Common Drug Review
Clinical Review Report

August 2015

Drug	Ranibizumab (Lucentis) (10 mg/mL solution for intravitreal injection, 0.5 mg dose with monthly re-treatment as needed)
Indication	Visual impairment due to choroidal neovascularization secondary to pathologic myopia
Listing request	As per indication
Manufacturer	Novartis Pharmaceuticals Canada Inc.

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

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

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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

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ABBREVIATIONS

AE	adverse event
AMD	age-related macular degeneration
ANOVA	analysis of variance
BCVA	best corrected visual acuity
CCB	Canadian Council of the Blind
CDEC	Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CI	confidence interval
CNIB	Canadian National Institute for the Blind
CNV	choroidal neovascularization
CRT	central retinal thickness
CSR	Clinical Study Report
D	dioptre
ETDRS	Early Treatment Diabetic Retinopathy Study
EQ-5D	EuroQoL (Quality of Life)–5 Dimensions Questionnaire
FA	fluorescein angiography
FAS	full analysis set
FOCB	first observation carried back
LOCF	last observation carried forward
logMAR	logarithmic minimal angle of resolution
MCID	minimal clinically important difference
mCNV	myopic choroidal neovascularization
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire 25
OCT	optical coherence tomography
PM	pathologic myopia
PP	per-protocol
RPE	retinal pigment epithelium
SAE	serious adverse event
SD	standard deviation
TEAE	treatment-emergent adverse event
TRV	test–retest variability
VA	visual acuity
VEGF	vascular endothelial growth factor
vPDT	verteporfin photodynamic therapy
w/ran	with ranibizumab
WDAE	withdrawal due to adverse event
wo/ran	without ranibizumab
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

EXECUTIVE SUMMARY

Introduction

Pathologic myopia (PM) is caused by the progressive and excessive elongation of the axial length of the eyeball. Myopic choroidal neovascularization (CNV) is a complication of PM and is a serious threat to vision.[1] CNV is observed as an abnormal growth of blood vessels located between the neurosensory retina and the retinal pigment epithelium.[2] Symptoms include a decrease in vision, central scotoma, and/or metamorphopsia.[3] PM has a prevalence of 0.084% among adult Canadians,[4] and myopic CNV is a leading cause of visual disability among young adults.[3]

Verteporfin (Visudyne) photodynamic therapy (vPDT) is the standard of care for myopic CNV in Canada. vPDT retards vision loss in patients with subfoveal CNV and stabilizes, rather than improves, visual acuity (VA).[5] The anti-vascular endothelial growth factor (VEGF) therapies, ranibizumab (Lucentis) and bevacizumab (Avastin), have been used off-label as monotherapies for myopic CNV in Canada. Ranibizumab is approved in Canada for the treatment of neovascular (wet) age-related macular degeneration, the treatment of visual impairment due to macular edema secondary to retinal vein occlusion, and the treatment of visual impairment due to diabetic macular edema. Ranibizumab was recently approved by Health Canada for treating visual impairment due to CNV secondary to PM. Ranibizumab is supplied as a 10 mg/mL solution in single-use vials for intravitreal injection. The recommended dose is a single initial 0.5 mg injection followed by monthly injections, administered as needed based on signs of disease activity.

The objective of this review was to perform a systematic review of the beneficial and harmful effects of ranibizumab intravitreal injection for the treatment of visual impairment due to CNV secondary to PM in adults.

Results and interpretation

Included studies

A single study met the inclusion criteria for this review. The RADIANCE study (N = 277) was a 12-month, phase 3, multi-centre, randomized, double-masked, active-controlled study. Patients were adults with visual impairment due to CNV secondary to PM. Ranibizumab was administered to two treatment groups based on either stabilization of VA (Group I) or assessment of disease activity (Group II), while a third treatment group received vPDT (Group III).

Groups I and II both received an initial intravitreal injection of ranibizumab on day 1. Group I received a second injection one month later, after which there was no further ranibizumab treatment if VA remained stable (defined as no change in VA compared with two preceding monthly visits). If VA did not remain stable, patients were re-treated with monthly injections if there was a decrease in VA. Patients in Group II did not receive ranibizumab following the initial injection if no disease activity was observed (defined as vision impairment attributable to intra- or subretinal fluid or active leakage secondary to PM, as assessed by optical coherence tomography and/or fluorescein angiography), but were re-treated if disease activity was observed.

The study was designed with an initial three-month head-to-head phase to determine whether ranibizumab treatment was superior to vPDT. The primary outcome was the change in best corrected visual acuity (BCVA, defined as the best vision achieved with correction such as eyeglasses or contact lenses).

A secondary objective of the study was to determine whether the two ranibizumab treatment regimens were non-inferior to each other after six months. Other outcomes included changes in anatomical parameters such as changes in central retinal thickness (CRT), subretinal fluid, intraretinal edema, and CNV leakage. In addition, visual function was assessed using the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25), while quality of life and work productivity were measured using the EuroQoL Questionnaire – 5-Dimensions (EQ-5D) and the Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH), respectively.

Efficacy

The average improvement in BCVA compared with baseline was 11 letters in ranibizumab-treated patients versus two letters in vPDT-treated patients. After three months, ranibizumab treatment was associated with a statistically significant improvement in vision in BCVA compared with vPDT treatment. Specifically, the difference in the improvement in BCVA for Group I and Group II versus the vPDT group (Group III) was 8.5 letters (95% confidence interval [CI], [redacted]; $P < 0.00001$) and 8.6 letters (95% CI, [redacted]; $P < 0.00001$), respectively. In addition, between 62% and 66% of ranibizumab-treated patients achieved a gain in BCVA of at least 10 letters (or reached a BCVA of 84 letters), whereas 27% of vPDT-treated patients achieved the same threshold.

CADTH Common Drug Review (CDR) reviewers determined that the minimal clinically important difference (MCID) for the change in BCVA is likely between 10 letters and 15 letters, although some estimates suggest that the threshold might be lower. As the improvement in BCVA in ranibizumab-treated patients of approximately nine letters versus vPDT-treated patients was slightly lower than the MCID of 10 letters, there is some uncertainty as to the clinical meaningfulness of the improvement due to ranibizumab treatment versus vPDT. However, the increase in BCVA from baseline in ranibizumab-treated patients (an 11-letter improvement) did exceed the MCID, whereas vPDT-treated patients achieved only a two-letter improvement. Furthermore, the magnitude of treatment effect might have been greater (i.e., might have exceeded the MCID) had more severely visually impaired patients been included in the RADIANCE study, given that the definition of myopic CNV used to select patients was less stringent than guidance provided in the literature, and more severely affected patients tend to have a greater improvement in BCVA.

After six months, the difference between the two ranibizumab treatment groups was 0.1 letters (95% CI, −2.2 to 2.0), which was below the non-inferiority margin of five letters. This suggested that both ranibizumab treatment regimens were similarly efficacious. Over the 12-month study, the mean number of ranibizumab injections in Group I (4.6 injections/patient), which was re-treated based on stabilization of VA, was higher than that in Group II (3.5 injections/patient), which was re-treated based on disease activity. Since the regimen administered to Group II was non-inferior to Group I in terms of efficacy, the product monograph recommends use of the treatment regimen based on disease activity, which might reduce the occurrence of unnecessary injections.

CRT decreased by 61 µm to 78 µm in ranibizumab-treated patients compared with a decrease of 12 µm in vPDT-treated patients. Therefore, ranibizumab appeared to be more effective in reducing CRT, which is positively correlated with CNV progression. Similarly, changes in other anatomical parameters, subretinal fluid, intraretinal edema, and CNV leakage were numerically in favour of ranibizumab treatment compared with vPDT.

Visual function assessed using the NEI-VFQ-25 suggested that the improvement from baseline due to ranibizumab treatment (a 4- to 5-point improvement) exceeded the 4-point MCID, whereas no meaningful improvement was observed in the vPDT-treated group (0.3-point improvement). Changes in the EQ-5D and WPAI:GH scores were highly variable and inconsistent among treatment groups, and therefore no conclusions could be made regarding the relative efficacy of ranibizumab versus vPDT for these outcomes.

Harms

There were no withdrawals due to adverse events, and no deaths occurred during the study. Nevertheless, all patients who discontinued the study (4%) were treated with ranibizumab. The incidences of treatment-emergent adverse events were higher among patients who received ranibizumab, and the proportion of patients who experienced ocular adverse events (AEs) ranged from 37% to 43% in all patients who received ranibizumab. By contrast, patients treated with vPDT (and who did not receive ranibizumab after month 3) had a 27% incidence of ocular AEs. The most common ocular AEs were conjunctival hemorrhage (overall occurrence, 9%), punctate keratitis (5%), and increased intraocular pressure (5%), none of which occurred in vPDT-treated patients.

Non-ocular AE incidences were also higher among patients who received ranibizumab (43% to 50% across treatment groups who received ranibizumab at some point) compared with patients who did not receive ranibizumab (33%). The most common non-ocular AEs were nasopharyngitis (overall occurrence, 10%) and headache (7%). Patients who did not receive ranibizumab did not experience headache.

Serious adverse events (SAEs) occurred in 5% of ranibizumab-treated patients, whereas there were no SAEs in vPDT-treated patients. Most SAEs (85%) were non-ocular. Among notable ocular harms in the ranibizumab treatment groups, retinal tear (1% to 2%) and uveitis (1%) were reported. These AEs might be due to the injection itself and/or ranibizumab. In vPDT-treated patients, blindness (3% in vPDT-treated patients who also received ranibizumab; 7% in patients treated only with vPDT) and visual impairment (5% in patients treated only with vPDT) were reported, which may reflect damage to choroidal blood vessels and/or a lack of efficacy of vPDT.

The apparently higher incidence of harms that occurred in ranibizumab-treated patients in the RADIANCE study might be attributable to the study drug itself, but is likely also related to the procedure of injecting drug into the eye, because vPDT-treated patients did not receive a true sham intraocular injection. Overall, the harms observed in the study reflect those noted in the product monograph and reported elsewhere.

Other considerations

Patient groups expect that treatment with ranibizumab will allow patients to regain VA and expressed a willingness to tolerate adverse effects associated with ranibizumab treatment if it meant they would improve their vision.

Among treatment alternatives for CNV, the VEGF antibody bevacizumab is used for the treatment of myopic CNV in patients in jurisdictions in which ranibizumab is not reimbursed and in patients who are ineligible for coverage. However, bevacizumab is not approved in Canada for the treatment of visual impairment due to CNV secondary to PM, and consequently could not be considered to be a valid comparator for the purpose of this review.

Conclusions

The results of a single double-blind, multi-centre, randomized, active-controlled trial (RADIANCE) suggest that three months of ranibizumab treatment significantly improves VA compared with vPDT in adults with visual impairment due to CNV secondary to PM. Ranibizumab treatment was associated with a statistically significant improvement in vision in BCVA of nine Early Treatment Diabetic Retinopathy Study (EDTRS) letters compared with vPDT treatment. A greater proportion of patients treated with ranibizumab (62% to 66%) achieved an improvement in BCVA of at least 10 letters (or reached a BCVA of 84 letters) compared with vPDT-treated patients (27%). Changes in anatomical outcomes such as CRT, subretinal fluid, intraretinal edema, and CNV leakage favoured ranibizumab treatment over vPDT. The efficacy of ranibizumab treatment after six months at a treatment frequency based on stabilization of VA was similar to ranibizumab treatment at a frequency based on disease activity. All patients who discontinued the study (3.6%) were ranibizumab-treated patients, and ocular and non-ocular AEs and SAEs were more frequent in ranibizumab-treated patients compared with vPDT-treated patients. These differences in tolerability likely reflect differences in the mode of administration of the study drugs.

TABLE 1: SUMMARY OF RESULTS

Outcome	Radiance		
	Group I: Ranibizumab (Stabilization of VA[a])	Group II: Ranibizumab (Disease Activity[b])	Group III: vPDT
Month 1 through Month 3			
Baseline VA, mean (SD)	55.4 (13.43)	55.8 (12.59)	54.7 (13.84)
Average VA, mean (SD)	66.0 (12.98)	66.4 (12.28)	56.9 (14.49)
Average change in VA from baseline through Month 3, mean (SD)	10.5 (8.16)	10.6 (7.26)	2.2 (9.47)
Difference vs. vPDT, LSM (95% CI)	8.5 ([redacted])	8.6 ([redacted])	-
P value vs. vPDT	< 0.00001	< 0.00001	-
Month 1 through Month 6			
Baseline VA, mean (SD)	55.4 (13.43)	55.8 (12.59)	54.7 (13.84)
Average VA, mean (SD)	67.3 (12.40)	67.5 (12.34)	59.0 (14.24)
Average change in VA from baseline, mean (SD)	11.9 (8.81)	11.7 (8.24)	4.2 (9.26)
Difference vs. Group I, LSM (95% CI)	-	–0.1 (–2.2, 2.0)	NR
P value vs. Group I	-	< 0.00001	NR
Withdrawals, n/N (%)			
Prior to Month 3	1/106 (0.9)	0	0
Up to Month 12	6/106 (5.7)	4/116 (3.4)	0
SAEs, n/N (%)			
Ocular	1/106 (0.9)	1/118 (0.8)	0
Non-ocular	6/106 (5.7)	5/118 (4.2)	0
WDAEs			
Total	0	0	0
Notable harm(s), n/N (%)			
Blindness	0	0	2/53 (3.8)
Retinal tear	2/106 (1.9)	1/118 (0.8)	0
Uveitis	1/106 (0.9)	1/118 (0.8)	0
Visual impairment	0	0	2/53 (3.8)
Gastrointestinal hemorrhage	1/106 (0.9)	1/118 (0.8)	0

CI = confidence interval; LSM = least squares mean; n = number of patients with event; N = number of patients; SAEs = serious adverse events; SD = standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy; vs. = versus; WDAEs = withdrawal due to adverse events.

[a] This group received a 0.5 mg intravitreal injection of ranibizumab on day 1 and another injection one month after. Dosing was stopped if VA was stable. Treatment was resumed with monthly injections if there was a loss of VA. This treatment was continued until stable VA was reached again for three consecutive monthly assessments.

[b] This group received a 0.5 mg intravitreal injection of ranibizumab on day 1. Dosing was stopped if no disease activity was seen. Treatment was resumed if disease activity was observed. This treatment was continued until no disease activity was seen.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Pathologic myopia (PM) is caused by the progressive and excessive elongation of the axial length of the eyeball. There are some variations in how PM is defined clinically,[5] but PM is usually described as an axial length ≥ 26 mm with a visual correction > –6.0 dioptres (D).[6] PM causes a variety of ocular pathologies, among which myopic choroidal neovascularization (CNV) has the most serious effect on vision.[1] CNV is observed as an abnormal growth of blood vessels located between the neurosensory retina and the retinal pigment epithelium (RPE).[2] Symptoms of myopic CNV include a decrease in vision, central scotoma, and/or metamorphopsia.[3]

PM has a prevalence of 1% to 3% among individuals in the general population, with a higher prevalence in East Asians.[7] CNV secondary to PM occurs in 5% to 10% of such patients.[3] A Canadian study conducted in 70 family practice clinics in southwestern Ontario reported a prevalence of myopic CNV of 0.084% among adult patients.[4] Bilateral myopic CNV was observed in 10% of those patients.[4]

Myopic CNV is considered one of the leading causes of CNV[8] and visual disability[3] among young adults. Unlike CNV that occurs in age-related macular degeneration (AMD), more than 50% of patients affected by myopic CNV have a presenting age of 50 years or younger.[2]

1.2 Standards of Therapy

Verteporfin photodynamic therapy (vPDT) is the standard of care for myopic CNV in Canada. Verteporfin (Visudyne) is injected intravenously and is activated within the eye by exposure to a non-thermal diode laser. vPDT reduces pathological CNV by selectively damaging choriocapillary endothelium while sparing the neurosensory retina, the RPE, and the optic nerve.[2] vPDT attenuates vision loss in patients with subfoveal CNV and stabilizes, rather than improves, visual acuity (VA).[5]

Surgical excision and laser photocoagulation are additional therapeutic options, but according to a clinical expert consulted by CADTH Common Drug Review (CDR) reviewers, these therapies have been replaced in current practice by vPDT, which is safer and more effective.

The anti-vascular endothelial growth factor (VEGF) therapies, ranibizumab (Lucentis) and bevacizumab (Avastin), have been used off-label as monotherapies for myopic CNV in Canada. Due to its lower cost, bevacizumab has been used in clinical practice in Canada for treatment of myopic CNV in patients in jurisdictions in which ranibizumab is not reimbursed and in patients who are ineligible for coverage with ranibizumab (i.e., < 65 years of age).

