse event; VA = visual acuity.
Source: VIEW 1: T38, p. 124; VIEW 2: T37, p. 144.

TABLE 23: NON-OCULAR TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN AT LEAST 5% OF PATIENTS (SAFETY ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304 n (%)	N = 303 n (%)	N = 291 n (%)	N = 307 n (%)
Number of patients with at least 1 non-ocular TEAE	234 (77.0)	223 (73.6)	181 (62.2)	213 (69.4)
Infections and infestations	**123 (40.5)**	**104 (34.3)**	77 (26.5)	73 (23.8)
Nasopharyngitis	23 (7.6)	26 (8.6)	25 (8.6)	19 (6.2)
Upper respiratory tract infection	13 (4.3)	18 (5.9)	6 (2.1)	5 (1.6)
Urinary tract infection	17 (5.6)	13 (4.3)	9 (3.1)	5 (1.6)
Bronchitis	16 (5.3)	17 (5.6)	7 (2.4)	9 (2.9)
Sinusitis	8 (2.6)	11 (3.6)	NR	NR
Influenza	9 (3.0)	7 (2.3)	7 (2.4)	17 (5.5)
Pneumonia	14 (4.6)	6 (2.0)	NR	NR
Cellulitis	7 (2.3)	2 (0.7)	NR	NR
Cystitis	NR	NR	3 (1.0)	2 (0.7)
Investigations	**48 (15.8)**	**60 (19.8)**	43 (14.8)	61 (19.9)
Blood glucose increased	8 (2.6)	7 (2.3)	1 (0.3)	8 (2.6)
Protein urine present	7 (2.3)	10 (3.3)	NR	NR
Urine protein/creatinine ratio	3 (1.0)	6 (2.0)	NR	NR

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304 n (%)	N = 303 n (%)	N = 291 n (%)	N = 307 n (%)
increased				
Blood urine present	4 (1.3)	6 (2.0)	NR	NR
Blood pressure increased	4 (1.3)	9 (3.0)	NR	NR
Electrocardiogram T-wave inversion	NR	NR	5 (1.7)	7 (2.3)
Nervous system disorders	**35 (11.5)**	47 (15.5)	27 (9.3)	35 (11.4)
Headache	19 (6.3)	12 (4.0)	11 (3.8)	17 (5.5)
Dizziness	5 (1.6)	7 (2.3)	9 (3.1)	3 (1.0)
Injury, poisoning, and procedural complications	**42 (13.8)**	**45 (14.9)**	19 (6.5)	27 (8.8)
Fall	15 (4.9)	16 (5.3)	9 (3.1)	2 (0.7)
Contusion	4 (1.3)	3 (1.0)	NR	NR
Gastrointestinal disorders	**52 (17.1)**	**40 (13.2)**	30 (10.3)	45 (14.7)
Nausea	13 (4.3)	7 (2.3)	NR	NR
Diarrhea	9 (3.0)	5 (1.7)	10 (3.4)	14 (4.6)
Gastroesophageal reflux disease	6 (2.0)	6 (2.0)	NR	NR
Constipation	12 (3.9)	6 (2.0)	NR	NR
Abdominal pain upper	NR	NR	0 (0.0)	1 (0.3)
Vomiting	NR	NR	6 (2.1)	2 (0.7)
Musculoskeletal and connective tissue disorders	**54 (17.8)**	**41 (13.5)**	31 (10.7)	39 (12.7)
Arthralgia	11 (3.6)	5 (1.7)	8 (2.7)	3 (1.0)
Back pain	9 (3.0)	9 (3.0)	13 (4.5)	11 (3.6)
Osteoarthritis	5 (1.6)	7 (2.3)	4 (1.4)	6 (2.0)
Arthritis	9 (3.0)	2 (0.7)	NR	NR
Respiratory, thoracic, and mediastinal	**47 (15.5)**	**36 (11.9)**	24 (8.2)	24 (7.8)
Cough	11 (3.6)	10 (3.3)	7 (2.4)	3 (1.0)
Chronic obstructive pulmonary disease	6 (2.0)	7 (2.3)	NR	NR
Dyspnea	8 (2.6)	3 (1.0)	NR	NR
Cardiac disorders	**41 (13.5)**	**32 (10.6)**	32 (11.0)	40 (13.0)
Atrial fibrillation	11 (3.6)	6 (2.0)	3 (1.0)	5 (1.6)
Atrioventricular block – first degree	NR	NR	10 (3.4)	9 (2.9)
Vascular disorders	**34 (11.2)**	**28 (9.2)**	27 (9.3)	23 (7.5)
Hypertension	25 (8.2)	20 (6.6)	22 (7.6)	16 (5.2)
Metabolism and nutrition disorders	**29 (9.5)**	**24 (7.9)**	12 (4.1)	23 (7.5)
Hypercholesterolemia	5 (1.6)	7 (2.3)	NR	NR
Diabetes mellitus	NR	NR	4 (1.4)	7 (2.3)
Hyperglycemia	NR	NR	2 (0.7)	2 (0.7)
Skin and subcutaneous tissue disorders	22 (7.2)	20 (6.6)	18 (6.2)	14 (4.6)
General disorders and injection administration site conditions	19 (6.3)	22 (7.3)	18 (6.2)	13 (4.2)
Pyrexia	NR	NR	8 (2.7)	5 (1.6)
Neoplasms benign, malignant, and unspecified	22 (7.2)	22 (7.3)	6 (2.1)	8 (2.6)
Basal cell carcinoma	4 (1.3)	8 (2.6)	NR	NR

