Common Drug Review
Clinical Review Report

June 2016

Drug	aflibercept (Eylea) (40 mg/mL solution for intravitreal injection available as a 2 mg single-use vial)
Indication	Treatment of visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO)[a]
Listing request	List for the treatment of visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO), similar to ranibizumab
Manufacturer	Bayer Inc.

[a] Aflibercept is also indicated for the treatment of neovascular (wet) age-related macular degeneration and diabetic macular edema (DME), which have been reviewed separately.

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

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

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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

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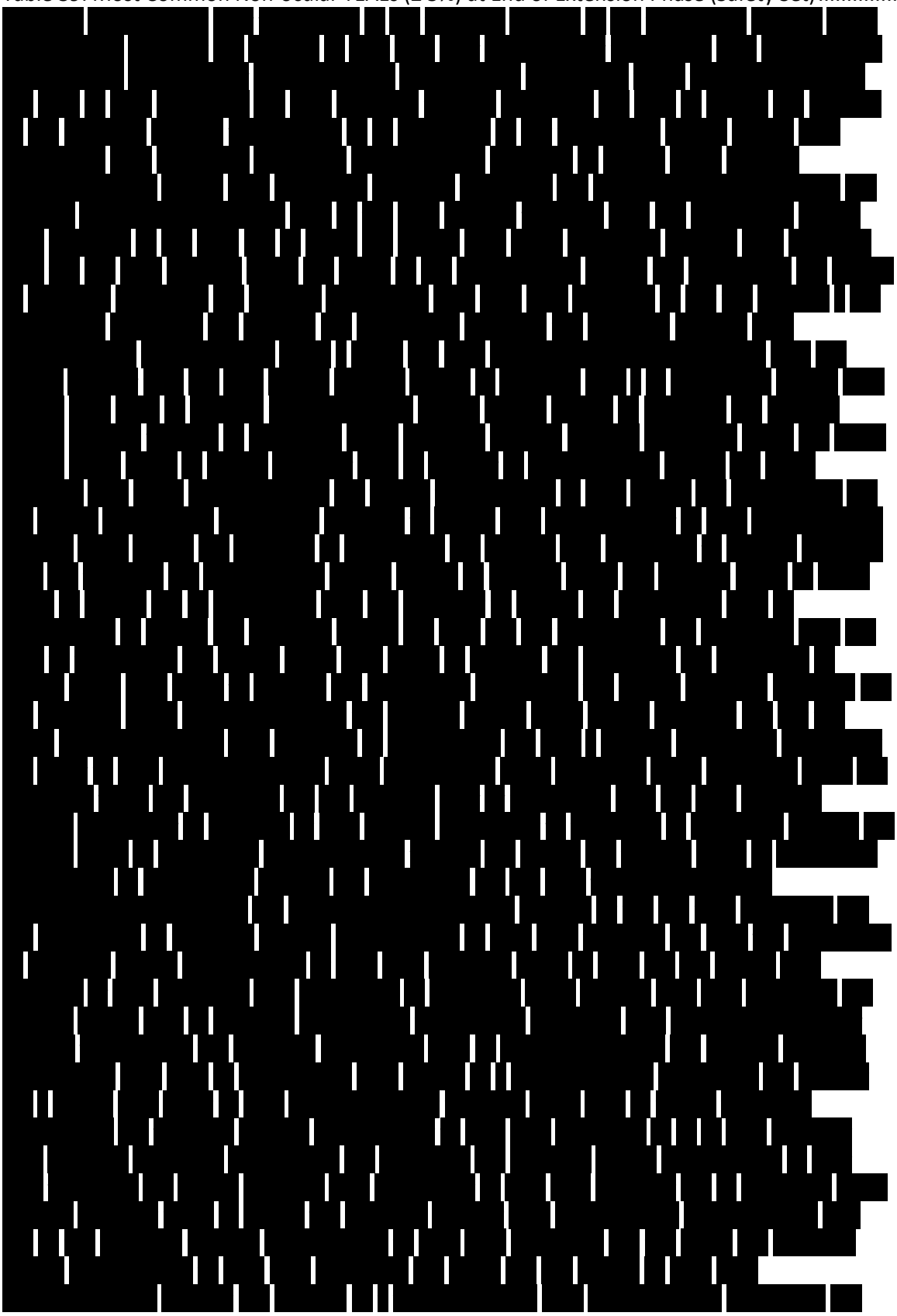
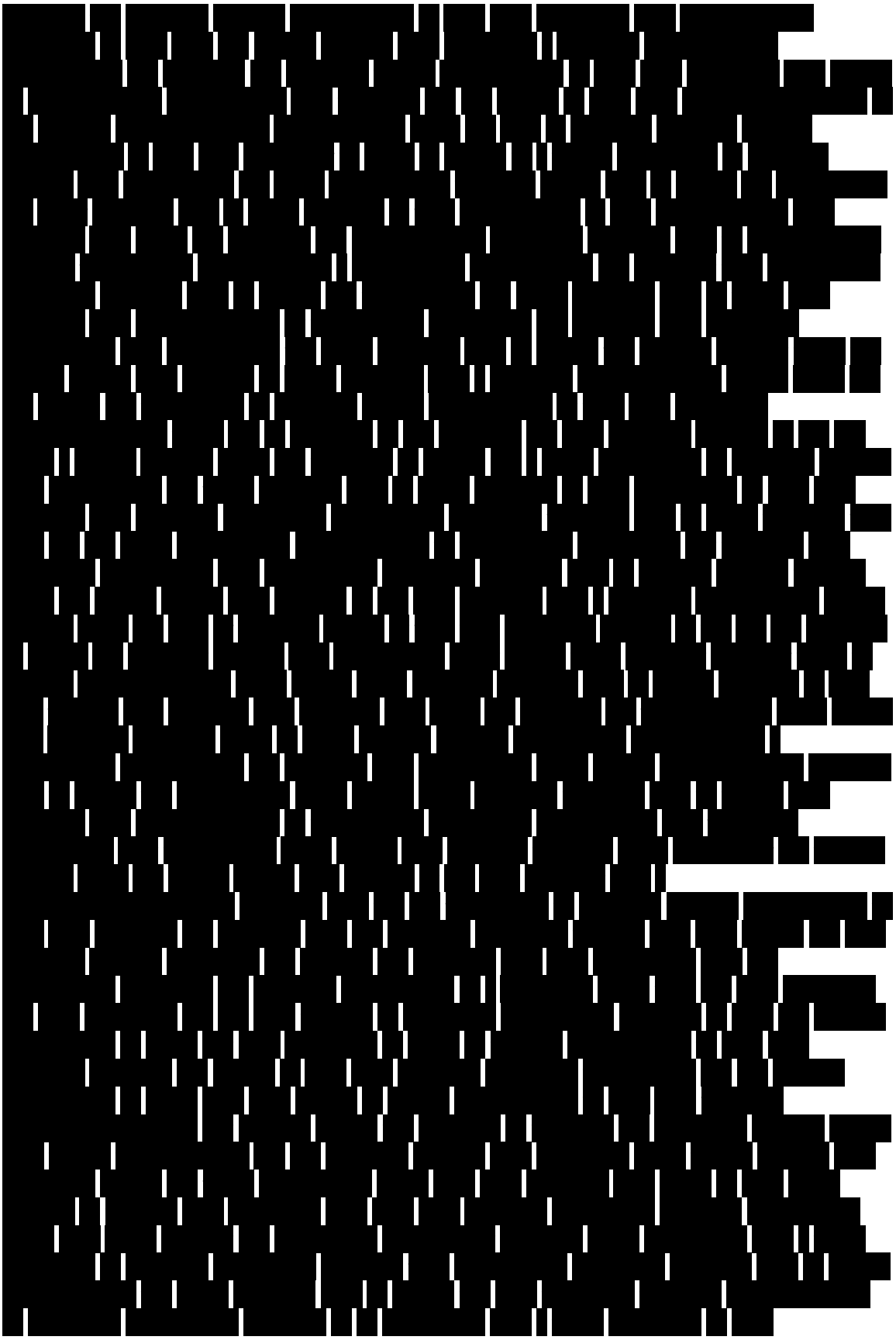
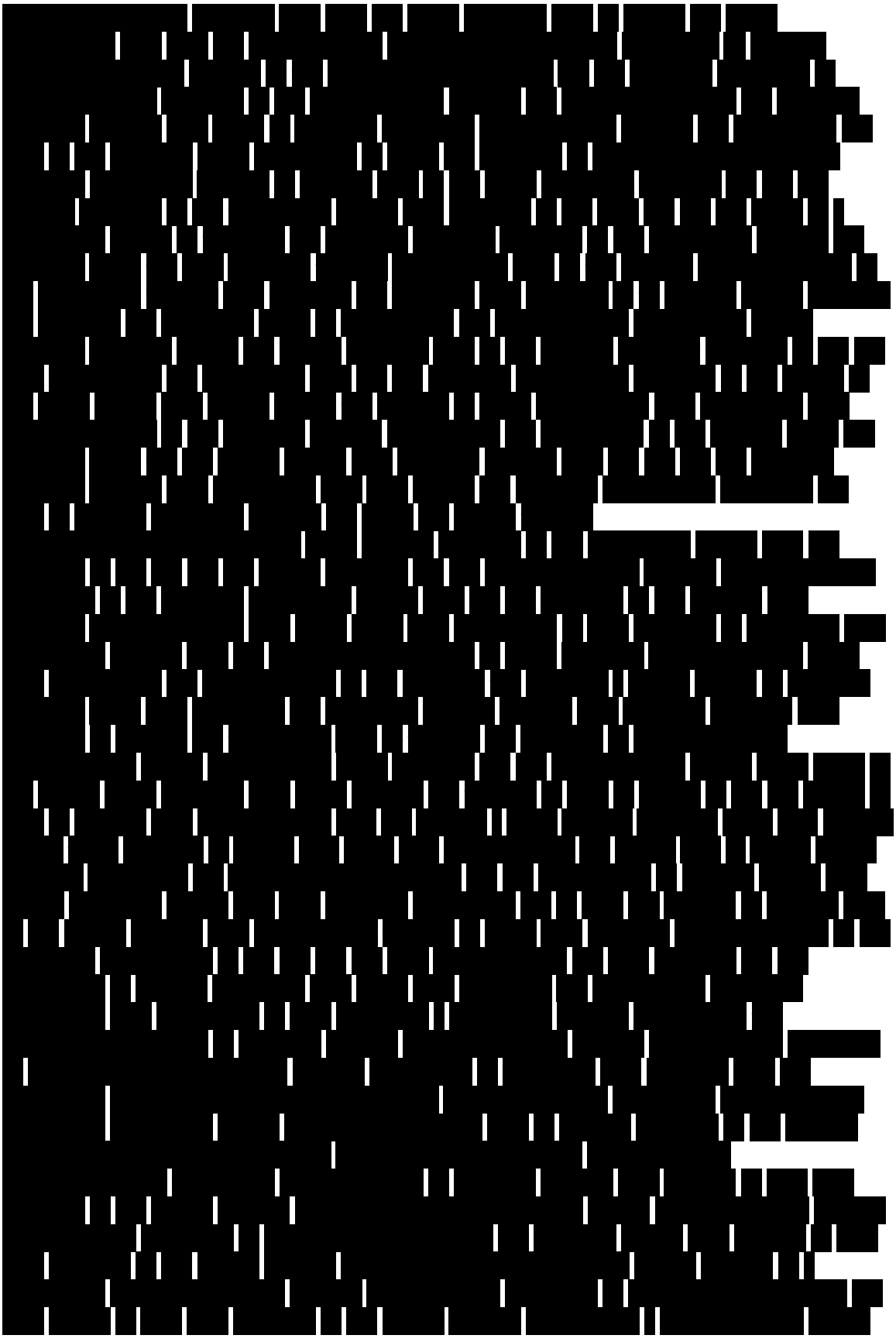
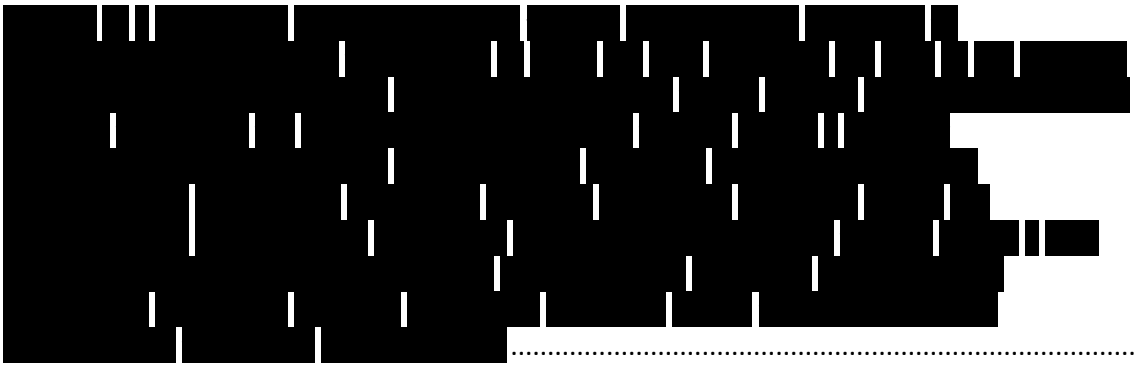
TABLE OF CONTENTS

Tables

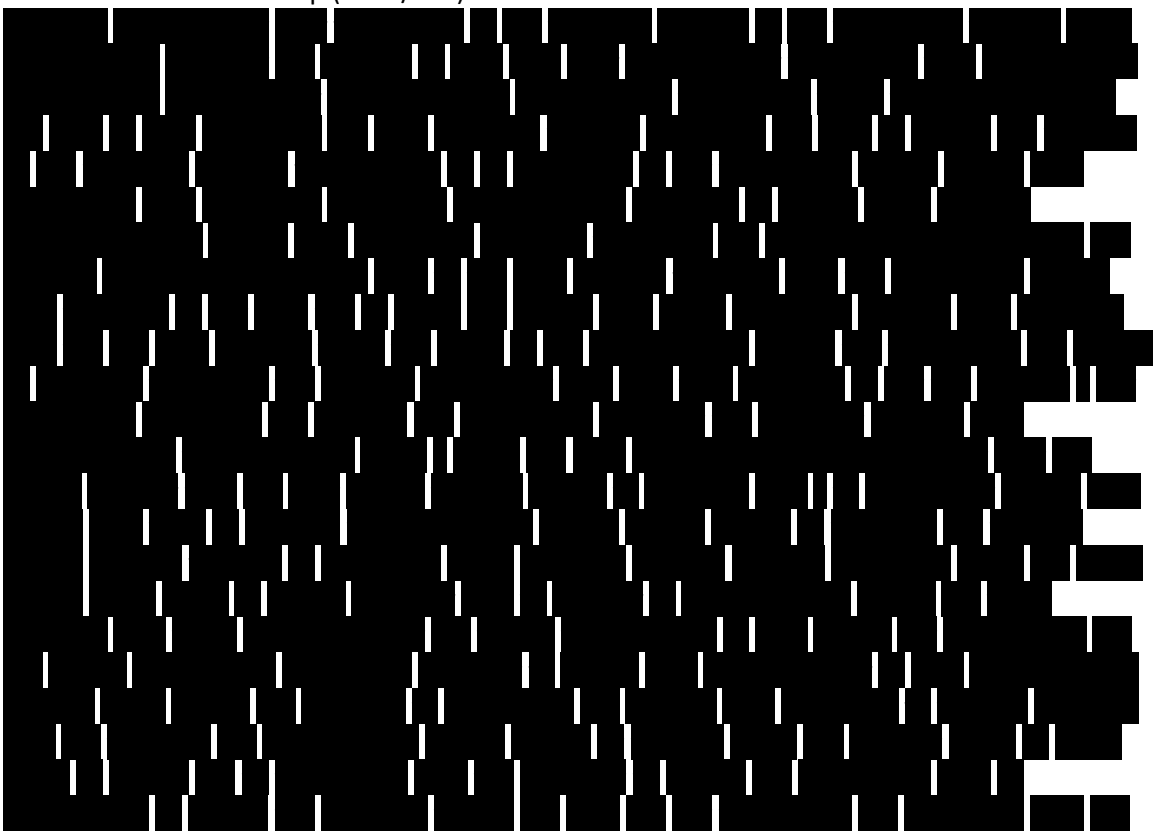


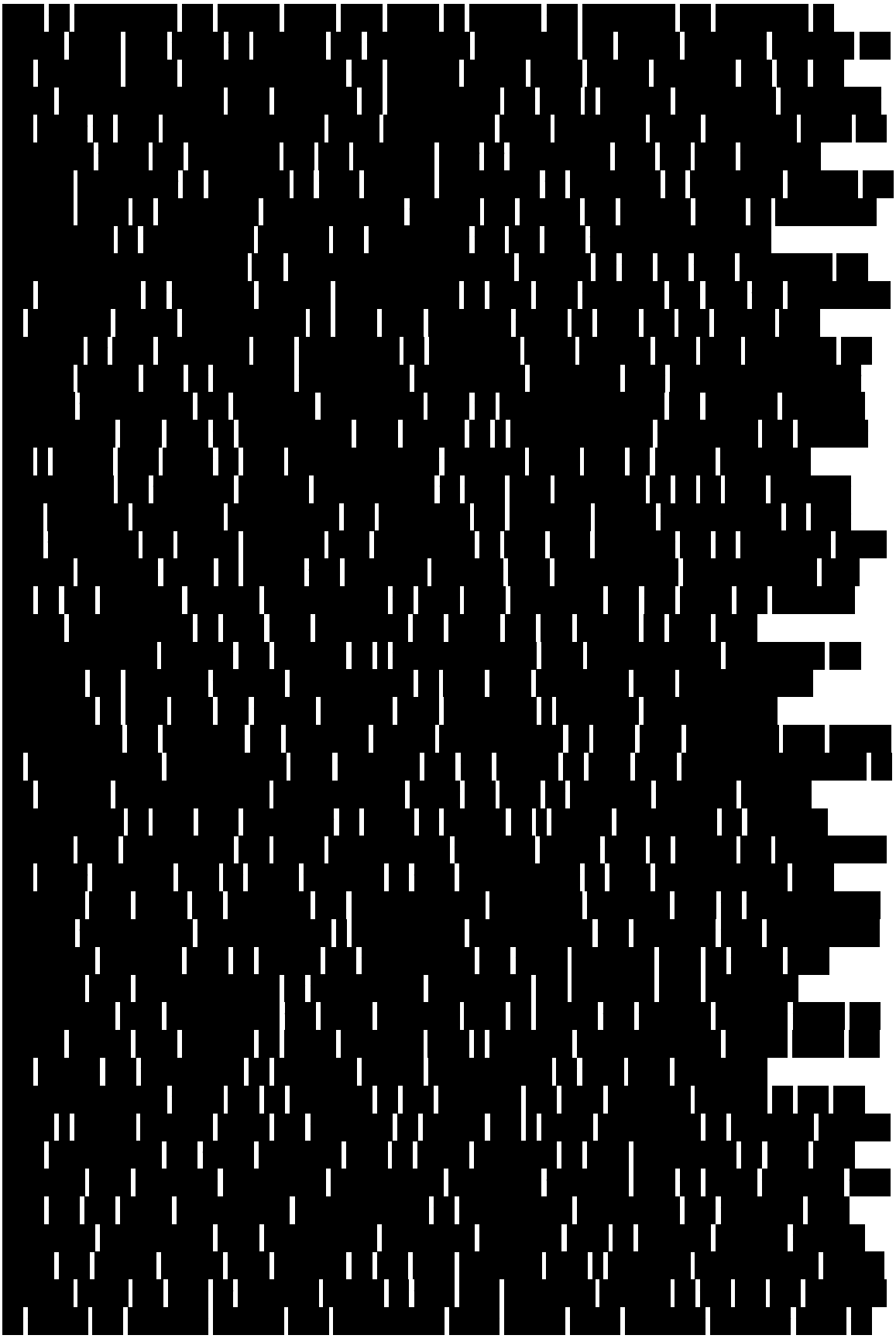


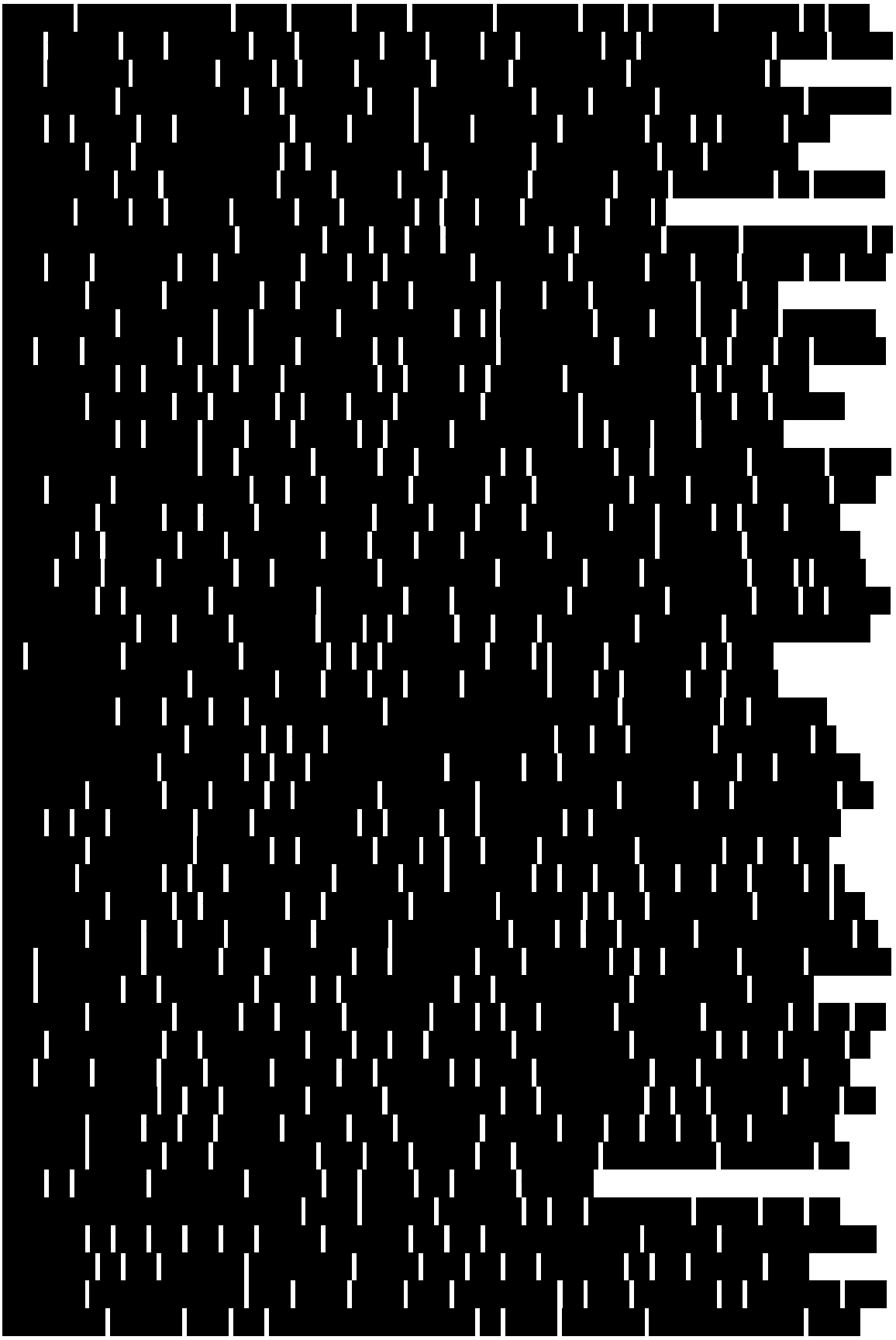


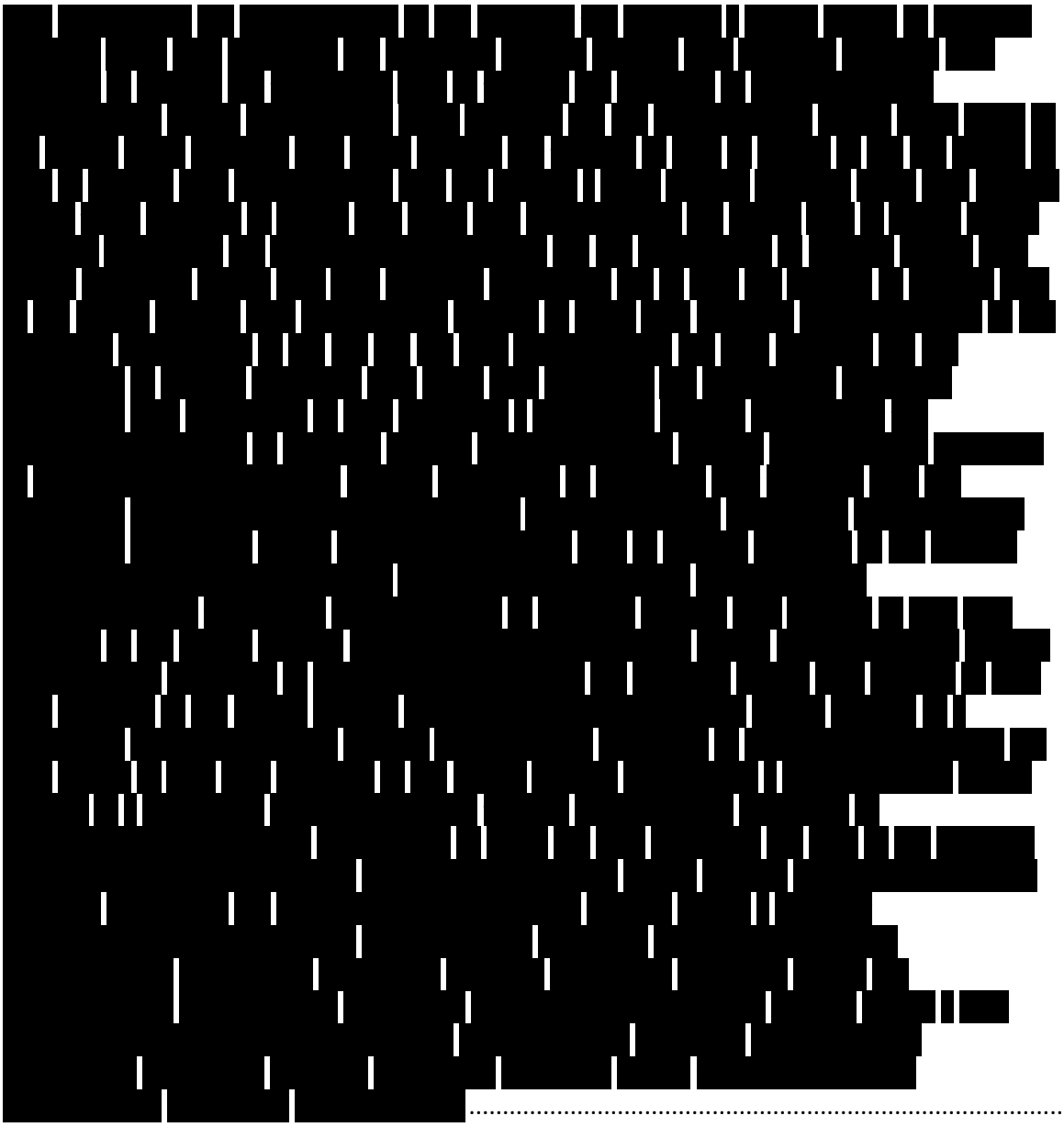


Figures









ABBREVIATIONS

AE	adverse event
ATE	arterial thromboembolic event
BCVA	best-corrected visual acuity
BRVO	branch retinal vein occlusion
CDR	CADTH Common Drug Review
CI	confidence interval
CRT	central retinal thickness
CRVO	central retinal vein occlusion
DME	diabetic macular edema
EQ-5D	EuroQol Five-Dimensions Questionnaire
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	full analysis set
IOP	intraocular pressure
IVI	intravitreal injection
IVT	intravitreal
LSMD	least squares mean difference
MCID	minimal clinically important difference
NEI VFQ-25	25-item National Eye Institute Visual Function Questionnaire
NMA	network meta-analysis
NVD	neovascularization of the optic disc
NVE	neovascularization of the retina elsewhere
OCT	optical coherence tomography
PP	per-protocol
PRN	as needed (pro re nata)
QoL	quality of life
PRP	panretinal photocoagulation
RCT	randomized controlled trial
RVO	retinal vein occlusion
SAE	serious adverse event
TEAE	treatment-emergent adverse event
VEGF	vascular endothelial growth factor
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Retinal vein occlusion (RVO) occurs when there is a blockage in the venous system of the retina. RVO is a common cause of vision loss and one of the most common retinal vascular diseases, second only to diabetic retinopathy.[1] Central retinal vein occlusion (CRVO) is caused by a blockage of the central retinal vein by a thrombus. It causes vision loss secondary to macular edema or ischemia and can cause blindness. CRVO is classified into two subtypes: non-ischemic (or perfused) and ischemic (or non-perfused).[2] The prevalence of CRVO is approximately 0.80 per 1,000 adults.[2]

The anti–vascular endothelial growth factor (VEGF) drug ranibizumab is currently first-line therapy in Canada for macular edema secondary to CRVO. Other pharmacological treatments include intravitreal injection of steroids (triamcinolone) or steroid-releasing implants (dexamethasone). Aflibercept is the second anti-VEGF to be approved in Canada for the treatment of visual impairment due to macular edema secondary to CRVO. The aim of this report was to review the efficacy and harms of aflibercept for the treatment of CRVO.

Results and Interpretation

Included Studies

Two studies met the criteria for inclusion in this review: GALILEO (N = 171) and COPERNICUS (N = 188). Both studies were randomized, multi-centre, double-masked, sham-controlled studies designed to assess the superiority of aflibercept over sham injection for the treatment of macular edema secondary to CRVO. GALILEO was a 76-week, two-arm randomized controlled trial (RCT) conducted in 10 countries in Europe and the Asia-Pacific region. COPERNICUS was a 100-week, two-arm RCT conducted in five countries, including Canada. The duration of the masked, controlled treatment period in both studies was 24 weeks. In both studies, patients were treatment-naive adults with macular edema secondary to CRVO and best-corrected visual acuity (BCVA) scores, measured with the Early Treatment Diabetic Retinopathy Study (ETDRS) acuity test, ranging from 20/40 (BCVA score of 73 letters) to 20/320 (BCVA score of 24 letters) in the study eye. In both studies, patients were randomized to receive either 2 mg intravitreal (IVT) aflibercept or a sham injection every four weeks. The primary efficacy outcome was the proportion of patients who gained at least 15 BCVA letters at week 24 compared with baseline.

