Common Drug Review
Clinical Review Report

July 2016

Drug	aflibercept (Eylea) (40 mg/mL solution for intravitreal injection available as a 2 mg single-use vial)
Indication	Treatment of diabetic macular edema (DME)[a]
Listing request	For the treatment of DME, in a manner similar to ranibizumab
Manufacturer	Bayer Inc.

[a] Aflibercept is also indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) and central retinal vein occlusion (CRVO), which have been reviewed separately.

This review report was prepared by 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.

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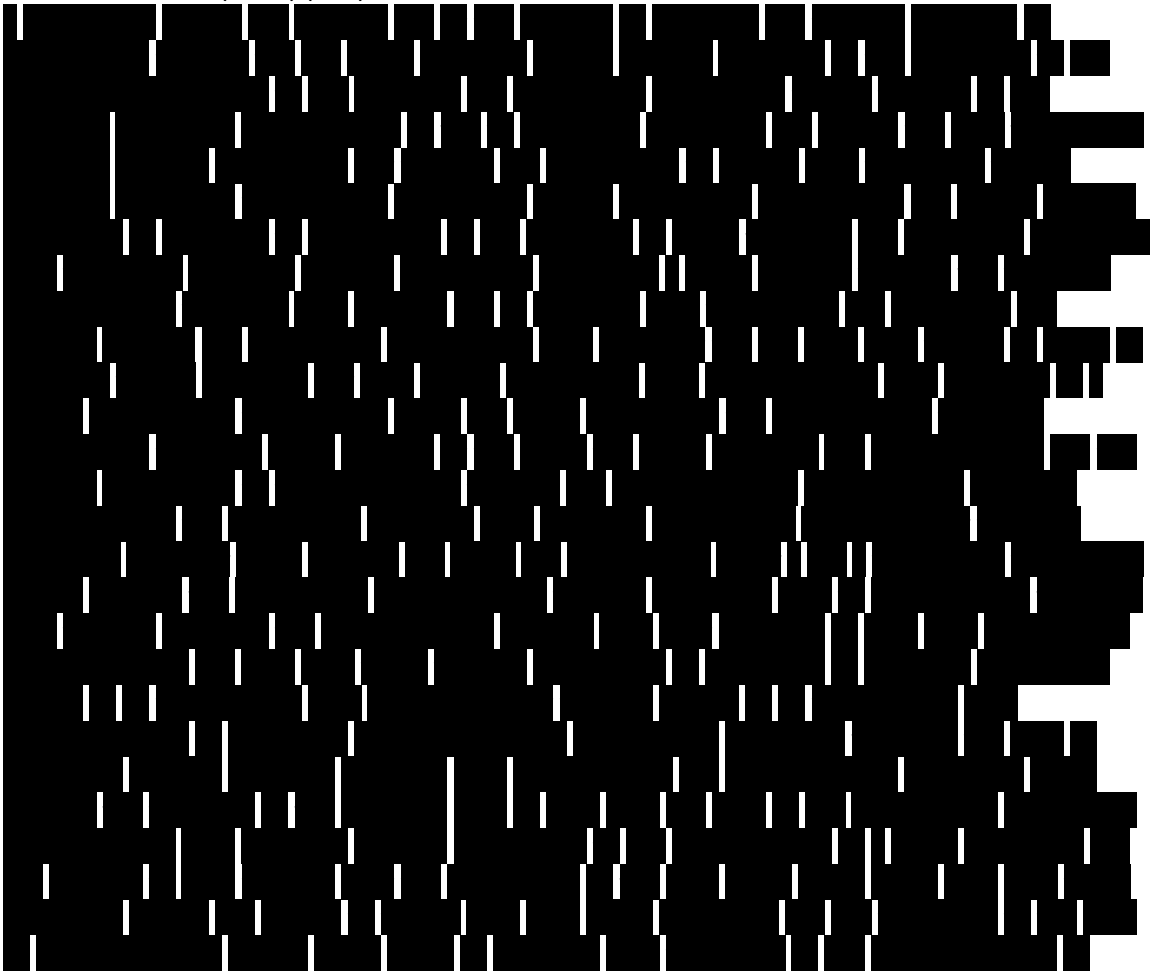
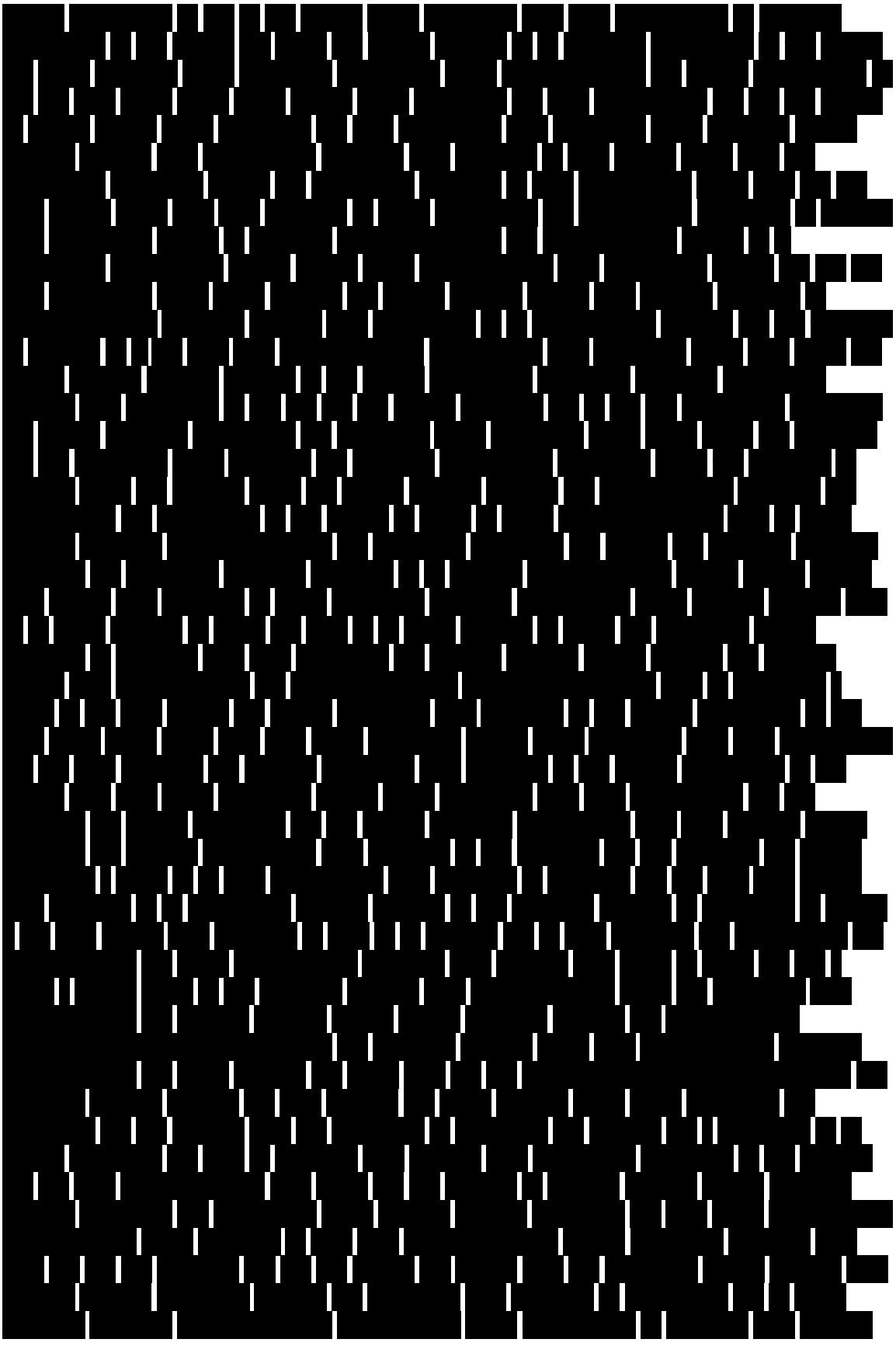
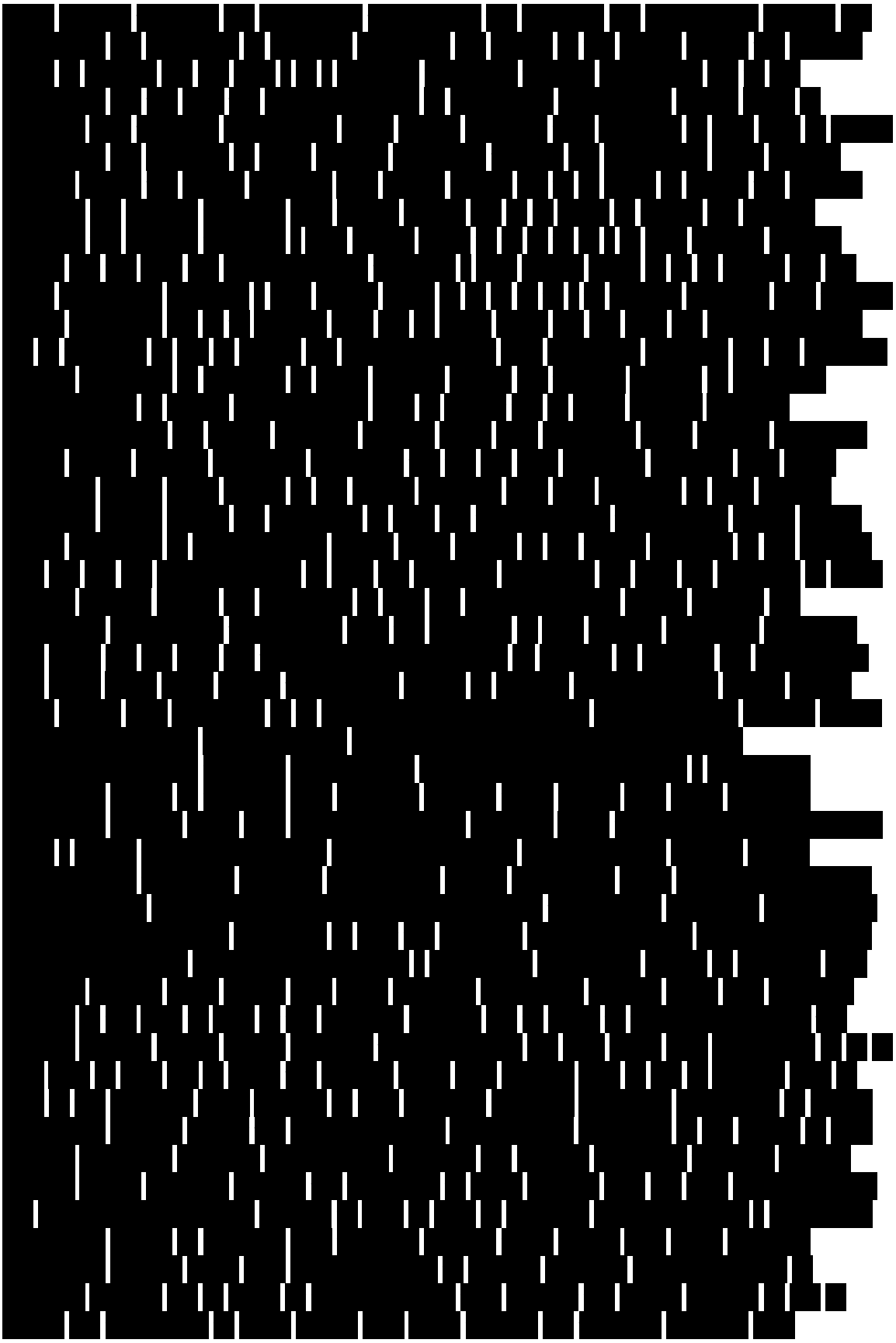
TABLE OF CONTENTS

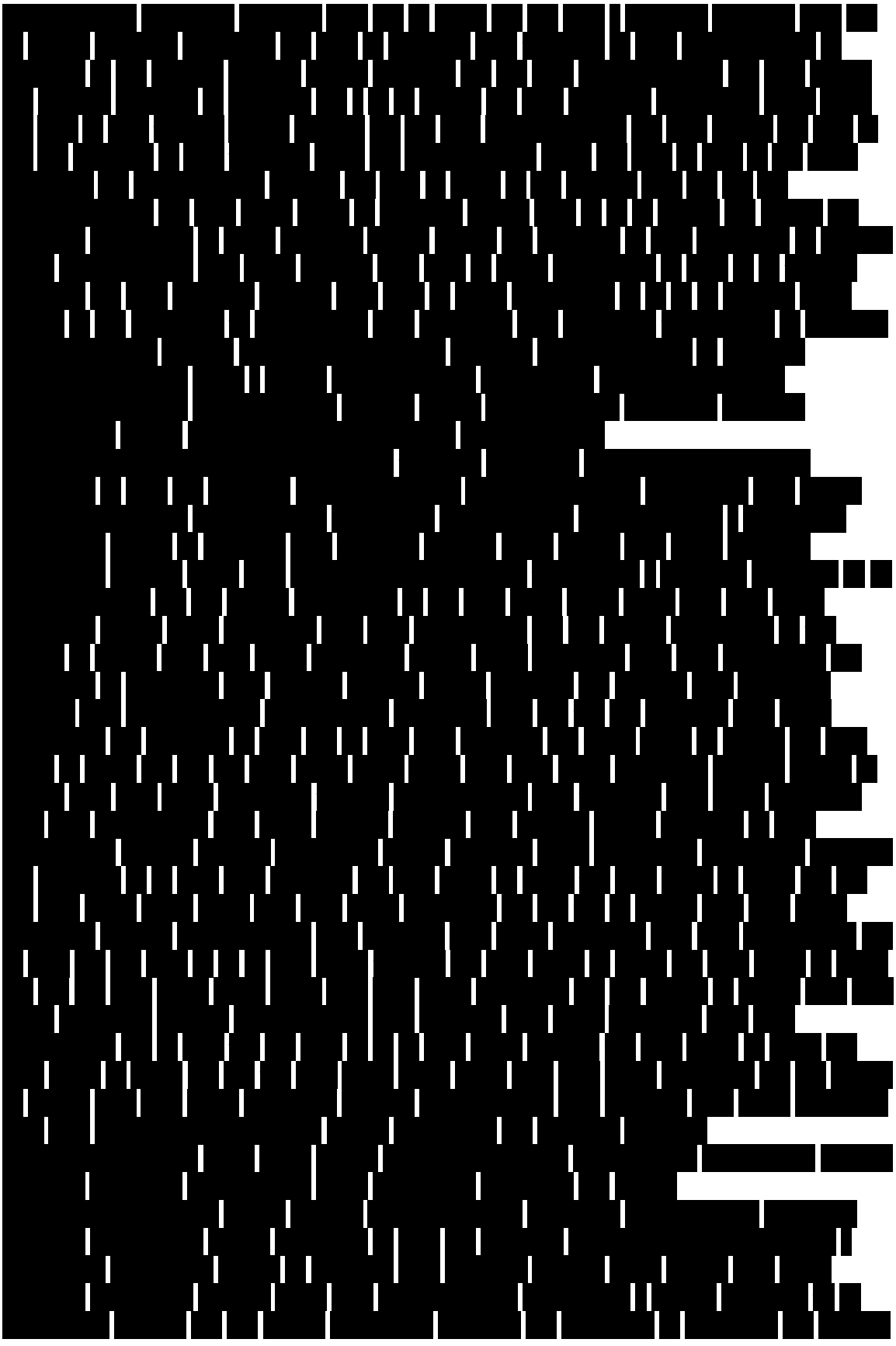
Tables

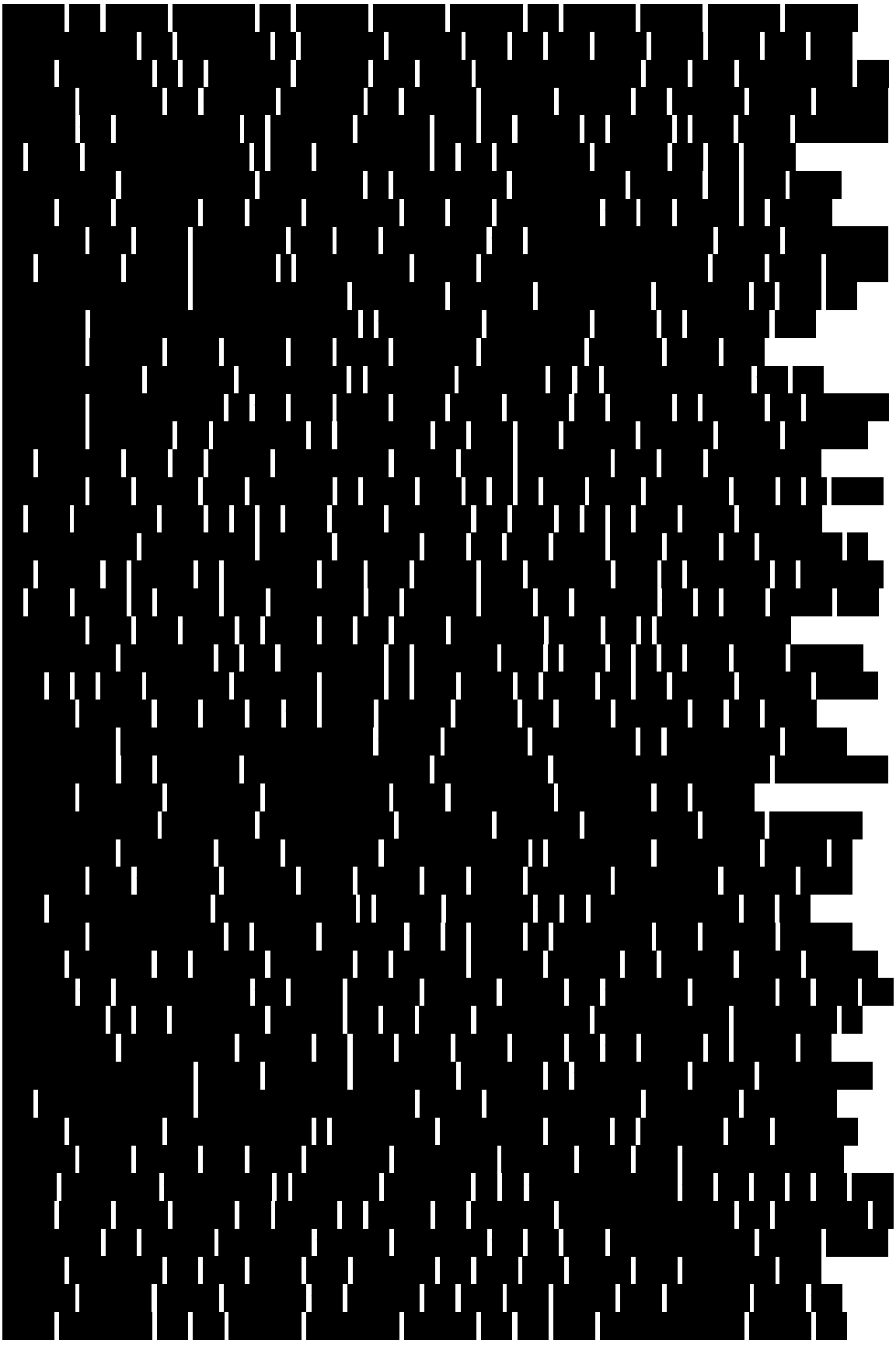
Figures

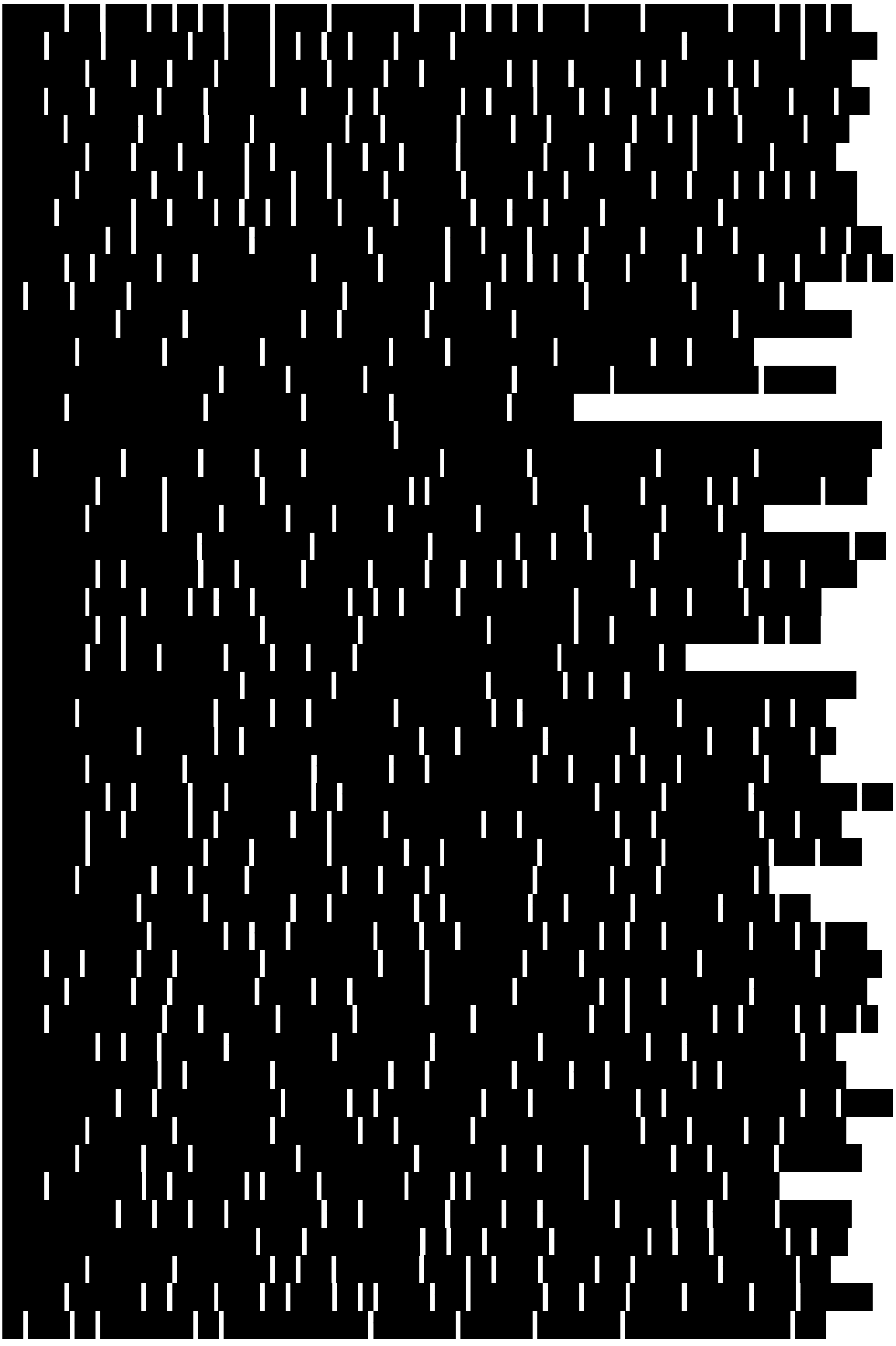


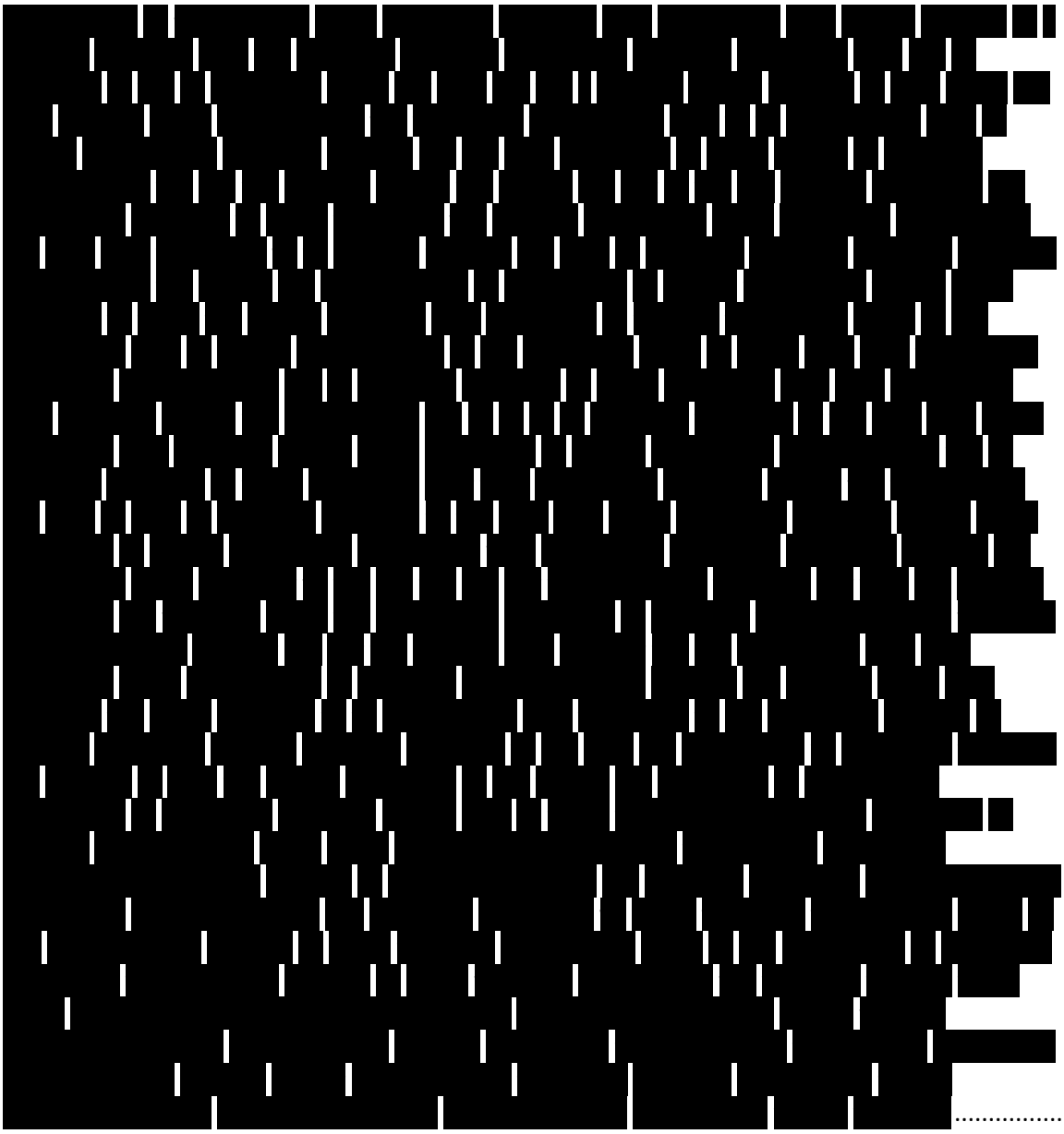












ABBREVIATIONS

A1C	glycated hemoglobin
AE	adverse event
AFL	aflibercept
aLOCF	last observation carried forward, including values observed after additional treatment
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
aOC	observed case including values observed after additional treatment
APTC	Antiplatelet Trialists' Collaboration
ATE	arterial thrombotic event
BCVA	best-corrected visual acuity
CDR	CADTH Common Drug Review
CHO	Chinese hamster ovary
CI	confidence interval
CRT	central retinal thickness
CST	central subfield thickness
CVA	cardiovascular accident
DME	diabetic macular edema
DR	diabetic retinopathy
DRSS	Diabetic Retinopathy Severity Score
EQ-5D	EuroQol Five-Dimension Health-Related Quality of Life Questionnaire
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	full analysis set
FDA	Food and Drug Administration
IVT	intravitreal
LOCF	last observation carried forward
Log MAR	logarithm of the minimal angle of resolution
LRT	laser-ranibizumab-triamcinolone
LRTforDME+PRP	Laser-Ranibizumab-Triamcinolone for Diabetic Macular Edema Plus Proliferative Diabetic Retinopathy (Study)
LRT for DME	Laser-Ranibizumab-Triamcinolone For Diabetic Macular Edema (Study)
LSM	least squares mean
MCID	minimal clinically important difference
MI	myocardial infarction
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
OC	observed case
OCT	optical coherence tomography
PIGF	placental growth factor
PPS	per-protocol set
PRP	proliferative diabetic retinopathy

QoL	quality of life
RAN	ranibizumab
RCT	randomized controlled trial
RR	risk ratio
SAE	serious adverse event
SAF	safety analysis set
SD	standard deviation
TEAE	treatment-emergent adverse event
VA	visual acuity
VEGF	vascular endothelial growth factor
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Diabetic macular edema (DME) is a microvascular complication of diabetes mellitus. DME is defined as retinal thickening at, or within one disc diameter of, the centre of the fovea.[1-3] DME is the leading cause of vision loss, visual disability, and legal blindness in people with diabetes mellitus.[4]

Macular laser photocoagulation had been the mainstay therapy for DME prior to the introduction of anti–vascular endothelial growth factor (anti-VEGF) drugs.[3] Since its approval in 2011, the standard of care of the pharmacological treatment for DME has been the anti-VEGF drug ranibizumab (RAN),[1] although bevacizumab is also used off-label to treat DME. Aflibercept (AFL; Eylea) is a novel anti-VEGF drug that is also indicated for the treatment of DME.[5] The recommended regimen for treating DME with AFL is intravitreal (IVT) injection (40 mg/mL) with 2 mg AFL every eight weeks after five initial monthly injections.

Results and Interpretation

Two similarly designed, double-blind, multi-centre, active-controlled, randomized trials (VIVID[6] and VISTA[7]) met the inclusion criteria for the review. These studies assessed whether AFL was superior to laser photocoagulation for the treatment of DME. The primary outcome was the change in best-corrected visual acuity (BCVA), as assessed by the change in the number of Early Treatment Diabetic Retinopathy Study (ETDRS) letters after 52 weeks of treatment with AFL 2 mg every eight weeks after five initial monthly injections compared with laser treatment. (Data for AFL 2 mg every four weeks were not included in this review, as this regimen does not conform to the dosing regimen recommended in the product monograph.)[5] Patients could receive additional (rescue) treatment starting at week 24, based on predefined criteria for worsening of visual acuity (VA). The VIVID and VISTA studies were designed to be carried out over three years. As the primary outcome was the change in VA at 52 weeks, the results presented in this review are derived from data from the first year of treatment;[6,7] the results reported for the second treatment year[8,9] are summarized in Appendix 7. The results for the third treatment year were unavailable at the time of this review.

Included Studies

Efficacy

Compared with the laser group, AFL treatment was associated with a statistically significant improvement in BCVA in both studies at 52 weeks. Specifically, patients treated with AFL gained 9.1 (97.5% confidence interval [CI], 6.3 to 11.8) and 10.4 (97.5% CI, 7.7 to 13.2) ETDRS letters in VIVID and VISTA, respectively. Similarly, a statistically significant greater proportion of patients treated with AFL achieved an improvement of at least 15 ETDRS letters compared with those treated with laser therapy (24% and 23% more patients in VIVID and VISTA, respectively). The clinical importance of the improvement in VA observed in AFL-treated patients versus laser-treated patients is uncertain, because the minimal clinically important difference (MCID) for the change in ETDRS letters is thought to be at least 10 letters. The results of several sensitivity analyses in which alternative analysis sets were used — including values observed after additional treatment (last observation carried forward, including measurements after additional treatment was given [aLOCF]), observed case (OC), and observed case including values observed after additional treatment (aOC) — were consistent with the findings from the primary analysis. In addition, the greater improvement in BCVA observed in AFL-treated patients was consistent across various subgroup analyses, including those based on baseline disease severity and glycated hemoglobin (A1C) levels.

VA measured using the ETDRS Diabetic Retinopathy Severity Score (DRSS) also showed that a statistically significantly greater proportion of AFL-treated patients achieved an improvement of at least two steps on the DRSS at week 52 (between-group difference in proportion [97.5% CI]: 19.3 [6.6 to 32.1] and 14.9 [4.4 to 25.4] in VIVID and VISTA, respectively). A previous study had suggested that patients with at least two steps of ETDRS DRSS deterioration over six years were significantly more likely to develop proliferative diabetic retinopathy than those without progression.[10] Therefore, improvement of two or more steps in the DRSS observed in response to AFL treatment in VIVID and VISTA likely represents a clinically meaningful improvement in VA.

Quality of life and vision-related function were measured using the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) total score. Although more patients treated with AFL had improved NEI VFQ-25 scores at 52 weeks compared with laser treatment in both VIVID and VISTA, the differences between treatments were not statistically significant different.

AFL-treated patients had a statistically significantly greater reduction in central retinal thickness (CRT) at 52 weeks compared with laser-treated patients in both studies (least squares mean [LSM] difference [97.5% CI]: –142.8 [–179.3 to –106.3] and –113.5 [–144.19 to –82.75] in VIVID and VISTA, respectively).The clinical significance of these changes in CRT is uncertain, due to the lack of information regarding the MCID for this outcome; nevertheless, the lack of any meaningful increase in CRT in the AFL-treated patients reflects an absence in these patients of the increased thickening of the retina that characterizes progression of DME.

