Common Drug Review
Clinical Review Report

July 2016

Drug	Aflibercept (Eylea)
Indication	Treatment of Visual Impairment due to Macular Edema Secondary to Branch Retinal Vein Occlusion (BRVO)
Reimbursement request	EYLEA (aflibercept) be reimbursed for the treatment of visual impairment due to macular edema secondary to branch retinal vein occlusion (BRVO), in a manner similar to Lucentis (ranibizumab).
Dosage form(s)	40 mg/mL Solution for Intravitreal Injection available as a 2 mg single-use vial
NOC date	December 10, 2015
Manufacturer	Bayer Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
AMD	age-related macular degeneration
BCVA	best corrected visual acuity
BRVO	branch retinal vein occlusion
CRT	central retinal thickness
CRVO	central retinal vein occlusion
CI	confidence interval
DME	diabetic macular edema
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	full analysis set
IDC	indirect comparison
FDA	Food and Drug Administration
IOP	intraocular pressure
IVT	intravitreal injection
MCID	minimal clinically important difference
NA	not available
NEI VFQ-25	National Eye Institute Visual Function Questionnaire-25
LOCF	last observation carried forward
OCT	optical coherence tomography
PP	per-protocol
RCT	randomized controlled trial
RVO	retinal vein occlusion
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
VEGF	vascular endothelial growth factor

EXECUTIVE SUMMARY

Introduction

Retinal vein occlusion (RVO) is an obstruction of the retinal venous system. It has an abrupt onset[1] and is the second most common cause of retinal vascular disease leading to vision loss, after diabetic retinopathy.[2] Branch retinal vein occlusion (BRVO) is the most common form of RVO;[3,4] if left untreated, it can have a significant detrimental impact on vision acuity and the quality of life of affected patients and caregivers.[5] In Canada, an annual incidence of BRVO has been reported at 0.056%, or 56 per 100,000 population.

Aflibercept (Eylea) is a recombinant fusion protein with anti–vascular endothelial growth factor (anti-VEGF) and anti-placental growth factor properties.[6] Aflibercept is approved by Health Canada for the treatment of neovascular (wet) age-related macular degeneration (wAMD), diabetic macular edema (DME), visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO), and visual impairment due to macular edema secondary to BRVO.[6]

CADTH has previously reviewed aflibercept in the context of a therapeutic review of anti-VEGF drugs for use in retinal conditions.[7] Based on this therapeutic review, the CADTH Canadian Drug Expert Committee (CDEC) issued several recommendations, including the recommendation that bevacizumab is the preferred initial anti-VEGF therapy for the treatment of patients with RVO, although ranibizumab or aflibercept can be used as alternative treatment options in patients who do not respond to bevacizumab[a] or if they experience thromboembolism following the initiation of bevacizumab treatment or are at a high risk of cardiovascular adverse events[b].[7]

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Results and Interpretation

Included Studies

Our systematic search of the literature identified one study for inclusion. The VIBRANT study was a phase 3, double-masked, randomized, active-controlled, parallel-group study. It randomized 183 BRVO patients to either 2 mg aflibercept once every four weeks, or laser treatment. The study's primary outcome was the proportion of patients who gained 15 or more letters in best corrected visual acuity

[a] For all retinal conditions considered, an inadequate response to treatment is defined as not achieving any improvement in BCVA at three months or not achieving an improvement in BCVA at six months of at least 15 Early Treatment Diabetic Retinopathy Study letters compared with the baseline (pre-treatment) BCVA.

[b] Individuals are considered to be at a high risk of cardiovascular adverse events if there is clinical evidence of atherosclerosis or they have had a previous myocardial infarction, have undergone coronary or arterial revascularization, or have a history of cerebrovascular disease (including transient ischemic attack) or peripheral arterial disease.

(BCVA) (Early Treatment Diabetic Retinopathy Study [ETDRS]) at 24 weeks, with a subsequent follow-up of 28 weeks, to a total study period of 52 weeks. Limitations of the study included lack of power to assess relevant safety outcomes, lack of generalizability to patients who received previous treatment for BRVO or have concomitant retinal disease, and lack of direct evidence to compare against other anti-VEGF therapies used currently for macular edema.

In addition to VIBRANT, two indirect comparison (IDC) studies provided relevant evidence: an IDC provided by the manufacturer[8] and a published study by Regnier et al. (2015).[9] Both IDCs compared aflibercept to different interventions for macular edema secondary to BRVO. The manufacturer's IDC was of better overall quality, with the main limitation being a weak connection between aflibercept and the rest of the network. Regnier et al. (2015) omitted reporting some information needed to judge the overall quality of the IDC and, in addition, the network was smaller than the manufacturer's IDC, as it excluded bevacizumab and triamcinolone — two commonly used treatments for the management of macular edema.

Efficacy

The VIBRANT study demonstrated that a statistically significantly greater proportion of patients treated with aflibercept gained ≥ 15 ETDRS letters from baseline to week 24 than those treated with laser (52.7% versus 26.7%, $P = 0.0003$). Patients treated with aflibercept also gained an average of 17.0 ETDRS letters (± 11.88) at week 24 from baseline compared with 6.9 letters for those treated with laser ($P < 0.0001$). In addition, the aflibercept group showed greater improvement in central retinal thickness (CRT) than the laser group (mean difference in CRT change between aflibercept and laser = –148.6 µm [95% confidence interval (CI), –179.8 to –117.4]). At week 24, no patient in the aflibercept arm lost ≥ 15 ETDRS letters from baseline, while four patients (4.4%) lost ≥ 15 ETDRS letters from baseline in the laser arm. Aflibercept was not associated with a statistically significant improvement in the health-related quality of life measure (National Eye Institute Visual Function Questionnaire-25) compared with the laser group. However, while both groups did perceive improvements in the quality of life from baseline, it is possible that because BRVO commonly affects one eye only, and the other eye is usually fully functional, patients may not perceive differences in small or gradual improvements in quality of life.

At week 52, patients in the aflibercept arm showed similar outcomes to week 24 across all measures. However, outcomes at 52 weeks are exploratory in nature and should only be used for hypothesis generation.

The available indirect evidence from two IDCs suggested that aflibercept is not associated with any significant differences in outcomes when compared with the other anti-VEGFs, bevacizumab and ranibizumab.

Harms

Harms reported for the VIBRANT study were largely related to the mode of administration (intravitreal injection) rather than aflibercept itself. Potentially serious concerns of anti-VEGF treatment include the theoretical increased risk of cardiovascular events, as well as the serious complication of endophthalmitis. Whereas aflibercept-treated patients did not appear to experience increased rates of adverse events for either of these categories of harm in the VIBRANT study, the study was underpowered to capture and detect any true differences in between the two interventions for such relatively infrequent harms. Indeed, there was no synthesis of safety evidence in either of the IDC reports reviewed herein. This reflects the large statistical power and long follow-up needed to detect

any meaningful differences in important safety outcomes. However, overall, the safety profile of aflibercept is consistent with what has been observed in previous indications.

Conclusions

The results of the VIBRANT study are consistent with the conclusion that aflibercept administered at a dose of 2 mg in 0.05 mL volume is superior to laser treatment in improving BCVA at 24 weeks in patients with macular edema secondary to BRVO. Evidence from two IDCs suggested that there are no statistically significant differences in the efficacy of aflibercept in patients with macular edema secondary to BRVO compared with bevacizumab or ranibizumab. The indirect evidence, however, is associated with a high degree of uncertainty, as only one study was available to connect aflibercept to the network of interventions. Direct evidence from the VIBRANT study suggested that most commonly reported adverse events are related to the procedure of intravitreal administration rather than to aflibercept itself, although this study was not powered to detect differences in potentially serious harms of interest — specifically endophthalmitis and cardiovascular adverse events.

TABLE 1: SUMMARY OF RESULTS

Outcome	VIBRANT	
	Aflibercept (N = 91)	Laser (N = 90)
Gain of ≥ 15 ETDRS letters at week 24		
N (%)	48 (52.7)	24 (26.7)
***P* value**	0.0003	
Mean difference from baseline in BCVA at week 24		
Baseline, mean (SD)	58.6 (11.4)	57.7 (11.3)
Mean change from baseline (SD)	17.0 (11.88)	6.9 (12.91)
Difference between aflibercept and laser treatment, mean difference (95% CI)	10.5 (7.1 to 14.0)	
***P* value**	< 0.0001	
Mean change in central retinal thickness at week 24		
Baseline, mean (SD)	558.9 (185.9)	553.5 (188.1)
Mean change from baseline (SD)	–280.5 (189.7)	–128.0 (195.02)
Difference between aflibercept and laser treatment, mean difference (95% CI)	–148.6 (–179.8 to –117.4)	
***P* value**	< 0.0001	
Mean change from baseline in NEI VFQ-25 total score at week 24		
Baseline, mean (SD)	77.8 (15.4)	75.6 (16.4)
Mean change from baseline (SD)	7.7 [redacted]	6.3 [redacted]
Difference between aflibercept and laser treatment, mean difference (95% CI)	2.6 (–0.3 to 5.5)	
***P* value**	0.0833	
Discontinued before 24 weeks		
N (%)	6 (6.6)	9 (9.7)
Discontinued before 52 weeks		
N (%)	18 (19.8)	15 (16.3)
Ocular SAEs throughout the study (52 weeks)		
N (%)	1 (1.1)	0 (0.0)
Systemic SAEs throughout the study (52 weeks)		
N (%)	6 (6.6)	7 (7.6)
WDAEs throughout the study (52 weeks)		
N (%)	4 (4.4)	0 (0.0)

BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.
Source: Campochiaro 2015,[10] Clark 2016,[11] and clinical study reports.[12,13]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Retinal vein occlusion (RVO) is an obstruction of the retinal venous system. It has an abrupt onset[1] and is the second most common cause of retinal vascular disease leading to vision loss, after diabetic retinopathy.[2] RVOs are classified into three types, depending on the location of the occlusion: central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), and hemispheric retinal vein occlusion.[3,4] BRVO is the most common form of RVO;[3,4] if left untreated, it can have a significant detrimental impact on vision acuity and the quality of life of affected patients and caregivers.[5]

In Canada, an annual incidence of BRVO has been reported at 0.056%, or 56 per 100,000 population.[14] A prevalence figure in Canada was not found. However, a pooled data analysis of population studies from the United States, Europe, Asia, and Australia showed a prevalence of BRVO of 4.42 per 1,000 (95% confidence interval [CI], 3.65 to 5.19), or 442 per 100,000 population.[15]

1.2 Standards of Therapy

Anti–vascular endothelial growth factor (VEGF) treatments are widely accepted as being more effective than laser treatment. Unlike laser treatment, which aims only to prevent further deterioration, anti-VEGF treatment aims to improve visual acuity and regain some of the lost vision. In the 1980s, the Branch Vein Occlusion Study[16] established laser treatment as the preferred method to manage BRVO. Recent Canadian consensus and guidelines,[5] however, have established anti-VEGF treatment as the preferred first-line treatment for BRVO, with laser treatment now viewed as second-line to these drugs. Table 2 provides a summary of key characteristics of the different anti-VEGFs and laser treatment. Anti-VEGF treatments that are used currently to treat BRVO include aflibercept and ranibizumab. Although bevacizumab has not been approved for use to treat retinal conditions,[17] this drug is used widely in clinical practice in Canada for intravitreal injection (IVT) and is currently reimbursed for the treatment of several retinal conditions by several of the public drug plans that participate in the CADTH Common Drug Review (CDR) process.[18-21]

CADTH has previously reviewed aflibercept in the context of a therapeutic review of anti-VEGF drugs for use in retinal conditions.[7] Based on this therapeutic review, the CADTH Canadian Drug Expert Committee (CDEC) issued several recommendations, including the recommendation that bevacizumab be the preferred initial anti-VEGF therapy for the treatment of patients with RVO, although ranibizumab or aflibercept can be used as alternative treatment options in patients who do not respond to bevacizumab[c] or if they experience thromboembolism following the initiation of bevacizumab treatment or are at a high risk of cardiovascular adverse events[d].[7]

1.3 Drug

Aflibercept is a recombinant fusion protein with anti-VEGF and anti-placental growth factor properties, formulated as an iso-osmotic solution for intravitreal administration.[6] Aflibercept is approved by Health

[c] For all retinal conditions considered, an inadequate response to treatment is defined as not achieving any improvement in BCVA at three months or not achieving an improvement in BCVA at six months of at least 15 ETDRS letters compared with the baseline (pre-treatment) BCVA.

