CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

Brolucizumab (BEOVU)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Treatment of Neovascular (wet) Age-Related Macular Degeneration (AMD)

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

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Abbreviations

AE	adverse event
AMD	age-related macular degeneration
ANOVA	analysis of variance
BCVA	best-corrected visual acuity
CATT	Comparison of AMD Treatments Trials
CNIB	Canadian National Institute for the Blind
CNV	choroidal neovascularization
CrI	credible interval
CRT	central retinal thickness
CSFT	central subfield thickness
DIC	diagnostic information criterion
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	full analysis set
HRQoL	health-related quality of life
IRC	intraretinal cyst
IRF	intraretinal fluid
ITC	indirect treatment comparison
IVT	Intravitreal
LOCF	last observation carried forward
nAMD	neovascular age-related macular degeneration
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire–25
OCT	optical coherence tomography
PPS	per-protocol analysis set
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
SE	standard error
SRF	subretinal fluid
SF-36	Short Form (36) Health Survey
TD-OCT	time-domain optical coherence tomography
VEGF	vascular endothelial growth factor

Drug	Brolucizumab (BEOVU)
Indication	Pre-NOC proposed: Treatment of neovascular (wet) age-related macular degeneration (AMD)
Reimbursement request	As per indication
Dosage form(s) and route of administration)/strength(s)	120 mg/mL solution for intravitreal injection in single-use, pre-filled syringe
NOC date	March 12, 2020
Manufacturer	Novartis Pharmaceuticals Canada Inc.

Executive Summary

Introduction

Age-related macular degeneration (AMD) is a degenerative disease of the macula. In Canada, it affects approximately 2 million people. In North America, it is the leading cause of vision loss in people older than 50 years. There are two basic types of AMD: dry and neovascular (wet). Neovascular AMD (nAMD) is a chronic degenerative eye disease characterized by the formation of abnormal blood vessels underneath the central retina (macula) that can lead to progressive, irreversible vision loss. The majority of patients (90%) develop dry AMD, but those with nAMD account for more than 90% of advanced vision loss due to AMD. In 2004, it was estimated that there were 17,100 new nAMD cases in Canada (2004 population: 32.5 million).

Anti–vascular endothelial growth factor (anti-VEGF) therapies represent the gold standard of care for nAMD as recommended in international guidelines. In Canada, ranibizumab and aflibercept are indicated by Health Canada as anti-VEGF drugs for the treatment of nAMD. In addition, bevacizumab is commonly used in practice as an anti-VEGF drug without a Health Canada indication.

Brolucizumab is a humanized, monoclonal, single-chain variable fragment antibody directed against human VEGF.

The objective of this review is to perform a systematic review of the beneficial and harmful effects of brolucizumab for the treatment of nAMD. The systematic review protocol for the current review was established prior to the anticipated issuance of the Health Canada Notice of Compliance for brolucizumab, expected on March 12, 2020. The expected recommended dose for brolucizumab is 6 mg (50 µL) administered by intravitreal (IVT) injection every four weeks for the first three doses and every 12 weeks thereafter.

Stakeholder Engagement

Patient Input

CADTH received one joint patient group submission, which was prepared jointly by Fighting Blindness Canada, the Canadian Council of the Blind, the Canadian National Institute for the Blind (CNIB) Foundation, and Vision Loss Rehabilitation Canada. Half of respondents with nAMD considered their disease to be “very serious.” The submission noted that

respondents thought about the disease frequently despite the relatively long periods of time between treatments (monthly or once every two months injections). Respondents with nAMD indicated that the following activities were difficult or impossible to do: reading (65% of respondents), driving (46%), interacting with others (37%), navigating public spaces (23%), travelling (21%), cooking (16%), interacting online (15%), interacting socially (13%), doing housework (11%), and networking (6%). Just under a fifth of respondents (18%) indicated that there were no activities they found difficult or could no longer do.

Patients were generally satisfied with their current treatment for nAMD, with 50% saying they were "very satisfied," 40% "fairly satisfied," 10% "neither satisfied nor unsatisfied," and 1% "fairly unsatisfied." However, 64% of respondents also indicated "yes" when asked if a treatment that could be taken less often would be preferred. No other information was presented on any other unmet needs with current treatment. Although patients were polled on whether they were aware of alternative medications or treatment (70% indicated "no"), additional expectations for improved treatment were not reported, other than the potential prospect of a curative stem cell therapy in the future and a cheaper alternative to Lucentis, an existing anti-VEGF treatment.

Clinician Input

The central treatment goal is to stabilize and/or improve vision. Improving or maintaining driving vision is desirable for all patients, as this can improve or stabilize quality of life (QoL) and reduce the chance of crashes, thereby reducing the possibility of fractures and loss of independence. Given that treatment with anti-VEGF drugs requires repeated administration to maintain or improve vision, clinicians also aim to reduce the burden of follow-up visits and treatment visits while improving vison and preserving and enhancing vision-related QoL.

Currently, some patients can become refractory to treatment. Increasing the number of available treatment options may prove useful to such patients. Also, there is a strong need for a treatment option that reduces the need for frequent follow-ups and injections.

Brolucizumab is an anti-VEGF. As such, it has the same mechanism of action as other anti-VEGFs available on the market. However, the indicated regimen for brolucizumab is once every 12 weeks after the loading phase, which would make it the only indicated anti-VEGF with such an extended period. The current paradigm of care will be altered dramatically if fewer visits and treatments are required and if visual acuity and function are optimized. The treatment burden on patients and caregivers will be reduced, and a reduction in direct medical costs per patient will be achieved.

The appropriate target patient population for brolucizumab would be treatment-naive patients who have recently been diagnosed with nAMD. Acute nAMD patients who are symptomatic and have early and small (in size) neovascular lesions would be excellent candidates for treatment with brolucizumab.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two studies met the inclusion criteria for this systematic review: HAWK and HARRIER. Both were phase III, noninferiority, multi-centre, double-masked, active-controlled, parallel,

randomized trials. Both lasted a total of 96 weeks. In HAWK, 1,082 patients with nAMD were randomized in a 1:1:1 ratio to brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg. Given that only the 6 mg dose is recommended by Health Canada, this review does not include results for the brolucizumab 3 mg treatment group. In HARRIER, 743 patients with nAMD were randomized in a 1:1 ratio to brolucizumab 6 mg or aflibercept 2 mg. All patients received three monthly loading IVT injections followed by maintenance doses every 12 weeks for brolucizumab and every eight weeks for aflibercept. Patients receiving brolucizumab every 12 weeks could be permanently switched to an injection frequency of every eight weeks if an investigator determined the presence of continuous disease activity based on pre-specified criteria.

Both studies aimed to establish the noninferiority of brolucizumab 6 mg to aflibercept 2 mg through the primary outcome of the change in best-corrected visual acuity (BCVA) from baseline to week 48 and through a key secondary outcome of change in BCVA from baseline to the average BCVA of week 35 to week 48. The noninferiority margin was specified as four letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. The end point was analyzed using a pairwise analysis of variance (ANOVA) model, including treatment, baseline BCVA categories (≤ 55 letters, 56 to 70 letters, or ≥ 71 letters), and age categories (< 75 years or ≥ 75 years) as factors. In addition, HAWK included a statistical hierarchy and an alpha spending method to control for multiple testing and allow for additional secondary outcomes testing. Secondary outcomes included measures for retinal thickness, retinal fluids, and health-related QoL.

Overall, patients randomized into the treatment arms had similar baseline characters within each study and across studies in terms of age, gender, number of eyes affected, BCVA, and central subfield thickness. HARRIER had a higher proportion of white patients compared to HAWK and a greater proportion of patients with a disease duration of more than three months. Within the HARRIER study, there was a higher proportion of patients with subretinal fluid in the aflibercept arm compared to the brolucizumab arm (72.6% versus 67.8%).

Efficacy Results

Between-treatment differences in both studies were within the noninferiority margin. In HAWK, the mean difference of brolucizumab 6 mg versus aflibercept 2 mg for the primary outcome of change in BCVA from baseline to week 48 was –0.2 (95% confidence interval [CI], –2.1 to 1.8); in HARRIER, it was –0.7 (95% CI, –2.4 to 1.0). Sensitivity analyses reported by the sponsor show similar results to the base case. Results at week 96 indicate that the improvement reported at week 48 was maintained. An assessment of the proportion of patients at week 48 who gained greater than or equal to 15 letters from baseline or had a BCVA of greater than or equal to 84 letters at week 48 showed a higher numerical proportion in brolucizumab 6 mg (33.6%) than aflibercept 2 mg (25.4%) in HAWK. However, these results are numerically similar in HARRIER, with 29.3% for brolucizumab 6 mg and 29.9% for aflibercept 2 mg. On the other hand, the proportion of patients with greater than or equal to 15 letters' loss from baseline at week 48 was similar within and across trials, with 6.4% and 3.8% in the brolucizumab 6 mg groups in HAWK and HARRIER, respectively, and 5.5% and 4.8% in the aflibercept groups in HAWK and HARRIER, respectively.

Anatomical-related outcomes (such as retinal thickness) and the proportion of patients with subretinal or intraretinal fluids showed statistically significant improvements in patients treated with 6 mg of brolucizumab compared to those treated with aflibercept in the HAWK

study at week 48. These findings are supported numerically by the results in the HARRIER study. Other outcomes show numerically similar results for the brolucizumab and aflibercept groups within and across studies, including for the reported health-related quality of life (HRQoL) measure, the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) composite score.

By the end of the first year, almost half of the patients randomized to brolucizumab had been switched to receiving treatment once every eight weeks while the rest continued to receive treatment once every 12 weeks. The majority of the patients who were switched to receiving treatment every eight weeks were identified at week 16 and week 20. From baseline to week 48, the mean numbers of active injections received by patients in the brolucizumab groups were 6.2 in HAWK and 6.4 in HARRIER, while patients in the aflibercept group received 6.8 in HAWK and 6.9 in HARRIER.

Harms Results

Overall, and up until 96 weeks, ocular adverse events (AEs) were reported by 61.6% and 55.8% of patients in HAWK in each of the brolucizumab 6 mg and aflibercept 2 mg arms. In HARRIER, these proportions were 47.0% and 47.7% in each of the brolucizumab 6 mg and aflibercept 2 mg arms. Ocular serious adverse events (SAEs) were experienced by a numerically higher proportion in the brolucizumab arms compared to the aflibercept arms in both studies. Specifically, of patients who received brolucizumab 6 mg treatment, 3.3% and 3.5% experienced at least one ocular SAE in HAWK and HARRIER, respectively. Among patients who received aflibercept, 1.4% and 1.6% experienced at least one ocular SAE, respectively. The most common ocular SAEs in the brolucizumab arms were endophthalmitis, uveitis, retinal tear, and retinal pigment epithelial tear. Non-ocular SAEs were experienced in a numerically higher proportion of patients in the aflibercept arms in both studies compared with the brolucizumab arms. Specifically, of patients who received aflibercept 2 mg, 30.6% and 23.0% experienced at least one non-ocular SAE in HAWK and HARRIER, respectively. Among patients who received brolucizumab 6 mg treatment, 23.6% and 18.6% experienced at least one ocular SAE. There was no cluster of any specific non-ocular SAE. The most common non-ocular SAE was pneumonia.

Table 1: Summary of Key Results From Pivotal and Protocol Selected Studies

	Total N	Baseline	End-of-treatment time point	Treatment group difference versus control		
		Mean (SD)	Mean change from baseline (SD)	Mean difference (95% CI)[a]	P value (treatment difference)	P value (noninferiority)
BCVA change from baseline at week 48 (FAS – LOCF)						
HAWK						
Brolucizumab 6 mg	360	60.8 (13.66)	6.4 (14.40)	–0.2 (–2.1 to 1.8)	0.8695	< 0.001
Aflibercept 2 mg	360	60.0 (13.92)	7.0 (13.16)	REF	REF	REF
HARRIER						
Brolucizumab 6 mg	370	61.5 (12.59)	6.9 (11.47)	–0.7 (–2.4 to 1.0)	0.4199	< 0.001
Aflibercept 2 mg	369	60.8 (12.93)	7.6 (12.47)	REF	REF	REF
	Total N		**n (%)**	**Difference (95% CI)**	**P value[a]**	
Patients with ≥ 15 letters gain from baseline or BCVA of ≥ 84 letters at week 48 (FAS – LOCF)						
HAWK						
Brolucizumab 6 mg	360		119 (33.6)	8.2 (2.2 to 15.0)	0.0136[a]	
Aflibercept 2 mg	360		93 (25.4)	REF	REF	
HARRIER						
Brolucizumab 6 mg	370		109 (29.3)	–0.6 (–7.1 to 5.8)	0.8600[a]	
Aflibercept 2 mg	369		110 (29.9)	REF	REF	
Patients with ≥ 15 letters loss from baseline at week 48 (FAS – LOCF)						
HAWK						
Brolucizumab 6 mg	360		23 (6.4)	0.9 (–2.7 to 4.3)	0.6198[a]	
Aflibercept 2 mg	360		20 (5.5)	REF	REF	
HARRIER						
Brolucizumab 6 mg	370		14 (3.8)	–1.0 (–3.9 to 2.2)	0.5079[a]	
Aflibercept 2 mg	369		18 (4.8)	REF	REF	
	Total N	**Baseline**	**End-of-treatment time point**			
		Mean (SD)	**N**	**Mean (SD)**	**Mean change from baseline (SD)**	
NEI VFQ-25 composite score: change from baseline week 48 (FAS – Observed)						
HAWK						
Brolucizumab 6 mg	358	77.4 (15.90)	324	81.6 (15.02)	4.1 (12.58)	
Aflibercept 2 mg	359	77.0 (16.39)	317	81.6 (15.45)	4.5 (10.64)	
HARRIER						
Brolucizumab 6 mg	368	74.6 (17.32)	347	79.7 (16.14)	4.8 (11.57)	
Aflibercept 2 mg	369	76.0 (17.02)	346	80.2 (15.91)	3.6 (11.88)	

	Total N	Baseline	End-of-treatment time point	Treatment group difference versus control[a]		
		Mean (SD)	Mean change from baseline (SD)	Mean difference (95% CI)	P value (one-sided)	P value (two-sided)
CSFT-total (micro m): change from baseline at week 48 (FAS – LOCF)[a]						
HAWK						
Brolucizumab 6 mg	360	463.1 (166.62)	–170.8 (142.58)	–29.0 (–47.6 to 10.4)	0.0012	0.0023
Aflibercept 2 mg	360	457.9 (146.37)	–145.4 (145.57)	REF	REF	REF
HARRIER						
Brolucizumab 6 mg	370	473.6 (171.39)	–189.8 (158.35)	–49.9 (–68.9 to 30.9)	NA	< 0.0001[b]
Aflibercept 2 mg	369	465.3 (151.21)	–147.8 (144.97)	REF	NA	REF
	Total N	**n (%)**		**Difference (95% CI)[a]**	**P value (one-sided)**	**P value (two-sided)**
Patients with presence of SRF and/or IRF at week 48 (FAS – LOCF)						
HAWK						
Brolucizumab 6 mg	360	112 (31.2)		–13.5 (–20.7 to –6.1)	0.0001	0.0002[b]
Aflibercept 2 mg	360	161 (44.6)		REF	REF	REF
HARRIER						
Brolucizumab 6 mg	370	96 (25.8)		–18.1 (–24.9 to –11.8)	NA	< 0.0001[b]
Aflibercept 2 mg	369	161 (43.9)		REF	NA	REF
	HAWK		**HARRIER**			
	Brolucizumab 6 mg (N = 360)	**Aflibercept 2 mg (N = 360)**	**Brolucizumab 6 mg (N = 370)**	**Aflibercept 2 mg (N = 369)**		
Patients with ≥ 1 ocular adverse event						
n (%)	220 (61.1)	201 (55.8)	174 (47.0)	176 (47.7)		
Patients with ≥ 1 non-ocular adverse event						
n (%)	289 (80.3)	303 (84.2)	282 (76.2)	272 (73.7)		
Patients with ≥ 1 ocular SAE						
n (%)	12 (3.3)	5 (1.4)	13 (3.5)	6 (1.6)		
Patients with ≥ 1 non-ocular SAE						
n (%)	85 (23.6)	110 (30.6)	69 (18.6)	85 (23.0)		
Patients who permanently stopped treatment due to AEs						
n (%)	11 (3.1)	12 (3.3)	13 (3.5)	6 (1.6)		
Deaths						
n (%)	8 (2.2)	12 (3.3)	4 (1.1)	7 (1.9)		
Notable harms						
Any intraocular inflammation	21 (5.8)	2 (0.6)	11 (3.0)	5 (1.4)		

	HAWK		HARRIER	
	Brolucizumab 6 mg (N = 360)	Aflibercept 2 mg (N = 360)	Brolucizumab 6 mg (N = 370)	Aflibercept 2 mg (N = 369)
Iritis	9 (2.5)	1 (0.3)	0 (0.0)	1 (0.3)
Uveitis	8 (2.2)	1 (0.3)	3 (0.8)	0 (0.0)
Vitritis	2 (0.6)	1 (0.3)	1 (0.3)	2 (0.5)
Anterior chamber inflammation	1 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)
Iridocyclitis	1 (0.3)	0 (0.0)	2 (0.5)	1 (0.3)
Chorioretinitis	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Anterior chamber cell	1 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)
Anterior chamber flare	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)
Eye inflammation	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Vitreous haze	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Endophthalmitis, n (%)	3 (0.8)	0 (0.0)	1 (0.3)	1 (0.3)
Eye infection, n (%)	NR	NR	NR	NR
Retinal tear, n (%)	6 (1.7)	3 (0.8)	3 (0.8)	2 (0.5)
Retinal detachment, n (%)	2 (0.6)	1 (0.3)	2 (0.5)	1 (0.3)
Increased IOP, n (%)	13 (3.6)	15 (4.2)	14 (3.8)	15 (4.1)
Glaucoma, n (%)	2 (0.6)	4 (1.1)	0 (0.0)	1 (0.3)
Surgical intervention for glaucoma treatment, n (%)	NR	NR	NR	NR
Conjunctival hemorrhage, n (%)	29 (8.1)	32 (8.9)	17 (4.6)	19 (5.1)
Vitreous hemorrhage, n (%)	2 (0.6)	1 (0.3)	0 (0.0)	2 (0.5)
Arteriothrombotic event	11 (3.1)	11 (3.1)	11 (3.0)	10 (2.7)

AE = adverse event; BCVA = best-corrected visual acuity; CI = confidence interval; CSFT = central subfield thickness; FAS = full analysis set; IOP = intraocular pressure; LOCF = last observation carried forward; IRF = intraretinal fluid; NA = not applicable; NR = not reported; REF = reference treatment; SAE = serious adverse event; SD = standard deviation; SRF = subretinal fluid; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire–25.