The data available through the second year of treatment (at 100 weeks) indicate that the relatively greater improvements in VA in AFL-treated patients observed in the first year of each study were maintained through the second year of treatment,[8,9] suggesting that the differential efficacy of AFL compared with laser treatment is likely preserved over the longer term.

Harms

The frequency of ocular treatment-emergent adverse events (TEAEs) was slightly higher in laser-treated patients in both studies (62% to 67% for laser treatment versus 57% to 59% for AFL). While the incidence of ocular TEAEs was slightly higher in laser-treated patients in both studies (8% to 10% for laser versus 5% for AFL), the overall frequency of non-ocular TEAEs was similar between the treatment groups. Conjunctival hemorrhage, eye pain, cataract, and vitreous floaters were the most common adverse events (AEs), although none of these were reported in more than 3% of patients.

There were relatively few ocular serious adverse events (SAEs) in VIVID and VISTA. The most common ocular SAEs were vitreous hemorrhage, diabetic retinopathy, and retinal revascularization, each of which occurred in fewer than 2% of patients (except for retinal revascularization, which occurred in 2.3% of patients in the laser group in VIVID). There was no clear imbalance in the frequency of non-ocular SAEs across studies: in VIVID, more non-ocular SAEs were observed in the AFL group than in the laser group (14% for laser versus 19% for AFL), whereas in VISTA, more non-ocular SAEs were observed in the laser-treated patients than in AFL-treated patients (32% for laser treatment versus 26% for AFL). More laser-treated patients withdrew from both studies than AFL-treated patients, and this was reflected in a higher rate of withdrawals due to non-ocular SAEs in both studies (2% to 3% for laser versus 0% to 1% for AFL). The most common non-ocular SAEs were acute myocardial infarction, peripheral ischemia, and hyperglycemia, each of which occurred in fewer than 2% of patients.

Harms of particular clinical relevance were relatively rare. Specifically, endophthalmitis occurred in only two patients, both of whom were treated with laser. Retinal detachment occurred in three patients (in the VIVID study only). Arterial thrombotic events occurred in eight and 10 laser- and AFL-treated patients, respectively, and there was no notable imbalance in the distribution of these events between treatments. In VIVID, one death was reported in the laser treatment group and four in the AFL treatment group. The only death that occurred in VISTA was in the laser treatment group.

The harms data available through 100 weeks of treatment were consistent with those reported after 52 weeks, and no new safety issues were observed.

Other Considerations

None of the included studies included RAN as a comparator, and there are no published studies of clinical trials that directly compared AFL with RAN in the treatment of DME.[a] However, a review of three indirect comparisons[12-14] (including a network meta-analysis submitted by the manufacturer) that included AFL and RAN as treatments suggested that AFL is at least as effective as RAN in improving VA in DME patients. In addition, the three indirect comparisons were consistent in their finding that the safety profiles of AFL and RAN are similar.

Patient input received by CADTH for this review indicated that patients expect AFL will present them with an alternative option to treatments available at present. Patients also expected that that AFL will require fewer injections than the current standard of treatment, RAN, but whether this expectation will be met is not known.

Conclusions

The results of the two double-blind, multinational, randomized, active-controlled trials (VIVID and VISTA) suggest that AFL is superior to laser photocoagulation for improving VA in patients with DME. A statistically significantly greater improvement of 9.1 to 10.5 more ETDRS letters was observed after 52 weeks of treatment in AFL-treated patients compared with laser therapy in both studies. A statistically significantly greater proportion of AFL-treated patients in both studies achieved a gain of at least 15 ETDRS letters compared with laser treatment. There were no statistically significant differences between treatments in either study with respect to quality of life. The incidences of TEAEs, SAEs, and withdrawal due to adverse events over 52 weeks were similar for both treatments in both studies, suggesting that the treatment harms associated with AFL and laser treatment are similar. Data available through week 100 suggest that the comparative efficacy and harms of AFL and laser therapy at 52 weeks persist through 100 weeks of treatment. The results of the manufacturer's indirect comparison and a recently published study suggest that patients treated with AFL have statistically significantly greater gains in BCVA than those treated with RAN, although the clinical significance of this is unclear. Two

[a] Recently, a study assessing the comparative effectiveness of AFL, bevacizumab, and RAN was completed.[11] The results of this study are presented and discussed in Appendix 8, and they suggest that, in patients with DME, one year of treatment with aflibercept (2 mg per injection every four weeks) is associated with a statistically significantly greater improvement in VA compared with ranibizumab (0.3 mg per injection every four weeks). The difference in the improvement in VA between treatments (13 letters versus 11 ETDRS letters for aflibercept and ranibizumab, respectively) was not clinically meaningful and was driven by baseline VA, such that patients with worse baseline VA (less than 69 ETDRS letters) tended to do relatively better with aflibercept. However, any differences between treatments in this study might not be generalizable to Canada, because a lower dose of ranibizumab (0.3 mg) was used in this US-based study than that used in Canada (0.5 mg). Safety data from this study indicated that aflibercept and ranibizumab have similar potential harms.

other indirect comparisons suggest that the efficacy and safety profile of these two anti-VEGF drugs are similar for the treatment of DME.

TABLE 1: SUMMARY OF RESULTS

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Change from baseline to week 52 in ETDRS letter score in the study eye (FAS, LOCF)				
Baseline, mean (SD)	60.8 (10.6)	58.8 (11.2)	59.7 (10.9)	59.4 (10.9)
At 52 weeks, mean (SD)	62.0 (14.3)	69.5 (11.9)	60.0 (16.5)	70.1 (12.6)
LSM change (SE)	0.9 (1.0)	10.0 (0.9)	0.1 (1.0)	10.6 (0.7)
LSM change difference (97.5% CI) (AFL – laser)	9.1 (6.3 to 11.8)		10.4 (7.7 to 13.2)	
P value	< 0.0001		< 0.0001	
Patients gained ≥ 15 letters in the ETDRS letter score in the study eye at week 52 (FAS, LOCF)[a]				
n /N (%)	12/132 (9.1)	45 /135 (33.3)	12/154 (7.8)	47 /151(31.1)
Difference in proportion, % (97.5% CI) (AFL – laser)	24.2 (13.5 to 34.9)		23.3(13.5 to 33.1)	
NNT	[redacted]		[redacted]	
P value	< 0.0001		< 0.0001	
RR (95% CI) (AFL vs. laser)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Proportion of patients with a ≥ 2-step improvement from baseline to week 52 in the ETDRS DRSS (FAS, LOCF)				
n /N (%)	6/80 (7.5)	23/83 (27.7)	22/154 (14.3)	44/151 (29.1)
Difference in proportion, % (97.5% CI) (AFL – laser)	19.3 (6.6 to 32.1)		[redacted]	
P value	0.0006		0.0017	
NNT	[redacted]		[redacted]	
RR (CI 95%)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Withdrawal from the study				
n/N (%)	20/132 (14.8)	15/135 (11.1)	11/154 (7.1)	10/151 (6.5)
Ocular SAEs				
n/N (%)	6/132 (4.5)	3/135 (2.2)	6/154 (3.9)	2 /151(1.3)
RR (95% CI)	[redacted]		[redacted]	
ARR (AFL – laser)	[redacted]		[redacted]	
NNH	[redacted]		[redacted]	
Non-ocular SAE				
n/N (%)	18/132 (13.5)	25/135 (18.5)	47/154 (30.5)	39/151 (25.7)
RR (95% CI)	[redacted]		[redacted]	
ARR (AFL – laser)	[redacted]		[redacted]	
NNH	[redacted]		[redacted]	
WDAEs				
n/N (%)	8 / 132(5.9)	4/135 (3.0) b	3/154 (1.9)	2 /151(1.3)
RR (95% CI)	[redacted]		[redacted]	
ARR	[redacted]		[redacted]	
NNH	[redacted]		[redacted]	

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Notable harm(s)				
Injection-related ocular TEAE				
n/N (%)	17 (12.8)	50 (37.0)	59 (38.3)	62 (40.8)
RR (95% CI)	[redacted]		[redacted]	
ARR	[redacted]		[redacted]	
NNH	[redacted]		[redacted]	

2Q8 = 2 mg every eight weeks; AFL = aflibercept; ARR = absolute risk reduction; 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; RR = risk ratio; SAE = serious adverse event; SD = standard deviation; SE = standard error; TEAE = treatment-emergent adverse event; VA = visual acuity; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Difference is AFL minus laser; CI was calculated using a normal approximation. LSM differences were calculated using the 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). In the VIVID study, an ANCOVA model was used with baseline BCVA measurement as a covariate and treatment group and geographic region (Europe, Japan) as fixed factors for the primary analysis. In the VISTA study, an ANCOVA model with treatment as the main effect, history of myocardial infarction or correct visual acuity as a fixed effect, and baseline BCVA measurement as the covariate was used for the primary analysis.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Diabetic macular edema (DME) is a microvascular complication of diabetes mellitus. DME is defined as retinal thickening at, or within one disc diameter of, the centre of the fovea.[1-3] DME is the leading cause of visual loss, visual disability, and legal blindness in people with diabetes mellitus. Its prevalence has been shown to increase with the severity of non-proliferative diabetic retinopathy. DME prevalence was found to be 3% in mild non-proliferative diabetic retinopathy, rising to 38% in eyes with moderate to severe non-proliferative diabetic retinopathy, and reaching in excess of 70% for patients with proliferative diabetic retinopathy.[4]

Vascular endothelial growth factor (VEGF) plays a key role in the pathophysiology of DME.[15] Specifically, anti-VEGF induces angiogenesis and neovascularization and increases vascular permeability. Besides anti-VEGF, hypoxia-induced placental growth factor (PlGF) is instrumental in contributing to vascular permeability.[16] It acts in synergy with VEGF and contributes to the vessel abnormalities and retinal changes occurring in early diabetic retinopathy. DME usually presents as a slowly progressive vision loss. The degree of vision loss can vary considerably and depends on the severity, duration, and location of intraretinal fluid, among other factors. Symptoms may include blurred or distorted vision, colours appearing "washed out" or faded, changes in contrast sensitivity, impaired colour vision, gaps in vision (scotomas), and loss of central vision (blindness). Such progressive visual impairment results in significant decrements in daily functioning and quality of life (QoL) for patients with DME,[17,18] and indirect costs due to lost productivity are high if DME is left untreated.[19] Therefore, early detection and treatment of DME is vital.[20] The Early Treatment Diabetic Retinopathy Study (ETDRS) chart is the gold standard for measuring changes in vision.[21] Each line contains five letters, which proportionally decrease in size as the patient reads down the chart. Table 1 illustrates that even one line of vision loss negatively affects a patient's QoL. The Canadian Diabetes Association estimates that in 2010, 2.7 million (7.6%) Canadians had diabetes. This number is estimated to grow to 4.2 million (10.8%) by 2020.[22] The prevalence of DME among patients with diabetes in 2008–2009 was estimated to be 16%, and the prevalence of visual impairment due to DME was estimated to be 2.6%.[2] With the increasing prevalence of diabetes in Canada, more Canadians will be at risk for DME, making effective treatment options critical.

1.2 Standards of Therapy

The treatment strategies for DME encompass lifestyle modification, exercise, smoking cessation, as well as better blood sugar control and thus better blood sugar, blood pressure, blood lipids, and body mass index values.

Macular laser photocoagulation (including focal or grid laser) for DME had been the mainstay therapy for more than 25 years before the introduction of anti-VEGF drugs.[3] Laser photocoagulation, which is still widely used following anti-VEGF therapy, has been shown to slow or stabilize vision loss but has been minimally effective in restoring vision. Laser also has the disadvantage of causing permanent destruction of retinal tissue during treatment.[23-25] Since 2011, the standard of care of pharmacological treatment for DME has been the anti-VEGF drug ranibizumab (RAN)[1] (Table 2). RAN is a humanized recombinant monoclonal antibody fragment with anti-VEGF activity. It was the first of the anti-VEGF drugs to be approved in Canada for the treatment of DME[26] and has recently become the standard of care in this disease area.[3] The recommended dose of RAN is 0.5 mg, given as a single intravitreal injection monthly until stable visual acuity (VA) is achieved for three monthly consecutive assessments. This is followed by monthly monitoring and a "treatment as needed" regimen (PRN).[26]

Although bevacizumab (Avastin), another anti-VEGF drug, is sometimes used as an off-label treatment for DME, bevacizumab is not approved for use in DME patients in Canada and was not considered to be a valid comparator for this review.

1.3 Drug

Aflibercept (AFL; Eylea) is a solution for intravitreal (IVT) injection (40 mg/mL) at a dose of 2 mg every eight weeks after five initial monthly injections. AFL is indicated for the treatment of patients with DME in Canada.[5] AFL 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. AFL is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology. In the eye, AFL acts as a soluble decoy receptor that binds anti-VEGF and PlGF with higher affinity than their natural receptors, thereby inhibiting the binding and activation of these cognate VEGF receptors.[5] AFL differs from other VEGF inhibitors in that it has a strict one-to-one binding ratio and an approximately 100-fold higher binding affinity for VEGF than RAN. AFL, unlike RAN, also binds PlGF, which may be advantageous in certain disease situations.[27] The key characteristics of AFL and RAN are presented in Table 2.

Indication under review
Treatment of diabetic macular edema (DME)[a]
Listing criteria requested by sponsor
For the treatment of DME, in a manner similar to ranibizumab (RAN)

[a] Aflibercept is also indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) and central retinal vein occlusion (CRVO), which have been reviewed separately.

TABLE 2: KEY CHARACTERISTICS OF AFLIBERCEPT AND RANIBIZUMAB

	Aflibercept	Ranibizumab
Mechanism of Action	Recombinant fusion protein that binds VEGF and PIGF with higher affinity than their natural receptors, thereby inhibiting the binding and activation of these cognate VEGF receptors[5]	Recombinant monoclonal antibody fragment that binds VEGF isoforms that contribute to the progression of DME[26]
Indication[a]	Treatment of DME	
Route of Administration	Intravitreal injection	
Recommended Dose	2 mg every 8 weeks after initial 5 monthly injections	0.5 mg once a month
Serious Side Effects/Safety Issues	• SAEs: cataract, increased intraocular pressure, and retinal detachment • Contraindications: patients who are hypersensitive to this drug, who have ocular or periocular infection, and who have active intraocular inflammation	• SAEs: 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

DME = diabetic macular edema; IOP = intraocular pressure; PIGF = placental growth factor; SAE = serious adverse event; VEGF = vascular endothelial growth factor.
[a] Health Canada indication. Aflibercept is also indicated for the treatment of neovascular (wet) age-related macular degeneration and central retinal vein occlusion, which have been reviewed separately.
Source: Product monographs for aflibercept[5] and ranibizumab.[26]

2. OBJECTIVES AND METHODS

2.1 Objectives

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

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 the CADTH Common Drug Review (CDR), as well as those meeting the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with DME Subgroups • baseline visual acuity • baseline A1C
Intervention	Aflibercept (40 mg/mL solution for intravitreal injection), 2 mg intravitreal injection monthly (once every 4 weeks) for the first 5 consecutive doses, followed by one injection every 2 months (8 weeks)
Comparators	Ranibizumab[a] Laser photocoagulation Corticosteroid: triamcinolone acetonide
Outcomes	**Efficacy outcomes** • Change from baseline in visual acuity[b] • Proportion of patients with ≥ 2-step improvement from baseline in ETDRS DRSS • Quality of life and/or vision-related function (assessed by validated measures such as EQ-5D, NEI VFQ-25) • Blindness (legal) • Change in CRT **Harms outcomes** • AE • SAE (ocular or non-ocular) • WDAE • Notable AEs: endophthalmitis, retinal detachment, ATE
Study Design	Published and unpublished DB, phase 3 RCTs

A1C = glycated hemoglobin; AE = adverse event; ATE = arterial thrombotic event; CRT = central retina thickness; DB = double-blind; DME = diabetic macular edema; DRSS = Diabetic Retinopathy Severity Score; ETDRS = Early Treatment Diabetic Retinopathy Study; EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; RCT = randomized controlled trial; SAE = serious adverse events; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; WDAE = withdrawal due to adverse events.

[a] Standard pharmacotherapy available in Canada.

[b] Visual acuity change from baseline consists of absolute change, and percentage of patients maintaining vision (defined as percentage of patients with vision acuity worsening from baseline of ≤ 15 letters, with improvement or worsening from baseline of ≥ 15 letters visual acuity, and with severe vision loss [loss of ≥ 30 letters visual acuity]).

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.

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 via Ovid; Embase (1974–) via 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 concepts were Eylea (aflibercept) and diabetic macular edema.

Methodological filters were not applied to limit retrieval to specific study designs. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on November 24, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on April 8, 2015. 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 Grey Matters checklist (www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials 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 through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished 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 4 and described in section 3.2.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

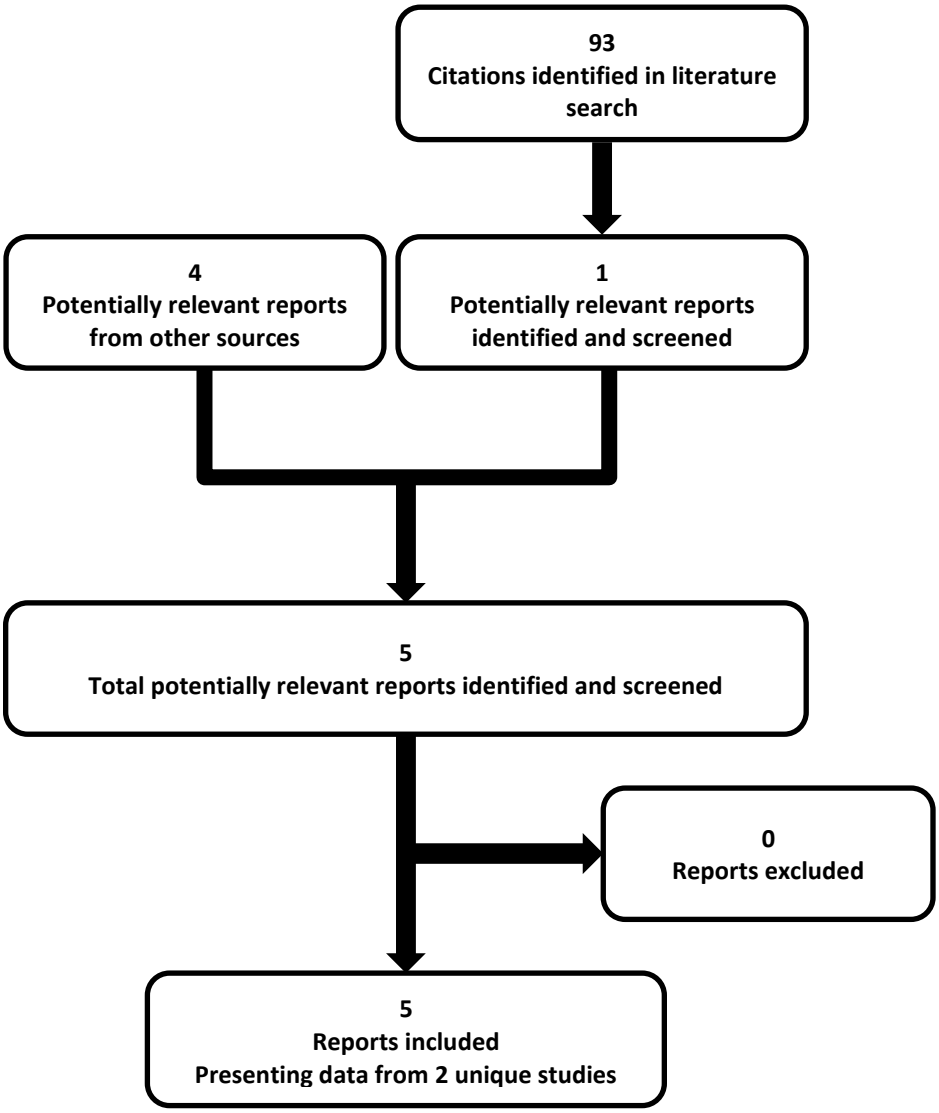


TABLE 4: DETAILS OF INCLUDED STUDIES

		VIVID6	VISTA7
DESIGNS AND POPULATIONS	**Study Design**	Phase 3, DB, multi-centre, active-controlled RCT	
	Locations	73 centres in Japan, European countries, and Australia	54 centres in the US
	Randomized (N)[a]	270 in total (in laser and aflibercept [2Q8]) (136 in 2Q4 group)	310 (in laser and aflibercept [2Q8]) (156 in 2Q4 group)
	Inclusion Criteria	• Adults ≥ 18 years with type 1 or 2 diabetes mellitus • Patients with DME secondary to diabetes mellitus involving the centre of the macula (central subfield on OCT) in the study eye • Decrease in vision determined to be primarily the result of DME in the study eye • BCVA ETDRS letter score of 73 to 24 (20/40 to 20/320) in the study eye • Willing and able to comply with clinic visits and study-related procedures • Provide a signed informed consent form • Only 1 eye per patient was enrolled in the study	
	Exclusion Criteria	• Ocular conditions with a poorer prognosis in the untreated eye than in the study eye • History of vitreoretinal surgery in the study eye • Laser photocoagulation (panretinal or macular) in the study eye within 90 days of day 1 • More than 2 previous macular laser treatments in the study eye or, in the opinion of the investigator, the patient had no potential to benefit from laser treatments (e.g., if too many laser treatments had been applied in the past) • Previous use of intraocular or periocular corticosteroids in the study eye within 120 days of day 1 • Previous treatment with anti-angiogenic drugs in either eye (pegaptanib sodium, bevacizumab, ranibizumab, etc.) within 90 days of day 1[b] • Active proliferative DR in the study eye • History of idiopathic or autoimmune uveitis in the study eye and other severe eye conditions, or other severe medical conditions • Only 1 functional eye even if that eye was otherwise eligible for the study • Uncontrolled diabetes mellitus, as defined by glycated hemoglobin (A1C) > 12% in VIVID study; no A1C cut-off was provided in VISTA study • Pregnant or breastfeeding women • Allergy to fluorescein	
DRUGS	**Intervention**	• AFL 2Q8 IVT injection after 5 initial monthly injections • With sham LPCT, as appropriate	
	Comparator(s)[c]	• Macular LPCT[c] • With sham IVT injection	
	Phase		
	Screen phase	21 days (day –21 to day 0)	
	Run-in	None	
	First year DB: Primary efficacy phase	Week 0 to 52	
	Second year: DB phase	Week 52 to 100	

		VIVID6	VISTA7
	Laser group patients treated with AFL as needed phase	Through 100 week 148	
OUTCOMES	**Primary End Point**	Change in BCVA in ETDRS letter score from baseline to week 52	
	Other End Points	• Mean change in BCVA; gain or loss ≥ 15 letters • The proportion of patients who achieved a ≥ 2-step improvement in the ETDRS DRSS from baseline to week 52 • Change in total NEI VFQ-25 score • Central retinal thickness • Adverse events	
NOTES	**Publications**	Korobelnik et al. (2014)[28]	

2Q8 = 2 mg every 8 weeks; 2Q4 = 2 mg every 4 weeks; AFL = aflibercept; BCVA = best-corrected visual acuity; DB = double-blind; DME = diabetic macular edema; DR = diabetic retinopathy; DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; IVT = intravitreal; LPCT = laser photocoagulation treatment; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25; OCT = optical coherence tomography; RCT = randomized controlled trial; VEGF = vascular endothelial growth factor.

[a] Patients were randomized in a 1:1:1 ratio to the following regimens: 2Q4; 2Q8 after 5 initial monthly injections at weeks 0, 4, 8, 12, and 16 (to maintain masking, sham injections were given at the interim 4-week visits after week 8); or LPCT. 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.[30] In this review, only 2Q8 after first five monthly injections and LPCT are reported.

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

[c] LPCT: at day 1 and at visits at which patients met any of the criteria for laser re-treatment (but no more often than every 12 weeks).

Note: In addition to the one published article, three additional reports and documents were included: one submission package[29] and two Clinical Study Reports.[6,7]

Source: Korobelnik et al. (2014).[28]

3.2 Included Studies

3.2.1 Description of studies

Two studies (VISTA[7] and VIVID[6]) that met the inclusion criteria for the review were identified. Both studies were superiority-designed, double-blind, and randomized (1:1 ratio) controlled trials that examined the efficacy and safety of AFL versus laser treatment for patients with DME. VIVID was conducted at 73 centres in Japan, European countries, and Australia (N = 270),[6] and VISTA was conducted at 54 sites (N = 310) in the US.[7] The entire trial duration was designed for three years. The primary outcome was measured at week 52. During year 3 (from week 100 to week 148), patients randomized to the laser treatment group will receive AFL, administered as IVT injection as needed; if AFL re-treatment criteria are met, patients randomized to the AFL treatment groups will maintain their randomized treatment to the end of the study (week 148) (Figure 2). The primary objective of the two studies was to assess the efficacy of IVT-injected AFL compared with laser photocoagulation treatment in improving best-corrected visual acuity (BCVA) in patients with DME at week 52.

In the included two trials, there were three treatment groups: laser photocoagulation treatment, AFL 2 mg every four weeks throughout, and AFL 2 mg every eight weeks after five initial monthly injections at weeks 0, 4, 8, 12, and 16. (To maintain masking, sham injections were given at the interim

four-week visits after week 16.) In this report, we focus primarily on the comparative efficacy and safety profile of AFL every eight weeks after five initial monthly injections with laser treatment at week 52, because AFL 2 mg every four weeks is not a recommended dose regimen in Canada (see section 3.2.3). The results observed at year 2 are briefly summarized in Appendix 6.

AFL injection (2 mg every eight weeks) patients were administered AFL 2 mg IVT every four weeks until week 16 (i.e., five initial monthly doses) and every eight weeks thereafter. After week 16, a sham injection was given every eight weeks at the visits at which AFL was not administered. Therefore, every four weeks, the patients received either AFL or a sham injection to maintain masking. Patients in this group also received a sham laser treatment at baseline, that is, at the initial dosing visit. Patients were assessed for sham laser re-treatment beginning at week 12. With the macular laser photocoagulation treatment with sham IVT injection, patients received an active macular laser photocoagulation treatment using the modified ETDRS protocol at baseline, that is, at the initial dosing visit, and sham injections at every visit. Patients were assessed for laser re-treatment beginning at week 12.

Patients were assessed for additional treatment criteria starting at week 24. Patients receiving additional treatment continued with the study and their randomized treatment while maintaining all masking measures. Additional treatment included AFL (2 mg every eight weeks, after five initial monthly doses) for patients undergoing laser treatment and active laser treatment for the AFL patients (section 3.2.3).

3.2.2 Populations

a) Inclusion and exclusion criteria

The key selection criteria included patients aged 18 years or older with type 1 or 2 diabetes mellitus; patients with DME secondary to diabetes mellitus involving the centre of the macula (defined as the area of the centre subfield of optical coherence tomography [OCT]) in the study eye; decrease in vision determined to be primarily the result of DME in the study eye; retinal thickness as assessed by OCT of ≥ 300 µm in the study eye; and BCVA ETDRS letter score of 73 to 24 (20/40 to 20/320) in the study eye.[6,7] Patients who met any of the following criteria at either the screening visit or day 1 visit were excluded from the study: ocular conditions with a poorer prognosis in the untreated eye than in the study eye; history of vitreoretinal surgery and/or including scleral buckling in the study eye; laser treatment in the study eye within 90 days of day 1 of the study; more than two previous treatments with laser photocoagulation in the study eye or the patient had no potential to benefit from laser treatments (e.g., if too many laser treatments had been applied in the past); previous use of intraocular or periocular corticosteroids in the study eye within 120 days of day 1; previous treatment with anti-angiogenic drugs in either eye (pegaptanib sodium, bevacizumab, RAN, etc.) within 90 days of day 1; active proliferative diabetic retinopathy (DR) in the study eye; or uncontrolled diabetes mellitus, as defined by glycated hemoglobin (A1C) > 12% in VIVID[6] (no A1C cut-off was provided in VISTA[7]).

b) Baseline haracteristics

Overall, the demographic and baseline characteristics of the patients included in the studies were balanced between treatment groups in both studies (Table 5). Two hundred and seventy patients in VIVID and 310 patients in VISTA were randomized to the two groups (laser treatment or AFL 2 mg every eight weeks) (Table 4). The mean age of the randomized patients was 62 to 64 years (range from 36 to 86 years old). More male patients (59% to 65% in VIVID and 51% to 55% in VISTA) were included in both trials. Patients were predominantly Caucasian (79% to 81% in VIVID and 83% to 85% in VISTA). The mean baseline BCVA letter scores were 59 to 61 (range 24 to 80) and were similar between the two treatment groups (Table 5). The mean central retinal thickness (CRT) was 490 µm to 540 µm and was comparable in both treatment groups in either of the two studies (Table 10 in Appendix 4). The proportion of

patients with prior anti-VEGF IVT treatment was 10% to 11% in VIVID and 41% to 45% in VISTA. Mean baseline National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) total scores were 69 to 78 out of a total of 100 possible points (Table 5). The patients with A1C > 8% were 31% to 33% in VIVID and 62% to 70% in VISTA. The majority of patients (91% to 93%) had type 2 (rather than type 1) diabetes in VISTA. More detailed information on baseline characteristics is presented in Table 9, Table 10, and Table 11 in Appendix 4.

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

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Sex, n (%)				
Male	78 (59.1)	88 (65.2)	85 (55.2)	78 (51.7)
Female	54 (40.9)	47 (34.8)	69 (44.8)	73 (48.3)
Age, years				
Mean (SD)	63.9 (8.6)	64.2 (7.8)	61.7 (8.65)	63.1 (9.39)
A1C, %				
Mean (SD)	7.7 (1.3)	7.7 (1.4)	7.6 (1.7)	7.9 (1.6)
A1C, % by category				
Mean (SD), ≤ 8%	89 (67.4)	91 (67.4)	108 (70.1)	94 (62.3)
Mean (SD), > 8%	42 (31.8)	44 (32.6)	45 (29.2)	57 (37.7)
Duration of diabetes (years)				
Mean (SD)	14.5 (9.8)	14.1 (8.9)	17.2 (9.6)	17.6 (11.5)
Prior intravitreal anti-VEGF treatment, n (%)	13 (9.8)	15 (11.1)	63 (40.9)	68 (45.0)
BCVA				
Mean (SD)	60.8 (10.6)	58.8 (11.2)	59.7 (11.0)	59.4 (10.9)
Baseline total NEI VFQ-25 score				
Mean (SD)	77.5 (15.2)	71.2 (17.8)	68.7 (18.1)	70.5 (17.1)

2Q8 = 2 mg every 8 weeks after first five monthly injections; A1C = glycated hemoglobin; AFL = aflibercept; BCVA = best-corrected visual acuity; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; SD = standard deviation; VEGF = vascular endothelial growth factor.
Source: VIVID Clinical Study Report T13, p. 93–94; VISTA Clinical Study Report T12, p. 75–77; VIVID Clinical Study Report T14, p. 95; VISTA Clinical Study Report T13, p. 78–79.

3.2.3 Interventions

In both trials, there were three treatment groups. Only the Health Canada–recommended dosage and regimen are discussed in this report; that is, AFL 2 mg every eight weeks after five monthly injections and macular laser photocoagulation treatment (laser treatment).

In the AFL 2 mg every eight weeks group, to maintain masking, sham injections were given at the interim four-week visits after week 16. Patients in this group also received a sham laser treatment at baseline; i.e., at the initial dosing visit. Patients were assessed for sham laser re-treatment beginning at week 12 and for additional treatment criteria starting at week 24.

In the laser treatment group, patients received an active macular laser treatment using the modified ETDRS protocol at baseline, i.e., at the initial dosing visit, and sham injections at every visit. Patients

were assessed for laser re-treatment beginning at week 12 and for additional treatment criteria starting at week 24.

Patients were assessed for laser re-treatment beginning at week 12 according to the following criteria for both groups: the investigator expected that the patient would benefit from another laser treatment, and one of the following: thickening of the retina at or within 500 µm of the centre of the macula; hard exudates at or within 500 µm of the centre of the macula, if associated with thickening of adjacent retina; or a zone or zones of retinal thickening one disc area or larger, any part of which is within one disc diameter of the centre of the macula. For patients randomized to the AFL groups, if laser re-treatment criteria were met, sham laser treatment was performed on the same day, before the AFL IVT injection, but not more often than every 12 weeks. For patients randomized to the laser group, if laser re-treatment criteria were met, laser photocoagulation therapy was performed on the same day, before the sham IVT injection, but not more often than every 12 weeks.

a) Additional treatment (rescue) starting at week 24

Patients were also considered for additional treatment at each visit starting at week 24. If at least one of the following conditions were met (as assessed by masked personnel), the patient was considered for additional treatment: loss of 15 letters or more from the best previous measurement, but actual BCVA not better than baseline, at any study visit; or loss of 10 letters or more from the best previous measurement, but actual BCVA not better than baseline, at any study visit, confirmed at a consecutive visit at least seven days later (consecutive visit may be an unscheduled visit). Patients receiving additional treatment continued with the study and their randomized treatment while maintaining all masking measures. Additional treatment included AFL (2 mg every eight weeks, after five initial monthly doses) for the laser-treated patients and active laser treatment for the AFL patients.

b) Fellow eye treatment

The untreated eye was not considered an additional study eye. Any therapy of the untreated eye was considered as routine medical care rather than a study intervention. If the untreated eye had DME with central involvement requiring treatment, standard of care (including AFL IVT) therapy was administered (Table 16).