1.3 Drug

Ranibizumab is a recombinant humanized monoclonal antibody fragment that binds human vascular endothelial growth factor A (VEGF-A) to prevent it binding its receptors, thereby suppressing neovascularization. The mechanism of action of ranibizumab is similar to other VEGF-targeting therapies.

Ranibizumab is supplied as a 10 mg/mL solution in single-use vials for intravitreal injection. The recommended dose is a single initial 0.5 mg injection followed by monthly injections, administered as needed based on signs of disease activity.

Health Canada recently approved ranibizumab for the treatment of visual impairment due to CNV secondary to PM. In addition, ranibizumab is approved in Canada for three other indications: treatment of neovascular (wet) AMD; treatment of visual impairment due to macular edema secondary to retinal vein occlusion (RVO); and treatment of visual impairment due to diabetic macular edema (DME). Previously, the Canadian Drug Expert Advisory Committee (CEDAC)/Canadian Drug Expert Committee (CDEC) made positive listing recommendations for ranibizumab in each of these indications, and most public health plans list ranibizumab for various indications.

Indication under review
Treatment of visual impairment due to choroidal neovascularization secondary to pathologic myopia
Listing criteria requested by sponsor
As per indication

TABLE 2: KEY CHARACTERISTICS OF RANIBIZUMAB AND VERTEPORFIN

	Ranibizumab	Verteporfin
Mechanism of Action	Humanized recombinant monoclonal antibody fragment targeted against human VEGF-A. Binds with high affinity to all active VEGF-A isoforms, preventing the neovascularization and vascular leakage that contribute to the progression of AMD, macular edema causing visual impairment.	Circulating verteporfin appears to preferentially accumulate in neovasculature, including choroidal neovasculature. Light activation of verteporfin results in local damage to neovascular endothelium, resulting in vessel occlusion.
Indication[a]	Treatment of visual impairment due to CNV secondary to PM.	Treatment of predominantly classic subfoveal CNV in patients with PM.
Route of Administration	Intravitreal injection.	Intravenous infusion and activation with light from a non-thermal diode laser.
Recommended Dose	Dose of 0.5 mg with monthly re-treatment as needed.	Infusion: 6 mg/m^2 BSA, diluted in 30 mL solution, given by a 10-minute IV infusion. Photoactivation: dose of 50 J/cm^2 with a 689 nm laser at an intensity of 600 mW/cm^2 over 83 seconds.
Serious Side Effects and Safety Issues	SAEs: endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract, intraocular inflammation, and increased IOP. Contraindications: patients who are hypersensitive to this drug, active or suspected ocular or periocular infections, and patients with active intraocular inflammation.	SAEs: hypersensitivity to light, severe vision decrease, severe vasovagal reaction. Contraindications: patients who are hypersensitive to this drug, porphyria, and severe hepatic impairment.

AMD = age-related macular degeneration; BSA = body surface area; CNV = choroidal neovascularization; IOP = intraocular pressure; IV = intravenous; J = joule; mW = milliwatt; nm = nanometre; PM = pathologic myopia; SAEs = serious adverse events; VEGF-A = vascular endothelial growth factor A.

[a] Health Canada indication.

Source: Product monographs.[9,10]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of ranibizumab intravitreal injection for the treatment of visual impairment due to CNV secondary to PM in adult patients.

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal study supporting the Health Canada indication (provided by the manufacturer) and those meeting the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with visual impairment due to choroidal neovascularization secondary to pathologic myopia. Subgroup: CNV location (subfoveal vs. non-subfoveal).
Intervention	Ranibizumab (10 mg/mL for intravitreal injection), 0.5 mg initial dose with monthly re-treatments as needed.
Comparators	vPDT.[a]

Outcomes	***Efficacy outcomes:***
	• Change from baseline in visual acuity[b]
	• Change in CRT
	• Quality of life and vision function
	• Legal blindness.
	Harms outcomes:
	• AEs
	• SAEs
	• WDAEs
	• Mortality
	• Notable AEs:
	  ○ Non-ocular: arterial thromboembolic events (including nonfatal stroke, nonfatal myocardial infarction, vascular death), gastrointestinal perforation.
	  ○ Ocular: unilateral blindness, endophthalmitis, retinal detachments, retinal tear, uveitis, visual impairment.

Study Design	Published and unpublished RCTs.

AEs = adverse events; CNV = choroidal neovascularization; CRT = central retinal thickness; RCTs = randomized controlled trials; SAEs = serious adverse events; vPDT = verteporfin photodynamic therapy; vs. = versus; WDAEs = withdrawals due to adverse events.

[a] Standard pharmacotherapy available in Canada. Bevacizumab has been used off-label in Canada.

[b] Visual acuity change from baseline comprised absolute change and proportion of patients with improvement or worsening of visual acuity from baseline.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were ranibizumab (Lucentis) and myopic choroidal neovascularization or pathological myopia.

No methodological, publication year or language filters were applied to limit retrieval. Conference abstracts were excluded from the search results.

The initial search was completed on August 29, 2014. Regular alerts were established to update the search until the meeting of CDEC on January 21, 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 (http://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
- Databases (free)
- Internet Search.

Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

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

3. RESULTS

3.1 Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 4 and described in Section 3.2.

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

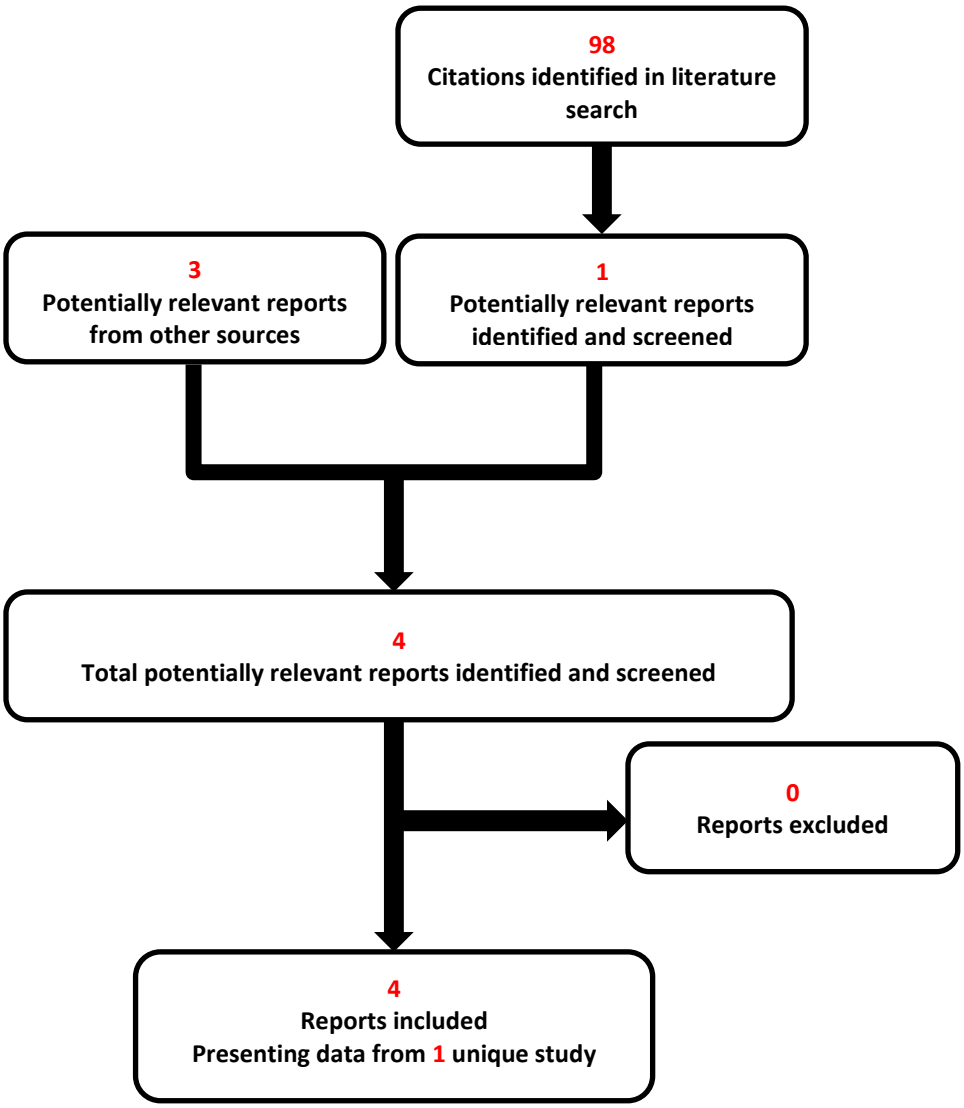

TABLE 4: DETAILS OF INCLUDED STUDIES

			Radiance
DESIGNS & POPULATIONS	**Study Design**		Double-masked, multi-centre, active-controlled RCT.
	Locations		76 centres in 20 countries throughout Asia, Europe, and Canada.
	Randomized (N)		277
	Inclusion Criteria		• Male or female patients, ≥ 18 years of age. • Active CNV secondary to PM with greater than –6 D of spherical equivalence and axial length ≥ 26 mm. • Presence of posterior changes compatibles with PM (any signs of attenuation of RPE and choroids, mottling of the RPE, titled disc, geographic atrophy of RPE, Fuchs spot, posterior staphyloma, submacular hemorrhage, lacquer cracks) seen by fundus ophthalmoscopy and fundus photography. • Presence of active leakage from CNV seen by FA. • Presence of intra- or subretinal fluid or increase of CRT seen by OCT. • At least one of the following lesion types in the study eye: subfoveal, juxtafoveal, extrafoveal, margin of the optic disc. • BCVA ≥ 24 letters and ≤ 78 letters tested at 4 m starting distance using ETDRS-like VA chart (approximate 20/32 to 20/320 to Snellen Chart). • Visual loss due to the presence of any eligible types of CNV related to PM based on clinical ocular findings, FA, and OCT.
	Exclusion Criteria		• History of hypersensitivity to the study drugs, drugs of similar chemical classes, fluorescein or any other component of fluorescein formulation. • History of malignancy other than localized basal or squamous cell carcinoma of the skin in the past 5 years. • History of stroke. • Any type of disease or its treatment that could interfere with outcome evaluations. • Ocular disorders in the study eye that could confound interpretation of results, compromised VA, or required medical intervention during the study. • History of pan-retinal or focal or grid laser photocoagulation with involvement of the macular area in the study eye. • History of intraocular treatment with any anti-VEGF or vPDT in the study eye. • History of intraocular surgery or treatment with corticosteroids within 3 months prior to the randomization in the study eye.
DRUGS	**Intervention**		0.5 mg Ranibizumab (10 mg/mL for intravitreal injection), 0.5 mg dose with monthly re-treatment as needed.
	Comparator(s)		Verteporfin IV infusion (6 mg/m^2 BSA, diluted in 30 mL solution given in a 10-minute infusion). Photoactivation: dose of 50 J/cm^2 with a 689 nm laser at an intensity of 600 mW/cm^2 over 83 seconds, 15 minutes after start of the infusion.
DURATION	**Phase**		
	Screening		2 weeks
	Double-blind	Period 1	3 months
		Period 2	9 months
	Follow-up		None

		Radiance
OUTCOMES	**Primary End Point**	BCVA
	Other End Points	CRT Presence of active leakage Number of re-treatments Quality of life AEs
NOTES	**Publications**	Wolf, 2014

AEs = adverse events; BCVA = best corrected visual acuity; BSA = body surface area; CNV = choroidal neovascularization; CRT = central retinal thickness; D = dioptre; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; IV = intravenous; J = joule; mW = milliwatt; nm = nanometre; OCT = optical coherence tomography; PM = pathologic myopia; RCT = randomized controlled trial; RPE = retinal pigment epithelium; VA = visual acuity; VEGF = vascular endothelial growth factor; vPDT = verteporfin photodynamic therapy.
Note: Three additional reports were included: the manufacturer's submission[11] and Clinical Study Report,[12] the Health Canada report.[13]
Source: Clinical Study Report.[12]

3.2 Included Study

3.2.1 Description of study

A single study was included. The RADIANCE study was a phase 3, multi-centre, randomized, double-masked, active-controlled study that compared two different frequency treatment regimens of ranibizumab (i.e., two treatment groups, namely Group I and Group II) with vPDT (Group III). The primary objective of the study was to assess whether ranibizumab was superior to vPDT for improving best corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters after three months in patients with myopic CNV. The key secondary objective was to compare the two ranibizumab treatment regimens (Group I: re-treatment based on stabilization of VA versus Group II: re-treatment based on disease activity) for non-inferiority based on BCVA after six months. The study design of this 12-month trial is summarized in Table 5.

TABLE 5: RADIANCE STUDY DESIGN

Radiance				
Period	**Time**	**Group I: Ranibizumab (Stabilization of VA) N = 106**	**Group II: Ranibizumab (Disease Activity) N = 116**	**Group III: vPDT N = 55**
1	Day 1 to Month 3	Two monthly injections and then re-treated, as needed, following a decrease of VA	One injection and then re-treated, as needed, following signs of disease activity	A single vPDT treatment
2	Month 4 to Month 12	Same as period 1	Same as period 1	Based on disease activity, subjects could receive either ranibizumab, vPDT, or both

N = number of patients; VA = visual acuity; vPDT = verteporfin photodynamic therapy.

The RADIANCE study enrolled 277 patients randomized to three groups at a ratio of 2:2:1. Patients were given a treatment on day 1 and were monitored on a monthly basis (4 weeks ± 7 days).

Patients were given a treatment on day 1. Ranibizumab treatment groups (Groups I and II) received 0.5 mg intravitreal injections of ranibizumab and sham vPDT treatment. Group III (vPDT) received a vPDT treatment and a sham injection. Group I received a second mandatory 0.5 mg intravitreal injection of ranibizumab one month later. Ranibizumab-treated patients could be re-treated with ranibizumab following stabilization of VA (Group I) or disease activity (Group II). vPDT-treated patients were not re-treated through month 3, after which they could receive ranibizumab, vPDT, or a combination of both.

[redacted].

3.2.2 Populations

a) Inclusion and exclusion criteria

In the RADIANCE study, adult patients with visual impairment due to CNV secondary to PM were included. Patients had to show: high myopia (greater than –6 dioptre (D) of spherical equivalence); axial length of the eye ≥ 26 mm; presence of posterior changes in line with PM; presence of active leakage from CNV; presence of intra- or subretinal fluid or increase in central retinal thickness (CRT); at least one lesion in the central macular area; a BCVA ≥ 24 letters and ≤ 78 letters using the ETDRS chart; and a visual loss due only to the presence of any eligible types of CNV due to PM. Subjects with the following features were excluded: high blood pressure; use of anticoagulant medications; hypersensitivity to any of the study drugs; history of malignancy in the past five years; history of stroke; advanced, severe, or unstable disease; intraocular infection or inflammation; high intraocular pressure; history of anti-VEGF, vPDT, or laser photocoagulation; or history of corticosteroid or intraocular surgery in the last three months. If both eyes were eligible, the eye with worse VA was selected as the study eye. In some cases, the investigator could select the eye with better VA based on medical reasons and according to local ethical requirements.

b) Baseline characteristics

As shown in Table 6, the demographic and baseline characteristics of participants in the RADIANCE study were uniformly distributed among each group. The mean age of randomized participants across treatment groups was from 54.0 to 57.4 years old (range [redacted]). Caucasians represented 56.6% to 60.3% of group subjects, while Asians represented 39.7% to 42.5% of these groups. Baseline VAs were similar among all groups with means ranging from 54.7 letters to 55.8 letters among the three groups. Some differences among treatment groups could be observed (e.g., higher or lower proportion of patients [more than 10% difference] in a specific subgroup) when axial length and refraction sphere of the eye were stratified (see Table 12). The characteristics of the study eye assessed by optical coherence tomography (OCT), fluorescein angiography (FA) and colour fundus photography are also summarized in Table 6. No difference in regard to CRT (means from 350.2 µm to 373.1 µm) or CNV location (67.0% to 69.9% subfoveal) was observed among groups. A more complete summary of the demographic and ocular characteristics is given in Table 11, Table 12, and Table 13 in Appendix 3. A total of [redacted] patients ([redacted]%) were taking concomitant ocular medications before the study (Table 14).