[d] Individuals are considered to be at a high risk of cardiovascular adverse events if there is clinical evidence of atherosclerosis or they have had a previous myocardial infarction, have undergone coronary or arterial revascularization, or have a history of cerebrovascular disease (including transient ischemic attack) or peripheral arterial disease.

Canada for the treatment of neovascular (wet) age-related macular degeneration (wAMD), treatment of diabetic macular edema (DME), treatment of visual impairment due to macular edema secondary to CRVO, and treatment of visual impairment due to macular edema secondary to BRVO.

In Canada, the recommended dosing regimen for Eylea for the treatment of BRVO is 2 mg (0.05 mL or 50 microlitres) administered by IVT once every month (four weeks). The interval between two doses should not be shorter than one month. The treatment interval may be extended up to three months (12 weeks) based on visual and anatomic outcomes. Prescribers are advised to periodically assess (every one to two months) the need for continued therapy.[6]

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TABLE 2: KEY CHARACTERISTICS OF ANTI-VEGFS AND LASER TREATMENT FOR RETINAL CONDITIONS

	Aflibercept	Ranibizumab	Bevacizumab	Laser Photocoagulation
Mechanism of Action	Inhibition of VEGF			Cauterize abnormal blood vessels
Indication	BRVO, CRVO, AMD, DME	BRVO, CRVO, AMD, DME, and CNV due to PM	Not reviewed by Health Canada but used for BRVO, CRVO, AMD, DME, and CNV due to PM	Most retinal conditions, including BRVO, CRVO, DME, AMD, and CNV due to PM
Route of Administration	IVT			Intraocular laser
Recommended Dose	2 mg in solution monthly	0.5 mg in solution monthly	1.25 mg in solution monthly	Operator-dependent
Serious Side Effects / Safety Issues	Potential for thrombotic events			Loss of peripheral vision/ worsening visual acuity
Other	Endophthalmitis, increased IOP			Intraocular hemorrhage

AMD = age-related macular degeneration; BRVO = branch retinal vein occlusion; CNV = choroidal neovascularization; CRVO = central retinal vein occlusion; DME = diabetic macular edema; IOP = intraocular pressure; IVT = intravitreal injection; PM = pathologic myopia; VEGF = vascular endothelial growth factor.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of aflibercept 40 mg/mL for the treatment of visual impairment due to macular edema secondary to BRVO.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Other phase 3 studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with visual impairment due to macular edema secondary to BRVO
Intervention	Aflibercept (40 mg/mL solution for intravitreal injection), 2 mg IVT every one to three months as monotherapy
Comparators	• Ranibizumab • Bevacizumab • Dexamethasone intravitreal implant • Triamcinolone • Laser photocoagulation • Sham injections

Outcomes	**Key efficacy outcomes:**
	• Change from baseline in BCVA, specifically:
	  ○ Number of patients with a BCVA gain ≥ 15 letters
	  ○ Number of patients with a BCVA loss ≥ 15 letters
	  ○ Mean difference in BCVA change from baseline
	• Blindness (legal)
	Other efficacy outcomes:
	• QoL (assessed by validated measures)
	• Change from baseline in CRT
	Harms outcomes:
	• AE
	• SAE
	• WDAE
	• Mortality
	• Notable harms: Arterial thromboembolic events, cardiovascular events**,** increased intraocular pressure, bacterial endophthalmitis, and retinal detachment

Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CRT = central retinal thickness; CRVO = central retinal vein occlusion; DB = double-blind; IVT = intravitreal injection; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse events.

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 retinal vein occlusion.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See APPENDIX 2: LITERATURE SEARCH STRATEGY for the detailed search strategies.

The initial search was completed on January 14, 2016. Regular alerts were established to update the search until the meeting of CDEC on May 18, 2016. 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 (https://www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug regulatory approvals, advisories and warnings, drug class reviews, and databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

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 0.

3. RESULTS

3.1 Findings From the Literature

A total of one unique study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 4 and described in section 3.2. There were no excluded studies.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

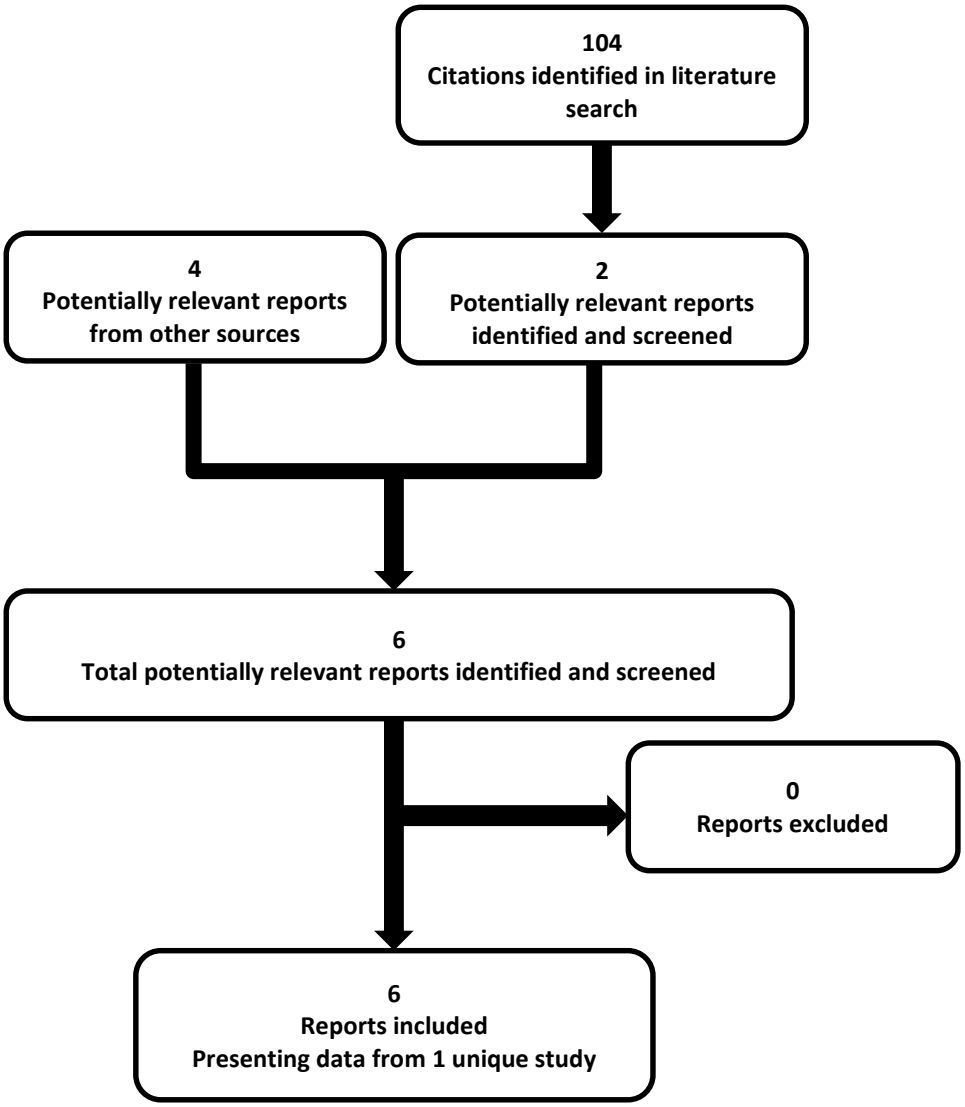


TABLE 4: DETAILS OF INCLUDED STUDIES

		VIBRANT
DESIGNS & POPULATIONS	**Study Design**	Double-blind, active-controlled, phase 3, randomized controlled trial
	Locations	Canada, United States, Japan
	Randomized (N)	183
	Inclusion Criteria	• Adults ≥ 18 years of age with foveal centre–involved macular edema following BRVO diagnosed within 12 months before the screening visit • BCVA of 24 to 73 (ETDRS)
	Exclusion Criteria	• A history of vitreoretinal surgery or anticipation of such within 12 months or any intraocular surgery within the last 3 months • Reductions in visual acuity from causes other than BRVO • Presence of diabetic macular edema or retinopathy • Ocular inflammation, or uncontrolled glaucoma • Periocular corticosteroid use within the last 3 months • Prior treatment with intraocular corticosteroids or antiangiogenic drugs, scatter or panretinal laser, macular grid laser, or sector laser
DRUGS	**Intervention**	• 2 mg IVT aflibercept every 4 weeks until 24 weeks, then every 8 weeks until 48 weeks • Sham laser treatment and sham injections were also administered to maintain blinding
	Comparator(s)	1 initial laser treatment with sham injections until week 24, then rescue treatment with aflibercept was available based on clinical criteria until week 48
DURATION	**Phase**	
	Run-in	3 weeks
	Double-blind	52 weeks
	Follow-up	NA
OUTCOMES	**Primary End Point**	Proportion of eyes that gained ≥ 15 ETDRS letters from baseline BCVA at week 24
	Other End Points	• Proportion of eyes with ≥ 15 letters ETDRS loss at week 24 • Mean change from baseline BCVA at week 24 • Mean change in CRT at week 24 • Mean change from baseline in the NEI VFQ-25 total score at week 24 • Proportion of eyes that gained ≥ 15 ETDRS letters from baseline BCVA at week 52 • Proportion of eyes with ≥ 15 letters ETDRS loss at week 52 • Mean change from baseline BCVA at week 52 • Mean change in CRT at week 52 • Mean change from baseline in the NEI VFQ-25 total score at week 52
NOTES	**Publications**	Campochiaro et al. (2015),[10] Clark et al. (2016)[11]

BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CRT = central retinal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; IVT = intravitreal injection; NA = not applicable; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25.
Note: Two additional reports were included (CADTH Common Drug Review submission,[6] and Health Canada reviewer's report[22]).
Source: Campochiaro 2015,[10] Clark 2016,[11] and clinical study reports.[12,13]

3.2 Included Studies

3.2.1 Description of Studies

The systematic search of the literature identified one study for inclusion. The VIBRANT study was a phase 3, double-masked, randomized, active-controlled, parallel-group study. Investigators randomized 183 BRVO patients to either aflibercept or laser treatment. The study's primary outcome was the proportion of patients who gained 15 or more letters in best corrected visual acuity (BCVA) (Early

Treatment Diabetic Retinopathy Study [ETDRS]) at 24 weeks, with a subsequent follow-up of 28 weeks, to a total study period of 52 weeks.

3.2.2 Populations

a) Inclusion and exclusion criteria

Eligible patients were adults with macular edema secondary to BRVO if the occlusion occurred within 12 months, and BCVA was between 73 and 24 letters ETDRS. BRVO was defined by the presence of retinal hemorrhages or other biomicroscopic evidence of RVO and a dilated venous system in less than two quadrants of the retina drained by the same vein. Only one eye from each patient was included in the study. In addition to excluding patients with possible conditions or interventions that would affect BCVA, it is worth noting that patients with any prior retinal treatment were excluded, effectively enrolling only treatment-naive patients.

b) Baseline characteristics

Overall, patients randomized into the two treatment arms had similar baseline characteristics in terms of BCVA, central retinal thickness (CRT), and vision-related quality of life. The two groups, however, showed some discrepancies in mean age (63.9 mean age in laser treatment versus 67.0 in the aflibercept arm), gender (40.0% women in laser treatment versus 51.6% in the aflibercept arm), race (68.9% white in laser treatment versus 76.9% in the aflibercept arm), and retinal perfusion status (68.9% perfused retina in laser treatment versus 60.4% in the aflibercept arm).

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Characteristics	VIBRANT	
	2 mg IVT aflibercept (n = 91)	**Laser treatment (n = 90)**
Age, mean (SD) years	67.0 (10.4)	63.9 (11.4)
Women, n (%)	47 (51.6)	36 (40.0)
Race: white, n (%)	70 (76.9)	62 (68.9)
Time since diagnosis of BRVO, mean, days (SD)	42.4 (43.4)	43.1 (38.8)
Perfused retina, n (%)	55 (60.4)	62 (68.9)
BCVA baseline (ETDRS) Mean (SD)	58.6 (11.4)	57.7 (11.3)
BCVA < 35 letters, n (%)	6 (6.6)	7 (7.8)
Mean central retinal thickness, µm (SD)	558.9 (185.9)	553.5 (188.1)
NEI VFQ-25 total score Mean (SD)	77.8 (15.4)	75.6 (16.4)

BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; ETDRS = Early Treatment Diabetic Retinopathy Study; IVT = intravitreal injection; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25; SD = standard deviation.
Source: Campochiaro 2015,[10] Clark 2016,[11] and clinical study reports.[12,13]

3.2.3 Interventions

Patients in the VIBRANT study were randomized to either the laser treatment arm or aflibercept arm. Patients randomized to the aflibercept arm received 2 mg aflibercept in 0.05 mL volume IVTs once every four weeks for the first 24 weeks, along with an initial sham laser treatment to maintain blinding. Patients in the laser treatment arm received a single laser treatment session on day 1, along with a sham injection; they continued to receive sham injections once every four weeks during the first 24 weeks.