[a] Logistic regression models with baseline fluid status, age categories (< 75 years, ≥ 75 years) and treatment as fixed-effects factors are used.
[b] The outcome was outside the statistical testing hierarchy.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Critical Appraisal

Limitations of the HAWK and HARRIER studies include lack of stratification by geographic region, lack of adjustment for multiplicity in HARRIER, and potential risk of unmasking treatment assignment through the use of sham injections and an unmasked injection physician. In addition, generalizability of the results is limited to the treatment-naive population. Also, the applicability of the results measuring the proportion of patients receiving treatment every eight weeks or every 12 weeks might be limited in practice for several reasons. First, information regarding development, validation, and the extent of use by investigator of the criteria described in the two studies to determine disease activity is not available; second, in clinical practice, it is unlikely that patients would be ineligible to start receiving treatment every 12 weeks after being administered treatment every eight weeks. In addition, neither HAWK nor HARRIER assessed the comparative injection

frequency of brolucizumab versus aflibercept under a pre-specified statistical testing method. This is a major limitation, as no inference can be made regarding the results related to the number of injections. The generalizability value of the injection frequency measures is further reduced with the common use of treat-and-extend protocols in clinical practice. Finally, no direct evidence comparing brolucizumab with ranibizumab or bevacizumab is available.

Indirect Comparisons

Description of Studies

One indirect treatment comparison (ITC) was submitted by the sponsor and included in this review. No additional ITCs were identified in the literature. The sponsor performed a network meta-analysis (NMA) to estimate the efficacy of brolucizumab in patients with nAMD versus other anti-VEGFs. The authors of the sponsor-submitted ITC used a Bayesian approach through Markov Chain Monte Carlo methods. Non-informative priors were chosen for the analysis. For the outcome of BCVA at one year, the authors analyzed 21 trials under a fixed-effects model.

Efficacy Results

In the ITCs, brolucizumab 6 mg every 12 weeks or every eight weeks was significantly more effective than sham treatments. All other comparisons included zero in the 95% credible interval (CrI). Also, wide CrIs were noted in several comparisons. At two years, the network for the BCVA outcome was much sparser than it had been at one year, including only nine trials. As in the one-year results, brolucizumab was significantly better than sham, but wide CrIs were more prominent at the two-year outcome than at the one-year outcome. For the outcome of retinal thickness, at one year, the authors analyzed 18 randomized controlled trials (RCTs) under a fixed-effects model. The results showed brolucizumab to be significantly better than all comparators except ranibizumab 0.5 mg as needed with extension after a loading phase and brolucizumab 3 mg every 12 weeks or every eight weeks after a loading phase. However, the CrIs are notably large in all of the results. At two years, the authors analyzed eight trials, with the results showing larger CrIs than in the one-year results and the null included in comparisons that were significant in the one-year analysis.

Harms Results

No comparative safety outcomes were reported in the sponsor-submitted ITC.

Critical Appraisal

Limitations to the sponsor's ITC include: lack of reporting on informative items (e.g., diagnostic information criterion [DIC] values, graphic representation of the baseline characteristics across trials, results of the random-effects model); considerable heterogeneity in some baseline characteristics (most notably, the variation in values for retinal thickness and the method of assessing retinal thickness); lack of inconsistency assessment; and weak connections between brolucizumab and the rest of the network, with only one study directly informing the network (as also evidenced in the wide CrIs). These limitations pose considerable challenges with regard to arriving at a conclusive decision on the validity of the results to inform clinical practice.

Other Relevant Evidence

Description of Studies

Because the HAWK and HARRIER studies delivered brolucizumab in a formulation that differed from that of the product intended for commercialization, the FDA recommended collecting clinical data from at least 50 patients originally enrolled in the pivotal trials and studying the patients for an additional six months while treating them with the brolucizumab 6 mg product intended for commercialization. Compared with the core study, patients in the extension study had a greater mean age. A greater proportion were also female, and a greater proportion had been diagnosed with nAMD within one month of the core study baseline. Disease activity was assessed at week 16 and week 20; investigators determined disease activity status using on their own expert judgment. Descriptive statistics were reported for patients with a BCVA loss of at least five letters, 10 letters, 15 letters, and 30 letters in the study eye from baseline to each study visit, as well as a gain in BCVA for the same time points and thresholds. The mean change in BCVA from baseline to each study visit was also reported.

Efficacy Results

In patients who received brolucizumab, there was no notable change in mean BCVA from baseline to week 24, regardless of the dosage received in the core study (overall change: –1.0 letters; standard error [SE]: 7.67 letters). The percentages of patients who gained and lost five letters (16.8% and 18.7%), 10 letters (5.6% and 11.2%), and 15 letters (2.8% for both) were similar. One patient experienced a loss of at least 30 letters; none experienced a gain of at least 30 letters. Sensitivity analyses for mean BCVA using observed values only were consistent with the main analyses.

Harms Results

In patients receiving brolucizumab, 18.7% had at least one ocular AE in the study eye, with cataract, nAMD, and retinal hemorrhage each occurring in 2.8% of patients. (Other ocular AEs were reported by fewer than 2% of patients). The percentage of patients with an ocular SAE in the study eye was 0.9%, with one patient experiencing both retinal artery occlusion (a notable harm, according to the systematic review protocol) and retinal vein occlusion. In terms of non-ocular AEs, 47.7% of brolucizumab patients reported at least one AE and 5.6% reported at least one SAE.

Critical Appraisal

The extension study provided descriptive results that lacked control and randomization. It supports the finding that the improvements gained in the core studies are maintained.

Conclusions

The results of the two double-blind, multinational, randomized, active-controlled trials (HAWK and HARRIER) indicate that in terms of mean change of BCVA from baseline for treatment-naive patients with nAMD at week 48, three loading, monthly IVT injections of brolucizumab 6 mg followed by one IVT injection every 12 weeks or every eight weeks is noninferior to three loading, monthly IVT injections of aflibercept 2 mg followed by one IVT injection every eight weeks. Almost half of the patients treated with brolucizumab 6 mg required treatment every eight weeks by the end of the first year. The sponsor's ITC demonstrated results that suggest brolucizumab 6 mg every 12 weeks or every eight weeks to be significantly better than sham in BCVA outcomes, and significantly better than most other comparators in the retinal thickness outcome. However, due to the high heterogeneity in the retinal thickness baseline values and definition, and because of the low statistical robustness of the model as evidenced by the wide CrIs in most outcomes, no confident conclusion can be made regarding the similarity or superiority of brolucizumab versus other anti-VEGFs. Safety data from the two studies indicate that the most common ocular SAEs in the brolucizumab arms were endophthalmitis, uveitis, retinal tear, and retinal pigment epithelial tear.

Introduction

Disease Background

AMD is a degenerative disease of the macula.[2] In Canada, it affects approximately 2 million people.[3] Given the aging population, this number is expected to double over the next 25 years.[4] AMD is the leading cause of vision loss in people older than 50 years in North America.[5] Considering the impact of blindness on QoL and independence, and considering the aging Canadian population, AMD will become an even more important health issue.[6]

There are two basic types of AMD: dry and neovascular (wet). The latter, nAMD, is a chronic degenerative eye disease characterized by the formation of abnormal blood vessels underneath the central retina (macula) that can lead to progressive, irreversible vision loss.[2,7] The majority of patients (90%) develop dry AMD, but those with nAMD account for more than 90% of the advanced vision loss due to AMD.[8,9] In 2004, it was estimated that there were 17,100 new nAMD cases in Canada (2004 population: 32.5 million).[10] Risk factors associated with the development of nAMD include age (over 75 years), gender (female), smoking status (current smoker), and genetic background.[11]

The defining feature of nAMD is choroidal neovascularization (CNV), which occurs in response to abnormally high levels of pro-inflammatory and angiogenic cytokines, including VEGF. These novel blood vessels disrupt the structural integrity of the retina.[12] In addition, these newly formed vessels are fragile and leak fluid, which accumulates in the retina as subretinal fluid (SRF) and intraretinal fluid (IRF), leading to generalized thickness of the retina.[13]

Standards of Therapy

Anti-VEGF therapies represent the gold standard of care for nAMD as recommended in international guidelines.[4,14-16] In Canada, ranibizumab and aflibercept are indicated by Health Canada as anti-VEGF drugs for the treatment of nAMD. In addition, bevacizumab is commonly used in practice as another anti-VEGF drug that does not have a Health Canada indication.[3]

Drug

Brolucizumab is a humanized, monoclonal, single-chain variable fragment antibody directed against human VEGF. It binds with high affinity to VEGF-A isoforms (e.g., VEGF110, VEGF121, and VEGF165), preventing VEGF-A from binding to receptors VEGFR-1 and VEGFR-2. By inhibiting VEGF-A binding, brolucizumab suppresses endothelial cell proliferation, thereby reducing pathologic neovascularization and decreasing vascular permeability.

At the time of this systematic review, brolucizumab's anticipated Health Canada–approved indication was for the treatment of nAMD. (The Notice of Compliance from Health Canada was issued after the conduct of this review on March 12, 2020.) The anticipated recommended dose of brolucizumab is 6 mg (50 µL) administered by IVT injection every four weeks for the first three doses and every 12 weeks thereafter. The physician may individualize treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. The treatment interval could be as frequent as every eight weeks.[17]

The sponsor is requesting reimbursement of brolucizumab per the indication.

Stakeholder Engagement

Patient Group Input

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

About the Patient Groups and Information Gathered

One patient group submission, prepared jointly by Fighting Blindness Canada, the Canadian Council of the Blind, the CNIB Foundation, and Vision Loss Rehabilitation Canada, was received by CADTH for this review. Fighting Blindness Canada, a charitable organization, is Canada's leading private funder of vision research and focuses on all blinding eye diseases. The Canadian Council of the Blind is a not-for-profit community of peers that works to improve QoL for individuals and communities of people who are blind, deaf-blind, or living with low vision. The CNIB Foundation is a not-for-profit organization whose mission is to change what it means to be blind through programs and advocacy that enable Canadians affected by blindness to live the lives they choose. Vision Loss Rehabilitation Canada is a health services organization that is a part of the CNIB Foundation. It provides training that enables people who are blind or partially sighted to develop or restore key daily living skills, enhancing their independence, safety, and mobility.

The patient group submission was informed by an online survey that garnered 157 responses from individuals living with AMD. Of these, 97 reported having nAMD (the indication under review) and 60 reported having dry AMD. The mean time since diagnosis of nAMD was 14 years. Most provinces and territories were represented in the responses; the highest concentrations of respondents were in Ontario, Alberta, and British Columbia. In the group with nAMD, 17 reported an ocular comorbidity, with the most common being glaucoma. The patient groups did not receive external help to complete the submission or to collect or analyze the data used in the submission.

Disease Experience

Half of respondents with nAMD considered their disease to be "very serious," while 23% considered it "fairly serious" and 23% considered it "moderately serious." Also, 80% reported thinking about nAMD "very often (at least once a day)," while 18% thought about it "often (at least once a week)" and 11% thought about it "occasionally (at least once a month)." It was noted in the submission that respondents thought about the disease frequently despite the relatively long periods of time between treatments (injections every four or eight weeks).

Respondents with nAMD indicated that the following activities were difficult or impossible to do: reading (65%), driving (46%), interacting with others (37%), navigating public spaces (23%), travelling (21%), cooking (16%), interacting online (15%), interacting socially (13%), doing housework (11%), and networking (6%). Just under a fifth of respondents (18%) indicated that there were no activities they found difficult or could no longer do. In the open-ended "Other" category, one response indicated difficulty with *"sewing, knitting, stained glass, writing, embroidery, etc."* Another response described how bright lights are painful yet necessary for performing certain activities, such as cooking. In summary, nAMD can negatively affect patients' ability to perform some activities of daily living and recreational activities and can negatively affect their social well-being. With regard to the latter issue, in an open-ended response to a question about overall challenges, one respondent reported, *"Every month getting more isolated."*

The following overall challenges were also cited by respondents: concern over deterioration of sight (80%), frequency of visits to the eye doctor (44%), frequency of medication or treatment (43%), loss of independence (32%), anxiety (28%), depression (20%), strain on family members or friends (17%), and general mobility (4%). In addition, 12% reported "no challenges." In summary, it appears that potential deterioration of vision with nAMD is a common concern and, although not explicitly stated, may be a source of anxiety and depression. Also, nAMD can negatively affect patients' independence. One respondent mentioned *"Loss of job, loss of income"* as a consequence of the impacts of nAMD. There can also be a significant burden associated with the management of nAMD, including frequent health care appointments and treatments and strain on family or friends. Respondents indicated that they rely on support from a variety of sources, most commonly family and friends (70%).

Experience With Treatment

Most respondents with nAMD (86%) indicated that they were taking medication or receiving treatment; 59% were receiving some type of injected treatment (one of the anti-VEGF treatments or an unspecified "injection," "shot," or "needle"). In addition, 12% of respondents selected the "Other" category, with responses about other treatments that included *"injections and a shunt in my one eye,"* *"herbal medications,"* *"Vitalux,"* and *"injection in the eye when required, and eye drops daily."* While 63% of respondents indicated that their medication or treatment routine did not affect their QoL, others reported impacts related to limited vision, pain, or other unspecified side effects for one to three days following injection as well as inconvenience, disruption, and expense associated with transportation to and from treatment appointments. Treatment burden also affects family members (as indicated by 70% of respondents), with the need for them to provide transportation to appointments and treatments commonly cited as a reason.

Although 90% of respondents indicated that they did not experience financial difficulties paying for medications and treatment, the rest noted financial challenges with paying for Vitalux (a lutein and zeaxanthin supplement), paying for treatment when in the US, and paying for transportation-related costs.

The most common challenges associated with taking medications or receiving treatment for nAMD were related to transportation — that is, the amount of time spent and the cost and availability of someone to take the patient to appointments. "Fear of knowing the disease is getting worse" was selected by 37% of respondents as a common challenge. Another theme was difficulty in getting diagnosis or treatment: 7% indicated "wait time to see specialist is too long," while 7% "did not know how important it was." One open-ended response recalled that *"initial diagnosis was delayed to the point that it was too late to save my right eye."* Despite the identified challenges, the survey results showed that, for the most part, patients adhere to the treatment regimens prescribed by their eye specialists.

Improved Outcomes

Patients are generally satisfied with their current treatments for nAMD, with 50% saying they are "very satisfied," 40% saying they are "fairly satisfied," 10% saying they are "neither satisfied nor unsatisfied," and 1% saying they are "fairly unsatisfied." However, 64% of respondents also answered "yes" when asked if they would prefer a treatment that could be taken less often. No other information was presented on any other unmet needs with current treatment. Although patients were polled on whether they were aware of alternative medications or treatment (70% indicated "no"), additional expectations for improved treatment were not reported, other than the potential prospect of stem cell therapy in the

future (with no further therapy) and a cheaper alternative to Lucentis, an anti-VEGF treatment.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by a clinical specialist with expertise in the diagnosis and management of AMD.

Description of the Current Treatment Paradigm for the Disease

Current treatments do not modify underlying disease mechanisms. The current standard of treatment is to use anti-VEGF intravascular injections. The current anti-VEGF therapies suppress VEGF activity, thereby reducing abnormal permeability of neovascular tissue within neovascular nAMD lesions, resulting in a drying effect within the macular retina and involution of neovascular membranes. This reduces the tendency for bleeding and subsequent disciform scar formation, preserving and, in some cases, enhancing visual acuity. Anti-VEGF drugs target the visual symptoms of macular vision loss and usually improve them.

Treatment Goals

The central goal of treatment is to stabilize and/or improve vision. Improving or maintaining driving vision is desirable for all patients, given that this will improve or stabilize their QoL, reduce the chance crashes, and thereby reduce the possibility of fractures and loss of independence. Because treatment with anti-VEGF drugs requires repeated administration to maintain or improve vision, we also aim to reduce the burden of follow-up and treatment visits while improving vison and preserving and enhancing vision-related QoL.

Overall, the goal of improving and stabilizing vision is to increase the patient's ability to maintain employment and independence as well as to reduce the burden on caregivers.

Unmet Needs

Some patients can become refractory to treatment. Increasing treatment options may prove useful to such patients. Also, there is a strong need for a treatment option that reduces the need for frequent follow-ups and injections.

Place in Therapy

Brolucizumab is an anti-VEGF therapy. As such, it has the same mechanism of action as other anti-VEGFs available on the market. However, the indicated regimen for brolucizumab is once every 12 weeks after the loading phase, which would make it the only indicated anti-VEGF with this extended period. The current paradigm of care could be altered dramatically if fewer visits and treatments were required and if visual acuity and function were optimized. The treatment burden on patients and caregivers would be reduced. As well, a reduction in direct medical costs per patient would be achieved.

Patient Population

The appropriate target patient population for brolucizumab would be treatment-naive patients who have recently been diagnosed with nAMD. Acute nAMD patients who are symptomatic and have early and small (in size) neovascular lesions would be excellent candidates for treatment with brolucizumab. In addition, patients who are poor responders to other anti-VEGF drugs could try brolucizumab to see if they might experience benefits from it.

On the other hand, if there is very poor initial visual acuity and structural damage to the macular retina in the form of fibrous scarring, treatment with a novel new therapy might be futile. Similarly, if a patient has had a long disease duration and unsuccessful therapy with an anti-VEGF for more than two years, they are unlikely to benefit from a newer drug.

Assessing Response to Treatment

After the completion of the loading dose (three monthly injections), an assessment at eight weeks to 12 weeks should show stabilization or improvement in visual acuity. The outcomes used in the clinical trials (e.g., BCVA) are appropriate for clinical practice.

Discontinuing Treatment

Stopping rules do not exist in the early phases of therapy. It may be appropriate to discontinue treatment if disciform macular fibrous scarring has occurred with loss of central vision to count fingers or worse, or where a long interval has passed without therapy due to missed appointments and where vision remains good and there are no signs of disease activity clinically or on optical coherence tomography (OCT). However, in the latter case, frequent clinical and OCT monitoring are essential.

Prescribing Conditions

For the correct diagnosis to be made, the availability of high-quality ocular imaging services is essential. This includes trained technical personnel, fundus photography, fluorescein angiography, OCT, and OCT angiography. Given that this drug would especially benefit treatment-naive patients, conditioning prescription on the failure of other drugs is not appropriate.

Clinical Evidence

The clinical evidence included in the review of brolucizumab is presented in three sections. Section 1, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. Section 2 includes indirect evidence from the sponsor (if submitted) and indirect evidence selected from the literature that met the selection criteria specified in the review. Section 3 includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of brolucizumab 6 mg (50 µL) IVT injection for the treatment of nAMD.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 2.

Table 2: Inclusion Criteria for the Systematic Review

Patient population	Adults with nAMD Subgroups: • Baseline visual acuity • Duration of disease • History of cerebrovascular or cardiovascular disease
Intervention	Brolucizumab (120 mg/mL solution for IVT injection), 6 mg IVT injection every 12 weeks after 3 initial monthly injections
Comparators	• Ranibizumab • Aflibercept • Bevacizumab[a]
Outcomes	**Efficacy outcomes:** • Change from baseline in visual acuityb • HRQoLb • Vision-related functionb (e.g., NEI VFQ-25) • Blindness (legal)b • Change in CRT • Presence of intraretinal or subretinal fluid **Harms outcomes:** • AEs • SAEs • WDAEs • Mortality

	Notable harms: endophthalmitis, eye inflammation, eye infections, retinal tear, retinal detachment, increased IOP, glaucoma, surgical intervention for glaucoma treatment, ATE, conjunctival hemorrhage, vitreous hemorrhage
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; CRT = central retinal thickness; HRQoL = health-related quality of life; IOP = intraocular pressure; IVT = intravitreal; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire–25; nAMD = neovascular age-related macular degeneration; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Used in Canada outside of Health Canada's approved indication.

[b] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[18]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid; Embase (1974–) through Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was brolucizumab. Clinical trial registries were searched, including the US National Institutes of Health's clinicaltrials.gov and WHO's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters were applied to limit retrieval by study type. Retrieval was not limited by publication date or language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on December 12, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on April 15, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[19] Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review 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.

Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Figure 1. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

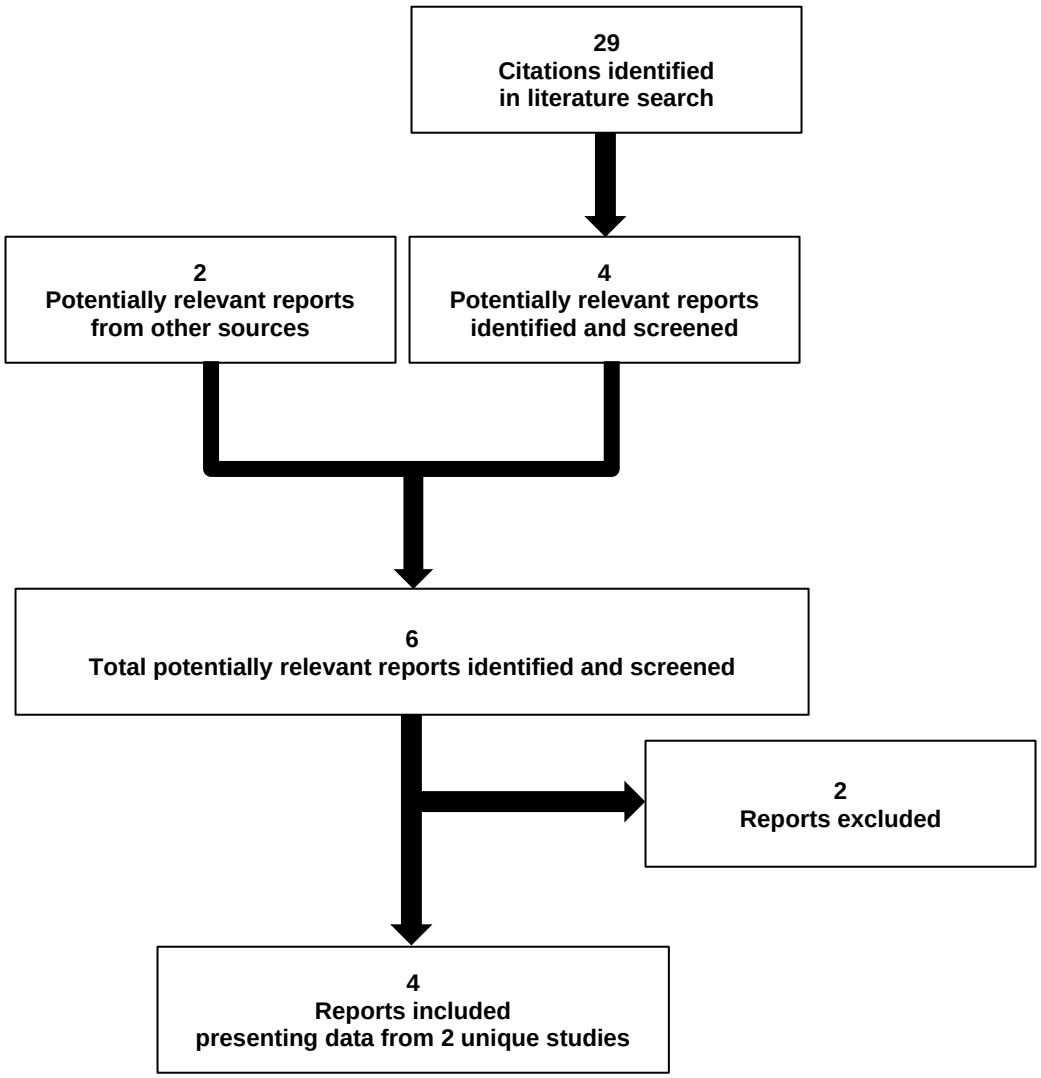


Table 3: Details of Included Studies

		HAWK	HARRIER
Designs & Populations	**Study design**	Randomized, double-masked, multi-centre, three-arm, noninferiority study	Randomized, double-masked, multi-centre, two-arm, noninferiority study
	Locations	Argentina, Australia, Canada, Colombia, Israel, Japan, Mexico, New Zealand, Panama, Puerto Rico, US	Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, South Korea, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Russia, Singapore, Slovakia, Spain, Switzerland, Taiwan, Turkey, UK, Vietnam
	Randomized (N)	1,082	743
	Inclusion criteria	• 50 years of age or older at screening • Active CNV lesions secondary to AMD that affected the central subfield (including retinal angiomatous proliferation lesions with a CNV component) in the study eye at screening • Total area of CNV (including both classic and occult components) comprised > 50% of the total lesion area in the study eye at screening • Intraretinal and/or subretinal fluid affecting the central subfield of the study eye at screening • BCVA between 78 letters and 23 letters, inclusive, in the study eye at screening and baseline using ETDRS testing	
	Exclusion criteria	• Any active intraocular or periocular infection or active intraocular inflammation in either eye at baseline • Central subfield of the study eye affected by fibrosis or geographic atrophy or total area of fibrosis ≥ 50% of the total lesion in the study eye at screening • Subretinal blood affecting the foveal centre point and/or ≥ 50% of the lesion of the study eye at screening • Any approved or investigational treatment for nAMD in the study eye at any time • Retinal pigment epithelial rip/tear in the study eye at screening or baseline, or current vitreous hemorrhage, or history of vitreous hemorrhage in the study eye within 4 weeks prior to baseline • Stroke or myocardial infarction in the 90-day period prior to baseline	
Drugs	**Intervention**	• Brolucizumab solution for IVT injection, 3 mg/50 µL (three monthly loading doses followed by maintenance therapy at 12-week or 8-week intervals) • Brolucizumab solution for IVT injection, 6 mg/50 µL (three monthly loading doses followed by maintenance therapy at 12-week or 8-week intervals)	• Brolucizumab solution for IVT injection, 6 mg/50 µL (three monthly loading doses followed by maintenance therapy at 12-week or 8-week intervals)
	Comparator(s)	• Aflibercept solution for IVT injection, 2 mg/50 µL (three monthly loading doses followed by maintenance therapy at 8-week intervals)	
Duration	**Phase**		
	Run-in	2 weeks	
	Double-blind	96 weeks	
	Follow-up	NA	

		HAWK	HARRIER
Outcomes	**Primary end point**	Change from baseline in BCVA at week 48	
	Secondary and exploratory end points	**Key secondary outcomes:** • Average change from baseline in BCVA (letters read) between week 36 and week 48 • Proportion of patients with positive q.12.w. treatment status at week 48 • Proportion of patients with positive q.12.w. treatment status at week 48 among the patients with no q.8.w. treatment needed during the first q.12.w. cycle (week 16, week 20) **Additional secondary and exploratory end points:** • Change in BCVA from baseline to each post-baseline visit • Average change in BCVA from baseline from week 84 to week 96; for each patient, this end point was derived as the average of the changes from baseline to weeks 84, 88, 92, and 96 • Average change in BCVA from baseline from week 4 to week 48; for each patient, this end point was derived as the average of the monthly changes from baseline up to week 48 • Average change in BCVA from baseline from week 4 to week 96; for each patient, this end point was derived as the average of the monthly changes from baseline up to week 96 • Average change in BCVA from baseline from week 12 to week 48; for each patient, this end point was derived as the average of the monthly changes from baseline to week 12 up to week 48 • Average change in BCVA from baseline from week 12 to week 96; for each patient, this end point was derived as the average of the monthly changes from baseline to week 12 up to week 96 • Number and percentage of patients with a gain in BCVA from baseline to each post-baseline visit using the following criteria: ≥ 15-letter gain, ≥ 10-letter gain, and ≥ 5-letter gain (patients with BCVA values of ≥ 84 letters at a post-baseline visit were considered as responders for the corresponding end point to account for a ceiling effect; e.g., for the ≥ 15-letter gain end point for patients with BCVA values at baseline ≥ 70 letters) • Number and percentage of patients with a BCVA of ≥ 73 letters at each post-baseline visit • Number and percentage of patients with a loss in BCVA from baseline to each post-baseline visit using the following criteria: ≥ 15-letter loss, ≥ 10-letter loss, and ≥ 5-letter loss • q.12.w. treatment status at week 96 (only for patients randomized to brolucizumab 3 mg and 6 mg); this end point was analyzed using the Kaplan-Meier method as given for the corresponding week 48 end point • q.12.w. treatment status at week 96 among patients with no q.8.w. need during the first (“initial”) q.12.w. cycle (week 16 and week 20) for patients randomized to brolucizumab only; this end point was analyzed using the Kaplan-Meier method as given for the corresponding week 48 end point q.8.w. treatment need at week 16 • Change in CSFT from baseline to each post-baseline visit • Average change in CSFT from baseline from week 36 to 48 • Average change in CSFT from baseline from week 84 to week 96 • Average change in CSFT from baseline from week 4 to week 48 • Average change in CSFT from baseline from week 4 to week 96 • Change in CSFTns from baseline to each post-baseline visit • Average change in CSFTns from baseline from week 36 to week 48 • Average change in CSFTns from baseline from week 84 to week 96 • Change in area of CNV within the lesion (CNV lesion size) from baseline to weeks 12, 48, and 96 • Number and percentage of patients with CNV lesion area > 0 mm2 at week 12, week 48, and week 96 • Number and percentage of patients with presence of SRF and/or IRF (central subfield) at each post-baseline visit • Number of visits with presence of SRF and/or IRF (central subfield) during week 36 to week 48 • Number and percentage of patients with presence of SRF (central subfield) at each post-baseline visit • Number of visits with presence of SRF (central subfield) during week 36 to week 48 • Number and percentage of patients with presence of IRF (central subfield) at each post-baseline visit	

		HAWK	HARRIER
		• Number of visits with presence of IRF (central subfield) during week 36 to week 48 • Number and percentage of patients with presence of sub-RPE fluid (central subfield) at each post-baseline visit • Number of visits with presence of sub-RPE fluid (central subfield) during week 36 to week 48 • Number of patients with presence of subretinal hemorrhage (central subfield) at each assessment visit (based on the FA assessment) • Number of patients with presence of intraretinal hemorrhage (central subfield) at each assessment visit (based on the FA assessment) • Change in patient-reported outcomes (NEI VFQ-25) total and subscale scores from baseline to weeks 24, 48, 72, and 96	
Notes	**Publications**	Dugel 2019	

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; CSFT = central subfield thickness; CSFTns = CSFT-neurosensory area; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; IRF = intraretinal fluid; IVT = intravitreal; NA = not available; nAMD = neovascular age-related macular degeneration; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; RPE = retinal pigment epithelium; SRF = subretinal fluid; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire–25.

Note: Two additional reports were included.[20,21]

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Description of Studies

Two studies (HAWK and HARRIER) that met the inclusion criteria for the review were identified. Both studies were phase III, noninferiority, double-masked, active-controlled, parallel, randomized trials. Both were identical in design, with the exception that HAWK (N = 1,082) was a three-arm trial (brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept 2 mg) while HARRIER (N = 743) was a two-arm trial (brolucizumab 6 mg and aflibercept 2 mg). Given that only the 6 mg dose is recommended by Health Canada, we will only report information relevant to the brolucizumab 6 mg arm. The studies' primary outcome was change from baseline in BCVA at week 48. Both studies were designed for a 96-week double-masked period.

Populations

Inclusion and Exclusion Criteria

Eligible patients were 50 years of age and older with untreated, active CNV lesions secondary to AMD affecting the central subfield and with BCVA scores between 78 ETDRS chart letters and 23 ETDRS chart letters. With IRF and/or SRF affecting the central subfield of the study eye, only one eye from each patient was included in the study. For the selection of the study eye, if both eyes were eligible at screening and baseline, the eye with the worse BCVA at baseline was to be selected. If both eyes had the same BCVA, it was recommended that the right eye be selected. The studies excluded patients with possible conditions or interventions that would affect BCVA or who had any prior retinal treatment. Effectively, they enrolled only treatment-naive patients.

Baseline Characteristics

Overall, patients randomized into the treatment arms had similar baseline characters within each study and across studies in terms of age, gender, number of eyes affected, BCVA, and central subfield thickness. HARRIER had a higher proportion of white patients compared to HAWK and a higher proportion of patients with a disease duration of longer

than three months. The HARRIER study had a higher proportion of patients with SRF in the aflibercept arm compared to the brolucizumab arm (72.6% versus 67.8%).

Table 4: Summary of Baseline Characteristics (Full Analysis Set)

	HAWK		HARRIER	
	Brolucizumab 6 mg (N = 360)	Aflibercept 2 mg (N = 360)	Brolucizumab 6 mg (N = 370)	Aflibercept 2 mg (N = 369)
Age (years)				
Mean (SD)	76.7 (8.95)	76.2 (8.80)	74.8 (8.58)	75.5 (7.87)
Female				
n (%)	205 (56.9)	194 (53.9)	210 (56.8)	212 (57.5)
Race n (%)				
White	285 (79.2)	287 (79.7)	340 (91.9)	341 (92.4)
Black or African American	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)
American Indian Or Alaska Native	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Asian	61 (16.9)	53 (14.7)	22 (5.9)	23 (6.2)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	9 (2.5)	17 (4.7)	5 (1.4)	4 (1.1)
Multiple	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Time since diagnosis of nAMD n (%)				
< 1 month	159 (44.2)	154 (42.8)	136 (36.9)	139 (37.7)
1 to 3 months	184 (51.1)	190 (52.8)	191 (51.8)	197 (53.4)
> 3 months	17 (4.7)	16 (4.4)	42 (11.4)	33 (8.9)
Unilateral versus bilateral nAMD n (%)				
Unilateral	271 (75.3)	268 (74.4)	268 (72.4)	255 (69.1)
Bilateral	89 (24.7)	92 (25.6)	102 (27.6)	114 (30.9)
BCVA (ETDRS chart letters read)				
Mean (SD)	60.8 (13.66)	60.0 (13.92)	61.5 (12.59)	60.8 (12.93)
≤ 55 letters, n (%)	101 (28.1)	116 (32.2)	102 (27.6)	107 (29.0)
56 letters to 70 letters, n (%)	157 (43.6)	153 (42.5)	171 (46.2)	170 (46.1)
≥ 71 letters, n (%)	102 (28.3)	91 (25.3)	97 (26.2)	92 (24.9)
CSFT-total (µm)				
Mean (SD)	463.1 (166.62)	457.9 (146.37)	473.6 (171.39)	465.3 (151.21)
< 400 µm, n (%)	157 (43.6)	146 (40.6)	148 (40.0)	130 (35.2)
≥ 400 µm,	203 (56.4)	214 (59.4)	222 (60.0)	239 (64.8)

	HAWK		HARRIER	
	Brolucizumab 6 mg (N = 360)	Aflibercept 2 mg (N = 360)	Brolucizumab 6 mg (N = 370)	Aflibercept 2 mg (N = 369)
n (%)				
Type of CNV n (%)				
Predominantly classic	113 (31.4)	116 (32.3)	154 (41.6)	144 (39.5)
Minimally classic	39 (10.8)	34 (9.5)	33 (8.9)	34 (9.3)
Occult	208 (57.8)	209 (58.2)	183 (49.5)	187 (51.2)
Area of lesion associated with CNV (mm^2)				
Mean (SD)	4.6 (4.08)	4.4 (3.72)	2.6 (2.76)	2.9 (3.95)
Presence of subretinal fluid n (%)				
Present	250 (69.4)	245 (68.1)	251 (67.8)	268 (72.6)
Absent	110 (30.6)	115 (31.9)	119 (32.2)	101 (27.4)
Presence of intraretinal fluid/cyst n (%)				
Present	194 (53.9)	194 (53.9)	149 (40.3)	139 (37.7)
Absent	166 (46.1)	166 (46.1)	221 (59.7)	230 (62.3)
Presence of SRF and/or IRF n (%)				
Present	334 (92.8)	336 (93.3)	330 (89.2)	332 (90.0)
Absent	26 (7.2)	24 (6.7)	40 (10.8)	37 (10.0)
Presence of sub-RPE fluid n (%)				
Present	168 (46.7)	158 (43.9)	125 (33.8)	127 (34.4)
Absent	192 (53.3)	202 (56.1)	245 (66.2)	242 (65.6)

BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; CSFT = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; IRF = intraretinal fluid; nAMD = neovascular age-related macular degeneration; RPE = retinal pigment epithelium; SD = standard deviation; SRF = subretinal fluid.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Interventions

Patients in HAWK were randomized on a 1:1:1 ratio to brolucizumab 6 mg, aflibercept 2 mg, or brolucizumab 3 mg (which is not covered in this review). Patients in HARRIER were randomized on a 1:1 ratio to either brolucizumab 6 mg or aflibercept 2 mg. Randomization and treatment assignment were established at baseline using an interactive response system. Randomization of patients in Japan was stratified by the presence or absence of polypoidal choroidal vasculopathy.

Patients randomized to the brolucizumab arm received 6 mg brolucizumab in 50 µL volume once monthly for the first three injections (day 0, week 4, and week 8) followed by

maintenance therapy every 12 weeks unless a disease activity assessment indicated ongoing disease activity in the patient. In that case, maintenance therapy was changed to every eight weeks. Patients randomized to the aflibercept arm received 2 mg aflibercept in 50 µL volume once monthly for the first three injections (day 0, week 4, and week 8) followed by maintenance therapy every eight weeks.

Disease activity assessment was conducted at pre-specified assessment visits for all enrolled patients. Assessments were conducted by a masked investigator with guidance from the study protocol regarding the definition of an ongoing disease activity. Once a patient was determined to have ongoing disease activity, they were switched to the every-eight-weeks regimen until the conclusion of the trial.

The first assessment visit at week 16 provided the following criteria as guidance to determine ongoing disease activity: decrease in BCVA of ≥ five letters compared with baseline; decrease in BCVA of ≥ three letters and increase in CRT of ≥ 75 µm compared with week 12; decrease in BCVA of ≥ 5 letters due to nAMD disease activity compared with week 12; new or worse IRF or intraretinal cysts compared with week 12. Assessment visits at weeks 20, 32, and 44 determined ongoing disease activity as a decrease in BCVA of ≥ 5 letters due to nAMD disease activity compared with week 12. Assessment visits at weeks 56, 68, 80, and 92 determined ongoing disease activity as a decrease in BCVA of ≥ 5 letters due to nAMD disease activity compared with week 48.

As a double-masked study, all of the enrolled patients and involved staff were masked to the treatment assignment with the exception of the unmasked study centre personnel and unmasked injecting physician. Sham injections, in which a needless injection is pressed against the eye to mimic the pressure of an actual IVT injection, were administered to establish identical monthly injection schedules across treatment arms.

Outcomes

ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between letters and rows. There are 14 lines (i.e., 70 letters) in total. The ability to read more lines (i.e., more letters) indicates better visual acuity.

In both studies, the primary efficacy outcome was the change in BCVA from baseline to week 48. Both trials also included three key secondary outcomes: the average change from baseline in BCVA (letters read) from week 36 to week 48, where for each patient, this end point was defined as the average of the changes from baseline to weeks 36, 40, 44, and 48; the proportion of patients with positive q12w treatment status (i.e., patients who were receiving brolucizumab IVT injections at 12-week intervals) at week 48; and the proportion of patients with positive q12w treatment status at week 48 among those with no q8w treatment needed during the first q12w cycle (week 16, week 20).