Although GALILEO and COPERNICUS were methodologically rigorous, some limitations were identified. First, in both studies, there were differential dropout rates between the studies' aflibercept groups (9% and 4%, respectively) compared with the sham-injection groups (21% and 19%). Although the higher discontinuation rates in sham-treated patients could have led to a bias in favour of the relative effect of aflibercept versus sham injection, this was counterbalanced by a corresponding loss of statistical power needed to demonstrate superiority of the aflibercept treatment. Second, the primary outcome in GALILEO and COPERNICUS was measured at 24 weeks; subsequent to this time point, the treatment regimens and assignments varied, which limits the available comparative data to six months of treatment. Finally, there were no data available to directly assess the comparative efficacy of aflibercept against ranibizumab, the other anti-VEGF approved for treating CRVO in Canada. However, evidence available from indirect comparisons of aflibercept and ranibizumab was reviewed and is presented in this report.

Efficacy

In GALILEO and COPERNICUS, aflibercept was superior to sham injection for improving vision in CRVO patients. Specifically, a significantly greater proportion of aflibercept-treated patients (adjusted difference [AD] = 38.3%; 95% confidence interval [CI], 24.4% to 52.1% and AD = 44.8%; 95% CI, 33.0% to 56.0% for GALILEO and COPERNICUS, respectively) achieved an improvement of at least 15 BCVA letters compared with sham-injected patients at 24 weeks. The difference between treatments appeared to be clinically meaningful. Subgroup analyses indicated that aflibercept was superior to sham injection for improving BCVA by at least 15 letters in patients with non-perfused CRVO (AD = 47.0% to 64.3% across studies) as well as in patients with perfused CRVO (AD = 32.5% to 42.4% across studies) at 24 weeks. At 52 weeks, aflibercept remained superior to sham injection. Although the difference between treatment was smaller than at 24 weeks (AD = 27.9%; 95% CI, 13.0% to 42.7% and AD = 25.9%; 95% CI, 11.8% to 40.1% for GALILEO and COPERNICUS, respectively), this might be attributable to the changes in dosing that occurred after 24 weeks.

Aflibercept treatment was associated with a statistically significantly greater improvement in baseline visual acuity compared with sham injection. Specifically, at 24 weeks, the least squares mean difference (LSMD) for change from baseline BCVA between the aflibercept and sham-injection groups was 14.7 letters (95% CI, 10.8 to 18.7) in GALILEO, and 21.7 letters (95% CI, 17.4 to 26.0 letters) in COPERNICUS. At 52 weeks, aflibercept remained superior to sham injection, although the difference between treatments was smaller than at 24 weeks (LSMD = 13.2 letters; 95% CI, 8.2 to 18.2 letters and LSMD = 12.7 letters; 95% CI, 7.7 to 17.7 letters for GALILEO and COPERNICUS, respectively), which might be attributable to the changes in dosing that occurred after 24 weeks.

In addition to improving visual acuity, measurement of quality of life (QoL) at 24 weeks using the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) suggested that, compared with sham injection, aflibercept was associated with a greater improvement in vision-related QoL. Specifically, aflibercept was associated with an improvement in least squares mean NEI VFQ-25 total scores of 4.5 points compared with 0.3 points in the GALILEO sham-injection group (LSMD = 4.2 points; 95% CI, 1.7 to 6.8 points); in COPERNICUS, the LSMD was 6.26 points (95% CI, 2.61 to 9.91 points). At 52 weeks, the effect of aflibercept on NEI VFQ-25 scores remained superior to sham injection in GALILEO, although the difference between treatments was smaller than at 24 weeks (LSMD = 3.6 points; 95% CI, 1.1 to 6.0 points), which might be attributable to the changes in dosing that occurred after 24 weeks. By contrast, at 52 weeks, there was no significant difference between treatments in COPERNICUS. In GALILEO, QoL was also measured using the EuroQol five-dimensions questionnaire (EQ-5D). There were no statistically significant differences between the aflibercept treatment group and the sham-injection group at any time point.

The effects of aflibercept on the anatomical features of CRVO were assessed by measuring changes in central retinal thickness (CRT) in both GALILEO and COPERNICUS. In both studies, aflibercept treatment was associated with a significantly greater decrease in CRT compared with sham injection. Specifically, aflibercept-treated patients at 24 weeks had a statistically significantly greater decrease in CRT compared with the sham-injected group (LSMD = –239 µm [95% CI, –286 µm to –192 µm] and LSMD = –311 µm [95% CI, –389 µm to –234 µm] in GALILEO and COPERNICUS, respectively). At 52 weeks in GALILEO, aflibercept treatment was still associated with a statistically significantly greater reduction in CRT compared with sham treatment (LSMD = –167 µm; 95% CI, –216 µm to –118 µm), although the difference between treatments was smaller than at 24 weeks. As noted above, this might be attributable to the changes in dosing that occurred after 24 weeks. At 52 weeks in COPERNICUS, there was no longer a statistically significant difference in CRT between treatments.

Harms

In GALILEO and COPERNICUS, there were fewer serious adverse events in the aflibercept treatment groups (8.7% and 9.6% for GALILEO and COPERNICUS, respectively) compared with the sham-injection groups (14.7% and 21.6%, respectively) through 24 weeks. In GALILEO and COPERNICUS, a smaller proportion of aflibercept-treated patients discontinued treatment due to adverse events through 24 weeks (1.9% and 1.8%, respectively) compared with sham-injected patients (8.8% and 6.8%, respectively).

Only two deaths occurred across studies through 52 weeks of treatment, and both occurred within the sham treatment group. Arterial thromboembolic events were infrequent (fewer than seven overall through 52 weeks across both studies). In COPERNICUS, fewer aflibercept-treated patients (2.6%) experienced a ≥ 10 mm Hg increase in intraocular pressure compared with the sham-injection group (9.5%), but there was little difference between treatments in GALILEO (4.8% versus 5.9% for aflibercept-treated versus sham-treated patients, respectively). Endophthalmitis was reported for COPERNICUS only, and only one event occurred through 52 weeks (in the aflibercept group). There were no reports of retinal detachment in either study through 52 weeks.

Data from the extension phases of both studies suggested that the greater improvement in visual acuity observed at week 52 in the aflibercept-treated patients compared with the sham-injected patients was maintained beyond 52 weeks: up to 76 weeks and 100 weeks for GALILEO and COPERNICUS, respectively. Adverse events appeared to be largely similar in frequency and type across treatment groups in both extension studies.

Other Considerations

In the absence of a direct comparison between aflibercept and ranibizumab, evidence regarding the relative efficacy of these two drugs was reviewed. The results of an indirect comparison submitted by the manufacturer that compared aflibercept, ranibizumab, and dexamethasone suggested that while both anti-VEGFs are significantly more efficacious than dexamethasone in improving visual acuity in CRVO patients over six months, aflibercept and ranibizumab are similar to each other in terms of efficacy. Although conclusions related to comparative harms were somewhat uncertain due to heterogeneity, the manufacturer's analysis suggested that the harms profiles of the three treatments were largely similar. The conclusions of the indirect comparison provided by the manufacturer were similar to those of an independent indirect comparison retrieved from the published literature; the conclusions suggest that aflibercept and ranibizumab are similar with respect to efficacy and harms in CRVO patients.

Bevacizumab (Avastin), an anti-VEGF that is approved in Canada for the treatment of certain types of cancer, was not considered to be a valid comparator for the purpose of this review because it is not approved in Canada for the treatment of CRVO. However, bevacizumab is reimbursed for CRVO treatment in some of the jurisdictions that participate in the CADTH Common Drug Review (CDR) process. In addition, according to the clinical expert consulted for the purpose of this review, bevacizumab is used off label in Canada for the treatment of CRVO in jurisdictions in which ranibizumab is not reimbursed and in patients who are ineligible for coverage.

Conclusions

The results of the two double-masked, sham-controlled, randomized controlled studies (COPERNICUS and GALILEO) suggest that 24 weeks of treatment with 2 mg of aflibercept every four weeks is superior to sham injection for improving visual acuity in patients with CRVO. Specifically, compared with sham injection, aflibercept significantly improved BCVA by at least 15 letters in 38% and 45% more patients in GALILEO and COPERNICUS, respectively. Similarly, aflibercept significantly improved BCVA more than sham injection in GALILEO and COPERNICUS (by 15 letters and 22 letters, respectively). The significant improvements in vision that occurred after 24 weeks in both studies were sustained through 52 weeks. Aflibercept was also associated with significantly greater improvement in vision-related QoL at 24 weeks (NEI VFQ-25 scores) compared with sham injection in both studies. Vision-related QoL improvement persisted through 52 weeks in GALILEO, but not in COPERNICUS, and there was no evidence to suggest that aflibercept improved overall QoL. Aflibercept was associated with significantly greater decreases in CRT compared with sham injection in both studies at week 24, although the difference between treatments remained significant through 52 weeks only in one of the two studies (GALILEO). In both studies, aflibercept was associated with a lower incidence of adverse events compared with sham-injected patients through 52 weeks. Data available through 76 weeks (GALILEO) and 100 weeks (COPERNICUS) of follow-up treatment did not raise any notable safety concerns. Although there was no direct comparative evidence to assess the efficacy and harms of aflibercept versus other anti-VEGFs, the results of two indirect comparisons suggested that after six months of treatment, the efficacy of aflibercept and ranibizumab are similar, but the comparative safety could not be appraised.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Retinal vein occlusion (RVO) is a common cause of vision loss and one of the most common retinal vascular diseases, second only to diabetic retinopathy.[1] RVO has a prevalence of approximately 1% to 2% in individuals older than 40 years of age; the disease appears to particularly affect those over 70 years of age.[1] RVO occurs when there is a blockage in the venous system of the retina. The primary cause is often thrombus (blood clot) formation, but other causes can include external compression or vasculitis.[1] Systemic hypertension is the most common independent risk factor associated with RVO, particularly in patients older than 50 years.[1] Other risk factors include glaucoma, diabetes mellitus, dyslipidemia, cigarette smoking, and renal disease. Vision loss is secondary to macular edema or ischemia. RVO is classified into two subtypes: branch RVO (BRVO) or central RVO (CRVO), based on the specific occlusion site (i.e., localized to a branch retinal vein [BRVO] or in the main retinal vein at the optic nerve [CRVO]). CRVO is a potentially blinding disorder caused by a blockage of the central retinal vein by a thrombus. It causes painless vision loss, usually occurring with sudden onset. It is diagnosed by funduscopy.[3] CRVO is classified into two subtypes: non-ischemic (or perfused) where there is reduced blood supply to the retina, or ischemic (or non-perfused) where blood supply remains relatively normal.[2] No single test reliably differentiates the two subtypes with 100% sensitivity and specificity during the early acute phase of CRVO.[2] The annual Canadian incidence of CRVO is 0.021%.[4] The age- and sex-standardized prevalence of CRVO has been estimated at 0.80 per 1,000 people (95% confidence interval [CI], 0.61 to 0.99), which is an estimated global burden of 2.5 million affected adults.[2]

1.2 Standards of Therapy

Currently, there is no established standard of care for the prevention or treatment of macular edema secondary to CRVO.[5,6] The treatment strategies approved in Canada include ranibizumab, aflibercept, and dexamethasone intravitreal injection (IVI) implant.[7-9] Anti–vascular endothelial growth factor (VEGF) drugs are the primary treatment for macular edema secondary to CRVO. The drugs include IVI ranibizumab, bevacizumab, aflibercept, and pegaptanib. Ranibizumab is a humanized recombinant monoclonal antibody fragment with anti-VEGF-A activity. It was the first of the anti-VEGF drugs to be approved in Canada for the treatment of macular edema secondary to RVO. The recommended dose of ranibizumab is 0.5 mg given as a single monthly IVI until stable visual acuity is achieved for three monthly consecutive assessments. This is followed by monthly monitoring, and treatment is resumed when monthly monitoring indicates a loss of visual acuity.[9] A summary of the key characteristics of the Health Canada–approved treatments for macular edema secondary to CRVO is provided in Table 1.

Bevacizumab (Avastin), a VEGF antibody that is approved for the treatment of cancers, such as colorectal and lung cancer, has been used off label as monotherapy as an intravitreal treatment for macular edema secondary to CRVO in some patients in some Canadian jurisdictions where ranibizumab is not reimbursed, or in patients who are ineligible for coverage. There may be other uses in routine Canadian clinical practice for treatment of macular edema secondary to CRVO.

1.3 Drug

Aflibercept is a VEGF; it acts as a soluble decoy receptor that binds VEGF-A and placental growth factor with higher affinity than their natural receptors; thus, aflibercept can inhibit the binding and activation of these cognate VEGF receptors.[10] Aflibercept is indicated for the treatment of visual impairment due to macular edema secondary to CRVO at a recommended dose of 2 mg (0.05 mL) administered monthly by IVI.[10] Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2

extracellular domains fused to the Fc portion of human IgG1 and formulated as an iso-osmotic solution for IVI. Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

Indication under review
Treatment of visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO)
Listing criteria requested by sponsor
List for the treatment of visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO), similar to ranibizumab

TABLE 1: KEY CHARACTERISTICS OF AFLIBERCEPT, RANIBIZUMAB, AND DEXAMETHASONE INTRAVITREAL IMPLANT (FROM PRODUCT MONOGRAPHS)

	Aflibercept[a]	Ranibizumab	Dexamethasone Intravitreal Implant
Mechanism of action	Inhibition of VEGF	Inhibition of VEGF	Anti-inflammatory activity and possible inhibition of VEGF
Indication[b]	Treatment of visual impairment due to macular edema secondary to CRVO	Treatment of visual impairment due to macular edema secondary to RVO	Treatment of macular edema following CRVO
Route of administration	IVI	IVI	IVI
Recommended dose	2 mg in solution monthly	0.5 mg in solution monthly	One 0.7 mg implant approximately every 6 months; no more than 2 consecutive injections
Serious side effects/ safety issues	Potential for thrombotic events	Potential for thrombotic events	Conjunctival hemorrhage
Other	Increased IOP	Increased IOP	Increased IOP

CRVO = central retinal vein occlusion; IOP = increased intraocular pressure; IVI = intravitreal injection; RVO = retinal vein occlusion; VEGF = vascular endothelial growth factor.

[a] Aflibercept is also indicated for the treatment of neovascular (wet) age-related macular degeneration and diabetic macular edema, which have been reviewed separately.

[b] Health Canada indication.

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 central retinal vein occlusion (CRVO).

2.2 Methods

All manufacturer-provided studies considered pivotal by Health Canada were included in the systematic review. Other studies were selected for inclusion based on the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with visual impairment due to macular edema secondary to central retinal vein occlusion Subgroups: Hemi-central retinal vein occlusion Ischemic versus non-ischemic central retinal vein occlusion
Intervention	Aflibercept (40 mg/mL solution for intravitreal injection), 2 mg IVT every one to three months as monotherapy
Comparators	• Ranibizumab • Intravitreal steroids
Outcomes	**Key efficacy outcomes** • Change from baseline in BCVA • Blindness (legal) **Other efficacy outcomes** • QoL (assessed by validated measures) • Change from baseline in CRT **Harms outcomes** • AEs • SAEs • WDAEs • Mortality • Notable harms: arterial thromboembolic events, cardiovascular events, increased intraocular pressure, bacterial endophthalmitis, and retinal detachment.
Study Design	E.g., published and unpublished phase 3 RCTs

AE = adverse event; BCVA = best-corrected visual acuity; CRT = central retinal thickness; IVT = intravitreal; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

2.2.1 Supplemental Issues

- Validity of outcome measures
- Summary of extension studies
- Summary and critical appraisal of the manufacturer's network meta-analysis.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's

MeSH (Medical Subject Headings), and keywords. The main search concepts were Eylea-aflibercept (drug name) and CRVO (indication).

Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on December 9, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on April 8, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, and Clinical Studies. 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.

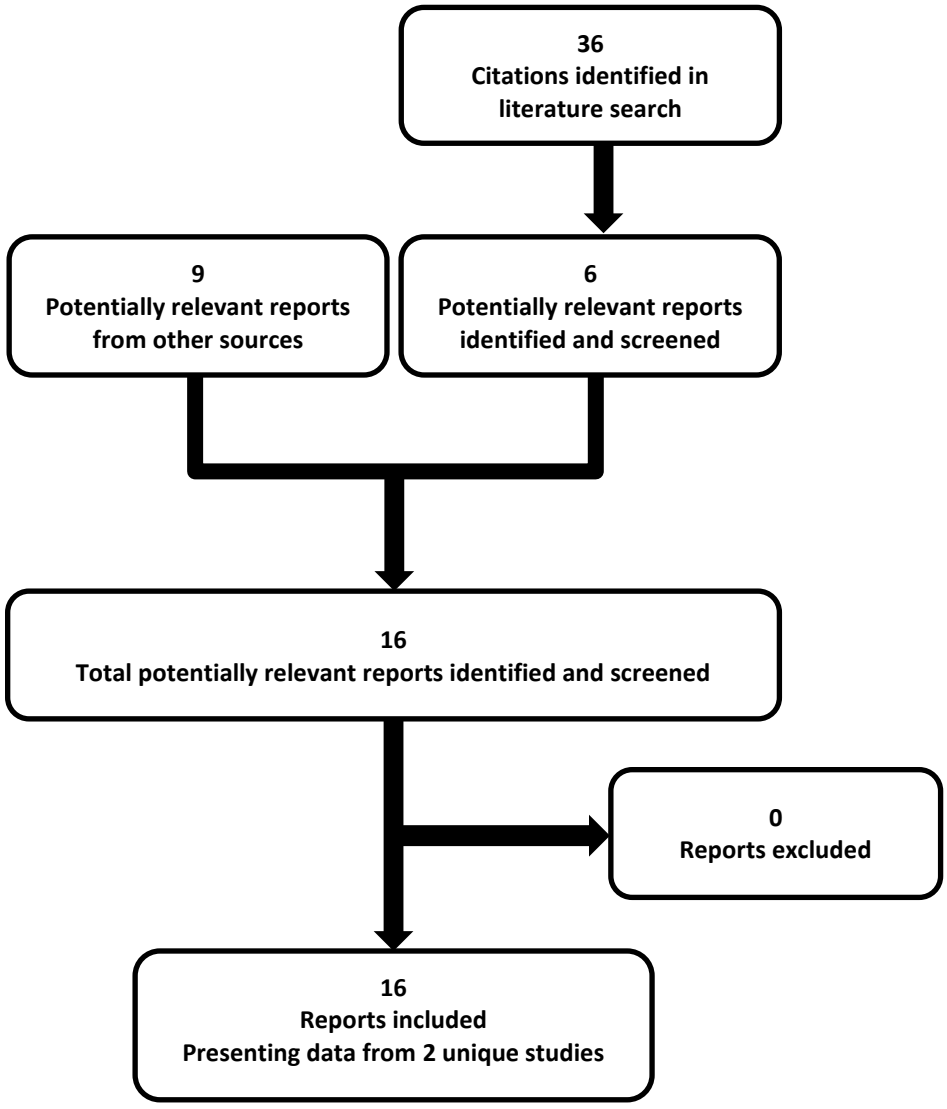
Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers 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 3; excluded studies (with reasons) are presented in Appendix 3: Excluded Studies.

3. RESULTS

3.1 Findings From the Literature

A total of 16 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 3 and described in section 3.2. A list of excluded studies is presented in Appendix 3: Excluded Studies.

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



QUOROM = Quality of Reporting of Meta-analyses.

TABLE 3: DETAILS OF INCLUDED STUDIES

		GALILEO	COPERNICUS
DESIGNS & POPULATIONS	**Study Design**	DB, randomized, multi-centre, double-masked, sham-controlled trial	DB, randomized, multi-centre, double-masked, sham-controlled trial
	Locations	Australia, Austria, France, Germany, Hungary, Italy, Japan, Latvia, Singapore, and South Korea	Argentina, Canada, Colombia, India, Israel, and the US
	Randomized (N)	171	188
	Inclusion Criteria	• Treatment-naive • Adults ≥ 18 years • Centre involved macular edema secondary to CRVO diagnosed within 9 months of study initiation • Eye with mean CRT ≥ 250 µm on OCT • ETDRS BCVA of 20/40 to 20/320 (73 to 24 letters) in the study eye	
	Exclusion Criteria	• History of vitreoretinal surgery in the study eye or anticipated surgery within the next 12 months • Bilateral manifestation of RVO • Previous treatment with anti-VEGF drugs, panretinal or macular laser photocoagulation or intraocular corticosteroids • Prior PRP or macular laser photocoagulation in the study eye • History or presence of AMD, DME, or diabetic retinopathy • Concurrent disease in the study eye that would have compromised visual acuity or required medical or surgical intervention during the study period • Cataract surgery in the study eye within three months • Uncontrolled glaucoma • Any ocular disorders in the study eye that may have confounded the interpretation of study results • Previous treatment with anti-angiogenic drugs in the study eye.	
DRUG	**Intervention**	2 mg IVT aflibercept every four weeks	
	Comparator(s)	Sham injections every four weeks	
DURATION	**Phase**	3	
	Screening	3 weeks	
	Masked (Controlled and 2Q4)	76 weeks (24 weeks)	52 weeks (24 weeks)
	Follow-up	76 weeks	100 weeks
OUTCOMES	**Primary End Point**	Proportion of patients gaining ≥ 15 letters in BCVA at 24 weeks	
	Other End Points	Change in BCVA score at 24 weeks Changes in vision-related QoL assessed by NEI VFQ-25 and EQ-5D Change from baseline CRT at 24 weeks	

		GALILEO	COPERNICUS
NOTES	**Publications**	Clinical Study Report A52377 (24 weeks)[11] Holz et al. (2013)[12] Clinical Study Report A59664 (52 weeks)[13] Korobelink et al. (2014)[14] Clinical Study Report (76 weeks) PH-36935[15] Ogura et al. (2014)[16] Eylea CDR submission[17]	Clinical Study Report R-8733 (24 weeks)[18] Boyer et al. (2012)[19] Clinical Study Report R-8734 (52 weeks)[20] Brown et al. (2013)[21] Clinical Study Report R-8742 (100 weeks)[22] Heier et al. (2014)[23] Eylea CDR submission[17]

2Q4 = 2 mg every four weeks; AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CDR = CADTH Common Drug Review; CRT = central retinal thickness; CRVO = central retinal vein occlusion; DB = double blind; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; EQ-5D = EuroQol five-dimensions questionnaire; IVT = intravitreal; NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; OCT = optical coherence tomography; PRP = panretinal photocoagulation; QoL = quality of life; RVO = retinal vein occlusion; VEGF = vascular endothelial growth factor.
Source: Clinical Study Reports A52377[11] and R-8733.[20]

3.2 Included Studies

3.2.1 Description of Studies

The literature search identified two randomized controlled trials (RCTs) that met the criteria for inclusion in the review: GALILEO and COPERNICUS. GALILEO (N = 171) and COPERNICUS (N = 188) were randomized, multi-centre, double-masked, sham-controlled studies designed to evaluate aflibercept for the treatment of macular edema secondary to CRVO. Both GALILEO and COPERNICUS were considered pivotal studies by Health Canada.[24] GALILEO was a 76-week, two-arm RCT conducted in 10 countries in Europe and the Asia-Pacific region. COPERNICUS was a 100-week, two-arm RCT conducted in five countries, including Canada. In both studies, patients were treatment-naive adults with macular edema secondary to CRVO diagnosed within nine months of study initiation and best-corrected visual acuity (BCVA) scores measured with Early Treatment Diabetic Retinopathy Study (ETDRS) of 20/40 (73 letters) to 20/320 (24 letters) in the study eye. Only one eye was enrolled per patient in the study. In both studies, patients were randomized to one of two treatment groups (3:2 ratio): 2 mg intravitreal (IVT) aflibercept every four weeks, and sham injections every four weeks from day 1 through to week 20. Randomization was stratified by region (Europe versus Asia-Pacific) and baseline BCVA (> 20/200 versus ≤ 20/200). The duration of the masked, controlled treatment periods in both studies was 24 weeks.

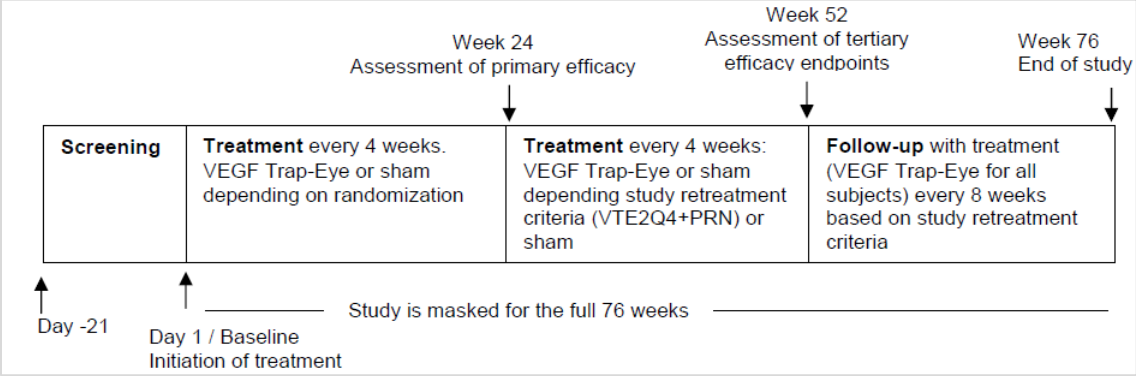
In GALILEO, patients in the 2 mg IVT aflibercept group received 2 mg IVT aflibercept by IVT injection every four weeks from day 1 through week 20.

In GALILEO, after 24 weeks, patients in the 2 mg IVT aflibercept group were eligible for re-treatment if they met the re-treatment criteria. If the re-treatment criteria were not met at a given visit during this treatment phase, patients received a sham injection in order to maintain masking. Patients were retreated with aflibercept if any of the following re-treatment criteria were met: increase of ≥ 50 μm in central retinal thickness on optical coherence tomography (OCT) compared with lower previous measurement, new or persistent cystic retinal damages of subretinal fluid on OCT or persistent diffuse edema of ≥ 250 μm in the central subfield on OCT, or a loss or gain of five letters or more between the current and most recent visit.[24,25] In the sham-injection group, treatment was continued through week 48. At 52 weeks, patients in the sham-injection group were eligible to receive 2 mg IVT aflibercept based on

the study re-treatment criteria every eight weeks. Treatment was masked for the full 76 weeks (Figure 2).

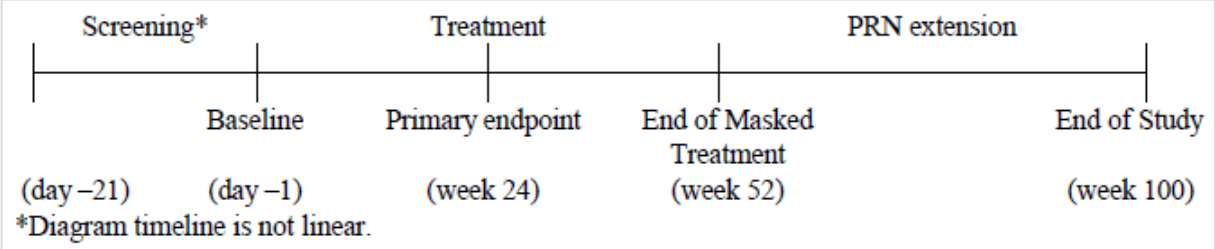
In COPERNICUS after 24 weeks through to 48 weeks, patients in the 2 mg IVT aflibercept group were evaluated monthly to receive either 2 mg IVT aflibercept injections as needed (PRN) or sham injections based on the treatment protocol. Patients in the sham-injection group starting at 24 weeks through 48 weeks were eligible for VEGF Trap-Eye injections PRN or sham injections according to the re-treatment criteria as described for GALILEO.

FIGURE 2: GALILEO TRIAL DESIGN



2Q4 = every four weeks; PRN = as needed; VEGF = vascular endothelial growth factor; VTE = VEGF Trap-Eye.
Source: Clinical Study Report A52377.[11]

FIGURE 3: COPERNICUS TRIAL DESIGN



PRN = as needed.
Source: Clinical Study Report R-8733.[20]

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Eligibility criteria for GALILEO and COPERNICUS were similar. To be eligible for both studies, patients were required to be treatment-naive adults diagnosed with macular edema secondary to CRVO diagnosed within nine months of study initiation. A study eye was required to have a mean retinal thickness of ≥ 250 μm and meet the ETDRS BCVA criteria described above. Women and men of childbearing/impregnating potential must have been willing to utilize adequate contraception and not become pregnant (or impregnate their partner) during the full course of the study.

Exclusion criteria included having only one functional eye; bilateral manifestation of RVO; history of vitreoretinal surgery in the study eye or anticipated surgery within the next months following day 1;

and previous treatment with intraocular or periocular corticosteroids, or anti-VEGF drugs in the study eye or fellow eye.

b) Baseline Characteristics

Demographic and baseline characteristics in GALILEO and COPERNICUS are displayed in Table 4. Patients were predominantly Caucasian. The mean age of patients was similar in both studies (61.5 and 66.3 years of age), as well as across treatment groups within the individual studies. The proportion of male and female patients was approximately equal across the two studies, with slightly more than half of the patients in both studies being male (56% and 57% in GALILEO and COPERNICUS, respectively). The proportions of males and females were generally similar within the GALILEO trial; however, in COPERNICUS the proportion of males (61%) in the 2 mg IVT aflibercept treatment group was greater than males in the sham-injection group (52%).