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304 n (%)	N = 303 n (%)	N = 291 n (%)	N = 307 n (%)
Renal and urinary disorders	19 (6.3)	15 (5.0)	5 (1.7)	13 (4.2)
Psychiatric disorders	21 (6.9)	14 (4.6)	7 (2.4)	10 (3.3)
Anxiety	7 (2.3)	4 (1.3)	NR	NR
Immune system disorders	8 (2.6)	16 (5.3)	NR	NR
Seasonal allergy	4 (1.3)	9 (3.0)	NR	NR
Blood and lymphatic system disorders	10 (3.3)	9 (3.0)	11 (3.8)	10 (3.3)
Anemia	NR	NR	6 (2.1)	7 (2.3)
Ear and labyrinth disorders	7 (2.3)	11 (3.6)	4 (1.4)	9 (2.9)
Vertigo	4 (1.3)	8 (2.6)	NR	NR
Reproductive system and breast disorders	3 (1.0)	7 (2.3)	4 (1.4)	8 (2.6)

AFL = aflibercept; NR = not reported; RAN = ranibizumab; TEAE = treatment-emergent adverse event.
Source: VIEW 1: T39, p. 126–127; VIEW 2: T38, p. 146–147.

TABLE 24: ALL OCULAR, INJECTION-RELATED TREATMENT-EMERGENT ADVERSE EVENTS (≥ 2%) IN THE STUDY EYE BY PATIENT (SAFETY ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304 n (%)	N =3 03 n (%)	N = 291 n (%)	N = 307 n (%)
Number of patients with at least 1 ocular injection-related TEAE in study eye	182 (59.9)	163 (53.8)	93 (32.0)	90 (29.3)
Conjunctival hemorrhage	140 (46.1)	127 (41.9)	21 (7.2)	29 (9.4)
Eye pain	25 (8.2)	16 (5.3)	25 (8.6)	20 (6.5)
Vitreous floaters	20 (6.6)	9 (3.0)	10 (3.4)	5 (1.6)
Eye irritation	10 (3.3)	7 (2.3)	2 (0.7)	4 (1.3)
Sensation of foreign body in eyes	9 (3.0)	13 (4.3)	9 (3.1)	4 (1.3)
Injection site pain	11 (3.6)	11 (3.6)	8 (2.7)	8 (2.6)
Increased intraocular pressure	12 (3.9)	8 (2.6)	15 (5.2)	12 (3.9)
Increased lacrimation	2 (0.7)	8 (2.6)	2 (0.7)	3 (1.0)
Ocular hyperemia	8 (2.6)	2 (0.7)	17 (5.8)	5 (1.6)
Injection site hemorrhage	5 (1.6)	6 (2.0)	5 (1.7)	4 (1.3)
Ocular discomfort	7 (2.3)	1 (0.3)	0 (0.0)	0 (0.0)
Punctate keratitis	2 (0.7)	1 (0.3)	6 (2.1)	3 (1.0)
Conjunctival hyperemia	3 (1.0)	1 (0.3)	8 (2.7)	1 (0.3)
Corneal erosion	NR	NR	7 (2.4)	4 (1.3)

AFL = aflibercept; NR = not reported; RAN = ranibizumab; SAF = safety analysis set; TEAE = treatment-emergent adverse event.
Source: VIEW 1: T44, p. 137–138; VIEW 2: T43, p. 157.

TABLE 25: ALL OCULAR SERIOUS ADVERSE EVENTS IN THE STUDY EYE (SAFETY ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304 n (%)	N = 303 n (%)	N = 291 n (%)	N = 307 n (%)
Number of patients with ≥ 1 serious TEAE[a] (study eye)	10 (3.3)	3 (1.0%)	9 (3.1)	9 (2.9)
Endophthalmitis	3 (1.0%)	0	NR	NR
Reduced VA	2 (0.7%)	0	1 (0.3)	5 (1.6)
Retinal hemorrhage	2 (0.7%)	2 (0.7%)	1 (0.3)	1 (0.3)
Cataract	0	0	1 (0.3)	1 (0.3)
Retinal degeneration	0	0	1 (0.3)	0 (0.0)
Retinal detachment	0	0	1 (0.3)	0 (0.0)
Retinal edema	1 (0.3%)	0	NR	NR
Retinal pigment epithelial tear	0	1 (0.3%)	1 (0.3)	1 (0.3)
Retinal tear	1 (0.3%)	0	NR	NR
Incorrect dose administered	1 (0.3%)	0	NR	NR
Increased intraocular pressure	1 (0.3%)	0	0 (0.0)	1 (0.3)
Posterior capsule opacification	NR	NR	2 (0.7)	0 (0.0)
Cataract cortical	NR	NR	1 (0.3)	0 (0.0)
Hyphema	NR	NR	1 (0.3)	0 (0.0)
Macular cyst	NR	NR	0 (0.0)	1 (0.3)
Macular degeneration	NR	NR	0 (0.0)	1 (0.3)

AE = adverse event; AFL = aflibercept; NR = not reported; RAN = ranibizumab; TEAE = treatment-emergent adverse event; VA = visual acuity.