TABLE 6: SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

	Radiance			
	Group I: Ranibizumab (Stabilization of VA) (N = 106)	Group II: Ranibizumab (Disease Activity) (N = 116)	Group III: vPDT (N = 55)	Total (N = 277)
Age (years)				
Mean (SD)	54.0 (14.00)	56.1 (14.35)	57.4 (12.82)	55.5 (13.94)
[redacted]				
Predominant race, n (%)				
Caucasian	60 (56.6)	70 (60.3)	32 (58.2)	162 (58.5)
Asian	45 (42.5)	46 (39.7)	23 (41.8)	114 (41.2)
Other	1 (0.9)	0	0	1 (0.4)
VA (letters)				
Mean (SD)	55.4 (13.38)	55.8 (12.59)	54.7 (13.84)	55.4 (13.11)
[redacted]				
VA subgroup (letters), n (%)				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Central retinal thickness (µm)				
[redacted]				
Mean (SD)	350.2 (95.12)	373.1 (127.44)	355.1 (102.35)	360.6 (110.98)
[redacted]				
CNV location, n (%)				
Subfoveal	71 (67.0)	81 (69.8)	38 (69.1)	190 (68.6)
Non-subfoveal	33 (31.1)	27 (23.3)	17 (30.9)	77 (27.8)
[redacted]				

CNV = choroidal neovascularization; D = dioptre; n = number of patients with event; N = number of patients; OCT = optical coherence tomography; SD = standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy; µm = micrometre.
Note: Percentages are based on the total number of patients in the randomized set. Refraction sphere values were collected as negative D but are presented as positive values to facilitate interpretation. Central retinal thickness and central foveal thickness represent all data irrespective of types of OCT machines.
Source: Clinical Study Report: Table 11-3, p. 127; Table 11-4, p. 129; Table 11-5, p. 130.

3.2.3 Interventions

Treatment was assigned with the lowest available randomization number given on day 1 visit. This number assigned the patient to one of the study groups. Only one eye (the study eye) was selected for treatment.

a) Group I (N = 106 patients): ranibizumab treatment based on VA stabilization

Patients received a 0.5 mg intravitreal injection of ranibizumab on day 1 and a second injection one month later (at month 1). The first timepoint to assess stabilization criteria was month 2. No further

treatment was administered if VA was stable. VA stabilization was defined as no change in BCVA as compared to two preceding monthly visits. Treatment was resumed at a frequency of one injection per month if there was a decrease in VA. This treatment was continued until VA had stabilized for three consecutive monthly assessments.

b) Group II (N = 116 subjects): ranibizumab treatment based on disease activity

Patients received a 0.5 mg intravitreal injection of ranibizumab at day 1. If no disease activity was observed, there was no further treatment. Disease activity was defined as vision impairment attributable to intra- or subretinal fluid or active leakage secondary to PM as assessed by OCT or fluorescein angiography. Treatment was resumed at a frequency of one injection per month if disease activity was observed. This treatment was continued until no disease activity was seen.

The main difference between these two treatment regimens is that for one dose regimen (Group I), an additional injection was provided mandatorily for each patient at month 1, regardless of their VA status.

c) Group III (N = 55 subjects): vPDT treatment

Patients received vPDT treatment at day 1 and were not re-treated through month 3. From month 4 to month 11, the treating investigator had the following options to treat disease activity: a 0.5 mg intravitreal injection of ranibizumab; vPDT treatment; or a combination of both. Criteria for choosing one of these options were not clearly stated in the Clinical Study Report (CSR). Treatment with vPDT was performed as per label (see Table 2). No further treatment was administered if there was no disease progression. Treatment was resumed if disease activity was observed and continued until there was no disease progression.

Even if the two study medications had very different appearances and routes of administration, treatment masking was attempted to be maintained in all groups during the entire 12-month duration. In an attempt to preserve masking, sham intravitreal injections (mimics of injections with a needle-free syringe) and sham vPDT treatments (laser treatments with sham [vehicle] injections) were given throughout the trial following a detailed laminated study plan. The masking of the investigator was preserved by using an assessing investigator (masked to the treatment assignment) and a treating investigator (unmasked to the treatment assignment).

Medications given for ocular procedures used during the trial, such as fluorescein, dilating drops, topical antibiotics, and topical anesthetics were allowed. Treatments for PM or other diseases in the fellow eye were permitted at any time. The concomitant drug most often used during the trial is [redacted] (Table 14), likely used for dry eye treatment according to the clinical expert consulted by CDR reviewers. It has been used [redacted].

3.2.4 Outcomes

Efficacy outcomes were based on VA and anatomical parameters. The BCVA was tested using the ETDRS VA testing protocol at a distance of 4 m. BCVA was assessed at every visit. The OCT was assessed at every visit except at follow-up visit after treatment (day 8). FA was performed after colour fundus photography to assess the choroids and retinal vasculature as needed during the trial and at the end of the study. Quality of life was measured with the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25) and the EuroQoL (Quality of Life) Questionnaire-5 Dimensions (EQ-5D) instruments. Functionality was measured with the Work Productivity and Activity Impairment Questionnaire: General

Health (WPAI:GH) instrument. Safety was monitored through the collection of ocular and non-ocular adverse events (AEs) and concomitant medications.

a) Primary and key secondary outcomes

The primary and key secondary outcomes were based on BCVA measures. The primary outcome was the difference from baseline of the average level of BCVA over all monthly post-baseline assessments from month 1 to month 3. The key secondary outcome was the difference from baseline of the average level of BCVA over all monthly post-baseline assessments from month 1 to month 6.

The BCVA assessed with the ETDRS chart is a validated outcome (see Appendix 4). ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between letters and rows. There are a total of 14 lines (i.e., 70 letters). Reading more lines (i.e., more letters) indicates better VA.[14] The FDA recommends a mean change of 15 letters or more on an ETDRS chart, or a statistically significant difference in the proportion of patients with a 15 or greater letter change in VA, as clinically relevant outcome measures in trials of interventions for macular edema.[15] However, this threshold has been questioned in the literature. The generally accepted minimal clinically important difference (MCID) is between 10 letters and 15 letters.[16,17]

b) Other secondary outcomes

Best corrected visual acuity

Some other secondary outcomes were also based on BCVA. The difference between the average level of BCVA over all monthly post-baseline assessments from month 1 to month 12 and the baseline level of BCVA; the time-course of BCVA changes from baseline; and the proportion of patients with ≥ 10 letters and ≥ 15 letters gain or reaching 84 letters for each month between treatment groups were all based on VA. According to the clinical expert consulted by CDR reviewers, the 84-letter threshold is used by clinicians as the aimed BCVA, which is just below a perfect VA.

Anatomical outcomes

These outcomes include changes from baseline in CRT, and proportion of patients with presence of active leakage over time up to month 12. Numbers of patients with subretinal fluid, intraretinal edema, and intraretinal cysts were also reported.

Number of treatments

Also reported was the proportion of patients treated with ranibizumab by visit and number of ranibizumab re-treatments from baseline in Groups I and II.

Safety

Safety and tolerability of each of the two regimens with ranibizumab versus vPDT, and between the two regimens of ranibizumab were assessed. Mortality, ocular, and non-ocular serious adverse events (SAEs), overall AEs, and potential AEs with special clinical interest (i.e., notable AEs) were reported.

c) Exploratory objectives

Quality of life, visual functionality, and general functionality

The impact of treatment on patient functioning and quality of life was assessed by the NEI-VFQ-25 and EQ-5D. The amounts of absenteeism, presenteeism, and daily activity impairment attributable to the ocular health status were captured through the WPAI:GH.

The NEI-VFQ-25 includes 25 items relevant to 11 vision-related constructs, in addition to a single-item general health component.[18,19] A 4-point improvement from baseline was considered to be the MCID.[20] EQ-5D is a generic quality-of-life instrument that has been applied to a wide range of health conditions.[21,22] Reported MCIDs for this scale have ranged from 0.033 to 0.074.[23] The WPAI:GH instrument is a self-administered questionnaire that captures lost time from work and productivity challenges due to health problems.[24] No MCIDs have been reported for this instrument. The changes in NEI-VFQ-25 score (composite score), EQ-5D (thermometer) score, and total WPAI:GH score from baseline to month 3 were measured.

d) Comparison with protocol

The primary outcome, the key secondary outcome and other secondary outcomes of the RADIANCE study were based on VA, which was identified as the outcome of primary importance in our protocol, and on CRT, which was identified as the second outcome of importance. Quality of life and vision function were identified as the third outcome of importance, but this outcome (NEI-VFQ-25, EQ-5D, and WPAI:GH) was assessed only among the exploratory outcomes in the study, limiting its validity. Blindness has been monitored among the harms outcomes of the study.

3.2.5 Statistical analysis

The primary outcome analysis was the superiority of ranibizumab treatment groups (Groups I and II) versus vPDT (Group III) in terms of difference from baseline of the average level of BCVA over all monthly post-baseline assessments from month 1 to month 3. The comparisons were performed using the stratified Cochran–Mantel–Haenszel (CMH) test on the full analysis set (FAS) with the observed values as scores. Stratification was done based on categories of baseline BCVA (i.e., ≤ 60 letters versus > 60 letters). The cut-point of 60 represents the approximate median baseline BCVA level. The primary variable was also assessed by parametric statistical methods. The two-sided 95% confidence interval (CI) for the absolute BCVA and the average changes in BCVA, and the corresponding pairwise difference between treatments were calculated using the least square means from an analysis of variance (ANOVA) model with treatment and baseline BCVA category (≤ 60 letters versus > 60 letters) as factors. Additionally, an unstratified CMH test was conducted. A modified last observation carried forward (LOCF) approach, using the mean of the last observation before and the first observation after, has been used for missing values.

The key secondary outcome analysis was the non-inferiority of the ranibizumab injections driven by the disease activity re-treatment criteria (Group II) versus the ranibizumab injections driven by the VA stabilization criteria (Group I). The differences from baseline of the average level of BCVA over all monthly post-baseline assessments from month 1 to month 6 were compared. The two-sided 95% CI of the average changes in BCVA and the corresponding pairwise difference between treatments was calculated using the least squares means from an ANOVA model with treatment and baseline BCVA category (≤ 60 letters versus > 60 letters) as factors. The non-inferiority margin of five letters was based on health authority feedbacks on Visudyne. This analysis was performed with the FAS using modified LOCF for the imputation of missing values.

The sample size calculation was performed as follows. With 110 patients in each of the ranibizumab treatment groups and 55 patients in the vPDT group, based on pairwise treatment group comparisons using CMH tests at multiple one-sided 0.001 (Hochberg procedure), assuming a treatment difference of eight letters between each of the ranibizumab treatment groups and vPDT and a standard deviation of 10 letters, the power to reject at least one of the null hypotheses was ≥ 91%. The power calculation was performed using PASS/NCSS 2002 (Wilcoxon test based on normal distribution). It is assumed that the

stratification planned in the primary analyses has a tendency to further increase the power, and that the impact by dropouts at month 3 is negligible. It is further assumed that the standard deviation (SD) for the difference between the average level of BCVA (letters) over all monthly post-baseline assessments from month 1 to month 3 is approximately 85% of the SD for change from baseline at month 3 and month 6.

Sensitivity analyses for the primary and the key secondary analyses were performed by using the per-protocol (PP) set, by using observed values only, by using a standard LOCF approach, and by using a first observation carried back (FOCB) approach. Subgroup analyses of the primary outcome in regard to ethnicity (Japanese versus Caucasian) and clinical types of macular (and peripapillary) CNV lesions were pre-specified. Other subgroup analyses such as sex, race (Caucasian, Asian, other), baseline BCVA (< 45, 45 < 60, 60 < 73, ≥ 73), baseline axial length (< 28 mm, 28 mm to < 30 mm, ≥ 30mm) were also performed.

a) Analysis populations

The randomized set consists of all randomized patients.

The FAS consists of all patients who received at least one application of study treatment and had at least one post-baseline efficacy assessment. Patients in this set were analyzed according to treatment assigned. The FAS has been used for the efficacy outcomes.

The safety set consists of all patients who received at least one application of study treatment and had at least one post-baseline safety assessment. Patients in this set were analyzed according to treatment received.

The PP set consists of all patients in the FAS who received study treatment as randomized and completed the trial to a certain timepoint (month 3 or month 6) without clinically significant protocol deviations.

3.3 Patient Disposition

Information on patient disposition in the RADIANCE study is summarized in Table 7, whereas more complete data are shown in Table 15. Although the overall discontinuation rate after 12 months was only 3.6 %, discontinuations were higher in the ranibizumab treatment groups (5.7% and 3.4% for Groups I and II, respectively, versus 0% in the vPDT treatment group). The most common reasons for discontinuation were “lost to follow-up” (four patients) and “withdrawal of consent” (three patients).

TABLE 7: PATIENT DISPOSITION

	Radiance			
Disposition Reason	**Group I: Ranibizumab (Stabilization of VA)**	**Group II: Ranibizumab (Disease Activity)**	**Group III: vPDT**	**Total**
Screened, N				334
Randomized, N (%)	106 (100.0)	116 (100.0)	55 (100.0)	277 (100.0)
Completed 3 months, n (%)	105 (99.1)	116 (100.0)	55 (100.0)	276 (99.6)
Discontinued study prior to month 3, n (%)	1 (0.9)	0	0	1 (0.4)
Completed 6 months, n (%)	103 (97.2)	116 (100.0)	55 (100.0)	274 (98.9)
Discontinued study prior to month 6, n (%)	3 (2.8)	0	0	3 (1.1)
Completed study (12 months)	100 (94.3)	112 (96.6)	55 (100.0)	267 (96.4)
Discontinued study prior to month 12, n (%)	6 (5.7)	4 (3.4)	0	10 (3.6)
FAS, N (%)	105 (99.1)	116 (100.0)	55 (100.0)	276 (99.6)
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety, N (%)	106 (100.0)	118 (101.7)[a]	53 (96.4)	277 (100.0)

FAS = full analysis set; n = number of patients with event; N = number of patients; PP = per-protocol analysis set; VA = visual acuity; vPDT = verteporfin photodynamic therapy.
[a] Two patients randomized to vPDT each received one ranibizumab injection prior to month 3.
Percentages are based on the total number of patients in the randomized set.
Source: Clinical Study Report: Table 10-1, p. 123; Table 11-1, p. 126.

3.4 Exposure to Study Treatments

Detailed information of medication exposure is presented in Table 8 (and in Appendix 3, Table 16, Table 17, Table 18, Figure 2, and Figure 3). When comparing numbers of injections of ranibizumab at month 12, patients in Group I (stabilization of VA, 4.6 injections) received one more injection per patient than patients in Group II (disease activity, 3.5 injections), which is in line with the number of initial injections received.

During the trial, the use of concomitant medications [redacted] (see Table 14). [redacted] was the most commonly used ocular medication.

TABLE 8: SUMMARY OF EXPOSURE TO STUDY TREATMENTS (SAFETY SET)

	Radiance		
	Group I: Ranibizumab (Stabilization of VA)	Group II: Ranibizumab (Disease Activity)	Group III: vPDT
Number of ranibizumab injections			
Prior to Month 3[a]			
N	106	118[b]	53
[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	2.5 (0.57)	1.8 (0.82)	0.0 (0.00)
Median	2.0	2.0	0.0
Prior to Month 12[c]			
N	106	118[b]	38
[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	4.6 (2.59)	3.5 (2.92)	3.2 (2.54)
Median	4.0	2.5	2.0

N = number of patients and number of study eyes; SD = standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy.
[a] Two injections in Group II and one in Group III could not be classified as sham or active ranibizumab due to missing or invalid injection identification numbers. These injections are not included in the analysis presented here.
[b] In the vPDT group (Group III), two patients received ranibizumab prior to month 3 and these were included in Group II.
[c] Three injections in Group II could not be classified as sham/active ranibizumab due to missing or invalid injection identification numbers. These injections are not included in the analysis presented here.
Source: Clinical Study Report: Table 12-1, p. 155; Table 12-4, p. 158–159.