In COPERNICUS, the mean time since diagnosis for patients in the sham-injection group was approximately two months before compared with three months for the 2 mg IVT aflibercept group. Mean time since diagnosis was not reported in GALILEO. In the GALILEO trial, approximately equal proportions of patients were diagnosed < 2 months or ≥ 2 months before in both the sham-injection group and the 2 mg IVT aflibercept group. However, in the COPERNICUS trial, there was a greater proportion of patients diagnosed ≤ 2 months before in the sham-injection group (71.2%) compared with the 2 mg IVT aflibercept group (56.1%). Overall, in the COPERNICUS trial there was a greater proportion of patients who were diagnosed with CRVO ≤ 2 months before (62%); in GALILEO there was a greater proportion of patients who were diagnosed < 2 months before (53%). The majority of patients in both studies were perfused (or non-ischemic) at baseline. Overall, a greater proportion of patients in GALILEO were perfused (84%) compared with COPERNICUS (68%). In GALILEO, a greater proportion of patients in the 2 mg IVT aflibercept group were perfused (86%) compared with the sham-injection group (79%). In COPERNICUS, there were similar proportions of patients in the 2 mg IVT aflibercept and sham-injection groups perfused at baseline (67% and 68%, respectively). In GALILEO, the mean baseline BCVA scores were similar in the sham-injection and 2 mg IVT aflibercept treatment groups at approximately (51 letters and 54 letters, respectively). In COPERNICUS, baseline BCVA scores were similar in the sham-injection and 2 mg IVT aflibercept treatment groups (49 letters and 51 letters, respectively). BCVA proportions were similar within the GALILEO and COPERNICUS studies. However, in the GALILEO trial, there was a greater proportion of patients who could read ≥ 35 letters compared with COPERNICUS (83% versus 75%, respectively). Baseline retinal thickness was similar between GALILEO and COPERNICUS and within the treatment groups of the studies. Quality of life measured with the NEI VFQ-25 [redacted] Quality of life was assessed with the EQ-5D in GALILEO only. [redacted]

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS (FULL ANALYSIS SET)

Characteristics	GALILEO		COPERNICUS	
	Sham (N = 68)	2 mg IVT Aflibercept 2Q4 (N = 103)	**Sham (N = 73)**	2 mg IVT Aflibercept 2Q4 (N = 114)
Age, mean (SD) years Range	63.8 (13.3) 37 to 88	59.9 (12.4) 29 to 81	67.5 (14.29) 26 to 89	65.5 (13.57) 22 to 88
Male, n (%)	37 (54.4)	58 (56.3)	38 (52)	69 (61)
Race, Caucasian, n (%)	49 (72.1)	74 (71.8)	59 (80.8)	88 (77.2)

Characteristics	GALILEO		COPERNICUS	
	Sham (N = 68)	2 mg IVT Aflibercept 2Q4 (N = 103)	**Sham (N = 73)**	2 mg IVT Aflibercept 2Q4 (N = 114)
Months since diagnosis of CRVO, mean (SD) Range ≥ 2 months[a] or > 2 months,[b] n (%) < 2 months[a] or ≤ 2 months,[b] n (%)	[redacted] 33 (48.5) 35 (51.5)	[redacted] 46 (44.7) 55 (53.4)	1.88 (2.19) 0.0 to 9.2 21 (28.8) 52 (71.2)	2.73 (3.1) 0.0 to 18.2 49 (43.0) 64 (56.1)
Baseline retinal perfusion; n (%)				
Perfused (< 10 DA of capillary non-perfusion)	54 (79.4)	89 (86.4)	50 (68.5)	77 (67.5)
Non-perfused (≥ 10 DA of capillary non-perfusion)	7 (10.3)	7 (6.8)	12 (16.4)	17 (14.9)
Indeterminate	7 (10.3)	7 (6.8)	11 (15.1)	20 (17.5)
BCVA baseline (ETDRS)				
Mean (SD) Range	50.9 (15.4) 14 to 82	53.6 (15.8) [redacted]	48.9 (14.42) 20 to 73	50.7 (13.9) [redacted]
BCVA distribution				
BCVA > 20/200 (letters read ≥ 35) BCVA ≤ 20/200 (letters read ≤ 34)	56 (82.4) 12 (17.6)	86 (83.5) [redacted](16.5)	55 (75.3) 18 (24.7)	86 (75.4) 28 (24.6)
Baseline retinal thickness by OCT (µm)				
Mean (SD) Range	638.7 (224.7) 219.0 to 1,386.1	683.2 (234.5) 138.0 to 1,405.6	672.4 (245.3) 197 to 1,366	661.7 (237.4) [redacted]
NEI VFQ-25 total score				
Mean (SD) Range	78.9 (14.0) 44.2 to 96.3	[redacted]	77.8 (16.2) 23.5 to 97.4	77. 7 (16.0) 24.5 to 98.2
Baseline EQ-5D score				
Mean (SD) Range	[redacted]	[redacted]	NR	NR

2Q4 = every four weeks; BCVA = best-corrected visual acuity; CRVO = central retinal vein occlusion; DA = disc areas; ETDRS = Early Treatment Diabetic Retinopathy Study; IVT = intravitreal; NEI VFQ-25 = National Eye Institute 25-Item Visual Function Questionnaire; NR = not reported; OCT = optical coherence tomography; PRN = as needed; SD = standard deviation.
[a] GALILEO only.
[b] COPERNICUS only.
Source: Clinical Study Reports A52377[11] and R-8733.[20]

3.2.3 Interventions

2 mg IVT aflibercept was administered by IVIs to patients in the 2 mg IVT aflibercept treatment groups of GALILEO and COPERNICUS as 2 mg injections every four weeks. In GALILEO and COPERNICUS, 2 mg IVT aflibercept was supplied at a concentration of 40 mg/mL in sealed 3 mL single-use vials, each with a volume of 0.5 mL that could be withdrawn. Sham injections involved using a syringe, without a needle, to exert pressure on the eye, and did not involve intraocular penetration or injection of any substance. The sham kits were prepared to resemble the treatment in most facets including the same labelling and storage information. However, the kits differed in that there were no needles in the sham-injection kit. Patients in the sham-injection group received treatment every four weeks, as well.

In GALILEO, patients in the 2 mg IVT aflibercept group received 2 mg aflibercept by IVT injection every four weeks from day 1 through week 20. No treatment was received at week 24 prior to the collection of

data for the primary efficacy end point. Treatment was given at week 24 through week 52 based on the re-treatment criteria. If the re-treatment criteria were not met at a given visit during this treatment phase, subjects received a sham injection in order to maintain masking. Patients in the sham-injection group received sham injections every four weeks from day 1 through week 20. No treatment was received at week 24 prior to the collection of data for the primary efficacy end point. Sham injection was then given at all visits from week 24 through week 52.

In COPERNICUS, patients in the 2 mg IVT aflibercept group received 2 mg IVT aflibercept by IVT injection every four weeks from day 1 through week 20. No treatment was received at week 24 prior to the collection of data for the primary efficacy end point. Patients in the 2 mg IVT aflibercept group received 2 mg of active treatment PRN from week 24 through week 48. Patients in the sham-injection group received sham injection every four weeks through week 20. Starting at week 24 through week 48, patients in the sham plus PRN group were eligible to receive 2 mg IVT aflibercept.

Any other medication that was considered necessary for the patient's welfare, and that was not expected to interfere with the evaluation of the study drug, could be given at the discretion of the investigator. Patients were not allowed to receive any medications for their CRVO in the study eye other than the assigned study treatment. All patients who progressed to anterior segment neovascularization, neovascularization of the optic disc (NVD), or clinically relevant neovascularization of the retina elsewhere (NVE) could receive panretinal photocoagulation (PRP) at any time during the study. In addition, patients who received treatment in the fellow eye were not required to be withdrawn from the study.

3.2.4 Outcomes

a) Primary Outcome

In both GALILEO and COPERNICUS, the primary efficacy outcome was the proportion of patients who gained at least 15 BCVA letters at week 24 compared with baseline (patients who discontinued prior to week 24 were judged as failures).

b) Secondary Outcomes

Visual Acuity Measured With Early Treatment Diabetic Retinopathy Study

Change from baseline in BCVA as measured by ETDRS letter score at 24 weeks was a secondary outcome. To our knowledge, there has been no derivation of a minimal clinically important difference (MCID) for the ETDRS in CRVO. For macular edema, the US Food and Drug Administration (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.[26] A cut point for clinically meaningful change in patients with advanced eye disease should be higher than in healthy individuals, with a suggested range of between 10 and 15 letters.[27]

Change in Central Retinal Thickness

Change in central retinal thickness (CRT) was a secondary outcome evaluated using OCT on the study eye at 24 weeks. 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.[28] CRT is defined as the thickness of the centre subfield (the area of the retina using a 1 mm diameter around the centre of the macula).

Quality of Life and Visual Function

In both GALILEO and COPERNICUS, quality of life and vision function were evaluated using the NEI VFQ-25 at 24 weeks as secondary outcomes. 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). An improvement from baseline of between 3.3 points to 6.1 points was considered to be an MCID.[29-31] An MCID for the subscales was not determined from our review of the literature.

Quality of life was also measured using the EuroQol five-dimensions questionnaire (EQ-5D) in GALILEO. EQ-5D is a generic quality of life instrument that has been applied to a wide range of health conditions. The instrument consists of five scales: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels, reflecting no health problems, moderate health problems, and extreme health problems. The possible range of the EQ-5D total score is between 0 (worst imaginable health state) and 100 (best imaginable health state). No published evidence of validation and an MCID for the EQ-5D for patients with macular edema secondary to CRVO (or with other vision-related disorders) was found.[32,33]

Safety Outcomes

Various harms outcomes were reported, including mortality, serious adverse events (SAEs), and adverse events.

3.2.5 Statistical Analysis

a) Efficacy Criteria

The primary analysis plans for GALILEO and COPERNICUS were nearly identical. The primary analyses for both studies were statistical evaluations of superiority of 2 mg IVT aflibercept compared with sham injection for the proportion of patients who gained at least 15 BCVA letters (using the ETDRS chart) at 24 weeks, conducted using the full analysis set (FAS). If the primary efficacy analysis for the FAS was successful, the efficacy tests for superiority of 2 mg IVT aflibercept treatment over sham treatment in the secondary variables were to be considered confirmatory if they fulfilled sequential testing by preserving an alpha level of 0.05. A two-sided Cochran–Mantel–Haenszel (CMH) test was conducted at alpha level 0.05 stratified by regions (North America versus rest of the world or Europe versus Asia-Pacific) and baseline BCVA (BCVA > 20/200 and BCVA < 20/200).

The 2 mg IVT aflibercept treatment was considered to be superior to sham injection if the estimated proportion of patients who gained at least 15 letters on the BCVA (compared with baseline at 24 weeks) was greater in the aflibercept treatment group than in the sham-injection group, and the two-sided *P* value of the CMH statistic was ≤ 0.05. Patients in both studies were randomly assigned based on a ratio of 3:2 (2 mg IVT aflibercept: sham injection). A difference of 25% was expected between the two treatment groups in the proportion of patients gaining at least 15 letters, assuming proportions in the sham-injection group and 2 mg IVT aflibercept group of 15% and 40%, respectively.

In GALILEO, it was determined that a total sample size of at least 150 patients (60 in the sham-injection group and 90 in the 2 mg IVT aflibercept group) would be needed to detect the expected difference between the two treatments with a power of 90% in the two-sided Fisher's exact test at a level of 5%. Accounting for an anticipated 10% dropout rate, 165 patients (66 sham injection and 99 2 mg IVT aflibercept) were earmarked to be randomized and treated. This sample size would provide at least a 90% power for the primary analysis using the CMH test. In COPERNICUS, sample size calculations were nearly identical, with the exception of the expected dropout rate. To account for an expected dropout rate of 9%, 165 patients were planned to be enrolled (66 sham injection and 99 2 mg IVT aflibercept). In

the primary analysis, missing values were considered as failures. Baseline retinal perfusion status was determined by fluorescein angiography (FA) for each patient using the following criteria:

- Non-perfused: ≥ 10 disc areas of capillary non-perfusion on FA
- Perfused: < 10 disc areas of capillary non-perfusion on FA.

The proportion of patients achieving ≥ 15-letter improvement was reported for this subgroup of patients, along with an unadjusted difference in the proportions.

b) Analysis Populations

Three datasets were analyzed in both studies. The datasets were defined as follows:

Full analysis set: This included all randomized patients who received any investigational product, had a baseline efficacy assessment, and had at least one post-baseline assessment; it was based on the treatment allocated (as randomized).

Per-protocol set (PPS): This included all patients in the FAS who received at least five injections of study drug or sham, with the exception of patients excluded due to major protocol violations, where a major protocol violation was one that could have affected the interpretation of study results. The PPS was used for the efficacy analysis. The PPS was analyzed as treated.

Safety set: This included all randomized patients who received any investigational product; it was based on the treatment received (as treated). A maximum of one incorrect injection was allowed.

3.3 Patient Disposition

The disposition of patients is presented in Table 5. The overall study discontinuation rate among randomized patients was 14.1% in GALILEO and 10.1% in COPERNICUS at 24 weeks. In both studies, discontinuation rates were greater in the sham-injection groups compared with the 2 mg IVT aflibercept treatment groups (21.1% versus 9.4% and 18.9% versus 4.3% in GALILEO and COPERNICUS, respectively). The most common reason for discontinuation from the study before 24 weeks in the sham-injection groups was lack of efficacy or treatment failure (7.0% and 5.4% in GALILEO and COPERNICUS, respectively). The most frequent reason for discontinuation from the study before 24 weeks in the 2 mg IVT aflibercept group of GALILEO was protocol violation (4.7%); in COPERNICUS, it was withdrawal of consent (2.6%). At 52 weeks, findings were similar for the most frequent reason for discontinuation of study before 52 weeks for both treatment groups of GALILEO. IN COPERNICUS, findings were similar for the most frequent reason for discontinuation of study before 52 weeks in the 2 mg IVT aflibercept group; however, for the sham-injection group, the most frequent reason for discontinuation of study at 52 weeks was adverse events (5.4%). The proportion of patients who completed 24 weeks of VEGF treatment was high (91% to 96%), and the frequency of completion remained high at 52 weeks (86% to 93%). The proportion of patients who completed 24 weeks (79% to 81%) and 52 weeks (73% to 77%) was lower in the sham-injection groups.

TABLE 5: PATIENT DISPOSITION (ALL RANDOMIZED PATIENTS)

Disposition	GALILEO		COPERNICUS	
	Sham (N = 71)	2 mg IVT Aflibercept 2Q4 + PRN (N = 106)	Sham + PRN (N = 74)	2 mg IVT Aflibercept 2Q4 + PRN (N = 115)
Screened, N	240		273	
Randomized, N (%)	71 (100)	106 (100)	74 (100)	115 (100)
At 24 weeks				
Completed 24 weeks N (%)	56 (78.9)	96 (90.6)	60 (81.1)	110 (95.7)
Discontinued from study before 24 weeks, N (%)	15 (21.1)	10 (9.4)	14 (18.9)	5 (4.3)
Adverse event	4 (5.6)	0	3 (4.1)	0
Protocol violation	2 (2.8)	5 (4.7)	1 (1.4)	0
Withdrawal of consent	3 (4.2)	3 (2.8)	1 (1.4)	3 (2.6)
Lack of efficacy or treatment failure	5 (7.0)	0	4 (5.4)	0
Lost to follow-up	0	1 (0.9)	2 (2.7)	1 (0.9)
Completed study drug	53 (74.6)	95 (89.6)	60 (81.1)	110 (95.7)
Discontinued study drug before 24 weeks, N (%)	18 (25.4)	11 (10.4)	14 (18.9)	5 (4.3)
Adverse event	8 (11.3)	2 (1.9)	3 (4.1)	1 (0.9)
Lack of efficacy or treatment failure	4 (5.6)	0	4 (5.4)	0
Lost to follow-up	0	1(0.9)	2 (2.7)	1 (0.9)
Other	1 (1.4)	0	1 (1.4)	0
Protocol violation or deviation	2 (2.8)	5 (4.7)	1 (1.4)	0
Withdrawal of consent	3 (4.2)	3 (2.8)	1 (1.4)	3 (2.6)
FAS, N (%)	68 (95.8)	103 (97.2)	73 (98.6)	114 (99.1)
PP, N (%)	51 (71.8)	87 (82.1)	60 (81.1)	108 (93.9)
Safety, N (%)	68 (95.8)	104 (98.1)	74 (100)	114 (99.1)
At 52 weeks				
Completed 52 weeks	52 (73.2)	91 (85.8)	57 (77.0)	107 (93.0)
Discontinued study before week 52	19 (26.8)	15 (14.2)	17 (23.0)	8 (7.0)
Adverse event	4 (5.6)	4 (3.8)	4 (5.4)	0
Protocol violation	2 (2.8)	5 (4.7)	2 (2.7)	0
Withdrawal of consent	6 (8.5)	4 (3.8)	1 (1.4)	5 (4.3)
Lack of efficacy	6 (8.5)	0	NA	NA
Lost to follow-up	0	1 (0.9)	2 (2.7)	0
Discontinued treatment before week 52[a]	25 (35.2)	21 (19.8)	18 (24.3)	8 (7.0)
Adverse event	9 (12.7)	6 (5.7)	4 (5.4)	1 (0.9)
Protocol violation	2 (2.8)	5 (4.7)	2 (2.7)	0
Withdrawal of consent	3 (4.2)	4 (3.8)	1 (1.4)	5 (4.3)
Lack of efficacy or treatment failure	5 (7.0)	0	4 (5.4)	0
Lost to follow-up	0	1 (0.9)	3 (4.1)	2 (1.7)
Completed[b]	[redacted]	[redacted]	[redacted]	[redacted]

2Q4 = every four weeks; FAS = full analysis set; IVT = intravitreal; NA = not applicable; PP = per-protocol; PRN = as needed.
[a] Five patients are in the database as having discontinued (no reason provided). Following database lock, however, it was determined that these patients had not discontinued.
[b] These patients did not discontinue treatment. They actually completed the study and their final week-76 status was erroneously included in the 52-week database used for this Clinical Study Report.
Source: Clinical Study Report A52377 (week 24),[11] Clinical Study Report R-8733 (week 24),[18] Clinical Study Report A59664 (week 52),[13] and Clinical Study Report R-8734 (week 52).[20]

3.4 Exposure to Study Treatments

Detailed information on medication exposure is presented in Table 6 and Table 7. In GALILEO and COPERNICUS, a greater proportion of patients in the 2 mg IVT aflibercept treatment groups received 6 injections at 24 weeks (89.5% and 92.1%, respectively) compared with the sham-injection groups (79.5% and 89.2%, respectively). At 24 and 52 weeks, in GALILEO and COPERNICUS the duration of treatment was longer for patients in the 2 mg IVT aflibercept treatment groups compared with the sham-injection groups. In GALILEO, the proportion of patients with 100% compliance in the first 24 weeks in the 2 mg IVT aflibercept treatment [redacted]. In COPERNICUS, the proportion of patients who received 100% of planned injections in the first 24 weeks was high in both treatment groups, with greater compliance in the 2 mg IVT aflibercept group (92%) compared with the sham-injection group (89%). [redacted] Table 12[redacted]. In both studies, all patients, regardless of treatment group, were eligible to receive PRP during the study if they progressed to anterior segment neovascularization, NVD, or clinically relevant NVE. Through week 24, patients who underwent concomitant PRN treatment (2 mg IVT aflibercept versus sham injection) were: GALILEO: 1 (1.0%) versus 3 (4.4%); COPERNICUS: 0 (0%) versus 4 (5.5%).[24]

TABLE 6: TREATMENT EXPOSURE DURING 24 WEEKS (SAFETY ANALYSIS SET)

	GALILEO		COPERNICUS	
	Sham (N-68)	2 mg IVT Aflibercept 2Q4 + PRN (N = 104)	Sham + PRN (N = 74)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114)
Number of patients with the injections n (%)				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
6	[redacted] (79.4)	[redacted] (8.5)	[redacted]	[redacted]
Frequency count				
Mean (SD)	5.3 (1.5)	5.7 (0.9)	5.3 [redacted]	5.8 [redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Total amount (mg)				
Mean (SD)	0	[redacted]	0	[redacted]
Median	0	[redacted]	0	[redacted]
Range	0	[redacted]	0	[redacted]
Duration of treatment (days)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	28 to 184	[redacted]	[redacted]

2Q4 = every four weeks; PRN = as needed; SD = standard deviation.
Source: Clinical Study Report A52377 (week 24)[11] and Clinical Study Report R-8733 (week 24).[18]

TABLE 7: TREATMENT EXPOSURE DURING 52 WEEKS (SAFETY ANALYSIS SET)

		GALILEO	COPERNICUS	
	Sham (N = 68)	2 mg IVT Aflibercept 2Q4 + PRN (N = 104)	Sham (N = 74)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114)
Number of patients with injections n (%)				
1	[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]
7	0	[redacted]	2 (2.7)	[redacted]
8	2 (2.9)	[redacted]	NA	[redacted]
9	1 (1.5)	[redacted]	1 (1.4)	[redacted]
10	0	[redacted]	1 (1.4)	[redacted]
11	2 (2.9)	[redacted]	[redacted]	[redacted]
12	1 (1.5)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Frequency count				
Mean (SD)	10.5 (4.2)	11.8 (2.8)	10.6 (3.85)	12.2 (2.07)
Range	1.0 to 13.0	[redacted]	1.0 to 13.0	[redacted]
Total amount (mg)				
Mean (SD)	0.0 (0.0)	16.0 (4.7)	6.3 (4.69)	16.8 (3.94)
Median	0.0	[redacted]	6.0	[redacted]
Range	0	[redacted]	0 to 13	[redacted]
Duration of treatment (days)				
Mean (SD)	297.0 (119.9)	333.6 (85.7)	308.9 (113.14)	351.1 (58.17)
Median	364	[redacted]	364.0	[redacted]
Range	28 to 371	[redacted]	28 to 379	[redacted]

2Q4 = every four weeks; IVT = intravitreal; PRN = as needed; SD = standard deviation.
Source: Clinical Study Report A59664 (week 52)[13] and Clinical Study Report R-8734 (week 52).[20]

3.5 Critical Appraisal

3.5.1 Internal Validity

The included studies were double-masked, multi-centre, randomized, sham-controlled superiority studies. The randomization process, including allocation concealment and masking method, was well described and performed. Overall, the important baseline characteristics were similar between the two treatment groups with both studies. 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 or medical records, another strength of this trial.

However, there were some limitations to the included studies. There is a lack of direct comparisons between aflibercept and other active treatments listed in the systematic review protocol. This includes ranibizumab and dexamethasone IVI implant (the only treatments licensed in Canada for CRVO). Any

patient could have received PRP as a rescue treatment if he or she progressed to anterior segment neovascularization, NVD, or clinically relevant NVE at any time during the study. At 24 weeks, the overall proportion of patients who underwent concomitant PRN treatment was relatively low (0% to 1% in the VEGF groups and 4% to 6% in the sham-injection group). In both studies, a greater proportion of patients receiving rescue therapy in the sham-injection groups may have biased the results against detecting superiority of aflibercept compared with sham injection.

In both GALILEO and COPERNICUS, there were differential dropout rates between the 2 mg IVT aflibercept treatment groups (9% and 4%, respectively) compared with the sham-injection groups (21% and 19%). A difference in the rates of discontinuation is a cause for concern with respect to biases arising from imbalances between treatment groups over the course of the study. [redacted]

In addition, sham injection kits were similar to 2 mg IVT aflibercept; however, they did not include a needle in the package. There was no intraocular penetration; thus, the physician and drug handler were unmasked to treatment. The unmasked physician prepared and administered the 2 mg IVT aflibercept or sham injection. The treating physician was aware of the patient's treatment allocation and could have consciously or unconsciously revealed the patient's treatment assignment during the course of the study. Moreover, patients may have been able to distinguish between having an injection into the eye versus the sham procedure, which consisted of simply having pressure applied. Although the visual acuity and OCT examiner were blinded, patient's knowledge of treatment allocation may have affected outcome measures, particularly subjective outcomes such as quality of life.

The included studies followed patients for a maximum of 24 weeks after initial treatment with aflibercept. Although data for 76 weeks and 100 weeks of follow-up are available for patients from GALILEO and COPERNICUS, respectively, these are non-comparative, observational data in which everyone received aflibercept as needed (with the exception of the sham-injection patients in GALILEO until week 52).

3.5.2 External Validity

Patients with eye disease or comorbidities other than macular edema secondary to CRVO — such as history of any vitreous hemorrhage or vitrectomy — were excluded from the study. Therefore, the safety profiles as demonstrated in the studies may not reflect real-world clinical practice. Patients were excluded if they had had any prior or concomitant therapy or surgery for macular edema secondary to CRVO. Therefore, the effect of the study drug compared with sham injection was demonstrated only in a treatment-naive population based on the two included studies for this review. The findings of these studies cannot be applied to a treatment-experienced population. The superiority aflibercept compared with sham injection was assessed at 24 weeks. Therefore, the durability of this effect beyond 24 weeks may be considered uncertain.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (see section 2.2, Table 2). For detailed efficacy data, see Appendix 4: Detailed Outcome Data.

3.6.1 Blindness

No data were reported in GALILEO and COPERNICUS on the number of cases of blindness.

3.6.2 Best-Corrected Visual Acuity

At 24 weeks, the proportion of patients who had an improvement of ≥ 15 BCVA letters was similar in the 2 mg IVT aflibercept groups of GALILEO (60%) and COPERNICUS (56%). In the sham-injection groups, a greater proportion of patients had an improvement of ≥ 15 letters in GALILEO (22.1%) compared with COPERNICUS (12.3%). In GALILEO and COPERNICUS, the 2 mg IVT aflibercept treatment groups demonstrated superiority to sham injection in the FAS (adjusted difference [AD] = 38.3%; 95% CI, 24.4 to 52.1% and AD = 44.8%; 95% CI, 33.0 to 56.0%, respectively) (Table 8). In GALILEO and COPERNICUS, the findings for the proportion of patients who had an improvement of ≥ 15 BCVA letters were generally similar in the per-protocol population.

For the subgroup of patients categorized as non-perfused (ischemic) versus perfused (non-ischemic), unadjusted differences between the 2 mg IVT aflibercept groups and sham-injection groups were reported in GALILEO and COPERNICUS (Table 16). In GALILEO, [redacted] in COPERNICUS, for non-perfused patients, the proportion of patients achieving an improvement of ≥ 15 BCVA letters was greater in the 2 mg IVT aflibercept group (51.4%) compared with the sham-injection group (4.3%); the difference was 47.0% (95% CI, 28.9 to 65.1%). For perfused patients, the proportion achieving an improvement of ≥ 15 BCVA letters was greater in the 2 mg IVT aflibercept group (58.4%) compared with the sham-injection group (16.0%); the difference was 42.4% (95% CI, 27.5 to 57.4).

At 52 weeks, the adjusted difference between the 2 mg IVT aflibercept treatment groups of GALILEO and COPERNICUS and sham-injection groups for the proportion of patients who demonstrated an improvement of ≥ 15 BCVA letters was smaller than at 24 weeks (AD = 27.9%; 95% CI, 13.0 to 42.7% and AD = 25.9%; 95% CI, 11.8 to 40.1%) (Table 9). Findings for the non-perfused versus perfused subgroups were not reported in the data sources examined at 52 weeks.

At 24 weeks, the least squares mean change from baseline in BCVA score between the 2 mg IVT aflibercept and sham-injection groups was statistically significant in GALILEO, supporting the superiority of 2 mg IVT aflibercept to sham injection (least square mean difference [LSMD] = 14.7 letters; 95% CI, 10.8 to 18.7 letters) (Table 9). Similarly, in COPERNICUS the difference in least squares mean change from baseline in BCVA score between the 2 mg IVT aflibercept and sham-injection groups was statistically significant, supporting the superiority of 2 mg IVT aflibercept to sham (LSMD = 21.7 letters; 95% CI, 17.4 to 26.0 letters) (Table 8). At 52 weeks, the difference in least square mean change from baseline ETDRS letter score between the 2 mg IVT aflibercept and sham-injection groups was statistically significant, supporting the superiority of 2 mg IVT aflibercept to sham injection (LSMD = 13.2 letters; 95% CI, 8.2 to 18.2 letters and LSMD = 12.7; 95% CI, 7.7 to 17.7 letters, in GALILEO and COPERNICUS, respectively) (Table 8). At 52 weeks, the effect sizes were smaller than reported at 24 weeks.

3.6.3 Quality of Life and Visual Function

In GALILEO, NEI VFQ-25 mean total scores were similar between treatment groups at baseline. At 24 weeks, a greater improvement in least squares mean scores was observed in the 2 mg IVT aflibercept group (4.5 points) compared with the sham-injection group (0.3 points) (LSMD = 4.2 points; 95% CI, 1.7 points to 6.8 points) (Table 8). At 52 weeks, the findings were similar, as the difference between the 2 mg IVT aflibercept group and sham-injection group was statistically significant in favour of the 2 mg IVT aflibercept group (LSMD = 3.6, 95% CI, 1.1 to 6.0) (Table 9). In COPERNICUS, mean NEI VFQ-25 total scores were similar between treatment groups at baseline. At week 24, a greater improvement in mean scores was observed in the 2 mg IVT aflibercept group (7.2 points) compared with the sham-injection group (0.8 points) (LSMD = 6.26 points; 95% CI, 2.61 to 9.91) (Table 8). At 52 weeks, there was no significant difference between the 2 mg IVT aflibercept and sham-injection groups for the mean change from baseline in NEI VFQ-25 scores (Table 9).

Quality of life was also measured with the EQ-5D in GALILEO only. At baseline, patients in the sham and 2 mg IVT aflibercept group had similar mean EQ-5D scores. At 24 weeks, a greater improvement in EQ-5D scores was observed in the 2 mg IVT aflibercept group (0.013) compared with the sham-injection group (–0.031). However, the difference between the groups was not statistically significant (Table 8). At 52 weeks, a greater improvement in EQ-5D was observed in the 2 mg IVT aflibercept group (0.026) compared with the sham-injection group (0.013). However, the difference between the two groups was not statistically significant (Table 9).

3.6.4 Central Retinal Thickness

At baseline in GALILEO, mean CRT was similar in the VEGF group and sham-injection group. At 24 weeks, the adjusted least squares mean change from baseline values showed a statistically significantly greater decrease in the 2 mg IVT aflibercept group (–447.97 μm) compared with the sham-injection group (–208.55 μm [LSMD = –239.42 μm; 95% CI, –286.31 to –192.53 μm]) (Table 8). At 52 weeks, the adjusted least squares mean change from baseline values showed a statistically significantly greater decrease in the 2 mg IVT aflibercept group (–441.62 μm) compared with sham-injection group (–274.15 μm [LSMD = –167.47 μm; 95% CI,–216.62 to –118.33]). At baseline in COPERNICUS, mean CRT was similar between the 2 mg IVT aflibercept group and the sham-injection group. At 24 weeks, the adjusted mean change from baseline values showed a greater decrease in the 2 mg IVT aflibercept group (–487.1 μm) compared with the sham-injection group (–175.2 μm [LSMD = –311.9 μm; 95% CI, –389.4 to –234.4]). At 52 weeks, there were no significant differences between the 2 mg aflibercept group and sham-injection group.