[a] Serious ocular AE was defined as follows: AE causing a decrease in VA of > 30 letters (compared with the most recent assessment of VA) and lasting more than one hour; AE causing a decrease in VA to the level of light perception or worse lasting > one hour post-injection; AE requiring surgical intervention to prevent permanent loss of vision; AE associated with severe intraocular inflammation; AE may require medical intervention to prevent permanent loss of sight.

Source: VIEW 1: T46, p. 140; VIEW 2: T45, p. 160.

TABLE 26: OCULAR SERIOUS ADVERSE EVENTS IN THE FELLOW EYE BY PATIENT (SAFETY ANALYSIS SET)

	VIEW 1 RAN N = 304 n (%)	VIEW 1 AFL N = 303 n (%)	VIEW 2 RAN N = 291 n (%)	VIEW 2 AFL N = 307 n (%)
Number of patients with ≥ 1 serious TEAE (fellow eye)	3 (1.0)	2 (0.7)	3 (1.0)	3 (1.0)
Reduced VA	1 (0.3)	0	0 (0.0)	1 (0.3)
Retinal hemorrhage	0	1 (0.3)	1 (0.3)	0 (0.0)
Retinal tear	0	1 (0.3)	NR	NR
Endophthalmitis	1 (0.3)	0	NR	NR
Posterior capsule opacification	1 (0.3)	0	NR	NR
Cataract	NR	NR	3 (1.0)	1 (0.3)
Choroidal neovascularization	NR	NR	1 (0.3)	1 (0.3)
Vitreous hemorrhage	NR	NR	1 (0.3)	0 (0.0)
Macular degeneration	NR	NR	0 (0.0)	1 (0.3)
Maculopathy	NR	NR	0 (0.0)	1 (0.3)

AFL = aflibercept; NR = not reported; RAN = ranibizumab; TEAE = treatment-emergent adverse event; VA = visual acuity.
Source: VIEW 1: T47, p. 141; VIEW 2: T46, p. 162.

TABLE 27: ALL NON-OCULAR SERIOUS ADVERSE EVENTS (SAFETY ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304 n (%)	N = 303 n (%)	N = 291 n (%)	N = 307 n (%)
Number of patients with at least 1 non-ocular serious TEAE	57 (18.8)	51 (16.8)	26 (8.9)	38 (12.4)
Pneumonia	7 (2.3)	5 (1.7)	0 (0.0)	2 (0.7)
Cellulitis	2 (0.7)	0	NR	NR
Gastroenteritis	1 (0.3)	2 (0.7)	NR	NR
Atrial fibrillation	2 (0.7)	3 (1.0)	2 (0.7)	3 (1.0)
Congestive cardiac failure	2 (0.7)	3 (1.0)	NR	NR
Myocardial infarction	3 (1.0)	2 (0.7)	2 (0.7)	3 (1.0)
Coronary artery disease	4 (1.3)	0	NR	NR
Squamous cell carcinoma of skin	3 (1.0)	3 (1.0)	NR	NR
Transient ischemic attack	0	1 (0.3)	0 (0.0)	0 (0.0)
Cerebrovascular accident	0	3 (1.0)	1 (0.3)	2 (0.7)
Fall	5 (1.6)	6 (2.0)	2 (0.7)	0 (0.0)
Subdural hematoma	1 (0.3)	2 (0.7)	NR	NR
Gastrointestinal disorders	5 (1.6)	3 (1.0)	0 (0.0)	6 (2.0)
Chronic obstructive pulmonary disease	2 (0.7)	2 (0.7)	NR	NR
Hypertension	2 (0.7)	0	NR	NR
Osteoarthritis	3 (1.0)	0	NR	NR
Mental status changes	2 (0.7)	0	NR	NR

AFL = aflibercept; NR = not reported; RAN = ranibizumab; TEAE = treatment-emergent adverse event.
Source: VIEW 1: T48, p. 143–148; VIEW 2: T43, p. 157, p. 164 (for VIEW 1 and VIEW 2: ≥ 2%).