3.5 Critical Appraisal

3.5.1 Internal validity

The only included study (RADIANCE) was a double-masked, multi-centre, randomized, active-controlled trial with a primary analysis of superiority. The randomization process including allocation concealment was well described but did not mention any stratification in regard to study centre. Thus, the possibility of having patients in the same treatment group clustered in a few study centres is not ruled out. Because the two study medications had very different appearances and routes of administration, the masking conditions were not ideal. Firstly, the sham injections were mimics of an injection with a needle-free syringe and an empty vial. This could be quite easily noticed by the patients who could deduce their assignation. Secondly, the study used an unmasked treating investigator and a masked assessing investigator. An unmasked treating investigator may give different care when the treatment is a sham intervention and, once again, this could have been noticed by patients. This way of conducting the study, with partial blinding, was likely inevitable due to ethics and logistics considerations. However, patients who had uncovered their treatment assignations, more likely those in the vPDT treatment group (i.e., sham injection with a needle-free syringe and an empty vial), could have biased their VA assessments (on a decrease), which is in favour of the study drug.

The baseline characteristics of patients were similar between each group. Even if baseline ocular characteristics of the study eye were not equally distributed when the characteristics were subgrouped for severity, which could have affected the magnitude of the response, a clear tendency of disequilibrium in favour of one treatment group was not observed. Whether this could be a source of bias is uncertain.

The key secondary outcome was the non-inferiority of the ranibizumab treatment regimen driven by disease activity over the ranibizumab treatment regimen driven by VA stabilization after six months. As the trial was primarily designed and conducted to show superiority, the conduction of the study was not likely to be biased toward non-inferiority.

An intention-to–treat analysis on the FAS with a modified LOCF approach was used for the primary and key secondary outcomes. Both analyses were tested for sensitivity by using different approaches to handle missing data (observed values, standard LOCF, FOCB) and by using the PP set. These sensitivity analyses produced results that were similar to the original analyses. Statistical tests, stratified for baseline VA, were appropriate since this baseline parameter affects the responsiveness of the patient.[16,25] A sample size calculation was performed with credible assumptions for the primary and key secondary outcomes. The power to reject the null hypothesis was of 91% for both analyses.

The 12-month study had an overall completion rate of 96.4% and only one patient discontinued before month 3. The possibility of attrition bias is very weak.

Concomitant medications [redacted] (Groups I and II). The most common concomitant medication was [redacted]. According to the clinical expert consulted by CDR reviewers, this medication did not likely affect the results of the study.

3.5.2 External validity

In terms of baseline ocular characteristics, the study population reflected patients seen in Canadian clinics. Although quite stringent, inclusion and exclusion criteria were in line with common medical practice. In terms of demographic characteristics, the study population may not reflect the Canadian population. Two study centres were in Canada and many from Europe, but a high proportion of patients were from Asian study centres. Hence, the proportion of Asian patients enrolled in the study is high (41.2%). Racial populations other than Caucasian or Asian are under-represented in the study with only 0.4%, which does not reflect the Canadian population. However, according to the clinical expert consulted by CDR reviewers, race is not likely to change the management of the disease.

The dosing, administration, and treatment regimens of the study drugs were appropriate and reflected what is performed in clinics. The use of vPDT was judicious as it is the standard of care for this indication in Canada and is the most effective on-label drug available.

Most of the outcomes in the study were based on improvement of VA, which is probably the most relevant end point for a patient with vision loss. This is also in line with the indication that is visual impairment and not disease activity. Other outcomes were based on anatomic observations reflecting signs of the disease. Those were of less importance compared with VA and were treated accordingly by the investigators (i.e., secondary outcomes). Quality of life, visual functionality, and general functionality were self-reported outcomes and were considered as exploratory outcomes.

The design of the study allowed a head-to-head comparison of the two treatments over only three months. This short follow-up period exposed data on the efficacy of the response with ranibizumab or vPDT, but did not address the long-term sustainability of the response and the recurrence of the disease.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (Section 2.2, Table 3) are reported in Table 9. See APPENDIX 3: DETAILED OUTCOME DATA for detailed efficacy data from Table 19 to Table 29.

3.6.1 Average change in BCVA from baseline to month 1 through month 3

Treatment with ranibizumab was associated with a statistically significant improvement in BCVA from baseline to month 1 through month 3 (averaged difference). The differences versus vPDT were 8.5 letters (95% CI, [redacted]; $P < 0.00001$) and 8.6 letters (95% CI, [redacted]; $P < 0.00001$) for ranibizumab treatment groups, Group I (re-treatment based on stabilization of VA) and Group II (re-treatment based on disease activity), respectively. When compared with the MCID of 10 letters to 15 letters, the differences versus vPDT do not reach the threshold for a clinically meaningful response. For within-group differences, BCVA showed differences of 10.5 letters, 10.6 letters, and 2.2 letters from baseline to month 1 to month 3 in Groups I, II (ranibizumab treatment groups), and III (vPDT), respectively (see Table 9).

The results of the sensitivity analyses performed on the FAS (observed data, LOCF, and FOCB) and on the PP set (modified LOCF, observed data, LOCF, FOCB) were consistent with the primary analysis.

Subgroup analyses were carried out based on age, sex, race, baseline BCVA, baseline axial length, and baseline location of CNV subtype (see Table 19). In all subgroups, the gains in BCVA were similar to the overall results. It was also observed that patients with a higher baseline BCVA achieved a generally lower gain of BCVA following treatment. Moreover, in terms of BCVA improvement in the ranibizumab treatment groups, patients with an extrafoveal CNV had a numerically lower response (i.e., from 3.7 letters to 7.2 letters lower) compared with patients with a subfoveal or a juxtafoveal CNV. However, this observation is based on a very small sample of extrafoveal CNV and could be further explained by the better baseline VA of those patients.

3.6.2 Average change from baseline to month 1 through month 6 in BCVA

The key secondary analysis was a non-inferiority comparison between the ranibizumab injections driven by the disease activity re-treatment criteria (Group II) versus the ranibizumab injections driven by the stabilization criteria (Group I). At month 6, the average BCVA changes from baseline were of 11.9 letters and 11.7 letters for Group I and Group II, respectively (see Table 9). The difference between the two groups was –0.1 letters (95% CI, –2.2 to 2.0) and the statistical test for non-inferiority was significant ($P < 0.00001$). The measured difference was below the pre-specified five letters non-inferiority margin. Therefore, improvement of BCVA was similar between both regimens of ranibizumab injections.

The results of the sensitivity analyses (same analyses as for primary outcome) were consistent with the results of the key secondary analysis.

3.6.3 Proportion of patients with ≥ 10 letters and ≥ 15 letters gain or loss or reaching 84 letters

Proportions of patients achieving categorized BCVA change from baseline at month 3, month 6, and month 12 are shown in Table 9.

In Group I (ranibizumab, re-treatment based on stabilization of VA), the proportion of patients who gained ≥ 15 letters or reached 84 letters at month 3 was 38.1%, and the proportion of patients who gained ≥ 10 letters or reached 84 letters was 61.9%. Numbers were quite similar in Group II (ranibizumab, re-treatment based on disease activity). In Group III (vPDT), the proportion of patients

who gained ≥ 15 letters or reached 84 letters was 14.5% (month 3), and the proportion of patients who gained ≥ 10 letters or reached 84 letters was 27.3% (month 3). At all timepoints, the proportions of patients with the aforementioned categorized BCVA improvements were higher in the ranibizumab treatment groups than in the vPDT group. The proportions of patients with categorized BCVA deteriorations were higher in the vPDT group at all timepoints, except for the ≥ 10 letter loss at month 12, where patients in the vPDT group could have received ranibizumab.

3.6.4 Central retinal thickness changes from baseline

The mean CRT changes from baseline to month 3, month 6, and month 12 are reported in Table 9. In Groups I and II (ranibizumab-treated patients), the mean change from baseline to month 3 in CRT was –61.0 µm and –77.6 µm, respectively, and –12.0 µm in Group III (vPDT-treated patients). From baseline to month 6, the mean changes in CRT were –66.1 µm, –74.8 µm, and –51.5 µm for patients of Groups I, II, and III, respectively, and the mean change from baseline to month 12 was –66.6 µm, –71.3 µm, and –60.8 µm for Groups I, II, and III, respectively. Then, the changes of CRT, which reflect the state of the disease, numerically favoured ranibizumab treatments over vPDT.

3.6.5 Impact of treatment on patient functioning, quality of life, and work productivity

Self-reported outcomes were assessed with the NEI-VFQ-25 (Table 27), the EQ-5D (see Table 28), and the WPAI:GH (see Table 29) instruments as part of the exploratory efficacy results. At month 3, patients in Groups I, II (ranibizumab treatment groups), and III (vPDT) had a mean change of NEI-VFQ-25 composite score from baseline of 5.3, 4.3, and 0.3, respectively. At month 3, patients had a mean change of EQ-5D thermometer score from baseline of [redacted] and [redacted] in Group I, II (ranibizumab treatment groups), and III (vPDT), respectively. At the same timepoint, the mean change of WPAI:GH total score from baseline was of [redacted] and [redacted] for Groups I, II, and III, respectively.

3.6.6 Other anatomic outcomes

The proportion of patients with subretinal fluid (Table 23) or intraretinal edema (Table 24) is shown in Appendix 3. At month 3, the general trend on subretinal fluid (Group I [ranibizumab, re-treatment based on stabilization of VA]: [redacted], Group II [ranibizumab, re-treatment based on disease activity]: [redacted], Group III [vPDT]: [redacted] of definite presence) and intraretinal edema (Group I: [redacted], Group II: [redacted], Group III: [redacted] of definite presence) is that ranibizumab treatment groups have better improvement over vPDT. Those differences tend to disappear after month 3. The proportion of patients with intraretinal cysts at baseline, month 3, month 6, and month 12 is shown in Table 25. Benefits from ranibizumab were less clear for this outcome with [redacted], [redacted] and [redacted] of definite presence at month 3 for Groups I, II, and III, respectively. The proportion of patients with CNV leakage at baseline and month 12 is shown in Table 26. At month 12, numbers were in favour of Group I (21.0 %) and Group II (19.0%) (ranibizumab treatment groups) versus vPDT (Group III) (29.1%) in terms of definite presence of CNV leakage.

TABLE 9: KEY EFFICACY OUTCOMES

	Radiance		
	Group I: Ranibizumab (Stabilization of VA) N = 105	**Group II: Ranibizumab (Disease Activity) N = 116**	**Group III: vPDT N = 55**
VISUAL ACUITY (ETDRS LETTERS) CHANGE FROM BASELINE TO MONTH 1 THROUGH MONTH 3			
Baseline, mean (SD)	55.4 (13.43)	55.8 (12.59)	54.7 (13.84)
Average VA from month 1 to month 3,[a] mean (SD)	66.0 (12.98)	66.4 (12.28)	56.9 (14.49)
Average VA change from baseline, mean (SD)	10.5 (8.16)	10.6 (7.26)	2.2 (9.47)
Difference vs. vPDT, LSM (95% CI)[b]	8.5 ([redacted])	8.6 ([redacted])	-
P value[c]	< 0.00001	< 0.00001	-
VISUAL ACUITY (ETDRS LETTERS) CHANGE FROM BASELINE TO MONTH 1 THROUGH MONTH 6			
Baseline, mean (SD)	55.4 (13.43)	55.8 (12.59)	54.7 (13.84)
Average VA from month 1 to month 6, mean (SD)	67.3 (12.40)	67.5 (12.34)	59.0 (14.24)
Average VA change from baseline, mean (SD)	11.9 (8.81)	11.7 (8.24)	4.2 (9.26)
Difference vs. Group I, LSM (95% CI)[b]	-	–0.1 (–2.2 to 2.0)	NR
Non-inferiority *P* value[d]	-	< 0.00001	NR
CATEGORIZED BCVA GAINS AT MONTHS 3, 6, AND 12			
Month 3			
Number of patients who gained ≥ 15 letters or reached 84 letters, n (%)	40 (38.1)	50 (43.1)	8 (14.5)
Number of patients with ≥ 15 letters loss, n (%)	2 (1.9)	0	4 (7.3)
Number of patients who gained ≥ 10 letters or reached 84 letters, n (%)	65 (61.9)	76 (65.5)	15 (27.3)
Number of patients with ≥ 10 letters loss, n (%)	2 (1.9)	1 (0.9)	9 (16.4)
Month 6			
Number of patients who gained ≥ 15 letters or reached 84 letters, n (%)	49 (46.7)	52 (44.8)	15 (27.3)
Number of patients with ≥ 15 letters loss, n (%)	0	1 (0.9)	2 (3.6)
Number of patients who gained ≥ 10 letters or reached 84 letters, n (%)	75 (71.4)	75 (64.7)	25 (45.5)
Number of patients with ≥ 10 letters loss, n (%)	2 (1.9)	3 (2.6)	2 (3.6)

	Radiance		
	Group I: Ranibizumab (Stabilization of VA) N = 105	**Group II: Ranibizumab (Disease Activity) N = 116**	**Group III: vPDT N = 55**
Month 12			
Number of patients who gained ≥ 15 letters or reached 84 letters, n (%)	56 (53.3)	60 (51.7)	18 (32.7)
Number of patients with ≥ 15 letters loss, n (%)	2 (1.9)	1 (0.9)	2 (3.6)
Number of patients who gained ≥ 10 letters or reached 84 letters, n (%)	73 (69.5)	80 (69.0)	27 (49.1)
Number of patients with ≥ 10 letters loss, n (%)	5 (4.8)	2 (1.7)	2 (3.6)
CHANGE FROM BASELINE IN CRT			
Month 3			
Baseline, mean (SD)	349.2 (95.05)	373.1 (127.44)	352.5 (101.52)
Value at visit, mean (SD)	288.3 (70.14)	295.6 (71.93)	340.5 (106.03)
Change from baseline, mean (SD)	−61.0 (67.46)	−77.6 (102.25)	−12.0 (65.84)
Month 6			
Baseline, mean (SD)	349.2 (95.05)	373.1 (127.44)	355.1 (102.35)
Value at visit, mean (SD)	283.1 (67.43)	298.3 (81.16)	303.5 (76.81)
Change from baseline, mean (SD)	−66.1 (73.63)	−74.8 (97.05)	−51.5 (79.98)
Month 12			
Baseline, mean (SD)	349.2 (95.05)	373.1 (127.44)	355.1 (102.35)
Value at visit, mean (SD)	282.6 (68.62)	301.8 (88.16)	294.3 (83.25)
Change from baseline, mean (SD)	−66.6 (82.63)	−71.3 (100.91)	−60.8 (80.04)

BCVA = best corrected visual acuity; CI = confidence interval; CRT = central retinal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; LSM = least squares mean; n = number of patients with event; N = number of patients; NR = not reported; SD = standard deviation; VA = visual acuity; vs. = versus; vPDT = verteporfin photodynamic therapy.

[a] Average of visual acuity assessments during this period.

[b] Differences in LSM and the two-sided 95% CIs are estimated from pairwise ANOVA (stratified) model. Stratified analysis includes baseline visual acuity (≤ 60 letters, > 60 letters) as factors.

[c] One-sided *P* values for treatment difference are derived from the two-sided stratified Cochran–Mantel–Haenszel test using the row means score statistics.

[d] This *P* value for non-inferiority is from a CMH test (stratified), is one-sided and based on the null hypothesis: Group II (by disease activity) is not more than five letters worse than Group I (by stabilization), against the alternative hypothesis: Group II (by disease activity) is more than five letters worse than Group I (by stabilization).

Source: Clinical Study Report: Table 11-6, p. 133; Table 11-8, p. 135; Table 14.2-2.1, p. 692; Table 14.2-2.53 p. 3183, 3186, 3192; Table 11-14, p. 145.

3.7 Harms

Only harms identified in the review protocol (see 2.2.1, Protocol) are reported in Table 10. See APPENDIX 3: DETAILED OUTCOME DATA for detailed harms data in Table 30 to Table 32. All AEs that occurred during this study were classified as either ocular AEs or non-ocular AEs. Harms data from the included study are reported as treatment-emergent adverse events (TEAEs). In addition, serious AEs, mortality, and withdrawals due to adverse events (WDAEs) and notable AEs identified with the clinical expert involved in the review are reported.

3.7.1 Adverse events

After month 12, 43.4% of patients in Group I (ranibizumab, re-treatment based on stabilization of VA), 37.3% of patients in Group II (ranibizumab, re-treatment based on disease activity), 42.1% of patients in Group III (vPDT) who had ranibizumab after month 3, and 26.7% of patients in Group III (vPDT) who did not have ranibizumab after month 3 reported ocular TEAEs during the study. The incidences of ocular TEAEs were higher in the ranibizumab treatment groups and among patients in Group III who had ranibizumab compared to patients who did not have ranibizumab injections. The most common reported ocular AEs were conjunctival hemorrhage (Group I: 11.3%, Group II: 10.2%, Group III with ranibizumab [w/ran]: 5.3%, Group III without ranibizumab [wo/ran]: 0%), punctate keratitis (Group I: 7.5%, Group II: 2.5%, Group III w/ran: 5.3%, Group III wo/ran: 0%) and increased intraocular pressure (Group I: 2.8%, Group II: 5.9%, Group III w/ran: 10.5%, Group III wo/ran: 0%).