3.2.4 Outcomes

a) Primary outcome

The primary outcome was the change from baseline in BCVA, as measured by ETDRS letters at week 52. ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between 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 US FDA recommends a mean change of 15 letters or more on an ETDRS chart, or a statistically significant difference in the proportion of patients with a 15 or greater letter change in VA as clinically relevant outcome measures in trials of interventions for macular edema.[31]

b) Secondary outcomes

The secondary efficacy outcomes include the following:

Proportion of eyes that gained 15 letters from baseline

With regard to the proportion of patients who gained at least 15 letters of vision from baseline to week 52, a gain of three lines (15 letters) is usually considered a moderate degree of change and is commonly used as an outcome in clinical trials.[32]

Proportion of eyes with a two-step improvement in the ETDRS Diabetic Retinopathy Severity Scale Score at week 52

The Diabetic Retinopathy Severity Scale (DRSS) consists of 13 levels of graded photographic characteristics that were defined to categorize severity of diabetic retinopathy for individual eyes, ranging from no retinopathy to severe vitreous hemorrhage. Step progression refers to an increase in photographic level that can be used to describe change in DR over time.[10,33] In the ETDRS, the proportion of eyes with progression of two or more levels at follow-up was relatively similar among all severity categories at the one-year follow-up time point, establishing two-step progression as a reasonable outcome measure for all baseline retinopathy levels.[33] The FDA-recommended end points for DR clinical trials include a "statistically significant difference in the percentage of patients at 3 years with a ≥ 3-step change on the ETDRS retinopathy scale."[25] The Wisconsin Epidemiologic Study of Diabetic Retinopathy indicated that patients with one or more steps of ETDRS DRSS progression over six years (years 4 to 10 of follow-up) were significantly more likely to develop proliferative DR than those without ETDRS DRSS step progression.[10]

Quality of life and vision-related function

QoL and vision-related function were evaluated using the NEI VFQ-25 in both VIVID and VISTA. The NEI VFQ-25 includes 25 items relevant to 11 vision-related constructs, in addition to a single-item general health component.[34] 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).[35] The change in total NEI VFQ-25 score from baseline to week 52 was measured. In the two included studies, the NEI VFQ-25 subscales included a near activity subscale and a distance activity subscale. The EuroQol Five-Dimension Health-Related Quality of Life Questionnaire (EQ-5D) is a generic QoL instrument that has been applied to a wide range of health conditions.[36] The MCID of EQ-5D in patients with DME is unknown.

Change in central retinal thickness

Change from baseline in central subfield thickness or CRT was evaluated using OCT on the study eye. No MCID for CRT is specified.

Safety outcomes

Mortality, ocular and non-ocular serious adverse events (SAEs), overall adverse events (AEs), potential AEs of special clinical interest, and injection-related AEs were also reported.

3.2.5 Statistical analysis

a) Primary outcome analysis

In both studies, the primary outcome analysis is the change from baseline to week 52 in BCVA. For the analysis, an analysis of covariance (ANCOVA) model was used, with baseline BCVA measurement as a covariate and treatment group and geographic region (Europe and Australia, and Japan) as fixed factors in VIVID.[6] In contrast to the classical ANCOVA model, separate variances were estimated for each of the treatment groups, as the variances for AFL and laser treatment were not assumed to be equivalent. In VISTA,[7] the primary efficacy analysis was the change in BCVA from baseline to week 52 in the AFL 2 mg every eight weeks group versus the laser treatment group. An ANCOVA model with treatment as the main effect, history of myocardial infarction (MI) or cardiovascular accident (CVA) as a fixed effect, and baseline BCVA measurement as the covariate, was used for the primary analysis. For the primary efficacy analysis, measurements obtained after the initiation of additional treatment were censored. Missing or censored values were imputed using the last non-censored value (last observation carried forward [LOCF]). Baseline values were not carried forward.

In both studies, in order to control the nominal family-wise type 1 error rate of 5%, the Bonferroni multiple comparison test was used to adjust the comparisons between study treatments and control; i.e., AFL group versus laser group comparison was tested independently at the 2.5%, two-sided significance level. This extended to the secondary end points in a hierarchical manner, assuming that the statistical significance of the primary end point at week 52 for a given dose was met.[7] According to the US statistical analysis plan, among all secondary outcomes, only the proportion of patients who gained 15 ETDRS letters or more from baseline to week 52 is considered in the hierarchy of secondary end points. All other end points are considered exploratory for the US-specific analysis.

Sample size: In both studies, the sample size calculation was based on the primary outcome "change from baseline in BCVA in ETDRS letters to week 52" in the AFL 2 mg every eight weeks group versus the laser treatment group. A sample size of 92 patients per group was needed to provide 90% power to reject each of the null hypotheses with a two-sided *t*-test at the 2.5% (5%/2) significance level. Assuming a dropout rate up to 25% in VIVID[6] and up to 30% in VISTA,[7] approximately 125 patients per group were required in VIVID and 134 patients per group in VISTA. This resulted in a total of approximately 250 patients in VIVID and 268 patients in VISTA for the two groups (AFL 2 mg every eight weeks group versus the laser treatment group). [redacted]

Secondary outcome analyses

For the secondary analysis, the model described for the primary analysis was used but additionally included interaction terms for treatment[6,7] and region[6] as well as treatment and baseline value.[6,7] As a secondary analysis, a logistic regression analysis was performed using the same covariates as for the primary analysis of the primary variable, i.e., geographic region[6] and baseline BCVA.[6,7] If the AFL group was shown to be superior to the laser treatment group for the primary end point, additional comparisons of this AFL group with the laser treatment group were made with respect to secondary end points. The analyses for all secondary efficacy variables were conducted in the full analysis set (FAS) population and were tested for superiority of the AFL group over the laser treatment group. [redacted]

Sensitivity analyses

In both studies, to assess the robustness of the main analysis results, several sensitivity analyses were performed to address the impact of missing data due to dropouts or receipt of additional treatment. All sensitivity analyses for the primary efficacy outcome were analyzed on the FAS. [redacted]

[redacted]

Subgroup analyses

Key subgroup analyses by baseline VA (< 40 letters, ≥ 40 to < 55 letters, ≥ 55 to <65 letters, and ≥ 65 letters); by baseline A1C (> 8% and ≤ 8%) were performed on primary outcomes and key secondary outcomes (Table 1 as well as Table 24, Table 25, Table 26, and Table 27 in Appendix 4).

Analysis populations

The following three analysis sets were used for all statistical analyses: FAS, per-protocol set (PPS), and safety analysis set (SAF). The FAS included all randomized patients who received any study treatment, had a baseline measurement of BCVA, and had at least one post-baseline assessment of BCVA. The analysis on the FAS was performed according to the treatment assigned at baseline (as randomized). All efficacy outcomes were analyzed using the FAS. The efficacy analysis on the FAS was considered to be the primary analysis (statistical evaluation of superiority). The PPS included all patients in the FAS who did not have any major protocol deviations during the first 52 weeks. Analysis of the PPS was performed according to the treatment the patient actually received (as treated). The "as treated" assignment differed from "as randomized" if the patient was systematically receiving treatment from an alternative treatment group. However, isolated incorrect treatments did not constitute a change in the "as treated" assignment. Only the primary end point was evaluated using the PPS. The safety analysis set (SAF) included all patients who received at least one study treatment (active or sham). Patients were summarized according to the treatment actually received (as treated); additional treatment was not considered when determining "as treated" status.

3.3 Patient Disposition

Information on patient disposition in VIVID and VISTA is summarized in Table 6. The discontinuation rate from the study was similar between the AFL (2 mg every eight weeks) and the laser treatment groups in both studies, although the discontinuation rate was higher in VIVID than that in VISTA (14.8% to 11.1% and 7.1% to 6.5%, respectively). In VIVID, the primary reason for discontinuation was an AE (18 patients [4.4%]), followed by "withdrawal by the patient" (12 patients [3%]). Five (1.2%) patients were lost to follow-up, and 4 (1.0%) patients discontinued due to death (all in the AFL 2 mg every eight weeks group). In VISTA, the primary reason for both premature study discontinuation and [redacted] discontinuation was "withdrawal by the patient" (14 patients [3.0%] and [redacted] patients, respectively). The reasons for and incidence of premature discontinuation from the study and from study medication were similar across the treatment groups (Table 6). From 24 weeks after randomization, 24% to 31% patients in the laser treatment group received rescue AFL treatment; 8% of patients in VIVID and 1% patient in VISTA received additional laser treatment (Table 14 and Table 15 in Appendix 4). More detailed information on patient disposition is presented in Table 12 in Appendix 4.

TABLE 6: PATIENT DISPOSITION

	VIVID		VISTA	
	Laser	AFL 2Q8	Laser	AFL 2Q8
Screened, n	604 (in total)		687 in total	
Randomized, n (%)	135	135	156	154
Completed 52 weeks, n (%)[a]	115 (85.2)	120 (88.9)	145 (92.9)	144 (93.5)
Discontinued treatment before week 52, n (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued study before week 52, n (%)[a]	20 (14.8)	15 (11.1)	11 (7.1)	10 (6.5)
Adverse event	8 (5.9)	4 (3.0)	3 (1.9)	2 (1.3)
Death	1[b]	4 (3.0)[c]	1 (0.6)	0
FAS[c]	132 (97.8)	135 (100.0)	154 (98.7)	151 (98.1)
PPS[c]	[redacted]	[redacted]	[redacted]	[redacted]
Safety	133 (98.5)	135 (100.0)	154 (98.7)	152 (98.7)

AFL = aflibercept; FAS = full analysis set; Max = maximum; Min = minimum; n = number of patients; N = total number of patients; PPS = per-protocol analysis; SD = standard deviation; 2Q8 = 2 mg every 8 weeks after 5 monthly injection.
[a] Percentages are based on all randomized patients.
[b] One patient in the laser treatment group discontinued the study due to an AE (acute myocardial infarction) and died approximately three months later.
[c] [redacted].
Source: VIVID Clinical Study Report T7, p. 85; VISTA Clinical Study Report T7, p. 88–89.

3.4 Exposure to Study Treatments

Detailed information on medication exposure and compliance is presented in Table 13, Table 14, Table 15, Table 16, and Table 17 in Appendix 4. During the first year of treatment, planned exposure to AFL 2 mg every eight weeks was nine injections, or laser therapy at baseline (day 1) and then as needed (but no more often than every 12 weeks). All patients received the correct treatment per randomization. The mean number of active injections during the first year of AFL 2 mg every eight weeks treatment for patients was 8.7 injections in VIVID and 8.4 injections in VISTA; the mean number of active laser treatments for the laser treatment group was 2.1 in VIVID and 2.7 (1.15) in VISTA, respectively. During the study, patients did not receive any treatment (approved or investigational) for their DME in the study eye other than the study treatment until they had completed week 148.

3.5 Critical Appraisal

3.5.1 Internal validity

The included studies were double-masked, multi-centre, randomized, active laser controlled trials. The randomization process, including allocation concealment and masking method, was well described and performed. Overall, the important baseline characteristics were similar between the two treatment groups, although the mean CRT was numerically higher in the laser treatment group than in the AFL group in VIVID. Approximately 10% to 11% patients in VIVID and 41% to 45% patients in VISTA had been previously treated with anti-VEGF drugs (with a three-month washout period), demonstrating efficacy in eyes that were not totally naive to anti-VEGF therapy. Less than 15% of patients dropped out of the PPS analysis.

Multiplicity of testing for secondary outcomes was performed to control for type 1 error in both trials. In the VIVID study, which was conducted in Japan, Europe, and Australia, the primary analysis was also adjusted by study region. In VISTA, conducted in the US, the primary analysis was also adjusted by history of MI or CVA as a fixed effect, and baseline BCVA measurement as the covariate was used for

the primary analysis. The robustness of the primary analysis results was confirmed by various sensitivity analyses, including observed case (OC) analysis, last observation carried forward, including measurements after additional treatment was given (aLOCF), and observed values obtained after the initiation of additional treatment (aOC).

While the studies were considered well designed overall, the methodological quality could potentially be limited because randomization was not stratified by region, and the main analyses were adjusted by region only in VIVID, but not in VISTA. However, because VISTA was conducted in the US only, where the management of DME is highly consistent across the country, significant treatment response variation between investigation sites is unlikely. The randomization was not stratified based on the baseline VA, although subgroup analysis showed the results are consistent with the main primary analysis. One more potential concern involves the study conduct and the claimed magnitude differences between the AFL and laser treatment groups in the BCVA change from baseline. Based on current guidelines on laser treatment for DME, laser re-treatment could be given at 12, 24, and 36 weeks if clinically significant DME was still present, in accordance with standard clinical practice at the time.[38,39] At week 52, 39% patients in VIVID and 20% patients in VISTA randomized to the laser treatment group received only one laser treatment. Whether the patients in the laser group were undertreated is uncertain, which was also pointed out in Health Canada's review report.[40] However, similar numbers of laser treatments are seen in previously published RAN trials in DME (mean: 2.1 laser treatments)[41-43] and in VIVID/VISTA overall (mean of 2.1 and 2.7 laser treatments).[6,7] The assessment of any improvements in QoL (NEI VFQ-25) as an effect of the treatments in study eyes may have been compromised by the treatments that the untreated eyes received at study entry or during the course of the study. The dropout rate at week 52 was greater than 10% in VIVID (14.8% in the laser treatment group and 11.1% in the AFL group, respectively), which might have an impact on the validity of the findings. However, the findings from sensitivity analysis based on the OC were consistent with that of full analysis (LOCF, FAS). No true intention to treat analysis was performed; however, less than 2% of patients were not included in the full analysis. The significant impact of non–intention-to-treat analysis on the comparative efficacy comparing AFL with laser treatment is unlikely expected.

3.5.2 External validity

Patients were excluded if they had uncontrolled diabetes (A1C > 12% in VIVID; no cut-off was specified in VISTA) or active proliferative DR. Therefore, whether the superiority effect of AFL 2 mg every eight weeks to laser treatment demonstrated in the included studies can be generalized to uncontrolled diabetes or active proliferative DR patients is uncertain. No Canadian patients participated in the studies. However, VISTA was conducted in the US, where clinical management in patients with DME is very similar to that in Canada.

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. In this report, we focus primarily on the comparative efficacy and safety profile of AFL compared with laser treatment at week 52. The results observed at week 100 are briefly summarized in Appendix 6.

3.6.1 Change from baseline to week 52 in ETDRS letter score

Baseline BCVA was similar between treatment groups in the FAS. A BCVA improvement of 10 to 11 letters was observed in AFL groups in both studies, while a BCVA improvement of less than one letter was observed in the laser treatment group (Figure 3 and Table 4). The least squares mean (LSM) treatment group difference in BCVA improvement from baseline (AFL minus laser treatment groups,

mean [97.5% CI]) was 9.1 (6.3 to 11.8) in VIVID and 10.4 (7.7 to 13.2) in VISTA. Statistically significant difference between the two treatment groups was observed in both studies (Table 7). In VIVID, the results for the change in mean BCVA in ETDRS letter score for the PPS population were similar to those for the FAS (Table 19, Appendix 4). The results of the sensitivity analyses for the FAS population were consistent with the LOCF analysis used in the primary analysis. In both the aLOCF and aOC analyses, after additional treatment was given, results were still significantly in favour of the AFL groups despite the expected improved outcomes in the laser treatment group (Table 20, Appendix 4). In terms of subgroup analysis based on baseline BCVA ETDRS letters and A1C level, in general, results of the evaluable subgroups on the change in BCVA in ETDRS letter score from baseline to week 52 were qualitatively consistent with those in the overall population and for most subgroups, the 95% CI of the difference from the laser treatment group did not cross 0, despite the usual underpowered nature of subgroup analysis, except in the ETDRS letter score < 40 group (Figure 5 and Figure 6).

3.6.2 Proportion of patients who gained 15 ETDRS letters or more from baseline to week 52 (LOCF) (FAS)

In VIVID, at week 52, the proportion of patients who made a gain in vision of 15 letters or more in the AFL (2 mg every eight weeks) group showed superior improvement compared with the laser treatment group (45 [33.3%] versus 12 [9.1%], respectively; adjusted difference = 24.2; 97.5% CI, 13.5 to 34.9; *P* < 0.0001). In VISTA, in the AFL 2 mg every eight weeks group, 47 (31.1%) patients gained 15 ETDRS letters or more at week 52 versus 12 (7.8%) patients for the laser treatment group (adjusted difference = 23.3%; 97.5% CI, 13.5 to 33.1; *P* < 0.0001) (Table 22).

In VIVID, results of the sensitivity analyses performed on the proportion of patients experiencing an increase in ETDRS letter score of at least 15 letters at week 52 for the aLOCF analysis in the FAS population are shown in Table 28 and this analysis demonstrated results similar to those in the FAS, LOCF analysis. Table 23 [redacted] (Table 23).

In both studies, the results by subgroup (for A1C and BCVA ETDRS letters) using the LOCF, OC, aLOCF, and aOC methods as well as the proportion of patients who gained 15 ETDRS letters or more from baseline to week 52 were qualitatively consistent with those in the overall population.

The proportion of patients who experienced greater than 15 ETDRS letters lost is presented in Table 31, Appendix 4. The results were all shown to be in favour of AFL compared with laser treatment.

3.6.3 Legal blindness

No data were reported for legal blindness in either of the two included studies.

3.6.4 Proportion of patients with two-step or greater improvement from baseline to week 52 in the ETDRS DRSS (LOCF) (FAS)

In VIVID, the proportion of patients experiencing an improvement of at least two steps on the ETDRS DRSS at week 52 from baseline in the FAS population is shown in Table 28 and and Table 29.

At week 52, the AFL 2 mg every eight weeks groups showed superior improvement in the proportion of patients who achieved a two-step or greater improvement from baseline on the ETDRS DRSS compared

with the laser treatment group (23 [27.7%] versus 6 [7.5%], adjusted difference = 19.3; 97.5% CI, 6.6 to 32.1; *P* = 0.0006) (Table 28).

[redacted]

In VISTA, at week 52, the AFL 2 mg every eight weeks groups both showed a statistically significant improvement in the proportion of patients who achieved a two-step or greater improvement on the DRSS compared with the laser group (Table 28). In the AFL 2 mg every eight weeks group, 44 (29.1%) patients achieved a two-step or greater improvement on the DRSS at week 52 versus 22 (14.3%) patients for the laser treatment group (adjusted difference = 14.9%; 97.5% CI, 4.4 to 25.4; *P* = 0.0017). [redacted] (Table 28).

[redacted] (Table 29).

The proportion of patients who experienced DRSS improvement of greater than three steps or DRSS worsening of greater than two or three steps is provided in Table 30, Appendix 4. The results were all in favour of AFL compared with laser treatment.

3.6.5 Quality of life and vision-related function

NEI VFQ-25 total, near activities, and distance activities scores were assessed in both studies. [redacted] Table 32. A similar trend was observed in near activities or distance activities. No statistically significant difference was observed between the AFL and laser treatment groups in terms of the improvement from baseline in near or distance activities (Table 33 and Table 34).

The change from baseline in mean EQ-5D total score for the FAS population was reported in VIVID, but not in VISTA. In VISTA, data from the EQ-5D questionnaire were collected but were not analyzed. There were minimal changes from baseline to week 52 in each of the treatment groups (Table 37).

3.6.6 Central retinal thickness

Baseline CRT was similar between treatment groups in both studies, although the central retina was thicker in VIVID than in VISTA in the FAS (518 µm to 540 µm in VIVID and 479 µm to 483 µm in VISTA, respectively). At week 52, in VIVID, CRT decreased from baseline by –66 µm and –192 µm in the laser treatment group and AFL groups, respectively. The between-group difference in the change from baseline (LSM, 97% CI) was –142.8 µm (–179.3 µm to –106.3 µm), *P* < 0.001, in favour of the treatment group (Table 35 and Figure 7). In VISTA, CRT decreased from baseline by –73 µm and –183 µm in the laser treatment group and AFL groups, respectively. The between-group difference in the change from

baseline (LSM, 97% CI) was –113.47 µm (–144.19 µm to –82.75 µm), *P* < 0.001, in favour of the treatment group (Table 35 and Figure 8). In VIVID, the results of the sensitivity analyses (aLOCF) for the FAS population demonstrated results similar to those in the FAS, LOCF (Table 36).

TABLE 7: KEY EFFICACY OUTCOMES

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Change from baseline to week 52 in ETDRS letter score in the study eye (FAS, LOCF)				
Baseline, mean (SD)	60.8 (10.61)	58.8 (11.23)	59.7 (10.9)	59.4 (10.9)
At 52 weeks, mean (SD)	62.0 (14.3)	69.5 (11.9)	60.0 (16.5)	70.1 (12.6)
LSM change (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LSM change difference, (97.5% CI for the difference) (AFL – laser)	9.1 (6.3 to 11.8)		10.4 (7.7 to 13.2)	
P value	< 0.0001		< 0.0001	
Patients who gained ≥ 15 letters in the ETDRS letter score in the study eye at week 52 (FAS, LOCF)[b]				
n / N (%)	12 /132(9.1)	45/135 (33.3)	12/154(7.8)	47/151 (31.1)
Adjusted difference in proportion, % (97.5% CI) (AFL – laser)	24.2 (13.5 to 34.9)		23.3 (13.5 to 33.1)	
NNT	[redacted]		[redacted]	
P value	< 0.0001		< 0.0001	
RR (CI) (AFL vs. laser)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Proportion of patients with a ≥ 2-step improvement from baseline to week 52 in the ETDRS DRSS (LOCF) (FAS)				
n /N (%)	6/80 (7.5)	23/83 (27.7)	22/154 (14.3)	44/151(29.1)
Difference in proportion, % (97.5% CI) (AFL – laser)	19.3 (6.6 to 32.1)		14.9 (4.4 to 25.4)	
P value	0.0006		0.0017	
NNT	[redacted]		[redacted]	
RR (CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Change from baseline to week 52 in NEI VFQ-25 (total score) (FAS, LOCF)				
Baseline				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
At 52 weeks				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 52, mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LSM between-group difference in changes from baseline, % (97.55% CI) (AFL – laser)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Change from baseline to week 52 in CRT (FAS, LOCF)				
Baseline				
Mean (SD), µm	540.3 (152.4)	518.4 (147.4)	483.4 (152.9)	479.0 (153.9)
At 52 weeks				

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Mean (SD), µm	474.2 (177.6)	326.0 (109.3)	410.1 (155.7)	295.9 (84.3)
Change from baseline at week 52				
Mean (SD),	–66.2 (139.0)	–192.4 (149.9)	–73.3 (176.7)	–183.1 (153.5)
LSM between-group difference in changes from baseline, µm (97.55% CI) (AFL – laser)	–142.8 (–179.3 to –106.3)		–113.5 (–144.19 to –82.75)	
P value	< 0.0001		< 0.0001	

AFL = aflibercept; BCVA = best-corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; CVA = cardiovascular accident; DRSS = Diabetic Retinopathy Severity Score; ETDRS = Early Treatment Diabetic Retinopathy Study; FAS = full analysis set; LOCF = last observation carried forward; LSM = least squares mean; MI = myocardial infarction; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; NNT = number needed to treat; RR = relative risk; SD = standard deviation; SE = standard error; vs. = versus.
Note: In VIVID, an ANCOVA model was used with baseline BCVA measurement as a covariate, and treatment group and geographic region (Europe, Japan) as fixed factors for the primary analysis. In VISTA, an ANCOVA model with treatment as the main effect, history of MI or CVA as a fixed effect, and baseline BCVA measurement as the covariate was used for the primary analysis.

3.7 Harms

Only those harms identified in the review protocol are reported in section 2.2.1, Protocol. See Appendix 4: Detailed Outcome Data for detailed harms data. All AEs occurring during this study were classified as either ocular or non-ocular AEs. Harms data from the included studies are reported as treatment-emergent adverse events (TEAEs). In addition, serious AEs, mortality, withdrawals due to adverse events (WDAEs), injection-related TEAEs, laser procedure-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, 60% to 62% of patients in VIVID and 57% to 67% in VISTA reported TEAEs (that occurred in 2% or more of patients, in the study eye) during the first year of the study (Table 8). The incidences of ocular TEAEs and treatment emergent surgeries were reported numerically higher in the laser treatment group than in the AFL groups in both studies (Table 8, Table 38, and Table 39). The overall non-ocular TEAEs (Table 40) were similar between the treatment groups. More non-ocular TEAEs were reported in AFL-treated patients than in the laser treatment group in VIVID (laser versus AFL: 61% versus 73%), but more non-ocular TEAEs were reported in the laser treatment group in VISTA (86% versus 78%). Injection-related ocular TEAEs in AFL groups were reported to be 37% in VIVID and 41% in VISTA (Table 41). The incidence of laser-related ocular TEAEs in the laser treatment group were 9% in VIVID and 3% in VISTA. The most commonly reported ocular AEs were conjunctival hemorrhage, retinal hemorrhage, vitreous floaters, eye pain, macular fibrosis, reduced VA, and vitreous hemorrhage and retinal aneurysm (Table 38).

3.7.2 Serious adverse events

a) Ocular serious adverse events in the study eye

Overall, the incidence of ocular treatment-emergent SAEs was very low. There were numerically more SAEs in the laser treatment group than in the AFL group. The incidence of treatment emergent SAEs was numerically higher in the laser treatment group (3.9% to 4.3%) than in the AFL groups (1.3% to 2.2%) in VIVID and VISTA (Table 8). The reported ocular SAEs in the study eye included mainly vitreous hemorrhage, DR, and retinal revascularization (Table 43).

b) Non-ocular serious adverse events

The overall incidence of non-ocular SAEs was similar in both treatment groups (13.5% versus 18.5% in the laser treatment group and the AFL group, respectively, in VIVID; and 35.5% versus 25.7% in the laser treatment group and the AFL group, respectively, in VISTA) (Table 44).

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

Only one patient (0.7%) experienced the sole ocular injection–related SAE; that is, retinal detachment in the study eye in the AFL group in either VIVID or VISTA. None of them were reported in the laser treatment group (Table 45).

d) Laser procedure-telated SAE

In VIVID, laser procedure–related SAEs were reported in 9% of patients in the laser treatment group and 7% of those in the AFL group. The laser procedure–related SAEs mainly included conjunctivitis (1.5%) and maculopathy (1.5%) (Table 46).

3.7.3 Withdrawal due to adverse events

In VIVID, four patients (3.0%) in the laser treatment group and none in the AFL group withdrew from the study due to an ocular TEAE in the study eye. Withdrawals from the study due to non-ocular TEAEs were 2.3% and 0.7% in the laser treatment and AFL groups, respectively. In VISTA, no patient withdrew from the study due to an ocular TEAE in the study eye. Only one patient (0.7%) withdrew from the study due to a non-ocular TEAE in either of the groups (Table 47).

3.7.4 Mortality

In VIVID, one death (0.7%) in the laser group and four deaths (3.0%) in the AFL group were reported during the first year. A single death was considered to be possibly related to the study drug. In VISTA, one death was reported (0.6%) in the laser treatment group and none in the AFL groups (Table 8). The death was considered to be related to the laser procedure.

3.7.5 Notable harms

After consultation 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 VIVID, endophthalmitis occurred in one patient (0.6%) in the laser treatment group in both VIVID and VISTA,[6,7] but none in the AFL (2 mg every eight weeks) group. In VIVID, retinal detachment was reported in one patient (0.8%) in the laser treatment group and two patients (1.5%) in the AFL (2 mg every eight weeks) group. None were reported in either group in VISTA (Table 38). Potential ATEs were evaluated according to criteria formerly applied and published by the Antiplatelet Trialists' Collaboration (APTC) criteria.[20,24] According to these criteria, an APTC event is defined as a non-fatal MI, non-fatal ischemic stroke, non-fatal hemorrhagic stroke, or death owing to vascular or unknown causes. In VIVID, numerically more ATEs occurred in the AFL than in the laser treatment group (1.5% versus 3%, respectively), but in VISTA, ATEs were similar in both groups (Table 48).

TABLE 8: HARMS

	VIVID		VISTA	
	Laser (N = 133)	AFL2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
AE, n (%)				
Patients with ≥ 1 TEAEs, occurring in ≥ 2% of patients (study eye)	82 (61.7)	80 (59.3)	103 (66.9)	87 (57.2)
Patients with ≥ 1 ocular treatment emergent surgeries (study eye)	9 (6.8)	7 (5.2)	16 (10.4)	7 (4.6)
Patients with ≥ 1 non-ocular AE, occurring in ≥ 5% of patients	81 (60.9)	98 (72.6)	132 (85.7)	119 (78.3)
SAE, n (%)				
Patients with ≥ 1 serious ocular TEAE (study eye)	6 (4.5)	3 (2.2)	6 (3.9)	2 (1.3)
Patients with ≥ 1 serious non-ocular TEAE (≥ 1%)	18 (13.5)	25 (18.5)	47 (30.5)	39 (25.7)
Most common ocular SAEs[a]				
Vitreous hemorrhage	1 (0.8)	0	3 (1.9)	1
Diabetic retinopathy	1 (0.8)	0	2	0
Cataract	0	2 (1.5)	1 (0.6)	0
Retinal neovascularization	3 (2.3)	0	NR	NR
WDAE				
WDAEs, n (%) (discontinuation from study)	8 (5.9)	4 (3.0)	3 (1.9)	2 (1.3)
Deaths				
Number of deaths, n (%)	1	4 (3.0)	1 (0.6)	0
Notable Harms				
Endophthalmitis	1[a]	0	1[b]	0
Retinal detachment	1 (0.8)	2 (1.5)	NR	NR
ATE	2 (1.5)	4 (3.0)	6 (3.9)	6 (3.9)

AE = adverse event; AFL = aflibercept; ATE = arterial thrombotic event; NR = not reported; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

[a] Occurred in both eyes in one patient.

[b] Occurred in untreated eye.

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was derived from two similarly designed double-blind, randomized, active-controlled superiority trials, VIVID and VISTA, that compared AFL (2 mg per eight weeks after five initial monthly injections) with laser photocoagulation therapy in patients with DME. The aim of these studies was to determine whether AFL was superior to laser treatment in improving BCVA in patients with DME. The primary outcome was the change from baseline in BCVA (ETDRS letters) at week 52. Secondary outcomes included the proportion of patients with an improvement of 15 ETDRS letters or more, the proportion of patients with a two-step improvement in the ETDRS DRSS score, QoL assessed using the NEI VFQ-25, and change in CRT.

Baseline characteristics were similar across studies for all treatment groups. Dropout rates were similar between groups within each study and were consistently less than 15%. There were no serious violations of internal validity. Although there was no placebo group in either study, the magnitude of changes in BCVA in the laser treatment group were consistent with previous studies.[41-43]

4.2 Interpretation of Results

4.2.1 Efficacy

Compared with the laser treatment group, AFL treatment was associated with a statistically significant improvement in BCVA, as reflected by a gain of nine more ETDRS letters in AFL-treated than in laser-treated patients in both studies. The magnitude of the difference in the improvement in ETDRS letters between AFL and laser treatment is slightly smaller than the threshold for clinically meaningful improvement of 10 to 15 letters (see Appendix 5). However, a 9.1 to 10.5 ETDRS letter improvement reflects an improvement of about two lines on the ETDRS chart; according to the clinical expert consulted for this review, this degree of improvement can be considered clinically relevant, especially for patients with poor VA.

If VA deteriorated to a degree that met predefined criteria, patients were eligible for additional (rescue) therapy with the alternative study treatment starting at week 24. Of the patients who received AFL treatment, 8% in VIVID and 0.7% in VISTA also received (rescue) laser treatment. By contrast, of the patients who received laser treatment, 24% in VIVID and 31% in VISTA also received AFL treatment. The larger proportion of patients who received rescue treatment with AFL would potentially bias the results against AFL by reducing the magnitude of the difference between the treatments. In order to assess the effect of the additional treatment on the comparative effective of AFL and laser treatment, various sensitivity analyses were conducted (aLOCF, OC, aOC). The results of BCVA change from baseline from these sensitivity analyses were consistent with the primary analysis. Furthermore, in terms of BCVA, similar findings were observed across different subgroup analyses based on baseline severity of VA reduction (ETDRS letters) and baseline A1C level. The improvement in the laser treatment group is consistent with the findings reported previously,[41,42] although it was not reported whether this improvement from baseline in both the laser treatment and AFL groups was statistically significant.

In addition to recommending a mean change of 15 letters or more on an ETDRS chart, the FDA recommends a statistically significant difference be demonstrated in the proportion of patients with 15-letter or greater change in VA, as a clinically relevant outcome measure in trials of interventions for macular edema.[31] In both VIVID and VISTA, this criterion was met; specifically, a statistically significantly greater proportion of patients treated with AFL achieved an improvement of at least 15 letters

compared with the proportion treated with laser photocoagulation (24% and 23% more in VIVID and VISTA, respectively).