Subsequent to the first 24 weeks and until week 48, patients in the aflibercept arm received 2 mg/0.05 mL aflibercept once every eight weeks, with sham injections replacing the removed aflibercept doses. Meanwhile, patients in the laser treatment arm were eligible to receive aflibercept 2mg/0.05 mL if they exhibited any of the following criteria:

- > 50 µm increase in CRT on optical coherence tomography (OCT) compared with the lowest previous measurement
- New or persistent cystic retinal changes or subretinal fluid on OCT, or persistent diffuse edema in the central subfield on OCT
- A loss of five or more letters from the best previous measurement due to BRVO, in conjunction with any increase in retinal thickness in the central subfield on OCT from the best previous measurement.

Rescue treatment — defined by the criteria mentioned earlier — for patients in the aflibercept arm was available from week 12 and onward in the form of laser treatment, while rescue treatment for patients in the laser arm from week 12 and until week 24 was also in the form of another laser treatment session. [redacted]

FIGURE 2: [redacted]

Source: CADTH Common Drug Review submission.[6]

3.2.4 Outcomes

a) Primary Outcome

The primary efficacy outcome was the proportion of patients who gained at least 15 BCVA ETDRS letters at week 24 compared with baseline. 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 visual acuity. The FDA recommends a mean change of 15 letters or more on an ETDRS chart, or a statistically significant difference in the proportion to patients with a ≥ 15 letter change in visual acuity, as clinically relevant outcome measures in trials of interventions for macular edema.[23,24]

b) Secondary Outcomes

The secondary efficacy outcomes include the following:

Proportion of eyes with ≥ 15 letters ETDRS gain at 52 weeks

The proportion of patients who gained at least 15 BCVA ETDRS letters at week 52 compared with baseline.

Visual acuity measured with ETDRS

Mean change from baseline in BCVA, as measured by ETDRS letter score at 24 weeks and 52 weeks, was a secondary outcome. To our knowledge, there has been no derivation of a minimal clinically important difference (MCID) for the ETDRS in BRVO. For macular edema in general, the 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 letter change in visual acuity, as clinically relevant outcomes in studies.[23,24] A cut-point for clinically meaningful change in patients with advanced eye disease should be higher than in healthy individuals, and has been suggested to range between 10 and 15 letters.[25]

Proportion of eyes with ≥ 15 letters ETDRS loss

Another secondary outcome was the proportion of eyes with with at least a 15 BCVA ETDRS letter loss at week 24 and week 52 compared with baseline.

Change in central retinal thickness

Change in CRT, as evaluated using OCT on the study eye at 24 weeks and 52 weeks, was a secondary outcome. OCT is a validated technique used to create cross-sectional maps of the retinal structures and to quantify retinal thickness in patients with macular edema.[26] CRT is defined as the thickness of the centre subfield (i.e., the area of the retina using a 1 mm diameter around the centre of the macula).

Quality of life / vision-related function

Quality of life and vision-related function were evaluated using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25). The NEI VFQ-25 is a validated scale that includes 25 items relevant to 11 vision-related constructs (general vision, ocular pain, near vision, distance vision, social functioning, mental health, role functioning, dependency, driving, peripheral vision, and colour vision), in addition to a single-item general health component. The possible range of the NEI VFQ-25 total score is between 0 (worst possible) and 100 (best possible). Our literature search did not identify a BRVO-specific MCID. However, in other macular edema conditions, an improvement from baseline between 3.3 and 6.1 points was considered to be an MCID.[27-30]

c) Safety Outcomes

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

3.2.5 Statistical Analysis

The study was designed for superiority testing, with a hypothesis that aflibercept is superior to laser treatment. The sample size was determined from the assumption that 55% of aflibercept-treated patients will gain 15 letters or more, and 30% of laser-treated patients will gain 15 letters or more. As such, a sample size of 81 patients would provide 90% power for rejecting the null hypothesis at a two-sided 5% significance level. The manufacturer assumed a 10% drop rate, leading to the decision to enrol 90 patients per arm.

The primary efficacy analysis was conducted for the proportion of patients who gained at least 15 BCVA ETDRS letters at week 24 compared with baseline. The two treatment groups were compared using the Cochran–Mantel–Haenszel test at a two-sided test level of 5%, with stratification adjustment for geographical region (Japan and North America) and baseline BCVA (letter score of 35 to 73, and 24 to 34). Missing data were imputed using last observation carried forward (LOCF).

Secondary outcomes at week 24 followed a hierarchical testing model: if the primary outcome was significant, then change from baseline in BCVA was tested; if this was statistically significant, then change from baseline in CRT was tested; if this was statistically significant, then change from baseline in the NEI VFQ-25 total score was tested. Between-group differences in secondary outcomes were analyzed using two-way analysis of covariance. Missing data were imputed using LOCF.

Outcomes measured at week 52 were not adjusted for multiplicity. They are considered exploratory in nature and any *P* value reported is nominal and cannot inform for purposes beyond hypothesis generation.

a) Analysis populations

Full analysis set

All randomized patients who received any investigational product had a baseline BCVA assessment, and at least one post-baseline BCVA assessment. All efficacy outcomes were analyzed using the full analysis set (FAS).

Per-protocol set

The per-protocol (PP) set consisted of all patients in the FAS except those patients excluded due to major protocol violations.

Safety analysis set

The safety analysis set (SAS) comprised all randomized patients who received any investigational product.

3.3 Patient Disposition

Of 281 screened patients, 183 were randomized: 92 into the laser treatment arm and 91 into the aflibercept arm. At week 24, nine patients discontinued from the laser treatment group (six withdrew consent, one protocol deviation, one death, and one lost to follow-up), as opposed to six discontinued patients in the aflibercept arm (three AEs and three withdrew consent). After week 24 and until [redacted]

[redacted]

Up to week 24, both arms had a dropout rate of less than 10%. It is notable that there were more dropouts in the laser treatment arm (9.7%) than the aflibercept arm (6.6%). At week 52, the dropout rate was > 10% in both arms, with a higher dropout rate in the aflibercept arm (19.8%) than in the laser treatment arm (16.3%).

TABLE 6: PATIENT DISPOSITION

	VIBRANT	
	2 mg IVT Aflibercept	**Laser Treatment**
Screened, N	281	
Randomized, N	91	92
Discontinued before 24 weeks, N (%)	6 (6.6%)	9 (9.7%)
Reasons for discontinuation up until week 24		
Adverse events	3	0
Withdrew consent	3	6
Lost to follow-up	0	1
Protocol violation	0	1
Death	0	1
Discontinued before 52 weeks, N (%)	18 (19.8%)	15 (16.3%)
[redacted]		
FAS, N at 24 weeks	91	90
FAS, N at 52 weeks	91	90
PP set, N at 24 weeks	90	85
PP set, N at 52 weeks	NA	NA
Safety, N at 24 weeks	91	92
Safety, N at 52 weeks	91	92

FAS = full analysis set; IVT = intravitreal injection; NA = not available; PP = per-protocol.
Source: Campochiaro 2015,[10] Clark 2016,[11] and clinical study reports.[12,13]

3.4 Exposure to Study Treatments

Up to week 24, patients in the aflibercept arm received 2 mg/0.05 mL IVT every four weeks, achieving a mean of 5.7 injections. Patients in the laser treatment arm were not exposed to aflibercept.

From week 24 to 52, patients in the aflibercept arm received a 2 mg/0.05 mL IVT once every eight weeks, achieving a mean number of 3.6 active injections for that period. Patients in the laser treatment arm were allowed to receive aflibercept during this period if they met specific criteria; a total of 295 aflibercept injections were given to patients in the laser treatment arm, achieving 4.4 mean numbers of injections. Table 7 provides more detail regarding exposure to aflibercept in the VIBRANT study.

TABLE 7: EXPOSURE TO STUDY TREATMENTS

		VIBRANT	
		2 mg IVT aflibercept	**Laser treatment**
Exposure to aflibercept	**Period**	Baseline to week 24	
	Total number of active injections, N	515	0
	Total number of sham injections, N	0	508
	Mean number of active injections (SD)	5.7 (0.75)	NA
	Period	Week 24 to week 52	
	Total number of active injections, N	305	295
	Total number of sham injections, N	231	235
	Mean number of active injections (SD)	3.6 (0.76)	4.4 (1.02)
	Period	Baseline to week 52 (total study period)	
	Total number of active injections, N	820	295
	Total number of sham injections, N	231	743
	Mean number of active injections (SD)	9.0 (1.76)	4.4 (1.02)
Exposure to laser treatment	**Period**	Baseline to week 24	
	Total number of active laser treatments, N	0	153
	Total number of sham laser treatments, N	115	0
	Mean number of active laser treatments (SD)	NA	1.7 (0.48)
	Period	Week 24 to week 52	
	Total number of active laser, N	9	1
	[redacted]	[redacted]	[redacted]
	Period	Baseline to week 52 (total study period)	
	[redacted]	[redacted]	[redacted]

IVT = intravitreal injection; SD = standard deviation.

3.5 Critical Appraisal

3.5.1 Internal Validity

The included study was a double-masked, multi-centre, randomized, active laser treatment, controlled, superiority study. The randomization process, including allocation concealment and masking method, was well described and performed. Stratification by geographic region and baseline BCVA was an additional strength of the study design. Because the study drug was administered at the study site, compliance could be monitored by a review of the patient's clinical and medical records, adding another strength to this trial.

The lack of adjustment for multiple outcomes at week 52 meant that all comparisons at that time point are nominal in nature and can only be used as exploratory outcomes for hypothesis generation.

Baseline characteristics were slightly different between the two arms in terms of mean age (63.9 mean age in laser treatment versus 67.0 in the aflibercept arm), gender (40.0% women in laser treatment versus 51.6% in aflibercept arm), race (68.9% white in laser treatment versus 76.9% in aflibercept arm), and retinal perfusion status (68.9% perfused retina in laser treatment versus 60.4% in aflibercept arm).

It is unclear whether these small differences can bias the results in any direction. However, the clinical expert involved suggested that these differences are unlikely to significantly influence the outcomes tested.

Dropout rates exhibited discrepancy between the two arms; up until week 24, the laser treatment arm had a higher dropout rate than the aflibercept arm (9.7% laser treatment versus 6.6% aflibercept). This could potentially have biased results at 24 weeks in favour of aflibercept, although the small difference between treatments is unlikely to have meaningfully biased the results. Subsequent to week 24, at week 52, the dropout rate in the aflibercept arm was higher than the dropout rate in the laser treatment arm (19.8% aflibercept versus 16.3% laser treatment); this discrepancy seemed to be mainly driven from the higher number of patients who withdrew their consent in the aflibercept arm (11 patients) compared with the laser arm (nine patients). The effect of this dropout rate, however, is not important, as the nature of outcomes at 52 weeks is exploratory in nature and holds no decision-making value.

3.5.2 External Validity

There were no direct comparisons between aflibercept and other active treatments listed in the systematic review protocol including ranibizumab and bevacizumab. The manufacturer provided an indirect treatment comparison (IDC) to compare aflibercept to other anti-VEGFs. In addition one IDC was also identified in the literature search. Both are summarized and appraised in **Error! Reference source not found.** and the results are considered in the Discussion and Conclusion.

Patients with eye disease or comorbidities other than macular edema secondary to BRVO, such as a history of any vitreous hemorrhage or vitrectomy, were excluded from the study. Therefore, the efficacy profiles as demonstrated in the studies may not reflect in such subset of patients with concomitant ocular conditions. Patients were excluded if they had had any prior or concomitant therapy, or surgery for macular edema. Therefore, the effect of the study drug versus laser treatment was demonstrated only in a treatment-naive population. The findings of this study cannot be applied to a treatment-experienced population, as none of the study participants had been treated previously with another anti-VEGF. The superiority of aflibercept compared with laser treatment was assessed for statistical significance at 24 weeks, and although patients were followed until 52 weeks, the efficacy results at 52 weeks were exploratory in nature and did not provide testing for statistical significance. As such, while results at 52 weeks can be viewed as supportive information, they cannot provide statistically significant evidence of the efficacy of aflibercept at 52 weeks. Therefore, the durability of treatment effect beyond the 24 weeks may be considered uncertain.