After month 12, 45.3% of patients in Group I (ranibizumab, re-treatment based on stabilization of VA), 43.2% of patients in Group II (ranibizumab, re-treatment based on disease activity), 50.0% of patients in Group III (vPDT) who had ranibizumab, and 33.3% of patients in Group III (vPDT) who did not have ranibizumab reported non-ocular TEAEs during the study. Overall, the incidences of non-ocular TEAEs were also higher in the ranibizumab treatment groups. The most common reported non-ocular AEs were nasopharyngitis (Group I: 11.3%, Group II: 10.2%, Group III w/ran: 2.6%, Group III wo/ran: 13.3%) and headache (Group I: 7.5%, Group II: 9.3%, Group III w/ran: 2.6%, Group III wo/ran: 0%).

3.7.2 Serious adverse events

The total numbers of SAEs in the study were 6.6% in Group I (ranibizumab, re-treatment based on stabilization of VA), 5.1% in Group II (ranibizumab, re-treatment based on disease activity), and 0% in Group III (vPDT). Most were non-ocular SAEs with incidences of 5.7% and 4.2% for Group I and Group II, respectively. Those non-ocular SAEs are reported in Table 32. Only two cases of ocular SAEs occurred: one patient with corneal erosion (Group I) and one patient with retinoschisis (Group II).

3.7.3 Withdrawals due to adverse events

No WDAEs occurred during the study.

3.7.4 Mortality

No mortality occurred during the study.

3.7.5 Notable harms

After consultation with the clinical expert involved in the review, the following notable ocular harms (i.e., ocular AEs with special clinical interest) were identified: unilateral blindness, endophthalmitis, retinal detachment, retinal tear, uveitis, and visual impairment. The notable non-ocular harms were arterial thromboembolic events (ATEs) and gastrointestinal perforation. Blindness (Group III w/ran: 2.6%, Group III wo/ran: 6.7%) and visual impairment (Group III w/ran: 5.3%) occurred only in Group III (vPDT). Retinal tear (Group I: 1.9%, Group II: 0.8%), uveitis (Group I: 0.9%, Group II: 0.8%), and gastrointestinal hemorrhage (Group I: 0.9%, Group II: 0.8%) were reported only in the ranibizumab treatment groups. No ATEs were reported in the study.

TABLE 10: HARMS

	Radiance			
	Group I: Ranibizumab (Stabilization of VA) (N = 106)	Group II: Ranibizumab (Disease Activity) (N = 118)	Group III: vPDT	
			With Ranibizumab From Month 3 (N = 38)	Without Ranibizumab From Month 3 (N = 15)
TEAEs				
Subjects with > 0 ocular TEAEs up to month 12, n (%)				
Total	46 (43.4)	44 (37.3)	16 (42.1)	4 (26.7)
Most common ocular TEAEs[a]				
Conjunctival hemorrhage	12 (11.3)	12 (10.2)	2 (5.3)	0
Punctate keratitis	8 (7.5)	3 (2.5)	2 (5.3)	0
Dry eye	4 (3.8)	2 (1.7)	0	1 (6.7)
Eye pain	4 (3.8)	4 (3.4)	1 (2.6)	1 (6.7)
Injection site hemorrhage	3 (2.8)	3 (2.5)	2 (5.3)	0
Intraocular pressure increased	3 (2.8)	7 (5.9)	4 (10.5)	0
Subjects with > 0 non-ocular TEAEs up to month 12, n (%)				
Total	48 (45.3)	51 (43.2)	19 (50.0)	5 (33.3)
Most common non-ocular TEAEs[a]				
Nasopharyngitis	12 (11.3)	12 (10.2)	1 (2.6)	2 (13.3)
Headache	8 (7.5)	11 (9.3)	1 (2.6)	0
Hypertension	3 (2.8)	5 (4.2)	3 (7.9)	0
SAEs				
Total	7 (6.6)	6 (5.1)	0	0
Ocular SAEs[b]	1 (0.9)	1 (0.8)	0	0
Non-ocular SAEs	6 (5.7)	5 (4.2)	0	0
WDAEs	0	0	0	0
Death	0	0	0	0
Notable harms				
Blindness	0	0	1 (2.6)	1 (6.7)
Retinal tear	2 (1.9)	1 (0.8)	0	0
Uveitis	1 (0.9)	1 (0.8)	0	0
Visual impairment	0	0	2 (5.3)	0
Gastrointestinal hemorrhage	1 (0.9)	1 (0.8)	0	0

n = number of patients with event; N = number of patients; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events; VA = visual acuity; vPDT = verteporfin photodynamic therapy; WDAEs = withdrawals due to adverse event.
[a] Frequency > 5%.
[b] Two ocular SAEs were corneal erosion and retinoschisis.
Source: Clinical Study Report: Table 12-11, p. 167; Table 12-4, p. 170; Table 12-35, p. 183; Table 14.3.1-3.1.1, p. 5892; Table 14.3.1-3.1.2, p. 5897; Table 14.3.1-3.2.1, p. 5910.

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence used for this review was derived from a single, double-masked, multi-centre, active-controlled trial that compared two different treatment regimens of ranibizumab (Groups I and II) against vPDT (Group III) in 277 patients with myopic CNV. The 12-month study consisted of a three-month double-blinded phase (Period 1), during which no changes in treatment assignment were allowed, and a second phase (Period 2; month 4 through month 12), during which the vPDT treatment group could continue with vPDT and/or receive ranibizumab.

The primary objective was to determine whether ranibizumab was superior to vPDT in improving BCVA over three months. This was assessed by comparing the average change in BCVA through month 1 and month 3 between the ranibizumab-treated groups and the vPDT-treated group. A secondary objective was to determine whether the ranibizumab treatment regimen based on disease activity (Group I) was non-inferior to the ranibizumab treatment regimen based on stabilization of VA (Group II), and this was assessed by comparing the average change in BCVA through month 1 and month 6 between the two ranibizumab treatment groups. In addition to these objectives, BVCA gains were compared among treatments at months 3, 6, and 12 after categorizing visual improvement according to the gain in EDTRS letters. Other outcomes measured at months 3, 6, and 12 included anatomical parameters such as changes in CRT, subretinal fluid, intraretinal edema, and CNV leakage. Visual function was assessed using the NEI-VFQ-25, while quality of life and work productivity were measured using the EQ-5D and WPAI:GH instruments, respectively.

Baseline characteristics were similar in all treatment groups. While there were minor imbalances among treatment groups after stratification (subgrouping) by age, sex, race, baseline BCVA, baseline axial length, and location of CNV, none of these differences was associated with any clear or systematic bias. The definition of myopic CNV used to select patients for inclusion in the RADIANCE study (–6 D refraction sphere, ≥ 26 mm axial length) was somewhat less restrictive than that used in the literature (–8 D refraction sphere, ≥ 30 mm axial length), which might have resulted in a bias against detecting a superior response in the ranibizumab groups (see below). The use of unmasked treating investigators and the nature of the sham injections (no injection to the eye itself) make it likely that patients were unblinded to the study treatment, which might have biased the estimates of BCVA. Specifically, if patients in the vPDT treatment group were aware of their treatment assignment, they could potentially have provided VA assessments that were biased against vPDT. Nevertheless, the effects of this potential bias on the study results are unclear.

4.2 Interpretation of Results

4.2.1 Efficacy

The results of the RADIANCE study suggest that ranibizumab is superior to vPDT for improving vision in adults with myopic CNV. When compared with vPDT, ranibizumab was associated with a statistically significant greater improvement in BCVA of approximately nine additional ETDRS letters. This result is in agreement with the superiority of anti-VEGF therapies over vPDT in patients with myopic CNV that has been reported elsewhere.[26] Ranibizumab-treated patients in the RADIANCE study exhibited an increase in VA from baseline of approximately 11 EDTRS letters, which is similar to the magnitude of vision improvement observed in other studies of anti-VEGF therapies,[26] whereas the improvement in BCVA of two letters in the vPDT-treated group reflected stabilization rather than improvement of VA.

While ranibizumab was statistically superior to vPDT in improving vision in the RADIANCE study, the magnitude of the treatment difference between ranibizumab and vPDT (nine additional EDTRS letters attained in the ranibizumab treatment groups) was slightly smaller than the MCID of 10 to 15 letters (see Appendix 4). By contrast, the improvement in VA from baseline of 11 letters attributable to ranibizumab exceeded the MCID of 10 to 15 letters. Therefore, while the improvement in vision from baseline in ranibizumab-treated patients was likely clinically meaningful, it is less certain whether the improvement in vision in ranibizumab-treated patients over vPDT treatment was clinically meaningful. However, it should be noted that there is some uncertainty regarding the precise value of the MCID: while the FDA prefers the higher value of 15 letters, the available evidence supports the lower value of 10 letters, and some have proposed that MCID may be lower than 10 letters (see Appendix 4). As noted above, the somewhat less restrictive definition of myopic CNV used to recruit patients for the RADIANCE study might have led to the inclusion of patients with slightly less severe VA, which in turn would have produced a slightly smaller magnitude of improvement (due to the inverse relationship between the magnitude of improvement and baseline VA). If a more stringent definition of myopic CNV had been used, the nine-letter improvement in BCVA might have been higher and could potentially have exceeded the 10-letter threshold.

While the between-treatment difference in vision improvement of nine letters did not exceed the MCID of 10 to 15 letters, greater proportions of ranibizumab-treated patients did achieve these clinical thresholds compared with vPDT-treated patients. Specifically, an improvement of at least 15 letters (or achievement of 84 letters) was observed in 38% to 43% of ranibizumab-treated patients versus 15% of vPDT-treated patients, while an improvement of at least 10 letters was observed in 62% to 66% of ranibizumab-treated patients versus 27% of vPDT-treated patients. While this was not the primary outcome used in the RADIANCE study, this categorical method of comparing vision improvement is the same as that used in the VIP trial, a pivotal study of the use of verteporfin for the treatment of visual impairment due to CNV secondary to PM.[27,28]

The secondary key finding of the RADIANCE study was the demonstration that the ranibizumab treatment regimen that was based on re-treatment according to disease activity was non-inferior to the regimen based on re-treatment according to stabilization of VA. Therefore, the treatment regimen in which re-treatment is based on assessment of disease activity is the regimen that is recommended in the product monograph. Patients treated with the aforementioned regimen received an average of one fewer injection over 12 months (3.5 injections per patient) compared with patients treated according to stabilization of VA (4.6 injections/patient). Since the regimen administered to Group II was non-inferior to Group I in terms of efficacy, the recommendation to use the treatment regimen based on disease activity might reduce the occurrence of unnecessary injections in practice.

Other secondary outcomes were based on anatomical observations. The mean changes from baseline to month 3 in CRT were greater in ranibizumab-treated patients (decreases of 61 µm to 78 µm) compared with vPDT-treated patients (a decrease of 12.0 µm). While this was not a primary outcome of the study, the difference in the diminution of CRT thickness reflects a greater effect of ranibizumab on an anatomical feature that is positively correlated with CNV progression. A similar trend in favour of ranibizumab was observed for other anatomical outcomes including the presence of subretinal fluid, intraretinal edema, and CNV leakage.

The impact of ranibizumab on patient functioning, quality of life, and work productivity were assessed as exploratory outcomes. In terms of change from baseline, the increase in NEI-VFQ-25 composite scores at month 3 in ranibizumab-treated patients (4- to 5-point increase) was higher than observed in vPDT-treated patients (0.3-point increase). As the improvement in the ranibizumab-treated patients from baseline met or exceeded the MCID for this instrument of 4 points, ranibizumab appeared to have had a clinically meaningful effect on patient-rated visual function, whereas vPDT did not. Differences between treatments for changes in EQ-5D (generic quality of life) and WPAI:GH (work productivity and activity impairment) scores were too variable to allow for meaningful conclusions.

A limitation of the RADIANCE study is the relatively short follow-up period for the primary and secondary outcomes (three and six months, respectively). The short duration of the initial three-month double-blind phase is too brief to allow for meaningful conclusions regarding the long-term relative efficacy of ranibizumab compared with vPDT, nor does it allow for a long-term comparison of the two different ranibizumab treatment regimens. However, the short duration of the head-to-head comparison phase is likely due to ethical considerations aimed at giving patients the best treatment available. Nevertheless, the fact that most patients require fewer than five monthly ranibizumab injections suggests that a period of approximately six to 12 months is not an unreasonable trial duration. While a duration of 12 months would be adequate to assess the initial treatment response, the mean interval between initial treatment and first recurrence has been reported to be 24 months.[29] Therefore, it is unlikely that the duration of RADIANCE was sufficient to capture the comparative efficacy of ranibizumab and vPDT for treating recurrent CNV. This is not a trivial issue, because at least one long-term retrospective study demonstrated that the proportion of recurrence of myopic CNV over a 71-month period was 46%.[29] Regarding the long-term effect of ranibizumab, it is of interest to mention the results of a 24-month retrospective, non-randomized comparative study on 85 myopic CNV patients that favoured ranibizumab over vPDT for outcomes likes BCVA, CRT, closure of CNV, and chorioretinal atrophy size.[30] Of note, the manufacturer has a large observational study ongoing assessing the long-term efficacy and safety of ranibizumab over five years for all approved indications including myopic CNV.[31]

4.2.2 Harms

The proportion of patients who experienced ocular AEs ranged from 37.3% to 43.4% among all patients who received ranibizumab, which was a higher incidence than that observed in patients treated with vPDT alone (26.7%). The most common ocular AEs (conjunctival hemorrhage: 9.4%; punctate keratitis: 4.7%; increased intraocular pressure: 5.1%) occurred exclusively in the ranibizumab-treated patients. Similarly, SAEs occurred in 4.7% of ranibizumab-treated patients whereas there were no SAEs in vPDT-treated patients. It is not clear whether these differences were due to the administration of intravitreal injections (which occurred only in patients who received ranibizumab) and/or due to the study drug itself. According to the clinical expert consulted by CDR reviewers, the aforementioned AEs are reversible and do not markedly affect the tolerability of ranibizumab treatment. Indeed, no patients discontinued due to adverse events. Nevertheless, all subjects who discontinued the study (3.6%) were ranibizumab-treated patients.

Among notable ocular harms in the ranibizumab treatment groups, retinal tear (1% to 2%) and uveitis (1%) were reported. These AEs might be due to the injection itself and/or ranibizumab. In vPDT-treated patients, blindness (3% in vPDT-treated patients who also received ranibizumab; 7% in patients treated only with vPDT) and visual impairment (5% in patients treated only with vPDT) were reported, which may reflect damage to choroidal blood vessels and/or a lack of efficacy of vPDT.

The apparently higher incidence of harms that occurred in ranibizumab-treated patients in the RADIANCE study are likely attributable to the study drug itself and/or to the procedure of injecting drug into the eye, because vPDT-treated patients did not receive a true sham intraocular injection. Nevertheless, the overall harms profile of ranibizumab observed in the RADIANCE study is in line with the harms described in the product monograph, which have been reported on extensively for various other indications.

4.3 Other Considerations

The outcomes assessed in the RADIANCE study are in line with the priorities expressed by patients. Patients expressed a desire for improved VA, better functionality, and an improvement in quality of life. The current standard of care for treatment of myopic CNV is vPDT, yet this treatment stabilizes but does not improve vision. Therefore, while there is no robust evidence from the RADIANCE study in favour of ranibizumab improving function or quality of life, ranibizumab did appear to meet patients' desire to improve VA. In addition, patients expressed a desire to avoid the photosensitivity that is associated with vPDT therapy. However, the RADIANCE study demonstrated that patients treated with ranibizumab will likely experience more side effects compared with vPDT treatment. Despite this, patients appear to be willing to accept the higher rate of AEs associated with ranibizumab if they can improve their vision. For this reason, according to the clinical expert consulted by CDR reviewers, ranibizumab is likely to replace vPDT as first-line therapy in clinical practice.

It should be noted that bevacizumab (Avastin) is not approved in Canada for the treatment of visual impairment due to CNV secondary to PM. Consequently, it was not considered to be a valid comparator for the purpose of this review. However, according to the clinical expert consulted by CDR reviewers, bevacizumab is used off-label for the treatment of myopic CNV in patients in jurisdictions where ranibizumab is not reimbursed and in patients who are ineligible for coverage, primarily because it is less costly than ranibizumab.