TABLE 8: KEY EFFICACY OUTCOMES AT 24 WEEKS (FULL ANALYSIS SET)

	GALILEO		COPERNICUS	
Proportion of Patients Gained ≥ 15 Letters on the BCVA at 24 Weeks, n (%)	**Sham (N = 68)**	**2 mg IVT Aflibercept 2Q4 (N = 103)**	**Sham + PRN (N = 73)**	**2 mg IVT Aflibercept 2Q4 (N = 114)**
Efficacy outcomes at 24 weeks				
Week 24, n (%)	15 (22.1)	62 (60.2)	9 (12.3)	64 (56.1)
Adjusted difference[a] (%) (95% CI)	38.3[b] (24.4 to 52.1)		44.8[b] (33.0 to 56.6)	
BCVA at week 24				
Baseline mean (SD)	50.9 (15.4)	53.6 (15.8)	48.9 (NR)	50.7 (NR)
Mean at week 24 (SD)	54.3 (20.2)	71.6 (17.1)	44.8 (NR)	68.0 (NR)
LS mean[c]	3.0	17.7	–5.33	16.36
LSMD (95% CI)	14.7[b] (10.8, 18.7)		21.7[b] (17.4 to 26.0)	

Proportion of Patients Gained ≥ 15 Letters on the BCVA at 24 Weeks, n (%)	GALILEO		COPERNICUS	
	Sham (N = 68)	2 mg IVT Aflibercept 2Q4 (N = 103)	Sham + PRN (N = 73)	2 mg IVT Aflibercept 2Q4 (N = 114)
Change from baseline NEI VFQ-25 total score at week, N	65	96	59	104
Baseline mean (SD)	[redacted]	[redacted]	78.0 (16.25)	77.7 (15.96)
Mean at week 24 (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change (unadjusted) at 24 weeks	3.5	7.5	0.8	7.2
LS mean change[c]	0.3	4.5	2.54	8.80
LSMD (95% CI)	4.2[d] (1.7 to 6.8)		6.23[e] (2.6, 9.9)	
Change from baseline in EQ-5D score from baseline at week 24, N	[redacted]	[redacted]	NR	NR
Baseline mean (SD)	[redacted]	[redacted]	NR	NR
Mean at 24 weeks (SD)	[redacted]	[redacted]	NR	NR
LS mean change[c]	–0.031	0.013	NR	NR
LSMD (95% CI)	0.044(–0.002 to 0.090)		NR	NR
CRT at week 24, N (%)	68	103	65	112
Baseline mean (SD)	638.7 (224.7)	683.2 (234.5)	664.0 (NR)	661.7 (NR)
Mean	464.9 (205.5)	234.6 (109.3)	519.2	204.5
LS mean change[c]	–208.55	–447.97	–175.2	–487.1
LSMD (95% CI)	–239.4[b] (–286.3 to –192.5)		–311.9[b] (–389.4 to –234.4)	

2Q4 = every four weeks; ANCOVA = analysis of covariance; BCVA = best-corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; EQ-5D = EuroQol five-dimensions questionnaire; IVT = intravitreal; LS = least squares; LSMD = least squares mean difference; NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; NR = not reported; PRN = as needed.

[a] Adjusted differences were calculated using a weighting scheme adjusted by regions (Europe versus Asia-Pacific or North America versus rest of world) and baseline BCVA (BCVA > 20/200 and BCVA ≤ 20/200).

[b] $P < 0.0001$.

[c] LS mean changes were calculated using an ANCOVA model with treatment group, region, and baseline BCVA (BCVA < 20/200 and BCVA ≤ 20/200) as fixed factors.

[d] $P < 0.05$.

[e] $P < 0.001$.

Source: Clinical Study Report A52377 (week 24),[11] Clinical Study Report R-8733 (week 24),[18] Clinical Study Report A59664 (week 52),[13] and Clinical Study Report R-8734 (week 52).[20]

TABLE 9: KEY EFFICACY OUTCOMES AT 52 WEEKS (FULL ANALYSIS SET)

	GALILEO		COPERNICUS	
	Sham (N = 68)	2 mg IVT Aflibercept 2Q4 + PRN (N = 103)	Sham + PRN (N = 73)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114)
Proportion of who patients gained ≥ 15 letters in BCVA at 52 weeks, N (%)	22 (32.4)	62 (60.2)	22 (30.1)	63 (55.3)
Adjusted difference[a] (%) (95% CI)	27.9[b] (13.0, 42.7)		25.9[b] (11.8 to 40.1)	
BCVA score at week 52				
Mean (SD)	54.7 (21.8)	70.4 (18.6)	52.7	66.8
LS mean[c]	4.9	18.1	1.3	14.0
LSMD (95% CI)	13.2[d] (8.2 to 18.2)		12.7[d] (7.7, 17.7)	

	GALILEO		COPERNICUS	
	Sham (N = 68)	2 mg IVT Aflibercept 2Q4 + PRN (N = 103)	Sham + PRN (N = 73)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114)
Change from baseline NEI VFQ-25 total score				
Week 52 mean	[redacted]	[redacted]	[redacted]	[redacted]
Mean change (unadjusted) at 52 weeks	4.5	7.8	5.1	7.5
LS mean change[c]	1.7	5.3	6.91	9.28
LSMD (95% CI)	3.6[e] (1.1 to 6.0)		2.4 (–1.4 to 6.2)	
Change from baseline in EQ-5D score from baseline at week 52				
Mean	[redacted]	[redacted]	NR	NR
Change (unadjusted) at 52 weeks	0.029	0.029	NR	NR
LS mean change[c] (SD)	0.013 (NR)	0.026 (NR)	NR	NR
LSMD (95% CI)	0.013 (–0.021 to 0.047)		NR	NR
CRT week 52				
Mean	414.90 (202.99)	259.68 (136.39)	282.2	248.7
LS mean change[c]	–274.15	–441.62	–426.7	–455.1
Change from baseline CRT score at week 52, LSMD (95% CI)	–167.47[d] (–216.62 to –118.33)		–28.4 (–121.22 to 64.34)	

2Q4 = every four weeks; BCVA = best-corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; EQ-5D = EuroQol five-dimensions questionnaire; IVT = intravitreal; LS = least squares; LSMD = least squares mean difference; NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; PRN = as needed; SD = standard deviation.

[a] Adjusted differences were calculated using a weighting scheme adjusted by region (Europe versus Asia-Pacific or North America versus rest of world) and baseline BCVA (BCVA > 20/200 and BCVA ≤ 20/200).

[b] $P < 0.001$.

[c] LS mean changes were calculated using an ANCOVA model with treatment group, region and baseline BCVA (BCVA < 20/200 and BCVA ≤ 20/200) as fixed factors.

[d] $P < 0.0001$.

[e] $P < 0.05$.

Source: Clinical Study Report A52377 (week 24),[11] Clinical Study Report R-8733 (week 24),[18] Clinical Study Report A59664 (week 52),[13] and Clinical Study Report R-8734 (week 52).[20]

3.7 Harms

Only those harms identified in the review protocol are reported subsequently (see 2.2.1, Protocol). For detailed harms data, see Appendix 4: Detailed Outcome Data.

3.7.1 Treatment-Emergent Adverse Events

In both studies, there was a lower rate of treatment-emergent adverse events (TEAEs) in aflibercept-treated patients compared with sham-treated patients, although the differences between treatments were generally small and never exceeded 10%. In GALILEO, there was a smaller proportion of TEAEs in the 2 mg IVT aflibercept group (68.3%) compared with the sham-injection group (77.9%) at 24 weeks. At 52 weeks, the proportion of TEAEs increased in both treatment groups with a smaller proportion of TEAEs in the 2 mg IVT aflibercept group (82.7%) and sham-injection group (86.8%) (Table 10). In COPERNICUS, there was a slightly smaller proportion of TEAEs in the 2 mg IVT aflibercept group (81.6%) compared with the sham-injection group (83.8%) at 24 weeks. At 52 weeks, the proportion of TEAEs increased in both treatment groups with a higher proportion of TEAEs in the 2 mg IVT aflibercept group (97.4%) compared with the sham-injection group (91.9%) (Table 10).

a) 24 Weeks

At 24 weeks, in both studies there was a lower rate of ocular adverse events (AEs) in the aflibercept treatment groups compared with the sham-injection groups; the differences between treatments were generally small and never exceeded 10%. At 24 weeks in GALILEO, a smaller proportion of patients in the 2 mg IVT aflibercept group experienced an ocular AE in the study eye (54.8%) compared with the sham-injection group (64.7%) (Table 10). The most frequently occurring ocular AEs in the 2 mg IVT aflibercept treatment groups of GALILEO and COPERNICUS were eye pain (11.5% and 14.0%, respectively) and conjunctival hemorrhage (8.7% and 14.9%, respectively)(Table 18). Overall, in COPERNICUS, a smaller proportion of patients in the 2 mg IVT aflibercept group experienced an ocular AE in the study eye (63.2%) compared with the sham-injection group (66.2%) (Table 10). The most frequent ocular TEAEs in the sham-injection group of GALILEO were macular edema (16.2%), eye irritation (10.3%) and visual acuity reduced (10.3%) at 24 weeks. In COPERNICUS, the most frequently occurring ocular TEAEs in the sham-injection group at 24 weeks were conjunctival hemorrhage (17.6%) and reduced visual acuity (17.6%) (Table 18).

At 24 weeks, the results concerning the frequency of non-ocular AEs were inconsistent. At 24 weeks in GALILEO, the frequency of non-ocular AEs was lower in 2 mg IVT the aflibercept group (45.2%) compared with the sham-injection group (54.4%) (Table 10). At 24 weeks in COPERNICUS, the frequency of non-ocular AEs was higher in the aflibercept group (50.9%) compared with the sham-injection group (48.6%). The most frequently occurring non-ocular AEs for the 2 mg IVT aflibercept treatment groups were nasopharyngitis in GALILEO and COPERNICUS (7.7% and 4.4%, respectively), headache (6.7% in GALILEO), and hypertension (8.8% in COPERNICUS) (Table 20). For non-ocular TEAEs, the most frequently occurring TEAEs in the GALILEO sham-injection groups were nasopharyngitis (8.8%) and arthralgia (7.4%). In the COPERNICUS sham-injection group, the most frequent non-ocular TEAEs were nasopharyngitis (5.4%) and hypertension (5.4%).

b) 52 Weeks

At 52 weeks, in both studies there was no evidence to suggest there may be a lower proportion of ocular AEs for the aflibercept group compared with the sham-injection group. At 52 weeks in GALILEO, a smaller proportion of patients in the 2 mg IVT aflibercept group experienced an ocular AE in the study eye (72.1%) compared with (75.0%) the sham-injection group (Table 10). At 52 weeks in COPERNICUS, the proportion of patients experiencing an ocular AE in the study eye was the same for the 2 mg IVT aflibercept group (78.4%) and the sham-injection group (78.9%) (Table 10). The most frequent ocular AEs in the GALILEO 2 mg IVT aflibercept group were macular edema (33.7%) and eye pain (14.4%) (Table 19). At 52 weeks, the most frequent ocular AEs in the COPERNICUS 2 mg IVT aflibercept group were reduced visual acuity (18.4%) and eye pain (15.8%). At 52 weeks, the most frequent ocular AEs for in the GALILEO sham-injection group were macular edema (22.1%), reduced visual acuity (11.8%), retinal vascular disorder (11.8%), and retinal hemorrhage (11.8%). The most frequent ocular AEs in the COPERNICUS sham-injection group were reduced visual acuity (21.6%) and conjunctival hemorrhage (18.9%) (Table 19).

At 52 weeks, in both studies there was no evidence to suggest there was a difference in non-ocular AEs between the aflibercept and sham-injection groups. At 52 weeks in GALILEO, the frequency of non-ocular AEs was similar for the 2 mg IVT aflibercept group (66.3%) compared with the sham-injection group (66.2%). At 52 weeks in COPERNICUS, the frequency of non-ocular AEs was similar for the 2 mg IVT aflibercept group (74.6%) and the sham-injection group (73.0%). The most frequently occurring non-ocular AEs for the 2 mg IVT aflibercept treatment groups in GALILEO were nasopharyngitis (13.5%) and headache (9.6%) (Table 21). The most frequent non-ocular AE for the 2 mg IVT aflibercept group in

COPERNICUS were hypertension (14.9%), nasopharyngitis (7.9%), and upper respiratory tract infection (7.9%) (Table 22). The most frequently occurring non-ocular AEs for the GALILEO sham-injection group were nasopharyngitis (22.1%), arthralgia (8.8%), and hypertension (8.8%). The most frequent non-ocular AEs for the COPERNICUS sham-injection group were hypertension (9.5%), protein urine present (6.8%), increased blood glucose (6.8%), and nasopharyngitis (6.8%).

3.7.2 Serious Adverse Events

a) 24 Weeks

In both studies, there was a lower rate of SAEs in aflibercept-treated patients compared with sham-treated patients, although the differences between treatments were generally small and never exceeded 12% at 24 weeks. In GALILEO, there was a smaller proportion of SAEs in the 2 mg IVT aflibercept group (8.7%) compared with the sham-injection group (14.7%) at 24 weeks. In COPERNICUS, there was a smaller proportion of SAEs in the 2 mg IVT aflibercept group (9.6%) versus the sham-injection group (21.6%) at 24 weeks. In GALILEO, no individual reason for ocular SAEs accounted for more than two events in either treatment group (Table 23). The proportion of ocular SAEs was lower in the 2 mg IVT aflibercept group (2.9%) compared with the sham-injection group (8.8%). In COPERNICUS, the proportion of ocular SAEs was lower in the 2 mg IVT aflibercept group (3.5%) compared with the sham-injection group (13.5%); no individual reason for ocular SAE accounted for more than one event in the 2 mg IVT aflibercept group. In the sham-injection group, the most frequent reason for ocular SAE was vitreous hemorrhage (5.4%) (Table 23).

In both studies, there was a lower rate of non-ocular SAEs in the aflibercept group compared with the sham-injection group at 24 weeks. In GALILEO at 24 weeks, there was a smaller proportion of non-ocular SAEs in the 2 mg IVT aflibercept group (5.8%) compared with the sham-injection group (7.4%) (Table 25). In COPERNICUS at 24 weeks, the proportion of non-ocular SAEs was lower in the 2 mg IVT aflibercept group (5.3%) compared with the sham-injection group (8.1%) (Table 25). There was no individual reason for non-ocular SAEs that occurred more than once in any GALILEO or COPERNICUS treatment group.

a) 52 Weeks

At 52 weeks, there was some evidence in COPERNICUS only to suggest that aflibercept may have a lower rate of ocular SAEs compared with sham injection. In GALILEO at 52 weeks, there were similar proportions of ocular SAEs in the 2 mg IVT aflibercept group (9.6%) and sham-injection group (8.8%) (Table 24). In COPERNICUS at 52 weeks, there was a smaller proportion of ocular SAEs in the 2 mg IVT aflibercept group (5.3%) compared with the sham-injection group (16.2%). In GALILEO, the most frequent reason for ocular SAEs were four (3.8%) occurrences of macular edema in the 2 mg IVT aflibercept treatment group. In COPERNICUS, no individual reason for ocular SAEs accounted for more than one event in the 2 mg IVT aflibercept treatment group. In GALILEO, no individual reason for ocular SAE accounted for more than two events in the sham-injection group. In COPERNICUS, the most frequent AEs in the sham-injection group were vitreous hemorrhage (6.8%) and glaucoma (4.1%) (Table 24). In both studies, there was some evidence to suggest that aflibercept offered a modest benefit compared with sham injection in terms of non-ocular SAEs, although the difference did not exceed 2.6%. In GALILEO at 52 weeks, the proportion of non-ocular SAEs was lower in the 2 mg IVT aflibercept group (10.6%) compared with the sham-injection group (13.2%) (Table 26). In COPERNICUS at 52 weeks, the proportion of non-ocular SAEs was lower in the 2 mg IVT aflibercept group (11.4%) compared with the sham-injection group (13.5%) (Table 28). In GALILEO and COPERNICUS, there was no individual reason for non-ocular SAEs that accounted for more than one event in the 2 mg IVT aflibercept treatment groups. The most frequent reason for non-ocular SAE in the sham-injection group of GALILEO was syncope (2.9%). The most frequent reason for non-ocular SAEs in the COPERNICUS sham-injection group was pancreatitis (2.7%) (Table 28).

3.7.3 Withdrawals Due to Adverse Events

b) 24 Weeks

In both studies, there was some evidence to suggest a smaller proportion of patients treated with aflibercept were withdrawn from the study due to adverse events (WDAE); however, the difference did not exceed 7% at 24 weeks. In GALILEO at 24 weeks, the proportion of patients who discontinued due to adverse events was lower for the 2 mg IVT aflibercept treatment group (1.9%) compared with the sham-injection group (8.8%) at 24 weeks. In COPERNICUS at 24 weeks, the proportion of patients who discontinued due to adverse events was lower in the 2 mg IVT aflibercept group (1.8%) compared with the sham-injection group (6.8%) at 24 weeks. No individual reason for WDAE accounted for more than one event in the 2 mg IVT aflibercept treatment groups of GALILEO and COPERNICUS. The most frequent reasons for WDAE in the sham-injection group of GALILEO were two occurrences of glaucoma (2.9%) and two of retinal neovascularization (2.9%). In the COPERNICUS sham-injection group, the most frequent reason for WDAE was vitreous hemorrhage (2.7%) (Table 29).

c) 52 Weeks

At 52 weeks, there continued to be evidence to suggest a smaller proportion of patients treated with aflibercept discontinued to due adverse events; however, the difference did not exceed 5% at 52 weeks. In GALILEO at 52 weeks, the proportion of patients who discontinued due to adverse events was lower in the 2 mg IVT aflibercept group (5.8%) compared with the sham-injection group (10.3%) (Table 30). In the GALILEO 2 mg IVT aflibercept treatment group, the most frequent reason for WDAE were two occurrences (1.9%) of iris neovascularization. In the COPERNICUS 2 mg IVT aflibercept group, no reason for WDAE accounted for more than one event. In the GALILEO sham-injection group, the most frequent reason for WDAE was retinal neovascularization (4.4%). In COPERNICUS at 52 weeks, the proportion of patients who discontinued due to adverse events was lower in the 2 mg IVT aflibercept group (1.8%) compared with the sham-injection group (6.8%). In the COPERNICUS sham-injection group, the most frequent reason for WDAE was vitreous hemorrhage (2.7%).

3.7.4 Mortality

There were no deaths in GALILEO at 24 weeks. In COPERNICUS, there were two deaths in the sham-injection group and no deaths in the 2 mg IVT aflibercept group. There were no additional deaths in either trial up to 52 weeks.

3.7.5 Notable Harms

Notable harms identified in the protocol included arterial thromboembolic events (ATEs), cardiovascular events, increased intraocular pressure (IOP), endophthalmitis, and retinal detachment. A summary of these events can be found in Table 10.

No ATEs were reported for GALILEO at 24 weeks. In COPERNICUS, at 24 weeks, there were ATEs (2.7%) reported in the sham-injection group, but none in the 2 mg IVT aflibercept group. In GALILEO at 52 weeks, there was one ATE (1.0%) in the 2 mg IVT aflibercept group and two in the sham injection control group (2.9%), but no ATEs in COPERNICUS at 52 weeks. However, using the Antiplatelet Trialists' Collaboration classification for ATEs, there was one ATE in the 2 mg IVT aflibercept group (0.9%) and two events in the sham control group reported at 52 weeks (2.7%).

Increased IOP occurred in both GALILEO and COPERNICUS. In GALILEO at 24 weeks, the same proportions of patients in the VEGF and sham-injection groups experiencing a ≥ 10 mm Hg increase in IOP (2.9% in both). In COPERNICUS at 24 weeks, there was a smaller proportion of patients who experienced a ≥ 10 mm Hg increase in IOP in the 2 mg IVT aflibercept group (2.6%) compared with the

sham-injection group (9.5%). In GALILEO at 24 weeks, similar proportions of patients had a pre-injection IOP absolute value of ≥ 21 mm Hg in the 2 mg IVT aflibercept group (4.8%) and sham-injection group (5.9%). In COPERNICUS at 24 weeks, the proportions of patients with a pre-injection IOP absolute value of ≥ 21 mm Hg in both treatment groups were higher than those of GALILEO. There was a smaller proportion of patients in the 2 mg IVT aflibercept group (14.9%) compared with the sham-injection group (20.3%) with a pre-injection IOP absolute value of ≥ 21 mm Hg at 24 weeks. Cases of pre-injection IOP absolute value of ≥ 35 mm Hg were infrequent at 24 weeks; there was one case in the sham-injection group only (1.5%) of GALILEO and two cases in the sham-injection group (2.7%) only of COPERNICUS.

In GALILEO at 52 weeks, similar proportions of patients in the 2 mg IVT aflibercept group and sham-injection treatment groups experienced a ≥ 10 mm Hg increase in IOP (7.7% and 7.4%, respectively). The proportion of patients with a pre-injection IOP absolute value of ≥ 21 mm Hg was greater in the 2 mg IVT aflibercept group (18.3%) compared with the sham-injection group (13.2%) at 52 weeks. The proportion of patients with a pre-injection IOP absolute value of ≥ 35 mm Hg was greater in the 2 mg IVT aflibercept group (5.8%) compared with the sham-injection group (2.9%) at 52 weeks. In COPERNICUS at 52 weeks, the proportion of patients experiencing a ≥ 10 mm Hg increase in IOP was lower in the 2 mg IVT aflibercept group (6.1%) compared with the sham-injection group (13.5%) at 52 weeks. The proportion of patients with a pre-injection IOP absolute value of ≥ 21 mm Hg was lower in the 2 mg IVT aflibercept group (21.9%) compared with the sham control group (28.4%) at 52 weeks. The proportion of patients with a pre-injection IOP absolute value of ≥ 35 mm Hg was lower in the 2 mg IVT aflibercept group (0.9%) compared with the sham-injection group (6.8%) at 52 weeks.

Endophthalmitis was reported in COPERNICUS only. At both 24 and 52 weeks, there was one occurrence of endophthalmitis reported in the 2 mg IVT aflibercept group (0.9%) and no occurrences reported in the sham-injection group. There were no occurrences of retinal detachment reported in GALILEO and COPERNICUS at 24 or 52 weeks.

TABLE 10: HARMS AT 24 AND 52 WEEKS (SAFETY ANALYSIS SET)

	GALILEO		COPERNICUS	
Summary of AEs, n (%)	**Sham (N = 68)**	**2 mg IVT Aflibercept (N = 104)**	**Sham + PRN (N = 74)**	**2 mg IVT Aflibercept 2Q4 + PRN (N = 114)**
Harms at 24 weeks				
Any TEAEs, N (%)	53 (77.9)	71 (68.3)	62 (83.8)	93 (81.6)
Any ocular AE, N (%)	44 (64.7)	58 (55.8)	51 (68.9)	78 (68.4)
Study eye, N (%)	44 (64.7)	57 (54.8)	49 (66.2)	72 (63.2)
Any non-ocular AE	37 (54.4)	47 (45.2)	36 (48.6)	58 (50.9)
Any SAEs, N (%)	10 (14.7)	9 (8.7)	16 (21.6)	11 (9.6)
WDAEs	6 (8.8)	2 (1.9)	5 (6.8)	2 (1.8)
Deaths	0	0	2 (2.7)	0
Notable harms at 24 weeks				
ATE	NR	NR	2 (2.7)	0
Acute myocardial infarction	NR	NR	1 (1.4)	0
Carotid artery stenosis	NR	NR	1 (1.4)	0
ATE based on APTC end point	NR	NR	2 (2.7)	0
IOP increased				

	GALILEO		COPERNICUS	
increase of ≥ 10 mm Hg from baseline in pre-injection IOP	2 (2.9)	3 (2.9)	7 (9.5)	3 (2.6)
Pre-injection IOP absolute value of ≥ 21 mm Hg	4 (5.9)	5 (4.8)	15 (20.3)	17 (14.9)
Pre-injection IOP absolute value of ≥ 35 mm Hg	1 (1.5)	0	2 (2.7)	0
Retinal detachment	0	0	NR	NR
Endophthalmitis	0	0	0	1(0.9)
Harms at 52 weeks				
Summary of AEs, n (%)	**Sham (N = 68)**	**2 mg IVT Aflibercept 2Q4 + PRN (N = 104)**	**Sham + PRN (N = 74)**	**2 mg IVT Aflibercept 2Q4 + PRN (N = 114)**
Patients with any TEAEs, N (%)	59 (86.8)	86 (82.7)	68 (91.9)	111 (97.4)
Any ocular AE N (%)	49 (72.1)	78 (75.0)	60 (81.1)	95 (83.3)
Study eye N (%)	49 (72.1)	78 (75.0)	58 (78.4)	90 (78.9)
Any non-ocular AE	45 (66.2)	69 (66.3)	54 (73.0)	85 (74.6)
Patients with ≥ 1 SAEs, N (%)	14 (20.6)	20 (19.2)	21 (28.4)	19 (16.7)
WDAEs (TEAE leading to discontinuation)	7 (10.3)	6 (5.8)	5 (6.8)	2 (1.8)
Deaths	0	0	2 (2.7)	0
Notable harms at 52 weeks				
ATE	2 (2.9)	1(1.0)	2 (2.7)	1(0.9)
ATE based on APTC end point	0	0	2 (2.7)	1 (0.9)
IOP increased				
increase of ≥ 10 mm Hg from baseline in Pre-injection IOP	5 (7.4)	8 (7.7)	10 (13.5)	7 (6.1)
Pre-injection IOP absolute value of ≥ 21 mm Hg	9 (13.2)	19 (18.3)	21 (28.4)	25 (21.9)
Pre-injection IOP absolute value of ≥ 35 mm Hg	2 (2.9)	6 (5.8)	5 (6.8)	1 (0.9)
Retinal detachment	NR	NR	NR	NR
Endophthalmitis	NR	NR	0	1 (0.9)

2Q4 = every four weeks; AE = adverse event; APTC = Antiplatelet Trialists' Collaboration; ATE = arterial thromboembolic; IVT = intravitreal; IOP = intraocular pressure; NR = not reported; PRN = as needed; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report A52377 (week 24),[11] Clinical Study Report R-8733 (week 24),[18] Clinical Study Report A59664 (week 52),[13] and Clinical Study Report R-8734 (week 52).[20]

4. DISCUSSION

4.1 Summary of Available Evidence

Evidence for this review was derived from the two pivotal double-masked, sham-controlled studies (GALILEO and COPERNICUS) that compared aflibercept (2 mg IVI every four weeks for 24 weeks) with sham injection in treatment-naive adults diagnosed with macular edema secondary to CRVO. The primary objective of each trial was to determine whether aflibercept is superior to sham injection in improving BCVA assessed using the ETDRS chart in patients with macular edema secondary to CRVO. The primary outcome in both studies was the proportion of patients who gained at least 15 BCVA letters compared with baseline at week 24.

Baseline characteristics were similar across treatment groups in both studies and there were no major limitations related to external validity. There were no major violations of internal validity, although the higher rates of discontinuation in the sham-injection groups mean it is possible the magnitude of the effect size of aflibercept could have been overestimated. However, this potential bias was mitigated by a corresponding decrease in the statistical power available to detect a significant difference between treatments.

4.2 Interpretation of Results

4.2.1 Efficacy

The proportion of patients who had an improvement of ≥ 15 BCVA letters in the aflibercept group of GALILEO (60%) and COPERNICUS (56%) was similar at 24 weeks. The clinical expert consulted for the CDR review suggested the gains observed in GALILEO and COPERNICUS were clinically meaningful. A significantly greater proportion of patients in the aflibercept group achieved an improvement of ≥ 15 letters compared with sham injection; the differences were 38% and 45% in GALILEO and COPERNICUS, respectively.

In addition, in both GALILEO and COPERNICUS, a statistically significant improvement in BCVA scores from baseline was observed with aflibercept compared with sham injection at 24 weeks; the mean difference in letters between aflibercept versus sham was approximately 15 and 22 letters, respectively. A difference of 10 to 15 letters in the BCVA scores has been considered a clinically meaningful difference (Appendix 5: Validity of Outcome Measures).

The differences observed for BCVA at 24 weeks were maintained through 52 weeks. The efficacy of aflibercept in terms of BCVA outcomes at 52 weeks is difficult to interpret given the possibility of PRN treatment received by patients in GALILEO and COPERNICUS. [redacted]

Data to assess efficacy over the longer term were derived from the extension phases of GALILEO (52 to 76 weeks) and COPERNICUS (52 to 100 weeks). The results of these extension phases suggest that the differences in efficacy observed at week 52 between the sham group and the active treatment group for BCVA outcomes are maintained beyond 52 weeks through approximately two years of treatment. The robustness of the treatment effect of aflibercept beyond two years is not known.

In Canada, besides aflibercept, dexamethasone IVI implant and ranibizumab are the only two other drugs that have a Health Canada–approved indication for the treatment of macular edema secondary to CRVO.[8,9] Previously, the Canadian Drug Expert Committee (CDEC) recommended that ranibizumab be listed with clinical criteria for CRVO.[34] CDEC reviewed dexamethasone IVI implant and recommended that it not be listed for CRVO.[35] The clinical expert consulted for the CDR review suggested ranibizumab is the standard of care in Canada.

However, while ranibizumab is the most appropriate comparator for assessing the comparative efficacy of aflibercept, there are no head- to-head studies comparing ranibizumab or dexamethasone IVI implant to aflibercept. As a result, the manufacturer supplied an indirect comparison to estimate the comparative efficacy and safety of aflibercept, ranibizumab, dexamethasone, and sham treatment. The aim was to evaluate the relative efficacy and safety of aflibercept (2 mg administered monthly) compared with ranibizumab (0.5 mg administered monthly) and dexamethasone (a single implant of 0.7 mg) for the treatment of reduced visual acuity due to macular edema following CRVO.[36] The network meta-analysis (NMA) was based on a systematic review[37] that followed the Cochrane Collaboration and National Institute for Health and Care Excellence (NICE) methods in order to meet NICE requirements.[38] The systematic review included RCTs with at least two groups and systematic reviews with meta-analyses. Interventions included aflibercept, dexamethasone, ranibizumab, bevacizumab, laser therapy, and placebo or sham or best supportive care. The outcomes of interest were visual acuity, health-related quality of life, and safety. The NMA indicated that aflibercept did not significantly differ in efficacy compared with other anti-VEGF drugs at six months in terms of the proportion of patients gaining ≥ 15 letters of BCVA from baseline, the proportion of patients losing ≥ 15 letters of BCVA from baseline, and the mean change in BCVA from baseline. Aflibercept had a significantly higher efficacy than dexamethasone at six months for the proportion of patients improving by ≥ 15 letters of BCVA from baseline and change in BCVA from baseline, but there were no data reported for dexamethasone on patients losing ≥ 15 letters of BCVA from baseline (Appendix 7: Summary of Indirect Comparisons).

In CADTH's targeted search of published literature for indirect comparison, including aflibercept for macular edema secondary to CRVO, a single indirect comparison[39] was identified in which an NMA based on a systematic review[40] was used to indirectly compare the clinical effectiveness of aflibercept, ranibizumab, bevacizumab, dexamethasone, and triamcinolone for the treatment of macular edema secondary to CRVO. The indirect comparison retrieved from published literature was very similar to the one submitted by the manufacturer. Indeed, both NMAs included the same studies for their common comparators as those treatments are also used in clinical practice. More patients treated with any active treatment except dexamethasone appeared to achieve the 15 letters of BCVA threshold compared with sham. No statistical difference was observed between aflibercept, bevacizumab, ranibizumab, and triamcinolone for this outcome. All active treatments showed an improvement in BCVA from baseline at six months compared with sham. Only patients treated with aflibercept appeared to gain statistically significantly more letters from baseline compared with triamcinolone. A statistical difference could not be observed between ranibizumab, aflibercept, and bevacizumab for the same outcome.

The conclusions of the NMA provided by the manufacturer were similar to those of an independent indirect comparison retrieved from the published literature. After six months, the efficacy of aflibercept is similar to that of ranibizumab and significantly better than dexamethasone.