Although the manufacturer attempted to capture AEs and provide a safety profile for aflibercept, the study is simply not powered sufficiently, nor does it have sufficient follow-up, to capture infrequent but serious ocular and systemic AEs theoretically associated with IVT anti-VEGF use, such as endophthalmitis, myocardial infarction, and gastrointestinal bleeding.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (see section 2.2, Table 3).

3.6.1 Proportion of Eyes That Gained ≥ 15 ETDRS Letters From Baseline BCVA at Week 24

Baseline BCVA was similar between treatment groups in FAS. A BCVA improvement of 15 letters or more was observed in 52.7% of patients in the aflibercept arm as opposed to 26.7% in the laser treatment arm. The difference in the proportion of patients with at least a 15-letter vision gain between the aflibercept and laser groups was 26.1% (95% CI, 13.0% to 40.1%, $P = 0.0003$). Using the PP set showed similar results to the FAS. The sensitivity analysis also showed similar results using the observed case as the base analysis using LOCF.

3.6.2 Change From Baseline in BCVA Score at Week 24

While both treatment groups exhibited an increase in the BCVA score from baseline, the magnitude of the improvement is much higher in the aflibercept arm (mean change from baseline = 17.0, standard deviation [SD] = 11.88) as opposed to the laser treatment arm (mean change from baseline = 6.9, SD = 12.91). The difference between the aflibercept and laser treatment groups was 10.5 ETDRS letters (95% CI, 7.1 to 14.0, $P < 0.0001$).

3.6.3 Change From Baseline in Central Retinal Thickness at Week 24

Mean CRT was similar between treatment groups at baseline in the FAS. Both treatment groups exhibited a reduction in CRT. However, the magnitude of the reduction in the aflibercept group was statistically significantly more than the laser group (mean difference in CRT change between aflibercept and laser = –148.6 µm [95% CI, –179.8 to –117.4]).

3.6.4 Mean Change From Baseline in the NEI VFQ-25 Total Score at Week 24

The mean NEI VFQ-25 total score was comparable between treatment groups at baseline. At week 24, the mean change from baseline in the NEI VFQ-25 total score was slightly higher in the aflibercept group (mean change 7.7 points compared with the laser group [mean change of 6.3]). The difference between the two groups, however, was not statistically significant (mean difference = 2.6 [95% CI, –0.3 to 5.5, $P = 0.0833$]).

3.6.5 Other Efficacy Outcomes

The following efficacy outcomes are considered exploratory in nature and can be used only for hypothesis generation. *P* values in these outcomes are nominal; the results are covered in Table 8:

- Proportion of eyes that gained ≥ 15 ETDRS letters from baseline BCVA at week 52
- Proportion of eyes that lost ≥ 15 ETDRS letters from baseline BCVA at week 24
- Proportion of eyes that lost ≥ 15 ETDRS letters from baseline BCVA at week 52
- Mean change from baseline BCVA at week 52
- Mean change in CRT at week 52
- Mean change from baseline in the NEI VFQ-25 total score at week 52.

TABLE 8: KEY EFFICACY OUTCOMES

	VIBRANT	
	2 mg IVT aflibercept, n = 91	Laser treatment (with rescue aflibercept treatment from week 24 to week 52), n = 90
Gain of ≥ 15 ETDRS letters at week 24		
N (%)	48 (52.7)	24 (26.7)
P value	0.0003	
Gain of ≥ 15 ETDRS letters at week 52		
N (%)	52 (57.1)	37 (41.1)
P value	nominal	
Loss of ≥ 15 ETDRS letters at week 24		
N (%)	0 (0)	4 (4.4)
P value	nominal	
Loss of ≥ 15 ETDRS letters at week 52		
N (%)	2 (2.2)	1 (1.1)
P value	nominal	
Mean difference from baseline in BCVA at week 24		
Baseline, mean (SD)	58.6 (11.4)	57.7 (11.3)
Mean change from baseline (SD)	17.0 (11.88)	6.9 (12.91)
Difference between aflibercept and laser treatment, mean difference (95% CI)	10.5 (7.1 to 14.0)	
P value	< 0.0001	
Mean difference from baseline in BCVA at week 52		
Baseline, mean (SD)	58.6 (11.4)	57.7 (11.3)
Mean change from baseline (SD)	17.1 (NA)	12.2 (NA)
Difference between aflibercept and laser treatment, mean difference (95% CI)	5.2 (1.7 to 8.7)	
P value	nominal	
Mean change in CRT at week 24		
Baseline, mean (SD)	558.9 (185.9)	553.5 (188.1)
Mean change from baseline (SD)	–280.5 (189.7)	–128.0 (195.02)
Difference between aflibercept and laser treatment, mean difference (95% CI)	–148.6 (–179.8 to –117.4)	
P value	< 0.0001	
Mean change in CRT at week 52		
Baseline, mean (SD)	558.9 (185.9)	553.5 (188.1)
Mean change from baseline (SD)	–283.9 (NA)	–249.3 (NA)
Difference between aflibercept and laser treatment, mean difference (95% CI)	–29.5 (–54.7 to –4.4)	
P value	nominal	

	VIBRANT	
	2 mg IVT aflibercept, n = 91	Laser treatment (with rescue aflibercept treatment from week 24 to week 52), n = 90
Mean change from baseline in NEI VFQ-25 total score at week 24		
Baseline, mean (SD)	77.8 (15.4)	75.6 (16.4)
Mean change from baseline (SD)	7.7 (11.1)	6.3 (12.3)
Difference between aflibercept and laser treatment, mean difference (95% CI)	2.6 (–0.3 to 5.5)	
P value	0.0833	
Mean change from baseline in NEI VFQ-25 total score at week 52		
Baseline, mean (SD)	77.8 (15.4)	75.6 (16.4)
Mean change from baseline (SD)	9.4 (NA)	8.3 (NA)
Difference between aflibercept and laser treatment, mean difference (95% CI)	2.5 (–0.5 to 5.4)	
P value	nominal	

BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CRT = central retinal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; CI = confidence interval; IVT = intravitreal injection; NA = not available; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25; SD = standard deviation.
Source: Campochiaro 2015,[10] Clark 2016,[11] and clinical study reports.[12,13]

3.7 Harms

Only those harms identified in the review protocol are reported below.

3.7.1 Adverse Events

A large proportion of AEs were likely associated with the nature of intravitreal and ocular administration of treatment. In the aflibercept group, conjunctival hemorrhage, increased intraocular pressure, eye pain, and eye irritation were most common. In the laser group, conjunctival hemorrhage and eye pain were most common. Other reported non-ocular AEs were unlikely to be related to treatment.

3.7.2 Serious Adverse Events

Only one patient was reported to have an ocular SAE. The patient developed traumatic cataract in the aflibercept group. This SAE is related to the procedure of introducing IVT, and not necessarily related to the aflibercept drug per se. Non-ocular SAEs included anemia (2.2% in aflibercept group), acute renal failure (1.1% in each group), myocardial infarction (1.1% in the laser group), pneumonia (1.1% in the laser group and 2.2% in the aflibercept group), and coronary artery disease (1.1% in the aflibercept group).

3.7.3 Withdrawals Due to Adverse Events

Four patients withdrew due to AEs; all were in the aflibercept group. One patient withdrew due to increased intraocular pressure; one patient withdrew due to traumatic cataract; one patient due to metastatic breast cancer; and the last patient withdrew due to small bowel obstruction and central pelvis abscess.

3.7.4 Mortality

There was a single death in the study: one patient in the laser group died due to pneumonia.

3.7.5 Notable Harms

A concern with intravitreal aflibercept is intraocular inflammation (endophthalmitis) and cardiovascular events. There were no recorded instances of endophthalmitis. One event of non-fatal myocardial infarction (1.1%) occurred in a patient in the laser group who had received aflibercept. One event of non-fatal stroke (1.1%) occurred in a patient in the laser group before receiving any aflibercept.

TABLE 9: HARMS (FULL STUDY PERIOD, 52 WEEKS)

	VIBRANT	
	2 mg IVT aflibercept	Laser treatment (with rescue aflibercept treatment from week 24 to week 52)
AEs		
Patients with > 0 ocular AEs, N (%)	52 (57.1%)	48 (52.2%)
Patients with > 0 ocular AEs, N (%)	52 (57.1%)	48 (52.2%)
Most common ocular AEs[a]		
Conjunctival hemorrhage	22 (24.2%)	14 (15.2%)
Eye pain	5 (5.5%)	7 (7.6%)
Eye irritation	7 (7.7%)	1 (1.1%)
Increased intraocular pressure	4 (4.4%)	1 (1.1%)
Patients with > 0 non-ocular AEs, N (%)	61 (67.0%)	63 (68.5%)
Most common non-ocular AEs[a]		
Nasopharyngitis	8 (8.8%)	8 (8.7%)
Urinary tract infection	3 (3.3%)	7 (7.6%)
Hypertension	10 (11.0%)	15 (16.3%)
Bronchitis	6 (6.6%)	2 (2.2%)
SAEs		
Patients with > 0 ocular SAEs, N (%)	1 (1.1%)	0 (0%)
Most common SAEs		
Traumatic cataract	1 (1.1%)	0 (0%)
Patients with > 0 non-ocular SAEs, N (%)	13 (14.3%)	10 (10.9%)
Most common SAEs		
Anemia	2 (2.2%)	0 (0%)
Acute renal failure	1 (1.1%)	1 (1.1%)
Myocardial infarction	0 (0.0%)	1 (1.1%)
Pneumonia	2 (2.2%)	1 (1.1%)
Coronary artery disease	1 (1.1%)	0 (0.0%)
Hypertension	1 (1.1%)	1 (1.1%)
Dehydration	0 (0.0%)	2 (2.2%)
WDAEs		
WDAEs, N (%)	4 (4.4%)	0 (0.0%)
Most common reasons		
Metastatic breast cancer	1 (1.1%)	0 (0.0%)
Traumatic cataract	1 (1.1%)	0 (0.0%)
Increased intraocular pressure	1 (1.1%)	0 (0.0%)
Small bowel obstruction and central pelvis abscess	1 (1.1%)	0 (0.0%)

	VIBRANT	
	2 mg IVT aflibercept	**Laser treatment (with rescue aflibercept treatment from week 24 to week 52)**
Deaths		
Number of deaths, N (%)	0 (0.0%)	1 (1.1%)
Most common reasons		
Pneumonia	0 (0.0%)	1 (1.1%)

AE = adverse event; IVT = intravitreal injection; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: Campochiaro 2015,[10] Clark 2016,[11] and clinical study reports.[12,13]

4. DISCUSSION

4.1 Summary of Available Evidence

One double-blinded, multi-centre, randomized controlled trial (VIBRANT) was included in this review, in which aflibercept treatment was compared with laser treatment for the management of macular edema secondary to BRVO over 24 weeks.[6,10-13] We also considered evidence from two IDCs of aflibercept to other BRVO treatment: one was submitted by the manufacturer (manufacturer's IDC),[8] and one was a published IDC study comparing several therapies for BRVO (Regnier et al. [2015]).[9]

4.2 Interpretation of Results

4.2.1 Efficacy

The VIBRANT study aimed to assess the efficacy and safety of intravitreal administration of aflibercept compared with laser treatment in patients with macular edema secondary to BRVO. A total of 183 patients were randomized across 58 sites in North America and Japan, including four sites in Canada. According to the clinical expert involved in this review, the inclusion and exclusion criteria in the VIBRANT trial were reflective of the majority of patients seen in practice in Canada. Randomization and allocation concealment in the VIBRANT trial were well described and executed. Although slight differences in some of baseline characteristics were observed (age, gender, and race, and retinal perfusion status), the clinical expert believed that they are not major factors that would exert significant influence on the outcome, especially when considering that other baseline characteristics that are more reflective of the clinical disease severity were equally distributed (ETDRS, CRT, and NEI VFQ-25). The VIBRANT study assessed patients for primary efficacy at 24 weeks. Subsequent to 24 weeks, patients in the laser group were allowed to receive aflibercept if they met specific criteria. The final follow-up was reported at week 52.

The VIBRANT study demonstrated that a statistically significantly greater proportion of patients treated with aflibercept gained ≥ 15 ETDRS letters from baseline to week 24 than those treated with laser (52.7% versus 26.7%, $P = 0.0003$). Patients treated with aflibercept also gained an average of 17.0 ETDRS letters (± 11.9) at week 24 from baseline compared with 6.9 letters for those treated with laser ($P < 0.0001$). In addition, patients in the aflibercept group showed better improvement in CRT than those in the laser group (mean difference in CRT change between aflibercept and laser = –148.6 µm [95% CI, –179.8 to –117.4]). The improvement in visual acuity with aflibercept-treated patients seemed to be maintained until week 52; the certainty of this observation, however, cannot be established due to the lack of testing for statistical significance at week 52.