Additional secondary and exploratory outcomes related to visual acuity, anatomical measures, and HRQoL measures were reported. Specifically, visual acuity outcomes were reported at every assessment point in terms of change in BCVA from baseline to every assessment visit; the proportion of patients who lost five, 10, and 15 ETDRS chart letters; the proportion who had BCVAs of ≥ 73 letters; and the proportion who gained five, 10, and 15 ETDRS chart letters, or who had BCVA values of ≥ 84 letters. Anatomical outcomes were reported in terms of change from baseline in retinal thickness, CNV lesion size, and the presence of SRF or IRF at each assessment point.

The HRQoL measure was reported as part of the exploratory outcomes in terms of the NEI VFQ-25 total and subscale score changes from baseline to various assessment points. The NEI VFQ-25 is a validated scale that includes 25 items relevant to 11 vision-related constructs (general vision, ocular pain, near vision, distance vision, social functioning, mental health, role functioning, dependency, driving, peripheral vision, and colour vision) in addition to a single-item, general-health component. NEI VFQ-25 total scores can range from 0 (worst possible) to 100 (best possible). Using results from two trials in patients with nAMD (N = 716 and N = 423), a 15-letter change in visual acuity in the study eye (typically the worse-seeing eye) corresponded to a change of 3.90 to 4.34 points in the composite score.[22] For the better-seeing eye, the clinically relevant difference for the NEI VFQ-25 composite score based on a three-line change was 7.35 to 8.18 points. In terms of responsiveness, a change of 9.61 to 10.57 points corresponded to a medium effect size.[22]

Safety outcomes were reported in terms of ocular and non-ocular SAEs, overall AEs, AEs of special clinical interest, and injection-related AEs.

Details regarding scoring, validity, and minimal clinically important difference (MCID) for the outcomes measures are presented in Appendix 4.

Statistical Analysis

Both the HAWK and HARRIER studies were designed to first test noninferiority of brolucizumab to aflibercept. To achieve noninferiority, the noninferiority margin was determined as –4 letters in BCVA. This margin was calculated based on the MARINA (ranibizumab versus sham) and ANCHOR (aflibercept versus verteporfin) trials, in which the results of the difference in BCVA change from baseline were observed to be 17.5 letters (95% CI, 14.8 to 20.2) and 21.1 letters (95% CI, 17.5 to 24.6), respectively. It was inferred that a noninferiority margin of –4 letters would guarantee an absolute treatment effect given a magnitude of at least 10 letters, even when taking the conservative approach of using the lower limits of these 95% CIs as reference points.

A power analysis based on a noninferiority margin of –4 letters in BCVA determined that a sample size of 297 patients per treatment arm was considered sufficient to demonstrate noninferiority (margin = –4 letters) of brolucizumab 6 mg versus aflibercept 2 mg with respect to the change in BCVA from baseline to week 48 at a two-sided alpha level of 0.05 with a power of approximately 90%, assuming equal efficacy and a common standard deviation (SD) of 15 letters. Assuming a 10% dropout rate, the study planned to randomize a total of 330 patients into each treatment arm.

In HARRIER, statistical hypotheses for the primary and first key secondary outcomes were established to be tested in a hierarchical sequence, where each hypothesis was assessed at a two-sided significance level of 0.05 while keeping the global type I error rate at 0.05:

- Null hypothesis: The brolucizumab 6 mg mean BCVA at 48 weeks minus the aflibercept 2 mg mean BCVA at 48 weeks is less than or equal to four ETDRS chart letters.
- Alternative hypothesis: The brolucizumab 6 mg mean BCVA at 48 weeks minus the aflibercept 2 mg mean BCVA at 48 weeks is greater than four ETDRS chart letters.
- Null hypothesis: The brolucizumab 6 mg average mean BCVA between 36 to 48 weeks minus the aflibercept 2 mg average mean BCVA between 36 to 48 weeks is less than or equal to four ETDRS chart letters.

- Alternative hypothesis: The brolucizumab 6 mg average mean BCVA between 36 to 48 weeks – the aflibercept 2 mg average mean BCVA between 36 to 48 weeks is greater than four ETDRS chart letters.

No additional formal statistical hypothesis testing was planned for any additional outcomes in HARRIER.

In HAWK, similar noninferiority statistical hypothesis testing was established with the additional 3 mg brolucizumab testing. In this setting, each hypothesis was assessed at a one-sided significance level of 0.025 while keeping the global type I error rate at 0.025.

However, unlike HARRIER, HAWK instated a parallel statistical hierarchy system to test for various secondary outcomes should the noninferiority hypothesis be confirmed for the primary end point. A graphic representation of this system is presented in Figure 2. All of the secondary outcomes statistical testing consisted of one-sided testing for superiority of brolucizumab versus aflibercept. The global one-sided alpha of 0.025 was split as follows to allow parallel testing:

- Testing in the central subfield thickness: 0.005
- Fluid status: 0.01
- Disease activity assessment: 0.01

Figure 2: Statistical Hierarchy System Employed in HAWK

1) H0: The mean BCVA of brolucizumab 6 mg at 48 weeks minus the mean BCVA of aflibercept 2 mg at 48 weeks is ≤ –4 ETDRS chart letters.
   Ha: The mean BCVA of brolucizumab 6 mg at 48 weeks minus the mean BCVA of aflibercept 2 mg at 48 weeks is > –4 ETDRS chart letters.
2) H0: The average mean BCVA of brolucizumab 6 mg between week 36 and week 48 minus the average mean BCVA of aflibercept 2 mg between week 36 and week 48 is ≤ –4 ETDRS chart letters.
   Ha: The average mean BCVA of brolucizumab 6 mg between week 36 and week 48 minus the average mean BCVA of aflibercept 2 mg between week 36 and week 48 is ≤ –4 ETDRS chart letters.
3) H0: The mean BCVA of brolucizumab 3 mg at 48 weeks minus the mean BCVA of aflibercept 2mg at 48 weeks is ≤ –4 ETDRS chart letters.
   Ha: The mean BCVA of brolucizumab 3 mg at 48 weeks minus the mean BCVA of aflibercept 2mg at 48 weeks is > –4 ETDRS chart letters.
4) H0: The average mean BCVA of brolucizumab 3 mg between week 36 and week 48 minus the average mean BCVA of aflibercept 2 mg between week 36 and week 48 is ≤ –4 ETDRS chart letters.
   Ha: The average mean BCVA of brolucizumab 3 mg between week 36 and week 48 minus the average mean BCVA of aflibercept 2 mg between week 36 and week 48 is ≤ –4 ETDRS chart letters.

Central subfield thickness

1. Change in CSFT total from baseline to week 16, 6 mg
2. Change in CSFT total from baseline to week 48, 6 mg
3. Average change in CSFT total from baseline from week 36 to week 48, 6 mg
4. Change in CSFT total from baseline week 16, 3 mg
5. Change in CSFT total from baseline to week 48, 3 mg
6. Average change in CSFT total from baseline from week 36 to week 48, 3 mg

Fluid status (yes, no)

1. Fluid at week 16, 6 mg
2. Fluid at week 48, 6 mg
3. Number of visits without fluid during week 36 to week 48, 6 mg
4. Fluid at week 16, 3 mg
5. Fluid at week 48, 3 mg
6. Number of visits without fluid during week 36 to week 48, 3 mg

Disease activity assessment (yes, no)

1. DAA at week 16, 6 mg
2. DAA at week 16, 3 mg

BCVA = best-corrected visual acuity; CSFT = central subfield thickness; DAA = disease activity assessment; ETDRS = Early Treatment Diabetic Retinopathy Study.

The primary and first key secondary efficacy end points were analyzed through pairwise ANOVA models with treatment, baseline BCVA categories (≤ 55 letters read, 56 to 70 letters read, and ≥ 71 letters read), and age categories (< 75 years or ≥ 75 years) as fixed effects. Least squares means for each treatment arm and treatment differences, together with corresponding two-sided 95% CIs, were derived from the ANOVA models.

Noninferiority was demonstrated if the lower limit of the two-sided 95% CI for the corresponding treatment difference was greater than −4 ETDRS chart letters.

Missing data in the primary and first secondary outcomes were handled using a last observation carried forward (LOCF) approach. Baseline data were used in cases where no post-baseline assessment was available. In patients who discontinued treatment but remained in the trial, efficacy data were censored when the patient started alternative anti-VEGF treatment in the study eye.

Sensitivity analyses for the primary and first secondary outcomes included using the per-protocol set (PPS) as opposed to the full analysis set (FAS) and using a mixed-effects model for repeated measures analysis with the FAS and PPS with observed data.

Subgroup analyses for the primary and first secondary outcomes (i.e., change in BCVA from baseline to week 48 and to average BCVA from week 36 to week 48) included: age category (< 75 years or ≥ 75 years), sex (male or female), baseline BCVA categories (≤ 55 letters, 56 to 70 letters, and ≥ 71 letters), baseline central subfield thickness (CSFT) category (< 400 µm and ≥ 400 µm), baseline lesion type (predominantly classic, minimally classic, or occult), baseline CNV lesion size, baseline lesion size by lesion type (predominant classic versus minimally classic or occult), and baseline fluid status (IRF, SRF, or subretinal pigment epithelium fluid).

Second and third key secondary outcomes were described through a Kaplan-Meier time-to-event analysis for the event of first need for treatment every eight weeks.

Analysis Populations

The following key analysis sets were used in the HAWK and HARRIER studies:

- The FAS included all randomized patients who received at least one IVT injection of study treatment. The FAS served as the primary analysis set for all efficacy analyses. The patients in the FAS were analyzed according to the treatment arm to which they had been assigned at randomization.
- The PPS was a subset of the FAS that excluded patients with protocol deviations and violations of analysis requirements that were expected to majorly affect the validity of the assessment of efficacy at week 48. Supportive analyses of the primary and secondary efficacy end points were performed using the PPS. The patients in the PPS were analyzed according to the treatment arm to which they had been assigned at randomization.
- The safety analysis set included all patients who received at least one IVT injection. Patients in the safety analysis set were analyzed according to the study treatment from which they had received the majority of their treatments up to and including week 44.

Results

Patient Disposition

In HAWK, of 1,775 screened patients, 1,082 were randomized, 361 into the brolucizumab 6 mg arm and 361 into the aflibercept 2 mg arm. In HARRIER, a total of 1,048 patients were screened. Among them, 743 were randomized, 372 to the brolucizumab 6 mg arm and 371 to the aflibercept 2 mg arm.

At week 48, the proportion of patients who had discontinued the study was higher overall in HAWK (a total of 8.6%) than in HARRIER (a total of 5%). Also, within HAWK, a higher proportion of patients discontinued in the aflibercept 2 mg arm (9.4%) than in the brolucizumab 6 mg arm (7.8%). A similar scenario was observed in the proportion of patients who discontinued treatment before week 48, with HAWK having a higher overall proportion than HARRIER and a higher proportion in the aflibercept arm than in the brolucizumab 6 mg arm. The most frequently reported reason for discontinuation in all cases was patient withdrawal. This was followed by AEs.

At week 96, the proportion of patients who discontinued the study was higher overall in HAWK (a total of 16.75%) than in HARRIER (a total of 9.7%). In both studies, the proportions of discontinuations were higher in the aflibercept arms than in the brolucizumab 6 mg arms. The most frequently reported reason for discontinuation was patient withdrawal. This was followed by AEs.

Table 5: Patient Disposition

	HAWK		HARRIER	
	Brolucizumab 6 mg	**Aflibercept 2 mg**	**Brolucizumab 6 mg**	**Aflibercept 2 mg**
Screened, N	1,775		1,048	
Randomized, N	361	361	372	371
Randomized and treated, N (%)	360 (99.7)	360 (99.7)	370 (99.5)	369 (99.5)
Completed week 48, n (%)	333 (92.2)	327 (90.6)	354 (95.2)	352 (94.9)
Discontinued the study prior to week 48, n (%)	28 (7.8)	34 (9.4)	18 (4.8)	19 (5.1)
Adverse event	7 (1.9)	8 (2.2)	5 (1.3)	1 (0.3)
Lack of efficacy	0 (0.0)	0 (0.0)	0 0.0)	2 (0.5)
Physician decision	1 (0.3)	4 (1.1)	0 0.0)	0 (0.0)
Protocol deviation	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)
Withdrawal by patient	15 (4.2)	11 (3.0)	9 (2.4)	7 (1.9)
Death	3 (0.8)	6 (1.7)	3 (0.8)	4 (1.1)
Lost to follow-up	2 (0.6)	3 (0.8)	0 (0.0)	4 (1.1)
Other reason	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Discontinued the study treatment prior to week 48, n (%)	37 (10.2)	46 (12.7)	25 (6.7)	24 (6.5)
Adverse event	11 (3.0)	8 (2.2)	12 (3.2)	4 (1.1)
Lack of efficacy	0 (0.0)	3 (0.8)	1 (0.3)	2 (0.5)
Physician decision	1 (0.3)	5 (1.4)	1 (0.3)	1 (0.3)
Progressive disease	0 (0.0)	7 (1.9)	0 (0.0)	0 (0.0)
Protocol deviation	1 (0.3)	2 (0.6)	0 (0.0)	1 (0.3)
Withdrawal by patient	19 (5.3)	11 (3.0)	7 (1.9)	7 (1.9)
Death	3 (0.8)	6 (1.7)	3 (0.8)	4 (1.1)
Lost to follow-up	2 (0.6)	3 (0.8)	0 (0.0)	4 (1.1)
Other reason	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.3)
Completed week 96, n (%)	304 (84.2)	297 (82.3)	342 (91.9)	329 (88.7)

	HAWK		HARRIER	
Discontinued the study prior to week 96, n (%)	57 (15.8)	64 (17.7)	30 (8.1)	42 (11.3)
Adverse event	8 (2.2)	12 (3.3)	9 (2.4)	4 (1.1)
Lack of efficacy	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.5)
Physician decision	2 (0.6)	8 (2.2)	0 (0.0)	1 (0.3)
Protocol deviation	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)
Withdrawal by patient	34 (9.4)	23 (6.4)	12 (3.2)	21 (5.7)
death	7 (1.9)	12 (3.3)	4 (1.1)	7 (1.9)
Lost to follow-up	5 (1.4)	6 (1.7)	1 (0.3)	6 (1.6)
Other reason	1 (0.3)	0 (0.0)	4 (1.1)	1 (0.3)
Discontinued the study treatment prior to week 96, n (%)	68 (18.8)	80 (22.2)	43 (11.6)	52 (14.0)
Adverse event	13 (3.6)	14 (3.9)	20 (5.4)	9 (2.4)
Lack of efficacy	1 (0.3)	4 (1.1)	2 (0.5)	5 (1.3)
Physician decision	2 (0.6)	10 (2.8)	1 (0.3)	3 (0.8)
Progressive disease	3 (0.8)	8 (2.2)	0 (0.0)	0 (0.0)
Protocol deviation	1 (0.3)	2 (0.6)	0 (0.0)	1 (0.3)
Withdrawal by patient	36 (10.0)	23 (6.4)	10 (2.7)	20 (5.4)
death	6 (1.7)	12 (3.3)	4 (1.1)	7 (1.9)
Lost to follow-up	5 (1.4)	6 (1.7)	1 (0.3)	6 (1.6)
Other reason	1 (0.3)	1 (0.3)	5 (1.3)	1 (0.3)
Full analysis set, N (%)	360 (99.7)	360 (99.7)	370 (99.5)	369 (99.5)
Safety analysis set, N (%)	360 (99.7)	360 (99.7)	370 (99.5)	369 (99.5)
Per-protocol analysis set, N (%)	328 (90.9)	312 (86.4)	351 (94.4)	341 (91.9)

Source: CADTH Common Drug Review submission: Beovu (brolucizumab single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Exposure to Study Treatments

During the loading phase, all patients were exposed to a mean of three active injections within and across studies. From baseline to week 48 (one year), patients in the brolucizumab groups received a mean number of active injections of 6.2 (HAWK) and 6.4 (HARRIER), while patients in the aflibercept groups received a mean number of active injections of 6.8 (HAWK) and 6.9 (HARRIER). From baseline to week 96 (two years), patients in the brolucizumab groups received a mean number of active injections of 10.8 (HAWK) and 11.3 (HARRIER), while patients in the aflibercept groups received a mean number of active injections of 12.3 (HAWK) and 12.6 (HARRIER). Table 6 provides more details regarding exposure to brolucizumab and aflibercept in the HAWK and HARRIER studies.

Table 6: Exposure to Study Treatments (Full Analysis Set)

	HAWK		HARRIER	
Assessment period	**Brolucizumab 6 mg (n = 360)**	**Aflibercept 2 mg (n = 360)**	**Brolucizumab 6 mg (n = 370)**	**Aflibercept 2 mg (n = 369)**
Loading: baseline to week 12				
Mean (SD)	3.0 (0.50)	3.0 (0.69)	3.0 (0.39)	3.0 (0.39)
Median	3.0	3.0	3.0	3.0
Min, max	1, 3	1, 3	1, 3	1, 3
Maintenance: week 12 to week 48				
Mean (SD)	3.3 (3.29)	3.9 (2.65)	3.4 (3.25)	3.9 (1.79)
Median	3.0	4.0	3.0	4.0
Min, max	0, 4	0, 4	0, 4	0, 5
1 year: baseline to week 48			370	369
Mean (SD)	6.2 (4.58)	6.8 (4.51)	6.4 (4.40)	6.9 (3.18)
Median	6.0	7.0	6.0	7.0
Min, max	1, 7	1, 7	1, 7	1, 8
2 years: week 48 to week 96				
Mean (SD)	4.8 (7.05)	5.8 (4.21)	5.0 (6.92)	5.8 (3.88)
Median	4.0	6.0	5.0	6.0
Min, max	0, 6	0, 6	0, 6	0, 6
2 years: baseline to week 96				
Mean (SD)	10.8 (17.74)	12.3 (16.32)	11.3 (16.13)	12.6 (11.96)
Median	10.0	13.0	11.0	13.0
Min, max	1, 13	1, 13	1, 13	1, 14

SD = standard deviation.
Source: CDR submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported in the next section. See Appendix 3 for detailed efficacy data.

Best-Corrected Visual Acuity

Change from baseline to week 48 in BCVA was the primary outcome in both studies. At week 48, patients randomized to the brolucizumab 6 mg arm had a mean change from baseline of 6.4 ETDRS chart letters in HAWK (SD = 14.40) and of 6.9 ETDRS chart letters in HARRIER (SD = 11.47). At week 48, patients randomized to the aflibercept 2 mg arm had a mean change from baseline of 7.0 ETDRS chart letters in HAWK (SD = 13.16) and 7.6 ETDRS chart letters in HARRIER (SD = 12.47).

The treatment group differences in both studies were within the noninferiority margin. In HAWK, the mean difference of brolucizumab 6 mg versus aflibercept 2 mg was –0.2 (95% CI, –2.1 to 1.8). In HARRIER, the mean difference of brolucizumab 6 mg versus aflibercept 2 mg was –0.7 (95% CI, –2.4 to 1.0). Sensitivity analyses reported by the sponsor show results similar to the base case.

Subgroup analyses results are graphically represented in Figure 5 and in Figure 6 in Appendix 3. In HARRIER, the subgroups with the largest observed differences between brolucizumab 6 mg and aflibercept 2 mg were patients with baseline BCVAs of less than or

equal to 55 letters, patients with IRF present at baseline (–2.6 letters in both categories), and patients with baseline BCVAs of greater than or equal to 71 letters (+1.0 letters). None of the subgroups of interest assessed excluded the null within their 95% CI.