TABLE 28: ALL OCULAR INJECTION-RELATED SERIOUS ADVERSE EVENTS IN THE STUDY EYE (SAFETY ANALYSIS SET)

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304 n (%)	N = 303 n (%)	N = 291 n (%)	N = 307 n (%)
Number of patients with ≥ 1 ocular injection-related serious TEAE (study eye)	4 (1.3)	0	1 (0.3)	1 (0.3)
Endophthalmitis	3 (1.0)	0	NR	NR
Incorrect dose administered	1 (0.3)	0	NR	NR
Increased intraocular pressure	1 (0.3)	0	NR	NR
Retinal pigment epithelial tear	NR	NR	1 (0.3)	1 (0.3)

AFL = aflibercept; NR = not reported; RAN = ranibizumab; TEAE = treatment-emergent adverse event.
Source: VIEW 1: T51, p. 152; VIEW 2: T14.3.2, p. 5,571.

TABLE 29: NUMBER OF PATIENTS WITH TREATMENT-EMERGENT ADVERSE EVENTS CAUSING DISCONTINUATION OF STUDY DRUG

	VIEW 1		VIEW 2	
	RAN	AFL	RAN	AFL
	N = 304 n (%)	N = 303 n (%)	N = 291 n (%)	N = 307 n (%)
Number of patients with at ≥ 1 TEAE causing withdrawal	4 (1.3)	3 (1.0)	4 (1.4)	10 (3.3)
Retinal hemorrhage	1 (0.3)	1 (0.3)	0	0
Reduced VA	0	1 (0.3)	0	0
Retinal detachment	0	0	1 (0.3)	0
Malignant hepatic neoplasm	1 (0.3)	0	0	0
Malignant lung neoplasm	1 (0.3)	0	0	0
Metastatic lung cancer	0	0	0	1 (0.3)
Esophageal carcinoma	0	0	1 (0.3)	0
Catheter site hematoma	0	1 (0.3)	0	0
Endophthalmitis	1 (0.3)	0	NR	NR
Cerebrovascular accident	0	0	0	2 (0.7)
Presyncope	0	0	0	1 (0.3)
Acute interstitial pneumonitis	0	0	0	1 (0.3)
Myocardial infarction	0	0	0	1 (0.3)
Angina pectoris	0	0	1 (0.3)	0
Acute pancreatitis	0	0	0	1 (0.3)
Investigations	0	0	0	1 (0.3)
Increased intraocular pressure	0	0	0	1 (0.3)
Urinary tract obstruction	0	0	0	1 (0.3)
Surgical and medical procedures	0	0	0	1 (0.3)
Hip surgery	0	0	0	1 (0.3)

AFL = aflibercept; NR = not reported; RAN = ranibizumab; TEAE = treatment-emergent adverse event; VA = visual acuity.
Source: VIEW 1: T52, p. 153; VIEW 2: T48, p.167–168.

TABLE 30: SUBGROUP ANALYSIS OF THE PROPORTION OF PATIENTS WITH VISION MAINTAINED (FULL ANALYSIS SET)

	VIEW 1			VIEW 2		
	RAN	AFL	Difference (%)[a] (95% CI)	RAN	AFL	Difference (%)[a] (95% CI)
BCVA category (ETDRS letter score)						
[redacted]						
[redacted]						
[redacted]						
CNV lesion size						
[redacted]						
[redacted]						
Lesion type						
[redacted]						
[redacted]						
[redacted]						

AFL = aflibercept; BCVA = best corrected visual acuity; CI = confidence interval; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study; FAS = full analysis set; RAN = ranibizumab.

[a] Difference is ranibizumab minus aflibercept. CI calculated using normal approximation.

Source: VIEW 1: T14.2.1/12, p. 638, p. 639, p. 640; VIEW 2: T14.2.1/30–32, p. 1524, p. 1,525, p. 1,526.

TABLE 31: SUBGROUP ANALYSIS OF CHANGE IN ETDRS LETTER SCORE AT WEEK 52 FROM BASELINE (FULL ANALYSIS SET)

		VIEW 1		VIEW 2	
		RAN	AFL	RAN	AFL
Baseline BCVA (ETDRS letter score)					
< 35	N				
	Baseline, mean				
	Change from baseline at week 52, mean				
	LSM difference (95% CI) (AFL – RAN)				
≥ 35 to < 50	N				
	Baseline, mean				
	Change from baseline at week 52, mean				
	LSM difference (95% CI) (AFL – RAN)				
≥ 50	N				
	Baseline, mean				
	Change from baseline at week 52, mean				
	LSM difference (95% CI) (AFL – RAN)				
Baseline CNV lesion size					
≤ 10.16 mm^2	N				
	Baseline, mean				
	Change from baseline at week 52, mean				
	LSM difference (95% CI) (AFL – RAN)				
> 10.16 mm^2	N				
	Baseline, mean				
	Change from baseline at week 52, mean				
	LSM difference (95% CI) (AFL – RAN)				
Baseline lesion type					
Occult	N				
	Baseline, mean				
	Change from baseline at week 52, mean				
	LSM difference (95% CI) (AFL – RAN)				
Minimally classic	n				
	Baseline, mean				
	Change from baseline at week 52, mean				
	LSM difference (95% CI) (AFL – RAN)				
Predominantly	n				

		VIEW 1		VIEW 2	
		RAN	AFL	RAN	AFL
classic	Baseline, mean	[redacted]	[redacted]	[redacted]	[redacted]
	Change from baseline at week 52, mean	[redacted]	[redacted]	[redacted]	[redacted]
	LSM difference (95% CI) (AFL – RAN)	[redacted]	[redacted]	[redacted]	[redacted]

AFL = aflibercept; BCVA = best corrected visual acuity; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; FAS = full analysis set; LSM = least squares mean; RAN = ranibizumab.
Source: VIEW 1: T14.2.2/14, p. 693–695; VIEW 2: T14.2.2/47, p. 1,668, 1,675, 1,683.