Whereas aflibercept was clearly superior to laser treatment in improving visual acuity and CRT, there was no statistically significant difference in the effects of these two treatments on quality of life (measured using the NEI VFQ-25). While patients in both groups did report improvements in quality of life from baseline, it is possible that the absence of significant differences between treatments for this outcome is due to the fact that BRVO commonly affects one eye only, while the other eye usually remains fully functional; therefore, the potential effects of changes in visual acuity on quality of life are likely blunted by the compensatory effect of the preservation of vision within one eye.

While the VIBRANT study provided evidence that aflibercept is superior to laser treatment for improving visual acuity in patients with BRVO, there is no direct evidence available to compare aflibercept with other anti-VEGF treatments that are commonly used in practice to manage macular edema — namely ranibizumab and bevacizumab. Therefore, evidence from IDCs of aflibercept to other anti-VEGFs was considered, including one IDC provided by the manufacturer that was based on a Bayesian network meta-analysis, and another IDC published by Regnier et al. (2015).[8,31]

The manufacturer's IDC was conducted and reported with methodological rigour. The only major limitation of the study was the weak connection between aflibercept and the rest of the network; this connection was informed by only one study, the VIBRANT study, which compared aflibercept to laser treatment. As such, the VIBRANT study was the only available connection to measure all indirect evidence between aflibercept and the rest of the interventions in the network. This limitation was reflected by the wide credible intervals observed frequently throughout many comparisons, specifically when these comparisons are made under the random-effects model. The same limitation was noted for the IDC published by Regnier et al. (2015), in which even fewer studies were included due to the exclusion from the network of two commonly used therapies, bevacizumab and triamcinolone. Despite these limitations, and across various outcomes, both IDCs were consistent in reporting that the effect of aflibercept was not meaningfully different from ranibizumab, or from bevacizumab as informed by the manufacturer's IDC, keeping in mind that these results are associated with a high degree of uncertainty due to the aforementioned limitation. Comparison of aflibercept with laser treatment in these IDCs revealed that aflibercept was associated with statistically significantly better results for all of the outcomes analyzed by the manufacturer analyses and for one of the two reported outcomes reported in Regnier et al. (2015).

4.2.2 Harms

The clinical expert involved in this review noted that most of the harms reported for the VIBRANT study appeared to be related to the mode of administration (IVT) rather than to the introduction of the aflibercept molecule itself. Traumatic cataract, conjunctival hemorrhage, eye pain, and eye irritation can all be directly associated with the manipulation and penetration of the eye while performing IVT. In contrast, there is no physiological or pharmacological mechanism to explain how aflibercept can cause nasopharyngitis, urinary tract infection, bronchitis, pneumonia, or dehydration.

A concern with all anti-VEGF treatments is a theoretical increased risk of cardiovascular events due to systemic inhibition of angiogenesis as a result of the potential diffusion of anti-VEGF molecules through the retina into the systemic circulation, as well as the serious complication of endophthalmitis. The VIBRANT study was underpowered to capture and detect any true differences in endophthalmitis and cardiovascular risk between the two interventions. As such, the VIBRANT trial cannot inform on these clinically important safety aspects of aflibercept. Nevertheless, the data that were available from the VIBRANT study did not reveal any notable differences between aflibercept and laser treatment with respect to cardiovascular harms and endophthalmitis. Neither IDC analyzed or reported on any safety or

adverse event data; as such, no information on the relative safety of aflibercept versus other anti-VEGFs can be derived from indirect evidence. Nevertheless, the overall safety profile of aflibercept is consistent with what has been observed in previous indications. In addition, comparisons of the safety of the anti-VEGFs in other retinal conditions, including AMD and DME, have revealed no notable differences among aflibercept, ranibizumab, and bevacizumab.[7,32-34]

4.3 Potential Place in Therapy[e]

The current standard of care for treatment of patients with macular edema associated with BRVO includes treatment with an anti-VEGF (ranibizumab or bevacizumab), steroids (triamcinolone acetonide, or dexamethasone implant), and laser therapy. Aflibercept represents another treatment option. Steroids are not an optimal option because of complications such as cataracts and increased intraocular pressure (IOP), and anti-VEGFs are superior to laser therapy. Therefore, anti-VEGFs are the preferred initial therapy. Aflibercept is used in a similar manner as ranibizumab for the treatment of macular edema secondary to BRVO. There is no barrier to identify appropriate patients in a consistent manner, and no specialized diagnostic test is required.

[e] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

5. CONCLUSIONS

The results of the VIBRANT study are consistent with the conclusion that aflibercept administered at a dose of 2 mg in 0.05 mL volume is superior to laser treatment in improving BCVA at 24 weeks in patients with macular edema secondary to BRVO. Evidence from two IDCs suggested that there are no statistically significant differences in the efficacy of aflibercept in patients with macular edema secondary to BRVO compared with bevacizumab or ranibizumab. The indirect evidence, however, is associated with a high degree of uncertainty, as only one study was available to connect aflibercept to the network of interventions. Direct evidence from the VIBRANT study suggested that most commonly reported AEs are related to the procedure of intravitreal administration rather than to aflibercept itself, although this study was not powered to detect differences in potentially serious harms of interest, specifically endophthalmitis and cardiovascular AEs.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff. No patient input was received from any group. The patient input summary presented below was adapted from the patient input received for reviews by the CADTH Common Drug Review (CDR) of aflibercept (Eylea) for diabetic macular edema, and aflibercept (Eylea) for macular edema secondary to central retinal vein occlusion.

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

The Canadian Council of the Blind (CCB) is a charitable organization. All officers and directors are blind or visually impaired, which gives a unique sensitivity to the needs of the blind community. The CCB has more than 65 chapters across Canada and, with more than 1,500 members, is the largest membership-based organization for the blind. In 2011, the CCB received support from the following: VIA Rail, Cannondale, Community Foundation of Ottawa, Lions Club, Keith Communications Inc., Employment and Social Development Canada (formerly Human Resources and Skills Development Canada [HRSDC]), and the following pharmaceutical companies: Bayer Inc., Merck Frosst, Novartis, and Pfizer Inc. CCB had nothing to declare regarding the compilation of the submission.

2. Condition-Related Information

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

Retinal vein occlusion (RVO) leads to loss of vision, which affects daily functioning and quality of life. Patients can no longer drive and need to find ways to attend medical appointments, shopping, and social activities. Vision loss can lead to an increased frequency of falls and injuries. Assistance is required for preparing meals, daily household chores, reading, etc. Patients with RVO are unable to read regular print (books, newspapers, food or medication labels, menus, greeting cards, etc.) as they could in the past. Because people don't know how to deal with the situation, vision loss has a negative impact on social life. Patients become isolated because they cannot move independently. The condition also changes family dynamics. Patients have to deal with new challenges as they arise. Depression can arise from the loss of independence, employment, driving privileges, and quality of life. The condition has an economic impact due to loss of employment and the cost of treatment.

Caregivers have to deal with all the emotional effects of vision loss in someone who had been previously independent, and deal also with their own emotions. Caregivers need to provide a safe environment for the patient. In addition, they may need to provide comfort and reassurance, and may need to do more household chores (especially if the patient lives alone). They may need to take time off work to transport the patient to medical appointments, shopping, etc. Caregivers are dealing with an added financial burden due to both patient and caregiver having to take additional time from employment or arranging child care for other family members as they care for a parent, and so on. Due to lack of knowledge or understanding, caregivers may not know how to deal with the personal feelings and/or depression of the patient.

3. Current Therapy-Related Information

CCB highlighted the lack of choice and coverage of drugs approved for the treatment of RVO. Current therapies include laser therapy, Vitalux, acetylsalicylic acid or ASA, lutein, Lucentis, and Avastin. Some are used "off-label". The off-label use is perceived as uncertain in terms of adverse events. Many patients have good results with the available treatments. Treatments with these drugs may need to be

repeated many times. Some patients have restricted treatment options because of the cost incurred from travelling to regional clinics. Also, some drug plans only partly reimburse the cost of an approved drug. Patients need alternatives to account for adverse drug reactions or drug shortages.

4. Expectations About the Drug Being Reviewed

It is expected that the lives of patients will be improved with Eylea, with decreased macular edema and improved vision. The hemorrhaging that occurs with RVO, along with the macular edema resulting in loss of vision, causes the patient to become very apprehensive. The need to stop bleeding is most important to prevent further vision loss, which would compound the above-mentioned problems. Also, the increased intraocular pressure — glaucoma — needs to be controlled to decrease the incidence of peripheral vision loss. It is expected that there will be improvement with this new drug by arresting the progress of vision loss and the patient possibly regaining sight. There is a lack of choice for approved therapies. Patients may have an adverse reaction to current therapy and therefore have no second choice of approved medication, and continue to lose vision. Eylea would now give the patient and physician two drugs to improve eye health. Dosing every eight weeks would mean fewer trips to the physician, less time for caregivers to miss work, and possibly alleviate adverse reactions or irritations.

If patients felt they were going to regain sight or prevent further vision loss, they would often be willing to experience some temporary adverse effects. Patients indicate that they would be willing to try a new drug, hoping to regain their sight. Regaining sight, controlling bleeding, having fewer hospital visits, returning to work, and regaining independence to a greater degree than prior to treatment would be considered adequate improvement and worth the risk of side effects. Mild irritation for a short time would be acceptable, but infection would not.

Eylea is also approved for wet age-related macular degeneration. The following advantages of Eylea have been mentioned by CCB:

- Fewer injections than ranibizumab
- Fewer and shorter clinic visits
- More predictability with a proactive approach treatment
- Low incidence of serious adverse events.

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:	January 14, 2016
Alerts:	Biweekly search updates until May 18, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical 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
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
.kw	Keywords defined by the author of the article
.kf	Keyword heading word (MEDLINE)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MUTLI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	(Eylea* or aflibercept* or "AVE 0005" or AVE0005 or "AVE 005" or AVE005 or Bay 86-5321 or Bay86-5321 or Zaltrap or Zivaflibercept or Ziv-aflibercept or VEGF trap* or vasculotropin trap or vascular endothelial growth factor trap or 15C2VL427D or 862111-32-8 or 924289-53-2).ti,ab,ot,kf,hw,rn,nm.
2	retinal vein occlusion/
3	(retina* adj2 (vein* or venous or vascular or vessel*) adj2 (obstruct* or occlusion* or occlud* or thrombos* or block* or embolism*)).ti,ab,kf.
4	(BRVO or branch).ti,ab,kf.
5	or/2-4
6	1 and 5
7	6 use pmez
8	*aflibercept/
9	(Eylea* or aflibercept* or "AVE 0005" or AVE0005 or Bay 86-5321 or Bay86-5321 or VEGF Trap* or Zaltrap or Zivaflibercept or Ziv-aflibercept or vasculotropin trap or vascular endothelial growth factor trap).ti,ab,kw.
10	or/8-9
11	retina vein occlusion/
12	branch retinal vein occlusion/
13	(retina* adj2 (vein* or venous or vascular or vessel*) adj2 (obstruct* or occlusion* or occlud* or thrombos* or block* or embolism*)).ti,ab,kw.
14	(BRVO or branch).ti,ab,kw.
15	or/11-14
16	10 and 15
17	16 not conference abstract.pt.
18	17 use oemezd
19	7 or 18
20	remove duplicates from 19

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. 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:	January 2016
Keywords:	Eylea (aflibercept), branch retinal vein occlusion (BRVO)
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 searching health-related grey literature* (https://www.cadth.ca/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

No excluded studies.

APPENDIX 4: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- Best corrected visual acuity (BCVA) measurement with the Early Treatment Diabetic Retinopathy Study (ETDRS) letters score
- Central retinal thickness (CRT) assessed by optical coherence tomography (OCT)
- National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25).

Findings

TABLE 10: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Evidence of Validation	MCID	References
ETDRS letters	ETDRS charts present a series of 5 letters of equal difficulty on each row, with standardized spacing between letters and rows; a total of 14 lines (70 letters).	Yes	15 letters	[23,24,35,36]
OCT	OCT is an instrument used to create cross-sectional maps of the retinal structures and to quantify retinal thickness in patients with macular edema.	Yes	Unknown	[26]
NEI VFQ-25	The NEI VFQ was developed as a means to measure vision-targeted quality of life. The NEI VFQ-25 is a shortened version of the NEI VFQ and includes 25 items relevant to 11 vision-related constructs, in addition to a single-item general health component.	Yes, but controversial[37,38]	Between 3.3 and 6.1 points	[27,29,30,39]

ETDRS = Early Treatment Diabetic Retinopathy Study; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire-25 items; OCT = optical coherence tomography.