In both VIVID and VISTA, a statistically significantly greater proportion of patients achieved an improvement of at least two steps on the DRSS score at week 52. A previous study demonstrated that patients who experience a deterioration in VA equivalent to at least two steps of ETDRS DRSS over six years are significantly more likely to develop proliferative DR than patients with a smaller degree of deterioriation.[10] Based on this finding, and in the opinion of the CDR clinical expert consulted for this review, the relatively greater improvement in the DRSS score observed in AFL-treated patients in the included studies likely reflects a clinically meaningful improvement in VA over laser treatment.

QoL and vision-related function were assessed using the change in the NEI VFQ-25 (and EQ-5D score in VIVID). While AFL-treated patients achieved higher NEI VFQ-25 scores compared with the laser-treated patients in both studies, no statistically significant differences were reported. QoL measured with EQ-5D in VIVID did not show any meaningful changes in either treatment group. It is difficult to determine whether there is truly no difference in QoL between the treatments or whether no difference was detected as a result of a lack of power, given that the QoL metrics were secondary outcomes in the included studies. In addition, the assessment of any improvements in QoL as an effect of the treatments received by the study eyes is confounded by the treatments that the non-study eyes received at study entry or during the course of the study.

The reduction in CRT at 52 weeks was statistically significantly greater in AFL-treated patients compared with laser-treated patients in both studies. Specifically, AFL was associated with a 114 µm to 143 µm greater decrease in CRT than laser treatment. The clinical significance of these changes is unknown due to the lack of information regarding the MCID for this outcome. Nevertheless, the marked reduction in CRT might reflect a lack of progression of DME, which is characterized by retinal thickening, in the AFL-treated patients.

Randomization and blinding in the VIVID and VISTA trials were maintained after 52 weeks, and the primary and secondary end points from the first year of treatment were evaluated at week 100 as exploratory end points.[6,7] The data available through 100 weeks of treatment (Appendix 4) indicate that the relatively greater improvements in VA in AFL-treated patients observed in the first year of each study were maintained through the second year of treatment,[8,9] suggesting that the differential efficacy of AFL compared with laser treatment may be preserved over the longer term.

4.2.2 Harms

Based on the harms data reported for the VIVID and VISTA studies, the overall safety profile of AFL and laser treatment appears to be similar. The frequency at which AEs occurred was slightly higher in laser-treated patients, but there were no substantial imbalances among the treatments across the two studies in the frequency of ocular and non-ocular AEs, and no individual AE occurred in more than 3% of patients.

Ocular SAEs were rare and, although the incidence of ocular AEs was slightly higher in the laser-treated patients in both studies, there were no substantial imbalances between the two treatments with respect to the frequency and type of SAEs. No individual ocular SAE occurred in more than 2% of patients, except retinal revascularization (2.3% in the laser treatment group in VIVID). More non-ocular SAEs were observed in the AFL group than in the laser group in VIVID, but more non-ocular SAEs were reported in the laser treatment group than in the AFL group in VISTA. Non-ocular SAEs mainly included acute MI,

peripheral ischemia, and hyperglycemia, and no individual non-ocular SAE was reported in more than 2% of patients.

Although a higher number of laser-treated patients withdrew from both studies due to AEs, the overall discontinuation rate due to AEs was low (< 6%) across treatment groups in both studies. Among the harms of special interest, endophthalmitis and retinal detachment occurred in fewer than 2% of patients. Although the FDA has warned of a potential risk of ATEs following intravitreal use of VEGF inhibitors (including AFL),[44] the number of patients who experienced an ATE was not markedly higher in AFL-treated patients (10 versus 8 for AFL-treated patients versus laser-treated patients, respectively, across both studies).

The data available through week 100 of treatment (see Appendix 7) were similar to the observations made regarding the treatment harms during the first year of study. In the laser treatment group, the most frequently reported TEAEs were related to reduced VA and retinal hemorrhage, which likely reflects the progression of DME in patients receiving laser therapy. In the AFL-treated patients, the most frequently reported TEAEs included VA reduction and conjunctival hemorrhage. The higher incidence of conjunctival hemorrhage in the AFL-treated patients was consistent with results reported at 52 weeks and likely reflects the injection procedure used in the AFL groups.

4.3 Other Considerations

RAN has supplanted laser photocoagulation as the current standard of care for patients with DME,[29] and RAN is reimbursed for the treatment of DME by most public drugs plans in Canada. Therefore, a comparison of the relative efficacy and harms of RAN and AFL is relevant to this review. However, as there are no published studies in which AFL and RAN have been compared directly in the treatment of DME, the only evidence available to compare AFL with RAN is that generated through indirect comparison (Appendix 6).[b] Accordingly, the manufacturer conducted an indirect comparison of AFL and RAN using network meta-analysis.[12] The results of this analysis were complemented by the results of two additional indirect comparisons of these anti-VEGF drugs identified in a literature search conducted by CDR.[13,14] These three indirect comparisons were based on essentially the same underlying studies, and the overall results of the analyses are consistent with the conclusion that AFL is at least as effective as RAN for improving VA in DME patients, and that AFL and RAN are not notably different in terms of their potential harms. The apparent absence of any notable differences between AFL and RAN based on the aforementioned indirect comparisons should be viewed in the context of the limitations within each analysis, as well as differences among the analyses, as noted in Appendix 6.

Patient input received by CADTH for this review indicated that patients expect that AFL will present them with an alternative option to treatments available at present. Patients also expect that that AFL will require fewer injections than the current standard of treatment, RAN. If AFL and RAN were dosed according to the regimens recommended in their respective product monographs (Table 2), this expectation would be met, as AFL requires eight or nine injections per year versus 12 injections per year for RAN. However,

[b] Recently, a study assessing the comparative effectiveness of AFL, BEV, and RAN was completed.[11] The results of this study are presented and discussed in Appendix 8, and they suggest that, in patients with DME, one year of treatment with aflibercept (2 mg per injection every four weeks) is associated with a statistically significantly greater improvement in VA compared with ranibizumab (0.3 mg per injection every four weeks). The difference in the improvement in VA between treatments (13 letters versus 11 ETDRS letters for aflibercept versus ranibizumab) was not clinically meaningful and was driven by baseline VA, such that patients with worse baseline VA (fewer than 69 ETDRS letters) tended to do relatively better with aflibercept. Safety data from this study indicated that aflibercept and ranibizumab have similar potential harms.

whether there will be a difference in clinical practice is not clear, because, according to the clinical expert consulted for this review, the number of injections of anti-VEGF drugs in practice is frequently lower than that recommended by the product monograph.

5. CONCLUSIONS

The results of the two double-blind, multinational, randomized, active-controlled trials (VIVID and VISTA) suggest that AFL is superior to laser photocoagulation treatment for improving VA in patients with DME. A statistically significantly greater improvement of 9.1 to 10.5 more ETDRS letters over laser treatment was observed after 52 weeks of treatment in AFL-treated patients compared with laser-treated patients in both studies. As well, a statistically significantly greater proportion of AFL-treated patients in both studies achieved a gain of at least 15 ETDRS letters compared with laser-treated patients. There were no statistically significant differences between treatments with respect to QoL in either study. The incidences of TEAEs, SAEs, and WDAEs over 52 weeks were similar for both treatments in both studies, suggesting that the treatment harms associated with AFL and laser treatment are similar. Data available through week 100 suggest that the comparative efficacy and harms of AFL and laser therapy at 52 weeks persist through 100 weeks of treatment. The results of the manufacturer's indirect comparison and a recently published study suggest that patients treated with AFL have statistically significantly greater gains in BCVA than those treated with RAN, although the clinical significance of this is unclear. Two other indirect comparisons suggest that the efficacy and safety profile of these two anti-VEGF drugs are similar for the treatment of DME.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review staff based on the input provided by patient groups. It has not been systematically reviewed.

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

One patient group, the Canadian Council of the Blind (CCB), submitted the input for this review. 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. With more than 1,500 members, it is the largest membership-based organization for the blind in the country.

CCB reported receiving support from the following sources in 2011: VIA Rail, Cannondale, Community Foundation of Ottawa, Lions Club, Keith Communications Inc., Human Resources and Skills Development Canada (HRSDC), 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

The CCB indicated that the information provided for this section was obtained from online literature searches, conversations with patients, and the Eylea (aflibercept) product monograph.

Diabetic macular edema (DME) and retinal vein occlusion lead to loss of vision, which affects daily functioning and quality of life. Patients can become unable to drive and read standard print (including books, newspapers, food and medication labels, menus, and greeting cards), and they may injure themselves more frequently. As a result, they often need assistance from caregivers to drive them to appointments or to run errands, or to help them with household chores and meal preparation. Patients may lose their jobs due to their impaired vision, which, combined with the cost of therapy, places a financial burden on patients with DME. There are also social and emotional implications to vision loss; patients may experience depression, a sense of isolation and loss of independence, and uncertainty regarding pending loss of vision and associated implications of impaired vision. Family dynamics often change, as patients become more reliant on those around them. Patients reported that “friends seem to disappear” because they do not know how to cope with the situation.

The lives of caregivers are also significantly affected as a result of a loved one’s diagnosis of DME. They must provide emotional support to those who have lost their vision and are less independent, while learning to cope with their own emotions regarding this change. This may be difficult if caregivers lack knowledge or understanding about the condition. Caregivers may also face increased responsibility in caring for patients who have lost their sight by ensuring the safety of their environment, taking time off work to accompany patients to medical appointments, and helping with household chores and errands. There may be new financial burdens associated with caring for patients with DME, resulting from unpaid leave from work or child care costs for young family members incurred when caregivers must focus on caring for the patient.

Lack of available treatment options and coverage of treatments for DME were identified as major issues associated with current therapy. Current therapy options include laser therapy, oral therapies (Vitalux, acetylsalicylic acid, Lutein), and injection therapies (ranibizumab [RAN; Lucentis] and bevacizumab [BEV; Avastin]). However, RAN is the only Health Canada–approved medication for DME. Many patients use

RAN with good results, but it may require more injections than Eylea. Some patients are receiving BEV, which has not been tested or approved by Health Canada for this indication. As a consequence, its long-term effects, including potential adverse effects, remain unknown. Physicians would benefit from being able to offer multiple Health Canada–approved options for the treatment of DME should one therapy be unavailable, cause adverse reactions, or fail to meet the needs of their patients. In addition, access to currently approved therapy is restricted for some patients due to either the cost of travel to regional clinics or the cost of the treatment itself when not completely covered by provincial drug plans. Patients expressed the desire to receive the best approved care for DME wherever they live, and they stated that these costs should not prevent them from receiving this care.

3. Related Information About the Drug Being Reviewed

Patients expect that Eylea will be effective for the treatment of DME by decreasing bleeding, arresting vision loss, and potentially improving sight. There may be a reduction in the number of doses with time, which may also be associated with reduced adverse reactions or irritation. Aflibercept may be administered every eight weeks, which is less frequently than current treatment and could result in fewer physician visits and less time for caregivers to miss from work. Patients also reported that Eylea will fulfill an unmet need by providing a second approved treatment option for DME should patients have adverse reactions to current therapy. Patients indicated that they would be willing to experience mild, temporary adverse effects (including mild irritation, but not including infection) with Eylea if there was a prospect of preventing further vision loss or regaining sight. They expect infection to be minimized as a result of Eylea's individual dosing preparation. Patients reported that regaining sight, controlling bleeding, making 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 adverse effects.

The CCB submission did not indicate whether the patients they contacted 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
- fewer injections per year
- fewer clinic visits
- no need for interim monitoring
- a predictable injection schedule.

Patients are in favour of Eylea being recommended for listing on all participating drug plans.

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:	November 24, 2014
Alerts:	Bi-weekly search updates until April 8, 2015
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAXGUIDE	
/	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
.po	Population group [PsycInfo only]
.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		
1	(Eylea* or aflibercept* or "AVE 0005" or AVE0005 or Bay 86-5321 or Bay86-5321 or VEGF Trap* or Zaltrap or Zivaflibercept or vasculotropin trap or vascular endothelial growth factor trap).ti,ab,rn,nm,sh,hw,ot.	2545
2	862111-32-8.rn,nm.	1540
3	or/1-2	2545
4	diabet*.ti,ab,hw.	1231325
5	DME.ti,ab.	3599

MULTI-DATABASE STRATEGY		
6	exp diabetes mellitus/	955309
7	or/4-6	1238574
8	and/3,7	340
9	8 use pmez	68
10	*aflibercept/	371
11	(Eylea* or aflibercept* or "AVE 0005" or AVE0005 or Bay 86-5321 or Bay86-5321 or VEGF Trap* or Zaltrap or Zivaflibercept or vasculotropin trap or vascular endothelial growth factor trap).ti,ab.	1251
12	or/10-11	1297
13	diabet*.ti,ab.	1032540
14	DME.ti,ab.	3599
15	exp diabetes mellitus/	955309
16	diabetic macular edema/	2098
17	or/13-16	1228483
18	and/12,17	148
19	18 use oemezd	91
20	conference abstract.pt.	1659862
21	19 not 20	79
22	or/9,21	147
23	remove duplicates from 22	100

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:	November 11–19, 2014
Keywords:	Eylea, Diabetic macular edema
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:

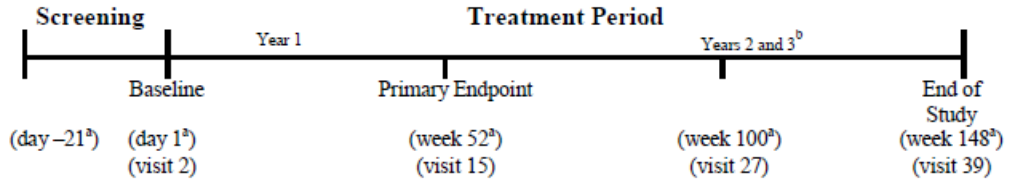
- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for exclusion

APPENDIX 4: DETAILED OUTCOME DATA

FIGURE 2: STUDY FLOW DIAGRAM



[a] Timeline is not linear (day versus week).
[b] During year 3, patients randomized to the laser treatment group will receive aflibercept by intravitreal (IVT) injection as needed, if aflibercept re-treatment criteria are met (study protocol, section 5.4 [Appendix 1.1]). Patients randomized to the aflibercept treatment groups will maintain their randomized treatment to the end of study (week 148).
Source: VISTA Clinical Study Report.[7]

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

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)		AFL 2Q8 (N = 135)
Sex; n (%)				
Male	78 (59.1)	88 (65.2)	85 (55.2)	78 (51.7)
Female	54 (40.9)	47 (34.8)	69 (44.8)	73 (48.3)
Age (years)				
Mean (SD)	63.9 (8.6)	64.2 (7.8)	61.7 (8.65)	63.1 (9.39)
Median	64.5	65.0	62.0	64.0
Min to Max	36 to 83	43 to 84	37 to 81	33 to 86
Age by category (year), n (%)				
< 55	15 (11.4)	13 (9.6)	26 (16.9)	26 (17.2)
≥ 55 to < 65	51 (38.6)	53 (39.3)	71 (46.1)	52 (34.4)
≥ 65 to < 75	53 (40.2)	55 (40.7)	45 (29.2)	60 (39.7)
≥ 75	13 (9.8)	14 (10.4)	12 (7.8)	13 (8.6)
Race; n (%)				
White	106 (80.3)	106 (78.5)	131 (85.1)	125 (82.8)
Black	1 (0.8)	1 (0.7)	16 (10.4)	19 (12.6)
Asian	25 (18.9)	27 (20.0)	3 (1.9)	2 (1.3)
Multiple[a]	0	1 (0.7)	NR	NR
Native Hawaiian or other Pacific Islander	NR	NR	2 (1.3)	2 (1.3)
Not reported	3 (2.3)	0	2 (1.3)	3 (2.0)
Ethnicity; n (%)				
Not Hispanic or Latino	128 (97.0)	130 (96.3)	133 (86.4)	125 (82.8)
Hispanic/Latino	1 (0.8)	5 (3.7)	21 (13.6)	26 (17.2)
Baseline weight (kg)				
n	132	134	154	150
Mean (SD)	80.6 (16.86)	80.5 (16.52)	91.1 (23.77)	90.8 (21.03)
Median	79.3	79.0	87.8	86.4
Min to Max	44.0 to 120.0	51.0 to 138.0	42 to 177	47 to 150
Baseline height (cm)				
n	132	133	154	150
Mean (SD)	167.3 (9.66)	167.3 (9.55)	168.6 (10.47)	168.4 (10.84)
Median	166.0	167.0	169.6	169.6

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)		AFL 2Q8 (N = 135)
Min to Max	144.0 to 190.0	150.0 to 191.0	142 to 191	142 to 198
Baseline BMI (kg/m^2), n (%)	132	133	154	150
≤ 30 kg/m²	82 (62.1)	91 (67.4)	69 (44.8)	71 (47.0)
> 30 to ≤ 35 kg/m²	37 (28.0)	27 (20.0)	41 (26.6)	34 (22.5)
> 35 kg/m²	13 (9.8)	15 (11.1)	44 (28.6)	45 (29.8)
Mean (SD)	28.7 (5.24)	28.8 (5.11)	31.9 (7.32)	32.0 (7.07)
Median	27.8	27.5	30.9	30.4
Min to Max	18.8 to 50.6	21.2 to 48.5	19 to 59	20 to 66
Geographic region; n (%)				
Non-Japanese	107 (81.1)	110 (81.5)	NR	NR
Japanese	25 (18.9)	25 (18.5)	NR	NR
Smoking history; n (%)				
Never	73 (55.3)	77 (57.0)	80 (51.9)	91 (60.3)
Former	50 (37.9)	49 (36.3)	56 (36.4)	52 (34.4)
Current	9 (6.8)	9 (6.7)	18 (11.7)	8 (5.3)
A1C, %				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
A1C (%) by category				
≤ 8%	[redacted]	[redacted]	[redacted]	[redacted]
> 8%	42 (31.8)	44 (32.6)	45 (29.2)	57 (37.7)
Unknown	1 (0.8)	0	1	0
Duration of diabetes (years)				
n	105	99	153	151
Mean (SD)	14.5 (9.8)	14.1 (8.9)	17.2 (9.55)	17.6 (11.46)
Median	14.0	14.0	17.0	17.0
Min to Max[b]	0 to 46	0 to 38	1 to 49	1 to 63
Prior intravitreal anti-VEGF treatment	13 (9.8)	15 (11.1)	63 (40.9)	68 (45.0)
Stratification factors				
Myocardial infarction	NR	NR	20 (13.0)	20 (13.2)
Cerebrovascular accident	NR	NR	11 (7.1)	10 (6.6)
Prior treatment for DME	NR	NR	101 (65.6)	108 (71.5)
Prior intravitreal steroids	NR	NR	31 (20.1)	42 (27.8)
Prior laser photocoagulation	NR	NR	77 (50.0)	80 (53.0)
No prior treatment for DME	NR	NR	53 (34.4)	43 (28.5)
Type of diabetes, n (%)				
Type 1 diabetes	NR	NR	14 (9.1)	10 (6.6)
Type 2 diabetes	NR	NR	140 (90.9)	141 (93.4)
Insulin-dependent	NR	NR	77 (50.0)	73 (48.3)
Non-insulin-dependent	NR	NR	60 (39.0)	65 (43.0)
Missing	NR	NR	3 (1.9)	3 (2.0)

2Q8 = 2 mg every eight weeks; A1C = glycated hemoglobin; AFL = aflibercept; BMI = body mass index; DME = diabetic macular edema; FAS = full analysis set; Max = maximum; Min = minimum; NR = not reported; SD = standard deviation; VEGF = vascular endothelial growth factor.
Source: VIVID Clinical Study Report T13, p. 93–94; VISTA Clinical Study Report T12, p. 75–77.

TABLE 10: BASELINE DISEASE CHARACTERISTICS IN THE STUDY EYE (FULL ANALYSIS SET)

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
BCVA				
Mean (SD)	60.8 (10.6)	58.8 (11.2)	59.7 (10.95)	59.4 (10.89)
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
Baseline BCVA (letters); n (%)				
< 40	[redacted]	[redacted]	[redacted]	[redacted]
≥ 40 to < 55	[redacted]	[redacted]	[redacted]	[redacted]
≥ 55 to < 65	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65	[redacted]	[redacted]	[redacted]	[redacted]
ETDRS DRSS at baseline[a]; n (%)				
10	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]
35	[redacted]	[redacted]	[redacted]	[redacted]
43	[redacted]	[redacted]	[redacted]	[redacted]
47	[redacted]	[redacted]	[redacted]	[redacted]
53	[redacted]	[redacted]	[redacted]	[redacted]
61	[redacted]	[redacted]	[redacted]	[redacted]
65	[redacted]	[redacted]	[redacted]	[redacted]
71	[redacted]	[redacted]	[redacted]	[redacted]
75	[redacted]	[redacted]	[redacted]	[redacted]
Cannot grade	[redacted]	[redacted]	[redacted]	[redacted]
Baseline CRT (µm)				
Mean (SD)	540.3 (152.4)	518.4 (147.4)	483.4 (152.88)	479.0 (153.95)
Median	525.0	505.0	458.5	457.0
Min to Max	284 to 1,183	283 to 1,074	238 to 955	231 to 1,179
Baseline IOP (mm Hg)			154	151
Mean (SD)	15.9 (2.42)	15.8 (2.71)	14.7 (3.25)	15.4 (3.52)
Median	16.0	16.0	14.0	15.0
Min to Max	10.0 to 22.0	10.0 to 23.0	8 to 22	6 to 24

2Q8 = 2 mg every eight weeks; AFL = aflibercept; BCVA = best-corrected visual acuity; CRT = central retinal thickness; DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; Max = maximum; Min = minimum; SD = standard deviation.

[a] Level 10 — None; levels 14, 15, 20, 35, 43 — Mild to moderate non-proliferative diabetic retinopathy; levels 47 and 53 — Moderately severe/severe non-proliferative diabetic retinopathy; levels 61, 65, 71, 75, 81, and 85 — Mild/moderate/high-risk/advanced proliferative diabetic retinopathy; "Cannot grade" cases appear as level 90 in the database.

Source: VIVID Clinical Study Report T14, p. 95; VISTA Clinical Study Report T13, p. 78–79.

TABLE 11: BASELINE NEI VFQ-25 AND EQ-5D SCORES (FULL ANALYSIS SET)

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Baseline total NEI VFQ-25 score				
n	131	135	NR	NR
Mean (SD)	77.5 (15.16)	71.2 (17.84)	NR	NR
Median	81.2	74.3	NR	NR
Min to Max	25.3 to 98.0	20.9 to 98.7	NR	NR
Baseline NEI VFQ-25 distance activities subscale score				
n	131	135	154	151
Mean (SD)	77.0 (20.86)	67.8 (22.89)	63.7 (23.32)	66.8 (22.47)
Median	83.3	66.7	66.7	66.7
Min to Max	0.0 to 100.0	8.3 to 100.0	8 to 100	17 to 100
Baseline NEI VFQ-25 near activities subscale score				
n	131	135	154	150
Mean (SD)	67.4 (22.24)	60.8 (23.50)	56.6 (23.06)	58.1 (22.94)
Median	66.7	58.3	58.3	58.3
Min to Max	8.3 to 100.0	8.3 to 100.0	0 to 100	0 to 100
Baseline NEI VFQ-25 vision dependency subscale				
n	NR	NR	153	151
Mean (SD)	NR	NR	70.8 (29.03)	74.2 (27.78)
Median	NR	NR	83.3	83.3
Min to Max	NR	NR	0 to 100	0 to 100
Baseline EQ-5D score				
n	131	135	NR	NR
Mean (SD)	0.83 (0.209)	0.82 (0.200)	NR	NR
Median	0.848	0.848	NR	NR
Min to Max	–0.02 to 1.00	–0.02 to 1.00	NR	NR

2Q8 = 2 mg every eight weeks; AFL = aflibercept; EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; Max = maximum; Min = minimum; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; NR = not reported; SD = standard deviation.
Source: VIVID Clinical Study Report T15, p. 96; VISTA Clinical Study Report T13, p. 78–79.

TABLE 12: PATIENT DISPOSITION (ALL ENROLLED PATIENTS) (DETAILED)

	VIVID		VISTA	
	Laser	AFL 2Q8	Laser	AFL 2Q8
Patients screened; n	604 in total		687 in total	
Patients randomized; n (%)	135 (100.0)	135 (100.0)	156 (100.0)	154 (100.0)
Patients treated; n (%)	133 (98.5)	135 (100.0)	154 (98.7)	152 (98.7)
Randomized but not treated	2 (1.5)	0 (0)	2 (1.3)	2 (1.3)
Completed 52 weeks; n (%)	115 (85.2)	120 (88.9)	145 (92.9)	144 (93.5)
Discontinued study before week 52, n (%)	20 (14.8)	15 (11.1)	11 (7.1)	10 (6.5)
Primary reason for premature discontinuation from the study during 52-week period, n (%)				
Adverse event	8 (5.9)	4 (3.0) b	3 (1.9)	2 (1.3)
Death	1 (0.7)	4 (3.0) (	1 (0.6)	0 (0)
Lack of efficacy (as assessed by the investigator)	1 (0.7)	0	NR	NR
Withdrawal of consent by patient	7 (5.2)	2 (1.5)	4 (2.6)	5 (3.2)
Protocol deviation	2 (1.5)	1 (0.7)	NR	NR

	VIVID		VISTA	
	Laser	AFL 2Q8	Laser	AFL 2Q8
Lost to follow-up	0	4 (3.0)	1 (0.6)	2 (1.3)
Physician decision	2 (1.5)	0	NR	NR
Prematurely discontinued study drug during 52-week period, n (%)				
Yes	7 (5.3)	1 (0.7)	14 (9.0)	14 (9.1)
Primary reason for discontinuation of study drug during 52-week period, n (%)				
Adverse event	NR	NR	4 (2.6)	3 (1.9)
Death	NR	NR	1 (0.6)	0
Withdrawal by patient	NR	NR	6 (3.8)	6 (3.9)
Lost to follow-up	NR	NR	1 (0.6)	4 (2.6)
FAS	132 (97.8)	135 (100.0)	154 (98.7)	151 (98.1)
PPS	[redacted]	[redacted]	[redacted]	[redacted]
Safety set	133 (98.5)	135 (100.0)	154 (98.7)	152 (98.7)

2Q8 = 2 mg every eight weeks; AFL = aflibercept; FAS = full analysis set; Max = maximum; Min = minimum; NR = not reported; PPS = per-protocol set; SD = standard deviation.
Note: Percentages are based on all randomized patients.
Source: VIVID Clinical Study Report T7, p. 85; VISTA Clinical Study Report T7, p. 68, 88–89.

TABLE 13: TREATMENT EXPOSURE (EXCLUDING ADDITIONAL TREATMENT) IN THE STUDY EYE IN THE FIRST 52 WEEKS (SAFETY ANALYSIS SET)

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
Total number of active laser treatments	273	0	418	0
Total number of sham laser treatments	2	256	0	342
Number of active laser treatments, n (%)				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
Summary of active laser treatments				
n	132	–	154	0
Mean (SD)	2.1 (1.1)	–	2.7 (1.15)	
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
Total number of active injections (AFL)	[redacted]	[redacted]	[redacted]	[redacted]
Total number of sham injections	[redacted]	[redacted]	[redacted]	[redacted]
Number of active injections, n (%)				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
8				
9				
10				
11				
12				
13				
Summary of active injections				
n	–	135	0	152
Mean (SD)	–	8.7 (1.2)		8.4 (1.35)
Median				
Min to Max				
Total amount, mg				
n				
Mean (SD)				
Median				
Min to Max				
Duration of treatment (weeks)				
n	133	135	154	152
Mean (SD)	47.86 (11.49)	50.70 (6.69)	50.8 (6.95)	50.2 (7.98)
Median	52.0	52.0	52.1	52.0
Min to Max	4.0 to 55.0	4.0 to 55.3	4 to 55	4 to 55

2Q8 = 2 mg every eight weeks; AFL = aflibercept; Max = maximum; Min = minimum; SD = standard deviation.
Note: Laser treatment includes laser therapy at baseline and when re-treatment criteria are met. Laser given in AFL groups for additional treatment is not included. AFL given in laser group for additional treatment is not included.
Source: VIVID Clinical Study Report T43, p. 146; VISTA Clinical Study Report T37, p. 125–126.

TABLE 14: EXPOSURE TO ADDITIONAL TREATMENT (LASER) IN THE AFLIBERCEPT GROUPS (SAFETY ANALYSIS SET)

	VIVID	VISTA
	AFL 2Q8 (N = 135)	AFL 2Q8 (N = 151)
Total number of additional treatments (laser) received		
Total number (%) of patients who received additional treatment	11 (8.1)	1 (0.7)
Total number of AFL injections given before additional treatment received		
n		
Mean (SD)		
Median		
Min to Max		
Number of additional treatments received (laser), n (%)		
1		
2		
Summary of additional treatments received		
n		
Mean (SD)		
Median		
Min to Max		

2Q8 = 2 mg every eight weeks; AFL = aflibercept; Max = maximum; Min = minimum; NE= not estimable; SD = standard deviation.
Source: VIVID Clinical Study Report T44, P. 148; VISTA Clinical Study Report T38 P127.

TABLE 15: EXPOSURE TO ADDITIONAL TREATMENT (AFLIBERCEPT) IN THE LASER GROUP (SAFETY ANALYSIS SET)

	VIVID	VISTA
	Laser (N = 133)	Laser (N = 154)
Total number of additional treatments (AFL) received	[redacted]	[redacted]
Total number (%) of patients who received additional treatment	32 (24.1)	48 (31.2)
Total number of laser treatments given before additional treatment received		
n	32	48
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]
Number of additional treatments received (AFL injections), n (%)		
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
Summary of additional treatments received		
n	[redacted]	[redacted]
Mean (SD)	4.2 (1.8)	4.4 (1.56)
Median	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]
Duration of additional treatment (weeks) received		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]

2Q8 = 2 mg every eight weeks; AFL = aflibercept; Max = maximum; Min = minimum; SD = standard deviation.
Source: VIVID Clinical Study Report T44, p. 148; VISTA Clinical Study Report T38, p. 127.

TABLE 16: EXPOSURE TO ANTI-VEGF TREATMENT IN THE FELLOW EYE IN THE FIRST 52 WEEKS (SAFETY ANALYSIS SET)

	VIVID				VISTA			
			Bilateral Treatment				Bilateral Treatment	
	Laser (N = 133)	Laser Without AT (N = 101)	Laser With AT (N = 32)	AFL 2Q8 (N = 135)	Laser (N = 154)	Laser Without AT (N = 106)	Laser With AT (N = 48)	AFL 2Q8 (N = 152)
Total number of fellow eye AFL injections, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of injections n (%)								
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	VIVID				VISTA			
			Bilateral Treatment				Bilateral Treatment	
	Laser (N = 133)	Laser Without AT (N = 101)	Laser With AT (N = 32)	AFL 2Q8 (N = 135)	Laser (N = 154)	Laser Without AT (N = 106)	Laser With AT (N = 48)	AFL 2Q8 (N = 152)
3	[redacted]							
4								
5								
6								
7								
8								
9								
10								
11								
12								

2Q8 = 2 mg every eight weeks; AFL = aflibercept; NR = not reported; SD = standard deviation; VEGF = vascular endothelial growth factor.
Source: VIVID Clinical Study Report T46, p. 151; VISTA Clinical Study Report T40, p. 130.

TABLE 17: TREATMENT COMPLIANCE DURING THE FIRST 52 WEEKS OF THE STUDY (FULL ANALYSIS SET)

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Number of patients receiving 100% planned injections (active or sham), n (%)	[redacted]			
Compliance during 52-week period, n (%)				
< 75%				
≥ 75%				
Compliance (%) during the first 52 weeks, n (%)				
n				
Mean (SD)				
Median				
Min to Max				

2Q8 = 2 mg every eight weeks; AFL = aflibercept; Max = maximum; Min = minimum; SD = standard deviation.
Source: VIVID Clinical Study Report T20, p. 102; VISTA Clinical Study Report T16, p. 85.