At week 96, patients randomized to the brolucizumab 6 mg arm had a mean change from baseline of 5.6 ETDRS chart letters in HAWK (SD = 15.62) and of 6.1 ETDRS chart letters in HARRIER (SD = 14.06). At week 96, patients randomized to the aflibercept 2 mg arm had a mean change from baseline of 5.6 ETDRS chart letters in HAWK (SD = 14.78) and of 6.6 ETDRS chart letters in HARRIER (SD = 12.47).

An outline of the results of the measures of change in BCVA from baseline is available in Table 7. BCVA by assessment visit is graphically presented in Figure 7 and Figure 8 in Appendix 3.

Table 7: Change From Baseline in Best-Corrected Visual Acuity (FAS – LOCF)

	Total N	Baseline	End-of-treatment time point	Treatment group difference versus control		
		Mean (SD)	Mean change from baseline (SD)	Mean difference (95% CI)[a]	P value (treatment difference)	P value (noninferiority)
BCVA: change from baseline at week 48 (FAS – LOCF)						
HAWK						
Brolucizumab 6 mg	360	60.8 (13.66)	6.4 (14.40)	–0.2 (–2.1 to 1.8)	0.8695	< 0.001
Aflibercept 2 mg	360	60.0 (13.92)	7.0 (13.16)	REF	REF	REF
HARRIER						
Brolucizumab 6 mg	370	61.5 (12.59)	6.9 (11.47)	–0.7 (–2.4 to 1.0)	0.4199	< 0.001
Aflibercept 2 mg	369	60.8 (12.93)	7.6 (12.47)	REF	REF	REF
BCVA: average change from baseline from week 36 to week 48 (FAS – LOCF)						
HAWK						
Brolucizumab 6 mg	360	60.8 (13.66)	6.5 (13.85)	0.0 (–1.9 to 1.9)	0.9791	< 0.001
Aflibercept 2 mg	360	60.0 (13.92)	6.9 (12.61)	REF	REF	REF
HARRIER						
Brolucizumab 6 mg	370	61.5 (12.59)	6.6 (11.10)	–1.2 (–2.8 to 0.5)	0.1582	< 0.001
Aflibercept 2 mg	369	60.8 (12.93)	7.7 (11.81)	REF	REF	REF
BCVA: change from baseline at week 96 (FAS – LOCF)						
HAWK						
Brolucizumab 6 mg	360	60.8 (13.66)	5.6 (15.62)	0.5 (–1.6 to 2.7)	0.6326[b]	NA
Aflibercept 2 mg	360	60.0 (13.92)	5.6 (14.78)	REF	REF	NA
HARRIER						
Brolucizumab 6 mg	370	61.5 (12.59)	6.1 (14.06)	–0.4 (–2.5 to 1.6)	0.6708[b]	NA
Aflibercept 2 mg	369	60.8 (12.93)	6.6 (14.55)	REF	REF	NA

BCVA = best-corrected visual acuity; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; NA = not applicable; REF = reference treatment; SD = standard deviation.

[a] Pairwise analysis of variance models with treatment, baseline BCVA categories (≤ 55, 56 to 70, and ≥ 71 letters read), and age categories (< 75 years or ≥ 75 years) as fixed effects.

[b] Outside the statistical testing hierarchy.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

The proportions of patients who gained greater than or equal to 15 letters from baseline or had a BCVA of greater than or equal to 84 letters at week 48 were 33.6% and 29.3% for the brolucizumab 6 mg groups in HAWK and HARRIER, respectively, while among those assigned to aflibercept 2 mg, the proportions who gained greater than or equal to 15 letters from baseline or had a BCVA of greater than or equal to 84 letters at week 48 were 25.4% and 29.9% in HAWK and HARRIER, respectively. On the other hand, the proportions of patients with a loss of greater than or equal to 15 letters from baseline at week 48 in the brolucizumab 6 mg groups were 6.4% and 3.8% in HAWK and HARRIER, respectively. These proportions were 5.5% and 4.8% for patients in the aflibercept groups in HAWK and HARRIER, respectively. An outline of these results is available in Table 8.

Table 8: Proportion of Patients With Change in BCVA of 15 ETDRS Chart Letters or Greater (FAS – LOCF)

	Total N	n (%)	Difference (95% CI)	P value[a]
Patients with ≥ 15 letters gain from baseline or BCVA of ≥ 84 letters at week 48 (FAS – LOCF)				
HAWK				
Brolucizumab 6 mg	360	119 (33.6)	8.2 (2.2 to 15.0)	0.0136[a]
Aflibercept 2 mg	360	93 (25.4)	REF	REF
HARRIER				
Brolucizumab 6 mg	370	109 (29.3)	–0.6 (–7.1 to 5.8)	0.8600[a]
Aflibercept 2 mg	369	110 (29.9)	REF	REF
Patients with ≥ 15 letters loss from baseline at week 48 (FAS – LOCF)				
HAWK				
Brolucizumab 6 mg	360	23 (6.4)	0.9 (–2.7 to 4.3)	0.6198[a]
Aflibercept 2 mg	360	20 (5.5)	REF	REF
HARRIER				
Brolucizumab 6 mg	370	14 (3.8)	–1.0 (–3.9 to 2.2)	0.5079[a]
Aflibercept 2 mg	369	18 (4.8)	REF	REF
Patients with ≥ 15 letters gain from baseline or BCVA of ≥ 84 letters at week 96 (FAS – LOCF)				
HAWK				
Brolucizumab 6 mg	360	121 (34.2)	7.2 (1.4 to 13.8)	0.0313[a]
Aflibercept 2 mg	360	99 (27.0)	REF	REF
HARRIER				
Brolucizumab 6 mg	370	108 (29.1)	–2.4 (–8.8 to 4.1)	0.4765[a]
Aflibercept 2 mg	369	116 (31.5)	REF	REF
Patients with ≥ 15 letters loss from baseline at week 96 (FAS – LOCF)				
HAWK				
Brolucizumab 6 mg	360	29 (8.1)	0.7 (–3.6 to 4.6)	0.7210[a]
Aflibercept 2 mg	360	27 (7.4)	REF	REF
HARRIER				
Brolucizumab 6 mg	370	26 (7.1)	–0.4 (–3.8 to 3.3)	0.8377[a]
Aflibercept 2 mg	369	28 (7.5)	REF	REF

CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; REF = reference treatment; SD = standard deviation.
[a] Outcome was outside the statistical testing hierarchy.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Health-Related Quality of Life and Vision-Related Function

Both HAWK and HARRIER measured HRQoL using the NEI VFQ-25 composite score. At baseline, scores were similar across and within the studies. At week 48, patients in the brolucizumab group experienced a mean change from baseline of 4.1 (SD = 12.58) in HAWK and of 4.8 (SD = 11.57) in HARRIER, while patients in the aflibercept 2 mg group experienced a mean change from baseline of 4.5 (SD = 10.64) in HAWK and 3.6 (SD = 11.88) in HARRIER. The results for mean change from baseline reported at 96 weeks were numerically less than those reported at week 48. These results are based on observed data only; no imputations were employed. An outline of these results is presented in Table 9.

Table 9: NEI VFQ-25 Composite Score: Descriptive Summary Results at Week 48 and Week 96 (FAS – Observed Data)

	Total N	Baseline	End-of-treatment time point		
		Mean (SD)	N	Mean (SD)	Mean change from baseline (SD)
NEI VFQ-25 Composite Score: change from baseline at week 48 (FAS – Observed)					
HAWK					
Brolucizumab 6 mg	358	77.4 (15.90)	324	81.6 (15.02)	4.1 (12.58)
Aflibercept 2 mg	359	77.0 (16.39)	317	81.6 (15.45)	4.5 (10.64)
HARRIER					
Brolucizumab 6 mg	368	74.6 (17.32)	347	79.7 (16.14)	4.8 (11.57)
Aflibercept 2 mg	369	76.0 (17.02)	346	80.2 (15.91)	3.6 (11.88)
NEI VFQ-25 Composite Score: change from baseline at week 96 (FAS – Observed)					
HAWK					
Brolucizumab 6 mg	358	77.4 (15.90)	301	81.7 (15.45)	3.8 (13.50)
Aflibercept 2 mg	359	77.0 (16.39)	296	80.8 (16.12)	2.8 (13.28)
HARRIER					
Brolucizumab 6 mg	368	74.6 (17.32)	338	79.2 (17.65)	3.8 (14.06)
Aflibercept 2 mg	369	76.0 (17.02)	329	79.3 (16.94)	2.6 (13.11)

FAS = full analysis set; SD = standard deviation; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire–25.
Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Legal Blindness

Not reported. See safety data.

Central Retinal Thickness

At baseline, retinal thickness was similar within and across studies. At week 48, patients in the brolucizumab group experienced a statistically significant mean change difference of –29.0 µm (95% CI, –47.6 to –10.4) compared to patients in the aflibercept group in HAWK and a mean change difference of –49.9 µm (95% CI, –68.9 to –30.9) compared to patients in the aflibercept group in HARRIER. At week 96, patients in the brolucizumab group experienced a mean change difference of –26.0 µm (95% CI, –46.2 to –5.9) compared to patients in the aflibercept group in HAWK and a mean change difference of –42.6 µm (95% CI, –62.0 to –23.3) compared to patients in the aflibercept group in HARRIER. Only the result of the comparison between brolucizumab 6 mg and aflibercept in the HAWK trial

was within the statistical hierarchy and adjusted for multiple testing. An outline of these results is presented in Table 10.

Table 10: CSFT-Total — Change From Baseline (FAS – LOCF)

	Total N	Baseline	End-of-treatment time point	Treatment group difference versus control[a]		
		Mean (SD)	Mean change from baseline (SD)	Mean difference (95% CI)	P value (one-sided)	P value (two-sided)
CSFT-total (µm): change from baseline at week 48 (FAS – LOCF)[a]						
HAWK						
Brolucizumab 6 mg	360	463.1 (166.62)	–170.8 (142.58)	–29.0 (–47.6 to –10.4)	0.0012	0.0023
Aflibercept 2 mg	360	457.9 (146.37)	–145.4 (145.57)	REF	REF	REF
HARRIER						
Brolucizumab 6 mg	370	473.6 (171.39)	–189.8 (158.35)	–49.9 (–68.9 to –30.9)	NA	< 0.0001[b]
Aflibercept 2 mg	369	465.3 (151.21)	–147.8 (144.97)	REF	NA	REF
CSFT-total (µm): change from baseline at week 96 (FAS – LOCF)[a]						
HAWK						
Brolucizumab 6 mg	360	463.1 (166.62)	–172.9 (156.38)	–26.0 (–46.2 to –5.9)	NA	0.0115 [b]
Aflibercept 2 mg	360	457.9 (146.37)	–150.7 (154.86)	REF	NA	REF
HARRIER						
Brolucizumab 6 mg	370	473.6 (171.39)	–193.6 (163.97)	–42.6 (–62.0 to –23.3)	NA	< 0.0001[b]
Aflibercept 2 mg	369	465.3 (151.21)	–159.3 (146.26)	REF	NA	REF

ANOVA = analysis of variance; CI = confidence interval; CSFT = central subfield thickness; FAS = full analysis set; LOCF = last observation carried forward; NA = not applicable; REF = reference treatment; SD = standard deviation.

[a] ANOVA model with baseline CSFT-total categories (< 400 µm and ≥ 400 µm), age categories (< 75 or ≥ 75 years), and treatment as fixed-effects factors.

[b] Outside the statistical testing hierarchy.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Presence of Intraretinal or Subretinal Fluid

The proportions of patients who had SRF or IRF at week 48 were 31.2% and 25.8% for those in the brolucizumab 6 mg groups in HAWK and HARRIER, respectively, while among those assigned to aflibercept 2 mg, the proportions at week 48 were 44.6% and 43.9% in HAWK and HARRIER, respectively. In HAWK, the difference between the brolucizumab 6 mg group and the aflibercept 2 mg group was statistically significant at –13.5 (95% CI, –20.7 to –6.1). At week 96, the proportions of patients with subretinal or intraretinal fluid were 24.0% and 24.4% for the brolucizumab 6 mg groups in HAWK and HARRIER, respectively, while among those assigned to aflibercept 2 mg, the proportions at week 96 were 36.9% and 38.5% in HAWK and HARRIER, respectively. An outline of these results is available in Table 11.

Table 11: Proportion of Patients With Presence of SRF and/or IRF at Week 48 and Week 96 (FAS – LOCF)

	Baseline n (%)	n (%)	Difference between groups (95% CI)[a]	P value (one-sided)	P value (two-sided)
Patients with presence of SRF and/or IRF at week 48 (FAS – LOCF)					
HAWK					
Brolucizumab 6 mg	334 (92.8)	112 (31.2)	–13.5 (–20.7 to –6.1)	0.0001	0.0002
Aflibercept 2 mg	336 (93.3)	161 (44.6)	REF	REF	REF
HARRIER					
Brolucizumab 6 mg	330 (89.2)	96 (25.8)	–18.1 (–24.9 to –11.8)	NA	< 0.0001[b]
Aflibercept 2 mg	332 (90.0)	161 (43.9)	REF	NA	REF
Patients with presence of SRF and/or IRF at week 96 (FAS – LOCF)					
HAWK					
Brolucizumab 6 mg	334 (92.8)	86 (24.0)	–12.9 (–19.7 to –6.6)	NA	0.0002[b]
Aflibercept 2 mg	336 (93.3)	133 (36.9)	REF	NA	REF
HARRIER					
Brolucizumab 6 mg	330 (89.2)	91 (24.4)	–14.1 (–21.3 to –7.2)	NA	< 0.0001[b]
Aflibercept 2 mg	332 (90.0)	141 (38.5)	REF	NA	REF

CI = confidence interval; FAS = full analysis set; IRF = intraretinal fluid; LOCF = last observation carried forward; NA = not applicable; REF = reference treatment; SRF = subretinal fluid.

[a] Logistic regression models with baseline fluid status, age categories (< 75 and ≥ 75 years), and treatment as fixed-effects factors are used.

[b] Outcome was outside the statistical testing hierarchy.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Other Outcomes: Switching From a Brolucizumab Injection Schedule of Every 12 Weeks to Every Eight Weeks

By the one-year mark, in both trials, almost half of the patients receiving brolucizumab 6 mg had switched to a regimen of treatment every eight weeks. However, the proportion of patients who required that regimen was less in the later weeks of the trial.

Table 12: Time to First Need for Treatment Every Eight Weeks (FAS – "Efficacy/Safety" Approach)

HAWK Brolucizumab 6 mg (N = 360)					
Time (week)	**Number of patients with first q.8.w. need at visit**	**Number of patients at risk at this visit**	**Number censored at the visit**	**Probability of maintaining on q.12.w. (survival)**	**95% CI for probability of maintaining on q.12.w.**
0	0	360	14	1.0000	1.0000 to 1.0000
16	83	346	4	0.7601	0.7115 to 0.8017
20	37	259	5	0.6515	0.5986 to 0.6993
32	19	217	10	0.5945	0.5404 to 0.6444
44	12	188	8	0.5565	0.5019 to 0.6077
56	18	168	8	0.4969	0.4418 to 0.5495
68	4	142	5	0.4829	0.4277 to 0.5358
80	6	133	3	0.4611	0.4059 to 0.5145
92	2	124	122	0.4537	0.3984 to 0.5072
HARRIER Brolucizumab 6 mg (N = 370)					
Time (week)	**Number of patients with first q.8.w. need at visit**	**Number of patients at risk at this visit**	**Number censored at the visit**	**Probability of maintaining on q.12.w. (survival)**	**95% CI for probability of maintaining on q.12.w.**
0	0	370	6	1.0000	1.0000 to 1.0000
16	83	364	8	0.7720	0.7253 to 0.8117
20	52	273	1	0.6249	0.5726 to 0.6727
28	13	220	6	0.5880	0.5351 to 0.6370
32	11	201	1	0.5558	0.5026 to 0.6057
40	6	189	4	0.5382	0.4849 to 0.5884
44	9	179	1	0.5111	0.4577 to 0.5619
52	5	169	2	0.4960	0.4426 to 0.5470
56	10	162	2	0.4654	0.4122 to 0.5168
64	6	150	1	0.4468	0.3938 to 0.4983
68	4	143	1	0.4343	0.3815 to 0.4858
76	4	138	2	0.4217	0.3691 to 0.4733
80	6	132	7	0.4025	0.3503 to 0.4541
88	5	119	0	0.3856	0.3336 to 0.4372
92	0	114	114	0.3856	0.3336 to 0.4372

CI = confidence interval; FAS = full analysis set; q.12.w. = every 12 weeks; q.8.w. = every 8 weeks.

Censored: Patients are considered no longer at risk of needing treatment every eight weeks at later visits.

Efficacy/safety approach: Censored data attributable to lack of efficacy and/or safety are imputed with the need for treatment every eight-weeks = Yes, at the next disease activity assessment visit.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Harms

Only those harms identified in the review protocol are reported in the following discussion. See Table 13 for detailed harms data.

Adverse Events

Overall and up to 96 weeks, ocular AEs were reported by 61.6% and 55.8% of patients in HAWK in the brolucizumab 6 mg and aflibercept 2 mg arms, respectively. In HARRIER, these proportions were 47.0% and 47.7% in the brolucizumab 6 mg and aflibercept 2 mg arms, respectively. Cataract as an AE was numerically higher in the aflibercept arm of the HARRIER study than the brolucizumab arm. The most commonly reported ocular AEs across studies and groups were conjunctival hemorrhage (4.6% to 8.9%) and reduced visual acuity (4.6% to 8.1%).

Serious Adverse Events

Overall and up to 96 weeks, ocular SAEs were experienced by a higher proportion of patients in the brolucizumab arms in both studies than by those in the aflibercept arms. Specifically, among patients who received brolucizumab 6 mg treatment, 3.3% and 3.5% experienced at least one serious ocular AE in HAWK and HARRIER, respectively, while among patients who received aflibercept treatment, 1.4% and 1.6% experienced at least one serious ocular AE. The most common ocular SAEs in the brolucizumab arms were endophthalmitis, uveitis, retinal tear, and retinal pigment epithelial tear. Conversely, non-ocular SAEs were experienced by a higher proportion of patients in the aflibercept arms in both studies than by those in the brolucizumab arms. Specifically, among patients who received aflibercept 2 mg treatment, 30.6% and 23.0% experienced at least one serious non-ocular AE in HAWK and HARRIER, respectively, while among patients who received brolucizumab 6 mg treatment, 23.6% and 18.6% experienced at least one serious ocular AE. There were no clusters of any specific SAE that would account for the majority of the non-ocular SAEs. The most common non-ocular SAE was pneumonia.

Withdrawal Due to Adverse Events

The sponsor reported that, overall, 3.1% and 3.5% of patients in the brolucizumab arms permanently discontinued treatment in the HAWK and HARRIER studies, respectively. Of the patients in the aflibercept arms, 3.3% and 1.6% permanently discontinued treatment in the HAWK and HARRIER studies, respectively. There was no specific most common AE that could be identified.

Mortality

A total of 20 patients passed away in the HAWK study, and a total of 11 passed away in the HARRIER study. Reasons for death are outlined in Table 13.