Quality of life was also an efficacy outcome of interest in this systematic review. In GALILEO and COPERNICUS, patients' visual function and quality of life were assessed using the NEI VFQ-25 questionnaire. The NEI VFQ-25 is a 25-item patient-reported questionnaire designed to assess the

influence of visual impairment on health-related quality of life. This instrument has been shown to have adequate reliability and validity to detect functional impairment associated with a wide range of ocular conditions, although studies have identified limitations to the instrument, including multidimensionality (measurement of more than one construct), and poor performance of the subscales (Table 31). The NEI VFQ-25 consists of a composite score and 11 visual subscale scores. The change from baseline in the NEI VFQ-25 composite score at 24 weeks was significantly improved for aflibercept when compared with sham injection in both GALILEO and COPERNICUS (4.2 points and 6.3 points, respectively). A review of the literature concerning the NEI VFQ-25 suggested a difference of at least 3.3 points to 6.1 points was clinically meaningful. However, benefits were not consistently observed for the subscales of near-activities, distance-activities, and dependency. A statistically significant difference in the near-activities subscale for patients in GALILEO was observed between the aflibercept group compared with sham injection. In GALILEO only, the difference observed at week 52 between the sham group and the active treatment group for NEI VFQ-25 was maintained at week 76. Thus, the response obtained with aflibercept appeared to be sustained. Because the design of COPERNICUS is not truly comparative after 24 weeks and because it is not blinded after week 52, the BCVA and NEI VFQ-25 results from GALILEO are more reliable than the BCVA and NEI VFQ-25 results from COPERNICUS. According to the clinical expert consulted for the CDR review, the eye with better vision is able to compensate for poor vision in the other eye to such an extent that the eye with better vision may be able to compensate for some of the deficits in overall visual function and quality of life. In contrast, patient input received by CADTH on aflibercept suggested quality of life is severely impacted by impaired vision.

In GALILEO, quality of life was also assessed using the EQ-5D. There were no statistically significant differences between aflibercept and sham injection at 24 or 52 weeks. The clinical expert consulted for the CDR review considered the lack of statistically significant differences between the aflibercept group and sham injection in GALILEO to be expected. Day-to-day living is not likely to be affected much by changes in visual impairment in the study eye, as patients may be able to compensate with the unaffected eye to limit the impact of CRVO on quality of life. Similar results were observed during the extension phase up to 76 weeks.

CRT was an outcome of interest in this systematic review that was assessed in both GALILEO and COPERNICUS. The clinical expert consulted for the CDR review suggested normal retinal thickness was approximately 250 µm. At 24 weeks, patients treated with aflibercept in both studies experienced a statistically significant reduction in CRT that was greater than in the sham-injection group. The end result for patients treated with aflibercept was mean CRT in the normal range in both GALILEO and COPERNICUS (234.6 µm and 204.5 µm). In addition, the difference between aflibercept and sham injection in both studies in terms of CRT outcome was statistically significant. Generally, the findings at 52 weeks were similar; however, in the GALILEO and COPERNICUS aflibercept groups, CRT increased to the limits of normality (259.7 µm and 248.7 µm, respectively). In addition, the difference between aflibercept and sham injection was statistically significant in GALILEO only. During the extension phases, CRT in all GALILEO and COPERNICUS treatment groups was above 250 µm. Although there were numerical reductions in CRT in the aflibercept and sham injection control groups in both studies, there were no statistically significant differences. In the short term (24 weeks), the results for CRT suggest clear reductions back into a normal range for patients treated with aflibercept. The effect waned after 52 weeks, but the CRT remained slightly above (GALILEO) or at (COPERNICUS) the threshold of 250 µm.

4.2.2 Harms

The overall incidence of SAEs was lower in the GALILEO and COPERNICUS aflibercept groups (8.7% and 9.6%, respectively) compared with the sham-injection groups (14.7% and 21.6%). The frequency of non-

ocular AEs was similar between treatment groups in both GALILEO and COPERNICUS at 24 and 52 weeks. The overall incidence of ocular SAEs was lower in the aflibercept group compared with sham injection in both GALILEO (2.9% versus 8.8%) and COPERNICUS (3.5% versus 13.5%). There is an inherent risk of intraocular infections with intravitreal injection; however, such events were rarely observed in the included studies. This finding is somewhat surprising considering the sham injection did not involve a needle applying treatment to the eye. Retinal detachment and increased IOP were identified as ocular harms of interest in this review. An increased risk of IOP elevation is of concern because sustained elevations in IOP can lead to vision problems, including blindness. There were no occurrences of retinal detachment reported in either GALILEO or COPERNICUS at 24 or 52 weeks. The clinical expert consulted by CDR indicated that an IOP of ≥ 35 mm Hg would be the greatest cause for concern. The frequency of a pre-injection IOP of ≥ 35 mm Hg was higher at 24 weeks in the sham group in both GALILEO (5.9%) and COPERNICUS (20.3%) compared with the aflibercept treatment groups (4.8% and 14.9%, respectively). However, at 52 weeks, the findings were inconsistent between studies concerning the risk of increased IOP as in GALILEO, the frequency of pre-injection IOP ≥ 35 mm Hg was higher in the aflibercept group (5.8%) compared with the sham-injection group (2.9%). However, in COPERNICUS, the frequency of pre-injection IOP ≥ 35 mm Hg was lower in the aflibercept group (0.9%) compared with the sham plus PRN group (6.8%). The findings at 52 weeks are difficult to interpret given the PRN nature of this phase and variability in results based on the categories of IOP examined.

Anti-VEGF drugs have been associated with non-ocular SAEs, including cardiovascular events and ATEs.[24] However, there were no clear safety signals associated with these events from either GALILEO or COPERNICUS. The manufacturer's provided NMA suggested aflibercept was associated with a lower incidence of vitreous hemorrhage compared with ranibizumab, dexamethasone, or sham injection.[24] However, some analyses were based on very small numbers of events, resulting in estimates with wide credible intervals and consequent uncertainty around the interpretation of the data. All other comparisons for AEs were not statistically significant in the manufacturer's NMA. Therefore, the evidence did not allow conclusions to be drawn regarding differences in the potential harms associated with aflibercept and ranibizumab. AEs were not evaluated in the NMA identified from a review of the literature.[39]

4.3 Other Considerations

During the 24-week treatment phase in GALILEO and COPERNICUS, the mean amount of aflibercept received was [redacted]. At 52 weeks in GALILEO and COPERNICUS, the mean amount of aflibercept received was 16 mg to 17 mg (the mean number of injections was 11.8 to 12.2). Patient input received by CADTH for the Eylea CRVO submission stated that patients expect aflibercept to require fewer injections than ranibizumab in line with the product monograph dosing.[10] However, the clinical studies do not provide much insight into whether this is likely to happen in practice.

Bevacizumab (Avastin), a VEGF antibody that has been approved for the treatment of certain types of cancer, is not approved in Canada for the treatment of CRVO and was not considered to be a valid comparator for the purpose of this review. However, bevacizumab is reimbursed for CRVO treatment in some of the jurisdictions that participate in the CDR process. In addition, according to the clinical expert, bevacizumab is used off-label for the treatment of CRVO in patients in jurisdictions in which ranibizumab is not reimbursed and in patients who are ineligible for coverage.

5. CONCLUSIONS

The results of the two double-masked, sham-controlled, randomized controlled studies (COPERNICUS and GALILEO) suggest that 24 weeks of treatment with 2 mg of aflibercept every four weeks is superior to sham injection for improving visual acuity in patients with CRVO. Specifically, aflibercept significantly improved BCVA by at least 15 letters in 38% and 45% more patients than sham injection in GALILEO and COPERNICUS, respectively. Similarly, aflibercept significantly improved BCVA by 15 letters and 22 letters more than sham injection in GALILEO and COPERNICUS, respectively. The significant improvements in vision that occurred after 24 weeks in both studies were sustained through 52 weeks. Aflibercept was also associated with significantly greater improvement in vision-related QoL at 24 weeks (NEI VFQ-25 scores) compared with sham injection in both studies. Vision-related QoL improvement persisted through 52 weeks in GALILEO, but not in COPERNICUS, and there was no evidence to suggest that aflibercept improved overall QoL. Aflibercept was associated with significantly greater decreases in CRT compared with sham injection in both studies at week 24, although the difference between treatments remained significant through 52 weeks only in one of the two studies (GALILEO). In both studies, aflibercept was associated with a lower incidence of adverse events compared with sham-injected patients through 52 weeks. Data available through 76 weeks (GALILEO) and 100 weeks (COPERNICUS) of follow-up treatment did not raise any notable safety concerns. Although there was no direct comparative evidence to assess the efficacy and harms of aflibercept versus other anti-VEGFs, the results of two indirect comparisons suggested that after six months of treatment, the efficacy of aflibercept and ranibizumab are similar. The comparative safety could not be correctly appraised.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH staff based on the input provided by patient groups.

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 makes them uniquely sensitive 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., Human Resources and Skills Development Canada (HRSDC), and the following pharmaceutical companies: Bayer, Merck Frosst, Novartis, and Pfizer. CCB had no conflicts to declare on the compilation of the submission.

2. Condition and Current Therapy–Related Information

Information was obtained by CCB from online literature searches, conversations with some patients, and printed sources, including the product monograph.

The CCB highlighted the lack of choice and lack of insurance coverage for drugs approved for the treatment of retinal vein occlusion (RVO). Quality of life and daily living is severely affected by impaired vision. Patients can no longer drive and need to find ways to attend medical appointments, shopping, and social activities. Vision loss can lead to 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 have in the past. Because people do not 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, of employment, of driving privileges, and of quality of life. The condition has an economic impact due to loss of employment and the cost of treatment.

Current therapies include laser therapy, Vitalux, acetylsalicylic acid, Lutein, Lucentis, and Avastin. Some are used “off label”; only one drug is approved. 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 due to 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.

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, etc. Due to lack of knowledge or understanding, they may not know how to deal with the patient’s personal feelings or depression.

3. Related Information 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 and resulting loss of vision, causes the patient to become very apprehensive. The need to stop the bleeding is most important to prevent further vision loss, which compounds the above problems. Also, the increased intraocular pressure — glaucoma — needs to be controlled to decrease the incidence of peripheral vision loss. It is expected that, by arresting the progress of the condition, there will be improvement and possible regaining of sight with this new drug. There is a lack of choice for approved therapies. Patients may have an adverse reaction to current therapy and therefore, with no approved medication available as a second choice, 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 missed by caregivers from work and, possibly, fewer adverse reactions or irritations.

If patients felt they were going to regain sight or prevent further loss, they would often be willing to experience some temporary adverse effects. Patients indicate they would be willing to try a new drug that offers them the hope of regaining their sight. Regaining sight, controlling bleeding, 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 not infection.

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

See section 2.2 (Methods) for more details on literature search methods.

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:	December 9, 2014
Alerts:	Bi-weekly search updates until project completion
Study types:	No search filters were applied
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(Eylea* or aflibercept* or "AVE 0005" or AVE0005 or Bay 86-5321 or Bay86-5321 or VEGF Trap* or Zaltrap or Zivaflibercept or vasculotropin trap or vascular endothelial growth factor trap).ti,ab,rn,nm,sh,hw,ot. (2598)
2	862111-32-8.rn,nm. (1573)
3	(central adj retina* adj (vein or venous) adj (obstruction* or occlusion*)).ti,ab,hw. (4236)
4	CRVO.ti,ab. (1594)
5	retinal vein occlusion/ (6338)

MULTI-DATABASE STRATEGY	
6	1 or 2 (2598)
7	3 or 4 or 5 (8843)
8	6 and 7 (114)
9	8 use pmez (20)
10	*aflibercept/ (379)
11	(Eylea* or aflibercept* or "AVE 0005" or AVE0005 or Bay 86-5321 or Bay86-5321 or VEGF Trap* or Zaltrap or Zivaflibercept or vasculotropin trap or vascular endothelial growth factor trap).ti,ab. (1282)
12	(central adj retina* adj (vein or venous) adj (obstruction* or occlusion*)).ti,ab. (3462)
13	CRVO.ti,ab. (1594)
14	central retina vein occlusion/ (2055)
15	10 or 11 (1328)
16	12 or 13 or 14 (4370)
17	15 and 16 (52)
18	17 use oemezd (35)
19	conference abstract.pt. (1671096)
20	18 not 19 (31)
21	or/9,20 (51)
22	remove duplicates from 21 (40)

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

Grey Literature

Dates for search:	November 24, 2014 – December 5, 2014
Keywords:	Eylea (aflibercept), central retinal vein occlusion (CRVO)
Limits:	No date or language limits used

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

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
None	None (not applicable)

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 11: TREATMENT COMPLIANCE DURING THE 24 WEEKS (FULL ANALYSIS SET)

	GALILEO		COPERNICUS	
	Sham (N = 68)	2 mg IVT Aflibercept 2Q4 (N = 103)	Sham (N = 73)	2 mg IVT Aflibercept 2Q4 (N = 114)
Patients with 100% compliance, n (%)	[redacted]	[redacted]	[redacted] (89.0)	[redacted] (92.1)
Patients with < 100% compliance, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Compliance in the first 24 weeks (%)				
Mean (SD)	90.1 [redacted]	96.5 [redacted]	[redacted]	[redacted]
Median	100	100	[redacted]	[redacted]
Range	17 to 100	17 to 100	[redacted]	[redacted]

2Q4 = every four weeks; IVT = intravitreal; NR = not reported; PRN = as needed; SD = standard deviation; VEGF = vascular endothelial growth factor.
Source: Clinical Study Report A52377 (week 24)[11] and Clinical Study Report R-8733 (week 24).[18]

TABLE 12: TREATMENT COMPLIANCE DURING THE 52 WEEKS (FULL ANALYSIS SET)

	GALILEO		COPERNICUS	
	Sham (N = 68)	2 mg IVT Aflibercept 2Q4 (N = 103)	Sham + PRN (N = 73)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114)
Patients with 100% compliance, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with < 100% compliance, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Compliance in the first 52 weeks (%)				
Mean (SD)	87.8 [redacted]	93.9 [redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]

2Q4 = every four weeks; IVT = intravitreal; NR = not reported; PRN = as needed; SD = standard deviation; VEGF = vascular endothelial growth factor.
Source: Clinical Study Report A59664 (week 52)[13] and Clinical Study Report R-8734 (week 52).[20]

TABLE 13: CHANGE FROM BASELINE IN VISUAL FUNCTION QUESTIONNAIRE SUBSCALES (NEI VFQ-25) AT 24 WEEKS (FULL ANALYSIS SET)

	GALILEO		COPERNICUS	
	Sham (N = 65)	2 mg IVT Aflibercept 2Q4 (N = 96)	Sham (N = 73)	2 mg IVT Aflibercept 2Q4 (N = 114)
Near-activities subscale				
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 mean	[redacted]	[redacted]	[redacted]	[redacted]
Mean change (unadjusted) at 24 weeks	1.6	10.4	1.84	8.25
LS mean change	–1.8	6.8	3.58	9.89

	GALILEO		COPERNICUS	
	Sham (N = 65)	2 mg IVT Aflibercept 2Q4 (N = 96)	Sham (N = 73)	2 mg IVT Aflibercept 2Q4 (N = 114)
LSMD (95% CI)	8.6 (4.0 to 13.2)[a]		6.31 (–0.55 to 13.16)	
Distance-activities subscale				
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 mean	[redacted]	[redacted]	[redacted]	[redacted]
Mean change (unadjusted) at 24 weeks	2.4	6.3	–0.64	6.09
LS mean change	–0.7	2.7	1.57	8.06
LSMD (95% CI)	3.5 (–0.3 to 7.2)		6.49 (0.56 to 12.42)	
Dependency subscale				
Baseline mean	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 mean	[redacted]	[redacted]	[redacted]	[redacted]
Mean change (unadjusted) at 24 weeks	2.4	3.7	1.13	7.13
LS mean change	–0.7	1.5	3.77	9.62
LSMD (95% CI)	2.1 (–1.6, 5.8)		5.84 (–0.76 to 12.45)	

2Q4 = every four weeks; CI = confidence interval; IVT = intravitreal; LS = least squares; LSMD = least squares mean difference; SD = standard deviation; VFQ-25 = Visual Function Questionnaire 25 (National Eye Institute).
[a] $P < 0.001$.
Source: Clinical Study Report A52377 (week 24)[11] and Clinical Study Report R-8733 (week 24).[18]

TABLE 14: PROPORTION OF PATIENTS WHO GAINED ≥ 15 LETTERS IN BCVA AT 24 WEEKS N (%) PP

	GALILEO		COPERNICUS	
Proportion of Patients Who Gained ≥ 15 Letters BCVA at 24 Weeks N (%) PP	Sham (N = 51)	2 mg IVT Aflibercept 2Q4 (N = 87)	Sham (N = 60)	2 mg IVT Aflibercept 2Q4 (N = 108)
BCVA at week 24, n (%)	13 (25.5)	56 (64.4)	[redacted]	[redacted]
Adjusted difference (%) (95% CI)	38.9 (22.7 to 55.0)[a]		[redacted]	

2Q4 = every four weeks; BCVA = best-corrected visual acuity; CI = confidence interval; IVT = intravitreal; PP = per-protocol; PRN = as needed; VEGF = vascular endothelial growth factor.
[a] $P < 0.001$.
Source: Clinical Study Report A52377 (week 24)[11] and Clinical Study Report R-8733 (week 24).[18]

TABLE 15: PROPORTION OF PATIENTS WHO LOST < 15 LETTERS IN BCVA AT 24 WEEKS N (%) FAS GALILEO (DISCONTINUED JUDGED AS FAILURES) AND COPERNICUS (LOCF)

	GALILEO		COPERNICUS	
	Sham (N = 51)	2 mg IVT Aflibercept 2Q4 (N = 87)	Sham (N = 60)	2 mg IVT Aflibercept 2Q4 (N = 108)
Proportion of patients who lost ≤ 15 letters or ≥ 15 letters BCVA at 24 weeks n (%)	[redacted]	[redacted]	[redacted] (27.4)	[redacted] (1.8)

2Q4 = every four weeks; BCVA = best-corrected visual acuity; FAS = full analysis set; IVT = intravitreal; LOCF = last observation carried forward.
Source: Clinical Study Report A52377 (week 24)[11] and Clinical Study Report R-8733 (week 24).[18]

TABLE 16: PROPORTION OF PATIENTS WHO GAINED ≥ 15 LETTERS IN BCVA BASED ON BASELINE PERFUSION STATUS AT 24 WEEKS (FULL ANALYSIS SET)

	GALILEO		COPERNICUS	
Proportion of Patients ≥ 15 Letters BCVA at 24 Weeks, n (%) PP	Sham (N = 68)	2 mg IVT Aflibercept 2Q4 (N = 103)	Sham (N = 73)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114)
Non-perfused	[redacted]	[redacted]	[redacted](4.3)	[redacted](51.4)
Difference (%) (95% CI)	[redacted]		47.0 (28.9 to 65.1)	
Perfused	[redacted]	[redacted]	[redacted](16.0)	[redacted] (58.4)
Difference	[redacted]		42.4 (27.5 to 57.4)	

2Q4 = every four weeks; BCVA = best-corrected visual acuity; CI = confidence interval; IVT = intravitreal; PP = per-protocol; PRN = as needed.

TABLE 17: CAPILLARY PERFUSION STATUS AT WEEK 24 (FULL ANALYSIS SET)

	GALILEO		COPERNICUS	
	Sham (N = 68)	2 mg IVT Aflibercept 2Q4 (N = 104)	Sham (N = 73)	2 mg IVT Aflibercept 2Q4 (N = 114)
Perfusion status				
Perfused (< 10 DA of capillary non-perfusion)	[redacted]	[redacted]	[redacted]	[redacted]
Non-perfused (≥ 10 DA of capillary non-perfusion)	[redacted]	[redacted]	[redacted](23.3)	[redacted](7.9)
Indeterminate	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]

2Q4 = every four weeks; DA = disc areas; IVT = intravitreal.

Harms

TABLE 18: OCULAR AES OCCURRING IN THE STUDY EYE IN ≥ 3% OF PATIENTS IN ANY GROUP DURING THE 24-WEEK TREATMENT PERIOD (SAFETY ANALYSIS SET)

	GALILEO		COPERNICUS	
	Sham (N = 68)	2 mg IVT Aflibercept 2Q4 (N = 104)	Sham (N = 74)	2 mg IVT Aflibercept 2Q4 (N = 114)
Ocular AE, total n (%) in study eye	44 (64.7)	57 (54.8)	49 (66.2)	72 (63.2)
Conjunctival hemorrhage	3 (4.4)	9 (8.7)	13 (17.6)	17 (14.9)
Visual acuity reduced	7 (10.3)	0	13 (17.6)	8 (7.0)
Eye pain	3 (4.4)	12 (11.5)	4 (5.4)	16 (14.0)
Increased intraocular pressure	4 (5.9)	10 (9.6)	5 (6.8)	7 (6.1)
Maculopathy	NA	NA	1 (1.4)	10 (8.8)
Retinal hemorrhage	NA	NA	6 (8.1)	5 (4.4)
Retinal vascular disorder	6 (8.8)	6 (5.8)	4 (5.4)	6 (5.3)
Vitreous detachment	NA	NA	5 (6.8)	5 (4.4)
Eye irritation	7 (10.3)	3 (2.9)	3 (4.1)	6 (5.3)
Optic disc vascular disorder	3 (4.4)	4 (3.8)	1 (1.4)	8 (7.0)
Vitreous floaters	0	5 (4.8)	2 (2.7)	6 (5.3)
Vitreous hemorrhage	NA	NA	6 (8.1)	2 (1.8)
Retinal exudates	5 (7.4)	7 (6.7)	0	7 (6.1)

	GALILEO		COPERNICUS	
	Sham (N = 68)	2 mg IVT Aflibercept 2Q4 (N = 104)	Sham (N = 74)	2 mg IVT Aflibercept 2Q4 (N = 114)
Iris neovascularization	NA	NA	6 (8.1)	0
Ocular discomfort	NA	NA	1 (1.4)	5 (4.4)
Punctate keratitis	NA	NA	3 (4.1)	3 (2.6)
Ocular hyperemia	4 (5.9)	5 (4.8)	0	4 (3.5)
Injection site pain	2 (2.9)	5 (4.8)	NA	NA
Macular edema	11 (16.2)	4 (3.8)	NA	NA
Foreign body sensation in eyes	5 (7.4)	6 (5.8)	NA	NA
Lacrimation increased	4 (5.9)	3 (2.9)	NA	NA
Macular ischemia	3 (4.4)	4 (3.8)	NA	NA
Papilledema	3 (4.4)	2 (1.9)	NA	NA
Retinal ischemia	3 (4.4)	1 (1.0)	NA	NA

2Q4 = every four weeks; AE = adverse event; IVT = intravitreal; NA = not applicable.
Source: Clinical Study Report A52377 (week 24)[11] and Clinical Study Report R-8733 (week 24).[18]

TABLE 19: OCULAR AES OCCURRING IN THE STUDY EYE IN ≥ 3% OF PATIENTS IN ANY GROUP DURING THE 52 WEEKS (SAFETY ANALYSIS SET)

	GALILEO		COPERNICUS	
	Sham (N = 68)	VEGF Eye-Trap 2Q4 (N = 104)	Sham + PRN (N = 74)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114)
Ocular AE, total n (%) in study eye	49 (72.1)	78 (75.0)	55 (74.3)	80 (70.2)
Macular edema	15 (22.1)	35 (33.7)	1 (1.4)	11 (9.6)
Retinal vascular disorder	8 (11.8)	11 (10.6)	5 (6.8)	9 (7.9)
Visual acuity reduced	8 (11.8)	11 (10.6)	16 (21.6)	21 (18.4)
Eye pain	4 (5.9)	15 (14.4)	7 (9.5)	18 (15.8)
Retinal hemorrhage	8 (11.8)	12 (11.5)	9 (12.2)	7 (6.1)
Retinal exudates	7 (10.3)	9 (8.7)	4 (5.4)	8 (7.0)
Conjunctival hemorrhage	3 (4.4)	12 (11.5)	14 (18.9)	19 (16.7)
Eye irritation	7 (10.3)	6 (5.8)	4 (5.4)	8 (7.0)
Macular ischemia	4 (5.9)	9 (8.7)	NR	NR
Optic disc vascular disorder	6 (8.8)	7 (6.7)	3 (4.1)	13 (11.4)
Foreign body sensation in eyes	5 (7.4)	6 (5.8)	3 (4.1)	1 (0.9)
Increased lacrimation	6 (8.8)	5 (4.8)	3 (4.1)	4 (3.5)
Ocular hyperemia	4 (5.9)	6 (5.8)	0	6 (5.3)
Vitreous detachment	1 (1.5)	7 (6.7)	6 (8.1)	10 (8.8)
Vitreous hemorrhage	2 (2.9)	5 (4.8)	8 (10.8)	3 (2.6)
Papilledema	3 (4.4)	4 (3.8)	2 (2.7)	4 (3.5)
Retinal neovascularization	5 (7.4)	2 (1.9)	NR	NR
Retinal vein occlusion	0	6 (5.8)	NR	NR
Vitreous floaters	0	6 (5.8)	3 (4.1)	8 (7.0)
Retinal ischemia	3 (4.4)	3 (2.9)	NR	NR
Ocular hypertension	1 (1.5)	4 (3.8)	NR	NR
Cystoid macular edema	0	5 (4.8)	3 (4.1)	8 (7.0)

	GALILEO		COPERNICUS	
	Sham (N = 68)	VEGF Eye-Trap 2Q4 (N = 104)	Sham + PRN (N = 74)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114)
Visual impairment	0	5 (4.8)	NR	NR
Iris neovascularization	0	5 (4.8)	6 (8.1)	0
Macular degeneration	0	4 (3.8)	NR	NR
Retinal edema	3 (4.4)	0	NR	NR
Eyelid edema	3 (4.4)	0	NR	NR
Injection site pain	2 (2.9)	6 (5.8)	NR	NR
Increased intraocular pressure	4 (5.9)	18 (17.3)	10 (13.5)	14 (12.3)
Visual acuity tests abnormal	1 (1.5)	5 (4.8)	NR	NR
Maculopathy	NR	NR	5 (6.8)	13 (11.4)
Retinal pigment epitheliopathy	NR	NR	7 (9.5)	5 (4.4)
Ocular discomfort	NR	NR	2 (2.7)	5 (4.4)
Punctate keratitis	NR	NR	4 (5.4)	3 (2.6)
Dry eye	NR	NR	3 (4.1)	3 (2.6)
Eye pruritus	NR	NR	2 (2.7)	4 (3.5)
Glaucoma	NR	NR	3 (4.1)	1 (0.9)

2Q4 = every four weeks; AE = adverse event; IVT = intravitreal; NR = not reported; PRN = as needed; VEGF = vascular endothelial growth factor.
Source: Clinical Study Report A59664 (week 52),[13] and Clinical Study Report R-8734 (week 52).[20]

TABLE 20: NON-OCULAR TEAES OCCURRING IN AT LEAST 3% OF PATIENTS IN ANY GROUP AT 24 WEEKS (SAFETY ANALYSIS SET)

	GALILEO		COPERNICUS	
	Sham PRN (N = 68)	2 mg IVT Aflibercept 2Q4 + PRN (N = 104)	Sham + PRN (N = 74)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114)
Non-ocular TEAE n (%)	37 (54.4)	47 (45.2)	16 (21.6)	22 (19.3)
Nasopharyngitis	6 (8.8)	8 (7.7)	4 (5.4)	5 (4.4)
Upper respiratory tract infection	NA	NA	2 (2.7)	6 (5.3)
Urinary tract infection	NA	NA	2 (2.7)	4 (3.5)
Hypertension	3 (4.4)	4 (3.8)	4 (5.4)	10 (8.8)
Increased urine protein or creatinine ratio	NR	NA	3 (4.1)	2 (1.8)
Nausea	NA	NA	3 (4.1)	0
Fall	3 (4.4)	0	NA	NA
Arthralgia	5 (7.4)	1 (1.0)	NA	NA
Back pain	3 (4.4)	3 (2.9)	NA	NA
Headache	4 (5.9)	7 (6.7)	NA	NA

2Q4 = every four weeks; IVT = intravitreal; NA = not applicable; NR = not reported; PRN = as needed; TEAE= treatment-emergent adverse event.
Source: Clinical Study Report A52377 (week 24)[11] and Clinical Study Report R-8733 (week 24).[18]

TABLE 21: NON-OCULAR TEAES OCCURRING IN AT LEAST 3% OF PATIENTS IN ANY GROUP AT 52 WEEKS (SAFETY ANALYSIS SET)

	GALILEO	
	Sham (N = 68)	2 mg IVT Aflibercept 2Q4 + PRN (N = 104)
Non-ocular TEAE, n (%)	45 (66.2)	69 (66.3)
Anemia	3 (4.4)	1 (1.0)
Nausea	4 (5.9)	0
Vomiting	3 (4.4)	0
Bronchitis	1 (1.5)	6 (5.8)
Influenza	2 (2.9)	7 (6.7)
Nasopharyngitis	15 (22.1)	14 (13.5)
Fall	4 (5.9)	1 (1.0)
Arthralgia	6 (8.8)	3 (2.9)
Back pain	3 (4.4)	6 (5.8)
Headache	5 (7.4)	10 (9.6)
Syncope	3 (4.4)	1 (1.0)
Hypertension	6 (8.8)	7 (6.7)

2Q4 = every four weeks; IVT = intravitreal; PRN = as needed; TEAE= treatment-emergent adverse event.
Source: Clinical Study Report A59664 (week 52)[13] and Clinical Study Report R-8734 (week 52).[20]

TABLE 22: NON-OCULAR TEAES OCCURRING IN AT LEAST 3% OF PATIENTS IN ANY GROUP AT 52 WEEKS — COPERNICUS (SAFETY ANALYSIS SET)

	COPERNICUS	
	Sham + PRN (N = 74)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114)
Non-ocular TEAE, n (%)	42 (56.8)	61 (53.5)
Nasopharyngitis	5 (6.8)	9 (7.9)
Upper respiratory tract infection	4 (5.4)	9 (7.9)
Sinusitis	3 (4.1)	7 (6.1)
Bronchitis	1 (1.4)	6 (5.3)
Influenza	1 (1.4)	6 (5.3)
Urinary tract infection	3 (4.1)	4 (3.5)
Pneumonia	3 (4.1)	2 (1.8)
Protein urine present	5 (6.8)	4 (3.5)
Increased urine protein or creatinine ratio	4 (5.4)	5 (4.4)
Blood glucose increased	5 (6.8)	3 (2.6)
Blood pressure increased	3 (4.1)	2 (1.8)
Hematocrit decreased	1 (1.4)	4 (3.5)
Increased blood pressure systolic	3 (4.1)	1 (0.9)
Blood urine present	3 (4.1)	1 (0.9)
Glucose urine present	3 (4.1)	1 (0.9)
Hypertension	7 (9.5)	17 (14.9)
Arthralgia	3 (4.1)	2 (1.8)
Osteoarthritis	1 (1.4)	4 (3.5)
Pain in extremity	3 (4.1)	2 (1.8)
Nausea	3 (4.1)	4 (3.5)