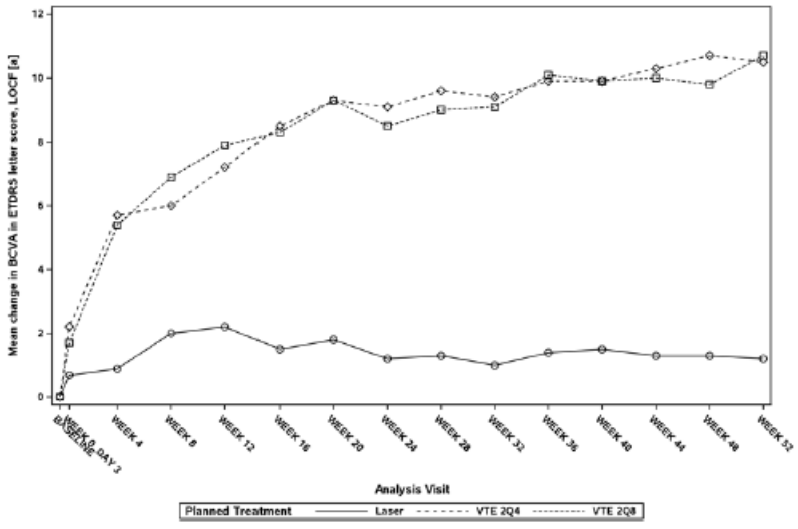
TABLE 18: CHANGE FROM BASELINE TO WEEK 52 IN EARLY TREATMENT DIABETIC RETINOPATHY STUDY LETTER SCORE IN THE STUDY EYE (LAST OBSERVATION CARRIED FORWARD) (FULL ANALYSIS SET)

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Baseline (absolute value)				
N				
Mean (SD)				
Median				
Min to Max				

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Week 52 (absolute value)				
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 (change from baseline)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	1.2 (10.7)	10.7 (9.3)	0.2 (12.5)	10.7 (8.2)
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LS mean change (97.5% CI for the difference) (AFL – laser)	[redacted]			[redacted]
P value		[redacted]		[redacted]

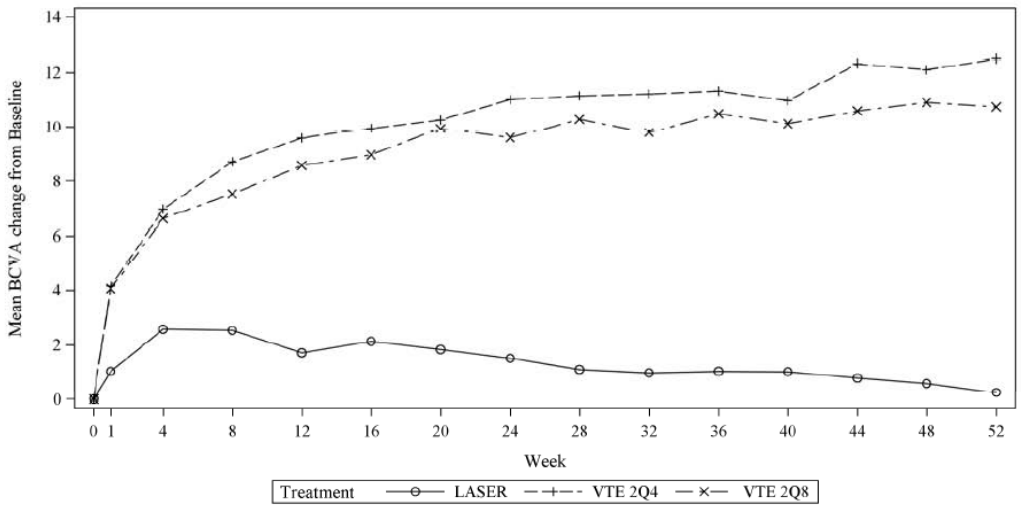
2Q8 = 2 mg every eight weeks; AFL = aflibercept; CI = confidence interval; LS = least squares; Max = maximum; Min = minimum; SD = standard deviation; SE = standard error.
Source: VIVID Clinical Study Report T21, p. 104; VISTA Clinical Study Report T17, p. 87.

FIGURE 3: VIVID STUDY MEAN CHANGE IN BEST-CORRECTED VISUAL ACUITY FROM BASELINE TO WEEK 52 BY VISIT (LAST OBSERVATION CARRIED FORWARD) (FULL ANALYSIS SET)



2Q4 = 2 mg every four weeks; 2Q8 = 2 mg every eight weeks; BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; FAS = full analysis set; LOCF = last observation carried forward; VTE = vascular endothelial growth factor Trap Eye (aflibercept).
Source: VIVID Clinical Study Report F2, p. 105.

FIGURE 4: VISTA STUDY MEAN CHANGE IN BEST-CORRECTED VISUAL ACUITY FROM BASELINE TO WEEK 52 (LAST OBSERVATION CARRIED FORWARD) (FULL ANALYSIS SET)



2Q4 = 2 mg every four weeks; 2Q8 = 2 mg every eight weeks; BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; FAS = full analysis set; LOCF = last observation carried forward; VTE = VEGF Trap Eye (aflibercept).
Source: VISTA Clinical Study Report F2, p. 88.

TABLE 19: CHANGE FROM BASELINE TO WEEK 52 IN BEST-CORRECTED VISUAL ACUITY IN EARLY TREATMENT DIABETIC RETINOPATHY STUDY LETTER SCORE (LAST OBSERVATION CARRIED FORWARD) (PER-PROTOCOL SET)

	VIVID		VISTA	
	Laser (N = 103)	AFL 2Q8 (N = 122)	Laser (N = 145)	AFL 2Q8 (N = 141)
Baseline (absolute value)				
N	103	122	145	141
Mean (SD)	61.0 (10.4)	58.3 (11.2)	59.8 (10.9)	59.5 (11.1)
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 (absolute value)				
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 (change from baseline)				
N	103	122	145	141
Mean (SD)	1.8 (10.5)	11.1 (9.4)	0.5 (12.6)	10.9 (8.4)
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LS mean change	[redacted]		[redacted]	
(97.5% CI for the difference)	(5.9 to 11.8)		(7.6 to 13.2)	
P value	< 0.0001		< 0.0001	

2Q8 = 2 mg every eight weeks; AFL = aflibercept; CI = confidence interval; LS = least squares; Max = maximum; Min = minimum; SD = standard deviation; SE = standard error.
Source: VIVID Clinical Study Report T22, p. 106; VISTA Clinical Study Report T18, p. 88.

TABLE 20: SENSITIVITY ANALYSES OF THE CHANGE FROM BASELINE TO WEEK 52 IN BEST-CORRECTED VISUAL ACUITY IN EARLY TREATMENT DIABETIC RETINOPATHY STUDY LETTER SCORE (FULL ANALYSIS SET)

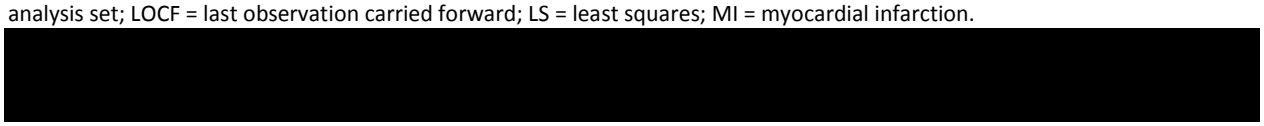
	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Observed values (OC analysis), n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE) BCVA change at Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LS mean change[a]		[redacted]		[redacted]
97.5% CI for the difference		[redacted]		[redacted]
P value		[redacted]		[redacted]
aLOCF; n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE) BCVA change at week 52	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LS mean change [a]		[redacted]		[redacted]
97.5% CI for the difference		[redacted]		[redacted]
P value		[redacted]		[redacted]
aOC; n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE) BCVA change at Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LS mean change [a]		[redacted]		[redacted]
97.5% CI for the difference		[redacted]		[redacted]
P value		[redacted]		[redacted]
Repeated measurements model, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE) BCVA change at week 52	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LS mean change [a]		[redacted]		[redacted]
97.5% CI for the difference		[redacted]		[redacted]
P value		[redacted]		[redacted]
Multiple imputation analysis, n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE) BCVA change at Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LS mean change [a]		[redacted]		[redacted]
97.5% CI for the difference		[redacted]		[redacted]
P value		[redacted]		[redacted]

2Q8 = 2 mg every eight weeks; AFL = aflibercept; aLOCF = last observation carried forward, including measurements after additional treatment was given; aOC = observed case, including measurements after additional treatment was given; BCVA = best-corrected visual acuity; CI = confidence interval; LS = least squares; OC = observed case; SD = standard deviation; SE = standard error. [redacted]

Source: VIVID Clinical Study Report T23, p. 107; VISTA Clinical Study Report T19, p. 90.

FIGURE 5: BEST-CORRECTED VISUAL ACUITY LS MEAN DIFFERENCE OF CHANGES FROM BASELINE (AFL 2 MG EVERY EIGHT WEEKS VERSUS LASER TREATMENT) BY SUBGROUP IN THE VIVID STUDY (LOCF) (FAS)

2Q8 = 2 mg every eight weeks; A1C = glycated hemoglobin; AFL = aflibercept; BCVA = best-corrected visual acuity; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; MI = myocardial infarction.



Source: VIVID Clinical Study Report F7, p. 112.

FIGURE 6: BEST-CORRECTED VISUAL ACUITY LS MEAN DIFFERENCE OF CHANGES FROM BASELINE (AFLIBERCEPT 2 MG EVERY EIGHT WEEKS VERSUS LASER TREATMENT) BY SUBGROUP IN THE VISTA STUDY (LOCF) (FAS)

2Q8 = 2 mg every eight weeks; A1C = glycated hemoglobin; AFL = aflibercept; BCVA = best-corrected visual acuity; FAS = full analysis set; LOCF = last observation carried forward, censoring measurements after additional treatment was given; LS = least squares; MI = myocardial infarction.

Source: VISTA Clinical Study Report F6, p. 93.

TABLE 21: OVERVIEW OF SECONDARY EFFICACY RESULTS (LAST OBSERVATION CARRIED FORWARD) (FULL ANALYSIS SET)

Test Order[a]	Secondary End Point	VIVID		VISTA	
		Adjusted Group Difference (AFL Versus Laser)		Adjusted Group Difference (AFL Versus Laser)	
		AFL 2Q8		AFL 2Q8	
		Estimate (97.5% CI)	*P* Value	Estimate (97.5% CI)	*P* Value
1	Proportion of patients who gained ≥ 10 ETDRS letters from baseline to week 52, %	27.5 (14.6 to 40.5)	< 0.0001	38.8 (27.2 to 50.3)	< 0.0001
2	Proportion of patients who gained ≥ 15 ETDRS letters from baseline to week 52,[b] %	24.2 (13.5 to 34.9)	< 0.0001	23.3 (13.5 to 33.1)	< 0.0001
3	Proportion of patients with a ≥ 2-step improvement from baseline in the ETDRS DRSS, %	19.3 (6.6 to 32.1)	0.0006	14.9 (4.4 to 25.4)	0.0017
4	Change in CRT from baseline to week 52, mean	–142.8 (–179.3 to –106.3)	< 0.0001	–113.47 (–144.2 to –82.8)	< 0.0001
5	NEI VFQ-25 near activities subscale change from baseline, to week 52,[c] mean	–1.21 (–5.8 to 3.4)	0.5537	4.36 (–0.2 to 8.9)	0.0323

Test Order[a]	Secondary End Point	VIVID		VISTA	
		Adjusted Group Difference (AFL Versus Laser)		Adjusted Group Difference (AFL Versus Laser)	
		AFL 2Q8		AFL 2Q8	
		Estimate (97.5% CI)	*P* Value	Estimate (97.5% CI)	*P* Value
6	NEI VFQ-25 distance activities subscale change from baseline to week 52, mean	–0.37 (–4.8 to 4.1)	0.8498	1.65 (–2.8 to 6.2)	0.4067

2Q8 = 2 mg every eight weeks; AFL = aflibercept; CI = confidence interval; CRT = central retinal thickness; DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25.
[a] Hierarchical testing procedure for control of type 1 error according to the global statistical analysis plan.
[b] According to the US statistical analysis plan, this is the only end point that is considered in the hierarchy of secondary end points. All other end points are considered exploratory for the US-specific analysis.
[c] The hierarchical testing procedure of statistical hypothesis tests for superiority of AFL was interrupted for both groups at this point. All *P* values presented after this point for the comparison of the AFL groups with laser treatment groups are provided for description only.
Source: VIVID Clinical Study Report T24, p. 113; VISTA Clinical Study Report T20, p. 94–95.

TABLE 22: PROPORTION OF PATIENTS WHO GAINED ≥ 15 EARLY TREATMENT DIABETIC RETINOPATHY STUDY LETTERS FROM BASELINE TO WEEK 52 (LAST OBSERVATION CARRIED FORWARD) (FULL ANALYSIS SET)

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
No. (%) of patients who gained at least 15 letters at week 52	12 (9.1)	45 (33.3)	12(7.8)	47 (31.1)
Difference,[a] %	24.2		23.3	
(97.5% CI for difference)	(13.5 to 34.9)		(13.5 to 33.1)	
P value	< 0.0001		< 0.0001	

2Q8 = 2 mg every eight weeks; AFL = aflibercept; CI = confidence interval.
[a] Difference between the AFL 2Q8 group minus the laser treatment group was adjusted by geographic region in VIVID and by medical history of myocardial infarction (MI) or cardiovascular accident (CVA) in VISTA.
Source: VIVID Clinical Study Report T27, p. 119; VISTA Clinical Study Report T23, p. 99.

TABLE 23: SENSITIVITY ANALYSES OF THE PROPORTION OF PATIENTS WHO GAINED ≥ 15 EARLY TREATMENT DIABETIC RETINOPATHY STUDY LETTERS FROM BASELINE TO WEEK 52 (LOCF) (FAS)

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
No. (%) of patients who gained at least 15 letters at week 52	[redacted]	[redacted]	[redacted]	[redacted]
Difference,[a] %		[redacted]		[redacted]
(97.5% CI for difference)		[redacted]		[redacted]
P value		[redacted]		[redacted]

2Q8 = 2 mg every eight weeks; AFL = aflibercept; CI = confidence interval; CVA = cardiovascular accident; FAS = full analysis set; LOCF = last observation carried forward; MI = myocardial infarction.
[a] Difference between the AFL 2Q8 minus the laser treatment group was adjusted by geographic region in VIVID and by medical history of MI or CVA in VISTA.
Source: VIVID Clinical Study Report T27, p. 119; VISTA Clinical Study Report T23, p. 99; VISTA Clinical Study Report T24, p. 101; VIVID Clinical Study Report T28, p. 120.

TABLE 24: ANALYSIS OF PROPORTION OF PATIENTS WHO GAIN ≥ 15 EARLY TREATMENT DIABETIC RETINOPATHY STUDY LETTERS FROM BASELINE TO WEEK 52 BY SUBGROUP (LAST OBSERVATION CARRIED FORWARD) (FULL ANALYSIS SET)

Subgroup	VIVID				VISTA			
	Treatment	Patients Who Gain ≥ 15 Letters at Week 52 k/n (%)	Difference,[a] % (97.5% CI)	CMH Test *P* Value	Treatment	Patients Who Gain ≥ 15 Letters at Week 52 n/N (%)	Adjusted Difference,[a] % (97.5% CI)	CMH Test *P* Value
Categorized A1C at baseline								
A1C > 8%	[redacted]							
A1C ≤ 8%	[redacted]							
Baseline BCVA category								
< 40	[redacted]							
≥ 40 to < 55	[redacted]							
≥ 55 to < 65	[redacted]							
≥ 65	[redacted]							

2Q8 = 2 mg every eight weeks; A1C = glycated hemoglobin; AFL = aflibercept; BCVA = best-corrected visual acuity; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; CVA = cardiovascular accident; MI = myocardial infarction.

[a] Difference between the AFL 2Q8 minus the laser treatment group was adjusted by geographic region in VIVID and by medical history of MI or CVA in VISTA.

Source: VIVID Clinical Study Report T14.2.2.2/13, p. 610; VISTA Clinical Study Report T14.02.03/13, p. 1499–1500.

TABLE 25: ANALYSIS OF PROPORTION OF PATIENTS WHO GAIN ≥ 15 EARLY TREATMENT DIABETIC RETINOPATHY STUDY LETTERS FROM BASELINE TO WEEK 52 BY SUBGROUP (OBSERVED CASE) (FULL ANALYSIS SET)

Subgroup Variable	VIVID				VISTA			
	Treatment	Patients Who Gain ≥ 15 Letters at Week 52, k/n (%)	Difference,[a] % (97.5 % CI)	CMH Test *P* Value	Treatment	Patients Who Gain ≥ 15 Letters at Week 52, n/N (%)	Adjusted Difference,[a] % (97.5% CI)	CMH Test, *P* Value
Categorized A1C at baseline								
A1C > 8%								
A1C ≤ 8%								
Baseline BCVA category								
< 40								
≥ 40 to < 55								
≥ 55 to < 65								
≥ 65								

A1C = glycated hemoglobin; AFL = aflibercept; BCVA = best-corrected visual acuity; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; CVA = cardiovascular accident; MI = myocardial infarction.

[a] Difference between the AFL 2Q8 minus the laser treatment group was adjusted by geographic region in VIVID and by medical history of MI or CVA in VISTA.

Note: Laser treatment includes laser therapy at baseline and when re-treatment criteria are met. Laser given in AFL groups for additional treatment is not included. AFL given in laser group for additional treatment is not included.

Source: VIVID Clinical Study Report T 14.2.2.2/14, p. 613; VISTA Clinical Study Report T14.02.03/14, p. 1504–1506.

TABLE 26: ANALYSIS OF PROPORTION OF PATIENTS WHO GAIN ≥ 15 EARLY TREATMENT DIABETIC RETINOPATHY STUDY LETTERS FROM BASELINE TO WEEK 52 BY SUBGROUP (LAST OBSERVATION CARRIED FORWARD) (FULL ANALYSIS SET)

	VIVID				VISTA			
Subgroup Variable	Treatment	Patients Who Gain ≥ 15 Letters at Week 52, n/N (%)	Difference,[a] % (97.5 % CI)	CMH Test, *P* Value	Treatment	Patients Who Gain ≥ 15 Letters at Week 52, n/N (%)	Adjusted Difference,[a] % (97.5% CI)	CMH Test, *P* Value
Categorized A1C at baseline								
A1C > 8%	[redacted]							
A1C ≤ 8%	[redacted]							
Baseline BCVA category								
< 40	[redacted]							
≥ 40 to < 55	[redacted]							
≥ 55 to < 65	[redacted]							
≥ 65	[redacted]							

A1C = glycated hemoglobin; BCVA = best-corrected visual acuity; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; CVA = cardiovascular accident; MI = myocardial infarction.

[a] Difference between the AFL 2Q8 minus the laser treatment group was adjusted by geographic region in VIVID and by medical history of MI or CVA in VISTA.

Note: Laser treatment includes laser therapy at baseline and when re-treatment criteria are met. Laser given in AFL groups for additional treatment is not included. AFL given in laser group for additional treatment is not included.

Source: VIVID Clinical Study Report T 14.2.2.2/15, p. 616; VISTA Clinical Study Report T14.02.03/15, p. 1509–1511.

TABLE 27: ANALYSIS OF PROPORTION OF PATIENTS WHO GAIN ≥ 15 EARLY TREATMENT DIABETIC RETINOPATHY STUDY LETTERS FROM BASELINE TO WEEK 52 BY SUBGROUP (AOC) (FULL ANALYSIS SET)

Subgroup Variable	VIVID				VISTA			
	Treatment	Patients Who Gain ≥ 15 Letters at Week 52, n/N (%)	Difference,[a] % (97.5 % CI)	CMH Test, *P* Value	Treatment	Patients Who Gain ≥ 15 Letters at Week 52, n/N (%)	Adjusted Difference,[a] % (97.5% CI)	CMH Test, *P* Value
Categorized A1C at baseline								
A1C > 8%	[redacted]							
A1C ≥ 8	[redacted]							
Baseline BCVA category								
< 40	[redacted]							
≥ 40 to < 55	[redacted]							
≥ 55 to < 65	[redacted]							
≥ 65	[redacted]							

A1C = glycated hemoglobin; AFL = aflibercept; aOC = values observed under additional treatment are included, only the values observed at week 52 will be used; BCVA = best-corrected visual acuity; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; CVA = cardiovascular accident; MI = myocardial infarction.

[a] Difference between the AFL 2Q8 minus the laser treatment group was adjusted by geographic region in VIVID and by medical history of MI or CVA in VISTA.

Note: Laser treatment includes at baseline and when re-treatment criteria are met. Laser given in AFL groups for additional treatment is not included. AFL given in laser group for additional treatment is not included.

Source: VIVID Clinical Study Report T 14.2.2.2/16, p. 619; VISTA Clinical Study Report T14.02.03/16, p. 1514–1516.

TABLE 28: PROPORTION OF PATIENTS WITH A TWO-STEP OR GREATER IMPROVEMENT FROM BASELINE TO WEEK 52 IN THE EARLY TREATMENT DIABETIC RETINOPATHY STUDY DIABETIC RETINOPATHY SEVERITY SCORE (LOCF) (FAS)

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
n/N (%) of patients with a ≥ 2-step improvement at week 52	6/80 (7.5)	23/83 (27.7)	22 (14.3)	44 (29.1)
Difference,[a] %	[redacted]		[redacted]	
(97.5% CI for difference)	[redacted]		[redacted]	
P value	0.0006		0.0017	

2Q8 = 2 mg every eight weeks; AFL = aflibercept; CI = confidence interval; CVA = cardiovascular accident; FAS = full analysis set; LOCF = last observation carried forward; MI = myocardial infarction.
[a] Difference between the AFL 2Q8 minus the laser treatment group was adjusted by geographic region in VIVID and by medical history of MI or CVA in VISTA.
Note: Laser treatment includes laser therapy at baseline and when re-treatment criteria are met. Laser given in AFL groups for additional treatment is not included. AFL given in laser group for additional treatment is not included.
Source: VIVID Clinical Study Report T29, p. 123; VISTA Clinical Study Report T25, p. 103.

TABLE 29: SENSITIVITY ANALYSES OF THE PROPORTION OF PATIENTS WITH TWO-STEP OR GREATER IMPROVEMENT FROM BASELINE TO WEEK 52 IN THE ETDRS DIABETIC RETINOPATHY SEVERITY SCORE (ALOCF) (FAS)

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
n/N (%) of patients with a ≥ 2-step improvement at week 52	8/80 (10.0)	22/84 (26.2)	28 (18.2)	44 (29.1)
Difference,[a] %	15.5		11.0	
(97.5% CI for difference)	(2.6 to 28.5)		(0.2 to 21.9)	
P value	0.0071		0.0232	

2Q8 = 2 mg every eight weeks; aLOCF = last observation carried forward, including after additional treatment; AFL = aflibercept; CI = confidence interval; CVA = cardiovascular accident; ETDRS = Early Treatment Diabetic Retinopathy Study; FAS = full analysis set; MI = myocardial infarction.
[a] Difference between the AFL 2Q8 minus the laser treatment group was adjusted by geographic region in VIVID and by medical history of MI or CVA in VISTA.
Note: Laser treatment includes laser therapy at baseline and when re-treatment criteria are met. Laser given in AFL groups for additional treatment is not included. AFL given in laser group for additional treatment is not included.
Source: VIVID Clinical Study Report T30, p. 124; VISTA Clinical Study Report T26, p. 104.

TABLE 30: PROPORTION OF PATIENTS WITH THREE-STEP OR GREATER IMPROVEMENT OR TWO- OR THREE-STEP OR GREATER WORSENING FROM BASELINE TO WEEK 52 IN THE ETDRS DRSS (LOCF) (FAS)

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
n/N (%) of patients with at least 3-step improvement at week 52	[redacted]	2/83 (2.4)	[redacted]	19 (12.6)
Difference,[a] %	[redacted]		[redacted]	
(97.5% CI for the difference)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
n/N (%) of patients with at least 2-step worsening at week 52	[redacted]	2/83 (2.4)	[redacted]	7 (4.6)
Difference,[a] %	[redacted]		[redacted]	
(97.5% CI for the difference)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
n/N (%) of patients with at least 3-step worsening at week 52	[redacted]	1/83 (1.2)	[redacted]	4 (2.6)
Difference,[a] %	[redacted]		[redacted]	
(97.5% CI for the difference)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

2Q8 = 2 mg every eight weeks; AFL = aflibercept; CI = confidence interval; CVA = cardiovascular accident; DRSS = Diabetic Retinopathy Severity Score; ETDRS = Early Treatment Diabetic Retinopathy Study; FAS = full analysis set; LOCF = last observation carried forward; MI = myocardial infarction.
[a] Difference between the AFL 2Q8 minus the laser treatment group was adjusted by geographic region in VIVID and by medical history of MI or CVA in VISTA.
Source: VIVID Clinical Study Report T39, p. 140; VISTA Clinical Study Report T35, p. 120.

TABLE 31: PROPORTION OF PATIENTS WHO LOST 15 OR MORE EARLY TREATMENT DIABETIC RETINOPATHY STUDY LETTERS FROM BASELINE TO WEEK 52 (LAST OBSERVATION CARRIED FORWARD) (FULL ANALYSIS SET)

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
n (%) of patients who lost ≥ 15 letters at week 52	14 (10.6)	0 (0.0)	14 (9.1)	1 (0.7)
Difference, %	[redacted]		[redacted]	
(97.5% CI for the difference)[a]	[redacted]		[redacted]	
P value[a]	< 0.0001		0.0007	

2Q8 = 2 mg every eight weeks; AFL = aflibercept; CI = confidence interval; CVA = cardiovascular accident; MI = myocardial infarction.
[a] CI and *P* value were adjusted by geographic region in VIVID and by medical history of MI or CVA in VISTA.
Source: VIVID Clinical Study Report T36, p. 136; VISTA Clinical Study Report T32, p. 115.

TABLE 32: CHANGE FROM BASELINE TO WEEK 52 IN TOTAL NEI VFQ-25 SCORE (LOCF) (FAS)

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Baseline (absolute value)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	77.4 (15.2)	71.2 (17.8)	68.7 (18.1)	70.5 (17.1)
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 (absolute value)				
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 (change from baseline)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE) at week 52	[redacted]	[redacted]	[redacted]	[redacted]
Difference[a] in LS mean change	[redacted]		[redacted]	
(97.5% CI for the difference)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

2Q8 = 2 mg every eight weeks; AFL = aflibercept; CI = confidence interval; CVA = cardiovascular accident; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; Max = maximum; MI = myocardial infarction; Min = minimum; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; SD = standard deviation; SE = standard error.

[a] Difference between the AFL 2Q8 minus the laser treatment group was adjusted by geographic region in VIVID and by medical history of MI or CVA in VISTA.

Source: VIVID Clinical Study Report T40, p. 141; VISTA Clinical Study Report T36, p. 121.

TABLE 33: CHANGE FROM BASELINE TO WEEK 52 IN NEI VFQ-25 NEAR ACTIVITIES SUBSCALE (LOCF) (FAS)

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Baseline				
N	131	135	154	150
Mean (SD)	67.4 (22.24)	60.8 (23.50)	56.6 (23.06)	58.1 (22.94)
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]
Week 52 (change from baseline)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE) at week 52	[redacted]	[redacted]	[redacted]	[redacted]
Difference[a] in LS mean change	[redacted]		[redacted]	
(97.5% CI for the difference)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

2Q8 = 2 mg every eight weeks; AFL = aflibercept; CI = confidence interval; CVA = cardiovascular accident; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; Max = maximum; MI = myocardial infarction; Min = minimum; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; SD = standard deviation; SE = standard error.

[a] Difference between the AFL 2Q8 minus the laser treatment group was adjusted by geographic region in VIVID and by medical history of MI or CVA in VISTA.

Source: VIVID Clinical Study Report T33, p. 132; VISTA Clinical Study Report T29, p. 110.

TABLE 34: CHANGE FROM BASELINE TO WEEK 52 IN NEI VFQ-25 DISTANCE ACTIVITIES SUBSCALE (LOCF) (FAS)

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Baseline				
N	131	135	154	151
Mean (SD)	77.0 (20.9)	67.8 (22.9)	63.7 (23.3)	66.8 (22.5)
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]
Week 52 (change from baseline)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE) at week 52	[redacted]	[redacted]	[redacted]	[redacted]
Difference[a] in LS mean change	[redacted]		[redacted]	
(97.5% CI for the difference)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

2Q8 = 2 mg every eight weeks; AFL = aflibercept; CI = confidence interval; CVA = cardiovascular accident; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; Max = maximum; MI = myocardial infarction; Min = minimum; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; SD = standard deviation; SE = standard error.

Note: Difference between groups (2Q8 minus laser group) was adjusted by geographic region in VIVID and by medical history of MI or CVA in VISTA.

Source: VIVID Clinical Study Report T34, p. 133; VISTA Clinical Study Report T30, p. 112.

TABLE 35: CHANGE FROM BASELINE TO WEEK 52 IN CENTRAL RETINAL THICKNESS (LOCF) (FAS)

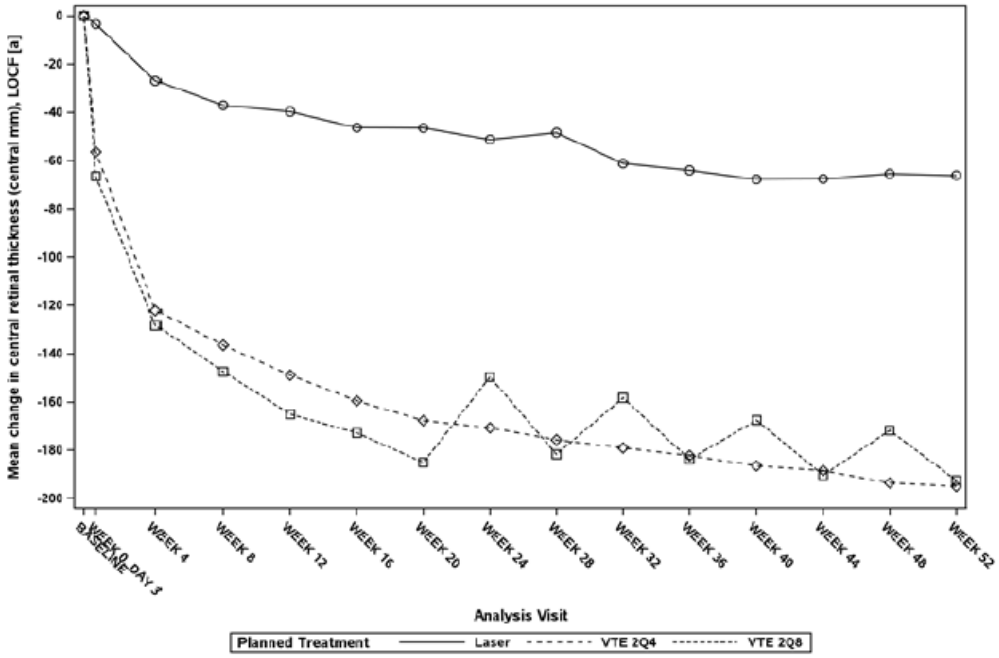
	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Baseline (absolute value)				
N	132	135	154	151
Mean, µm (SD)	540.3 (152.4)	518.4 (147.4)	483.4 (152.9)	479.0 (153.9)
Median, µm	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max, µm	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 (absolute value)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean, µm (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median, µm	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max, µm	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 (change from baseline)				
N	132	135	154	151
Mean, µm (SD)	–66.2 (139.0)	–192.4 (149.9)	–73.3 (176.7)	–183.1 (153.5)
Median, µm	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max, µm	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change, µm (SE) at week 52	–53.1 (14.1)	–196.0 (9.6)	–73.3 (12.1)	–186.8 (6.9)
Difference[a] in LS mean change, µm	–142.8		–113.4	
(97.5% CI for the difference)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

2Q8 = 2 mg every eight weeks; AFL = aflibercept; CI = confidence interval; CRT = central retinal thickness; CVA = cardiovascular accident; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; Max = maximum; MI = myocardial infarction; Min = minimum; SD = standard deviation; SE = standard error.

[a] Difference between the AFL 2Q8 minus the laser treatment group was adjusted by geographic region in VIVID and by medical history of MI or CVA in VISTA.

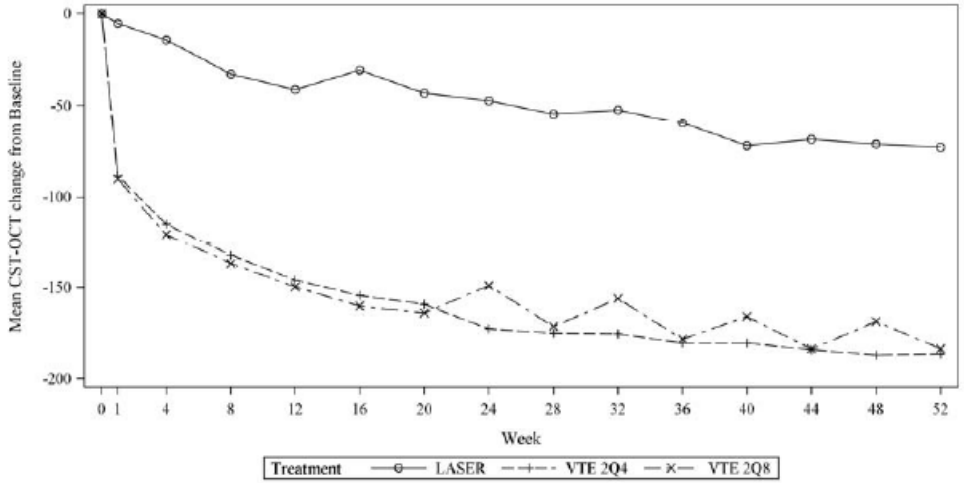
Source: VIVID Clinical Study Report T31, p. 127; VISTA Clinical Study Report T27, p. 106.