Notable Harms

Among the pre-specified notable harms, AEs related to eye inflammation were experienced by a higher proportion of patients in the brolucizumab group compared to the aflibercept group. Specifically, of patients who received brolucizumab 6 mg treatment, 5.8% and 3.0% experienced at least one eye infection event in HAWK and HARRIER, respectively, while among patients who received aflibercept treatment, 0.6% and 1.4% experienced at least one eye infection event.

Table 13: Summary of Harms

	HAWK		HARRIER	
	Brolucizumab 6 mg (N = 360)	Aflibercept 2 mg (N = 360)	Brolucizumab 6 mg (N = 370)	Aflibercept 2 mg (N = 369)
Patients with ≥ 1 ocular AE				
n (%)	220 (61.1)	201 (55.8)	174 (47.0)	176 (47.7)
Most common events[a]				
Conjunctival hemorrhage	29 (8.1)	32 (8.9)	17 (4.6)	19 (5.1)
Visual acuity reduced	22 (6.1)	29 (8.1)	32 (8.6)	26 (7.0)
Vitreous floaters	22 (6.1)	16 (4.4)	15 (4.1)	5 (1.4)
Retinal hemorrhage	21 (5.8)	20 (5.6)	12 (3.2)	4 (1.1)
Cataract	20 (5.6)	13 (3.6)	11 (3.0)	43 (11.7)
Vitreous detachment	19 (5.3)	19 (5.3)	10 (2.7)	8 (2.2)
Dry eye	19 (5.3)	26 (7.2)	10 (2.7)	11 (3.0)
Eye pain	18 (5.0)	21 (5.8)	13 (3.5)	19 (5.1)
Patients with ≥ 1 non-ocular AE				
n (%)	289 (80.3)	303 (84.2)	282 (76.2)	272 (73.7)
Most common events[a]				
Nasopharyngitis	38 (10.6)	44 (12.2)	43 (11.6)	31 (8.4)
Pneumonia	32 (8.9)	20 (5.6)	7 (1.9)	13 (3.5)
Urinary tract infection	27 (7.5)	41 (11.4)	16 (4.3)	19 (5.1)
Hypertension	25 (6.9)	24 (6.7)	28 (7.6)	25 (6.8)
Upper respiratory tract infection	18 (5.0)	16 (4.4)	6 (1.6)	14 (3.8)
Influenza	17 (4.7)	20 (5.6)	24 (6.5)	27 (7.3)
Arthralgia	15 (4.2)	21 (5.8)	14 (3.8)	13 (3.5)
Pain in extremity	15 (4.2)	10 (2.8)	9 (2.4)	4 (1.1)
Back pain	14 (3.9)	17 (4.7)	16 (4.3)	28 (7.6)
Diarrhea	14 (3.9)	13 (3.6)	10 (2.7)	6 (1.6)
Cough	13 (3.6)	17 (4.7)	12 (3.2)	8 (2.2)
Bronchitis	13 (3.6)	22 (6.1)	23 (6.2)	21 (5.7)
Patients with ≥ 1 ocular SAE				
n (%)	12 (3.3)	5 (1.4)	13 (3.5)	6 (1.6)
Endophthalmitis	3 (0.8)	0 (0.0)	1 (0.3)	1 (0.3)
Uveitis	2 (0.6)	0 (0.0)	3 (0.8)	0 (0.0)
Retinal detachment	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Visual acuity reduced	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)
Macular hole	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Cataract	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Retinal artery thrombosis	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Retinal depigmentation	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Retinopathy proliferative	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Vitritis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

	HAWK		HARRIER	
	Brolucizumab 6 mg (N = 360)	Aflibercept 2 mg (N = 360)	Brolucizumab 6 mg (N = 370)	Aflibercept 2 mg (N = 369)
Retinal artery occlusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Glaucoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cataract, subcapsular	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Retinal tear	0 (0.0)	0 (0.0)	2 (0.5)	1 (0.3)
Retinal pigment epithelial tear	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)
Anterior chamber inflammation	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Cataract, traumatic	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Blindness	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Dacryocystitis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Retinal artery embolism	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Dry age-related macular degeneration	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Patients with ≥ 1 non-ocular SAE				
n (%)	85 (23.6)	110 (30.6)	69 (18.6)	85 (23.0)
Most common events[b]				
Pneumonia	10 (2.8)	9 (2.5)	2 (0.5)	8 (2.2)
Cardiac failure, congestive	6 (1.7)	4 (1.1)	0 (0.0)	1 (0.3)
Chronic obstructive pulmonary disease	6 (1.7)	4 (1.1)	2 (0.5)	1 (0.3)
Atrial fibrillation	4 (1.1)	2 (0.6)	1 (0.3)	0 (0.0)
Cerebrovascular accident	4 (1.1)	3 (0.8)	0 (0.0)	4 (1.1)
Sepsis	4 (1.1)	1 (0.3)	1 (0.3)	1 (0.3)
Patients who permanently stopped treatment due to AEs				
n (%)	11 (3.1)	12 (3.3)	13 (3.5)	6 (1.6)
Most common events[b]				
No single event > 1% frequency				
Deaths				
n (%)	8 (2.2)	12 (3.3)	4 (1.1)	7 (1.9)
Cardiopulmonary failure	0	0	1	1
Myocardial infarction	0	1	1	0
Pulmonary edema	0	0	1	0
Chest injury	0	0	0	1
Natural cause	0	0	0	1
Renal failure	0	0	0	1
Cardiac arrest	1	2	0	1
Cerebrovascular accident	2	0	0	0

	HAWK		HARRIER	
	Brolucizumab 6 mg (N = 360)	Aflibercept 2 mg (N = 360)	Brolucizumab 6 mg (N = 370)	Aflibercept 2 mg (N = 369)
Lung carcinoma, cell type unspecified, stage IV	1	0	0	0
Non–small cell lung cancer	1	0	0	0
Emphysema	1	0	0	0
Arteriosclerosis	1	0	0	0
Sepsis	1	0	0	0
Chronic obstructive pulmonary disease	0	1	0	0
H1N1 influenza	0	1	0	0
Aortic stenosis	0	1	0	0
Acute respiratory failure	0	1	0	0
Pancreatic carcinoma, metastatic	0	1	0	0
Neoplasm, malignant	0	1	0	0
Not specified	0	2	0	2
Cardiorespiratory arrest	0	1	0	0
Hemorrhage of unknown etiology	0	0	1	0
Notable harms				
Endophthalmitis, n (%)	4 (1.1)	0 (0.0)	1 (0.3)	1 (0.3)
Any intraocular inflammation	21 (5.8)	2 (0.6)	11 (3.0)	5 (1.4)
Iritis	9 (2.5)	1 (0.3)	0 (0.0)	1 (0.3)
Uveitis	8 (2.2)	1 (0.3)	3 (0.8)	0 (0.0)
Vitritis	2 (0.6)	1 (0.3)	1 (0.3)	2 (0.5)
Anterior chamber inflammation	1 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)
Iridocyclitis	1 (0.3)	0 (0.0)	2 (0.5)	1 (0.3)
Chorioretinitis	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Anterior chamber cell	1 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)
Anterior chamber flare	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)
Eye inflammation	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Vitreous hate	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Endophthalmitis, n (%)	3 (0.8)	0 (0.0)	1 (0.3)	1 (0.3)
Eye infections, n (%)	NR	NR	NR	NR
Retinal tear, n (%)	6 (1.7)	3 (0.8)	3 (0.8)	2 (0.5)
Retinal detachment, n (%)	2 (0.6)	1 (0.3)	2 (0.5)	1 (0.3)
Increased IOP, n (%)	13 (3.6)	15 (4.2)	14 (3.8)	15 (4.1)
Glaucoma, n (%)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Surgical intervention for glaucoma treatment, n (%)	NR	NR		

	HAWK		HARRIER	
	Brolucizumab 6 mg (N = 360)	Aflibercept 2 mg (N = 360)	Brolucizumab 6 mg (N = 370)	Aflibercept 2 mg (N = 369)
Conjunctival hemorrhage, n (%)	29 (8.1)	32 (8.9)	17 (4.6)	19 (5.1)
Vitreous hemorrhage, n (%)	2 (0.6)	1 (0.3)	0 (0.0)	2 (0.5)
Arteriothrombotic event	11 (3.1)	11 (3.1)	11 (3.0)	10 (2.7)

AE = adverse event; IOP = intraocular pressure; NR = not reported; SAE = serious adverse event.

[a] Frequency > 5%.

[b] Frequency > 3%.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Critical Appraisal

Internal Validity

The included studies were double-masked, multi-centre, randomized, active-controlled, noninferiority trials. The randomization processes, including allocation concealment and masking method, were well described and performed. Overall, the important baseline characteristics were similar between the two treatment groups. Discontinuations were similar and less than 10% before the end point of the primary outcome. Given that the study drug was administered at the study site, compliance could be monitored by reviewing patients' clinical or medical records. The study approach to calculating the noninferiority margin and sample size was well justified. Data imputation methods and analysis population assumptions were tested in several sensitivity analyses. A multiplicity adjustment was performed for the primary and the first secondary outcomes at week 48 through a combination of alpha spending and statistical hierarchy. A further adjustment was employed through alpha spending and statistical hierarchy for some secondary outcomes in the HAWK study, but not in the HARRIER study.

While the studies were considered to be well designed overall, the methodological quality could have been improved through randomization stratified by geographic region. The statistical analysis model did not include geographic region as a covariate. The potential effect of not controlling for region is not clear.

The lack of multiplicity adjustment was a limitation in all outcomes in the HARRIER study beyond the primary and first secondary outcomes. In HAWK, the majority of reported additional secondary outcomes were also not adjusted for multiplicity. This limits the interpretation of any statistical testing, as all results should be interpreted with consideration of an increased risk of a type I error. In addition, considering that the noninferiority margin was only determined for the primary outcome, the interpretation of outcomes (beyond the primary outcome) that do not show statistically significant differences is not possible. While subgroup analysis was pre-specified in the studies protocol, it was not designed to test any hypothesis, and the results of the subgroup analyses are descriptive in nature.

In HAWK, the proportion of patients discontinuing the trial in the aflibercept arm (9.4%) was numerically higher than in the brolucizumab 6 mg arm (7.8%), representing a difference of six patients. Considering this differential discontinuation rate and the fact that the data imputation method was an LOCF, this could potentially bias the results in favour of

brolucizumab. However, the potential impact of this differential in discontinuation rate is unclear.

Sham injections were given to mask treatment assignment. These were administered by an unmasked physician, and it may have been possible for patients to distinguish them from real injections. This may pose a risk of revealing treatment assignment. However, the potential effect such a risk would cause on the internal validity of the study is unclear.

Finally, no true intention-to-treat (ITT) analysis was performed, as the FAS included patients who were randomized and received at least one injection. The difference between the FAS used and true ITT analysis would translate to four patients who were randomized and did not receive treatment. Considering that this is a noninferiority, active-controlled trial, the potential effects of this limitation are unclear. However, considering that almost all patients received at least one injection, any impact would be minimal.

External Validity

While HARRIER did not include any Canadian sites, HAWK included several. In addition, and according to the clinical expert included in this review, most patients newly diagnosed with nAMD would have been eligible to participate in these two studies. As a result, according to the clinical expert, the baseline characteristics reflect the nAMD patient population.

However, both studies only allowed the inclusion of treatment-naive patients, essentially limiting any inferences to patients newly diagnosed with nAMD. Thus, the efficacy of brolucizumab in treatment-experienced patients is not clear.

There were no direct comparisons between brolucizumab and ranibizumab or bevacizumab, two of the most commonly used anti-VEGFs. The sponsor provided an ITC to address this gap.

Finally, the applicability of the results measuring the proportion of patients on every-eight-week or every-12-week regimens might be limited in practice, for several reasons. First, information about the development, validation, and extent of the investigator's use of the criteria described in the two studies to determine disease activity is not available. Second, in clinical practice, it is unlikely that patients would be ineligible for treatment every 12-weeks after being administered treatment every eight weeks. In addition, neither HAWK nor HARRIER assessed the comparative injection frequency of brolucizumab versus aflibercept under a pre-specified statistical testing method. This is a major limitation, as no inference can be made about the results related to the number of injections. The generalizability value of the injection frequency measures is further reduced with the common use of treat-and-extend protocols in clinical practice.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

Due to the lack of direct evidence comparing brolucizumab with anti-VEGF other than aflibercept, the sponsor performed an NMA to estimate the efficacy of brolucizumab in patients with nAMD versus other anti-VEGFs. The objective of this section is to summarize and critically review the unpublished NMA performed by the sponsor. In addition, CADTH performed a literature search to identify any published indirect evidence of brolucizumab. None was identified.

Description of Indirect Comparison

One ITC submitted by the sponsor is discussed here. An overview of the submitted ITC is presented in Table 14.

Table 14: Study Selection Criteria and Methods for the Indirect Treatment Comparison

	Sponsor-submitted ITC: systematic review portion	Sponsor-submitted ITC: network meta-analysis portion
Population	Patients of any age undergoing treatment for nAMD	
Intervention	Brolucizumab	
Comparator	• Ranibizumab • Aflibercept • Pegaptanib • Photodynamic therapy with verteporfin • Laser photocoagulation therapy • Macular surgeries • Bevacizumab	• Ranibizumab • Aflibercept • Bevacizumab
Outcome	• Visual acuity (ETDRS chart letters or logMAR or Snellen equivalent) • Other measures of visual acuity (blindness and ≥15 letter gain/loss) • CRT • HRQoL • Severe ocular and systemic adverse events • Treatment discontinuation • Injection and monitoring frequencies	• Mean change in BCVA • Mean change in CRT • Proportion of patients gaining at least 15 ETDRS chart letters • Proportion of patients losing at least 15 ETDRS chart letters • Overall discontinuation • Injection frequencies • Adverse events
Study design	• Randomized controlled trials of 44 weeks or longer • Crossover RCTs (if data presented at the time of crossover) • Open-label extension studies of RCTs	
Publication characteristics	Peer-reviewed and published in journals or retrieved through hand searches on relevant Congress websites	
Exclusion criteria	Not matching the inclusion criteria	
Databases searched	Embase, MEDLINE, Cochrane Library	
Selection process	Two independent reviewers	
Data extraction process	One reviewer	
Quality assessment	The Cochrane Collaboration's tool for assessing risk of bias in randomized trials	

BCVA = best-corrected visual acuity; CRT = central retinal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; HRQoL = health-related quality of life; ITC = indirect treatment comparison; logMAR = logarithm of the minimum angle of resolution; nAMD = neovascular age-related macular degeneration; RCT = randomized controlled trial.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Methods of Sponsor-Submitted Indirect Treatment Comparison

Objectives

The objective of the ITC was to assess the comparative efficacy and safety of brolucizumab with relevant interventions that are listed in Table 14.

The original analysis of the sponsor's ITC excluded bevacizumab due to the lack of Health Canada indication for the treatment of nAMD. However, after discussion with CADTH, the sponsor submitted an expanded analysis that included bevacizumab as a relevant comparator in clinical practice in Canada.

Study Selection Methods

The authors developed a search strategy and searched three bibliographic databases (MEDLINE, Embase, and the Cochrane Library) with a manual screen of references of included studies. The population of interest was patients with nAMD. Both treatment-naive and experienced patients were included. The main intervention was defined as brolucizumab 6 mg every 12 weeks or every eight weeks (i.e., "Bro6 q.12.w./q.8.w."). Comparators were defined as follows:

- Bevacizumab 1.25 mg every eight weeks (Bev 1.25 mg q.8.w.)
- Bevacizumab 1.25 mg every six weeks (Bev 1.25 mg q.6.w.)
- Bevacizumab 1.25 mg every four weeks (Bev 1.25 mg q.4.w.)
- Bevacizumab 1.25 mg as needed (Bev 1.25 mg PRN)
- Bevacizumab with loading phase every six weeks, then every 12 weeks (LP [q.6.w.] -> Bev 1.25 mg q.12.w.)
- Bevacizumab with loading phase at six weeks, then as needed (LP [q.6.w.] -> Bev 1.25 mg PRN)
- Bevacizumab with loading phase, then as needed (LP -> Bev 1.25 mg PRN)
- Bevacizumab with treat-and-extend protocol (Bev 1.25 mg TRX)
- Ranibizumab 0.5 mg every four weeks (Rani 0.5 mg q.4.w.)
- Ranibizumab 0.5 mg as needed (Rani 1.25 mg PRN)
- Ranibizumab 0.5 mg loading phase, then as needed (LP -> Rani 0.5 mg PRN)
- Ranibizumab 0.5 mg loading phase, then as needed with potential to extend (LP -> Rani 0.5 mg PRNX)
- Ranibizumab 0.5 mg loading phase, then every eight weeks (LP -> Rani 0.5 mg q.8.w.)
- Ranibizumab 0.5 mg loading phase, then every 12 weeks (LP -> Rani 0.5 mg q.12.w.)
- Ranibizumab 0.5 mg loading phase, then treat-and-extend (LP -> Rani 0.5 mg TREX)
- Aflibercept 2 mg every four weeks (Afli 2 mg q.4.w.)
- Aflibercept 2 mg loading phase, then every eight weeks (LP -> Afli 2 mg q.8.w.)
- Aflibercept 2 mg loading phase, then as needed (LP -> Afli 2 mg PRN)
- Aflibercept 2 mg loading phase at 12 weeks, then as needed (LP [2 mg q.12.w.] -> Afli 2 mg PRN)
- Brolucizumab 3 mg loading phase, then every 12 weeks except in disease activity, then every eight weeks (LP -> Bro3 q.12.w./q.8.w.)
- Brolucizumab 6 mg loading phase, then injections every eight weeks until month 32, with a final injection at week 44 (LP -> Bro6 q.8.w. -> q.12.w.)

The criteria included English studies only and did not have a publication date limit. Two reviewers independently screened the retrieved reports at two stages, with any disagreement adjudicated by a third reviewer. Data extraction was handled by one

reviewer. Quality assessment was carried out using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials.

Visual acuity outcomes were defined as BCVA according to ETDRS chart letters. The definition of the retinal thickness outcome allowed the inclusion of various measures of retinal thickness, including mean change in retinal thickness, central retinal thickness (CRT), central macular thickness, CSFT, and central foveal thickness. No specific definitions for overall discontinuation, injection frequency, or AEs were specified beyond the standard reporting in each trial.

The sponsor's ITC reported outcomes at two end points: one year and two years. The one-year outcome included any result reported from week 48 to week 52, while the two-year outcome included any result reported from week 96 to week 104.

Indirect Treatment Comparison Analysis Methods

The authors of the sponsor-submitted ITC used a Bayesian approach through Markov chain Monte Carlo methods. Non-informative priors were chosen for the analysis. Convergence of the model was assessed using Brooks-Gelman-Rubin diagnostics.

The authors assessed model fit through the DIC and residual posterior heterogeneity. The authors constructed two models for each outcome: fixed-effects and random-effects models. The choice of model was based on a better fit, as indicated by a lower DIC value. A total of 20,000 iterations were used as burn-in followed by 20,000 iterations to monitor the parameters for the fixed-effects model, with 100,000 iterations as burn-in and 100,000 to monitor the parameters for the random-effects model.

The sponsor's ITC included a visual representation of the distribution of possible treatment-effect modifiers across included studies (not including the bevacizumab studies). In addition, assessment of heterogeneity in direct comparison was reported using the I-square measure. The sponsor attempted a meta-regression model to control for the impact of baseline BCVA value and type of treatment regimen, but it was not possible because the networks did not provide enough information to allow the models to converge. The authors planned and conducted sensitivity analyses for treatment-naive–only patients, spectral-domain OCT (not applied in the bevacizumab network), imputation of missing SD, and a sensitivity analysis that would exclude outcomes reported as a median.