5. CONCLUSIONS

The results of a single, double-blind, multi-centre, randomized, active-controlled trial (RADIANCE) suggest that three months of ranibizumab treatment significantly improves VA compared with vPDT in adults with visual impairment due to CNV secondary to PM. Ranibizumab treatment was associated with a statistically significant improvement in vision in BCVA of nine EDTRS letters compared with vPDT treatment. A greater proportion of patients treated with ranibizumab (62% to 66%) achieved an improvement in BCVA of at least 10 letters (or reached a BCVA of 84 letters) compared with vPDT-treated patients (27%). Changes in anatomical outcomes such as CRT, subretinal fluid, intraretinal edema, and CNV leakage favoured ranibizumab treatment over vPDT. The efficacy of ranibizumab treatment after six months at a treatment frequency based on stabilization of VA was similar to ranibizumab treatment at a frequency based on disease activity. All patients who discontinued the study (3.6%) were ranibizumab-treated patients, and ocular and non-ocular AEs and SAEs were more frequent in ranibizumab-treated patients compared with vPDT-treated patients. These differences in tolerability likely reflect differences in the mode of administration of the study drugs.

APPENDIX 1: PATIENT INPUT SUMMARY

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

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

The Canadian Council of the Blind (CCB) is a registered national charity. With more than 65 chapters and 1,500 members across Canada, it is the largest membership-based organization for the blind. All CCB officers and directors are blind or visually impaired, giving them a unique sensitivity to the needs of the blind community. Between 2011 and 2014, the CCB received support from the following pharmaceutical companies: Bayer, Merck Frosst, Novartis, and Pfizer. The CCB has declared no conflict of interest with respect to the preparation of this submission.

The Canadian National Institute for the Blind (CNIB) is a registered national charity, providing community-based support, knowledge, and a national voice to ensure that blind and partially sighted Canadians have the confidence, skills, and opportunities to fully participate in life. Each year, CNIB provides vision rehabilitation services to more than 10,000 new clients with vision loss. CNIB works with clients in their own homes and communities, participates in advocacy for equal access and an inclusive society, and promotes research and training into effective prevention, diagnosis, and treatment of eye disease. CNIB reports receiving support from the following pharmaceutical companies: Alcon, Bayer, Novartis, and Pfizer. CNIB has declared no conflict of interest with respect to the preparation of this submission.

2. Condition- and Current Therapy-related Information

Information for this submission was compiled from printed information from drug companies, online searches, one-on-one conversations with patients currently using the treatment, and professional conferences. CNIB notes having little specific information about vision loss from myopic choroidal neovascularization (mCNV), a low-prevalence disease; instead, CNIB based its submission on vision loss from choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

While mCNV is a low-prevalence disease, it is a major complication of pathologic myopia, which often results in irreversible central vision loss within five years if left untreated. Because of its prevalence among people of working age (i.e., 40 years to 50 years of age), CNV can have a major impact on a patient's career, independence, family dynamics and responsibilities, and quality of life. Patients may require help with preparing meals, completing daily household chores, and reading. The loss of one's independence, driving licence (which can make attending medical appointments, social activities, and shopping challenging) along with the potential loss of employment (which can affect affordability of treatments) and the uncertainty regarding one's quality of life without vision can lead to depression. Loss of vision also raises the risk of falls and injuries. Patients may become isolated with the loss of independent movement and the disappearance of friends, who may not know how to respond to the patient's vision loss. Few other eye diseases have this impact specifically on the working age population.

Current therapies for CNV include laser photocoagulation, photodynamic therapy with verteporfin (vPDT), surgery, and off-label drugs. vPDT stabilizes but does not improve VA, and is inconvenient because it requires multiple treatments per year and requires patients to avoid direct sunlight for some time post-injection, since it is a photosensitizing drug. Photocoagulation was believed to be of uncertain benefit, particularly in the long run when a potentially central, vision-threatening enlargement of a laser

scar could develop and result in a loss of independence or employment. Proximity to regional clinics may determine access to a given treatment. Costs associated with travel to clinics and the treatment may be unaffordable for some patients.

Caregivers are also affected by a diagnosis of CNV. They must provide emotional support to the patient, who was previously independent, a breadwinner, a driver, or a caregiver him- or herself, all the while dealing with their own emotions. Caregivers have to provide a safe physical environment for the patient. They may also need to take time off work to shuttle the patient to medical appointments or go shopping. Caregivers may also need to help with household chores. Caregivers have been shown to suffer from higher levels of depression, anxiety, and fatigue, with depression increasing as vision loss progresses. A medication that maintains or improves vision is expected to have a significant effect on the quality of life of the caregiver.

3. Related Information About the Drug Being Reviewed

Neither patient group included input from its patient members with mCNV who had used ranibizumab.

Based on clinical studies of ranibizumab in mCNV and patients' experiences with it in other retinal diseases, it is expected that patients with mCNV using ranibizumab will regain visual acuity. Patients treated with ranibizumab for other retinal disorders reported regaining lines on the Snellen Chart and driving privileges. Resumption of driving and working were identified as potential benefits from ranibizumab treatment. An unmet need exists for patients who do not tolerate or respond to the standard treatment because no alternative, approved therapy is currently available. It is expected that patients will have fewer treatments with ranibizumab than with vPDT, and will not have to be concerned about exposure to direct sunlight with ranibizumab. Patients are willing to tolerate some temporary adverse effects from a new therapy if they can regain sight or prevent further vision loss; specifically, mild irritation was acceptable, but infection was not. Outcomes that were identified as representing meaningful improvements from treatment and justifying a risk of adverse effects included regaining sight; controlling bleeding; having fewer medical appointments; returning to work; driving; regaining independence; and providing for the family. There is an expectation that ranibizumab will be easier to use compared with standard therapy due to a lower frequency of injections, and that long-term health will be improved.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	August 29, 2014
Alerts:	Bi-Weekly search updates until January 21, 2015 (date of CDEC meeting)
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.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	(lucentis* or ranibizumab* or rhuFab V2 or rhuFabV2 or Unii-ZL1R02VT79).ti,ot,ab,sh,rn,hw,nm.	5976
2	347396-82-1.rn,nm.	3744
3	or/1-2	5976
4	exp myopia/	31758
5	mCNV.ti,ab.	85
6	(myopic or myopia or myopias or myopes or myopy or myope or myoptic).ti,ab.	32198
7	or/4-6	41108
8	and/3,7	222
9	8 use pmez	78
10	*Ranibizumab/	1466
11	(lucentis* or ranibizumab* or rhuFab V2 or rhuFabV2 or Unii-ZL1R02VT79).ti,ab.	3543
12	or/10-11	3759
13	exp myopia/	31758
14	high myopia/	1789
15	(myopic or myopia or myopias or myopes or myopy or myope or myoptic).ti,ab.	32198
16	mCNV.ti,ab.	85
17	or/13-16	41327
18	and/12,17	156
19	conference abstract.pt.	1563817
20	18 not 19	152
21	20 use oemezd	85
22	or/9,21	163
23	remove duplicates from 22	97

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

Grey Literature

Dates for Search:	August 18-29, 2014
Keywords:	Ranibizumab (Lucentis), mCNV/pathological myopia
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: DETAILED OUTCOME DATA

TABLE 11: COMPLETE SUMMARY OF DEMOGRAPHIC CHARACTERISTICS

	Radiance			
	Group I: Ranibizumab (Stabilization of VA) (N = 106)	Group II: Ranibizumab (Disease Activity) (N = 116)	Group III: vPDT (N = 55)	Total (N = 277)
Age (years)				
Mean (SD)	54.0 (14.00)	56.1 (14.35)	57.4 (12.82)	55.5 (13.94)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
< 45, n (%)	24 (22.6)	24 (20.7)	7 (12.7)	55 (19.9)
45 to < 55, n (%)	27 (25.5)	21 (18.1)	16 (29.1)	64 (23.1)
55 to < 65, n (%)	30 (28.3)	34 (29.3)	14 (25.5)	78 (28.2)
≥ 65, n (%)	25 (23.6)	37 (31.9)	18 (32.7)	80 (28.9)
Sex, n (%)				
Male	24 (22.6)	29 (25.0)	15 (27.3)	68 (24.5)
Female	82 (77.4)	87 (75.0)	40 (72.7)	209 (75.5)
Predominant race, n (%)				
Caucasian	60 (56.6)	70 (60.3)	32 (58.2)	162 (58.5)
Asian	45 (42.5)	46 (39.7)	23 (41.8)	114 (41.2)
Other	1 (0.9)	0	0	1 (0.4)
[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]

n = number of patients with event; N = number of patients; SD = standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy.
Note: Percentages are based on the total number of patients in the randomized set.
Source: Clinical Study Report: Table 11-3, p. 127.

TABLE 12: COMPLETE SUMMARY OF BASELINE OCULAR CHARACTERISTICS OF THE STUDY EYE

	Radiance			
	Group I: Ranibizumab (Stabilization of VA) (N = 106)	Group II: Ranibizumab (Disease Activity) (N = 116)	Group III: vPDT (N = 55)	Total (N = 277)
VA (letters)				
Mean (SD)	55.4 (13.38)	55.8 (12.59)	54.7 (13.84)	55.4 (13.11)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Intraocular pressure (mmHg)				
Mean (SD)	15.1 (2.79)	15.1 (3.20)	14.8 (3.01)	15.0 (3.00)
[redacted]				
Axial length (mm)				
Mean (SD)	29.26 (1.929)	28.75 (1.846)	29.37 (1.850)	29.07 (1.892)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Refraction-sphere (D)				
Mean (SD)	13.727 (5.2305)	11.550 (4.6674)	12.150 (4.8669)	12.502 (5.0102)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

D = dioptre; mm Hg = millimetre of mercury; N = number of patients; SD = standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy.
Note: Percentages are based on the total number of patients in the randomized set. Refraction sphere values were collected as negative D but are presented as positive values to facilitate interpretation.
Source: Clinical Study Report: Table 11-4, p. 129.

TABLE 13: COMPLETE SUMMARY OF BASELINE OPTICAL COHERENCE TOMOGRAPHY AND FA/CF CHARACTERISTICS OF THE STUDY EYE

	Radiance			
	Group I: Ranibizumab (Stabilization of VA) (N = 106)	Group II: Ranibizumab (Disease Activity) (N = 116)	Group III: vPDT (N = 55)	Total (N = 277)
Central retinal thickness (µm)				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	350.2 (95.12)	373.1 (127.44)	355.1 (102.35)	360.6 (110.98)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CNV location, n (%)				
Subfoveal	71 (67.0)	81 (69.8)	38 (69.1)	190 (68.6)
Non-subfoveal	33 (31.1)	27 (23.3)	17 (30.9)	77 (27.8)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CF = colour fundus photography; CNV = choroidal neovascularization; FA = fluorescein angiography; n = number of patients with event; N = number of patients; OCT = optical coherence tomography; SD = standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy; µm = micrometre.
Note: Percentages are based on the total number of patients in the randomized set. Central retinal thickness and central foveal thickness represent all data irrespective of type of OCT machine.
Source: Clinical Study Report: Table 11-5, p. 130.

TABLE 14: SUMMARY OF CONCOMITANT OCULAR MEDICATIONS AND SIGNIFICANT NON-DRUG THERAPIES (TAKEN BY 2% OR MORE SUBJECTS) (SAFETY SET)

	Radiance		
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

[redacted]

TABLE 15: COMPLETE PATIENT DISPOSITION

	Radiance			
Disposition Reason	**Group I: Ranibizumab (Stabilization of VA)**	**Group II: Ranibizumab (Disease Activity)**	**Group III: vPDT**	**Total**
Screened, N				334
Randomized, N (%)	106 (100.0)	116 (100.0)	55 (100.0)	277 (100.0)
Completed 3 months, n (%)	105 (99.1)	116 (100.0)	55 (100.0)	276 (99.6)
Discontinued study prior to month 3, n (%)	1 (0.9)	0	0	1 (0.4)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed 6 months, n (%)	103 (97.2)	116 (100.0)	55 (100.0)	274 (98.9)
Discontinued study prior to month 6, n (%)	3 (2.8)	0	0	3 (1.1)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed study (12 months)	100 (94.3)	112 (96.6)	55 (100.0)	267 (96.4)
Discontinued study prior to month 12, n (%)	6 (5.7)	4 (3.4)	0	10 (3.6)
Unsatisfactory therapeutic effect	1 (0.9)	0	0	1 (0.4)
Subject withdrew consent	1 (0.9)	2 (1.7)	0	3 (1.1)
Lost to follow-up	3 (2.8)	1 (0.9)	0	4 (1.4)
Protocol deviation	1 (0.9)	1 (0.9)	0	2 (0.7)
FAS, N (%)	105 (99.1)	116 (100.0)	55 (100.0)	276 (99.6)
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety, N (%)	106 (100.0)	118 (101.7)[a]	53 (96.4)	277 (100.0)

FAS = full analysis set; n = number of patients with event; N = number of patients; PP = per-protocol analysis set; SD = standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy.

[a] Two patients randomized to vPDT each received one ranibizumab injection prior to month 3.

Note: Percentages are based on the total number of patients in the randomized set.

Source: Clinical Study Report: Table 10-1, p. 123; Table 11-1, p. 126.

TABLE 16: COMPLETE SUMMARY OF EXPOSURE TO STUDY TREATMENTS (SAFETY SET)

	Radiance		
	Group I: Ranibizumab (Stabilization of VA)	Group II: Ranibizumab (Disease Activity)	Group III: vPDT
Number of ranibizumab injections			
Prior to month 3[a]			
N	106	118[b]	53
[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	2.5 (0.57)	1.8 (0.82)	0.0 (0.00)
Median	2.0	2.0	0.0
Prior to month 6[c]			
N	106	118[b]	34
[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	3.5 (1.46)	2.5 (1.56)	1.9 (0.86)
Median	3.0	2.0	2.0
Prior to month 12[c]			
N	106	118[b]	38
[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	4.6 (2.59)	3.5 (2.92)	3.2 (2.54)
Median	4.0	2.5	2.0
Number of vPDT (sham or active) treatments received on day 1			
N	106	118[b]	53
n (type of treatment)	106 (sham)	118 (sham)	53 (active vPDT)
Mean (SD)	1.0 (0.00)	1.0 (0.00)	1.0 (0.00)
Median	1.0	1.0	1.0

n = number of patients with event; N = number of patients; SD = standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy.

[a] [redacted]

[b] [redacted]

[c] [redacted]

Source: Clinical Study Report: Table 12-1, p. 155; Table 12-2, p. 156; Table 12-4, p. 158–159; Table 12-5, p. 159.

TABLE 17: SUMMARY OF vPDT TREATMENTS RECEIVED BY PATIENTS RANDOMIZED TO vPDT GROUP

	Group III: vPDT	
	Group III Patients Who Had Ranibizumab From Month 3 N = 38	Group III Patients Who Did Not Have Ranibizumab From Month 3 N = 15
Total number of vPDT treatments received		
Total	38	17
Mean (SD)	1.0 (0.00)	1.1 (0.35)
Frequency of vPDT re-treatments, n (%)	0	2 (13.3)

n = number of patients with event; N = number of patients; SD = standard deviation; vPDT = verteporfin photodynamic therapy.
Source: Clinical Study Report: Table 14.3-1.4.2, p. 4724.

FIGURE 2: NUMBER OF ACTIVE AND SHAM INJECTIONS IN RANIBIZUMAB GROUP I, BY VISIT AND TREATMENT GROUP (SAFETY SET)

BSL = baseline; M = month.
Source: Clinical Study Report: Figure 12-1, p. 157.

FIGURE 3: NUMBER OF ACTIVE AND SHAM INJECTIONS IN RANIBIZUMAB GROUP II, BY VISIT AND TREATMENT GROUP (SAFETY SET)

BSL = baseline; M = month.
Source: Clinical Study Report: Figure 12-2, p. 157.

TABLE 18: SUBGROUP ANALYSIS OF THE MEAN NUMBER OF RANIBIZUMAB INJECTIONS RECEIVED PRIOR TO MONTH 12 (FULL ANALYSIS SET)

	Radiance			
Subgroup	n	Group I: Ranibizumab (Stabilization of VA) N = 105 Mean (SD)	n	Group II: Ranibizumab (Disease Activity) N = 116 Mean (SD)
Overall	105	4.6 (2.58)	116	3.5 (2.95)
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

BCVA = best corrected visual acuity; CNV = choroidal neovascularization; FAS = full analysis set; LOCF = last observation carried forward; n = number of patients with event; N = number of patients; SD = standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy.
Source: Clinical Study Report: Table 12-8, p. 163.