FIGURE 7: MEAN CHANGE FROM BASELINE IN CENTRAL RETINAL THICKNESS THROUGH WEEK 52 IN VIVID (LOCF) (FAS)



2Q4 = 2 mg every four weeks; 2Q8 = 2 mg every eight weeks; FAS = full analysis set; LOCF = last observation carried forward; VTE = VEGF Trap Eye (aflibercept).
Source: VIVID Clinical Study Report F14, p. 128.

FIGURE 8: MEAN CHANGE IN CENTRAL RETINAL THICKNESS FROM BASELINE TO WEEK 52 IN VISTA (LOCF) (FAS)



2Q4 = 2 mg every four weeks; 2Q8 = 2 mg every eight weeks; CST = centre subfield thickness; FAS = full analysis set; LOCF = last observation carried forward; OCT = optical coherence tomography; VTE = VEGF Trap Eye (aflibercept).
Source: VISTA Clinical Study Report F13, p. 107.

TABLE 36: SENSITIVITY ANALYSES OF THE CHANGE FROM BASELINE TO WEEK 52 IN CENTRAL RETINAL THICKNESS (LOCF, INCLUDING AFTER ADDITIONAL TREATMENT) (FAS)

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Baseline (absolute value)				
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]
Week 52 (change from baseline)				

	VIVID		VISTA	
	Laser (N = 132)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE) at week 52	[redacted]	[redacted]	[redacted]	[redacted]
Difference[a] in LS mean change	[redacted]		[redacted]	
(97.5% CI for the difference)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

2Q8 = 2 mg every eight weeks; AFL = aflibercept; CI = confidence interval; CVA = cardiovascular accident; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; Max = maximum; MI = myocardial infarction; Min = minimum; SD = standard deviation; SE = standard error.

[a] Difference between the AFL 2Q8 minus the laser treatment group was adjusted by geographic region in VIVID and by medical history of MI or CVA in VISTA.

Source: VIVID Clinical Study Report T32, p. 129; VISTA Clinical Study Report T28, p. 108.

TABLE 37: CHANGE FROM BASELINE TO WEEK 52 IN EQ-5D TOTAL SCORE (LOCF) (FAS)

	VIVID		VISTA	
	Laser (N = 131)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Baseline (absolute value)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 (absolute value)			[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 (change from baseline)			[redacted]	[redacted]
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 (absolute value)			[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]

	VIVID		VISTA	
	Laser (N = 131)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 151)
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]
Week 52 (change from baseline)			[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min to Max	[redacted]	[redacted]	[redacted]	[redacted]

2Q8 = 2 mg every eight weeks; AFL = aflibercept; EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; FAS = full analysis set; LOCF = last observation carried forward; Max = maximum; Min = minimum; SD = standard deviation.
Source: VIVID Clinical Study Report T42, p. 143.

TABLE 38: OCULAR TREATMENT-EMERGENT ADVERSE EVENTS IN THE STUDY EYE OCCURRING IN 2% OR MORE OF PATIENTS IN ANY TREATMENT GROUP (SAFETY SET)

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
	n (%)			
Number of patients with at least 1 ocular TEAE (study eye), n (%)	82 (61.7)	80 (59.3)	103 (66.9)	87 (57.2)
Blepharitis	1 (0.8)	3 (2.2)	3 (1.9)	6 (3.9)
Cataract	5 (3.8)	8 (5.9)	10 (6.5)	6 (3.9)
Cataract, cortical	0	3 (2.2)	3 (1.9)	4 (2.6)
Cataract, nuclear	2 (1.5)	2 (1.5)	4 (2.6)	0
Cataract, subcapsular	NR	NR	4 (2.6)	4 (2.6)
Conjunctival hemorrhage	3 (2.3)	31 (23.0)	47 (30.5)	42 (27.6)
Conjunctival hyperemia	4 (3.0)	1 (0.7)	NR	NR
Conjunctivitis	4 (3.0)	3 (2.2)	NR	NR
Conjunctivitis, allergic	2 (1.5)	3 (2.2)	NR	NR
Corneal erosion	2 (1.5)	5 (3.7)	NR	NR
Corneal abrasion	NR	NR	4 (2.6)	4 (2.6)
Cystoid macular edema	7 (5.3)	5 (3.7)	NR	NR

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
Diabetic retinal edema	5 (3.8)	2 (1.5)	NR	NR
Diabetic retinopathy	2 (1.5)	0	6 (3.9)	2 (1.3)
Dry eye	4 (3.0)	2 (1.5)	7 (4.5)	2 (1.3)
Eye inflammation	0	0	0	0
Eye irritation	1 (0.8)	3 (2.2)	9 (5.8)	7 (4.6)
Eye pain	3 (2.3)	3 (2.2)	15 (9.7)	18 (11.8)
Foreign body sensation in eyes	2 (1.5)	4 (3.0)	7 (4.5)	5 (3.3)
Increased intraocular pressure	9 (6.8)	6 (4.4)	1 (0.6)	6 (3.9)
Increased lacrimation	0	3 (2.2)	5 (3.2)	3 (2.0)
Macular cyst	3 (2.3)	0	NR	NR
Macular fibrosis	3 (2.3)	3 (2.2)	9 (5.8)	10 (6.6)
Macular edema	4 (3.0)	2 (1.5)	NR	NR
Maculopathy	3 (2.3)	0	NR	NR
Ocular hyperemia	1 (0.8)	6 (4.4)	11 (7.1)	5 (3.3)
Ocular hypertension	0	3 (2.2)	NR	NR
Photopsia	NR	NR	5 (3.2)	1 (0.7)
Posterior capsule opacification	2 (1.5)	3 (2.2)	6 (3.9)	3 (2.0)
Punctate keratitis	2 (1.5)	6 (4.4)	1 (0.6)	2 (1.3)
Retinal aneurysm	3 (2.3)	6 (4.4)	2 (1.3)	3 (2.0)
Retinal detachment	1 (0.8)	2 (1.5)	0	0
Retinal exudates	9 (6.8)	10 (7.4)	7 (4.5)	3 (2.0)
Retinal hemorrhage	10 (7.5)	8 (5.9)	11 (7.1)	4 (2.6)
Retinal neovascularization	6 (4.5)	0	7 (4.5)	2 (1.3)
Retinal pigment epitheliopathy	2 (1.5)	1 (0.7)	2 (1.3)	4 (2.6)
Retinal vascular disorder	1 (0.8)	3 (2.2)	0	3 (2.0)
Retinopathy	3 (2.3)	0	NR	NR
Vision blurred	1 (0.8)	2 (1.5)	5 (3.2)	3 (2.0)
Reduced visual acuity	17 (12.8)	10 (7.4)	8 (5.2)	5 (3.3)
Abnormal visual acuity tests	19 (14.3)	8 (5.9)	4 (2.6)	1 (0.7)
Visual impairment	2 (1.5)	2 (1.5)	5 (3.2)	3 (2.0)

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
Vitreous detachment	2 (1.5)	2 (1.5)	8 (5.2)	9 (5.9)
Vitreous floaters	1 (0.8)	2 (1.5)	8 (5.2)	11 (7.2)
Vitreous hemorrhage	3 (2.3)	3 (2.2)	8 (5.2)	1 (0.7)

2Q8 = 2 mg every eight weeks; AFL = aflibercept; NR = not reported; TEAE = treatment-emergent adverse event.
Source: VIVID Clinical Study Report T47, p. 155; VISTA Clinical Study Report T42, p. 132–133.

TABLE 39: SUMMARY OF OCULAR TREATMENT EMERGENT SURGERIES OF STUDY EYE BY PREFERRED TERM AND TREATMENT (SAFETY SET)

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
	n (%)			
Number of patients with at least 1 ocular surgery in of the study eye, n (%)	9 (6.8)	7 (5.2)	16 (10.4)	7 (4.6)
Cataract operation	0	2 (1.5)	5 (3.2)	1 (0.7)
Corneal sutures removal	0	1 (0.7)	NR	NR
Curettage of chalazion	1 (0.8)	1 (0.7)	0	1 (0.7)
Eye laser surgery	1 (0.8)	0	2 (1.3)	3 (2.0)
Iridotomy	1 (0.8)	0	0	0
Lens capsulotomy	2 (1.5)	2 (1.5)	1 (0.6)	0
Intraocular lens implant	NR	NR	0	1 (0.7)
Retinal laser coagulation	4 (3.0)	1 (0.7)	6 (3.9)	1 (0.7)
Retinopexy	0	1 (0.7)	0	0
Vitrectomy	0	1 (0.7)	1 (0.6)	1 (0.7)
Pterygium operation	NR	NR	1 (0.6)	0
Trabeculectomy	NR	NR	1 (0.6)	0

2Q8 = 2 mg every eight weeks; AFL = aflibercept; NR = not reported.
Source: VIVID Clinical Study Report T49, p. 1557; VISTA Clinical Study Report T43, p. 136.

TABLE 40: NON-OCULAR ADVERSE EVENT OCCURRING IN AT LEAST 5% OF ANY ONE TREATMENT GROUP BY PREFERRED TERM (SAFETY SET)

	VIVID		VISTA	
	Laser (n = 133)	AFL 2Q8 (n = 135)	Laser (n = 154)	AFL 2Q8 (n = 152)
	n (%)			
Number of patients with at least 1 non-ocular TEAE	81 (60.9)	98 (72.6)	132 (85.7)	119 (78.3)
Urinary tract infection	NR	NR	11 (7.1)	14 (9.2)
Nasopharyngitis	20 (15.0)	22 (16.3)	13 (8.4)	9 (5.9)
Influenza	5 (3.8)	7 (5.2)	NR	NR
Sinusitis	NR	NR	11 (7.1)	8 (5.3)
Cellulitis	NR	NR	5 (3.2)	8 (5.3)
Upper respiratory tract infection	NR	NR	7 (4.5)	8 (5.3)
Bronchitis	NR	NR	8 (5.2)	4 (2.6)
Vascular disorders	21 (15.8)	25 (18.5)	43 (27.9)	33 (21.7)
Hypertension	17 (12.8)	19 (14.1)	34 (22.1)	28 (18.4)
Diabetes mellitus	3 (2.3)	6 (4.4)	11 (7.1)	10 (6.6)
Investigations	15 (11.3)	20 (14.8)	40 (26.0)	28 (18.4)
Increased blood pressure	NR	NR	8 (5.2)	5 (3.3)
Diarrhea	NR	NR	9 (5.8)	4 (2.6)
Constipation	NR	NR	8 (5.2)	3 (2.0)
Edema, peripheral	NR	NR	6 (3.9)	10 (6.6)
Chest pain	NR	NR	8 (5.2)	5 (3.3)
Headache	NR	NR	13 (8.4)	6 (3.9)
Oropharyngeal pain	5 (3.8)	1 (0.7)		
Fall	NR	NR	6 (3.9)	8 (5.3)
Renal failure acute	9 (6.8)	8 (5.9)	8 (5.2)	7 (4.6)
Anemia	NR	NR	6 (3.9)	10 (6.6)

2Q8 = 2 mg every eight weeks; AFL = aflibercept; NR = not reported; TEAE = treatment-emergent adverse event.
Source: VIVID Clinical Study Report T40, p. 158; VISTA Clinical Study Report T44, p. 138.

TABLE 41: INJECTION PROCEDURE–RELATED OCULAR TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN 2% OR MORE OF PATIENTS IN ANY TREATMENT GROUP IN THE STUDY EYE (SAFETY SET)

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
	n (%)			
Number of patients with at least 1 injection-related ocular TEAE (study eye)	17 (12.8)	50 (37.0)	59 (38.3)	62 (40.8)
Cataract	0	2 (1.5)	NR	NR
Conjunctival hemorrhage	2 (1.5)	30 (22.2)	44 (28.6)	42 (27.6)
Eye irritation	1 (0.8)	3 (2.2)	8 (5.2)	6 (3.9)
Corneal erosion	1 (0.8)	3 (2.2)	NR	NR
Corneal abrasion	NR	NR	1 (0.6)	4 (2.6)
Ocular hyperemia	0	5 (3.7)	9 (5.8)	5 (3.3)
Eye pain	3 (2.3)	3 (2.2)	11 (7.1)	16 (10.5)
Increased lacrimation	0	3 (2.2)	2 (1.3)	2 (1.3)
Foreign body sensation in eyes	2 (1.5)	3 (2.2)	7 (4.5)	5 (3.3)
Increased intraocular pressure	3 (2.3)	4 (3.0)	0	4 (2.6)
Vision blurred	NR	NR	3 (1.9)	2 (1.3)
Injection site pain	1 (0.8)	2 (1.5)	0	2 (1.3)
Ocular hypertension	0	1 (0.7)	NR	NR
Retinal detachment	0	1 (0.7)	NR	NR
Vitreous floaters	0	1 (0.7)	5 (3.2)	10 (6.6)
Investigations	3 (2.3)	4 (3.0)	0	4 (2.6)

2Q8 = 2 mg every eight weeks; AFL = aflibercept; NR = not reported; TEAE = treatment-emergent adverse event.
Source: VIVID Clinical Study Report T55, p. 164–165; VISTA Clinical Study Report T48, p. 143–144.

TABLE 42: OCULAR LASER PROCEDURE–RELATED OCULAR TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN 2% OR MORE OF PATIENTS IN ANY TREATMENT GROUP IN THE STUDY EYE (SAFETY SET)

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
	n (%)			
Number of patients with at least 1 ocular laser procedure–related ocular TEAE (study eye)	12 (9.0)	10 (7.4)	4 (2.6)	0
Eye pain	1 (0.8)	0	3 (1.9)	0
Conjunctival hemorrhage	0	5 (3.7)	0	0
Retinal detachment	1 (0.8)	0	NR	NR

2Q8 = 2 mg every eight weeks; AFL = aflibercept; NR = not reported; TEAE = treatment-emergent adverse event.
Source: VIVID Clinical Study Report T56, p. 166; VISTA Clinical Study Report T50, p. 146.

TABLE 43: TREATMENT-EMERGENT OCULAR SERIOUS ADVERSE EVENTS IN THE STUDY EYE (SAFETY SET)

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
Number of patients with at least 1 ocular SAE in the study eye	6 (4.5)	3 (2.2)	6 (3.9)	2 (1.3)
Cataract	0	2 (1.5)	1 (0.6)	0
Vitreous hemorrhage	1 (0.8)	0	3 (1.9)	1 (0.7)
Diabetic retinopathy	1 (0.8)	0	2 (1.3)	0
Macular degeneration	1 (0.8)	0	NR	NR
Retinal detachment	0	1 (0.7)	NR	NR
Retinal exudates	1 (0.8)	0	NR	NR
Retinal neovascularization	3 (2.3)	0	NR	NR
Retinal hemorrhage	NR	NR	1 (0.6)	0
Increased intraocular pressure	NR	NR	0	1 (0.7)

2Q8 = 2 mg every eight weeks; AFL = aflibercept; NR = not reported; SAE = serious adverse events.
Source: VIVID Clinical Study Report T58, p. 169; VISTA Clinical Study Report T52, p. 148.

TABLE 44: NON-OCULAR SERIOUS ADVERSE EVENTS OCCURRING IN AT LEAST 1% OF ANY ONE TREATMENT GROUP BY PREFERRED TERM (SAFETY SET)

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
Number of patients with at least 1 non-ocular SAE	18 (13.5)	25 (18.5)	47 (30.5)	39 (25.7)
Cellulitis	NR	NR	2 (1.3)	5 (3.3)
Abscess limb	NR	NR	2 (1.3)	2 (1.3)
Pneumonia	NR	NR	2 (1.3)	1 (0.7)
Osteomyelitis	NR	NR	3 (1.9)	0
Sepsis	NR	NR	2 (1.3)	0
Cardiac failure congestive	0	1 (0.7)	1 (0.6)	4 (2.6)
Coronary artery stenosis	NR	NR	2 (1.3)	4 (2.6)
Myocardial infarction	NR	NR	1 (0.6)	2 (1.3)
Coronary artery disease	NR	NR	1 (0.6)	1 (0.7)
Acute myocardial infarction	2 (1.5)	0	3 (1.9)	1 (0.7)
Cardiac failure, acute	NR	NR	2 (1.3)	0
Renal failure, acute	NR	NR	5 (3.2)	5 (3.3)
Renal failure	0	2 (1.5)	2 (1.3)	1 (0.7)
Renal failure, chronic	NR	NR	1 (0.6)	2 (1.3)
Breast cancer	1 (0.8)	0	NR	NR
Squamous cell carcinoma of skin	NR	NR	0	2 (1.3)
Fall	NR	NR	2 (1.3)	4 (2.6)
Diabetic ketoacidosis	NR	NR	1 (0.6)	2 (1.3)
Hyperkalemia	NR	NR	2 (1.3)	0
Anemia	NR	NR	1 (0.6)	5 (3.3)
Transient ischemic attack	NR	NR	2 (1.3)	0
Vascular disorders	2 (1.5)	3 (2.2)	5 (3.2)	2 (1.3)
Hypertension	NR	NR	3 (1.9)	1 (0.7)
Orthostatic hypotension	NR	NR	2 (1.3)	0
Site conditions	NR	NR	2 (1.3)	5 (3.3)
Chest pain	NR	NR	0	3 (2.0)

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
Diabetic gastroparesis	NR	NR	2 (1.3)	0
Disorders	NR	NR	0	2 (1.3)
Tissue disorders	NR	NR	7 (4.5)	1 (0.7)
Osteoarthritis	NR	NR	3 (1.9)	0
Depression	NR	NR	2 (1.3)	0

2Q8 = 2 mg every eight weeks; AFL = aflibercept; NR = not reported; SAE = serious adverse events.
Source: VIVID Clinical Study Report T59, p. 170; VISTA Clinical Study Report T53, p. 149.

TABLE 45: NUMBER OF PATIENTS WITH SERIOUS OCULAR INJECTION PROCEDURE–RELATED TREATMENT-EMERGENT ADVERSE EVENTS OF STUDY EYE BY PRIMARY SYSTEM ORGAN CLASS AND PREFERRED TERM (SAFETY SET)

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
Number of patients (%) with at least 1 serious ocular injection procedure–related adverse event	0	1 (0.7)	0	1 (0.7)
Eye disorders	0	1 (0.7)	0	1 (0.7)
Retinal detachment	0	1 (0.7)	0	1 (0.7)
Vitreous hemorrhage	NR	NR	NR	1 (0.7)

2Q8 = 2 mg every eight weeks; AFL = aflibercept; NR = not reported.
Source: VIVID Clinical Study Report T14.3.1/17, p. 1003; VISTA Clinical Study Report T14.03.01/5-4, p. 1835.

TABLE 46: OCULAR LASER PROCEDURE–RELATED SERIOUS ADVERSE EVENTS (SAFETY SET)

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
	n (%)			
Number of patients with at least 1 ocular laser procedure–related SAE	12 (9.0)	10 (7.4)	NR	NR
Conjunctival hemorrhage	0	5 (3.7)	NR	NR
Conjunctival hyperemia	1 (0.8)	0	NR	NR

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
Conjunctival irritation	0	1 (0.7)	NR	NR
Conjunctivitis	2 (1.5)	0	NR	NR
Corneal disorder	0	1 (0.7)	NR	NR
Corneal erosion	1 (0.8)	0	NR	NR
Dry eye	1 (0.8)	0	NR	NR
Eye pain	1 (0.8)	0	NR	NR
Eye swelling	1 (0.8)	0	NR	NR
Macular degeneration	1 (0.8)	0	NR	NR
Macular edema	1 (0.8)	0	NR	NR
Maculopathy	2 (1.5)	0	NR	NR
Ocular hyperemia	0	1 (0.7)	NR	NR
Punctate keratitis	0	2 (1.5)	NR	NR
Retinal detachment	1 (0.8)	0	NR	NR
Retinal exudates	1 (0.8)	0	NR	NR
Retinal pigment epitheliopathy	0	1 (0.7)	NR	NR
Sudden visual loss	1 (0.8)	0	NR	NR
Vision blurred	0	1 (0.7)	NR	NR
Reduced visual acuity	1 (0.8)	1 (0.7)	NR	NR
Vitreous floaters	0	1 (0.7)	NR	NR

2Q8 = 2 mg every eight weeks; AFL = aflibercept; NR = not reported; SAE = serious adverse event.
Source: VIVID Clinical Study Report T61, p. 173; VISTA Clinical Study Report T14.03.01/5-7, p. 1838.

TABLE 47: OCULAR (STUDY EYE) AND NON-OCULAR TREATMENT-EMERGENT ADVERSE EVENTS LEADING TO DISCONTINUATION OF STUDY THROUGH WEEK 52 (SAFETY SET)

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
	n (%)			
Number of patients with at least 1 ocular TEAE of the study eye leading to discontinuation of the study	4 (3.0)	0	NR	NR
Diabetic retinopathy	1 (0.8)	0	NR	NR
Posterior capsule opacification	1 (0.8)	0	NR	NR
Retinal exudates	1 (0.8)	0	NR	NR
Retinal neovascularization	1 (0.8)	0	NR	NR
Retinopathy	1 (0.8)	0	NR	NR
Sudden visual loss	1 (0.8)	0	NR	NR
Reduced visual acuity reduced	1 (0.8)	0	NR	NR
Number of patients with at least 1 non-ocular TEAE leading to discontinuation of the study	3 (2.3)	1 (0.7)	1 (0.6)	1 (0.7)
Diffuse large B-cell lymphoma stage III	NR	NR	0	1 (0.7)
Investigations	NR	NR	1 (0.6)	0
Decreased hemoglobin	NR	NR	1 (0.6)	0
Acute myocardial infarction	2 (1.5)	0	NR	NR
Enterocolitis	1 (0.8)	0	NR	NR
Renal failure	1 (0.8)	0	NR	NR
Renal impairment	0	1 (0.7)	NR	NR

2Q8 = 2 mg every eight weeks; AFL = aflibercept; NR = not reported; TEAE = treatment-emergent adverse event.
Source: VIVID Clinical Study Report T62, p. 175; VISTA Clinical Study Report T54, p. 153.

TABLE 48: ANTIPLATELET TRIALISTS' COLLABORATION EVENTS (SAFETY SET)

	VIVID		VISTA	
	Laser (N = 133)	AFL 2Q8 (N = 135)	Laser (N = 154)	AFL 2Q8 (N = 152)
	n (%)			
Number of patients with at least 1 APTC event	2 (1.5%)	4 (3.0%)	6 (3.9%)	6 (3.9%)
Non-fatal myocardial infarction	1 (0.8%)	0	4 (2.6%)	3 (2.0%)
Non-fatal stroke	0	2 (1.5%)	NR	NR
Vascular death	1 (0.8%)	2 (1.5%)	NR	NR

2Q8 = 2 mg every eight weeks; AFL = aflibercept; APTC = Antiplatelet Trialists' Collaboration; NR = not reported.
Source: VIVID Clinical Study Report Table 63, p. 175; VISTA Clinical Study Report Table 55, p. 154.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts
- ETDRS Diabetic Retinopathy Severity Scale (DRSS)
- Optical coherence tomography (OCT)
- National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25)
- EuroQol Five-Dimension Health-Related Quality of Life Questionnaire (EQ-5D).

Findings

TABLE 49: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Validated	MCID	References
ETDRS charts	ETDRS charts were developed to measure visual acuity. They present a series of 5 letters of equal difficulty on each row, with standardized spacing between letters and rows; there are a total of 14 lines (70 letters).	Yes	10 to 15 letters	Kniestedt and Stamper 2003,[45] FDA Statistical Review[31]
ETDRS DRSS	The DRSS was developed to categorize severity of diabetic retinopathy based on several fundus photographic characteristics. There are 13 levels in the original ETDRS scale, and increase in the severity step or level is associated with an increased risk of retinopathy progression.	Yes	≥ 2 steps progression (at 1 year follow-up)	ETDRS Research Group 1991,[33] Klein et al. 2001[10]
NEI VFQ-25	The NEI VFQ-25 was developed as a means to measure vision-targeted quality of life. It includes 25 items relevant to 11 vision-related constructs, in addition to a single-item general health component.	Yes	3.33 points (SEM-based method), 6.13 points (one-half SD-based method)	Mangione et al. 2001,[46] Lloyd et al. 2013[35]
EQ-5D	EQ-5D is a general, non–disease-specific health-related quality of life questionnaire.	No	Unknown	Rabin 2001[36]
OCT	Optical coherence tomography (OCT) is a technique used to create cross-sectional maps of the retinal structures and to quantify retinal thickness in patients with macular edema.	Yes	Unknown	Goatman 2006[23]

DRSS = Diabetic Retinopathy Severity Scale; EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; ETDRS = Early Treatment Diabetic Retinopathy Study; MCID = minimal clinically important difference; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; OCT = optical coherence tomography; SD = standard deviation; SEM = standard error of measurement.

Early Treatment Diabetic Retinopathy Study Charts

The ETDRS charts are based on a design by Bailey and Lovie and are commonly used in clinical research.[45,47-50] ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between letters and rows, for a total of 14 lines (70 letters). 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.[45,51] ETDRS results can be converted to Snellen fractions, another common measure of visual acuity, 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.[45,52] ETDRS letters range from 58.18 mm to 2.92 mm in height, corresponding to Snellen visual acuity fractions of 20/200 to 20/10, respectively. Letter size increases 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 (logarithm of marginal angle of resolution [Log MAR]), suitable for statistical analysis, in which individual letters score 0.02 log units.

ETDRS charts may reliably identify changes in visual acuity of two lines (10 letters) or more, but not changes of one line (five letters) or less.[53] The reliability of ETDRS charts depends on the baseline visual acuity. For eyes with acuity better than 20/100, a change in visual acuity of five or more letters has a greater than 90% probability of being a real change, while for eyes worse than 20/100, a change of 10 or more letters is required for the same reliability.[54] A loss or gain of three lines (15 letters) is considered a moderate degree of change and is commonly used as a outcome in clinical trials.[32] The US FDA recommends a mean change of 15 letters or more on an ETDRS chart, or a statistically significant difference in the proportion of patients with greater than or equal to 15 letter change in visual acuity, as clinically relevant outcome measures in trials of interventions for macular edema.[31]

With regard to the relationship between visual acuity measurement and visual function, a loss of three or more lines (greater than or equal to 15 letters) on an ETDRS chart corresponds to a doubling of the visual angle and is considered moderate visual loss, while a loss of six or more lines (greater than or equal to 30 letters) corresponds to a quadrupling of the visual angle and is considered severe. However, visual acuity is only one component contributing to overall visual function and the ability to perform everyday visual tasks (e.g., reading, recognizing faces, driving, and using the telephone). Overall visual function also depends on variables such as contrast sensitivity, near vision, colour vision, and sensitivity to glare.[55] The various components of visual function will affect the performance of different vision-related tasks by varying degrees. For example, the use of distance acuity to measure the success of treatments for age-related macular degeneration is not optimal, given that distance vision is usually two ETDRS lines better than reading vision,[32] and difficulty with reading is a common complaint among persons with eye disease.[56] Rather, contrast sensitivity is a more important contributor to reading performance.[32,57]

ETDRS Diabetic Retinopathy Severity Scale

The ETDRS Research Group modified the Airlie House classification of diabetic retinopathy to create a diabetic retinopathy grading system based on stereoscopic fundus photographs.[58] Fundus photography displays ocular abnormalities, such as microaneurysms, hemorrhages, hard and soft exudates, venous abnormalities, new vessels, fibrous proliferations, retinal thickening, and clinically significant macular edema; these abnormalities are graded independently from single or multiple photographic fields.[58] A comparison of fundus photograph characteristics in patients with diabetic retinopathy over time led to the identification of photographic risk factors for progression from non-proliferative to proliferative

diabetic retinopathy.[33] As a result of these analyses, the DRSS was created. The DRSS consists of 13 levels of graded photographic characteristics that were defined to categorize severity of diabetic retinopathy for individual eyes, ranging from no retinopathy to severe vitreous hemorrhage.

Complete inter-rater agreement of fundus photography grading in the ETDRS was demonstrated with a frequency of 38%, agreement within one level occurred in 71%, and agreement within two levels in 87%.[33] The unweighted kappa statistic was 0.31, which increased to 0.71 with weighting of 1 for exact agreement, 0.9375 for one-level disagreement, and 0.75 for two-level disagreement.[33] Since its introduction, the ETDRS severity scale has been used extensively in research and has demonstrated sufficient reproducibility and validity to establish it as the "gold standard" instrument for diabetic retinopathy grading in clinical trials.[59]

Step progression refers to an increase in photographic level that can be used to describe change in diabetic retinopathy over time.[10,33] In the ETDRS, the proportion of eyes with progression of two or more levels at follow-up was relatively similar among all severity categories at the one year follow-up time point, establishing two-step progression as a reasonable outcome measure for all baseline retinopathy levels.[33] When assessing change in overall retinopathy severity for the patient and not just individual eyes, the scale was reproducible for progression in three or more steps for a longer period than one year follow-up.[33] The FDA-recommended end points for diabetic retinopathy clinical trials include a "statistically significant difference in the percentage of patients at three years with a ≥ three-step change on the ETDRS retinopathy scale."[25] The Wisconsin Epidemiology Study of Diabetic Retinopathy evaluated whether fewer than three steps of ETDRS DRSS progression were clinically meaningful by conducting a population-based study of diabetic patients with 10 years of follow-up.[10] The results indicated that patients with one or more or two or more steps of ETDRS DRSS progression over six years (years four to 10 of follow-up) were significantly more likely to develop proliferative diabetic retinopathy than those without ETDRS DRSS step progression.[10]

Optical Coherence Tomography

OCT is a fast, non-invasive technique used to create cross-sectional maps of the retinal structures and to quantify retinal thickness in patients with macular edema.[23] OCT uses lasers centred on infrared wavelengths to record light reflected from interfaces between materials with different refractive indices and from materials that scatter light. Third-generation OCT machines are able to differentiate three reflecting layers, thought to be the vitreous/retina, inner/outer photoreceptor segments, and the retinal pigment epithelium/choriocapillaris interfaces. Ultra-high-resolution machines can differentiate a fourth layer. During the OCT scan, a series of intersecting, radial cross-sections of the retina are measured. Resolution depends on the software as well as the hardware used and is better around the central axis than lateral areas.[23,60] A recent advancement in OCT device technology has been the shift from time domain (TD-OCT) to spectral domain OCT (SD-OCT), as the latter can acquire data at a higher speed with better image resolution and reduced motion artifact.[61]

Intra-device repeatability and inter-device reproducibility of measurements depend on a number of factors, including retinal pathology, retinal region, region size, OCT model, equipment settings, manual or automated analysis, and operator experience.[23] In eyes with diabetic macular edema (DME), a comparison of measurements with four different OCT devices found good intra-device repeatability, but statistically significant differences in retinal thickness values across different devices.[62] Another study that compared the reproducibility of retinal thickness measurements from OCT images of eyes with DME obtained by TD-OCT and SD-OCT instruments found that SD-OCT devices demonstrated less test-retest variability.[61] Inter-device differences in retinal thickness were also reported in this study, though

they were expected due to the different algorithms used by SD- and TD-OCT machines that define the anatomical structures serving as the boundaries for measurement. Additionally, the presence of macular edema can influence OCT measurement precision. In one study, the 95% limits of agreement (the scale at which an instrument can detect changes in a patient) for average foveal thickness in healthy eyes was 8 µm, while in patients with DME it was 36 µm.[63]

In patients with DME, the association between OCT-measured retinal thickness and best-corrected visual acuity has been evaluated. A moderate correlation between visual acuity and OCT centre point thickness has been observed (r = 0.52).[64] For every 100 µm decrease in centre point thickness, visual acuity increased by 4.4 letters (95% confidence interval [CI], 3.5 to 5.3).[64] Other studies have shown similarly modest correlations between visual acuity and central retinal thickness determined by OCT.[65,66] In eyes with DME treated by laser photocoagulation, changes in centre point thickness were associated with changes in visual acuity, with correlation coefficients of 0.44, 0.30, and 0.43 at 3, 5, 8, and 12 months, respectively. Retinal thickness, measured using OCT, may be a useful clinical tool to monitor macular edema and retinal changes in DME but is modestly correlated with changes in vision and cannot be used as a substitute for visual acuity or other patient reported outcomes.