The authors did not report on assessing the consistency assumption in the NMA.

Although the authors neither provided an a priori definition of what determines a significant result nor stated a clear null or alternate hypothesis to be rejected at certain thresholds, they commonly refer to results where the 95% CrI does not include the null (one in the odds ratio or zero in the mean difference) as a significant finding.

Table 15: Indirect Treatment Comparison Analysis Methods

ITC methods	Bayesian network meta-analysis
Priors	Non-informative
Assessment of model fit	Diagnostic information criterion
Assessment of consistency	Not reported
Assessment of convergence	Trace plots and Brooks-Gelman-Rubin diagnostics
Outcomes	• Mean change in BCVA • Mean change in retinal thickness • Proportion of patients gaining at least 15 ETDRS chart letters • Proportion of patients losing at least 15 ETDRS chart letters • Overall discontinuation
Follow-up time points	• One-year outcome included any result reported from week 48 to week 52 • Two-year outcome included any result reported from week 96 to week 104
Construction of nodes	Each node required the same dose and treatment regimen.
Sensitivity analyses	• Treatment-naive • Imputation of missing standard deviation • Exclude outcomes reported as a median
Subgroup analysis	None
Methods for pairwise meta-analysis	The inverse variance-weighted with Mantel-Haenszel method for continuity correction of zero events

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Results of Sponsor-Submitted Indirect Treatment Comparison

Summary of Included Studies

The authors included a total of 39 RCTs in the systematic review and conducted an NMA of a total of 22 RCTs. All trials were head-to-head except two trials that compared active treatments to sham IVT injection. Most of the trials (23 out of 39) were double-blind, and six included patients for open-label analysis. Study sizes ranged from 40 patients to 2,412 ITT patients. There was various heterogeneity in the way retinal thickness was measured and defined in the included trials.

The mean age at baseline ranged from 65 years to 83.3 years. The proportion of males across the studies ranged from 30% to 56%. The mean BCVA (ETDRS chart letters read) at baseline ranged from 53.5 letters to 61.5 letters. The retinal thickness at baseline ranged from 247 µm to 533 µm. Per-study data are not shown here, but were provided by the sponsor. The sponsor did not provide baseline data on disease duration. The authors provided a quality assessment for each of the included studies. A graphic representation is provided in Figure 3.

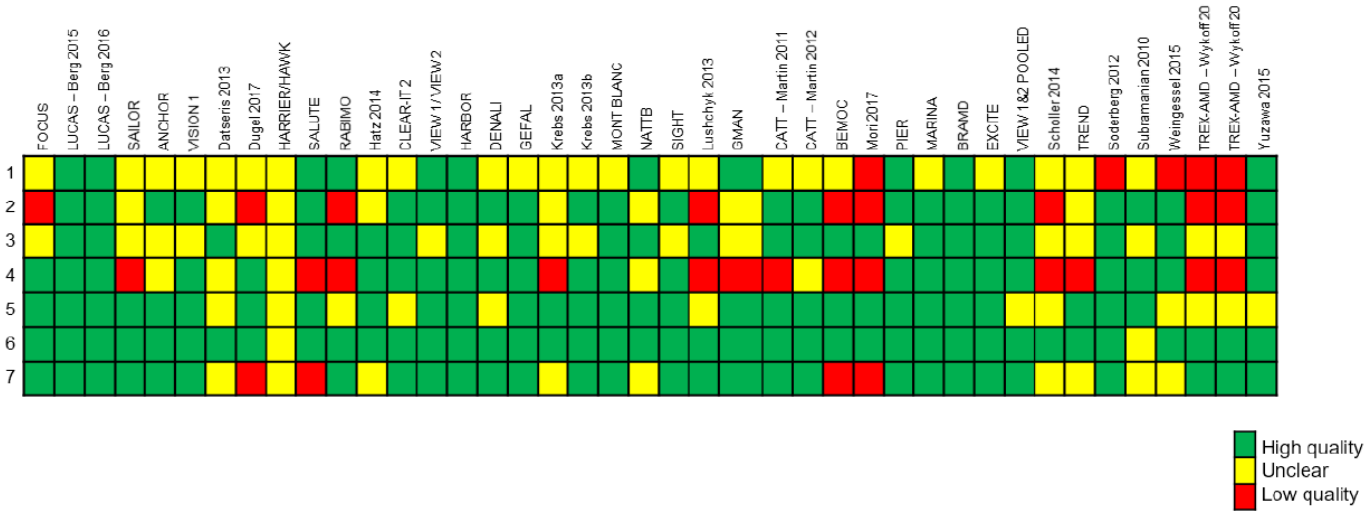
Table 16: Assessment of Homogeneity for Sponsor-Submitted Indirect Treatment Comparison

	Description and handling of potential effect modifiers
Disease severity	The authors reported baseline BCVA, age, and retinal thickness. Considerable heterogeneity was identified in retinal thickness between trials. Disease duration was not reported. The authors attempted to run regression models to control for baseline BCVA.
Treatment history	The sponsor reported previous treatment experience status for 14 of the included studies (did not report on the bevacizumab trials). Of these, 12 were treatment-naive. The sponsor planned a sensitivity analysis where only treatment-naive patients are included.
Clinical trial eligibility criteria	The sponsor reported reviewing the eligibility criteria of each trial. These have not been detailed in the submission. There was no clear decision regarding homogeneity of the included studies in their eligibility criteria.
Dosing of comparators	The authors treated each dose and regimen combination as a separate intervention or comparator.
Placebo response	Only two of the included trials had a sham or placebo arm.
Definitions of end points	Considerable heterogeneity was identified in retinal thickness. The authors reported using a sensitivity analysis to assess the effect of one of the definitions. However, this was not conducted on the analysis that included bevacizumab.
Timing of end point evaluation or trial duration	• The one-year outcome included any result reported from week 48 to week 52. • The two-year outcome included any result reported from week 96 to week 104.
Withdrawal frequency	Discontinuation was reported for 9 studies and ranged from 5% to 25%. The authors treated discontinuation as an outcome measure.
Study design	The majority of the included trials were double-masked, randomized, head-to-head trials.

BCVA = best-corrected visual acuity.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Figure 3: Quality Assessment of Included Studies



Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

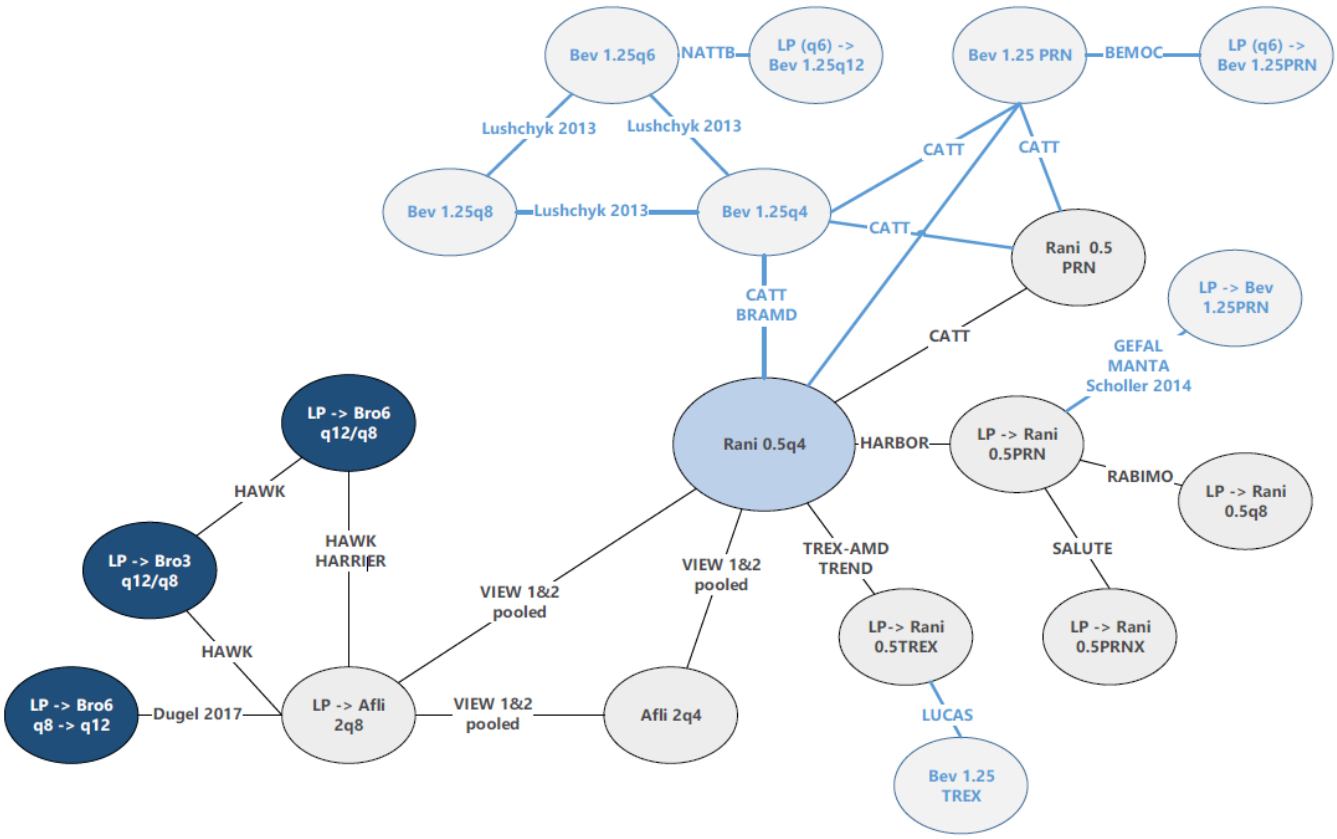
1. Was randomization carried out appropriately?
2. Was the concealment of treatment allocation adequate?
3. Were the groups similar at the outset of the study in terms of prognostic factors?
4. Were the care providers, participants, and outcome assessors blind to treatment allocation?
5. Were there any unexpected imbalances in drop-outs between groups?
6. Is there any evidence to suggest the authors measured more outcomes than they reported?
7. Did the analysis include an ITT analysis? If so, was this appropriate, and were appropriate methods used to account for missing data?

Results

BCVA

For the analysis of the outcome of BCVA at one year, the authors included 21 trials. The analysis was conducted using a fixed-effects model, as it had a smaller DIC than the random-effects model (numbers not reported for this network). A graphic representation of the evidence network is presented in Figure 4. Brolucizumab 6 mg every 12 weeks or every eight weeks was significantly better than sham. All other comparisons included zero in the 95% CrI. Also, wide CrIs were noted in several comparisons. At two years, the network was much sparser than it was at one year, including only nine trials. Similarly, brolucizumab was significantly better than sham, but wide CrIs were more prominent in the two-year outcome than in the one-year outcome. The comparative results are outlined in Table 17.

Figure 4: Evidence Network for the Outcome of BCVA at One Year



Afli = aflibercept; AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; Bev = bevacizumab; Bro6 = brolucizumab 6 mg; Bro3 = brolucizumab 3 mg; CATT = Comparison of AMD Treatments Trials; LP = loading phase; PRN = as needed; PRNX = as needed with potential to extend; q.4.w. = every 4 weeks; q.6.w = every 6 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; Rani = ranibizumab; TREX = treat-and-extend.
Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Table 17: Mean Difference (95% CrI) in BCVA – Indirect Treatment Comparison Results

	Mean difference [95% CrI] BCVA mean change from baseline at 1 year	Mean difference [95% CrI] BCVA mean change from baseline at 2 years
	Brolucizumab 6 mg q.12.w./q.8.w. versus	**Brolucizumab 6 mg q.12.w./q.8.w. versus**
Number of studies (patients), model	21 RCTs included, fixed-effects model	9 RCTs included, fixed-effects model
Rani 0.5 mg q.4.w.	–0.77 (–2.77 to 1.26)	–0.26 (–2.51 to 2.04)
LP -> Rani 0.5 mg PRN	1.14 (–1.82 to 4.12)	0.96 (–2.40 to 4.33)
Rani 0.5 mg PRN	1.08 (–1.83 to 4.00)	1.84 (–2.08 to 5.77)
LP -> Rani 0.5 mg PRNX	–3.3 (–12.16 to 5.46)	–
LP -> Rani 0.5 mg q.12.w.	0.76 (–6.7 to 8.20)	–
LP -> Rani 0.5 mg q.8.w.	–0.87 (–8.43 to 6.55)	–
LP -> Rani 0.5 mg TREX	0.98 (–1.78 to 3.74)	3.33 (–5.32 to 11.95)
LP -> Afli 2 mg q.8.w.	–0.44 (–1.72 to 0.85)	0.03 (–1.47 to 1.48)

	Mean difference [95% CrI] BCVA mean change from baseline at 1 year	Mean difference [95% CrI] BCVA mean change from baseline at 2 years
	Brolucizumab 6 mg q.12.w./q.8.w. versus	**Brolucizumab 6 mg q.12.w./q.8.w. versus**
Afli 2 mg q.4.w.	–1.35 (–3.34 to 0.67)	0.04 (–2.2 to 2.3)
LP -> Bev 1.25 mg PRN	–0.57 (–4.18 to 3.04)	–
Bev 1.25 mg PRN	1.97 (–1.11 to 5.08)	3.53 (–0.63 to 7.68)
Bev 1.25 mg q.4.w.	0.09 (–2.65 to 2.82)	0.75 (–3.65 to 5.17)
Bev 1.25 mg q.6.w.	0.47 (–5.17 to 6.15)	–
Bev 1.25 mg q.8.w.	–3.91 (–9.29 to 1.46)	–
Bev 1.25 mg TREX	1.27 (–2.55 to 5.1)	2.55 (–6.71 to 11.82)
LP (q.26.w.) -> Bev 1.25 mg PRN	1.8 (–4.39 to 8.03)	–
Sham IVT injection	**16.83 (13.29 to 20.37)**	**21.25 (17.43 to 25.11)**
LP -> Bro6 q.8.w. -> q.12.w.	0.79 (–5.57 to 7.13)	–
LP -> Bro3 q.12.w./q.8.w.	0.39 (–1.38 to 2.20)	0.00 (–2.03 to 2.02)
LP (q.26.w.) -> Bev 1.25 mg q.12.w.	2.95 (–4.29 to 10.26)	–
Comment	Sensitivity analyses with treatment-naive and data imputation show similar results. No inconsistency assessment was conducted.	Sensitivity analyses with treatment-naive and data imputation show similar results. No inconsistency assessment was conducted.

Afli = aflibercept; BCVA = best-corrected visual acuity; Bev = bevacizumab; Bro6 = brolucizumab 6 mg; Bro3 = brolucizumab 3 mg; CrI = credible interval; IVT = intravitreal; LP = loading phase; PRN = as needed; PRNX = as needed with potential to extend; q.4.w. = every 4 weeks; q.6.w = every 6 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; q.26.w. = every 26 weeks TREX = treat-and-extend; Rani = ranibizumab; RCT = randomized controlled trial.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Retinal Thickness

For outcomes measured at one year, the authors included 18 RCTs in the analysis under a fixed-effects model. The results showed brolucizumab to be significantly better than all comparators except for ranibizumab 0.5 mg administered as needed with extension after a loading phase, and for brolucizumab 3 mg administered every 12 weeks or every eight weeks after a loading phase. However, CrIs in these results are notably large in all results.

For outcomes measured at two years, the authors included eight trials in the analysis. The two-year results showed larger CrIs than the one-year results, and the null included comparisons that were significant in the one-year analysis (versus loading phase -> ranibizumab 0.5 mg treat-and-extend, bevacizumab 1.25 mg treat-and-extend, and bevacizumab 1.25 mg every six weeks). Results are outlined in Table 18.

Table 18: Indirect Treatment Comparison Results for Retinal Thickness

	Mean difference [95% CrI] Retinal thickness mean change from baseline at 1 year	Mean difference [95% CrI] Retinal thickness mean change from baseline at 2 years
	Brolucizumab 6 mg q.12.w./q.8.w. versus	**Brolucizumab 6 mg q.12.w./q.8.w. versus**
Number of studies (patients), model	18 RCTs included, fixed-effects model	8 RCTs included, fixed-effects model
Rani 0.5 mg q.4.w.	**–50.16 (–69.79 to –31.01)**	**–49.35 (–71.14 to –28.10)**
LP -> Rani 0.5 mg PRN	**–58.92 (–87.3 to –30.12)**	**–61.18 (–94.02 to –28.12)**
Rani 0.5 mg PRN	**–67.8 (–101.7 to –34.17)**	**–72.03 (–114.3 to –29.53)**
LP-> Rani 0.5 mg TREX	**–54.43 (–85.64 to –23.93)**	12.65 (–86.82 to 60.37)
LP -> Rani 0.5 mg q.8.w.	**–128.8 (–172.6 to –84.92)**	–
LP -> Rani 0.5 mg PRNX	–30.97 (–80.88 to 19.13)	–
LP -> Afli 2 mg q.8.w.	**–39.58 (–52.84 to –26.43)**	**–35.14 (–49.05 to –21.19)**
Afli 2 mg q.4.w.	**–40.36 (–59.82 to –20.82)**	**–40.29 (–61.92 to –18.67)**
LP -> Bev 1.25 mg PRN	**–70.22 (–103.1 to –36.71)**	–
LP (q.26.w.) -> Bev 1.25 mg q.12.w.	**–138.8 (–195.7 to –82.33)**	–
LP (q.26.w.) -> Bev 1.25 mg PRN	**–130.1 (–188.7 to –71.87)**	–
Bev 1.25 mg TREX	**–61.63 (–98.87 to –25.53)**	–21.3 (–98.05 to 54.69)
Bev 1.25 mg q.8.w.	**–79.55 (–123.4 to –35.31)**	–
Bev 1.25 mg q.6.w.	**–82.53 (–125.6 to –39.01)**	2.55 (–6.71 to 11.82)
Bev 1.25 mg q.4.w.	**–64.28 (–91.8 to –36.89)**	**–57.93 (–107.1 to –9.03)**
Bev 1.25 mg PRN	**–82.56 (–116.2 to –49.53)**	**–86.86 (–129.5 to –43.97)**
LP -> Bro3 q.12.w./q.8.w.	–10.38 (–28.03 to 7.13)	0.40 (–17.83 to 18.80)
LP -> Bro6 q.8.w. -> q.12.w.	**–22.63 (–77.47 to 31.42)**	–
Comment	A sensitivity analysis with various definitions of retinal thickness was not reported. An inconsistency assessment was not reported.	A sensitivity analysis with various definitions of retinal thickness was not reported. An inconsistency assessment was not reported.

Afli = aflibercept; Bev = bevacizumab; Bro6 = brolucizumab 6 mg; Bro3 = brolucizumab 3 mg; CrI = credible interval; LP = loading phase; PRN = as needed; PRNX = as needed with potential to extend; q.4.w. = every 4 weeks; q.6.w = every 6 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; Rani = ranibizumab; TREX = treat-and-extend.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) | [CONFIDENTIAL sponsor's submission].[1]

Patients Losing at Least 15 ETDRS Chart Letters

For the analysis of the outcome of patients losing at least 15 ETDRS chart letters at one year, the authors included 18 trials that were conducted using a fixed-effects model. Brolucizumab 6 mg every 12 weeks or every eight weeks was significantly better than both sham and ranibizumab as needed with loading phase. The credible interval of all other comparison included the value '1', which indicate no difference. Also, wide CrIs were noted in all comparisons except versus sham. At two years, the network was much sparser than it was at one year, including only eight trials. Similarly, brolucizumab was significantly better than sham, but wide CrIs were more prominent at the two-year outcome than at the one-year outcome. The comparative results are outlined in Table 19.