Early Treatment Diabetic Retinopathy Study

The ETDRS charts are based on a design by Bailey and Lovie, and are commonly used in clinical research.[35,40-45] ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between letters and rows; a total of 14 lines (70 letters). An ETDRS letter score can be calculated when 20 or more letters are read correctly at 4.0 metres; the visual acuity letter score is equal to the total number of letters read correctly at 4.0 m plus 30. If fewer than 20 letters are read correctly at 4.0 m, the visual acuity letter score is equal to the total number of letters read correctly at 4.0 m (the number recorded on line 1.0), plus the total number of letters read correctly at 1.0 m in the first six lines. Therefore, the ETDRS letter score could result in a maximum score of 100.[46,47] Charts are used in a standard light box, with a background illumination of approximately 150 cd/m^2. The standard chart testing distance is 4 m; however, shorter distances may be used when vision is severely impaired.[35,48] 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. Further 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 minimal angle of resolution score (logMAR) suitable for statistical analysis in which individual letters score 0.02 log units. 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 can read at 100 feet.[35,49] Holladay and Prager published the following formula to convert visual acuity scores derived from a Bailey-Lovie–style chart read at 2 m into a Snellen denominator, where X is the number of correctly read letters (see below).[50] Thus, reading all 70 letters on a Bailey-Lovie chart corresponds to a Snellen visual acuity of 20/10.

Snellen Acuity = 20 x 10[(55–X)/50]

Minimal Clinically Important Difference

To our knowledge, there has been no derivation of a minimal clinically important difference (MCID) for the ETDRS in BRVO. Clinical studies assessing ophthalmic interventions commonly use a loss or gain of three lines (15 letters), which corresponds to a moderate degree of change or a doubling a visual acuity, as the primary outcome of interest.[51] For macular edema, the 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 ≥ 15 letter change in visual acuity, as clinically relevant outcomes in studies.[23,24] The 15-letter reference point is still a topic of discussion for the FDA. A symposium was held by the National Institutes of Health and the FDA to discuss visual acuity measures as outcome measures for clinical studies. In particular, the symposium focused on discussing alternatives to the most commonly used cut-point of three-line gains and losses on eye charts for classifying outcomes, and discussing the relationship between statistically significant differences and clinically significant differences.[52]

The test–retest variability (TRV) of the measure can help guide what would be considered a clinically meaningful change. Literature-based estimates of TRV range from ± 0.07 to ± 0.19 logMAR.[36] This suggests that any change in score between baseline and follow-up of approximately four to 10 letters results in insufficient certainty that the difference in letters is not just due to chance alone. When TRV is high, the ability to detect a real change in score is low. For example, for a TRV of ± 0.19, the sensitivity of a 0.1 logMAR change (five letters) was 4% (0% to 14%). If the TRV is lowered to ± 0.11, the sensitivity of the test increases to 38% (25% to 53%). If the TRV remains at ± 0.11, and the threshold for change increases to a 0.2 logMAR change (10 letters), the sensitivity of the scale increases to 100% (93% to 100%).

The baseline visual acuity of a sample population will affect the TRV of ETDRS letter scores[46] and as a result will also affect what would reasonably be considered an MCID. A TRV of ± 0.11 has been found in healthy participants,[36] while higher levels of variability (± 0.15 to ± 0.20) have been cited for individuals with pathological changes in vision.[53] For eyes with acuity better than 20/100, a change in visual acuity of ≥ 5 letters has > 90% probability of being a real change, while for eyes worse than 20/100, a change of ≥ 10 letters is required for the same reliability.[54] A threshold for clinically meaningful change in patients with advanced eye disease should be higher than in healthy individuals, and has been suggested to range between 10 and 15 letters.[25] The studies contributing this discussion are summarized in Table 11.

TABLE 11: LITERATURE ASSESSING THE INTERPRETABILITY OF CHANGES IN ETDRS SCORES

Study	Population	Methods/Results	Key Findings	Strengths (S)/ Limitations (L)
Rosser et al. 2003[36]	n = 50 (healthy volunteers) **Age**: < 50 years **Snellen Acuity Measure**: ≥ 6/9 (20/30) **Other:** No ocular abnormalities or cognitive difficulties	**Methods:** 1. TRV was assessed using 2 different ETDRS charts at 4 m. 2. Participants were tested for visual acuity across varying distances to simulate real changes to visual acuity. **Results**: TRV ± 0.11 logMAR (literature values ranged from ± 0.07 to ± 0.19.). Sensitivity of a 0.1 logMAR change = 38% (25% to 53%); specificity = 96% (86% to 100%).	1. TRV was approximately 5 letters (logMAR = ± 0.11), suggesting that anything > 5 letters is likely to be considered a true change in vision acuity. However, the sensitivity of the test is low. 2. Literature-based estimates range from ± 0.07 to ± 0.19 logMAR. 3. At higher levels of TRV, the sensitivity of the ETDRS for detecting change is lower; sensitivity to detect > 0.30 logMAR is high. 4. Specificity is high for all TRVs.	S: TRV measure is mid-range compared with literature-based values. L: Sensitivity and specificity were not based on comparisons to other measures of change (visual acuity or QoL).
Beck et al. 2007[54]	8 clinical studies reporting a change in visual acuity as an outcome measure	**Discussion of analytical methods:** Binary outcome variable: lost information, misclassifying outcome, floor and ceiling effects (a person's baseline acuity measure) Continuous variable: No discussion of its disadvantages. In some situations, depending on the research question, binary may be better.	1. Visual acuity studies reported ranges of 6% to 32% differences between treatment and control groups for % of people with ≥ 15 letter worsening from baseline. This equated to a 2.9 to 19.4 mean difference between treatment and control groups for change in letter score from baseline. 2. Created artificial biases to show the effects of evaluating the significance of change in outcomes when using a binary outcome variable.	L: Non-systematic review of the literature. L: Used hypothetical biases to demonstrate effects.
Csaky et al. 2008[52]	Scientists, clinicians, and researchers (symposium held by NIH and FDA)	**Methods**: Roundtable discussion on visual acuity as an outcome measure.	4 representatives provided opinions on the 2 topics of discussion:	L: No discussion of the representation of participants. L: Opinion-based discussion.

Study	Population	Methods/Results	Key Findings	Strengths (S)/ Limitations (L)
		Two topics for discussion: 1. Identifying an alternative to the most commonly used threshold of 3-line gains and losses on eye charts for classifying outcomes 2. The relationship between statistically and clinically significant differences.	1. Question raised about using a lower than 15-letter change score in clinical studies. 2. Concern that up to a 15- letter change may not represent a real change. 3. Change score may depend on how rapidly disease progression occurs. 4. Standardization is important.	
Beck et al. 2003[46]	n = 251 (patients undergoing treatment of whom 20% had normal vision and 80% had a vision-related clinical diagnosis) **Age:** 50 years (± 22) **Visual acuity:** 20/20: 21% 20/20-20/40: 29% 20/40-20/100: 30% < 20/100: 20%	**Methods:** 1. Test–retest reliability of the ETDRS was done with back-to- back testing by the same technician. **Results:** 98% of patients had the results of their repeat test within 10 letters (0.2 logMARs); 87% were within 5 letters (0.1 logMAR). For patients with a baseline visual acuity of < 20/100, 83% of patients were within 5 letters (0.1 logMAR) after the retest.	1. Test–retest reliability varied according to the participant's baseline visual acuity.	L: Repeat test was completed immediately after first test. There is a risk of bias for remembering the sequence of letters.
Kiser et al. 2005[25]	N = 60 (Low-vision participants) with visual acuity problems identified from a previous research database, an eye institute, and a local institution; and N = 18 (healthy controls)	**Methods:** Each patient was tested for visual acuity at 4 to 5 visits every month using the ETDRS (under dim light and regular light). Contrast sensitivity was also tested. Coefficient of repeatability (CR.95) was used to identify the minimal change that must occur to be confident that visual acuity has truly changed.	The minimal change that must occur to be confident that visual acuity has truly changed in low-vision individuals is between 2 and 3 lines on the ETDRS.	L: Very few patients within each eye disease group. L: Patients are very low vision — defined as legally blind.

Study	Population	Methods/Results	Key Findings	Strengths (S)/ Limitations (L)
	Mean age: 61 years **Visual acuity:** Low-vision participants: legally blind (< 20/200) from retinal pigmentosa, macular degeneration, optic neuropathy, other retinal disease, or diabetic retinopathy. Healthy controls (> 20/25)	**Results**: Healthy controls (CR.95 ranged from 0.092 to 0.15); low- vision participants (CR.95 ranged from 0.13 to 0.36).		

ETDRS = Early Treatment Diabetic Retinopathy Study; NIH = National Institutes of Health; QoL = quality of life; TRV = test–retest variability.

Conclusion

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

Measures of high-contrast visual distance acuity, using ETDRS charts, are commonly used to assess treatment outcomes in clinical studies. A loss of ≥ 3 lines (≥ 15 letters) on an ETDRS chart corresponds to a doubling of the visual angle and is considered moderate visual loss, while a loss of ≥ 6 lines (≥ 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 upon 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, use of distance acuity to measure the success of treatments for age-related macular degeneration (AMD) is not optimal, given that distance vision is usually two ETDRS lines better than reading vision,[51] and difficulty with reading is a common complaint among persons with eye disease.[39] Rather, contrast sensitivity is a more important contributor to reading performance.[51,56]

Visual function and the resultant ability to perform everyday visual tasks have important implications for quality of life. Quality of life is very much a person-specific measure, which ultimately depends upon the value individuals place upon the ability to perform specific tasks. Quality-of-life instruments that do not include domains and tasks that are of importance to individuals will lack sensitivity to changes in a person's quality of life. Further, the impact of vision loss on quality of life may vary greatly, dependent upon the vision status of the fellow eye. For these reasons there are limitations in the use of quality-of-life instruments to compare treatment effectiveness.[55]

Optical Coherence Tomography

OCT is a fast, non-invasive instrument used to create cross-sectional maps of the retinal structures and to quantify retinal thickness in patients with macular edema.[26] 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. 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.[26,57] A recent advancement in OCT device technology has been the shift from time domain OCT (TD-OCT) to spectral domain OCT (SD-OCT), as the latter can acquire data at a higher speed and with better image resolution and reduced motion artifact.[58]

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.[26] 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.[59] 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 TRV.[58] Inter-device differences in retinal thickness were also reported in this study, although 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, whereas in patients with DME it was 36 µm.[60]

In patients with DME, the association between OCT-measured retinal thickness and BCVA has been evaluated. A moderate correlation between visual acuity and OCT centre point thickness has been observed (r = 0.52).[61] 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).[61] Other studies have shown similarly modest correlations between visual acuity and CRT determined by OCT.[62,63] 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 three, five, eight, and 12 months, respectively.

National Eye Institute Visual Function Questionnaire

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 consisting of persons with a number of common eye conditions (e.g., age-related cataracts, AMD, and diabetic retinopathy), and thus may be used to assess quality of life in a broad range of eye conditions.[39] The original 51-item questionnaire consists of 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.[28]

A shorter version of the original instrument, the VFQ-25, was subsequently developed, which retained the multidimensional nature of the original and is more practical and efficient to administer.[28,29] 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 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 VFQ-25 have been proposed.[27] 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. However, standard scoring is subject to floor and ceiling effects whereby the ability of the least visually able is overestimated and the ability of the most visually able is underestimated.[27]

Determination of what constitutes a clinically meaningful change in the NEI VFQ appears to be linked to its correlation with visual acuity. A three-line (15 letters) change in visual acuity has been used as the outcome of interest in clinical studies, and corresponding changes in the NEI VFQ are suggested as clinically meaningful end points. Specifically, for the study eye — which is typically the worse-seeing eye — a 15-letter change in visual acuity corresponds to a 4-point change in overall VFQ-25 score.[64] For the better-seeing eye, the clinically relevant difference for VFQ-25 scores based on a three-line change is 7 to 8 for overall score.[64] A psychometric validation study of the NEI VFQ-25 in patients with DME has more recently been conducted, and two distribution-based methods were employed to determine an MCID.[30] Using a half-standard deviation–based approach, the MCID for each VFQ-25 domain ranged from 8.80 (general vision) to 14.40 (role difficulties), producing a composite score MCID of 6.13 points. A standard error of measurement (SEM) approach yielded similar MCID estimates from 8.79 (driving) to 14.04 (role difficulties), with a composite score MCID estimate of 3.33 points.[30] Other studies have shown similar estimated clinically relevant differences.[65] The instrument showed weaker correlation or

was not responsive to changes in the visual acuity of the worse eye.[66,67] This may have implications when evaluating patients with unilateral disease.