National Eye Institute Visual Function Questionnaire-25

The NEI VFQ was developed as a means to measure vision-targeted quality of life. The original 51-item questionnaire was developed based on focus groups comprising persons with a number of common eye conditions (e.g., age-related cataracts, age-related macular degeneration, and diabetic retinopathy), and thus may be used to assess quality of life in a broad range of eye conditions.[56] 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.[67]

A shorter version of the original instrument, the NEI VFQ-25, was subsequently developed, which retained the multi-dimensional nature of the original but is more practical and efficient to administer.[46] With the exception of the expectations for future vision, all the constructs listed above were retained in the shortened version, with a reduced number of items within each. 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 are converted to a 0 to 100 scale, with 0 representing the worst 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.[34] 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.[34] However, standard scoring is prone 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.[34]

Determination of what constitutes a clinically meaningful change in the NEI VFQ-25 appears to be linked to its correlation with visual acuity. A three-line (15-letter) change in visual acuity 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. For patients with neovascular age-related macular degeneration (AMD), and specifically for the study eye, which is typically the worse-seeing eye, a 15-letter change in visual acuity corresponds to a four-point change in overall NEI VFQ-25 score.[68] 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 in patients with subfoveal choroidal neovascularization have shown similar estimated

clinically relevant differences.[69] The instrument showed weaker correlation or was not responsive to changes in the visual acuity of the worse eye in patients with AMD.[70,71] This may have implications when evaluating patients with unilateral disease. A psychometric validation study of the NEI VFQ-25, specifically in patients with DME, has recently been conducted, and two distribution-based methods were employed to determine a minimal clinically important difference (MCID) from baseline to week 54.[35] Using a one-half standard deviation-based approach, the MCID for each NEI VFQ-25 domain ranged from 8.80 (general vision) to 14.40 (role difficulties) and produced a composite score MCID of 6.13 points. The MCID for the near vision and distance vision subscales were 10.24 and 11.07, respectively. A standard error of measurement approach yielded similar MCID estimates from 8.79 (driving) to 14.04 (role difficulties), with a composite score MCID estimate of 3.33 points. This technique lowered the MCID estimates for the near and distance vision domains, which were reported as 9.17 and 10.19, respectively.

Both versions of the NEI VFQ were reported to be valid and reliable measures of health-related quality of life among patients with a wide range of eye conditions, including DME,[35,46,67,71] and all but two subscale scores (general health and ocular pain) have been shown to be responsive to changes in visual acuity in the better-seeing eye.[70,71] However, some assessments of the psychometric validity of the NEI VFQ-25 using Rasch scoring and principal component analysis in patients with various eye conditions have identified issues with multi-dimensionality (measurement of more than one construct) and poor performance of the subscales.[72,73] 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.[72,73] 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.[72,73] Considering the evidence of multi-dimensionality, the validity of the single composite score of the NEI VFQ-25 may be questioned.

Limitations of internal consistency due to the presence of single-item domains were also noted in a validation study in a DME-specific population.[35] The near vision and distance vision subscales are three-item domains on the NEI VFQ-25; their internal reliability, as represented by Cronbach's alpha, was reported as 0.73 and 0.58, respectively. Convergent validity analysis to examine the relationship between NEI VFQ-25 scores and other disease-related variables provided mixed results, and the NEI VFQ-25 domains collectively showed low to moderate correlations with ETDRS visual acuity score for both the study and untreated eyes. The Pearson correlation with ETDRS total letters in the study eye was reported as 0.35 for the near vision subscale and 0.34 for the distance vision subscale. A slightly stronger correlation was observed between the NEI VFQ-25 and the EQ-5D visual analogue scale (VAS), and the EQ-5D VAS along with ETDRS was a significant predictor of near and distance vision subscale scores, suggesting that general health-related quality of life, more than strictly vision-related information, was captured by the NEI VFQ-25. However, in support of known group validity, patients who saw more ETDRS letters also scored higher on the NEI VFQ-25 near and distance subscales as well as on the NEI VFQ-25 composite score. Overall, the authors concluded that, despite its documented limitations and the need for an improved instrument, the NEI VFQ-25 demonstrated a degree of validity to measure health-related quality of life in patients with DME.[35]

EuroQol Five-Dimension Health-Related Quality of Life Questionnaire

The EQ-5D questionnaire is a generic, non–disease-specific measure of health status.[36] The tool is based on self-report of five domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. It is accompanied by a VAS to provide self-rating of overall health.[36] The EQ-5D instrument does not contain a vision-specific component.

In a systematic review of studies using EQ-5D in adults with type 2 diabetes, EQ-5D was found to adequately capture the burden of disease of type 2 diabetes.[74] However, some studies have suggested that it may not be able to capture the impact of multiple complications and lacks discriminative power in patients with mild disease. In subgroup analysis, patients with retinopathy (not DME-specific) had lower pooled mean index scores (0.57; 95% CI, 0.46 to 0.69) compared with diabetic patients with no complications (0.76; 95% CI, 0.68 to 0.83), but overlapping confidence intervals suggest that the EQ-5D questionnaire may not be able to discriminate between vision-related outcomes and general diabetic quality of life. No comparison was provided for non-diabetic patients.

A recent study examined the construct validity and responsiveness of the EQ-5D in patients with type 2 diabetes.[75] The EQ-5D significantly discriminated between patients with and without diabetes-related health problems with a high overall effect size (0.74); however, this relationship was not seen when the comparison was limited to eye-related health problems (P = 0.12; effect size = 0.16). In addition, the EQ-5D displayed a low level of responsiveness to change over time, indicating a ceiling effect at baseline and follow-up. The authors suggested that a new, five-level version of this instrument, the EQ-5D-5L, may increase the sensitivity to change over time, although this has not yet been evaluated.

Conclusion

The validity of various instruments to measure visual acuity (ETDRS charts), diabetic retinopathy (ETDRS DRSS), retinal thickening (OCT), and health-related quality of life (NEI VFQ-25 and EQ-5D) was reviewed. Visual acuity, measured using the ETDRS charts, is a suitable outcome measure for statistical analysis in clinical trials. Visual function depends on several components, including visual acuity, contrast sensitivity, near vision, colour vision, and sensitivity to glare.[55] The various components of visual function affect performance of different vision-related tasks by varying degrees and have important implications for quality of life. The ETDRS DRSS was developed to categorize severity of diabetic retinopathy based on several fundus photographic characteristics and has become the reference standard for diabetic retinopathy grading in clinical trials. There are 13 levels in the original ETDRS scale, and severity step or level increase is associated with an increased risk of retinopathy progression.[10,33] OCT is a non-invasive technique used to create cross-sectional maps of the retinal structures and to quantify retinal thickness in patients with macular edema.[23] Intra- and inter-device reproducibility of measurements depend on several factors, including the OCT device and software and the retinal pathology.[23] Retinal thickness, measured using OCT, may be a useful clinical tool to monitor macular edema and retinal changes in patients with DME but cannot be used as a substitute for visual acuity or other patient-reported outcomes. The NEI VFQ-25 was developed to measure vision-targeted quality of life. It has been reported to be a valid and reliable measure of quality of life that is responsive to changes in visual acuity.[46,67,71] However, limitations to the instrument have been identified, including multi-dimensionality and poor performance of the subscales.[35,72,73] EQ-5D is a general quality of life questionnaire without a vision-specific component.[36] It has been found to adequately capture the burden of disease in patients with type 2 diabetes, but may not be adequately sensitive to retinopathy-related changes.[74,75]

APPENDIX 6: SUMMARY OF MIXED TREATMENT COMPARISON

Objective

To summarize and appraise a manufacturer-sponsored indirect comparison[12] of the efficacy of aflibercept (AFL) in a fixed treatment pattern (five doses of 2 mg every four weeks, followed by 2 mg every eight weeks) with sham laser treatment, versus 0.5 mg ranibizumab (RAN) treatment as needed with sham laser treatment for diabetic macular edema (DME). A systematic literature review was conducted by the CADTH Common Drug Review to compare the results of the indirect comparison performed by the manufacturer with other indirect comparisons found in the literature.

Methods

TABLE 50: INCLUSION CRITERIA FOR TRIALS ELIGIBLE FOR THE MANUFACTURER-PERFORMED SYSTEMATIC REVIEW

Population	Patients with diabetic macular edema
Interventions	• Eylea (VEGF Trap Eye/AFL) • Anti-VEGF treatments (any, including ranibizumab [Lucentis], bevacizumab [Avastin], pegaptanib [Macugen]) • Intravitreal steroids (any, including triamcinolone, fluocinolone [Iluvien], dexamethasone [Ozurdex], and implants) • Laser treatments

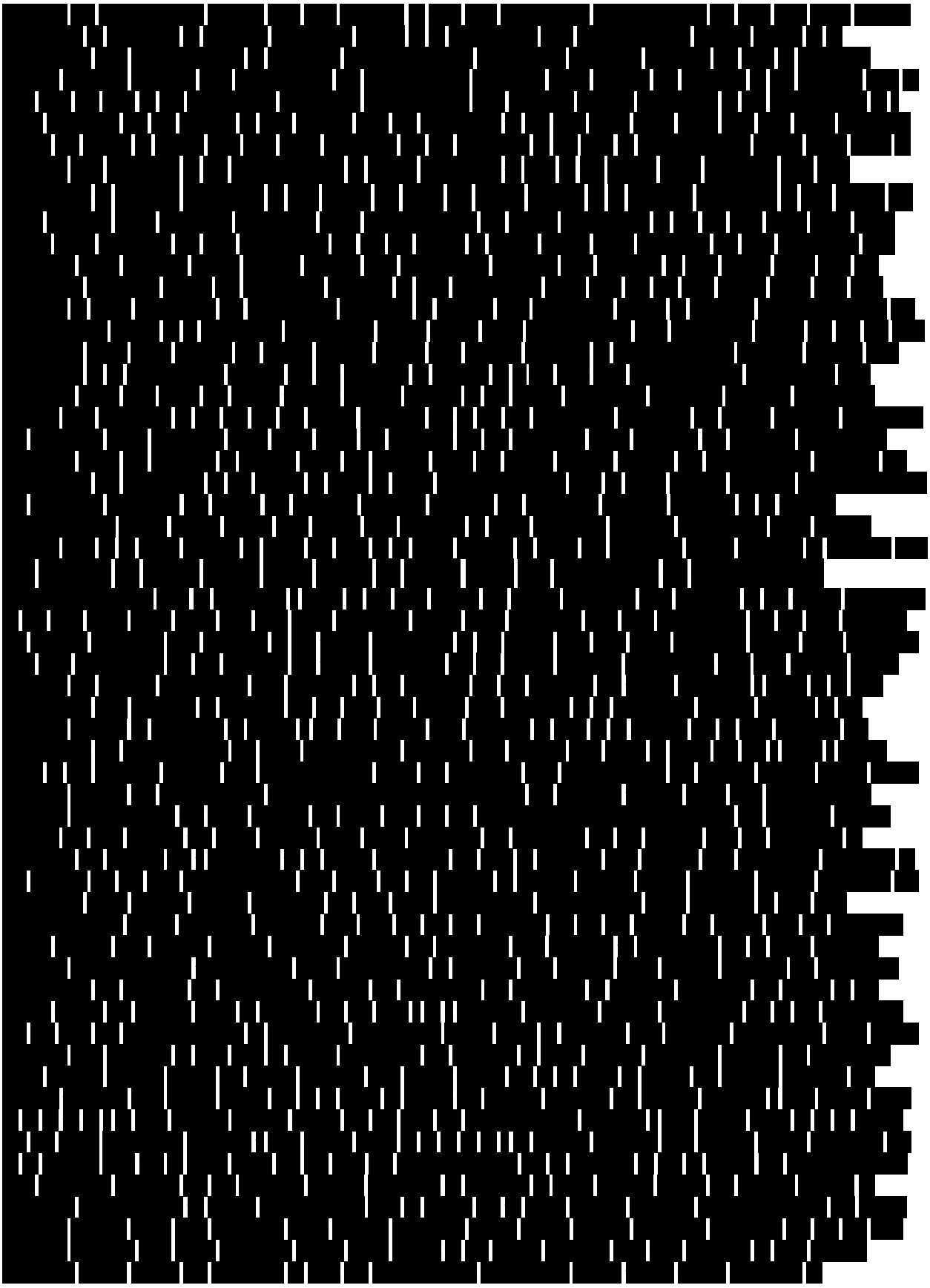
Outcomes	• BCVA (mean change from baseline, mean average change from baseline, as measured by ETDRS score or Snellen equivalent)
	• Visual acuity (% of patients who gain or lose, outcome vs. baseline):
	  • Loss of ≤ 15 letters in ETDRS score (maintained vision)
	  • Loss of ≥ 30 letters ETDRS score (severe vision loss)
	  • Loss of ≥ 15 letters ETDRS score (moderate vision loss)
	  • Gain of ≥ 15 letters

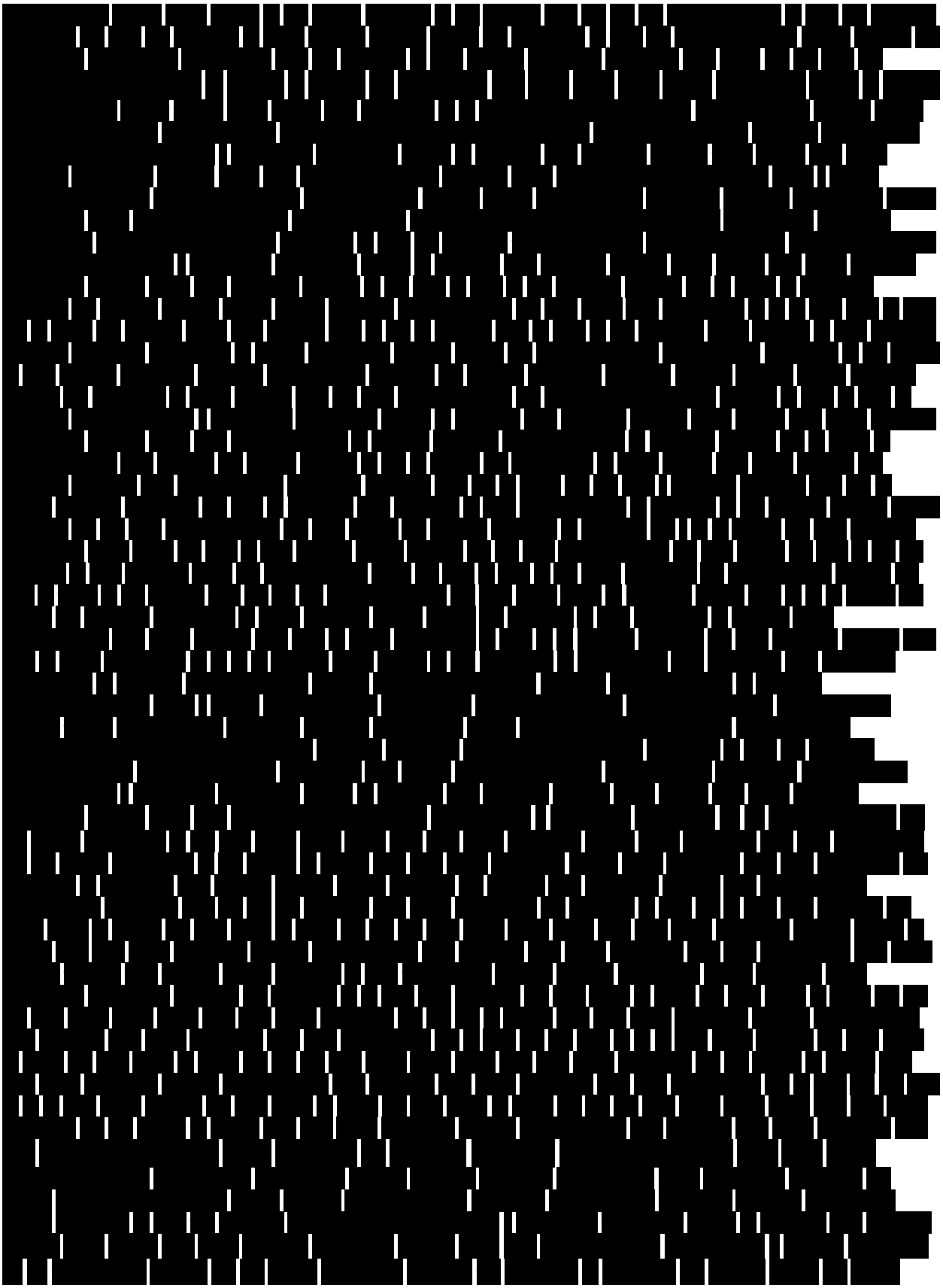
Comparators	• Placebo, best standard care, masked control, sham, eye drops • Any intervention (from those listed as interventions)
Study Design	Published and unpublished randomized controlled prospective clinical trials • Dose- or frequency-comparison trials • Ad hoc analyses of RCT data • Crossover RCTs

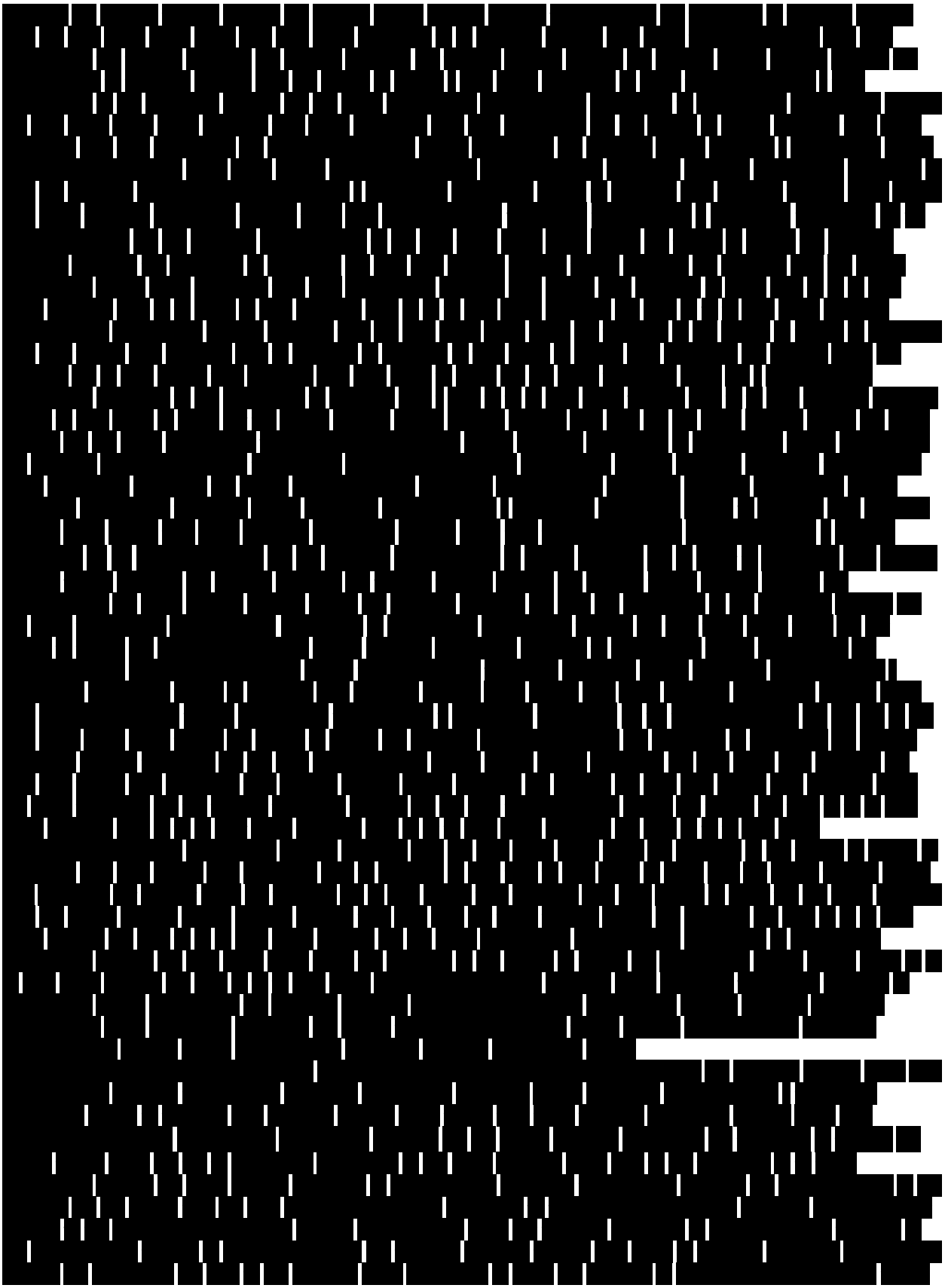
AFL = aflibercept; BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; RCT = randomized controlled trial, VEGF= vascular endothelial growth factor; vs. = versus.

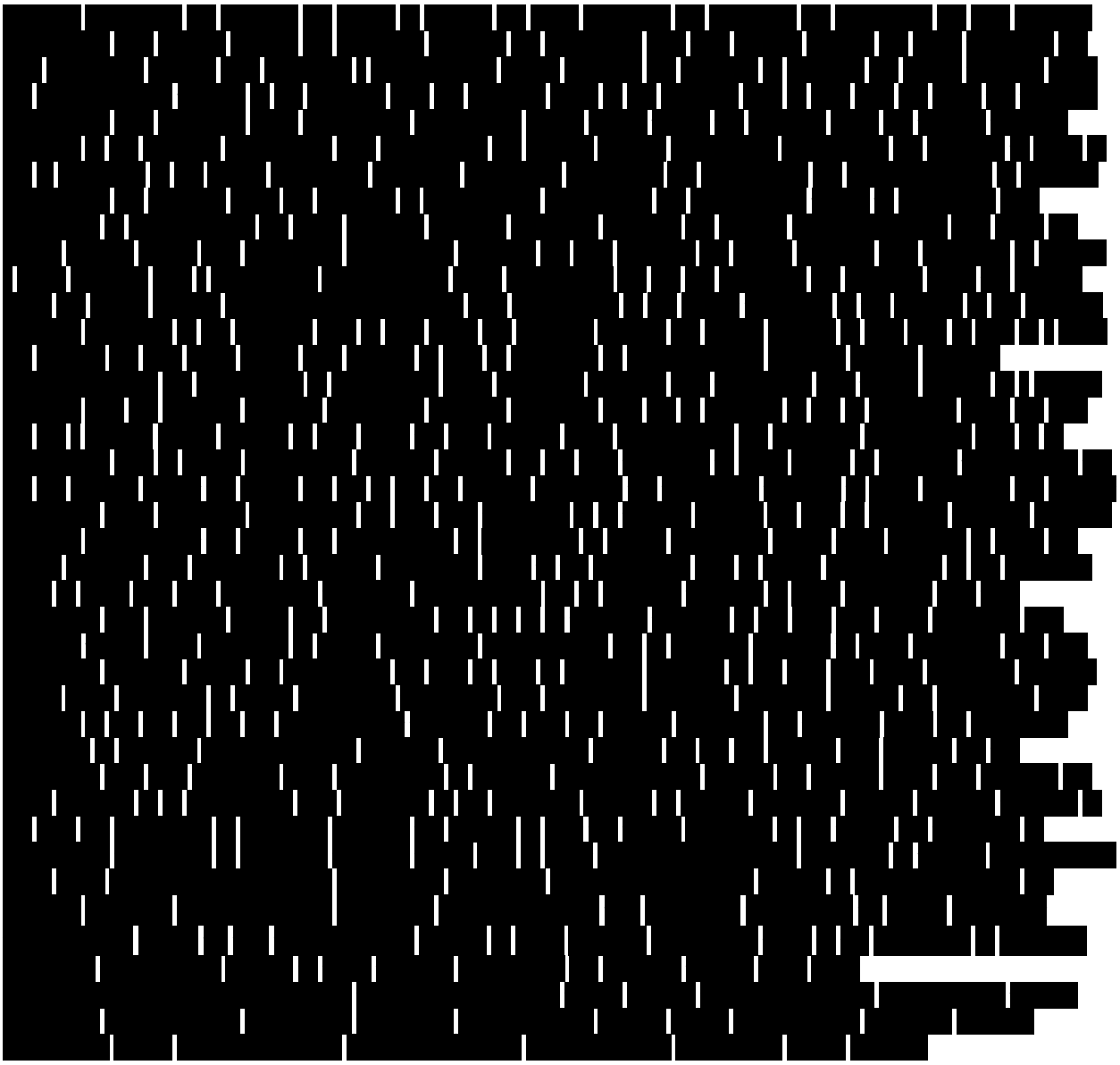
Manufacturer-Performed Systematic Review and Network Meta-analysis

[redacted]









Régnier et al. 2014[13]

A systematic review was carried out by the investigators to compare the efficacy of RAN, AFL, laser treatment, and sham in the first-line treatment of DME. Two independent reviewers assessed the data to establish whether relevant outcomes were sufficiently and appropriately reported. The following inclusion criteria were used: RCTs that reported the outcome of a gain in BCVA of at least 10 letters on the ETDRS scale for at least two comparators of interest (sham injections plus rescue laser treatment, RAN 0.5 mg, RAN 0.5 mg plus laser treatment, and AFL 2.0 mg bimonthly and prompt laser photocoagulation therapy). Studies with single treatment groups, and those not meeting inclusion criteria, were excluded. Included studies were required to have measured gain in BCVA of at least 10 letters on the ETDRS scale at 6 or 12 months. Study quality assessment was assessed using the Scottish Intercollegiate Guidelines Network (SIGN) tool. The investigators performed a Bayesian network meta-analysis with fixed and random treatment effects models. The analysis included baseline BCVA or CRT as covariates in the models. The relative treatment effect was the OR for the percentage of patients experiencing an improvement in BCVA of at least 10 letters on the ETDRS scale. A total of eight relevant RCTs (n = 1,978) were included in the analyses. Five studies (n = 1,320) investigated RAN, while three studies (n = 658) investigated AFL. The efficacy of RAN plus laser treatment was numerically, but not statistically, superior to AFL, with an OR (95% CrI) of 1.18 (0.45 to 3.66) at 12 months. Bayesian meta-analytical techniques were employed for the NMA using WinBUGS software. Results should be interpreted with caution, as there was heterogeneity in study designs; likely a result of the broad inclusion criteria for the systematic review. There is uncertainty regarding the methodological quality of the included studies, as only four of eight studies were deemed to have low risk of bias. It remains unclear whether there was heterogeneity between study populations, as the only reported baseline characteristics were BCVA and CRT. Safety outcomes were not assessed in the indirect comparison. In comparison with the manufacturer-submitted indirect comparison, only four studies (VIVID, VISTA, RESTORE, and LRT for DME) from the manufacturer's indirect comparison were included in the indirect comparison of Régnier et al. 2014.[13] The remaining studies included in Régnier et al. 2014[13] were not included from the manufacturer's indirect comparison, as the studies either had an irrelevant comparator, study design (measurement at 6 months only), or included the DA VINCI study (AFL monotherapy without active laser treatment). Given the differences in included studies, the comparison of findings from the NMAs performed by the manufacturer and by Régnier et al. 2014[13] is limited.

Ollendorf et al. 201314

A systematic review was carried out by the investigators to compare efficacy among anti-VEGF drugs, including RAN, AFL, pegaptanib (PEG), and bevacizumab (BEV), for the treatment of DME. It was not clear whether data were assessed by a single or multiple independent reviewers to establish whether relevant outcomes were sufficiently and appropriately reported. The following inclusion criteria were used: RCTs that reported all measures of change in visual acuity for all intravitreal anti-VEGF drugs (including RAN, PEG, BEV, and AFL) among patients with DME. The inclusion criteria for the systematic review was broad, as patients were not restricted by type of DME or by previous treatment (naive or experienced), treatments were not restricted by doses and regimens, and studies with treatments including concurrent therapy such as laser photocoagulation or intravitreal triamcinolone in addition to the anti-VEGF drugs were also included. No specific exclusion criteria were provided. Study quality assessment (rated as "good," "fair," or "poor" quality) was assessed using methods of the US Preventive Services Task Force. The investigators performed a series of Bucher pairwise indirect comparisons with random treatment effects models. The relative treatment effect was the MD in change in BCVA and the RR for the percentage of patients experiencing an improvement in BCVA of at least 10 letters on the ETDRS scale. A total of 15 relevant RCTs (n = 3,504) were included in the analyses. Six studies (n = 2,228) investigated RAN, six studies (n = 625) evaluated BEV, two studies (n = 432) assessed PEG, and one study

(n = 219) investigated AFL. Results revealed no statistically significant differences among BEV, RAN, and AFL for change in BCVA. There was a statistically significant difference favouring AFL compared with PEG with a MD of 0.92 (95%CI, 0.32 to 2.67). It remains unclear what time point was used, as the investigators provided a range between 6 and 24 months. Results should also be interpreted with caution, as the comparison with AFL is based solely on one study (DA VINCI study involving AFL monotherapy without active laser treatment). There were no statistically significant differences between anti-VEGF drugs in the likelihood of achieving a more than 10-letter gain. There was heterogeneity in study designs, likely a result of the broad inclusion criteria for the systematic review. There is uncertainty regarding the methodological quality of the included studies, as only two studies were deemed to be of "good" methodological quality. It remains unclear whether there was heterogeneity among study populations, as baseline characteristics were not provided and were not adjusted for in the analyses. Safety outcomes were pooled and assessed descriptively. Overall, the safety profiles of the anti-VEGFs were similar. In comparison with the manufacturer-submitted indirect comparison, only two studies (RESTORE and LRT for DME) from the manufacturer's indirect comparison were included in the indirect comparison of Ollendorf et al. 2013[14] (none of which assessed AFL). The remaining studies included in Ollendorf et al. 2013[14] were not included in the manufacturer's indirect comparison, as the studies either had irrelevant interventions and comparators, irrelevant study design (no measurements at 12 months), or included the DA VINCI study (AFL monotherapy without active laser treatment). Because no studies included combined treatment with AFL and laser photocoagulation, the results of this indirect comparison cannot be compared with the analysis performed by the manufacturer.

Summary

The results of the manufacturer's indirect comparison suggest that patients treated with ALF had statistically significantly greater gains in visual acuity than those treated with RAN. Two additional indirect comparisons identified in the literature suggest that AFL is at least as effective as RAN for improving visual acuity in patients with DME, and that AFL and RAN are not notably different in terms of potential harms.

APPENDIX 7: SUMMARY OF FINDINGS AT WEEK 100

Objective

To summarize the year 2 (week 100) findings of the VIVID[8] and VISTA[9] phase 3 studies of the efficacy and safety of intravitreal administration of aflibercept (AFL) in patients with diabetic macular edema (DME).

Findings

Study Characteristics

VIVID and VISTA were both phase 3, double-blind, randomized controlled trials (RCTs), planned for a total of three years to evaluate the clinical efficacy and safety of 2 mg intravitreal AFL injections compared with macular laser photocoagulation for the treatment of DME. Inclusion criteria for both RCTs included adults with type 1 or 2 diabetes mellitus, DME involving the central macula, associated vision loss, and a best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letters score of 24 to 73. An additional inclusion criterion for VIVID was retinal thickness of at least 300 μm in the study eye, as measured by optical coherence tomography.

Patients (N = 406 for VIVID and N = 466 for VISTA) were randomized 1:1:1 to receive laser treatment administered using the modified ETDRS protocols, AFL 2 mg every four weeks, or AFL 2 mg every four weeks for the first five doses, followed by 2 mg every eight weeks. Only the 2 mg every eight weeks group is discussed here. Patients also received sham laser treatment or sham injections, as appropriate, to maintain blinding. Patients were eligible for additional treatment based on BCVA criteria starting at week 24; those in the AFL groups would receive laser treatment, and those in the laser treatment group would receive AFL according to the 2 mg every eight weeks regimen.

The primary end point (change from baseline in BCVA) and secondary end points were reported at week 52 and were presented in the main body of this review. Key secondary end points included the proportions of patients who gained and lost at least 15 ETDRS letters from baseline, the proportions of patients who had at least a two-step improvement and worsening on ETDRS Diabetic Retinopathy Severity Scale (DRSS), the change from baseline in the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) total score, and the change from baseline in central retinal thickness. The three randomized groups and blinding were maintained as the VIVID and VISTA studies were continued through week 148, and the primary and secondary end points from the first year of the study were evaluated at week 100 as exploratory end points. Efficacy and safety results at week 100 are presented here.

Patient Disposition

A total of 406 patients were randomized for VIVID and 466 for VISTA. Of those patients randomized, 360 (88.7%) and 435 (93.3%) completed the first 52-week period of VIVID and VISTA, respectively. VIVID discontinuation rates were 14.8% and 11.1% in the laser treatment and AFL 2 mg every eight weeks groups, respectively, while VISTA discontinuation rates were 7.1% and 6.5% for the laser treatment and AFL 2 mg every eight weeks groups, respectively. Of those who completed the first 52-week study period, 330 VIVID and 385 VISTA patients continued to complete 100 weeks of treatment. Throughout the 100-week study period, VIVID discontinuation rates were 22.2% and 18.5% in the laser treatment and AFL 2 mg every eight weeks groups, respectively. VISTA discontinuation rates over 100 weeks were 14.7% and 17.5% in the laser treatment and AFL 2 mg every eight weeks groups, respectively. Deaths were reported more frequently in the AFL groups than in the laser treatment groups in both studies. Details on patient disposition and reasons for study discontinuation are shown in TABLE 51.

TABLE 51: PATIENT DISPOSITION (RANDOMIZED PATIENTS) THROUGH WEEK 100

	VIVID		VISTA	
	Laser N = 135	AFL 2Q8 N = 135	Laser N = 156	AFL 2Q8 N = 154
Patients randomized, n (%)	135 (100.0)	135 (100.0)	156 (100)	154 (100)
Patients treated, n (%)	133 (98.5)	135 (100.0)	154 (98.7)	152 (98.7)
Randomized but not treated, n (%)	2 (1.5)	0	2 (1.3)	2 (1.3)
Completed 52 weeks, n (%)	115 (85.2)	120 (88.9)	145 (92.9)	144 (93.5)
Completed 100 weeks, n (%)	105 (77.8)	110 (81.5)	133 (85.3)	127 (82.5)
Discontinued study before week 100, n (%)	30 (22.2)	25 (18.5)	23 (14.7)	27 (17.5)
Primary reason for premature discontinuation from the study before week 100, n (%)[a]				
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy (as assessed by the investigator)	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal of consent by patient	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

2Q8 = 2 mg every eight weeks; AFL = aflibercept. [redacted]

Source: VIVID Year 2 Clinical Study Report,[8] VISTA Year 2 Clinical Study Report.[9]

Baseline Characteristics

Baseline patient demographic and disease characteristics for the full analysis set were presented in the evaluation of the 52-week study period for both VIVID and VISTA. These characteristics were reported to be generally similar across treatment groups.