TABLE 32: SUBGROUP ANALYSIS OF THE PROPORTION OF PATIENTS WHO GAINED 15 OR MORE LETTERS (FULL ANALYSIS SET)

	VIEW 1			VIEW 2		
	RAN	AFL	Difference (%)[a] (95% CI)	RAN	AFL	Difference (%)[a] (95% CI)
BCVA category (ETDRS letters)						
< 35, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 35 to < 50, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 50, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CNV lesion size						
≤ 10.16 mm^2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 10.16 mm^2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lesion type						
Occult, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minimally classic, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Predominantly classic, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AFL = aflibercept; BCVA = best corrected visual acuity; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study; FAS = full analysis set; LSM = least squares mean; RAN = ranibizumab.
[a] Difference is ranibizumab minus aflibercept. CI calculated using normal approximation.
Source: VIEW 1: T14.2.3/9, p. 730–732; VIEW 2: T14.2.2/66, p. 1,698–1,770.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures used in the VIEW 1 and VIEW 2 studies.

- Vision acuity (VA) measurement: Early Treatment Diabetic Retinopathy Study (ETDRS) letters score and Snellen charts
- National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25).

Findings

TABLE 33: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCES OF OUTCOME MEASURES

Instrument	Type	Validated	MCID	Reference Number
ETDRS letters	ETDRS charts present a series of 5 letters of equal difficulty on each row, with standardized spacing between letters and rows — a total of 14 lines (70 letters).	Yes	≥ 15 letters	22
NEI VFQ-25	The NEI VFQ-25 was developed as a means to measure vision-targeted quality of life. There are 51 items in the original version (NEI VFQ-51).[35] The NEI VFQ-25, a short version of the NEI VFQ-51, was subsequently developed.[27] The NEI VFQ-25 includes 25 items relevant to 11 vision-related constructs, in addition to a single-item general health component.	Yes	4 points (NEI VFQ-25)	27

ETDRS = Early Treatment Diabetic Retinopathy Study; MCID = minimal clinically important difference; NEI VFQ-25 = National Eye Institute 25-Item Visual Function Questionnaire.

Measuring visual acuity

The Snellen eye chart is a commonly employed, well-recognized test of VA in clinical practice.[36,37] The chart presents a series of letters of decreasing size, with an increasing number of letters on subsequent lines. One or two mistakes per line are allowed and the smallest line that can be read corresponds to the VA. The resultant measure of VA is expressed as a Snellen fraction, in which the numerator indicates the distance at which the chart was read, and the denominator the distance at which a person may discern letters of a particular size. A larger denominator indicates worsening vision. For example, a person with 20/100 vision can read letters at 20 feet that a person with 20/20 vision could read at 100 feet. Snellen acuity may also be expressed in metric units. As 20 feet is roughly equivalent to 6 m, 20/20 vision may be expressed as 6/6, or 20/100 as 6/30. Snellen fractions may be expressed as decimal acuity where 20/20 is expressed as 1.00 and 20/100 as 0.2. Further, the logarithm of the reciprocal Snellen fraction may be calculated to produce a linear scoring system suitable for statistical analysis; Snellen fractions of 20/20 and 20/100 would correspond to log scores of 0.0 and 0.7 respectively.

A number of limitations of the Snellen charts, especially for clinical research, have been identified.[36,37] Specifically, the use of letters with different difficulty scores (A and L are more easily discernible than B, E, and F) and an unequal number of letters on each line allows for a different percentage of errors depending on the line read and number of errors made.[37] In addition, the change in letter size between chart lines is not uniform; thus, moving from line 20/25 to 20/20 represents a 20% improvement, compared with a 16% improvement when moving from line 20/30 to 20/25. Finally, differences in background luminance among charts, due to aging charts or different chart manufacturers, and the use of dusty or aging projector equipment can reduce contrast and may result in unreliable measures of VA.[37]

In response to the above limitations, alternative charts have been developed that are more appropriate in research.[36,37] The ETDRS charts are based on a design by Bailey and Lovie, and are commonly used in clinical research.[14,15,36,38,39] ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between letters and rows; there is a total of 14 lines (70 letters). The ETDRS letter score can be calculated when 20 or more letters are read correctly at 4.0 m, the VA letter score is equal to the total number of letters read correctly at 4.0 m plus 30. If fewer than 20 letters are read correctly at 4.0 m, the VA letter score is equal to the total number of letters read correctly at 4.0 m (the number recorded on line 1.0), plus the total number of letters read correctly at 1.0 m in the first six lines. The ETDRS letter score could therefore result in a maximum score of 100.[40,41]