	COPERNICUS	
	Sham + PRN (N = 74)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114)
Diarrhea	2 (2.7)	4 (3.5)
Abdominal pain	3 (4.1)	0
Depression	2 (2.7)	4 (3.5)
Anxiety	3 (4.1)	2 (1.8)
Seasonal allergy	2 (2.7)	5 (4.4)
Headache	3 (4.1)	4 (3.5)
Anemia	1 (1.4)	4 (3.5)
Hypercholesterolemia	3 (4.1)	2 (1.8)
Accident	3 (4.1)	0

2Q4 = every four weeks; IVT = intravitreal; PRN = as needed; TEAE = treatment-emergent adverse event.
Source: Clinical Study Report A59664 (week 52)[13] and Clinical Study Report R-8734 (week 52).[20]

TABLE 23: OCULAR SAES OCCURRING IN STUDY EYE BY PREFERRED TERM AT 24 WEEKS (SAFETY ANALYSIS SET)

	GALILEO		COPERNICUS	
	Sham (N = 68) n (%)	**2 mg IVT Aflibercept 2Q4 (N = 104) n (%)**	**Sham (N = 73) n (%)**	**2 mg IVT Aflibercept 2Q4 + PRN (N = 114) n (%)**
All SAEs in study eye with at least one TESAE in study, n (%)	6 (8.8)	3 (2.9)	10 (13.5)	4 (3.5)
Vitreous hemorrhage	1 (1.5)	0	4 (5.4)	0
Glaucoma	2 (2.9)	0	2 (2.7)	0
Iris neovascularization	0	1 (1.0)	2 (2.7)	0
Retinal hemorrhage	NA	NA	2 (2.7)	0
Reduced visual acuity	1 (1.5)	0	1 (1.4)	1 (0.9)
Corneal abrasion	NA	NA	0	1 (0.9)
Endophthalmitis	NA	NA	0	1 (0.9)
Retinal artery occlusion	NA	NA	0	1 (0.9)
Retinal tear	NA	NA	1 (1.4)	0
Retinal vein occlusion	NA	NA	1 (1.4)	0
Macular edema	NA	NA	NA	NA
Macular ischemia	0	1 (1.0)	NA	NA
Vitreous detachment	0	1 (1.0)	NA	NA

2Q4 = every four weeks; IVT = intravitreal; NA = not applicable; PRN = as needed; SAE = serious adverse event; TESAE = treatment-emergent serious adverse event.
Source: Clinical Study Report A52377 (week 24)[11] and Clinical Study Report R-8733 (week 24).[18]

TABLE 24: OCULAR SAES OCCURRING IN STUDY EYE BY PREFERRED TERM AT 52 WEEKS (SAFETY ANALYSIS SET)

	GALILEO		COPERNICUS	
	Sham (N = 68) n (%)	2 mg IVT Aflibercept 2Q4 + PRN (N = 104) n (%)	Sham + PRN (N = 74) n (%)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114) n (%)
All SAEs in study eye with at least one TESAE in study, n (%)	6 (8.8)	10 (9.6)	12 (16.2)	6 (5.3)
Macular edema	2 (2.9)	4 (3.8)	NR	NA
Glaucoma	2 (2.9)	0	3 (4.1)	0
Reduced visual acuity	1 (1.5)	1 (1.0)	1 (1.4)	0
Vitreous hemorrhage	1 (1.5)	1 (1.0)	5 (6.8)	1 (0.9)
Iris neovascularization	0	1 (1.0)	2 (2.7)	0
Macular fibrosis	0	1 (1.0)	NR	NA
Macular ischemia	0	1 (1.0)	NR	NA
Retinal vein occlusion	0	1 (1.0)	1 (1.4)	1 (0.9)
Vitreous detachment	0	1 (1.0)	NR	NA
Cataract	NR	NR	1 (1.4)	1 (0.9)
Retinal hemorrhage	NR	NR	2 (2.7)	0
Retinal tear	NR	NR	2 (2.7)	0
Corneal abrasion	NR	NR	0	1 (0.9)
Cystoid macular edema	NR	NR	0	1 (0.9)
Endophthalmitis	NR	NR	0	1 (0.9)
Retinal artery occlusion	NR	NR	0	1 (0.9)

2Q4 = every four weeks; IVT = intravitreal; NA = not applicable; NR = not reported; PRN = as needed; SAE = serious adverse event; TESAE = treatment-emergent serious adverse event.
Source: Clinical Study Report A59664 (week 52)[13] and Clinical Study Report R-8734 (week 52).[20]

TABLE 25: NON-OCULAR SAES OCCURRING IN STUDY EYE BY PREFERRED TERM AT 24 WEEKS — GALILEO (SAFETY ANALYSIS SET)

	GALILEO	
	Sham (N = 68) n (%)	2 mg IVT Aflibercept 2Q4 (N = 104) n (%)
All non-ocular SAEs occurring, n (%)	5 (7.4)	6 (5.8)
Furuncle	0	1 (1.0)
Gastroenteritis	1 (1.5)	0
Pneumonia	1 (1.5)	0
Fall	1 (1.5)	0
Hand fracture	0	1 (1.0)
Humerus facture	1 (1.5)	0
Radius fracture	1 (1.5)	0
Spinal compression fracture	0	1(1.0)
Intravertebral disc protrusion	1 (1.5)	0
Oropharyngeal cancer stage unspecified	0	1 (1.0)
Renal failure	1 (1.5)	0
Laryngeal granuloma	1 (1.5)	0
Ischemic heart disease prophylaxis	0	1 (1.0)
Circulatory collapse	0	1 (1.0)

2Q4 = every four weeks; IVT = intravitreal; SAE = serious adverse event.
Source: Clinical Study Report A52377 (week 24)[11] and Clinical Study Report R-8733 (week 24).[18]

TABLE 26: NON-OCULAR SAES OCCURRING IN STUDY EYE BY PREFERRED TERM AT 52 WEEKS — GALILEO (SAFETY ANALYSIS SET)

	GALILEO	
	Sham (N = 68) n (%)	2 mg IVT Aflibercept + 2Q4 (N = 104) n (%)
All non-ocular SAEs occurring, n (%)	9 (13.2)	11 (10.6)
Hepatic function abnormal	0	1 (1.0)
Furuncle	0	1 (1.0)
Gastroenteritis	1 (1.5)	0
Pneumonia	1 (1.5)	1 (1.0)
Vestibular neuronitis	1 (1.5)	0
Fall	1 (1.5)	0
Hand fracture	0	1 (1.0)
Humerus fracture	1 (1.5)	1 (1.0)
Radius fracture	1 (1.5)	0
Spinal compression fracture	0	1 (1.0)
Intervertebral disc protrusion	1 (1.5)	0
Breast cancer	0	1 (1.0)
Oropharyngeal cancer stage unspecified	0	1 (1.0)
Paresthesia	0	1 (1.0)
Syncope	2 (2.9)	1 (1.0)
Transient ischemic attack	1 (1.5)	0
Renal failure	1 (1.5)	0
Dyspnea	1 (1.5)	0
Laryngeal granuloma	1 (1.5)	0
Ischemic heart disease prophylaxis	0	1 (1.0)
Circulatory collapse	0	1 (1.0)

2Q4 = every four weeks; IVT = intravitreal; SAE = serious adverse event.
Source: Clinical Study Report A59664 (week 52)[13] and Clinical Study Report R-8734 (week 52).[20]

TABLE 27: NON-OCULAR SAES OCCURRING IN STUDY EYE BY PREFERRED TERM AT 24 WEEKS — COPERNICUS (SAFETY ANALYSIS SET)

	COPERNICUS	
	Sham + PRN (N = 74) n (%)	2 mg IVT Aflibercept 2Q4 (N = 114) n (%)
All non-ocular SAEs occurring, n (%)	6 (8.1)	6 (5.3)
Colon cancer	1 (1.4)	0
Non-small cell lung cancer	0	1(0.9)
Esophageal adenocarcinoma, stage IV	1(1.4)	0
Prostate cancer	1 (1.4)	0
Thyroid cancer	1 (1.4)	0
Abdominal adhesions	0	1 (0.9)
Dysphagia	0	1 (0.9)
Pancreatitis	1 (1.4)	0
Acute myocardial infarction	1 (1.4)	1 (0.9)

	COPERNICUS	
	Sham + PRN (N = 74) n (%)	2 mg IVT Aflibercept 2Q4 (N = 114) **n (%)**
Atrial fibrillation	0	1 (0.9)
Bronchitis, viral	0	1 (0.9)
Cellulitis	1 (1.4)	0
Clostridial infection	1 (1.4)	0
Pneumonia	1 (1.4)	0
Apnea	1 (1.4)	0
Pneumothorax	0	1(0.9)
Anemia	0	1 (0.9)
Cholecystitis	1 (1.4)	0
Abnormal loss of weight	0	1 (0.9)
Osteoarthritis	0	1(0.9)
Carotid artery stenosis	1 (1.4)	0
Mental status changes	1(1.4)	0
Renal failure chronic	1 (1.4)	0

2Q4 = every four weeks; IVT = intravitreal; SAE = serious adverse event; PRN = as needed.
Source: Clinical Study Report A52377 (week 24)[11] and Clinical Study Report R-8733 (week 24).[18]

TABLE 28: NON-OCULAR SAES OCCURRING IN STUDY EYE BY PREFERRED TERM AT 52 WEEKS — COPERNICUS (SAFETY ANALYSIS SET)

	COPERNICUS	
	Sham + PRN (N = 74) n (%)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114) **n (%)**
All non-ocular SAEs occurring, n (%)	10 (13.5)	13 (11.4)
Pancreatitis	2 (2.7)	0
Abdominal adhesions	0	1 (0.9)
Dysphagia	0	1 (0.9)
Gastrointestinal motility disorder	1 (1.4)	0
Inguinal hernia	0	1 (0.9)
Cellulitis	1 (1.4)	1 (0.9)
Pneumonia	2 (2.7)	0
Arthritis bacterial	0	1 (0.9)
Bronchitis	1 (1.4)	0
Bronchitis viral	0	1 (0.9)
Clostridial infection	1 (1.4)	0
Herpes esophagitis	1 (1.4)	0
Urinary tract infection	0	1 (0.9)
Colon cancer	1 (1.4)	0
Mantle cell lymphoma	1 (1.4)	0
Non-small cell lung cancer	0	1 (0.9)
Esophageal adenocarcinoma, stage IV	1 (1.4)	0
Prostate cancer	1 (1.4)	0
Squamous cell carcinoma of skin	0	1 (0.9)
Thyroid cancer	1 (1.4)	0

	COPERNICUS	
	Sham + PRN (N = 74) n (%)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114) **n (%)**
Renal failure acute	1 (1.4)	1 (0.9)
Obstructive uropathy	0	1 (0.9)
Renal failure chronic	1 (1.4)	0
Acute myocardial infarction	1 (1.4)	0
Atrial fibrillation	0	1 (0.9)
Coronary artery stenosis	0	1 (0.9)
Myocardial infarction	0	1 (0.9)
Anemia	0	1 (0.9)
Pernicious anemia	1 (1.4)	0
Chest discomfort	0	1 (0.9)
Generalized edema	0	1 (0.9)
Bile duct stone	1 (1.4)	0
Cholecystitis	1 (1.4)	0
Apnea	1 (1.4)	0
Pneumothorax	0	1 (0.9)
Accident	1 (1.4)	0
Femur fracture	1 (1.4)	0
Abnormal loss of weight	0	1 (0.9)
Osteoarthritis	0	1 (0.9)
Carotid artery stenosis	1 (1.4)	0
Mental status changes	1 (1.4)	0
Benign prostatic hyperplasia	0	1 (0.9)

2Q4 = every four weeks; IVT = intravitreal; PRN = as needed; SAE = serious adverse event.
Source: Clinical Study Report A59664 (week 52)[13] and Clinical Study Report R-8734 (week 52).[20]

TABLE 29: DURING THE 24-WEEK TREATMENT PERIOD (SAFETY ANALYSIS SET)

	GALILEO		COPERNICUS	
	Sham (N = 68) n (%)	2 mg IVT Aflibercept 2Q4 (N = 104) n (%)	Sham (N = 74)	2 mg IVT Aflibercept 2Q4 (N = 114)
TEAE leading to discontinuation	6 (8.8)	2 (1.9)	5 (6.8)	2 (1.8)
Glaucoma	2 (2.9)	0	1 (1.4)	0
Retinal neovascularization	2 (2.9)	0	NA	NA
Corneal edema	1 (1.5)	0	0	1 (0.9)
Macular edema	1 (1.5)	0	NA	NA
Retinal vein occlusion	1 (1.5)	0	NA	NA
Iris neovascularization	0	1 (1.0)	1(1.4)	0
Macular ischemia	0	1 (1.0)	NR	NR
Vitreous hemorrhage	NA	NA	2 (2.7)	0
Retinal artery occlusion	NA	NA	0	1 (0.9)
Retinal hemorrhage	NA	NA	1 (1.4)	0
Retinal tear	NA	NA	1 (1.4)	0
Reduced visual acuity reduced	NA	NA	1 (1.4)	0
Non-small cell lung cancer	NA	NA	0	1 (0.9)

2Q4 = every four weeks; IVT = intravitreal; NA = not applicable; NR = not reported; TEAE = treatment-emergent adverse event; WDAE = Withdrawal due to adverse event.
Source: Clinical Study Report A52377 (week 24)[11] and Clinical Study Report R-8733 (week 24).[18]

TABLE 30: WDAES AT 52 WEEKS (SAFETY ANALYSIS SET)

	GALILEO		COPERNICUS	
	Sham (N = 68) n (%)	2 mg IVT Aflibercept 2Q4 + PRN (N = 104) n (%)	Sham + PRN (N = 74) n (%)	2 mg IVT Aflibercept 2Q4 + PRN (N = 114) n (%)
TEAEs leading to discontinuation	7 (10.3)	6 (5.8)	5 (6.8)	2 (1.8)
Glaucoma	2 (2.9)	0	1 (1.4)	0
Iris neovascularization	0	2 (1.9)	1 (1.4)	0
Macular edema	2 (2.9)	0	NA	NA
Retinal neovascularization	3 (4.4)	0	NA	NA
Corneal edema	1 (1.5)	0	NA	NA
Retinal hemorrhage	1 (1.5)	0	1 (1.4)	0
Retinal vein occlusion	0	1 (1.0)	NA	NA
Macular ischemia	0	1 (1.0)	NA	NA
Vitreous hemorrhage	0	1 (1.0)	2 (2.7)	0
Hepatic function abnormal	0	1 (1.0)	NA	NA
Retinal artery occlusion	NA	NA	0	1 (0.9)
Retinal tear	NA	NA	1 (1.4)	0
Reduced visual acuity reduced	NA	NA	1 (1.4)	0
Non-small cell lung cancer	NA	NA	0	1 (0.9)

2Q4 = every four weeks; IVT = intravitreal; NA = not applicable; PRN = as needed; TEAE= treatment-emergent adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report A59664 (week 52)[13] and Clinical Study Report R-8734 (week 52).[20]

APPENDIX 5: 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 25-item Visual Function Questionnaire items (NEI VFQ-25)
- EuroQol five-dimensions questionnaire (EQ-5D).

Findings

TABLE 31: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE IN OUTCOME MEASURES

Instrument	Type	Evidence of Validation	MCID	References
ETDRS letters	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 rows (70 letters).	Yes	10 to 15 letters	[26,41,42]
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	[28]
NEI VFQ-25	The NEI VFQ was developed as a means to measure vision-targeted QoL. 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[43,44]	Between 3.3 and 6.1 points	[29-31]
EQ-5D	The EQ-5D is a generic QoL instrument consisting of five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/ depression) and a VAS for rating health today. Weighted scoring produces an EQ-5D index score.	No	None	[32,33]

ETDRS = Early Treatment Diabetic Retinopathy Study; EQ-5D = EuroQol five-dimensions questionnaire; MCID = minimal clinically important difference; NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; OCT = optical coherence tomography; QoL = quality of life; VAS = visual analogue scale.

Early Treatment Diabetic Retinopathy Study

The ETDRS charts are based on a design by Bailey and Lovie and are commonly used in clinical research.[36,41,45-52] ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between letters and rows. There are a total of 14 rows (70 letters). ETDRS scores can be calculated when 20 or more letters are read correctly at 4.0 metres (m); 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 (number recorded on row 1.0), plus the total number of letters in the first six rows read correctly at 1.0 m. Therefore, the ETDRS letter score could result in a maximum score of 100.[53,54] Charts are used in a standard light box with a background illumination of approximately 150 cd/m^2. Standard chart-testing distance is 4 m; however, shorter distances may be used when vision is severely impaired.[41,55] Letters

range in height from 58.18 mm to 2.92 mm, corresponding to Snellen visual acuity fractions of 20/200 to 20/10 respectively. Moving up the chart, letter sizes increase geometrically and equivalently in each row by a factor of 1.2589 (or 0.1 log unit). 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 Snellen fractions, 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.[41,56] 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.[57] Thus, reading all 70 letters on a Bailey-Lovie chart corresponds to a Snellen visual acuity of 20/10.

$$\text{Snellen visual acuity} = 20 \times 10^{([55-x]/50)}$$

Minimal Clinically Important Difference

To our knowledge, there has been no derivation of a MCID for the ETDRS in central retinal vein occlusion (CRVO). 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 of visual acuity, as the primary outcome of interest.[58] For macular edema, the US FDA recommends a mean change of 15 letters or more on an ETDRS chart, or a statistically significant difference in the proportion of patients with a change in visual acuity of ≥ 15 letters as clinically relevant outcomes in studies.[26] 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 or losses on eye charts for classifying outcomes, and discussing the relationship between statistically significant differences and clinically significant differences.[59]

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.[42] This suggests that any change in score between baseline and follow-up of approximately 4 to 10 letters results in insufficient certainty that the difference in letters is not 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 (five-letter) change is 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 (10-letter) change, 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[53] 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,[42] while higher levels of variability (± 0.15 to ± 0.20) have been cited for individuals with pathological changes in vision.[60] For eyes with acuity better than 20/100, a change in visual acuity of five letters or more has a greater than 90% probability of being a real change, while for eyes worse than 20/100, a change of 10 letters or more is required for the same reliability.[61] 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.[27] The studies contributing to this discussion are summarized in Table 32.

TABLE 32: LITERATURE ASSESSING THE INTERPRETABILITY OF CHANGES IN ETDRS SCORES

Study	Population	Methods/Results	Key Findings	Strengths and Limitations
Rosser et al. 2003[42]	n = 50 (healthy volunteers) **Age**: < 50 years **Snellen acuity measure**: ≥ 6/9 (20/30) **Other:** No ocular abnormalities or cognitive difficulties	**Methods:** 1. Test–retest variability was assessed using two different ETDRS charts at 4 m. 2. Participants were tested for visual acuity across varying distances to simulate real changes to visual acuity. **Results**: Test–retest variability ± 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 greater than 5 letters is likely to be considered a true change in VA; 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.	**Strengths:** TRV measure is mid-range compared with literature-based values. **Limitations:** Sensitivity and specificity were not based on comparisons to other measures of change (VA or QoL).
Beck et al. 2007[61]	8 clinical studies reporting a change in VA as an outcome measure	**Discussion of analytical methods:** • *Binary outcome variable:* lose 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. VA studies reported differences ranging from 6% to 32% 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.	**Limitations:** • Non-systematic review of the literature • Used hypothetical biases to demonstrate effects
Csaky et al. 2008[59]	Scientists, clinicians, and researchers (symposium held by NIH and FDA)	**Methods**: Roundtable discussion on VA as an outcome measure. **Two topics for discussion:** 1. Identifying an alternative to the most commonly used threshold of three-line gains or losses on eye charts for classifying outcomes 2. The relationship between statistically and clinically significant differences	Four representatives provided opinions on the two topics of discussion: 1. Question raised about using a change score of < 15 letters in clinical studies. 2. Concern that a change of up to 15 letters may not represent a real change. 3. Change score may depend on how rapidly disease progression occurs. 4. Standardization is important.	**Limitations:** • No discussion of the representation of participants • Opinion-based discussion

Study	Population	Methods/Results	Key Findings	Strengths and Limitations
Beck et al. 2003[53]	n = 251 (patients undergoing treatment, of whom 20% had normal vision and 80% had a vision-related clinical diagnosis) **Age:** 50 years (± 22 years) **VA:** • 20/20: 21% • 20/20 to 20/40: 29% • 20/40 to 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 logMAR); 87% were within 5 letters (0.1 logMAR). Of patients with a baseline VA of < 20/100, 83% were within 5 letters (0.1 logMAR) after the retest.	1. Test–retest reliability varied according to the participant's baseline VA.	**Limitations:** • Repeat test was completed immediately after first test. There is a risk of bias for remembering the sequence of letters.
Kiser et al. 2005[27]	N = 60 (low-vision participants with VA problems identified from a previous research database, an eye institute, and a local institution); and N = 18 (healthy controls) **Mean age:** 61 years **VA:** • Low-vision participants: legally blind (< 20/200) from retinitis pigmentosa, macular degeneration, optic neuropathy, other retinal disease, or diabetic retinopathy • Healthy controls: > 20/25	**Methods:** Each patient was tested for VA 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. **Results**: Healthy controls (CR.95 ranged from 0.092 to 0.15); low-vision participants (CR.95 ranged from 0.13 to 0.36).	The minimal change that must occur to be confident that VA has truly changed in low-vision individuals is between 2 and 3 lines on the ETDRS.	**Limitations:** • Very few patients within each eye disease group • Patients are very low-vision, defined as legally blind

CR = coefficient of repeatability; ETDRS = Early Treatment Diabetic Retinopathy Study; logMAR = logarithmic minimal angle of resolution; NIH = National Institutes of Health; QoL = quality of life; TRV = test–retest variability; VA = visual acuity.
Note: 0.1 logMAR = 1 row or 5 letters.

Relationship of Visual Acuity to Visual Function and Vision-Related Quality of Life

Measures of high-contrast visual distance acuity, using Early Treatment Diabetic Retinopathy Study (ETDRS) charts, are commonly used to assess treatment outcomes in clinical studies. A loss of three or more 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 six or more 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.[62] 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 is not optimal given that distance vision is usually two ETDRS lines better than reading vision,[58] and difficulty with reading is a common complaint among patients with eye disease.[29] Rather, contrast sensitivity is a more important contributor to reading performance.[58,63]

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 that ultimately depends upon the value individuals place on the ability to perform specific tasks. Quality-of-life instruments that do not include domains or tasks that are important to individuals will lack sensitivity to changes in their quality of life. Further, the impact of vision loss in one eye on quality of life may vary greatly depending on 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.[62]

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.[28] 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 and retina, inner and outer photoreceptor segments, and the retinal pigment epithelium and 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.[28,64] A recent advancement in OCT device technology has been the shift from time domain (TD-OCT) to spectral domain OCT (SD-OCT), as the latter can acquire data at a higher speed with better image resolution and reduced motion artifact.[65]

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.[28] 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.[66] Another study that compared the reproducibility of retinal thickness measurements from OCT images of eyes with DME obtained by TD-OCT versus SD-OCT instruments found that SD-OCT devices demonstrated less test–retest variability.[65] Inter-device differences in retinal thickness were also reported in this study, though they were expected due to the different algorithms used by SD-OCT and TD-OCT machines that define the anatomical structures serving as the boundaries for measurement. Additionally, the presence of macular edema can influence OCT measurement precision. In one study, the 95% limits of agreement

(the scale at which an instrument can detect changes in a patient) for average foveal thickness in healthy eyes was 8 µm, while in patients with DME it was 36 µm.[67]

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).[68] For every 100 µm decrease in centre-point thickness, visual acuity increased by 4.4 letters (95% CI, 3.5 to 5.3).[68] Other studies have shown similarly modest correlations between visual acuity and CRT determined by OCT.[69,70] 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 composed of individuals with a number of common eye conditions (e.g., age-related cataracts, age-related macular degeneration, and diabetic retinopathy), and thus may be used to assess quality of life in a broad range of eye conditions.[29] 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.[71]

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.[30,71] With the exception of the expectations for future vision, all the constructs listed in the previous paragraph 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.[72] Rasch modelling is used to obtain measurements from categorical data. When comparing standard scoring with 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.[72]

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-letter) 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 worst-seeing eye, a 15-letter change in visual acuity corresponds to a four-point change in overall VFQ-25 score.[73] 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.[73] 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.[31] Using a one-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 approach yielded similar MCID estimates from 8.79 (driving) to 14.04 (role difficulties), with a composite-score MCID estimate of 3.33 points.[31] Other studies have shown similar estimated clinically relevant differences.[74] The instrument showed weaker correlation, or was not

responsive to changes, in the visual acuity of the worse eye.[75,76] 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[30,71,76] 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.[75,76] However, more recent studies have indicated that the NEI VFQ measures visual functioning, not quality of life.[44] 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.[43,44] 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.[43,44] 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.[43,44] Considering this recent evidence of multidimensionality, the validity of the single composite score of the NEI VFQ may be questioned.

EuroQol Five-Dimensions Questionnaire

The EuroQol five-dimensions questionnaire is a generic quality of life instrument that may be applied to a wide range of health conditions and treatments.[32,33] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[32,33] The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
2. A population preference–weighted health index score based on the descriptive system.
3. A self-reported assessment of health status based on the EQ-VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores of less than zero represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported MCIDs for this scale have ranged from 0.033 to 0.074.[77]

The use of generic preference-based outcome measures to capture change in condition-specific populations, including visual impairments, was evaluated in a systematic review by Longworth and colleagues in 2014.[78] The EQ-5D was the most commonly used generic quality-of-life measure for vision-related studies. The identified studies included patients with glaucoma, age-related macular

degeneration, cataracts, diabetic retinopathy, conjunctivitis, and other eye conditions. The ability of the EQ-5D to distinguish between visual acuity groups varied according to the type of visual disorder, as did the construct validity of the EQ-5D with measures of visual acuity.[78] The authors found that half of the studies included did not find statistically significant correlations between the EQ-5D and measures of visual acuity, and two of three studies that assessed the responsiveness of the scale found statistically significant differences.[78]

The responsiveness of the EQ-5D may be of particular concern for patients with low levels of vision. A study assessing patients attending private and hospital-based outpatient clinics with low vision (i.e., 10% = < 20/500; 26% = 20/200 to 20/500; 34% = 20/70 to 20/200; 30% = > 20/70) reported that baseline utilities were highly skewed toward a value of 1.0 (mean = 0.74), while baseline visual ability as measured by the EQ-5D's Activity Inventory were normally distributed with a mean of 0.63.[79] The EQ-5D was unable to capture changes in visual ability as a result of rehabilitation, and following rehabilitation and the correlation of change scores between the two measures, was not statistically significant (Pearson correlation 0.056). Cohen's effect size was below 0.1 for EQ-5D utility scores and ranged from 0.2 and 0.7 for the domains of the activity inventory.[79] While the EQ-5D is the most common measure for assessing quality of life in vision-related studies, there are concerns with validity and responsiveness in this population. No published MCIDs could be found for the EQ-5D in CRVO or in other vision-related disorders.

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. The MCID is subject to change according to baseline visual acuity, therefore, a range of 10 to 15 letters may be used as MCID.

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 be identified as a measure of visual functioning. The NEI VFQ has a reported MCID of between 3.3 and 6.1 points.

The EQ-5D is well validated as a generic health-related quality-of-life measure. It is commonly used to measure changes in quality of life in the context of vision-related studies; however, its validity and responsiveness in CRVO is questionable. The psychometric properties of the EQ-5D are known to vary across eye conditions, with no study assessing the validity of the scale in CRVO. An appropriate MCID for use in studies assessing therapeutic interventions for eye disorders is unknown.

APPENDIX 6: SUMMARY OF THE EXTENDED PHASE OF GALILEO AND COPERNICUS

This section summarizes the extension phase of GALILEO from week 52 to week 76[15] and the extension phase of COPERNICUS from week 52 to week 100.[22]

Study Characteristics and Study Design

Study and patients characteristics were already described in section 3.2 (Included Studies) of the present report.

GALILEO had a double-blind, sham-controlled phase up to week 52, after which all patients were eligible to receive vascular endothelial growth factor (VEGF) Trap-Eye following re-treatment criteria up to week 76. Patients had visits every eight weeks and treatment was masked for the full period.

COPERNICUS had a double-blind, sham-controlled phase up to week 24, after which all patients were eligible for active treatment following re-treatment criteria assessed monthly. Starting at week 52, all patients were eligible to continue the as-needed (PRN) extension phase, but patients were monitored quarterly up to week 100. The masking was not maintained during the PRN extension phase.

Patient Disposition

In GALILEO, [redacted] and 85% of patients completed the extension phase in the sham group and the active treatment group, respectively. Between week 52 and week 76, [redacted] discontinued the study in the active treatment group, [redacted] observed in the sham group.

In COPERNICUS, 68% and 89% of patients completed the extension phase in the sham group and the active treatment group, respectively. Between week 52 and week 100, [redacted] patients discontinued the study in the sham group, while [redacted] patients discontinued the study in the active treatment group.