Both versions of the NEI VFQ were reported to be valid and reliable measures of health-related quality of life among patients with a wide range of eye conditions[28,29,67] 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.[66,67] However, more recent studies have indicated that the NEI VFQ measures visual functioning, not quality of life.[38] Assessments of the psychometric validity of the NEI VFQ-25 using Rasch scoring and principal component analysis have identified issues with multidimensionality (measurement of more than one construct) and poor performance of the subscales.[37,38] 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.[37,38] Re-engineering the NEI VFQ 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.[37,38] Considering this recent evidence of multidimensionality, the validity of the single composite score of the NEI VFQ may be questioned.

Conclusion

The ETDRS chart is the most widely used outcome measure to assess changes in visual acuity from a therapeutic intervention. It is a modified version of the Snellen chart and scores are based on the number of letters correctly read by a patient. A loss or gain of three lines (15 letters) is the most commonly used MCID in clinical studies.

Retinal thickness, measured using OCT, may be a useful clinical tool to monitor macular edema and retinal changes but is modestly correlated with changes in vision and 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. The NEI VFQ was reported to be a valid and reliable measure of health-related quality of life among patients with a wide range of eye conditions; however, recent studies have suggested that it may more appropriately identified as a measure of visual functioning. The NEI VFQ has a reported MCID between 3.3 and 6.1 points.

APPENDIX 5: SUMMARY OF INDIRECT COMPARISONS

A1.1 Introduction

A1.1.1 Background

The aim of this section is to review and critically appraise any indirect comparisons (IDCs) that compare aflibercept with any other treatment for macular edema secondary to branch retinal vein occlusion BRVO).

Aflibercept has been compared with laser treatment in the VIBRANT study.[10,11] However, no direct evidence exists in comparing aflibercept with other treatment options for BRVO that are commonly used in practice, specifically ranibizumab and bevacizumab. Therefore, IDCs that include aflibercept can provide information on the comparative effectiveness and safety of this drug to existing therapies, and would be relevant to this review by the CADTH Common Drug Review (CDR).

A1.1.2 Methods

One IDC submitted by the manufacturer was reviewed and critically appraised. In addition, a comprehensive literature search was performed by an information specialist to identify published IDCs. The details of the literature search are available in APPENDIX 2: LITERATURE SEARCH STRATEGY.

A1.2 Description of Indirect Comparisons Identified

The literature search identified one relevant IDC by Regnier et al. (2015),[9] in addition to the IDC submitted by the manufacturer.[8] The IDC by Regnier et al. aimed to compare the efficacy and safety of approved treatments for macular edema secondary to BRVO, which included aflibercept;[9] the manufacturer's IDC aimed to determine the relative efficacy and safety of aflibercept compared with other treatments for macular edema secondary to BRVO. Essentially, both IDCs had almost identical objectives.

A1.1.3 Review and Appraisal of Indirect Comparisons

Review of the Manufacturer's Indirect Comparison

[redacted]

Methods for Manufacturer's Indirect Comparison

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

FIGURE 3: [redacted]

[redacted]

FIGURE 4:

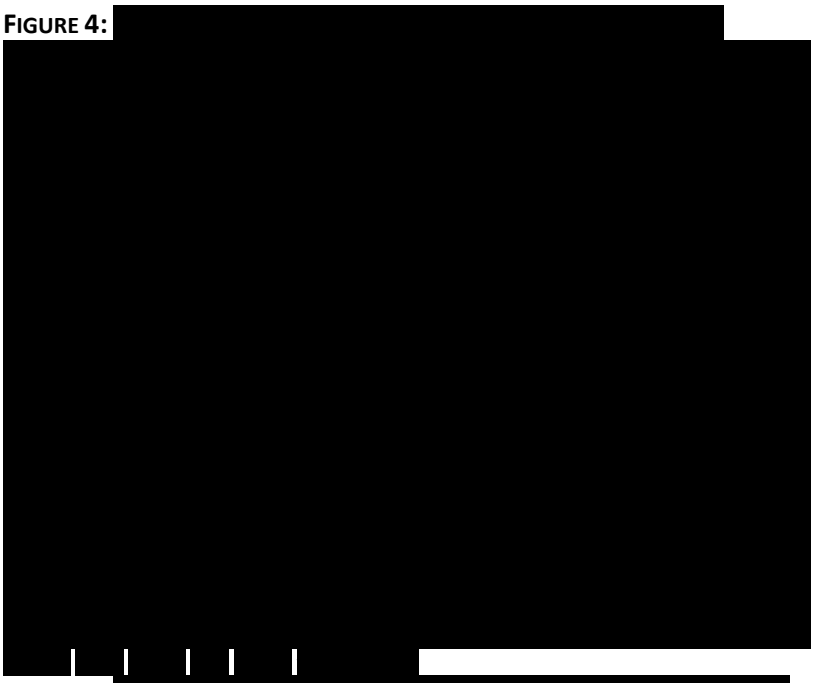


FIGURE 5:

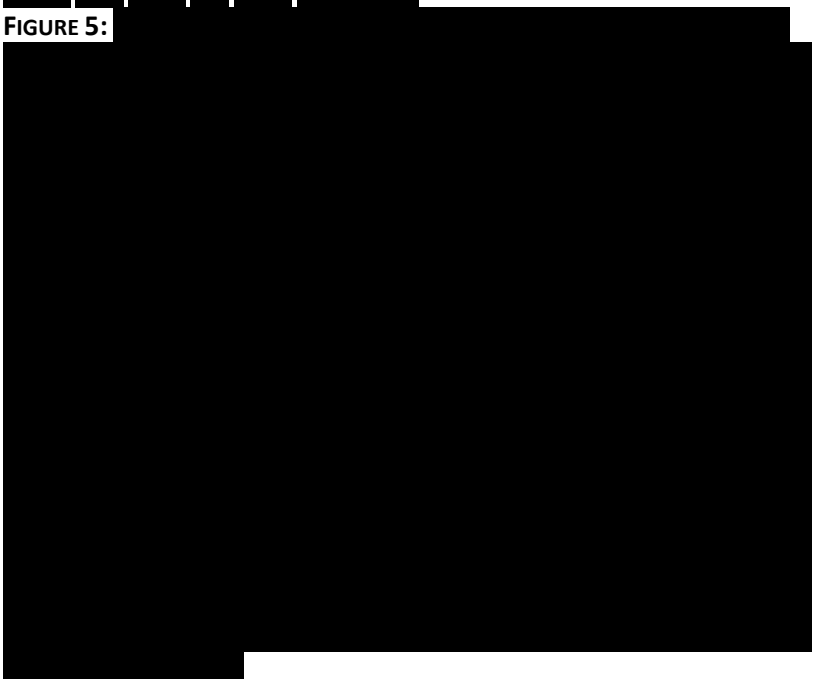
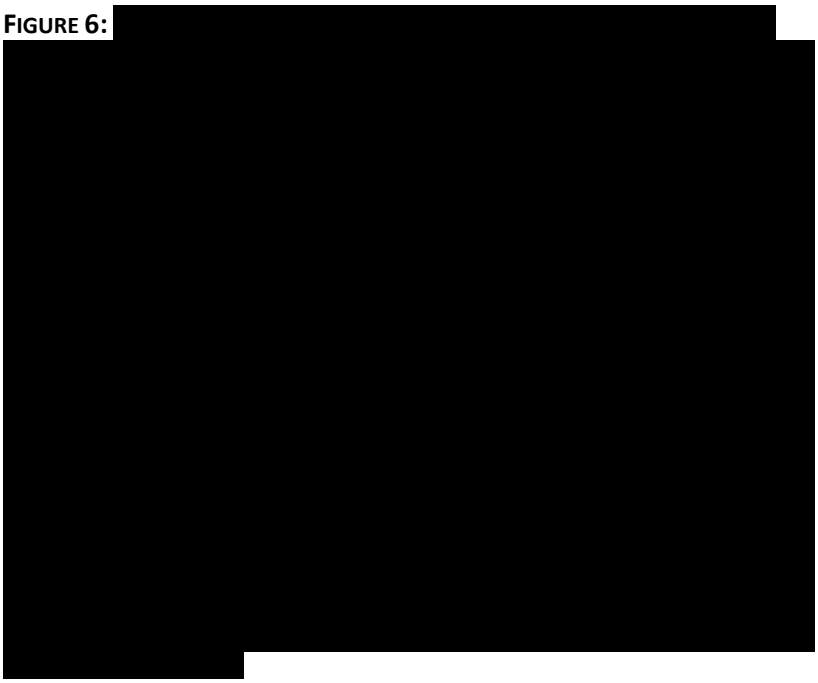


FIGURE 6: [redacted]



A1.1.4 Indirect Comparison Methods

[redacted]

Results

[redacted]

[redacted]

[redacted]

FIGURE 7: [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

TABLE 12: [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

TABLE 13: [redacted]

[redacted]		

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TABLE 14: [redacted]

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TABLE 15: [redacted]

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A1.1.5 Critical Appraisal

The manufacturer's IDC provided a research question that incorporated clear population, intervention, comparisons, and outcomes. The inclusion criteria would allow a population that is relevant for Canadian settings. The comparisons reported in this IDC have incorporated relevant treatments for Canadian settings, including treatments that have extensive clinical use but lack a formal review from Health Canada such as bevacizumab, which is commonly used in Canada.

The manufacturer's IDC used a search strategy sensitive enough to capture related citations. The manufacturer's IDC adhered to double screening and data extraction through two independent reviewers, and reconciled any differences with the involvement of a third independent reviewer.

Included trials were thoroughly assessed for quality and have proven to be of sufficiently good quality overall. In addition, the manufacturer's IDC transparently reported the characteristics of included trials.

The analysis of the extracted data followed the framework suggested by the National Institute for Health and Care Excellence (NICE), including using non-informative priors. The manufacturer's IDC reported on the number of burn-ins, convergence characteristics, deviance information criterion (DIC), and reported the fixed-effects and random-effects results.

A main limitation of the manufacturer's IDC is the weak connection between aflibercept and the rest of the network. This is observed throughout the reported outcomes. Aflibercept is connected to the network only through a single study, the VIBRANT study. Because of this, the statistical model would use the single arm available that compared aflibercept to laser treatment to inform all the rest of the included interventions. This has caused the results to be less credible and precise, thus explaining the wide credible intervals seen throughout the manufacturer's IDC and the unrealistic results associated with the random-effects model.

Another limitation caused by the weak connection of aflibercept to the network is our inability to test the assumption of transitivity and to assess consistency in the aflibercept comparisons. Consistency assessment requires comparison between direct and indirect evidence; i.e., we need to have closed loops within the network — this cannot be achieved with the aflibercept comparisons, as all evidence is indirect in nature and no closed loops that include aflibercept were available. Despite the lack of closed loops, the manufacturer's IDC could have tested the assumption of transitivity by comparing indirect evidence gained from a Bayesian network meta-analysis approach to indirect evidence gained from the Bucher method.

Review of Regnier et al. (2015)

Objectives and Rationale for Regnier et al.

Regnier et al. (2015) aimed to compare the efficacy and safety of licensed therapies for macular edema secondary to BRVO.

Methods for Regnier et al. 2015

Regnier et al. used a Bayesian network meta-analysis of data extracted from BRVO randomized controlled trials (RCTs).

Systematic review

Regnier et al. used a previous systematic review, Glanville et al. (2015), with a literature search update conducted in 2010.[31] However, unlike Glanville et al., Regnier et al. included only treatments for BRVO that are approved by the FDA. Specifically, a study had to have at least two of the following interventions of interest: laser, dexamethasone, aflibercept, or ranibizumab. As such, the Regnier et al. update meant removing some studies from Glanville et al. The updated search strategy was performed on August 4, 2014, using similar terms to Glanville et al. The search was conducted over MEDLINE, Embase, and the Cochrane Library, with a hand-search of relevant citations and clinicaltrials.gov to complement the search. For a study to be included in the review, it had to:

- report either mean change in BCVA from baseline, or percentage of patients gaining ≥ 15 letters from baseline
- have outcomes captured at six or 12 months
- have at least two of the interventions stated (sham, laser, dexamethasone, aflibercept, ranibizumab)

- have a population of anti-VEGF patients on a monthly or as-needed (PRN) regimen.

It is not clear how many reviewers screened the retrieved citations and whether quality control measures were in place to minimize human error.

Data extraction
It is not reported how the data were extracted and how missing data were handled.

Comparators
Sham injection, laser treatment, dexamethasone, aflibercept, and ranibizumab were the comparators used.