ETDRS charts are used in a standard light box with a background illumination of approximately 150 cd/m^2. Standard chart testing distance is 4 m; however, shorter distances may be used when vision is severely impaired.[36,42] Letters range from 58.18 mm to 2.92 mm in height, corresponding to Snellen VA fractions of 20/200 to 20/10 respectively. Letter size increases further geometrically and equivalently in every line by a factor of 1.2589 (or 0.1 log unit), moving up the chart. Scoring for ETDRS charts is designed to produce a logarithmic score (logMAR) suitable for statistical analysis, in which individual letters score 0.02 log units. Holladay and Prager published the following formula to convert VA scores derived from a Bailey and Lovie–style chart read at 2 m into a Snellen denominator, where X is the number of correctly read letters (see below).[43] Thus, reading all 70 letters on a Bailey–Lovie chart corresponds to a Snellen VA of 20/10.

$$\text{Snellen Acuity} = 20 \times 10\ [(55\text{-}X)/50]$$

ETDRS charts may reliably identify changes in VA of two lines (10 letters) or more, but not changes of one line (five letters) or fewer.[44] The reliability of ETDRS charts depends on the baseline VA. For eyes with acuity better than 20/100, a change in VA of five letters or more has a greater than 90% probability of being a real change, while for eyes worse than 20/100, a change of 10 letters or more is required for the same reliability.[29] A loss or gain of three lines (15 letters) is considered a moderate degree of change and is commonly used as an outcome in clinical trials.[26] The FDA recommends a mean change of ≥ 15 letters on an ETDRS chart, or a statistically significant difference in the proportion of patients with a change of ≥ 15 letters in VA, as clinically relevant outcome measures in trials of interventions for macular edema.[22]

Relationship of visual acuity to visual function and vision-related quality of life

Measures of high-contrast visual distance acuity, using ETDRS charts, are commonly used to assess treatment outcomes in clinical studies. A loss of three lines or more (≥ 15 letters) on an ETDRS chart corresponds to a doubling of the visual angle and is considered to be moderate vision loss, while a loss of six lines or more (≥ 30 letters) corresponds to a quadrupling of the visual angle and is considered to

be severe vision loss. However, VA is only one component contributing to overall visual function, the ability to perform everyday visual tasks (e.g., reading, recognizing faces, driving, and using the telephone). Overall visual function also depends upon variables such as contrast sensitivity, near vision, colour vision, and sensitivity to glare.[45] The various components of visual function affect the performance of different vision-related tasks by varying degrees. For example, use of distance acuity to measure the success of treatments for AMD is not optimal given that distance vision is usually two ETDRS lines better than reading vision,[26] and difficulty with reading is a common complaint among persons with eye disease.[35] Rather, contrast sensitivity is a more important contributor to reading performance.[26,46]

Visual function and the resultant ability to perform everyday visual tasks have important implications for QoL. QoL is very much a person-specific measure that ultimately depends upon the value individuals place on the ability to perform specific tasks. QoL instruments that do not include domains or tasks that are of importance to individuals lack sensitivity to changes in their QoL. Further, the impact of vision loss on QoL may vary greatly dependent upon the vision status of the fellow eye. For these reasons, there are limitations in the use of QoL instruments to compare treatment effectiveness.[45]

National Eye Institute 25-Item Visual Function Questionnaire

The NEI VFQ was developed as a means to measure vision-targeted QoL. The original 51-item questionnaire was developed based on focus groups consisting of persons with a number of common eye conditions (e.g., age-related cataracts, AMD, and diabetic retinopathy), and thus may be used to assess QoL in a broad range of eye conditions.[35] The original 51-item questionnaire comprises 12 subscales related to general vision, ocular pain, near vision, distance vision, social functioning, mental health, role functioning, dependency, driving, peripheral vision, colour vision, and expectations for future vision. In addition, the questionnaire includes one general health subscale.[47]

A shorter version of the original instrument, the NEI VFQ-25, was subsequently developed, which retained the multidimensional nature of the original and is more practical and efficient to administer.[27] With the exception of expectations for future vision, all of the constructs listed above were retained in the shortened version, with a reduced number of items within each construct. Thus, the NEI VFQ-25 includes 25 items relevant to 11 vision-related constructs, in addition to a single-item general health component. Responses for each item were converted to a 0 to 100 scale, with 0 representing the worst visual functioning and 100 the best visual functioning. Items within each construct, or subscale, are averaged to create 12 subscale scores, and averaging of the subscale scores produces the overall composite score. Different scoring approaches for the NEI VFQ-25 have been proposed.[48] Rasch modelling is used to obtain measurements from categorical data. When comparing standard scoring to Rasch analysis and an algorithm to approximate Rasch scores, all methods were highly correlated.[48] However, standard scoring is subject to floor and ceiling effects, whereby the ability of the least visually able is overestimated and the ability of the most visually able is underestimated.[48]

Determination of what constitutes a clinically meaningful change in the NEI VFQ-25 appears to be linked to its correlation with VA. A three-line (15 letters) change in VA has been used as the outcome of interest in clinical trials, and corresponding changes in the NEI VFQ-25 are suggested as clinically meaningful end points. Specifically, for the study eye, which is typically the worse-seeing eye, a 15-letter change in VA corresponds to a 4-point change in the overall NEI VFQ-25 score.[13] For the better-seeing eye, the clinically relevant difference for NEI VFQ-25 scores based on a three-line change is 7 to 8 for overall score. Other studies have shown similar estimated clinically relevant differences.[49] The

instrument showed weaker correlation or was not responsive to changes in the VA of the worse-seeing eye.[50,51] This may have implications when evaluating patients with unilateral disease.