Efficacy

The full analysis set with the last observation carried forward was used for all efficacy analyses. At week 52, the 2 mg every eight weeks group showed a statistically superior improvement in BCVA from baseline when compared with the laser treatment group in both VIVID and VISTA; this effect was maintained through week 100 in both studies. Likewise, the statistically significant differences between laser treatment and aflibercept 2 mg every eight weeks at week 52 reported for the secondary end points (e.g., gain in ETDRS letters, at least two-step improvement on the ETDRS DRSS, and change in central retinal thickness) were also observed at week 100 in both studies. A summary of key efficacy outcomes for both VIVID and VISTA at week 100 is presented in Table 52.

TABLE 52: KEY EFFICACY OUTCOMES AT WEEK 100

	VIVID		VISTA	
	Laser N = 132	AFL 2Q8 N = 135	Laser N = 154	AFL 2Q8 N = 151
Change from baseline to week 100 in ETDRS letter score (FAS, LOCF): Mean (SD)				
Baseline	60.8 (10.6)	58.8 (11.2)	59.7 (10.9)	59.4 (10.9)
At 100 weeks	61.5 (15.1)	68.2 (13.7)	60.6 (17.7)	70.5 (13.4)
LSM change (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group difference in LSM change (AFL – laser) (97.5% CI for the difference)	[redacted]		[redacted]	
P value	< 0.0001		< 0.0001	
Proportion of patients who gained ≥ 15 letters in the ETDRS letter score at week 100 (FAS, LOCF)				
n/N (%)	16/132 (12.1)	42/135 (31.1)	20/154 (13.0)	50/151 (33.1)
Adjusted difference in proportion (AFL – laser), % (97.5% CI)	[redacted]		[redacted]	
P value	0.001[d]		<0.0001[e]	
NNT	[redacted]		[redacted]	
Proportion of patients with a ≥ 2-step improvement on the ETDRS DRSS from baseline to week 100 (FAS, LOCF)				
n/N (%)	7/85 (8.2)	28/86 (32.6)	24/154 (15.6)	56/151 (37.1)
Adjusted difference in proportion (AFL – laser), % (97.5% CI)	[redacted]		[redacted]	
P value	< 0.0001[d]		< 0.0001[e]	
NNT	[redacted]		[redacted]	
Proportion of patients who lost ≥ 15 letters in the ETDRS letter score at week 100 (FAS, LOCF)				
n/N (%)	17/132 (12.9)	2/135 (1.5)	15/154 (9.7)	1/151 (0.7)
Adjusted difference in proportion (AFL – laser), % (97.5% CI)	[redacted]		[redacted]	
P value	0.0002[d]		0.0004[e]	
Proportion of patients with ≥ 2-step worsening on the ETDRS DRSS from baseline to week 100 (FAS, LOCF)				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted difference in proportion (AFL – laser), % (97.5% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Change from baseline to week 100 in total NEI VFQ-25 score (FAS, LOCF)				
Baseline				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
At 100 weeks				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 100				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
LSM change (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Between-group difference in LSM change (AFL – laser) (97.5% CI for the difference)	[redacted]		[redacted]	

	VIVID		VISTA	
	Laser N = 132	AFL 2Q8 N = 135	Laser N = 154	AFL 2Q8 N = 151
P value	[redacted]		[redacted]	
Change from baseline to week 100 in CRT (µm) (FAS, LOCF)				
Baseline				
Mean (SD), µm	540.3 (152.4)	518.4 (147.4)	483.4 (152.9)	479.0 (153.9)
At 100 weeks				
Mean (SD), µm	454.7 (181.3)	322.6 (118.7)	399.5 (160.4)	287.9 (86.9)
Change from baseline at week 100				
Mean (SD), µm	–85.7 (145.8)	–195.8 (141.7)	–83.9 (179.3)	–191.1 (160.7)
LSM change (SE)	–70.9 (14.6)	–197.7 (10.1)	–85.8 (12.6)	–196.8 (7.3)
Between-group difference in LSM change (AFL – laser) (97.5% CI for the difference)	[redacted]		[redacted]	
P value	< 0.0001		< 0.0001	

2Q8 = 2 mg every eight weeks; AFL = aflibercept; CI = confidence interval; CRT = central retinal thickness; CVA = cardiovascular accident; DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; FAS = full analysis set; LOCF = last observation carried forward; LSM = least squares mean; MI = myocardial infarction; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; NNT = number needed to treat; SD = standard deviation; SE = standard error.
[a] VISTA: The CI with *P* value is based on treatment difference (AFL group versus laser treatment) of the LS mean change using analysis of covariance (ANCOVA) model with baseline measurement as covariate and the treatment and medical history of myocardial infarction (MI) or cardiovascular accident (CVA) as fixed factors.
[b] VIVID: CI calculated using Mantel–Haenszel weighted scheme adjusted by geographic region.
[c] VISTA: Difference with CI was calculated using Mantel–Haenszel weighting scheme adjusted by medical history of MI or CVA.
[d] VIVID: *P* value is calculated using two-sided Cochran–Mantel–Haenszel test adjusted by geographic region.
[e] VISTA: *P* value was calculated using two-sided Cochran–Mantel–Haenszel test adjusted by medical history of MI or CVA.
Source: VIVID Year 2 Clinical Study Report[8], VISTA Year 2 Clinical Study Report.[9]

Harms

The incidences of adverse events (AEs) up to week 100 are reported in Table 53. The proportion of patients experiencing at least one ocular treatment-emergent AE (TEAE) in the study eye was similar among VIVID treatment groups (95 patients [71.4%] in the laser treatment group and 98 patients [72.6%] in the AFL 2 mg every eight weeks group), although, in the VISTA study, this number was slightly higher in the laser treatment group than in the AFL 2 mg every eight weeks group (120 patients [77.9%] compared with 108 patients [71.1%]).

The types of TEAEs most frequently experienced within each VIVID treatment group varied notably. Within the laser treatment group, the most frequently reported TEAEs were visual acuity tests abnormal [redacted] visual acuity reduced [redacted], and retinal hemorrhage [redacted] these events, as well as the incidence of several other ocular TEAEs in this group, were suggested to be attributable to the progression of DME in patients receiving laser therapy. In the AFL 2 mg every eight weeks group, the most frequently reported TEAEs were conjunctival hemorrhage ([redacted] cataract [redacted] and visual acuity reduced [redacted] The higher incidence of conjunctival hemorrhage in the 2 mg every eight weeks group compared with the laser treatment group was consistent with results reported at 52 weeks, and the VIVID authors suggested that this was related to the injection procedure in the AFL groups. However, patients in the laser treatment group also received sham injections, suggesting that this higher event rate may not be solely related to procedure. Similarly, conjunctival hemorrhage was the most common ocular TEAE in the study eye for all treatment groups in the VISTA study, and was experienced by 53 patients ([redacted] in the laser treatment group and 48 patients ([redacted] in the 2 mg every eight

weeks group; this was also consistent with results reported at week 52. Other commonly reported ocular TEAEs in the study eye (at least 10% frequency in any group) for VISTA at 100 weeks were eye pain (laser treatment and 2 mg every eight weeks), vitreous floaters (laser treatment and 2 mg every eight weeks), vitreous detachment (laser treatment and AFL 2 mg every eight weeks), cataract (laser treatment and 2 mg every eight weeks), and retinal hemorrhage (laser treatment and 2 mg every eight weeks). The authors of VISTA concluded that the slight intergroup variations in certain AE category frequencies were not regarded as clinically meaningful and thus did not suggest a safety concern.

The proportions of patients with ocular and non-ocular serious TEAEs were slightly lower in the 2 mg every eight weeks group than in the laser treatment group in both studies, with the exception of non-ocular serious TEAEs in the VIVID study (laser treatment, 2 mg every eight weeks). The incidence of arterial thrombotic events was slightly higher in the 2 mg every eight weeks group than in the laser treatment group in both studies (laser treatment, 2 mg every eight weeks in VIVID; laser treatment, 2 mg every eight weeks in VISTA). No occurrences of endophthalmitis were reported at week 100 for the AFL 2 mg every eight weeks group in either study.

In the VIVID study, deaths were reported during the first year (in the 2 mg every eight weeks group and in the laser treatment group), and there were an additional deaths by the second year: in the AFL 2 mg every four weeks group (colon cancer, brain herniation and two myocardial infarctions [MIs]), and in the AFL 2 mg every eight weeks group (MI and ventricular arrhythmia). Of the AEs leading to death reported up to week 100 of the study, hypertensive heart disease event in the 2 mg every eight weeks group and MI event in the AFL 2 mg every four weeks group were considered by the investigators to be related to the study drug. In the VISTA study, deaths were reported during the first year (in the laser treatment group and two in the AFL 2 mg every four weeks group), and there were an additional deaths reported by week 100: in the laser treatment group (cardiac arrest and multi-organ failure), in the AFL 2 mg every four weeks group (pulseless electrical activity, pneumonia, cardiac arrest, chronic renal failure, cerebrovascular accident, and acute cardiac failure), and in the 2 mg every eight weeks group (cardiac arrests, cerebrovascular accident, and arteriosclerosis). death in the VISTA study (cardiac arrest in the AFL 2 mg every four weeks group) was attributed to the study drug.

TABLE 53: KEY HARMS AT WEEK 100

	VIVID		VISTA	
	Laser N = 133	AFL 2Q8 N = 135	Laser N = 154	AFL 2Q8 N = 152
AE				
Patients with ≥ 1 TEAE, n (%)	128 (96.2)	126 (93.3)	150 (97.4)	148 (97.4)
Patients with ≥ 1 ocular TEAE (study eye), n (%)	95 (71.4)	98 (72.6)	120 (77.9)	108 (71.1)
Patients with ≥ 1 ocular treatment-emergent surgeries (study eye), n (%)				
Patients with ≥ 1 non-ocular TEAE occurring in ≥ 5% of patients, n (%)				
Patients with ≥ 1 injection procedure–related ocular TEAEs occurring in ≥ 2% of patients in the study eye, n (%)				
Patients with ≥ 1 ocular laser procedure–related ocular TEAEs occurring in ≥ 2% of patients in the study eye, n (%)				

	VIVID		VISTA	
	Laser N = 133	AFL 2Q8 N = 135	Laser N = 154	AFL 2Q8 N = 152
SAE				
Patients with ≥ 1 serious ocular TEAE (study eye), n (%)	10 (7.5)	7 (5.2)	7 (4.5)	4 (2.6)
Patients with ≥ 1 serious non-ocular TEAE occurring in ≥ 1% of patients, n (%)	30 (22.6)	38 (28.1)	67 (43.5)	56 (36.8)
Patients with serious ocular injection procedure–related TEAE (study eye), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with serious ocular laser procedure–related TEAEs (study eye), n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most common ocular SAEs				
Vitreous hemorrhage, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Diabetic retinopathy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Cataract, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Cataract operation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Retinal neovascularization, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
WDAE				
WDAEs, n (%) (discontinuation from study)	[redacted]	[redacted]	[redacted]	[redacted]
Ocular (study eye) and non-ocular TEAEs leading to discontinuation of study drug, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most common reasons				
Diabetic retinopathy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Acute myocardial infarction, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Deaths[a]				
Number of deaths, n (%)	1	6 (4.4)	3 (1.9)	4 (2.6)
Notable Harms				
Endophthalmitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Retinal detachment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
ATE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

2Q8 = 2 mg every 8 weeks; AE = adverse event; AFL = aflibercept; ATE = arterial thrombotic event; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.
[a] Includes all deaths reported from the start of the study until week 100.
Source: VIVID Year 2 Clinical Study Report[8], VISTA Year 2 Clinical Study Report.[9]

Summary

In patients with DME, AFL 2 mg every eight weeks significantly improved BCVA and indicators of diabetic retinopathy compared with macular laser photocoagulation at 52 weeks, and these efficacy results were maintained through week 100 of both the VIVID and VISTA studies. At week 100, conjunctival hemorrhage was the most commonly reported ocular TEAE in the study eye in both studies, and the rate of this event in the VIVID study was higher in the AFL groups than in the laser treatment group. By the second year of the study, there were seven deaths in VIVID and seven deaths in VISTA in the laser treatment and AFL 2 mg every eight weeks groups. No new safety signals were reported. As a continuation of the VIVID and VISTA studies, any limitations would be similar to those reported in the review of the results at 52 weeks; no new concerns were identified.

APPENDIX 8: SUMMARY OF DIABETIC RETINOPATHY CLINICAL RESEARCH NETWORK STUDY

Objective

To summarize a recently published multi-centre, randomized clinical trial undertaken by the Diabetic Retinopathy Clinical Research Network (DRCRN) and sponsored by the US National Institutes of Health, designed to compare the safety and efficacy of aflibercept, bevacizumab,[c] and ranibizumab in the treatment of diabetic macular edema (DME).[11]

Findings

Study Characteristics

The study was conducted in 89 sites in the US. The main eligibility criteria included:

- adult patients (≥ 18 years of age with type 1 or 2 diabetes)
- at least one eye with a best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letters of 78 to 24
- centre-involved DME
- no anti–vascular endothelial growth factor (VEGF) treatment within the previous 12 months.

Four hundred and forty-two patients were randomized to receive aflibercept (2.0 mg) or ranibizumab (0.3 mg). Randomization was performed at the DRCR.net study website, in permuted blocks and with stratification by study site and visual acuity (VA) in the study eye. Patients, reading-centre graders, and the medical monitor who reviewed all adverse events were unaware of the treatment group assignments. VA and optical coherence tomography technicians were unaware of the treatment group assignments at the one-year visit. However, investigators and study coordinators were aware of the treatment group assignments.

The study drugs were injected every four weeks unless VA was 20/20 or better with a central subfield thickness (CST) below the eligibility threshold and there was no improvement or worsening in response to the past two injections. Improvement was defined as an increase at least in five ETDRS letters or a decrease in the CST at least 10%; worsening was considered to be a decrease at least five ETDRS letters or an increase in the CST at least 10%. From week 24, an injection was withheld if there was no improvement or worsening after two consecutive injections, but treatment was reinitiated if the VA letter score or the CRT worsened. Laser photocoagulation therapy was initiated at or after the 24-week visit for persistent DME.

The primary outcome was the mean change in visual acuity at one year with adjustment for baseline visual acuity. The primary analysis was performed using an analysis of covariance model. The overall type 1 error rate was controlled with the use of the Hochberg method. The sample size was estimated on the basis of an expected largest between-group difference in the VA letter score of 4.0, a standard deviation (SD) of 11.4 with adjustment for baseline VA, an overall two-sided type 1 error rate of 0.049 (after an adjustment of 0.001 for interim monitoring), a rate of loss to follow-up of 7.5%, and a power of approximately 90%. The intention-to-treat analysis (included all eyes that were randomly assigned to a study drug) was performed. The Markov chain Monte Carlo method of multiple imputations was used to impute missing data for one-year VA on the basis of prior data.

[c] Note that the results for bevacizumab are not presented, because this treatment is not approved in Canada for the indication under review and is therefore excluded from the current report.

Baseline Characteristics and Patient Disposition

Baseline characteristics were similar between the two groups (Table 54). Four hundred and forty-two patients (mean age, 60 years, SD 10 years) with DME were randomized to receive intravitreal aflibercept (N = 224) or ranibizumab (N = 218). Among these, 46% were women and 67% were Caucasian. A total of 89% of the patients had type 2 diabetes, and the median duration of diabetes was 15 to 16 years in the aflibercept and ranibizumab groups, respectively. The median ETDRS letter score at baseline was 68 and 69 in the aflibercept and ranibizumab groups, respectively. The mean CST was 387 µm and 390 µm, respectively.

TABLE 54: BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS

Characteristics	AFL (N = 224)	RAN (N = 218)
Sex: female, N (%)	110 (49)	94 (43)
Age (years), median (25th to 75th percentile)	61 (54 to 66)	59 (53 to 67)
Mean (SD)	60 (10)	60 (11)
Race/ethnicity, N (%)		
Caucasian	145 (65)	146 (67)
Black	32 (14)	36 (17)
Hispanic	37 (17)	30 (14)
Other	10 (4)	6 (2)
Diabetes type, N (%)		
Type 1	22 (10)	16 (7)
Type 2	196 (88)	196 (90)
Uncertain	6 (3)	6 (3)
Duration of diabetes (years), median (25th to 75th percentile)	15 (8 to 21)	16 (11 to 23)
Hemoglobin A1C (%), median (25th to 75th percentile)	7.6 (6.8 to 9.1)	7.8 (6.9 to 9.2)
Prior myocardial infarction, N (%)	13 (6)	16 (7)
Prior coronary artery disease (without myocardial infarction), N (%)	22 (10)	34 (16)
Prior stroke, N (%)	8 (4)	10 (5)
Prior transient ischemic attacks, N (%)	6 (3)	10 (5)
Prior renal disease, N (%)	20 (9)	26 (12)
Prior hypertension, N (%)	177 (79)	175 (80)
Smoke cigarettes on a daily basis, N (%)		
Never	143 (64)	145 (67)
Prior	66 (29)	53 (24)
Current	15 (7)	20 (9)
Body mass index (kg/m^2), median (25th to 75th percentile)	31.8 (27.4 to 37.3)	32.3 (28.2 to 37.2)
Ocular characteristics		
Visual acuity		
Letter score, median (75th to 25th percentile)	69 (74 to 59)	68 (73 to 58)
Snellen equivalent, median (75th to 25th percentile)	20/40 (20/32 to 20/63)	20/50 (20/40 to 20/80)
20/50 or worse (letter score < 69), N (%)	112 (50)	110 (50)
20/32 to 20/40 (letter score 78 to 69), N (%)	112 (50)	108 (50)
OCT CST (µm), median (25th to 75th percentile)	387 (310 to 483)	390 (310 to 493)
Diabetic retinopathy severity (ETDRS level)		
Absent or minimal NPDR (level 10 to 20)	7 (3)	5 (2)

Characteristics	AFL (N = 224)	RAN (N = 218)
Mild to moderately severe NPDR (level 35, 43, or 47)	150 (68)	145 (67)
Severe NPDR (level 53)	17 (8)	18 (8)
Prior PRP; without current PDR (level 60)	17 (8)	16 (7)
Mild to moderate PDR (level 61 and 65)	28 (13)	23 (11)
High-risk PDR (level 71 and 75)	2 (1)	9 (4)
Prior focal or grid laser for DME, N (%)	80 (36)	80 (37)
Prior anti-VEGF for DME, N (%)	24 (11)	29 (13)
Prior other treatment for DME, N (%)	14 (6)	11 (5)
Prior PRP, N (%)	32 (14)	35 (16)

A1C = glycated hemoglobin; AFL = aflibercept; CST =central subfield thickness; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; NPDR = non-proliferative diabetic retinopathy; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; PRP = panretinal photocoagulation; RAN = ranibizumab; SD = standard deviation; VEGF = vascular endothelial growth factor.
Source: Diabetic Retinopathy Clinical Research Network study (2015),[11] Table S6, p. 21 in supplementary appendix.

Results

Study Drug Exposure

The median number of intravitreal injections was 9 in the aflibercept group and 10 in the ranibizumab group (maximum number of possible injections = 13) (Table 55). Laser photocoagulation was performed at least once between 24 and 48 weeks in 37% of aflibercept-treated eyes and 46% of ranibizumab-treated eyes. In patients with baseline best-corrected visual acuity (BCVA) of 20/32 to 20/40, the median number of injections was 9 in each group, with 36% of aflibercept-treated eyes, and 43% of ranibizumab-treated eyes receiving photocoagulation therapy. For patients with BCVA 20/50 or worse, the median number of injections was 10 in the aflibercept group and 10 in the ranibizumab group, with 37% and 50% of treated eyes receiving photocoagulation therapy (Table 55).

TABLE 55: TREATMENT EXPOSURE THROUGH 52 WEEKS

	AFL (N = 208)	RAN (N = 206)
IVT		
Total number of injections prior to 1 year (maximum = 13), N (%)		
0 to 2	0	0
3	0	0
4	3 (1)	3 (1)
5	4 (2)	3 (1)
6	17 (8)	16 (8)
7	23 (11)	21 (10)
8	24 (12)	26 (13)
9	45 (22)	27 (13)
10	27 (13)	37 (18)
11	40 (19)	34 (17)
12	17 (8)	29 (14)
13	8 (4)	10 (5)
Mean (SD)	9.2 (2.0)	9.4 (2.1)
Median (25th to 75th percentile)	9 (8 to 11)	10 (8 to 11)

	AFL (N = 208)	RAN (N = 206)
All visits, prior to 1 year, N (%)	N = 2,693	N = 2,607
Visits with injections received	1,991 (74)	2,011 (77)
Visits with injections deferred due to		
success	63 (2)	63 (2)
stability	606 (23)	509 (20)
failure	2 (< 1)	0
other reasons	31 (1)	24 (1)
Follow-up visits requiring re-injection per protocol based on OCT and VA criteria, N	N = 1,780	N = 1,805
Injection not given, N (%)	15 (1)	16 (1)
Reasons		
AE precluding treatment	6	9
Patient refused	1	2
Treatment not needed per investigator	6	3
Other	2	2
Injection received when protocol indicated deferral	1	4
Laser photocoagulation		
Total number of focal/grid laser treatments prior to 24 weeks	0	0
Total number of laser treatments between 24 weeks and 1 year, N (%)		
0	132 (63)	111 (54)
1	57 (27)	77 (37)
2	19 (9)	18 (9)
Eyes for which focal/grid laser treatment was indicated per visual acuity or OCT protocol criteria at 1 or more visit but not performed prior to 1 year, N (%)	15 (7)	10 (5)
Other		
Eyes receiving 1 or more alternative treatments for DME other than laser treatment, N (%)	2 (1)	1 (< 1)
Number of those eyes meeting failure criteria	1	0

AE = adverse event; AFL = aflibercept; IVT = intravitreal; OCT = optical coherence tomography; RAN = ranibizumab; SD = standard deviation; VA = vision acuity.
Source: Diabetic Retinopathy Clinical Research Network study (2015), [11] Table S7, p. 25 in supplementary appendix.

Best-Corrected Visual Acuity

The mean improvement in the ETDRS letters at one year was significantly greater in patients treated with aflibercept compared with those treated with ranibizumab (13.3 versus 11.2 ETDRS letter improvement, respectively; the mean between-group difference in the change from baseline = 2.1, *P* = 0.03) (Table 56). However, this difference lacked clinical applicability, because the magnitude of improvement in VA varied according to initial baseline VA, such that the difference was driven by the eyes with worse VA at baseline. Specifically, in patients with a baseline ETDRS score of 78 to 69 letters, the mean improvement from baseline was 8.0 ± 7.6 letters with aflibercept and 8.3 ± 6.8 with ranibizumab (Table 57), whereas in patients with a baseline ETDRS score < 69 letters, the mean improvement was 18.9 ± 11.5 and 14.2 ± 10.6, respectively. The mean between-group difference of the change from baseline was 4.7, *P* = 0.003; Table 57). It was also reported that, overall, statistically more patients achieved at least 15 ETDRS letters in the aflibercept group than in ranibizumab groups (mean difference in proportion: 8%, *P* = 0.068) (Table 56). The between-group difference of at least 15 ETDRS

letters in favour of aflibercept was observed only in patients with baseline BCVA less than 69, not in patients with baseline BCVA greater than 69 (Table 57).

TABLE 56: VISUAL ACUITY OUTCOMES OVERALL

	Observed Data		Between-Group Difference In Mean Change or in Proportions (Adjusted 95% CI) Adjusted *P* Value
ETDRS Letters	AFL (N = 208)	RAN (N = 206)	AFL vs. RAN
Baseline			
Mean (SD)	65.0 (11.8)	65.1 (11.1)	
Snellen equivalent	20/50	20/50	
1 Year			
Mean (SD)	78.4 (10.1)	76.3 (11.1)	
Snellen equivalent	20/32	20/32	
Change from baseline (letter score)			
Mean (SD)	13.3 (11.1)	11.2 (9.4)	2.1 (0.1 to 4.2), *P* = 0.034
≥ 15 letter improvement n (%)	87 (42)	66 (32)	Difference in proportion: 8% (0% to 17%), *P* = 0.068
≥ 15 letters worsening n (%)	3 (1)	3 (1)	Difference in proportion: 0% (–2% to 2%), *P* = 0.98

AFL = aflibercept; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; N = total number of patients; RAN = ranibizumab; SD = standard deviation; vs. = versus.
Note: Treatment group comparisons are from ANCOVA models adjusted for continuous baseline visual acuity or from binomial regression models adjusted for categorical baseline visual acuity. Reported *P* values have been adjusted for multiple treatment group comparisons to account for an overall type 1 error rate of 0.049.
Source: Diabetic Retinopathy Clinical Research Network study (2015), [11] Table S4, p. 17 in supplementary appendix.

TABLE 57: VISUAL ACUITY OUTCOMES

ETDRS Letter and Snellen Equivalent	AFL	RAN	AFL vs. RAN
			Between-Group Difference in Changes From Baseline (95% CI), *P* Value
ETDRS letters < 69 (equivalent to 20/50 or worse) at baseline			
No. of eyes	102	101	
VA at baseline			
Mean letter score (SD)	56.2 (11.1)	56.5 (9.9)	
Approximate Snellen equivalent	20/80	20/80	
VA at 1 year			
Mean letter score (SD)	75.2 (10.9)	70.7 (12.0)	
Approximate Snellen equivalent	20/32	20/40	
Change from baseline in letter score			
Mean improvement (SD)	18.9 (11.5)	14.2 (10.6)	4.7 (1.4 to 8.0), *P* = 0.003
Improvement of ≥ 15, no. (%)	68 (67)	50 (50)	18 (4 to 32), *P* = 0.008
Worsening of ≥ 15, no. (%)	1 (1)	2 (2)	−1 (−4 to 2), *P* = 0.85
ETDRS letters 78 to 69 (equivalent to 20/32 to 20/40) at baseline			
No. of eyes	106	105	
Visual acuity at baseline			

ETDRS Letter and Snellen Equivalent	AFL	RAN	AFL vs. RAN
			Between-Group Difference in Changes From Baseline (95% CI), *P* Value
Mean letter score (SD)	73.5 (2.6)	73.4 (2.7)	
Approximate Snellen equivalent	20/32	20/40	
Visual acuity at 1 year			
Mean letter score (SD)	81.4 (8.3)	81.6 (6.8)	
Approximate Snellen equivalent	20/25	20/25	
Change from baseline in letter score			
Mean improvement (SD)	8.0 (7.6)	8.3 (6.8)	−0.4 (−2.3 to 1.5), *P* = 0.69
Improvement of ≥ 15, no. (%)	19 (18)	16 (15)	4 (−5 to 12), *P* = 0.73
Worsening of ≥ 15, no. (%)	2 (2)	1 (1)	1 (−2 to 4), *P* = 0.99

AFL = aflibercept; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; RAN = ranibizumab; SD = standard deviation; VA = visual acuity; vs. = versus.
Source: Diabetic Retinopathy Clinical Research study (2015), [11] Table 1, p. 5.

Central Subfield Thickness

On average, at the one-year visit, the CST decreased by 169 µm (SD 138 µm) with aflibercept and 147 µm (SD 134 µm) with ranibizumab; the thickness was less than 250 µm in 66% and 58% of eyes in aflibercept and ranibizumab, respectively. The relative treatment effect on CST varied according to the baseline VA (*P* < 0.001 for interaction), such that the effect of aflibercept on VA outcomes was greater when pre-treatment thickness was greater (data not shown).

Adverse Events

Overall, there were no notable differences among the study groups in the rates of serious adverse events (SAEs), hospitalization, death, and major cardiovascular events (Table 58). At one year, the rate of SAEs was similar in the two treatment groups, as was the rate of hospitalization (Table 58). The rate of death from any cause was 1% in the aflibercept group and 2% in the ranibizumab group; the corresponding rates of vascular events (as defined by the Antiplatelet Trialists' Collaboration[24]) were 3% and 5%, respectively.

Ocular adverse events are presented in Table 58. Injection-related infectious endophthalmitis occurred in one aflibercept-treated eye and one ranibizumab-treated eye (Table 58). Ocular inflammation other than endophthalmitis was reported in two study eyes in each study-drug group, as well as in three non-study eyes in the aflibercept group, and no non-study eyes in ranibizumab group.

TABLE 58: ADVERSE EVENTS THROUGH ONE YEAR

Event	AFL (N = 224)	RAN (N = 218)
Prespecified ocular adverse events		
Study eyes		
No. of injections before 1 year	1,991	2,011
Events occurring at least once through 1 year, no. of eyes (%)		
Endophthalmitis	0	0
Inflammation	2 (1)	2 (1)
Retinal detachment or tear	0	1 (< 0.5)

Event	AFL (N = 224)	RAN (N = 218)
Vitreous hemorrhage	4 (2)	7 (3)
Injection-related cataract	2 (1)	0
Elevation in intraocular pressure	32 (14)	23 (11)
Non-study eyes treated with a study drug		
No. of eyes treated before 1 year	129	121
No. of injections before 1 year	753	766
Events occurring at least once from the first injection through 1 year, no. of eyes (%)		
Endophthalmitis	1 (1)	(1)
Inflammation	3 (2)	0
Retinal detachment or tear	0	0
Vitreous hemorrhage	5 (4)	3 (2)
Injection-related cataract	1 (1)	0
Elevation in intraocular pressure	15 (12)	11 (9)
Systemic events		
Vascular events occurring at least once through 1 year, no. of participants (%)		
Non-fatal myocardial infarction	4 (2)	3 (1)
Non-fatal stroke	0	4 (2)
Death from potential vascular cause or unknown cause	2 (1)	3 (1)
Any event	6 (3)	10 (5)
Prespecified events occurring at least once through 1 year, no. of participants (%)		
Death from any cause	3 (1)	4 (2)
Hospitalization	49 (22)	49 (22)
Serious adverse event	59 (26)	55 (25)
Gastrointestinal event	44 (20)	38 (17)
Renal event	28 (12)	24 (11)
Hypertension	26 (12)	26 (12)

AFL = aflibercept; no. = number; RAN = ranibizumab.
Source: Diabetic Retinopathy Clinical Research Network study (2015), [11] Table 3, p. 9.

Discussion

The DRCRN study is the first major study in which aflibercept has been compared directly with ranibizumab in the treatment of DME. The primary outcome was the mean change in VA at 1 year. The findings demonstrated that aflibercept is associated with a statistically significantly greater improvement in VA after one year of treatment than ranibizumab. However, the difference between these treatments was approximately two ETDRS letters, which is not a clinically meaningful difference. In addition, the difference between treatments was driven by baseline VA, such that patients with worse baseline VA (less than 69 ETDRS letters) appeared to do relatively better with aflibercept, whereas both treatments were equally efficacious in patients with relative better baseline VA (69 to 78 ETDRS letters).

The trial is a multi-centre, randomized, active-controlled study. One potential limitation of the study was the lack of information regarding masking. The investigators and study coordinators were aware of the treatment group assignments, although it is unclear whether this would have introduced any systematic bias into the results. One more potential limitation of the study is that the dosing regimen for

aflibercept (one injection every four weeks) was not exactly the same as that recommended in Canada (every four weeks for five months, followed by every eight weeks). This would normally threaten the external validity of the study findings; however, the fact that the average number of injections received by patients in this study (median of nine injections per eye through one year) is very close to that observed in the trials in the main report (median of nine injections per eye through one year [Table 13 in Appendix 4]) suggests that this is a minor issue and that the results of this study are likely applicable in the Canadian context. Similarly, the dose of ranibizumab used in the study is the US-approved dose of 0.3 mg, while the rest of the world, including Canada, uses this drug at a dose of 0.5 mg. Whether the result of this study would be the same if a dose of 0.5 mg were used for ranibizumab is unknown, although it is possible that a higher dose would have reduced and potentially eliminated the difference in the effect size of aflibercept compared with ranibizumab observed in this study.

Summary

The results of the DRCRN study suggest that, in patients with DME, one year of treatment with aflibercept (2 mg per injection every four weeks) is associated with a statistically significantly greater improvement in VA compared with ranibizumab (0.3 mg per injection every four weeks). The difference in the improvement in VA between treatments (13 letters versus 11 ETDRS letters for aflibercept versus ranibizumab) was not clinically meaningful and was driven by baseline VA, such that patients with worse baseline VA (less than 69 ETDRS letters) tended to do relatively better with aflibercept. Safety data from this study indicated that aflibercept and ranibizumab have similar potential harms.

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