Outcomes
The following outcomes were reported: mean change in BCVA from baseline to month 6; odds ratio (OR) for ≥ 15 letters gained; and OR for increase in intraocular pressure (IOP) or ocular hypertension (OH). It is not clear which outcomes were collected from the included studies.

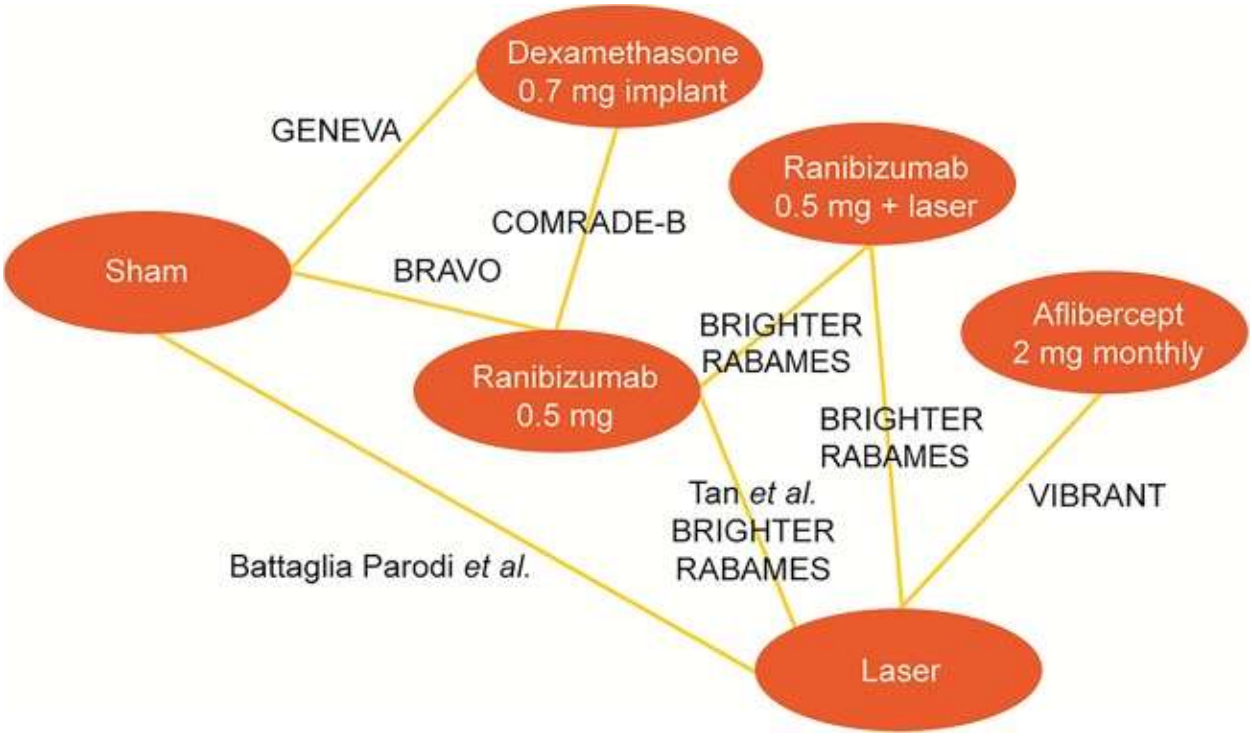
Quality assessment
Quality assessment of individual papers was performed using the NICE guidance quality checklist, and focused on the following areas:

- Selection bias
- Attrition bias
- Detection bias
- Performance bias.

It is not clear how the authors handled low-quality studies.

Evidence network
Figure 8 provides a network diagram for all the included trials in Regnier et al. (2015).

FIGURE 8: NETWORK DIAGRAM OF INCLUDED TRIALS IN REGNIER ET AL. (2015)



Reproduced with permission from: Regnier SA, Larsen M, Bezlyak V, Allen F. Comparative efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion: a network meta-analysis. BMJ Open [Internet]. 2015 [cited 2018 Feb 18];5(6):e007527. Figure 2: Meta-analysis study network. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4458587/pdf/bmjopen-2014-007527.pdf.

Meta-analysis and indirect comparison for Regnier et al. (2015)

A network meta-analysis using a Bayesian approach through Monte Carlo Markov chains was conducted in Regnier et al. (2015). No justification was given for following this specific approach. The authors do not report on the types of prior used. The authors report 27,000 iterations, excluding the results from the first 2,000 iterations. There was no mention of what methods were used to observe or measure convergence. A random-effects model was used and subsequently compared with the fixed-effects model in a sensitivity analysis; no DIC was provided. The authors performed node-splitting in which direct evidence was compared with indirect evidence, where possible.

Results of Regnier et al. (2015)

Included studies characteristics: A total of seven studies were included for evidence synthesis. Studies were all considered of good quality except one that did not report on a few related points. The number of patients enrolled in different arms in these studies ranged from 10 to 291. All but one study reported outcomes measured at six months. Baseline BCVA ranged from 39.5 to 65.6 ETDRS. The mean age ranged from 63.9 to 69.6, and the disease duration ranged from 1.4 to 5.2 months. There was no clear description of the specific RCT design, or the countries where the trials took place.

Intervention and comparators included in the review were: Sham injection, dexamethasone 0.7 mg implant, ranibizumab 0.5 mg + laser, ranibizumab 0.5 mg, laser, and aflibercept 2 mg.

Gaining 15 letters from baseline: For this outcome, aflibercept was compared with sham, ranibizumab 0.5 mg, laser, dexamethasone 0.7 mg implant, and ranibizumab 0.5 mg + laser. The results had wide credible intervals and no statistically significant result was observed. See Table 16.

TABLE 16: ODDS RATIO OF GAINING 15 LETTERS OR MORE WITH AFLIBERCEPT COMPARED WITH OTHER INTERVENTIONS

	NMA Results
Comparison	Random-effects model, OR (95% CrI)
Aflibercept versus sham	3.38 (0.28 to 31.36)
Ranibizumab 0.5 mg versus aflibercept	1.06 (0.16 to 8.94)
Laser versus aflibercept	0.33 (0.07 to 1.59)
Dexamethasone versus aflibercept	0.36 (0.04 to 4.54)
Ranibizumab 0.5 mg + laser versus aflibercept	0.94 (0.11 to 8.85)

CrI = credible interval; NMA = network meta-analysis; OR = odds ratio.

Change of BCVA from baseline: For this outcome, aflibercept was compared with sham injections, ranibizumab 0.5 mg, laser, dexamethasone, and ranibizumab + laser. The results, reported with the random-effects model, showed statistically significant improvement with aflibercept when compared to sham and to laser treatment. The rest of the comparisons showed no statistically significant results (see Table 17).

TABLE 17: MEAN DIFFERENCE IN BEST CORRECTED VISUAL ACUITY CHANGE FROM BASELINE

	NMA Results
Comparison	Random-effects model, mean difference (95% CrI)
Aflibercept versus sham	**9.2 (1.7 to 16.1)**
Aflibercept versus Ranibizumab 0.5 mg	−1.4 (−8.5 to 5.2)
Laser versus aflibercept	**−10.2 (−15.5 to −4.6)**
Dexamethasone versus aflibercept	−6.7 (−14.0 to 1.3)
Ranibizumab 0.5 mg + laser versus aflibercept	−0.0 (−7.4 to 7.6)

CrI = credible interval; NMA = network meta-analysis.
Note: Bold font indicates statistical significance.

Safety: Attempts to inform on safety using the outcome of IOP/OH were not possible, as the model did not converge sufficiently to produce any reliable and consistent results.

Critical Appraisal of Regnier et al. (2015)
The IDC provided a research question that incorporated clear population, intervention, comparisons, and outcomes. However, the inclusion of approved interventions only meant that important and relevant interventions were not part of this IDC. Namely, bevacizumab is extensively used in the Canadian setting for the management of macular edema; there are also published literature and high-quality RCTs that compared bevacizumab to other interventions for the treatment of macular edema. Another intervention that is not licensed, and as such not included, but is used for the treatment of macular edema, is triamcinolone. The exclusion of these two interventions meant that the power and reliability of the network is reduced considerably, as well as missing valuable information that could inform on health policy in Canada.

There are also several omissions and a lack of reporting on essential pieces of information regarding the conduct of the IDC. These include:

- Lack of reporting on the method of screening citations and a lack of reporting on the method of extracting data; we do not know what measure was taken to reduce human error and ensure high quality of the screening and extraction processes
- Lack of reporting on the type of priors used; therefore, it is not clear what, if any, role the priors had contributed in the outcomes results
- Lack of reporting on the methods used to detect and measure convergence, which leaves us uncertain as to the convergence of the simulations used
- Lack of reporting on the DIC values in different models; therefore, we are not sure of the extent of statistical fit.

In addition to the limitation associated with the lack of reporting key information, the specific connection between aflibercept and other interventions was very weak, as only one comparison (aflibercept versus laser) from one study (VIBRANT) served to inform on all produced evidence, and there is concern that such a connection could not have been powered sufficiently to detect differences.

A1.3 Discussion

Our search strategy identified one additional IDC outside the manufacturer's IDC — a review by Regnier et al. Whereas the manufacturer's IDC aimed to specifically compare aflibercept with any other intervention for macular edema secondary to BRVO, Regnier et al. compared all approved therapies for macular edema secondary to BRVO. As such, Regnier et al. (2015) contained fewer interventions and fewer studies and, subsequently, less power than the manufacturer's IDC. Despite having more included studies than Regnier et al. (2015), the manufacturer's IDC is still considered not strongly powered to compare aflibercept to the rest of the interventions, as only one comparison (aflibercept versus laser) from one study (VIBRANT) served to inform on all produced evidence, and this is reflected by the wide credible intervals produced from this network.

Despite this limitation, and across different outcomes, we consistently observe that aflibercept did not show any statistically significant differences when compared with bevacizumab or ranibizumab. When looking at aflibercept compared with dexamethasone or triamcinolone, we observed statistically significant differences in some of the outcomes and doses, whereas no statistically significant differences are observed in other outcomes or other doses. Coupling this observation with the wide credible intervals observed throughout both IDCs, and given that the point estimate was mostly in favour of aflibercept, it is likely that this indicates a possible difference in favour of aflibercept that is not very well observed due to the limitation in the available evidence, which stems largely from the single arm connection between aflibercept and the rest of the network. Comparison between aflibercept and laser was statistically significant in all of the manufacturer's IDC outcomes, and in one of the two reported outcomes in Regnier et al. (2015).

It is unfortunate that neither of the reviewed IDCs were able to synthesize any observation on safety-related issues. This is largely a reflection of the large statistical power and long follow-up needed to detect any meaningful differences in the safety outcomes.

A1.4 Conclusion

The manufacturer's IDC in addition to Regnier et al. (2015) compared aflibercept with different interventions for macular edema secondary to BRVO. These interventions included ranibizumab, bevacizumab, laser, dexamethasone, and triamcinolone. Regnier et al. (2015), however, did not include bevacizumab and triamcinolone, as they are not approved for the treatment of macular edema secondary to BRVO.

The manufacturer's IDC showed consistently that aflibercept was not statistically significantly different from bevacizumab or ranibizumab in terms of BCVA change from baseline, gains of ≥ 15 letters, loss of ≥ 15 letters, or change in CRT. The manufacturer's IDC showed conflicting results when aflibercept was compared with dexamethasone and triamcinolone, with some of the results showing statistically significant improvement in favour of aflibercept over some forms of these two drugs while some of the outcomes did not show a statistically significant improvement in the same comparison with the two drugs. Aflibercept was shown to be superior to laser in both direct and almost all indirect evidence in the manufacturer's IDC. The major limitation of the manufacturer's IDC is the weak connection between aflibercept and the rest of the network, which reduces the power, accuracy, precision, and credibility of the results.

Regnier et al. (2015), on the other hand, only showed statistically significant results in favour of aflibercept versus sham and laser in one of the two reported outcomes. This could largely be due to the small overall network and weak connection of aflibercept to the already small network. In addition, there are major omissions and lack of reporting important information in Regnier et al. (2015) that renders us unable to judge its overall credibility.

Overall, the available indirect evidence suggests that aflibercept is not statistically significantly different in efficacy from bevacizumab and ranibizumab; is inconclusively better than dexamethasone and triamcinolone; and has consistently showed statistically significant improvements over laser and sham injections. This evidence, however, is not very robust and is associated with high degree of uncertainty due to the small number of studies connecting aflibercept to the rest of the network; this limitation applies to all available comparisons between aflibercept and other treatments. This is reflected by the wide credible intervals produced in several comparisons. The safety of aflibercept compared with different interventions was not synthesized in any IDC, due to technical infeasibility, reflecting the need for a much larger network with longer follow-up time.

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