TABLE 19: MEAN AVERAGE CHANGE FROM BASELINE IN VISUAL ACUITY TO MONTH 1 THROUGH MONTH 3 BY BASELINE CHARACTERISTICS — SUBGROUP ANALYSIS (FULL ANALYSIS SET; MODIFIED LAST OBSERVATION CARRIED FORWARD)

	Radiance					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

TABLE 20: CHANGES FROM BASELINE IN VISUAL ACUITY AT MONTH 3, MONTH 6, AND MONTH 12 (FULL ANALYSIS SET; MODIFIED LAST OBSERVATION CARRIED FORWARD)

	Radiance		
	Group I: Ranibizumab (Stabilization of VA) N = 105	Group II: Ranibizumab (Disease Activity) N = 116	Group III: vPDT N = 55
Baseline, mean (SD)	55.4 (13.43)	55.8 (12.59)	54.7 (13.84)
Month 3			
Value at visit, mean (SD)	67.5 (13.17)	68.3 (12.40)	56.1 (15.44)
Change from baseline, mean (SD)	12.1 (10.18)	12.5 (8.81)	1.4 (12.21)
Month 6			
Value at visit, mean (SD)	69.2 (12.44)	68.4 (13.56)	62.7 (14.65)
Change from baseline, mean (SD)	13.7 (10.16)	12.7 (11.01)	7.9 (10.37)
Month 12			
Value at visit, mean (SD)	69.2 (14.84)	70.1 (12.91)	64.0 (17.30)
Change from baseline, mean (SD)	13.8 (11.42)	14.4 (10.20)	9.3 (11.33)

FAS = full analysis set; LOCF = last observation carried forward; N = number of patients; SD =standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy.
Source: Clinical Study Report: Table 11-10, p. 139.

TABLE 21: CHANGES FROM BASELINE IN VISUAL ACUITY AT MONTH 6 BY BASELINE CHARACTERISTICS — SUBGROUP ANALYSIS (FULL ANALYSIS SET; MODIFIED LAST OBSERVATION CARRIED FORWARD)

	Radiance			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TABLE 21 (CONT'D): CHANGES FROM BASELINE IN VISUAL ACUITY AT MONTH 6 BY BASELINE CHARACTERISTICS —SUBGROUP ANALYSIS (FULL ANALYSIS SET; MODIFIED LAST OBSERVATION CARRIED FORWARD)

	Radiance			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

TABLE 22: CHANGES FROM BASELINE IN VISUAL ACUITY AT MONTH 12 BY BASELINE CHARACTERISTICS — SUBGROUP ANALYSIS (FULL ANALYSIS SET; MODIFIED LAST OBSERVATION CARRIED FORWARD)

	Radiance			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

	Radiance			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

TABLE 23: NUMBER (%) OF PATIENTS WITH SUBRETINAL FLUID (VOLUME SCAN) OF THE STUDY EYE OVER TIME (FAS/LOCF)

Radiance					
Treatment	**Category**	**Baseline n (%)**	**Month 3 n (%)**	**Month 6 n (%)**	**Month 12 n (%)**
Ranibizumab 0.5 mg Group I					
	Definite	37 (35.2)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab 0.5 mg Group II					
	Definite	47 (40.5)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vPDT Group III					
	Definite	19 (34.5)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FAS = full analysis set; LOCF = last observation carried forward; n = number of patients with event; vPDT = verteporfin photodynamic therapy.
Source: Clinical Study Report: Table 11-15, p.146; [redacted]

TABLE 24: NUMBER (%) OF PATIENTS WITH INTRARETINAL EDEMA (VOLUME SCAN) OF THE STUDY EYE OVER TIME (FULL ANALYSIS SET/LAST OBSERVATION CARRIED FORWARD)

Radiance					
Treatment	**Category**	**Baseline n (%)**	**Month 3 n (%)**	**Month 6 n (%)**	**Month 12 n (%)**
Ranibizumab 0.5 mg Group I					
	Definite	89 (84.8)	[redacted]	[redacted]	3 (2.9)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab 0.5 mg Group II					
	Definite	92 (79.3)	[redacted]	[redacted]	5 (4.3)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vPDT Group III					
	Definite	48 (87.3)	[redacted]	[redacted]	1 (1.8)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FAS = full analysis set; LOCF = last observation carried forward; n = number of patients with event; vPDT = verteporfin photodynamic therapy.
Source: Clinical Study Report: Table 11-16, p.147; [redacted].

TABLE 25: NUMBER (%) OF PATIENTS WITH INTRARETINAL CYSTS (VOLUME SCAN) OF THE STUDY EYE OVER TIME (FULL ANALYSIS SET/LAST OBSERVATION CARRIED FORWARD)

Radiance					
Treatment	**Category**	**Baseline n (%)**	**Month 3 n (%)**	**Month 6 n (%)**	**Month 12 n (%)**
Ranibizumab 0.5 mg Group I					
	Definite	29 (27.6)	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ranibizumab 0.5 mg Group II					
	Definite	32 (27.6)	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
vPDT Group III					
	Definite	10 (18.2)	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FAS = full analysis set; LOCF = last observation carried forward; n = number of patients with event; vPDT = verteporfin photodynamic therapy.
Source: Clinical Study Report: Table 11-17, p. 148; [redacted]

TABLE 26: NUMBER (%) OF PATIENTS WITH CHOROIDAL NEOVASCULARIZATION LEAKAGE IN THE STUDY EYE AT BASELINE AND MONTH 12 (FULL ANALYSIS SET/LAST OBSERVATION CARRIED FORWARD)

Radiance			
Treatment	**Category[a]**	**Baseline n (%)**	**Month 12 n (%)**
Ranibizumab 0.5 mg Group I			
	Definite	101 (96.2)	22 (21.0)
	Questionable	1 (1.0)	0
	Absent	1 (1.0)	72 (68.6)
	Other	2 (1.9)	11 (10.5)
	Total	105 (100.0)	105 (100.0)
Ranibizumab 0.5 mg Group II			
	Definite	108 (93.1)	22 (19.0)
	Questionable	0	0
	Absent	1 (0.9)	81 (69.8)
	Other	7 (6.1)	13 (11.2)
	Total	116 (100.0)	116 (100.0)
vPDT Group III			
	Definite	55 (100.0)	16 (29.1)
	Questionable	0	1 (1.8)
	Absent	0	36 (65.5)
	Other	0	2 (3.6)
	Total	55 (100.0)	55 (100.0)

CNV = choroidal neovascularization; FAS = full analysis set; LOCF = last observation carried forward; n = number of patients with event; mg = milligram; vPDT = verteporfin photodynamic therapy.

[a] The category "Other" includes "Can't grade," "Not applicable," and "Missing." Percentages are based on the total number of patients at baseline.

Source: Clinical Study Report: Table 11-18, p. 149.

TABLE 27: CHANGES FROM BASELINE IN QUALITY OF LIFE (NEI-VFQ-25, COMPOSITE SCORE) AT MONTH 3, MONTH 6, AND MONTH 12 (FULL ANALYSIS SET; MODIFIED LAST OBSERVATION CARRIED FORWARD)

	Radiance		
	Group I: Ranibizumab (Stabilization of VA) N = 105	Group II: Ranibizumab (Disease Activity) N = 116	Group III: vPDT N = 55
Month 3			
n	88	91	44
Baseline, mean (SD)	69.3 (17.86)	71.0 (17.77)	71.9 (17.42)
Value at visit, mean (SD)	74.6 (16.81)	75.2 (17.24)	72.2 (18.37)
Change from baseline, mean (SD)	5.3 (13.96)	4.3 (10.09)	0.3 (12.63)
Differences vs. vPDT (95% CI)	5.3 (2.4, 8.3)	4.3 (2.2, 6.4)	0.3 (–3.5, 4.2)
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Month 12			
n	88	96	47
Baseline, mean (SD)	69.3 (17.86)	71.4 (17.55)	71.7 (17.08)
Value at visit, mean (SD)	75.9 (17.23)	76.5 (18.75)	76.5 (16.87)
Change from baseline, mean (SD)	6.6 (15.66)	5.1 (15.83)	4.9 (11.91)
Difference vs. Group I (95% CI)	-	–1.5 (–6.1 to 3.1)	NR

CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; n = number of patients with event; N = number of patients; NEI-VFQ-25 = National Eye Institute Visual Function Questionnaire 25; NR = not reported; SD = standard deviation; VA = visual acuity; vPDT = verteporfin photodynamic therapy; vs. = versus.
Source: Clinical Study Report: Table 14.2-4.7, p. 4198–4200; Table 14.2-4.8 p. 4276; Table 14.2-4.9, p. 4354, 4356.

TABLE 28: CHANGES FROM BASELINE IN QUALITY OF LIFE (EQ-5D, THERMOMETER SCORE) AT MONTH 3, MONTH 6, AND MONTH 12 (FULL ANALYSIS SET; MODIFIED LAST OBSERVATION CARRIED FORWARD)

	Radiance		
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

TABLE 29: CHANGES FROM BASELINE IN WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT (WPAI:GH, TOTAL SCORE) AT MONTH 3, MONTH 6, AND MONTH 12 (FULL ANALYSIS SET; MODIFIED LAST OBSERVATION CARRIED FORWARD)

	Radiance		
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

[redacted]

FAS = full analysis set; LOCF = last observation carried forward; WPAI:GH = Work Productivity and Activity Impairment Questionnaire: General Health.

TABLE 30: NUMBER (%) OF PATIENTS WITH OCULAR ADVERSE EVENTS OF THE STUDY EYE UP TO MONTH 12 (SAFETY SET)

	Radiance			
	Group I: Ranibizumab (Stabilization of VA) (N = 106)	Group II: Ranibizumab (Disease Activity) (N = 118)	Group III: vPDT	
			With Ranibizumab From Month 3 (N = 38)	Without Ranibizumab From Month 3 (N = 15)
Total	46 (43.4)	44 (37.3)	16 (42.1)	4 (26.7)
Conjunctival hemorrhage	12 (11.3)	12 (10.2)	2 (5.3)	0
Punctate keratitis	8 (7.5)	3 (2.5)	2 (5.3)	0
Vitreous floaters	5 (4.7)	1 (0.8)	0	0
Dry eye	4 (3.8)	2 (1.7)	0	1 (6.7)
Eye pain	4 (3.8)	4 (3.4)	1 (2.6)	1 (6.7)
Injection site hemorrhage	3 (2.8)	3 (2.5)	2 (5.3)	0
Intraocular pressure increased	3 (2.8)	7 (5.9)	4 (10.5)	0
Blepharitis	2 (1.9)	2 (1.7)	0	0
Conjunctivitis	2 (1.9)	1 (0.8)	0	0
Eyelid edema	2 (1.9)	0	0	0
Retinal tear	2 (1.9)	1 (0.8)	0	0
Cataract	1 (0.9)	2 (1.7)	0	1 (6.7)
Conjunctivitis allergic	1 (0.9)	5 (4.2)	1 (2.6)	0
Ocular hyperaemia	1 (0.9)	2 (1.7)	1 (2.6)	0
Retinal hemorrhage	1 (0.9)	3 (2.5)	0	0
Metamorphopsia	0	3 (2.5)	0	0
Visual impairment	0	0	2 (5.3)	0

N = number of patients; VA = visual acuity; vPDT = verteporfin photodynamic therapy.
Source: Clinical Study Report: Table 12-11, p. 167.

TABLE 31: NUMBER (%) OF PATIENTS WITH NON-OCULAR ADVERSE EVENTS UP TO MONTH 12 (SAFETY SET)

	Radiance			
	Group I: Ranibizumab (Stabilization of VA) (N = 106)	Group II: Ranibizumab (Disease Activity) (N = 118)	Group III: vPDT	
			With Ranibizumab From Month 3 (N = 38)	Without Ranibizumab From Month 3 (N = 15)
Total	48 (45.3)	51 (43.2)	19 (50.0)	5 (33.3)
Nasopharyngitis	12 (11.3)	12 (10.2)	1 (2.6)	2 (13.3)
Headache	8 (7.5)	11 (9.3)	1 (2.6)	0
Hypertension	3 (2.8)	5 (4.2)	3 (7.9)	0
Upper respiratory tract infection	3 (2.8)	4 (3.4)	1 (2.6)	0
Urinary tract infection	3 (2.8)	3 (2.5)	0	0
Abdominal pain	3 (2.8)	1 (0.8)	0	0
Back pain	2 (1.9)	4 (3.4)	0	0
Influenza	2 (1.9)	4 (3.4)	1 (2.6)	0
Bacteriuria	2 (1.9)	0	0	0
Diabetes mellitus	2 (1.9)	1 (0.8)	1 (2.6)	0
Intervertebral disc protrusion	2 (1.9)	0	0	0
Migraine	2 (1.9)	1 (0.8)	1 (2.6)	0
Nausea	2 (1.9)	1 (0.8)	1 (2.6)	0
Osteoporosis	2 (1.9)	0	0	0
Pain in extremity	2 (1.9)	1 (0.8)	0	1 (6.7)
Pharyngitis	2 (1.9)	0	0	0
Toothache	2 (1.9)	1 (0.8)	0	0
Vomiting	2 (1.9)	1 (0.8)	0	0
Arthralgia	1 (0.9)	2 (1.7)	0	0
Bronchitis	1 (0.9)	4 (3.4)	1 (2.6)	0
Cough	1 (0.9)	2 (1.7)	1 (2.6)	0
Cystitis	1 (0.9)	1 (0.8)	2 (5.3)	0
Hypercholesterolemia	1 (0.9)	2 (1.7)	0	0
Sciatica	1 (0.9)	2 (1.7)	0	0
Tendonitis	1 (0.9)	2 (1.7)	0	0
Dental caries	0	2 (1.7)	0	1 (6.7)
Fatigue	0	2 (1.7)	0	0
Hemorrhoids	0	2 (1.7)	0	0
Hyperglycemia	0	2 (1.7)	0	0
Hyperlipidemia	0	2 (1.7)	0	0
Seasonal allergy	0	2 (1.7)	0	0
Tinnitus	0	2 (1.7)	0	1 (6.7)
Tooth disorder	0	2 (1.7)	0	0
Urticaria	0	2 (1.7)	0	0

N = number of patients; VA = visual acuity; vPDT = verteporfin photodynamic therapy.
Source: Clinical Study Report: Table 12-14, p. 170.

TABLE 32: NON-OCULAR SERIOUS ADVERSE EVENTS UP TO MONTH 12 (SAFETY SET)

	Radiance			
	Group I: Ranibizumab (Stabilization of VA) (N = 106)	Group II: Ranibizumab (Disease Activity) (N = 118)	Group III: vPDT	
			With Ranibizumab From Month 3 (N = 38)	Without Ranibizumab From Month 3 (N = 15)
Total	6 (5.7)	5 (4.2)	0	0
Breast cancer in situ	1 (0.9)	0	0	0
Depression	1 (0.9)	0	0	0
Gastritis erosive[a]	1 (0.9)	0	0	0
Gastrointestinal hemorrhage[a]	1 (0.9)	0	0	0
Hepatic function abnormal	1 (0.9)	0	0	0
Joint dislocation	1 (0.9)	0	0	0
Myocarditis	1 (0.9)	0	0	0
Atrial tachycardia	0	1 (0.8)	0	0
Lung adenocarcinoma	0	1 (0.8)	0	0
Renal failure chronic	0	1 (0.8)	0	0
Spinal column stenosis	0	1 (0.8)	0	0
Subdural hematoma	0	1 (0.8)	0	0

N = number of patients; VA = visual acuity; vPDT = verteporfin photodynamic therapy.
Source: Clinical Study Report: Table 12-41, p. 186.

APPENDIX 4: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures used in the RADIANCE study.