TABLE 33: PATIENT DISPOSITION

	GALILEO (76 Weeks)		COPERNICUS (100 Weeks)	
	Sham + PRN (N = 71)	VEGF Trap-Eye 2Q4 + PRN (N = 106)	Sham + PRN (N = 74)	VEGF Trap-Eye 2Q4 + PRN (N = 115)
Completed 52 weeks, n (%)	52 (73.2)	91 (85.8)	57 (77.0)	107 (93.0)
Completed extension phase, n (%)	[redacted]	90 (84.9)	50 (67.6)	102 (88.7)
Discontinued study before end of extension phase, n (%)	19 (26.8))	16 (15.1)	24 (32.4)	13 (11.3)
Adverse event	5 (7.0)	5 (4.7)	4 (5.4)	4 (3.5)
Protocol violation or deviation	2 (2.8)	5 (4.7)	2 (2.7)	1 (0.9)
Withdrawal of consent	6 (8.5)	4 (3.8)	3 (4.1)	5 (4.3)
Lack of efficacy or treatment failure	5 (7.0)	0	4 (5.4)	[redacted]
Lost to follow-up	[redacted]	[redacted]	5 (6.8)	2 (1.7)
Death	[redacted]	[redacted]	4 (5.4)	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Completed week 52 under treatment, n (%)	[redacted]	[redacted]	57 (77.0)	107 (93.0)

	GALILEO (76 Weeks)		COPERNICUS (100 Weeks)	
	Sham + PRN (N = 71)	VEGF Trap-Eye 2Q4 + PRN (N = 106)	Sham + PRN (N = 74)	VEGF Trap-Eye 2Q4 + PRN (N = 115)
Completed extension phase under treatment, n (%)	50 (70.4)	87 (82.1)	51 (68.9)	100 (87.0)
Reasons for discontinuing study drug before end of extension phase, n (%)				
Adverse event	9 (12.7)	7 (6.6)	4 (5.4)	6 (5.2)
Protocol violation or deviation	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy or treatment failure	5 (7.0)	[redacted]	4 (5.4)	[redacted]
Lost to follow-up	0	[redacted]	4 (5.4)	[redacted]
Treatment unblinded	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	4 (5.4)	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

2Q4 = every four weeks; NR = not reported; PRN = as needed; VEGF = vascular endothelial growth factor.
Source: Clinical Study Report PH-36935 (week 76),[15] Clinical Study Report R-8742 (week 100).[22]

Efficacy

In GALILEO, the statistical difference between the sham group and the active treatment group for the proportion of patients gaining more than 15 letters observed at week 52 was maintained at week 76 (*P* = 0.0004) with a similar effect size (least squares mean difference [LSMD] of 28.0%; 95% confidence interval [CI], 13.3 to 42.6). The statistical difference between the sham group and the active treatment group in change from baseline in best-corrected visual acuity (BCVA) was maintained at week 76 (*P* = 0.007), but the effect size was lower at week 76 (7.6 letters [95% CI, 2.1 to 13.1]) compared with week 52 (13.2 letters [95% CI, 8.2 to 18.2]). In terms of change from baseline in the total 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) score, the statistical difference between the sham group and the active treatment group observed at week 52 was maintained to week 76 with a numerically lower effect size (2.9 letters [95% CI, 0.1 to 5.7], *P* = 0.0445) compared with week 52 (3.6 letters [95% CI, 1.1 to 6.0], *P* = 0.0049). Concerning the change from baseline in EQ-5D, as observed at week 52, no statistically significant difference was observed between the sham group and the treatment group at week 76 (0.030 letters [95% CI, –0.019 to 0.078], *P* = 0.2321). For the change from baseline in central retinal thickness (CRT), the statistical difference observed between the sham group and the active treatment group at week 52 was no longer observed at week 76 (–44.16 µm [95% CI, –98.76 to 10.44], *P* = 0.1122).

In COPERNICUS, the statistical difference between the sham group and the active treatment group for the proportion of patients gaining more than 15 letters observed at week 52 was maintained at week 100 (*P* = 0.0003) with a similar effect size (LSMD of 26.7% [95% CI, 13.1 to 40.3]). Concerning the change from baseline in BCVA, the statistical difference between the sham group and the active treatment group observed at week 52 was maintained to week 100 with a similar effect size (11.81 letters [95% CI, 6.65 to 16.79], *P* < 0.0001). For the change from baseline in total NEI VFQ-25 score, as observed at week 52, no statistically significant difference was observed between the sham group and the treatment group at week 100 (2.66 letters [95% CI, –2.02 to 7.34], *P* = 0.2628). In terms of change from baseline in CRT, as observed at week 52, no statistically significant difference was observed between the sham group and the treatment group at week 100 (–44.63 µm [95% CI, –141.8 to 52.58], *P* = 0.3661).

TABLE 34: KEY EFFICACY OUTCOMES AT THE END OF THE EXTENSION PHASE

	GALILEO (76 Weeks)		COPERNICUS (100 Weeks)	
	Sham + PRN (N = 68)	VEGF Trap-Eye 2Q4 + PRN (N = 103)	Sham + PRN (N = 73)	VEGF Trap-Eye 2Q4 + PRN (N = 114)
Proportion of patients ≥ 15 letters BCVA, n (%)	20 (29.4)	59 (57.3)	17 (23.3)	56 (49.1)
Adjusted difference (%) (95% CI)	28.0[a] (13.3 to 42.6)		26.7[a] (13.1 to 40.3)	
Change from baseline in BCVA at the end of the extension phase				
Baseline (SD)	50.9 (15.4)	53.6 (15.8)	48.9	50.7
Mean value at last visit (SD)	57.1 (21.3)	67.3 (21.4)	[redacted]	[redacted]
Mean change from baseline, unadjusted (SD)	6.2 (17.7)	13.7 (17.8)	1.5	13.0
LS mean change	7.4	15.0	–0.20	11.6
LSMD (95% CI)	7.6[b] (2.1 to 13.1)		11.81[c] (6.65 to 16.79)	
Change from baseline in NEI VFQ-25 total score				
n	67	98	[redacted]	[redacted]
Baseline	78.9	79.8	77.5	78.0
Mean value at last visit	83.8	87.2	[redacted]	[redacted]
Mean change from baseline, unadjusted	4.9	7.4	[redacted]	[redacted]
LS mean change	1.1	4.0	3.6	6.3
LSMD (95% CI)	2.9[b] (0.1 to 5.7)		2.66 (–2.02 to 7.34)	
Change from baseline in EQ-5D score from baseline				
n	67	97	NR	NR
Baseline	[redacted]	[redacted]	NR	NR
Mean value at last visit	[redacted]	[redacted]	NR	NR
Mean change from baseline, unadjusted	–0.001	0.017	NR	NR
LS mean change	[redacted]	[redacted]	NR	NR
LSMD (95% CI)	0.030 (–0.019 to 0.078)		NR	NR
Change from baseline in CRT at the end of the extension phase				
n	67	103	65	112
Baseline (SD)	638.66 (224.69)	683.20 (234.46)	664.0	661.7
Mean value at last visit (SD)	327.79 (191.58)	293.85 (173.01)	320.7	661.7
Mean change from baseline, unadjusted (SD)	–306.37 (246.85)	–389.35 (273.71)	–386.8	–431.4
LS mean change	–364.69	–408.85	–343.3	–390.0
LSMD (95% CI)	–44.16 (–98.76 to 10.44)		–44.63 (–141.8 to 52.58)	

2Q4 = every four weeks; BCVA = best-corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; EQ-5D = EuroQol five-dimensions questionnaire; LS = least squares; LSMD = least squares mean difference; NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; NR = not reported; PRN = as needed; SD = standard deviation; VEGF = vascular endothelial growth factor.

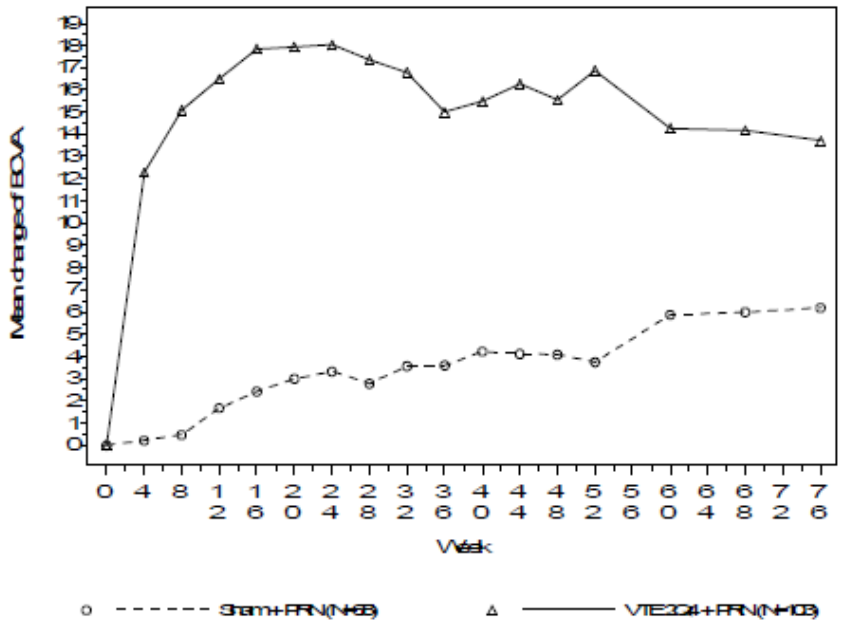
[a] $P < 0.001$.

[b] $P < 0.05$.

[c] $P < 0.0001$.

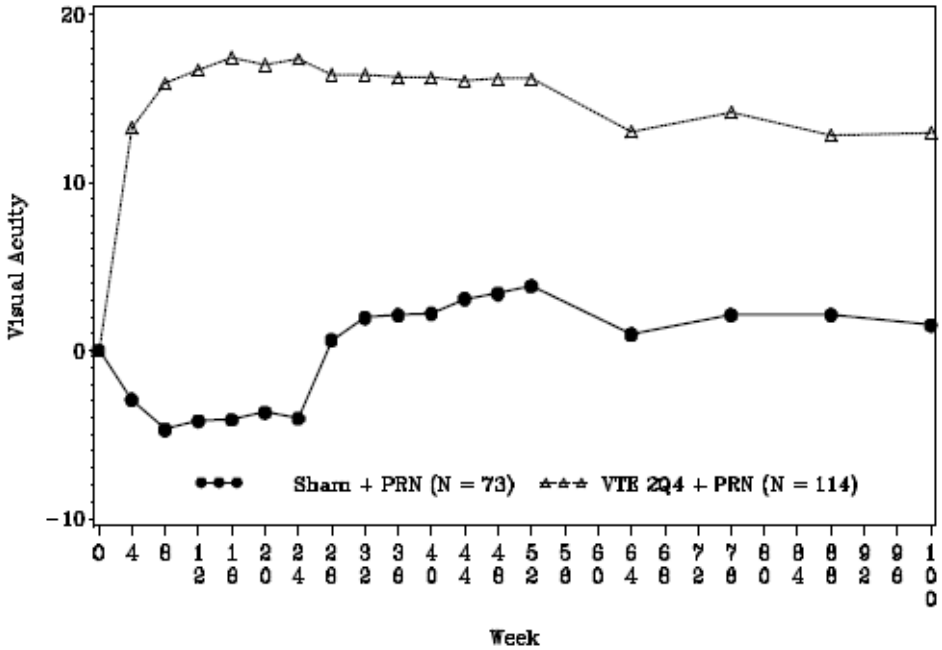
Source: Clinical Study Report PH-36935 (week 76)[15] and Clinical Study Report R-8742 (week 100).[22]

FIGURE 4: GALILEO — MEAN CHANGE FROM BASELINE IN BCVA THROUGH WEEK 76 BY TREATMENT GROUP (LOCF/FAS)



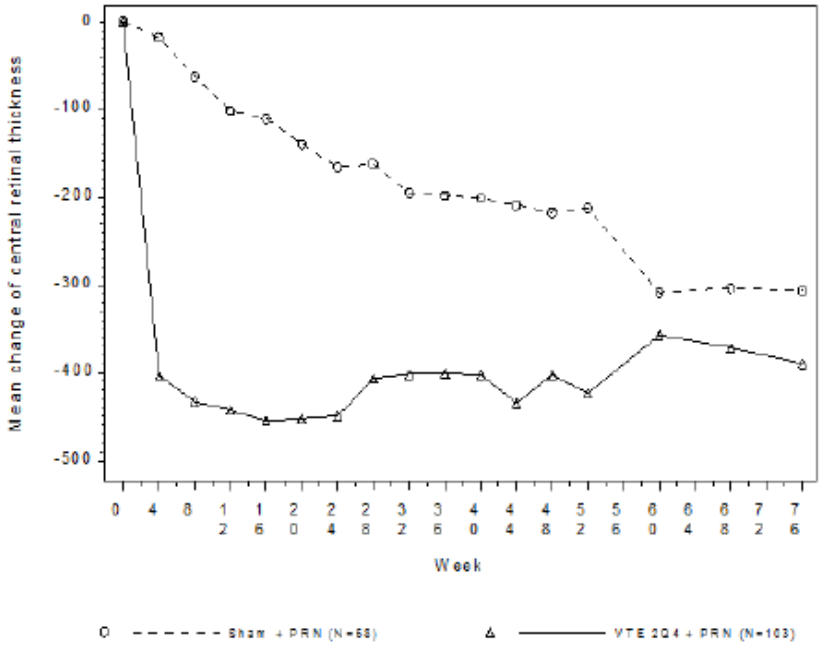
2Q4 = every four weeks; BCVA = best-corrected visual acuity; FAS = full analysis set; LOCF = last observation carried forward; PRN = as needed; VEGF = vascular endothelial growth factor; VTE = VEGF Trap-Eye.
Source: Clinical Study Report PH-36935 (week 76).[15]

FIGURE 5: COPERNICUS — MEAN CHANGE FROM BASELINE IN BCVA THROUGH WEEK 100 BY TREATMENT GROUP (LOCF/FAS)



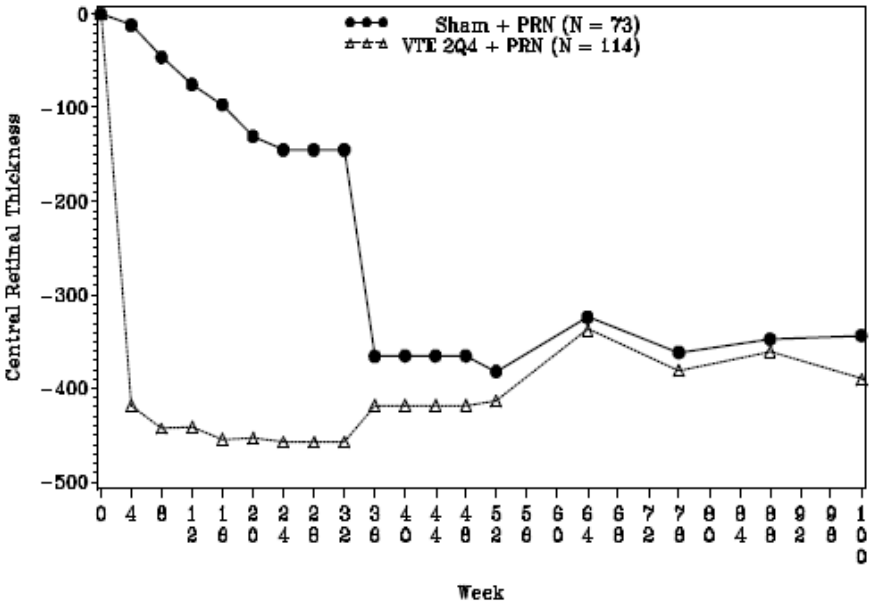
2Q4 = every four weeks; BCVA = best-corrected visual acuity; FAS = full analysis set; LOCF = last observation carried forward; PRN = as needed; VEGF = vascular endothelial growth factor; VTE = VEGF Trap-Eye.
Source: Clinical Study Report R-8742 (week 100).[22]

FIGURE 6: GALILEO — MEAN CHANGE FROM BASELINE IN CRT THROUGH WEEK 76 BY TREATMENT GROUP (LOCF/FAS)



2Q4 = every four weeks; CRT = central retinal thickness; FAS = full analysis set; LOCF = last observation carried forward; PRN = as needed; VEGF = vascular endothelial growth factor; VTE = VEGF Trap-Eye.
Source: Clinical Study Report PH-36935 (week 76).[15]

FIGURE 7: COPERNICUS — MEAN CHANGE FROM BASELINE IN CRT THROUGH WEEK 100 BY TREATMENT GROUP (LOCF/FAS)



2Q4 = every four weeks; CRT = central retinal thickness; FAS = full analysis set; LOCF = last observation carried forward; PRN = as needed; VEGF = vascular endothelial growth factor; VTE = VEGF Trap-Eye.
Source: Clinical Study Report R-8742 (week 100).[22]

Safety

The extent of study drug exposure in GALILEO and COPERNICUS is summarized in Table 35 and Table 36, respectively. At the end of GALILEO, patients in the sham group received approximately 2 mg aflibercept, which corresponds to a single injection, whereas patients in the active treatment group received approximately 18 mg (nine injections) aflibercept. For COPERNICUS, patients in the sham group received a mean of 6.4 injections at the end of the trial, while patients in the active treatment group received a mean of 11.8 injections.

The occurrence of treatment-emergent adverse events (TEAEs) is increased with the length of the study with COPERNICUS (94.6% to 98.2%) having more than GALILEO (87.5% and 89.7%) (Table 37). The number of ocular and non-ocular TEAEs was similar across treatment groups. The most commonly reported ocular TEAEs were macular edema (up to 39%), retinal hemorrhage (up to 16%), reduced visual acuity (up to 28%), conjunctival hemorrhage (up to 20%), retinal vascular disorder (up to 12%), eye pain (up to 18%), and increased intraocular pressure (up to 18%) (Table 38). Macular edema (for both studies), conjunctival hemorrhage (for GALILEO only), eye pain (for both studies) and increased intraocular pressure (for GALILEO only) occurred more frequently in the active treatment groups than in the sham groups. Of note, the number of macular edema events was much higher in GALILEO (39% in the active treatment group) than in COPERNICUS (18% in the active treatment group).

The most common non-ocular TEAEs were nasopharyngitis (up to 25%), hypertension (up to 19%), and headache (up to 12%) (Table 39). Nasopharyngitis was more frequent in the sham group (25%) of GALILEO compared with its active treatment group (15%) but, in general, the non-ocular TEAEs were not relevantly more frequent in one particular group.

Among notable harms (such as ATEs, retinal detachment, and endophthalmitis), ATEs were the most frequent, with an occurrence of 2% to 3%. None of the notable harms were observed more frequently in a particular group. The subgrouping of events with an increased intraocular pressure categorized according to pressure did not show an imbalance between groups. The numbers of TEAEs leading to discontinuation or interruption of study treatment were more or less balanced between groups. Four deaths (5.4%) occurred in the sham group of COPERNICUS. Two of them occurred within the 24 first weeks of the study when patients received sham treatment only. Those mortalities were not likely due to the study drug.

Differences in harms observed in GALILEO, but not observed in COPERNICUS, may be due to the design of those studies where patients in the sham group of COPERNICUS crossed over to active treatment after only 24 weeks, while patients in the sham group of GALILEO were not allowed to receive VEGF Trap-Eye (VTE) until week 52.

TABLE 35: EXPOSURE TO STUDY DRUG TO WEEK 76 — GALILEO (SAFETY SET)

	GALILEO (76 Weeks)	
Total Amount (mg)	**Sham + PRN (N = 68)**	**VEGF Trap-Eye (N = 104)**
Mean (SD)	2.5 [redacted]	18.2 [redacted]
Median	[redacted]	[redacted]

PRN = as needed; SD = standard deviation; VEGF = vascular endothelial growth factor.
Source: Clinical Study Report PH-36935 (week 76).[15]

TABLE 36: EXPOSURE TO STUDY DRUG TO WEEK 100 — COPERNICUS (SAFETY SET)

	COPERNICUS (100 Weeks)	
	Sham + PRN	VEGF Trap-Eye 2Q4 + PRN
Total amount (mg)		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Number of active injections[a]		
N	[redacted]	[redacted]
Mean (SD)	6.4 ([redacted])	11.8 (3.35)
Median	7.0	11.5

2Q4 = every four weeks; PRN = as needed; SD = standard deviation; VEGF = vascular endothelial growth factor.
[a] Safety set of patients who completed week 24.
Source: Clinical Study Report R-8742 (week 100).[22]

TABLE 37: HARMS AT END OF EXTENSION PHASE

	GALILEO (76 Weeks)		COPERNICUS (100 Weeks)	
Summary of AEs n (%)	Sham + PRN (N = 68)	VEGF Trap-Eye (N = 104)	Sham + PRN (N = 74)	VEGF Trap-Eye 2Q4 + PRN (N = 114)
TEAEs				
Patients with any TEAEs, n (%)	61 (89.7)	91 (87.5)	70 (94.6)	112 (98.2)
Any ocular TEAE, n (%)	52 (76.5)	82 (78.8)	65 (87.8)	103 (90.4)
Occurring in study eye, n (%)	51 (75.0)	82 (78.8)	63 (85.1)	100 (87.7)
Any non-ocular TEAEs	50 (73.5)	71 (68.3)	60 (81.1)	88 (77.2)
SAEs				
Patients with > 0 SAEs, N (%)	15 (22.1)	27 (26.0)	30 (40.5)	31 (27.2)
Notable harms				
ATE	2 (2.9)	1 (1.0)	2 (2.7)	3 (2.6)
ATE based on APTC end point	0	0	2 (2.7)	2 (1.8)
Retinal detachment	NR	NR	NR	NR
Endophthalmitis	NR	NR	0	1 (0.9)
WDAEs				
TEAEs leading to discontinuation of study treatment	7 (10.3)	7 (6.7)	6 (8.1)	4 (3.5)
TEAEs leading to interruption of study treatment	1 (1.5)	3 (2.9)	2 (2.7)	5 (4.4)
IOP increased				
Increase of ≥ 10 mm Hg from baseline in pre-injection IOP	5 (7.4)	10 (9.6)	10 (13.5)	8 (7.0)
Pre-injection IOP absolute value of ≥ 21 mm Hg	9 (13.2)	20 (19.2)	23 (31.1)	30 (26.3)
Pre-injection IOP absolute value of ≥ 35 mm Hg	1 (1.5)	3 (2.9)	5 (6.8)	2 (1.8)
Deaths	0	0	4 (5.4)	0

2Q4 = every four weeks; AE = adverse event; APTC = Antiplatelet Trialists' Collaboration; ATE = arterial thromboembolic event; IOP = intraocular pressure; NR = not reported; PRN = as needed; SAE = serious adverse event; TEAE = treatment-emergent adverse event; VEGF = vascular endothelial growth factor; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report PH-36935 (week 76)[15] and Clinical Study Report R-8742 (week 100).[22]

TABLE 38: MOST COMMON OCULAR TEAES (≥ 3%) AT END OF EXTENSION PHASE (SAFETY SET)

	GALILEO (76 Weeks)		COPERNICUS (100 Weeks)	
TEAEs, n (%)	Sham + PRN (N = 68)	VEGF Trap-Eye (N = 104)	Sham + PRN (N = 74)	VEGF Trap-Eye 2Q4 + PRN (N = 114)
Macular edema	17 (25.0)	41 (39.4)	3 (4.1)	21 (18.4)
Retinal hemorrhage	8 (11.8)	16 (15.4)	12 (16.2)	18 (15.8)
Reduced visual acuity	9 (13.2)	15 (14.4)	20 (27.0)	32 (28.1)
Conjunctival hemorrhage	5 (7.4)	18 (17.3)	15 (20.3)	22 (19.3)
Retinal vascular disorder	8 (11.8)	12 (11.5)	7 (9.5)	14 (12.3)
Eye pain	4 (5.9)	15 (14.4)	7 (9.5)	21 (18.4)
Macular ischemia	7 (10.3)	11 (10.6)	NR	NR
Retinal exudates	7 (10.3)	10 (9.6)	5 (6.8)	13 (11.4)
Macular fibrosis	8 (11.8)	6 (5.8)	6 (8.1)	12 (10.5)
Eye irritation	7 (10.3)	6 (5.8)	4 (5.4)	9 (7.9)
Ocular hyperemia	4 (5.9)	9 (8.7)	0	6 (5.3)
Optic disc vascular disorder	6 (8.8)	7 (6.7)	6 (8.1)	14 (12.3)
Foreign body sensation in eyes	5 (7.4)	7 (6.7)	3 (4.1)	2 (1.8)
Lacrimation increased	6 (8.8)	5 (4.8)	4 (5.4)	5 (4.4)
Retinopathy	3 (4.4)	6 (5.8)	NR	NR
Papilledema	3 (4.4)	5 (4.8)	3 (4.1)	5 (4.4)
Vitreous detachment	1 (1.5)	7 (6.7)	7 (9.5)	13 (11.4)
Vitreous floaters	1 (1.5)	7 (6.7)	4 (5.4)	9 (7.9)
Vitreous hemorrhage	3 (4.4)	5 (4.8)	9 (12.2)	3 (2.6)
Cystoid macular edema	1 (1.5)	6 (5.8)	5 (6.8)	15 (13.2)
Iris neovascularization	0	7 (6.7)	6 (8.1)	1 (0.9)
Increased intraocular pressure	4 (5.9)	18 (17.3)	13 (17.6)	14 (12.3)
Retinal pigment epitheliopathy	NR	NR	14 (18.9)	6 (5.3)
Cataract	2 (2.9)	3 2.9)	3 (4.1)	8 (7.0)
Dry eye	1 (1.5)	2 (1.9)	7 (9.5)	4 (3.5)

2Q4 = every four weeks; NR = not reported; PRN = as needed; TEAE = treatment-emergent adverse event; VEGF = vascular endothelial growth factor.
Source: Clinical Study Report PH-36935 (week 76)[15] and Clinical Study Report R-8742 (week 100).[22]

TABLE 39: MOST COMMON NON-OCULAR TEAES (≥ 3%) AT END OF EXTENSION PHASE (SAFETY SET)

	GALILEO (76 Weeks)		COPERNICUS (100 Weeks)	
TEAEs, n (%)	Sham + PRN (N = 68)	VEGF Trap-Eye (N = 104)	Sham + PRN (N = 74)	VEGF Trap-Eye 2Q4 + PRN (N = 114)
Nasopharyngitis	17 (25.0)	16 (15.4)	5 (6.8)	10 (8.8)
Hypertension	7 (10.3)	10 (9.6)	12 (16.2)	22 (19.3)
Headache	6 (8.8)	12 (11.5)	4 (5.4)	5 (4.4)
Arthralgia	6 (8.8)	5 (4.8)	3 (4.1)	4 (3.5)
Back pain	3 (4.4)	7 (6.7)	1 (1.4)	4 (3.5)
Influenza	2 (2.9)	8 (7.7)	4 (5.4)	9 (7.9)
Bronchitis	1 (1.5)	6 (5.8)	3 (4.1)	7 (6.1)
Protein urine present	NR	NR	6 (8.1)	6 (5.3)
Increased urine protein or creatinine ratio	NR	NR	6 (8.1)	6 (5.3)

2Q4 = every four weeks; NR = not reported; PRN = as needed; TEAE = treatment-emergent adverse event; VEGF = vascular endothelial growth factor.
Source: Clinical Study Report PH-36935 (week 76)[15] and Clinical Study Report R-8742 (week 100).[22]

Discussion

More patients discontinued the study in the sham groups of GALILEO and COPERNICUS than in their active treatment groups. Although adverse events were the most common reason for discontinuation, and more frequent than lack of efficacy, according to the clinical expert consulted by reviewers for the CADTH Common Drug Review, complications due to a lack of efficacy in the sham groups may be reported as adverse events.

In GALILEO, the differences in efficacy observed at week 52 between the sham group and the active treatment group for BCVA outcomes and NEI VFQ-25 scores were maintained at week 76. The difference observed at week 52 between the sham group and the active treatment group for CRT was not observed at week 76. In COPERNICUS, only the differences in efficacy between the sham group and the active treatment group for BCVA outcomes were maintained at week 100 compared with week 52. Thus, the response obtained with VTE appeared to be sustained.

In GALILEO, patients were masked to the nature of their treatment throughout the whole study. In COPERNICUS, patients were not blinded after 52 weeks. Because the measure of visual acuity can be subjective if the patient knows which treatment he received, and because NEI VFQ-25 is a patient-reported outcome, the BCVA and NEI VFQ-25 results from GALILEO are more reliable than the BCVA and NEI VFQ-25 results from COPERNICUS. Also, GALILEO allowed the study drug versus sham to be compared for 52 weeks, while this comparison was done for only 24 weeks in COPERNICUS. Hence, the long-term results of COPERNICUS are not comparative.

In GALILEO and COPERNICUS, the number of ocular or non-ocular TEAEs, withdrawals due to adverse events, and notable harms were similar across treatment groups. Macular edema, conjunctival hemorrhage, eye pain, and increased intraocular pressure appeared to be related to the active treatment groups. Those harms are not likely to limit the tolerance to treatment. Four deaths (5.4%) occurred in the sham group of COPERNICUS, but those were not likely due to the study drug.

Differences in harms observed in GALILEO, but not observed in COPERNICUS, may be due to the design of those studies where patients in the sham group of COPERNICUS crossed over to active treatment after only 24 weeks, while patients in the sham group of GALILEO were not allowed to receive VTE until week 52.

Conclusions

This section summarizes the extension phase of GALILEO from week 52 to week 76 and the extension phase of COPERNICUS from week 52 to week 100. More patients discontinued the study in the sham groups of GALILEO and COPERNICUS than in their active treatment groups, which probably reflects a lack of efficacy in the sham group. In GALILEO and COPERNICUS, the differences in efficacy observed at week 52 between the sham group and the active treatment group for BCVA outcomes were maintained at the end of the extension phase. In GALILEO only, the difference observed at week 52 between the sham group and the active treatment group for NEI VFQ-25 was maintained at week 76. Thus, the response obtained with VTE appeared to be sustained. Because COPERNICUS is not truly comparative after 24 weeks, and because it is not blinded after week 52, the BCVA and NEI VFQ-25 results from GALILEO are more reliable than the BCVA and NEI VFQ-25 results from COPERNICUS. The number of ocular and non-ocular TEAEs, withdrawals due to adverse events, and notable harms were similar across treatment groups in both studies. Macular edema, conjunctival hemorrhage, eye pain, and increased intraocular pressure appeared to be related to the active treatment groups, but those adverse events are not likely to limit the tolerance to treatment.

APPENDIX 7: SUMMARY OF INDIRECT COMPARISONS

1. Manufacturer-Submitted Indirect Comparison

Because the randomized controlled trials (RCTs) included in the systematic review of clinical evidence for the current submission were not designed to compare aflibercept directly with relevant active comparators, the manufacturer used an indirect comparison to estimate the comparative efficacy and safety of aflibercept, ranibizumab, dexamethasone, and sham treatment. The indirect comparison submitted by the manufacturer comprised a network meta-analysis (NMA) using data extracted from studies identified in a systematic literature review. The aim was to evaluate the relative efficacy and safety of aflibercept (2 mg administered monthly) compared with ranibizumab (0.5 mg administered monthly) and dexamethasone (a single implant of 0.7 mg) for the treatment of reduced visual acuity due to macular edema following central retinal vein occlusion (CRVO).[36] This section provides a summary and critical appraisal of the methods and main findings of the NMA.