Both versions of the NEI VFQ were reported to be valid and reliable measures of health-related QoL among patients with a wide range of eye conditions,[27,47,51] and all but two subscale scores (general health and ocular pain) have been shown to be responsive to changes in VA in the better-seeing eye.[50,51] However, more recent studies have indicated that the NEI VFQ-25 measures visual functioning, not QoL.[52] Assessments of the psychometric validity of the NEI VFQ-25 using Rasch scoring and principal component analysis have identified issues with multidimensionality (measurement of more than one construct) and poor performance of the subscales.[52,53] The NEI VFQ-25 subscales were found to have too few items and were unable to discriminate among the population under measurement, and thus were not valid.[52,53] Re-engineering the NEI VFQ-25 into two constructs (visual functioning and socio-emotional factors) and removing misfit items (e.g., pain around eyes, general health, and driving in difficult conditions) improved the psychometric validity of the scale in individuals with low vision.[52,53] Considering this recent evidence of multidimensionality, the validity of the single composite score of the NEI VFQ-25 may be questioned.

Summary

The validity of VA, NEI VFQ-25, and the relationship between VA, visual function, and QoL were reviewed.

VA, measured using the ETDRS charts, is a suitable outcome measure for statistical analysis in clinical trials. Visual function depends on several components, including VA, contrast sensitivity, near vision, colour vision, and sensitivity to glare.[45] The various components of visual function affect the performance of different vision-related tasks by varying degrees, and have important implications for QoL.

The NEI VFQ-25 is an outcome measure with 11 vision-related constructs and one single-item general health component that is subject to floor and ceiling effects.[48] In more recent studies, the NEI VFQ-25 has been shown to better measure visual functioning as opposed to QoL,[52] with issues arising regarding multidimensionality and poor subscale performance.[52,53] Hence, due to these issues, the NEI VFQ-25 single composite score may not be as valid in measuring health-related QoL.

APPENDIX 6: SUMMARY OF EXTENSION PHASE (96 WEEKS)

Objective

To summarize the 96-week results of the VIEW 1 and VIEW 2 studies.[30] Results from baseline to week 52 were examined in the main CADTH Common Drug Review (CDR) clinical report. The following summary is based on the publicly available trial publications.

Findings

Study design

VIEW 1 and VIEW 2 were randomized, double-masked, active-controlled, parallel group, multi-centre phase 3 clinical trials of 96 weeks' duration. From baseline to week 52, patients received study medications every four to eight weeks, following three initial monthly doses. From weeks 52 to 96, patients received the originally assigned study drug following an "as-needed" regimen, determined using predefined retreatment criteria, and mandatory treatment with at least one dose every 12 weeks.[30]

Criteria for retreatment were as follows:

- new or persistent fluid on optical coherence tomography (OCT)
- an increase in central retinal thickness (CRT) of 100 µm or more compared with the lowest previous value
- loss of five or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters from the best previous score in conjunction with recurrent fluid on OCT
- new-onset classic neovascularization
- new or persistent leak on fluorescein angiography
- new macular hemorrhage, or
- a time lapse of 12 weeks since the previous injection.

The primary outcome measure was the proportion of eyes that maintained best corrected visual acuity (BCVA) at week 96. Secondary outcomes included mean change in BCVA from baseline, the proportion of patients gaining ≥ 15 letters, mean change from baseline choroidal neovascularization size, and the proportion of patients without retinal fluid at week 96. Data from patients in the VIEW 1 and VIEW 2 studies were pooled and presented as the 96-week results.

Results

At 96 weeks, visual and anatomical improvements were similar between the 2 mg aflibercept every eight weeks (2q8) group and the ranibizumab group (Table 35 and Table 36); however, the aflibercept group received an average of five fewer injections over the 96 weeks of the study (Table 38). The most frequently reported serious ocular adverse events (SAEs) at 96 weeks were reduced visual acuity (VA), retinal hemorrhage, and endophthalmitis. The most frequently reported non-ocular AEs were pneumonia, fall, atrial fibrillation, and myocardial infarction (Table 37). The occurrence of ocular and non-ocular AEs was similar between groups. No new or unexpected AEs were reported between week 52 and week 96.