- Visual acuity measurement: Snellen charts and the Early Treatment Diabetic Retinopathy Study (ETDRS) Letters score
- National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ-25)
- EuroQoL (Quality of Life)–5 Dimensions Questionnaire (EQ-5D)
- Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH)

Findings

TABLE 33: VALIDITY AND MCID OF OUTCOME MEASURES FOR MYOPIC CNV

Instrument	Type	Validated	MCID	References
ETDRS letters	ETDRS charts present a series of 5 letters of equal difficulty on each row, with standardized spacing between letters and rows; a total of 14 lines (70 letters).[14]	Yes	10 to 15 letters	[15,32]
NEI-VFQ-25	The NEI-VFQ was developed as a means to measure vision-targeted quality of life.[33] The NEI-VFQ-25 is a shortened version of the NEI-VFQ[18] and includes 25 items relevant to 11 vision-related constructs, in addition to a single-item general health component.	Yes	4 points	[18]
EQ-5D	The EQ-5D is a generic QoL instrument consisting of 5 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.[21,22]	No	None	NA
WPAI:GH	The WPAI:GH was designed to measure work productivity and the ability to perform regular activities. It consists of 6 questions related to current employment status, the number of hours worked and missed from work, and the extent to which productivity and the ability to do regular daily activities has been affected by health problems over the past 7 days.[24]	No	None	NA

CNV = choroidal neovascularization; EQ-5D = EuroQoL (Quality of Life) Questionnaire–5 Dimensions; ETDRS = Early Treatment Diabetic Retinopathy Study; MCID = minimal clinically important difference; NA = not applicable; NEI-VFQ = National Eye Institute Visual Function Questionnaire; NEI-VFQ -25 = National Eye Institute Visual Function Questionnaire 25; QoL = quality of life; VAS = visual analogue scale; WPAI:GH = Work Productivity and Activity Index Questionnaire: General Health.

Measuring Visual Acuity

Snellen Eye Chart: The Snellen eye chart is a commonly employed, well-recognized test of visual acuity in clinical practice.[14,34] The chart presents a series of letters of decreasing size, with an increasing number of letters on subsequent lines. One or two mistakes per line are allowed and the smallest line that can be read corresponds to visual acuity. The resultant measure of visual acuity is expressed as a

Snellen fraction, in which the numerator indicates the distance at which the chart was read, and the denominator the distance at which a person may discern letters of a particular size. A larger denominator indicates worsening vision. For example, a person with 20/100 vision can read letters at 20 feet that a person with 20/20 vision could read at 100 feet. Snellen acuity may also be expressed in metric units. As 20 feet is roughly equivalent to 6 m, 20/20 vision may be expressed 6/6, or 20/100 as 6/30. Snellen fractions may be expressed as decimal acuity where 20/20 is expressed as 1.00 and 20/100 as 0.2. Further, the logarithm of the reciprocal Snellen fraction may be calculated to produce a linear scoring system suitable for statistical analysis; Snellen fractions of 20/20 and 20/100 would correspond to log scores of 0.0 and 0.7, respectively.

A number of limitations of the Snellen charts, especially for clinical research, have been identified.[14,34] Specifically, this includes the use of letters with different difficulty scores (e.g., A and L are more easily discernible than B E, and F) and an unequal number of letters on each line, which allows for different percentage errors depending on the line read and number of errors made.[34] In addition, the change in letter size between chart lines is not uniform; thus, moving from line 20/25 to 20/20 represents a 20% improvement, compared with a 16% improvement when moving from line 20/30 to 20/25. Finally, differences in background luminance between charts, due to aging or to different manufacturers, and the use of dusty or aging projector equipment can reduce contrast and may result in unreliable measures of visual acuity.[34]

Early Treatment Diabetic Retinopathy Study Letters: In response to the above limitations, alternative charts have been developed that are more appropriate in research.[14,34] The ETDRS charts are based on a design by Bailey and Lovie, and are commonly used in clinical research.[14,35-38] ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between letters and rows, for a total of 14 lines (70 letters). An ETDRS letter score can be calculated as follows: when 20 or more 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 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 line 1.0) plus the total number of letters read correctly at 1.0 m in the first six lines. Therefore, the ETDRS letter score could result in a maximum of 100.[25,39] 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.[14,40] Letters range from 58.18 mm to 2.92 mm in height, corresponding to Snellen visual acuity fractions of 20/200 to 20/10, respectively. Further, letter size increases geometrically and equivalently in every line by a factor of 1.2589 (or 0.1 log unit) moving up the chart. Scoring for EDTRS 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. Holladay and Prager published the following formula to convert visual acuity scores derived from a Bailey-Lovie-style chart read at 2 m into a Snellen denominator, where X is the number of correctly read letters (see below).[41] Thus, reading all 70 letters on a Bailey-Lovie chart corresponds to a Snellen visual acuity of 20/10.

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

Minimal Clinically Important Difference: To our knowledge, there has been no derivation of a minimal clinically important difference (MCID) for the ETDRS in myopic choroidal neovascularization (mCNV). Clinical trials assessing interventions for mCNV 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.[42] For other vision disorders such as macular edema, the FDA recommends a mean

change of 15 letters or more on an ETDRS chart, or a statistically significant difference in the proportion of patients with ≥ 15-letter change in visual acuity, as clinically relevant outcomes in trials.[15] 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 trials. 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.[43]

The test–retest variability (TRV) of the measure can help to guide what would be considered a clinically meaningful change. Literature-based estimates of TRV range from ± 0.07 logMAR to ± 0.19 logMAR.[32] 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 just due to chance alone. When TRV is high, the ability to detect a real change in score is low. For example, for a TRV of ± 0.19 logMAR, the sensitivity of a 0.1 logMAR change (5 letters) was 4% (0% to 14%). If the TRV is lowered to ± 0.11 logMAR, the sensitivity of the test increases to 38% (25% to 53%). If the TRV remains at ± 0.11 logMAR, and the threshold for change increases to a 0.2 logMAR (10 letters) 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[25] and as a result will also affect what would reasonably be considered an MCID. A TRV of ± 0.11 logMAR has been found in healthy participants,[32] while higher levels of variability (± 0.15 logMAR to ± 0.20 logMAR) have been cited for individuals with pathological changes in vision.[44] Eyes with acuity better than 20/100 and a change in visual acuity of ≥ 5 letters have > 90% probability of being a real change, while for eyes worse than 20/100, a change of ≥ 10 letters is required for the same reliability.[16] A cut point for clinically meaningful change in patients with advanced eye disease should be higher than in healthy individuals, and has been suggested to range between 10 and 15 letters.[17] The studies contributing to this discussion are summarized in Table 34 below.

TABLE 34: LITERATURE ASSESSING THE INTERPRETABILITY OF CHANGES IN ETDRS SCORES

Study	Population	Methods/Results	Key Findings	Strengths (S)/ Limitations (L)
Rosser et al. 2003[32]	n = 50 (healthy volunteers) **Age**: < 50 years **Snellen Acuity Measure**: ≥ 6/9 (20/30) **Other:** No ocular abnormalities or cognitive difficulties.	**Methods:** 1. TRV was assessed using 2 different ETDRS charts at 4 m. 2. Participants were tested for VA across varying distances to simulate real changes to visual acuity. **Results**: TRV ± 0.11 logMAR (literature values ranged from ± 0.07 logMAR to ± 0.19 logMAR). 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), which suggests 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 logMAR to ± 0.19 logMAR. 3. At higher levels of TRV, sensitivity of the ETDRS for detecting change is lower; sensitivity to detect >	S: TRV measure is mid-range compared with literature-based values. L: Sensitivity and specificity were not based on comparisons to other measures of change (VA or QoL).

Study	Population	Methods/Results	Key Findings	Strengths (S)/ Limitations (L)
			0.30 logMAR is high. 4. Specificity is high for all TRVs.	
Beck et al. 2007[16]	8 clinical trials reporting a change in VA as an outcome measure.	**Discussion of analytical methods:** Binary outcome variable: lose information, misclassifying outcome, floor/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 trials reported ranges of 6% to 32% differences between treatment and control groups for % of people with ≥ 15-letter worsening from baseline. This equated to a 2.9 to 19.4 mean difference between treatment and control groups for change in letter score from baseline. 2. Created artificial biases to show the effects of evaluating the significance of change in outcomes when using a binary outcome variable.	L: Non-systematic review of the literature. L: Used hypothetical biases to demonstrate effects.
Csaky et al. 2008[43]	Scientists, clinicians, and researchers (symposium held by NIH and FDA).	**Methods**: Round table discussion on VA as an outcome measure. **Two topics for discussion:** 1. Identifying an alternative to the most commonly used cut point of 3 line gains/losses on eye charts for classifying outcomes. 2. Relationship between statistically and clinically significant differences.	Four representatives provided opinions on the 2 topics of discussion: 1. Question raised about using a lower than 15 letter change score in clinical trials. 2. Concern that up to a 15-letter change may not represent a real change. 3. Change score may depend on how rapidly disease progression occurs. 4. Standardization is important.	L: No discussion of representation of participants. L: Opinion-based discussion.
Beck et al. 2003[25]	n = 251 (patients undergoing treatment, of whom 20% had normal vision and 80% had a vision-related clinical diagnosis)	**Methods:** Test–retest reliability of ETDRS was done with back-to-back testing by the same technician. **Results:** 98% of patients had results of their repeat test within 10 letters (0.2 logMAR); 87% were within 5 letters (0.1 logMAR). For patients with a	1. Test–retest reliability varied according to the participant's baseline VA.	L: Repeat test was completed immediately after first test. There is a risk of bias for remembering the sequence of letters.

Study	Population	Methods/Results	Key Findings	Strengths (S)/ Limitations (L)
	Age: 50 years (± 22) **VA:** 20/20: 21%; 20/20 to 20/40: 29%; 20/40 to 20/100: 30%; < 20/100: 20%	baseline VA < 20/100, 83% of patients were within 5 letters (0.1 logMAR) after retest.		
Kiser et al. 2005[17]	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 retinal 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 ETDRS (under dim 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 VA has truly changed. **Results**: Healthy controls (CR.95 ranged from 0.092 to 0.15); low-vision participants (CR.95, 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.	L: Very few patients within each eye disease group. L: Subjects are very low vision (defined as legally blind).

CR = coefficient of repeatability; ETDRS: Early Treatment Diabetic Retinopathy Study; L = limitations; logMAR = logarithmic minimal angle of resolution; n = number of patients with event; N = number of patients; NIH = National Institutes of Health; QoL = quality of life; S = strengths; TRV = test-retest variability; VA = visual acuity.
Note: logMAR of 0.10 = 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 ETDRS charts are commonly used to assess treatment outcomes in clinical studies. A loss of ≥ 3 lines (≥ 15 letters) on an ETDRS chart corresponds to a doubling of the visual angle and is considered moderate visual loss, while a loss of ≥ 6 lines (≥ 30 letters) corresponds to a quadrupling of the visual angle and is considered severe. However, visual acuity is only one component contributing to overall visual function — the ability to perform everyday visual tasks (e.g., reading, recognizing faces, driving, and using the telephone). Overall visual function also depends upon variables such as contrast sensitivity, near vision, colour vision, and sensitivity to glare.[45] The various components of visual function will affect the performance of different vision-related tasks by varying degrees. For example, use of distance acuity to measure the success of treatments for age-related macular degeneration (AMD) is not optimal, given that distance vision is usually two ETDRS lines better than reading vision,[42] and difficulty with reading is a common complaint among persons with eye disease.[33] Rather, contrast sensitivity is a more important contributor to reading performance.[42,46]

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 on the value individuals place upon the ability to perform specific tasks. Quality-of-life instruments that do not include domains or tasks that are of importance to individuals will lack sensitivity to changes. Further, the impact of vision loss 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.[45]

National Eye Institute Visual Function Questionnaire

The National Eye Institute Visual Function Questionnaire (NEI-VFQ) was developed as a means to measure vision-targeted quality of life. The original 51-item questionnaire was developed based on focus groups consisting of persons with a number of common eye conditions (e.g., age-related cataracts, AMD, and diabetic retinopathy), and thus may be used to assess quality of life in a broad range of eye conditions.[33] 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.[19]

A shorter version of the original instrument, the NEI-VFQ-25, was subsequently developed, which retains the multidimensional nature of the original and is more practical and efficient to administer.[18,19] With the exception of expectations for future vision, all constructs listed for the NEI-VFQ were retained in the shortened version, with a reduced number of items within each. Thus, the NEI-VFQ-25 includes 25 items relevant to 11 vision-related constructs, in addition to a single-item general health component. Responses for each item are converted to a 0 to 100 scale, with 0 representing the worst and 100 the best visual functioning. Items within each construct, or subscale, are averaged to create 12 subscale scores, and averaging of the subscale scores produces the overall composite score. Different scoring approaches for the NEI-VFQ-25 have been proposed.[47] Rasch modelling is used to obtain measurements from categorical data. When comparing standard scoring to Rasch analysis and an algorithm to approximate Rasch scores, all methods were highly correlated.[47] 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.[47]

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 trials, and corresponding changes in the NEI-VFQ are suggested as clinically meaningful endpoints. Specifically, for the study eye, which is typically the worse seeing eye, a 15-letter change in visual acuity corresponds to a 4-point change in overall NEI-VFQ-25 score.[20] For the better seeing eye, the clinically relevant difference for NEI-VFQ-25 scores based on a three-line change is 7 to 8 for overall score. Other studies have shown similar estimated clinically relevant differences.[48] The instrument showed weaker correlation or was not responsive to changes in the visual acuity of the worse eye.[49,50] 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[18,19,50] 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.[49,50] However, more recent studies have indicated that the NEI-VFQ measures visual functioning, not quality of life.[51] 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.[51,52] 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.[51,52] Re-engineering the NEI-VFQ into two constructs (visual functioning and socioemotional 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.[51,52] Considering this recent evidence of multidimensionality, the validity of the single composite score of the NEI-VFQ may be questioned.

EuroQoL (Quality of Life)–5 Dimensions Questionnaire

The EQ-5D is a generic quality-of-life (QoL) instrument that may be applied to a wide range of health conditions and treatments.[21,22] 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.[21,22] 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:

- A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- A population preference-weighted health index score based on the descriptive system
- 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 lower than 0 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.[23]

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 et al. in 2014.[53] The EQ-5D was the most commonly used generic quality-of-life measure for vision-related studies. The identified studies included patients with glaucoma, AMD, cataracts, diabetic retinopathy, conjunctivitis, and other eye conditions. The ability of the EQ-5D to distinguish between visual acuity groups varied according to type of visual disorder, as did the construct validity of the EQ-5D with measures of visual acuity.[53] 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.[53]

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; 3-% > 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 Activity Inventory (AI) was normally distributed with a mean of 0.63.[54] 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 AI.[54] 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 mCNV or in other vision-related disorders.

Work Productivity and Activity Impairment Questionnaire: General Health

The WPAI:GH was designed to assess the impact of therapeutic interventions on work productivity and the ability to perform regular activities.[24] The questionnaire consists of six questions related to current employment status, the number of hours worked and missed from work over the past seven days, and the extent to which productivity and the ability to do regular daily activities has been affected by health problems over the past seven days. The impact of health problems on productivity and the ability to do regular activities is measured on a scale of 0 to 10, with 0 representing "Health problems had no effect on my work (or activities)" and 10 representing "Health problems completely prevented me from working (or doing my daily activities)." Four main outcome scores can be calculated and expressed as percentages: level of absenteeism from work; level of impairment at work; overall impairment at work; and level of impairment with regular activities.[24]

The WPAI:GH was initially validated in a group of 106 employed individuals, between 30 and 50 years old.[24] The scale has since been adapted for use in various disease areas such as diabetes mellitus[55] and rheumatoid arthritis,[56,57] and has been translated and validated for use in various languages.[58-60] No studies have been found that use the WPAI:GH as an outcome measure for assessing the effectiveness of therapeutic interventions for vision-related disorders. Therefore, no MCID exists for this measure.

Conclusion

The validity of the ETDRS chart, NEI-VFQ-25, EQ-5D), WPAI:GH questionnaire, and the relationship between visual acuity, visual function, and quality of life were reviewed.

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 trials. Given the range of test–retest variability of the scale according to baseline visual acuity, a range of 10 to 15 letters may be a more appropriate MCID.

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 be more appropriately identified as a measure of visual functioning. The NEI-VFQ has a reported MCID of 4 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 this population 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 mCNV. An appropriate MCID for use in studies assessing therapeutic interventions for eye disorders is unknown.

The WPAI:GH is a useful measure to assess changes in work productivity and activity impairment in therapeutic intervention studies. It has been adapted for use in many disease areas including diabetes mellitus and rheumatoid arthritis; however, no adaptation has been made for use in studies for vision-related therapeutic interventions. The psychometric properties and MCID for the WPAI:GH in vision-related disorders is unknown.

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