Methods

Eligibility Criteria

[redacted]

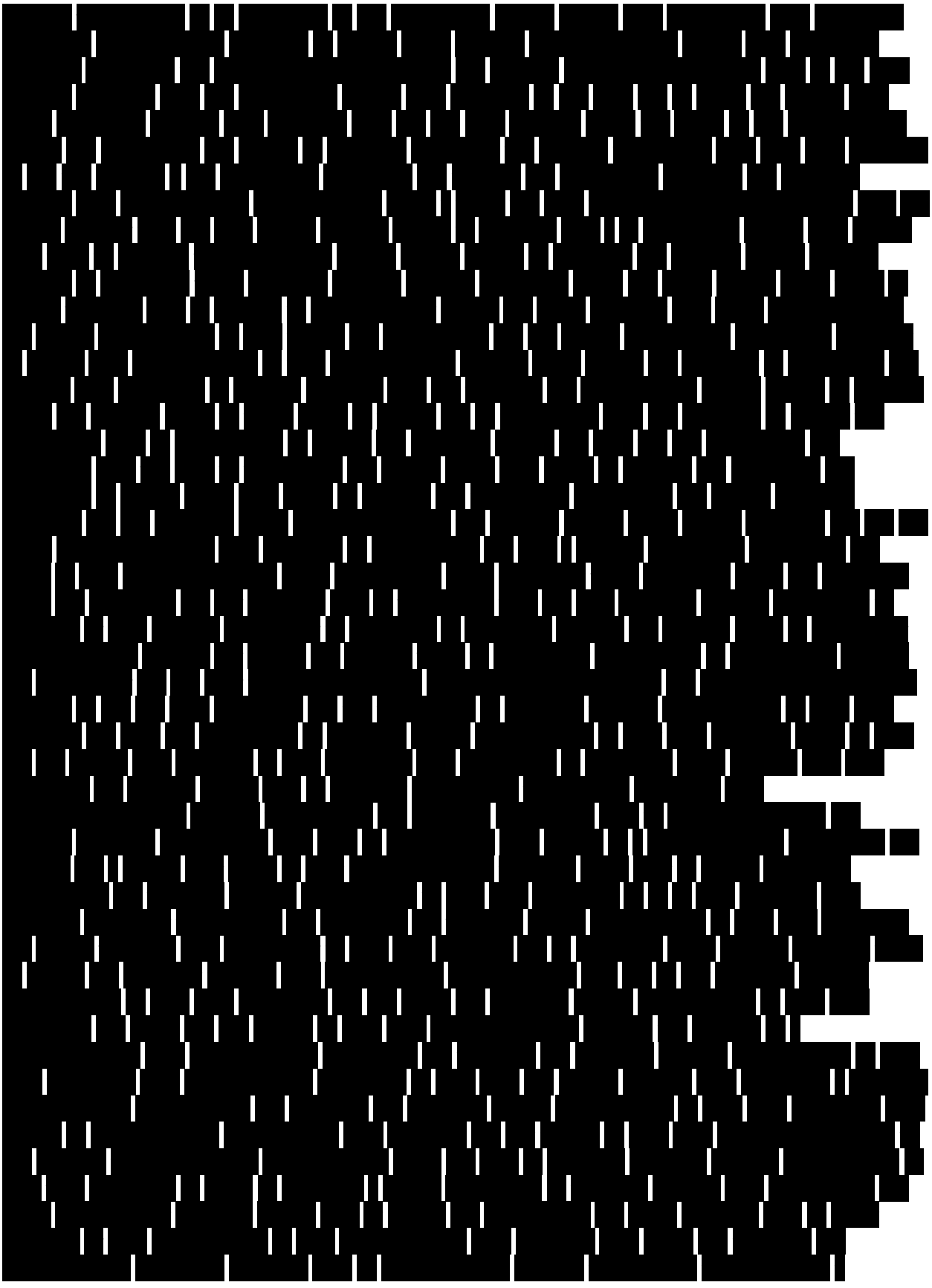
Network Meta-analysis

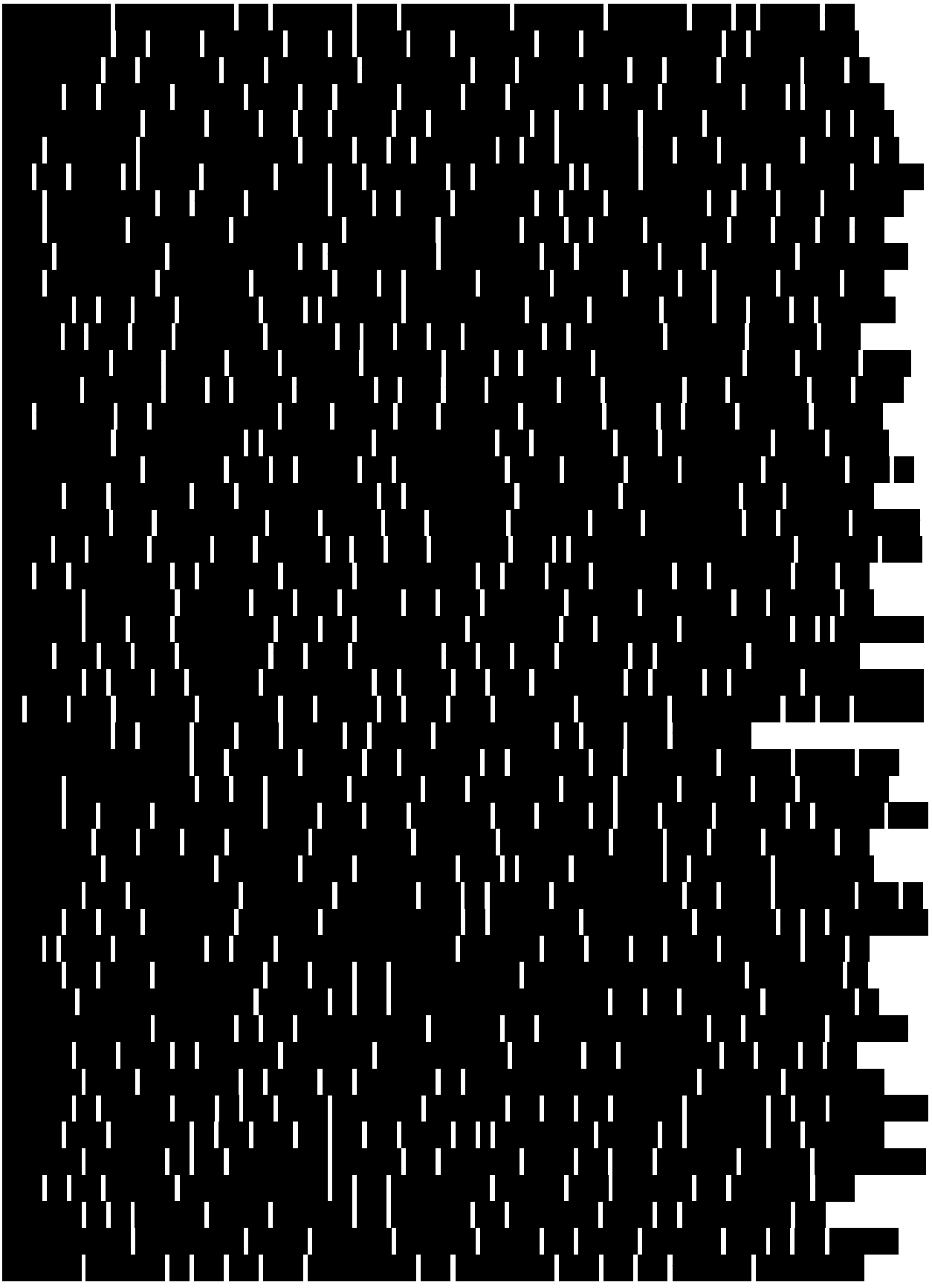
The analyses were carried out using WinBUGS v.1.4.3. Both fixed and random effects models were used. The deviance information criterion statistics and the total residual deviance were used to assess the overall fit of the model. Convergence was assessed using the Brooks–Gelman–Rubin diagnostic. A burn-in of at least 20,000 simulations was discarded. All results were presented on a further sample of at least 50,000 simulations. In each cycle, each treatment was ranked according to the estimated effect size. Then, the proportion of the cycles in which a given treatment ranks first out of the total number of cycles gave the probability that this treatment is the best. The Monte Carlo error was observed. All baseline and intervention-effect parameters were given flat normal (0, 10,000) priors. The between-study standard deviation was given flat uniform distributions. Study heterogeneity was tested [redacted]

Results

Systematic Literature Review

[redacted]





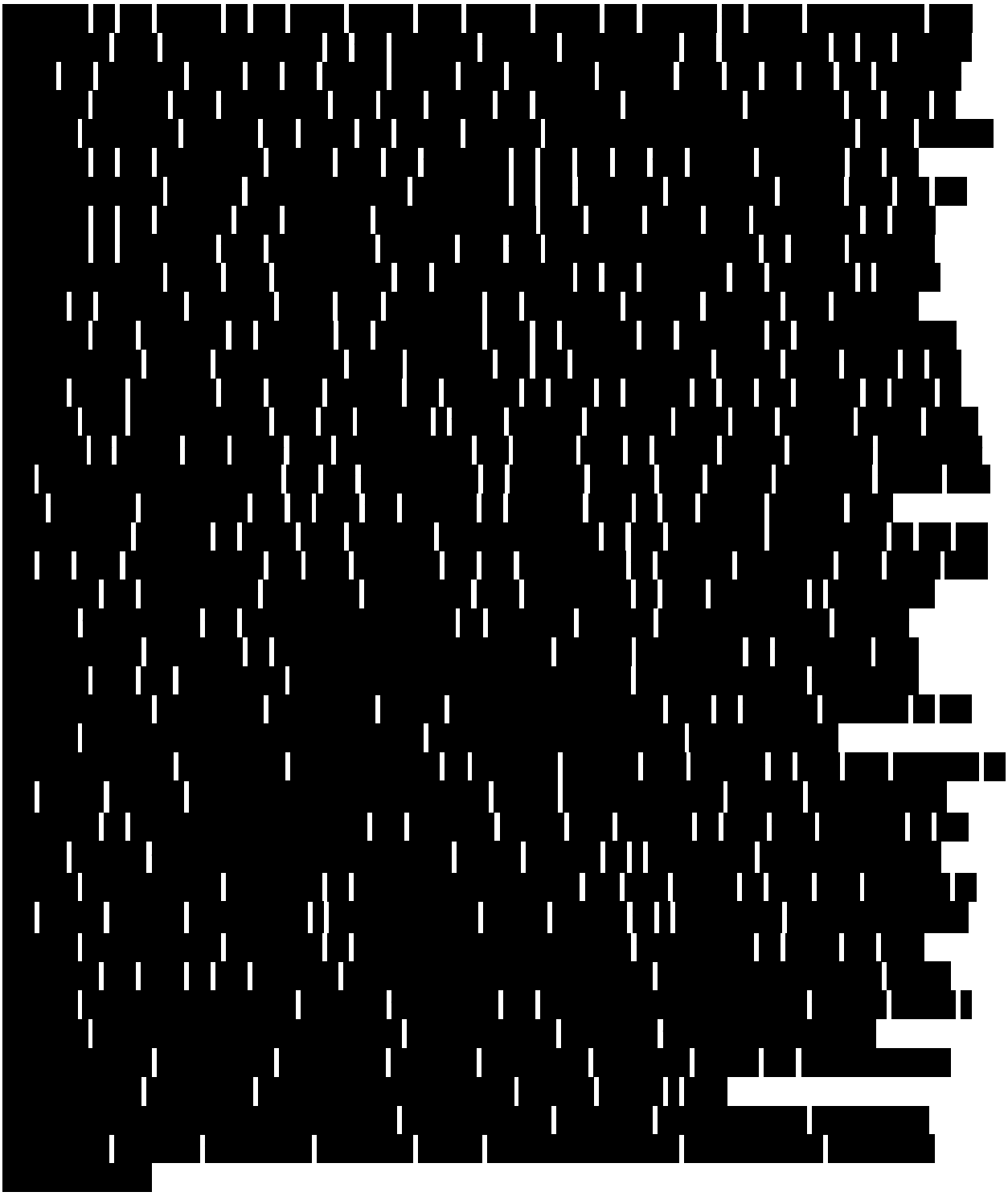


TABLE 40: APPRAISAL OF NETWORK META-ANALYSIS USING ISPOR CRITERIA

BCVA = best-corrected visual acuity; CRT = central retinal thickness; DIC = deviance information criterion; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; RCT = randomized controlled trial.

2. Indirect Comparisons From Published Literature

In our systematic review of published literature, a single indirect comparison[39] was identified in which an NMA based on a systematic review[40] was used to indirectly compare the clinical effectiveness of aflibercept, ranibizumab, bevacizumab, dexamethasone, and triamcinolone for the treatment of macular edema secondary to CRVO. The systematic review included RCTs with at least 12 months of

follow-up. Only doses that are used in clinical practice were included. Outcomes of interest were the proportion of patients gaining ≥ 15 letters from baseline to six months, the proportion of patients losing ≥ 15 letters from baseline to six months, and the mean change in BCVA from baseline to six months.

Methods for conducting the systematic review and the NMA were well described. The Cochrane Collaboration's tool was used for assessing risk of bias.

Eight studies were identified from the systematic review, seven of which were included in the NMA. The included studies are presented in Table 41. GENEVA was counted as two RCTs, but the results of the studies were reported together as in the manufacturer-submitted NMA.

The results for the proportions of patients gaining 15 letters or more from baseline showed that more patients treated with aflibercept, bevacizumab, triamcinolone, and ranibizumab appeared to achieve this end point compared with the patients treated with dexamethasone (Figure 11). Indeed, more patients treated with any active treatment except dexamethasone appeared to achieve the 15 letters of BCVA threshold compared with sham. No statistical difference was observed between aflibercept, bevacizumab, ranibizumab, and triamcinolone for this outcome. Triamcinolone had the highest probability of being best (nearly 40%) for this outcome and aflibercept had the highest probability of being second best (nearly 40%).

Compared with sham, fewer patients treated with aflibercept, ranibizumab, and triamcinolone appeared to lose 15 letters or more from baseline at six months compared with sham (Figure 12). Bevacizumab did not reach statistical significance for the same comparison. More patients treated with triamcinolone lost 15 letters or more from baseline than those treated with aflibercept and ranibizumab. Patients treated with aflibercept, ranibizumab, and bevacizumab were not statistically different in regard to this outcome. Ranibizumab had the highest probability of being best (nearly 70%) for this outcome and aflibercept had the highest probability of being second best (nearly 55%).

All active treatments showed an improvement in BCVA from baseline at six months compared with sham (Figure 13). Only patients treated with aflibercept appeared to gain statistically significantly more letters from baseline compared with triamcinolone. A statistical difference could not be observed between ranibizumab, aflibercept, and bevacizumab for the same outcome. Aflibercept had the highest probability of being best (60%).

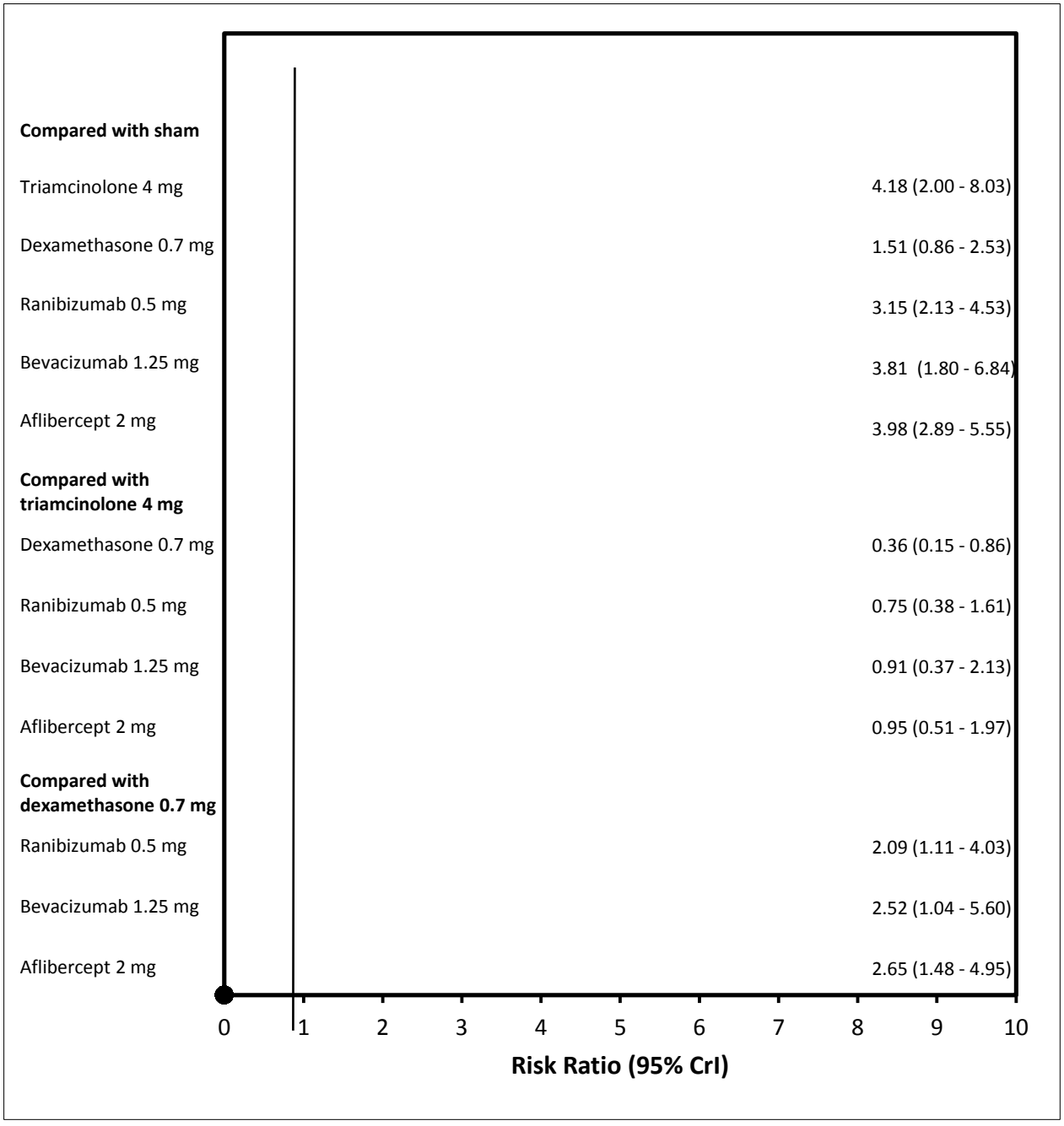
TABLE 41: LIST OF STUDIES INCLUDED IN THE NETWORK META-ANALYSIS (FORD ET AL. 2014)

Trial Name	Population	Randomized Interventions	Number of Patients	Duration	Included in Manufacturer-Submitted NMA
GENEVA 2010	Adults with visual acuity reduced because of macular edema due to CRVO or BRVO	DEX 0.7 mg DEX 0.35 mg Sham	n = 136 n = 154 n = 147	Primary end point at 6 months; open-label extension up to 12 months	Yes
SCORE 2009	Centre-involved macular edema secondary to CRVO	Triamcinolone 1 mg Triamcinolone 4 mg Sham	n = 92 n = 91 n = 88	Primary end point at 12 months	No

Trial Name	Population	Randomized Interventions	Number of Patients	Duration	Included in Manufacturer-Submitted NMA
COPERNICUS 2012	Adult patients with centre-involved CRVO for a maximum of 9 months	AFL 2 mg Sham	n = 114 n = 73	Primary end point at 24 weeks	Yes
GALILEO 2012	Treatment-naive patients with centre-involved CRVO for a maximum of 9 months	AFL 2 mg Sham	n = 103 n = 71	Primary end point at 24 weeks	Yes
CRUISE 2010	Patients with foveal centre-involved macular edema secondary to CRVO diagnosed within 12 months	RAN 0.3 mg RAN 0.5 mg Sham	n = 132 n = 130 n = 130	Primary end point at 6 months	Yes
EPSTEIN 2012	Patients with CRVO of ≤ 6 months	Bevacizumab 1.25 mg Sham	n = 30 n = 30	Primary end point at 6 months; open-label extension up to 12 months	No

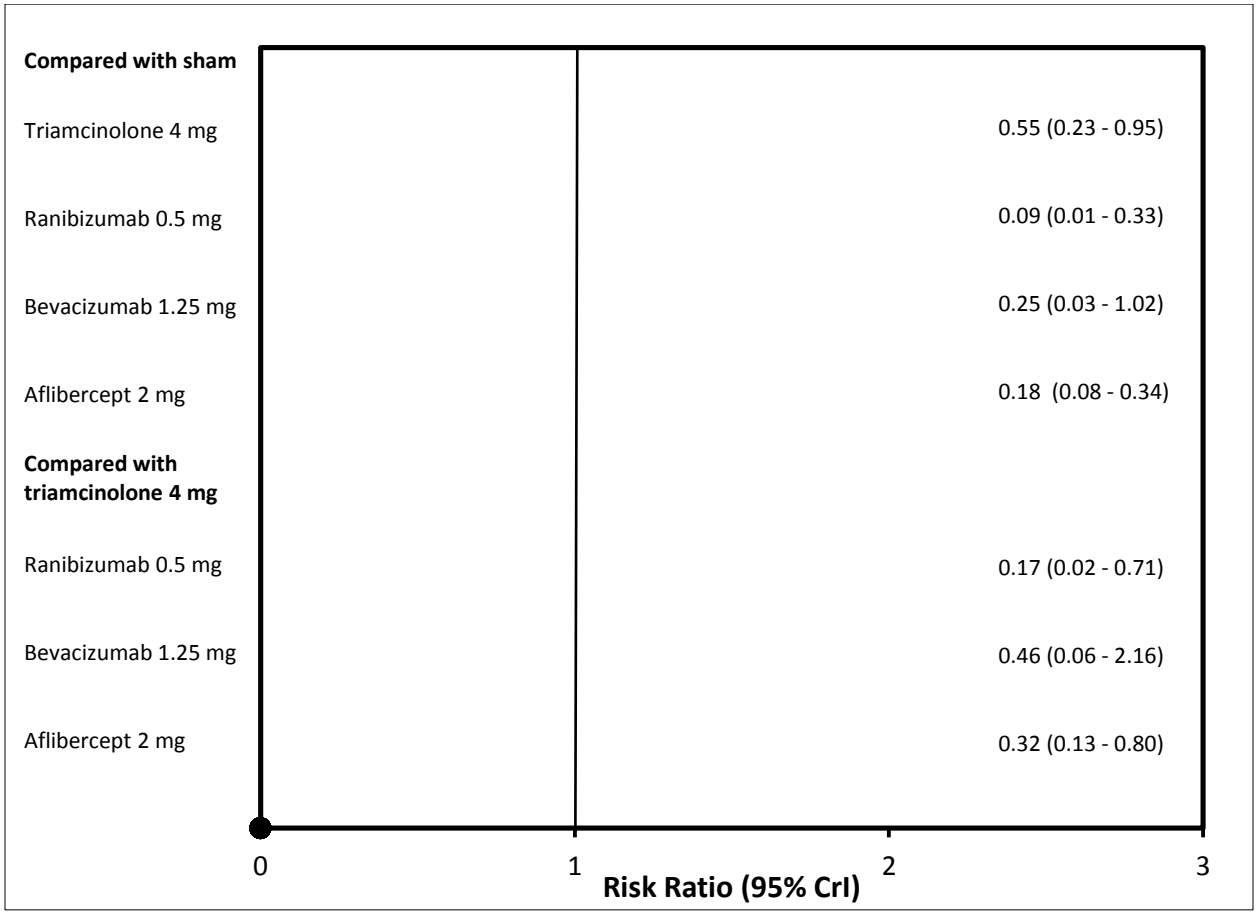
AFL = aflibercept; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; DEX = dexamethasone; NMA = network meta-analysis; RAN = ranibizumab.
Source: Ford et al. 2014[39]

FIGURE 11: PROPORTION OF PATIENTS GAINING 15 LETTERS OR MORE FROM BASELINE TO SIX MONTHS — FOREST PLOT (MODIFIED FROM FORD ET AL. 2014)



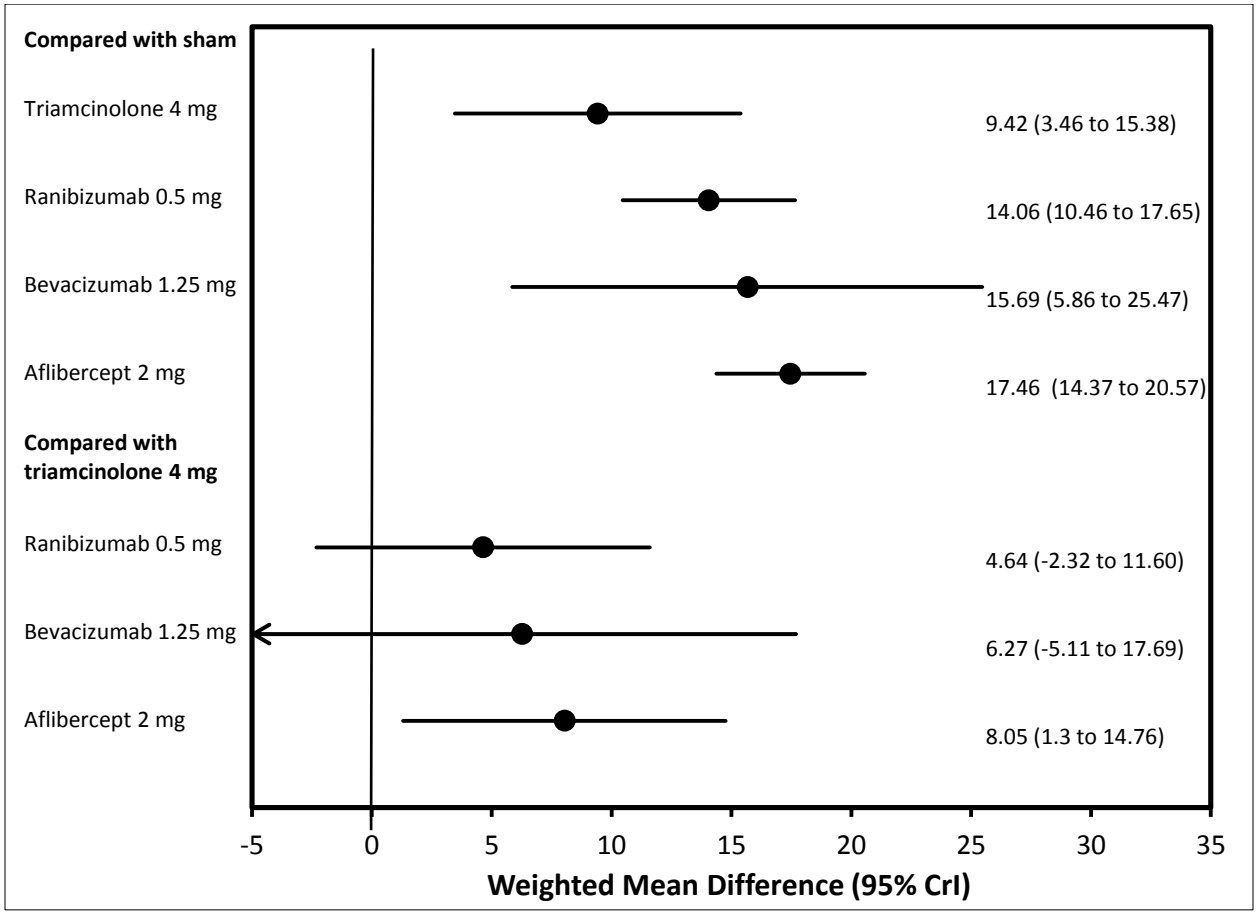
CrI = credible interval.
Source: Ford et al. 2014[39]

FIGURE 12: PROPORTION OF PATIENTS LOSING 15 LETTERS OR MORE FROM BASELINE TO SIX MONTHS — FOREST PLOT (MODIFIED FROM FORD ET AL. 2014)



CrI = credible interval.
Source: Ford et al. 2014[39]

FIGURE 13: MEAN BCVA CHANGE FROM BASELINE TO 6 MONTHS — FOREST PLOT (MODIFIED FROM FORD ET AL. 2014)



BCVA = best-corrected visual acuity; CrI = credible interval.
Source: Ford et al. 2014[39]

3. Discussion

The manufacturer's NMA had some limitations. The inclusion criteria for the NMA were not clear compared with the systematic review, even though the included studies were not the same for both. The patient baseline characteristics discussed in the indirect comparison report were not well reported. A significant proportion of non-ischemic patients were included in COPERNICUS and GALILEO, whereas CRUISE included less than 1% of those patients and GENEVA did not report this characteristic. This could have underestimated the efficacy of aflibercept versus ranibizumab. Baseline CRT was approximately 120 µm (18%) lower in the GENEVA trial compared with other studies. A lower disease severity in GENEVA could have overestimated the effect size of dexamethasone efficacy, but dexamethasone had a lower efficacy than aflibercept. The very limited number of studies available and the high heterogeneity observed for some efficacy outcomes could have increased the uncertainty (credible interval) around results, preventing us from observing a difference between aflibercept and ranibizumab. Most of the safety results were inconclusive because of their wide credible intervals due to very low numbers. No real sensitivity analyses were conducted.

The manufacturer-submitted NMA showed that aflibercept had statistically significantly better results for all three efficacy outcomes at six months compared with sham and dexamethasone, and when data allowed for comparison. For all three efficacy outcomes, aflibercept was not different from ranibizumab. [redacted]. Ranibizumab had the highest probability of being the best in regard to losing ≥ 15 letters in BCVA from baseline. [redacted] Aflibercept was not different from other comparators for other adverse events. However, the clinical expert consulted by CDR reviewers was skeptical of the conclusions of the safety outcomes, primarily because of the low number of events.

The indirect comparison retrieved from published literature was very similar to the one submitted by the manufacturer. Both included the same studies for their common comparators. As those treatments are also used in clinical practice, Ford et al. included bevacizumab (1.25 mg) and triamcinolone (4 mg) as valid comparators for their NMA. The outcomes of interest were the same for the two NMAs. The conclusions of the NMA were very similar, showing no clear difference in efficacy for all outcomes between aflibercept and other anti–vascular endothelial growth factor (anti-VEGF) drugs such as ranibizumab and bevacizumab. Both NMAs showed that aflibercept had statistically better efficacy than dexamethasone for the proportion of patients who gained ≥ 15 letters in BCVA from baseline at six months. The probabilities of being the best treatment for each outcome were also consistent between the NMAs when comparing the same interventions. It is worth noting that the study published by Ford et al. was not funded by industry and that the authors did not have any conflict of interest to declare.

4. Conclusion

In the absence of adequate head-to-head trial data for aflibercept and other active comparators, the manufacturer conducted a Bayesian NMA based on a systematic review of RCTs to compare the efficacy and safety of aflibercept with ranibizumab and dexamethasone. The NMA indicated that aflibercept did not have a significantly different efficacy compared with ranibizumab at six months in terms of the proportion of patients gaining ≥ 15 letters in BCVA from baseline and the mean change in BCVA from baseline. Aflibercept had a significantly higher efficacy than dexamethasone at six months for the proportion of patients gaining ≥ 15 letters in BCVA from baseline and change in BCVA from baseline. Although conclusions drawn from the safety results are uncertain, [redacted]. All other comparisons with aflibercept in regard to safety were inconclusive. The NMA did show some heterogeneity and only a few studies were available, but it was generally well conducted, although its inclusion criteria were not clear compared with the systematic review, and the baseline characteristics of patients were not well reported. The conclusions of the NMA provided by the manufacturer were similar to those of an independent indirect comparison retrieved from the published literature. In conclusion, after six months, the efficacy of aflibercept is not significantly different than other anti-VEGF drugs but is significantly higher than dexamethasone. However, no data are available for comparison beyond six months.

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