TABLE 34: SUMMARY OF RESULTS AT WEEK 96

	RAN (N = 609) n (%)	AFL (N = 616) n (%)
Patients completed week 52	560 (92.0)	560 (90.9)
Patients completed week 96	519 (85.2)	513 (83.3)
Patients discontinued before week 52	48 (8.0)	56 (9.1)
Patients discontinued before week 96	90 (14.8)	103 (16.7)
Consent withdrawal	32 (5.3)	35 (16.7)
Protocol deviation	5 (0.8)	1 (0.2)
Adverse event	16 (2.6)	25 (4.1)
Death	11 (1.8)	15 (2.4)
Lost to follow-up	14 (2.3)	15 (2.4)
Lack of efficacy	1 (0.2)	3 (0.5)
Other	11 (1.8)	9 (1.5)

AFL = aflibercept; RAN = ranibizumab.

TABLE 35: VISUAL OUTCOMES AT WEEK 96 — FULL ANALYSIS SET

	RAN (N = 595)	AFL (N = 607)
Mean change from baseline in BCVA (ETDRS letters)	7.9	7.6
Maintained visual acuity, n (%)	91.6%	92.4%
Gained 15 letters or more, n (%)	31.6%	33.4%

AFL = aflibercept; BCVA = best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; RAN = ranibizumab.

TABLE 36: ANATOMIC OUTCOMES AT WEEK 96 — FULL ANALYSIS SET

	Baseline to Week 52		Baseline to Week 96	
	RAN (N = 537)	AFL (N = 539)	RAN (N = 508)	AFL (N = 505)
Mean change from baseline CRT (µm)	–123	–139	–113	–133
Patients without retinal fluid on time-domain OCT	62.0%	67.7%	45.5%	50.1%

AFL = aflibercept; CRT = central retinal thickness; OCT = optical coherence tomography; RAN = ranibizumab.

TABLE 37: MOST FREQUENTLY REPORTED SERIOUS ADVERSE EVENTS — SAFETY ANALYSIS SET

	Baseline to Week 52		Baseline to Week 96	
	RAN (N = 595) N (%)	AFL (N = 610) N (%)	RAN (N = 595) N (%)	AFL (N = 610) N (%)
Total patients with ≥ 1 ocular SAE	**19 (3.2)**	**12 (2.0)**	**26 (4.4)**	**24 (3.9)**
Macular hole	0	0	0	0
Posterior capsule opacification	2 (0.3)	0	2 (0.3)	0
Retinal detachment	1 (0.2)	0	3 (0.5)	0
Retinal hemorrhage	3 (0.5)	3 (0.5)	4 (0.7)	5 (0.8)
Retinal pigment epithelial tear	1 (0.2)	2 (0.3)	1 (0.2)	3 (0.5)
Reduced VA	3 (0.5)	5 (0.8)	5 (0.8)	7 (1.1)
Endophthalmitis	3 (0.5)	0	5 (0.8)	0
Cataract	1 (0.2)	1 (0.2)	1 (0.2)	4 (0.7)
Macular degeneration	0	1 (0.2)	0	2 (0.3)
Increased ocular pressure	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.3)
Total patients with ≥ 1 non-ocular SAE	**83 (13.9)**	**89 (14.6)**	**146 (24.5)**	**154 (25.2)**
Atrial fibrillation	4 (0.7)	6 (1.0)	5 (0.8)	10 (1.6)
Myocardial infarction	5 (0.8)	6 (1.0)	10 (1.7)	6 (1.0)
Pneumonia	7 (1.2)	7 (1.1)	15 (2.5)	14 (2.3)
Fall	7 (1.2)	6 (1.0)	10 (1.7)	19 (3.1)
Congestive cardiac failure	2 (0.3)	3 (0.5)	5 (0.8)	9 (1.5)
Coronary artery disease	4 (0.7)	0	5 (0.8)	1 (0.2)
Transient ischemic attack	0	1 (0.2)	1 (0.2)	5 (0.8)
Cerebrovascular accident	1 (0.2)	5 (0.8)	4 (0.7)	7 (1.1)
Chronic obstructive pulmonary disease	2 (0.3)	3 (0.5)	3 (0.5)	7 (1.1)
Osteoarthritis	3 (0.5)	0	4 (0.7)	2 (0.3)

AFL = aflibercept; RAN = ranibizumab; SAE = serious adverse event; VA = visual acuity.

TABLE 38: NUMBER OF INJECTIONS DURING WEEKS 52 TO 96

Proportion of Patients	RAN (N = 513)	AFL (N = 511)
Fewer than 6 injections	73.5%	84.1%
6 or more injections	26.5%	15.9%
6 injections	8.4%	5.7%
7 injections	4.1%	4.1%
8 injections	4.9%	2.9%
9 injections	3.1%	0.6%
10 injections	2.3%	0.8%
11 injections	3.7%	1.8%

AFL = aflibercept; RAN = ranibizumab.

Summary

The goal of the extension study was to evaluate the long-term safety and efficacy of aflibercept. Visual and anatomical improvements appear to remain similar between 52 and 96 weeks in both treatment groups, with the aflibercept group receiving an average of five fewer injections over the 96-week study period. No new or unexpected safety issues were observed during the extension period.

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