Table 19: Patients Losing at Least 15 ETDRS Chart Letters – ITC Results

	Odds ratio [95% CrI] Patients losing 15 letters at 1 year	Odds ratio [95% CrI] Patients losing 15 letters at 2 years
	Brolucizumab 6 mg q.8.w./q.12.w. versus	
Number of studies (patients), model	18 RCTs included, fixed-effects model	8 RCTs, fixed effects model
Rani 0.5 mg q.4.w.	0.82 (0.39 to 1.68)	0.89 (0.50 to 1.57)
LP -> Rani 0.5 mg TREX	0.47 (0.16 to 1.34)	0.07 (0.00 to 1.09)
Sham IVT injection	**0.07 (0.03 to 0.19)**	**0.11 (0.05 to 0.23)**
Afli 2 mg q.4.w.	0.99 (0.47 to 2.06)	0.97 (0.54 to 1.72)
Bev 1.25 mg PRN	0.43 (0.16 to 1.12)	0.47 (0.17 to 1.23)
Bev 1.25 mg q.4.w.	0.53 (0.21 to 1.30)	0.76 (0.24 to 2.28)
Bev 1.25 mg q.6w.	0.32 (0.05 to 1.71)	–
Bev 1.25 mg q.8.w.	9.5 (0.47 to 5007)	–
Bev 1.25 mg TREX	0.54 (0.12 to 2.42)	0.1.00 (0.00 to 1.75)
LP (q.26.w.) -> Bev 1.25 mg q.12.w.	0.18 (0.02 to 1.70)	–
LP -> Afli 2 mg q.8.w.	0.97 (0.61 to 1.55)	1.00 (0.68 to 1.48)
LP -> Bev 1.25 mg PRN	0.34 (0.08 to 1.25)	–
LP -> Bro3 q.12.w./q.8.w.	1.00 (0.56 to 1.84)	0.89 (0.54 to 1.48)
LP -> Rani 0.5 mg PRN	**0.30 (0.08 to 0.98)**	0.55 (0.23 to 1.3)
LP -> Rani 0.5 mg PRNX	0.29 (0.04 to 2.04)	–
LP -> Rani 0.5 mg q.12.w.	0.75 (0.19 to 3.16)	–
LP -> Rani 0.5 mg q.8.w.	0.12 (0.00 to 2.16)	–
Rani 0.5 mg PRN	0.85 (0.30 to 2.41)	0.80 (0.29 to 2.17)
Comment	No inconsistency assessment was conducted.	No inconsistency assessment was conducted.

Afli = aflibercept; Bev = bevacizumab; Bro3 = brolucizumab 3 mg; CrI = credible interval; ETDRS = Early Treatment Diabetic Retinopathy Study; ITC = indirect treatment comparison; IVT = intravitreal; LP = loading phase; PRN = as needed; PRNX = as needed with potential to extend; q.4.w. = every 4 weeks; q.6.w = every 6 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; Rani = ranibizumab; TREX = treat-and-extend.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Patients Gaining at Least 15 ETDRS Chart Letters

To analyze the outcome of patients gaining at least 15 ETDRS chart letters at one year, the authors included 15 trials conducted using a fixed-effects model. Brolucizumab 6 mg every 12 weeks or every eight weeks was significantly better than sham. All other comparisons included the null value ‘one’ in the 95% CrI. Also, wide CrIs were noted in all comparisons. At two years, the network was sparser than it was at one year, including only nine trials. Similarly, brolucizumab was significantly better than sham, but wide CrIs were more prominent at the two-year outcome than at the one-year outcome. The comparative results are outlined in Table 20.

Table 20: Patients Gaining at Least 15 ETDRS Chart Letters – ITC Results

	Odds ratio [95% CrI] Patients gaining 15 letters at 1 year	Odds ratio [95% CrI] Patients gaining 15 letters at 2 years
	Brolucizumab 6 mg q.12.w./q.8.w. versus	
Number of studies (patients), model	15 RCTs included, fixed-effects model	9 RCTs, fixed-effects model
Rani 0.5 mg q.4.w.	1.12 (0.8 to 1.56)	1.22 (0.88 to 1.7)
LP -> Rani 0.5 mg PRN	1.36 (0.83 to 2.23)	1.30 (0.80 to 2.13)
Rani 0.5 mg PRN	1.64 (1.02 to 2.68)	1.35 (0.77 to 2.35)
LP -> Rani 0.5 mg PRNX	0.77 (0.24 to 2.36)	–
LP -> Rani 0.5 mg q.12.w.	7.60 (1.91 to 29.77)	–
LP -> Rani 0.5 mg q.8.w.	2.17 (0.53 to 9.36)	–
LP -> Rani 0.5 mg TREX	1.05 (0.64 to 1.71)	0.66 (0.16 to 2.45)
LP -> Afli 2 mg q.8.w.	1.19 (0.95 to 1.50)	1.11 (0.89 to 1.39)
Afli 2 mg q.4.w.	1.07 (0.77 to 1.49)	1.25 (0.9 to 1.73)
Bev 1.25 mg PRN	1.40 (0.86 to 2.27)	1.52 (0.86 to 2.65)
Bev 1.25 mg q.4.w.	1.12 (0.71 to 1.74)	1.28 (0.69 to 2.37)
LP -> Bev 1.25 mg TREX	1.12 (0.57 to 2.20)	0.64 (0.14 to 2.54)
LP -> Bev 1.25 mg PRN	1.34 (0.72 to 2.45)	–
Sham IVT	**11.02 (5.49 to 23.65)**	**16.19 (7.55 to 38.08)**
LP -> Bro3 q.12.w./q.8.w.	1.36 (1.01 to 1.86)	0.96 (0.72 to 1.29)
Comment	No inconsistency assessment was conducted.	No inconsistency assessment was conducted.

Afli = aflibercept; Bev = bevacizumab; Bro3 = brolucizumab 3 mg; CrI = credible interval; ETDRS = Early Treatment Diabetic Retinopathy Study; ITC = indirect treatment comparison; IVT = intravitreal; LP = loading phase; PRN = as needed; PRNX = as needed with potential to extend; q.4.w. = every 4 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; TREX = treat-and-extend; Rani = ranibizumab; RCT = randomized controlled trial.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) [CONFIDENTIAL sponsor's submission].[1]

Discontinuation

For the outcome of discontinuation at one year, the authors included 10 trials in the analysis. None of the results met the significance threshold of excluding the null of the CrI, and several results showed wide CrIs. No results were presented for the year 2 time point. The comparative results are outlined in Table 21.

Table 21: Discontinuation — Indirect Treatment Comparison Results

	Odds ratio [95% CrI] discontinuation at 1 year
	Brolucizumab 6 mg q.12.w./q.8.w. versus
Number of studies (patients), model	10 RCTs included, fixed-effects model
Rani 0.5 mg q.4.w.	1.00 (0.58 to 1.71)
LP -> Rani 0.5 mg PRN	1.34 (0.57 to 3.21)
LP -> Rani 0.5 mg q.8.w.	4.52 (0.64 to 47.1)
LP-> Rani 0.5 mg TREX	0.88 (0.42 to 1.82)
LP -> Afli 2 mg q.8.w.	0.87 (0.61 to 1.26)
Afli 2 mg q.4.w.	1.17 (0.67 to 2.03)

	Odds ratio [95% CrI] discontinuation at 1 year Brolucizumab 6 mg q.12.w./q.8.w. versus
Bev 1.25 mg q.4.w.	0.79 (0.36 to 1.7)
LP -> Bro6 q.8.w. -> q.12.w.	1.19 (0.23 to 6.98)
LP -> Bro3 q.12.w./q.8.w.	1.29 (0.81 to 2.1)
Comment	No inconsistency assessment was conducted.

Afli = aflibercept; Bev = bevacizumab; Bro3 = brolucizumab 3 mg; Bro6 = brolucizumab 6 mg; CrI = credible interval; LP = loading phase; PRN = as needed; q.4.w. = every 4 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; Rani = ranibizumab; RCT = randomized controlled trial; TREX = treat-and-extend.

Source: CADTH Common Drug Review submission: Beovu (brolucizumab, single-use, pre-filled syringe, 120 mg/mL solution for intravitreal injection) (CONFIDENTIAL sponsor's submission).[1]

Critical Appraisal of Sponsor-Submitted Indirect Treatment Comparison

The authors employed a comprehensive, transparent approach in their systematic review. They provided the search strategy, conducted the search over several databases, used two independent reviewers for screening, and outlined a comprehensive list of inclusion and exclusion criteria. The inclusion criteria would allow a population that is relevant for the Canadian settings. The comparisons reported in this ITC have incorporated relevant treatments for Canadian settings, including treatments that have extensive clinical use but lack a formal review from Health Canada, such as bevacizumab, which is commonly used in Canada.

The analysis of the extracted data followed the framework suggested by the National Institute for Health and Care Excellence, including using non-informative priors. The sponsor's ITC reported on the number of burn-ins and the convergence characteristics.

Limitations to the sponsor's ITC are outlined in the following points.

- Lack of reporting on informative items: Several items related to the assessment of the bevacizumab-included NMAs were not available, including the DIC values and a graphic representation of the baseline characteristics across trials. These items were reported for networks that did not include bevacizumab. Also, several sensitivity analyses were not conducted for the bevacizumab networks — most notably, the assessment of various retinal thickness definitions.
- Choice of fixed-effects model: The authors stated that if the difference in the DIC between the fixed-effects and random-effects models is less than three, then the fixed model is preferred. While this approach is practised, the choice of the fixed-effects model adds another assumption to the model that cannot be tested. The authors did not provide the results of the random-effects model for comparison; nor did they did not provide the DIC values for the bevacizumab-included networks to assess the DIC difference.
- Considerable heterogeneity in some baseline characteristics: Most notable are variations in the values of the retinal thickness and in the method of assessing retinal thickness. This heterogeneity adds a large degree of uncertainty to the related results.
- Lack of inconsistency assessment: There were several closed loops in the evidence network that would allow for testing of the consistency assumption. The lack of inconsistency assessment reduces the overall confidence in the results.
- Weak connection between brolucizumab and the rest of the network: Brolucizumab is only connected to the network through aflibercept in the two pivotal trials. Aflibercept, in turn, is connected to the rest of the network through two pooled trials. Also, the fact that

most of the interventions or comparators in the network are connected through one trial reduces the statistical robustness of the model. This is reflected in the wide CrIs throughout the comparative results, indicating high statistical uncertainty.

These limitations make it challenging to arrive at a conclusive decision about the validity of the results to inform clinical practice.

Summary

With the inclusion of up to 21 trials in an NMA, the sponsor's ITC has shown results that indicate brolucizumab 6 mg every 12 weeks or every eight weeks to be significantly better than sham in BCVA outcomes, and significantly better than most other comparators in retinal thickness outcomes. However, due to the high heterogeneity in the retinal thickness baseline values and definition, and because of the low statistical robustness of the model as evidenced by the wide CrI in the majority of outcomes, no confident conclusion can be drawn regarding the comparative indirect similarity or superiority of brolucizumab.

Other Relevant Studies

HAWK Extension Study

Because the HAWK and HARRIER studies delivered brolucizumab in a formulation that differed from the product intended for commercialization, the FDA recommended collecting clinical data from at least 50 patients originally enrolled in the pivotal trials and studying the patients for an additional six months while treating them with the brolucizumab product intended for commercialization.

Patients who completed the HAWK study were eligible to participate in the 24-week, double-masked, multi-centre HAWK extension study. The baseline visit in the extension study was to take place within 12 weeks of week 96 in the HAWK study. The HAWK extension study was conducted at 68 centres in the US.

Methods

Populations

Patients eligible to enrol in the extension study were those who were assessed at week 96 in the HAWK study and began baseline in the extension study within 12 weeks of week 96 in the HAWK study. Patients were excluded if they discontinued the HAWK study or HAWK study treatment, if they received standard of care treatment for nAMD following the HAWK study, or if they received investigational treatment for nAMD in the study eye, intraocular or periocular injections of steroids in the study eye, or systemic anti-VEGF therapy following the HAWK study.

Detailed information about the baseline characteristics of patients who received brolucizumab are presented in Table 22. HAWK extension study results were reported for patients receiving brolucizumab according to whether they received the 3 mg or 6 mg dose in the core study. Compared with patients in the core study, those in the extension study had a greater mean age. The core study also had a greater proportion of females and a greater proportion of patients diagnosed with nAMD within one month of the core study baseline. Other core study baseline characteristics of patients in the extension study listed in Table 22 were similar to those in the core study population.

In the brolucizumab group, duration from last active treatment with brolucizumab in the core study to first active treatment in the extension study ranged from three to 21 weeks (see Table 22 for further details). This duration was no more than four weeks longer than expected, according to treatment interval status at the end of the core study (i.e., every 12 weeks or every eight weeks) in 69.2% of the brolucizumab extension study group.

Table 22: Summary of Baseline Characteristics, HAWK Extension Study

	Brolucizumab 3 mg to 6 mg[a] N = 62	Brolucizumab 6 mg to 6 mg[a] N = 45	Brolucizumab combined N = 107
Mean age, years (SD)	81.0 (9.14)	80.0 (7.93)	80.6 (8.63)
Female, n (%)	45 (72.6)	24 (53.3)	69 (64.5)
Time since diagnosis of nAMD at core study baseline, n (%)			
< 1 month	52 (83.9)	43 (95.6)	95 (88.8)
1 month to 3 months	9 (14.5)	2 (4.4)	11 (10.3)
≥ 3 months	1 (1.6)	0	1 (0.9)
Type of choroidal neovascularization at core study baseline, n (%)			
Predominantly classic	20 (32.3)	14 (31.1)	34 (31.8)
Minimally classic	5 (8.1)	3 (6.7)	8 (7.5)
Occult	37 (59.7)	28 (62.2)	65 (60.7)
Subretinal fluid present at core study baseline, n (%)	43 (69.4)	32 (71.1)	75 (70.1)
Intraretinal fluid or cyst present at core study baseline, n (%)	37 (59.7)	22 (48.9)	59 (55.1)
Subretinal pigment epithelium fluid present at core study baseline, n (%)	28 (45.2)	15 (33.3)	43 (40.2)
Duration from last core study drug administration to baseline			
Mean, weeks (SD)	10.7 (4.66)	10.2 (4.21)	10.5 (4.46)
≤ 4 weeks, n (%)	4 (6.5)	7 (15.6)	11 (10.3)
> 4 weeks to ≤ 8 weeks, n (%)	20 (32.3)	8 (17.8)	28 (26.2)
> 8 weeks to ≤ 12 weeks, n (%)	14 (22.6)	15 (33.3)	29 (27.1)
> 12 weeks to ≤ 16 weeks, n (%)	18 (29.0)	12 (26.7)	30 (28.0)
> 16 weeks, n (%)	6 (9.7)	3 (6.7)	9 (8.4)

nAMD = neovascular age-related macular degeneration; SD = standard deviation.

[a] Brolucizumab 3 mg – 6 mg refers to patients who received brolucizumab 3 mg injections in the HAWK study and 6 mg injections in the extension study. Brolucizumab 6 mg – 6 mg refers to patients who received brolucizumab 6 mg injections in the HAWK study.

Source: Clinical Study Report for HAWK extension study.

Interventions

Patients who had received any dose of brolucizumab during the HAWK core study received 6 mg IVT injections in the extension study, with the study eye being the one selected in the HAWK core study. Brolucizumab was administered at baseline, week 8, and week 16 or week 20, depending on disease activity assessment at week 16. Patients with disease activity at week 16 were to be administered brolucizumab at week 16, while those without disease activity at week 16 were to be administered brolucizumab at week 20.

Patients who received aflibercept injections in the HAWK core study received aflibercept 2 mg IVT injections at baseline, week 8, and week 16, of the extension study.

Patients, investigators, and study personnel — aside from the physician and personnel administering study treatment — were masked to treatment assignment. Investigators performing study assessments were also masked. Sham injections, in which the tip of the injection syringe was used without the needle, were performed at week 16 or week 20 to preserve masking.

Disease activity was assessed at week 16 and week 20. Investigators determined disease activity status based on their own expert judgment.

The following treatments were prohibited: non-study anti-VEGF therapy, intraocular or periocular corticosteroids aside from treatment for AEs, laser treatment for AMD in the study eye, and systemic anti-VEGF therapy or any investigational drug, biologic, or device.

Outcomes

Efficacy was assessed using an ETDRS chart at a four-metre distance and OCT examination. These were performed at all study visits, which occurred every four weeks. Descriptive statistics were reported for patients with a loss in BCVA in the study eye from baseline to each study visit of at least five letters, 10 letters, 15 letters, and 30 letters, as well as a gain in BCVA for the same time points and thresholds. Mean change in BCVA from baseline to each study visit was also reported. CSFT on OCT was evaluated by the masked site investigator according to their standard clinical practice; change in CSFT from baseline to each study visit was reported for the study eye. Whether OCT was performed using a time-domain or spectral-domain system was not specified.

AEs were collected at each study visit. As well, slit-lamp examinations, intraocular pressure measurements with an applanation tonometer, and ophthalmoscopic fundus examinations were performed at all study visits.

Statistical Analysis

There was no planned formal hypothesis testing, and the results were presented as descriptive analyses for the brolucizumab group only. According to the statistical analysis plan for the extension study, patient selection and expected sample size did not support a valid comparison between brolucizumab and aflibercept.

LOCF imputation was used for missing BCVA and CSFT assessments; assessments were to be censored after the start of prohibited treatment in the study. Sensitivity analyses were also performed without imputation, using observed values only.

Subgroup analyses by core study treatment group in the brolucizumab group (brolucizumab 3 mg and 6 mg) were performed for BCVA and CSFT.

Analyses of efficacy and safety outcomes were performed in the safety set, which included all enrolled patients who received at least one dose of study medication in the extension study. In the analyses by core study treatment group, patients were reported under the treatment to which they were randomized in the core study.

Patient Disposition

A total of 150 patients were enrolled in the extension study (107 in the brolucizumab group and 43 in the aflibercept group). All enrolled patients received at least one dose of study treatment. Two patients in the brolucizumab group discontinued study treatment: one

discontinued treatment due to lack of efficacy, but continued with study visits; the other died during the study. One patient in the aflibercept group discontinued the study due to an AE.

Protocol deviations and missing assessments are presented in Table 23. There were no censored assessments, given that no prohibited concomitant medication use was reported. Patients with protocol deviations were included in the descriptive analyses.

Table 23: Protocol Deviations and Missing Assessments, HAWK Extension Study

	Brolucizumab 3 mg – 6 mg[a] N = 62	Brolucizumab 6 mg – 6 mg[a] N = 45	Brolucizumab combined N = 107
Patients with ≥ 1 protocol deviation, n (%)	5 (8.1)	7 (15.6)	12 (11.2)
Enrolled > 12 weeks after completing core study	0	1 (2.2)	1 (0.9)
Received brolucizumab at week 16 despite no disease activity	4 (6.5)	5 (11.1)	9 (8.4)
Missed active treatment for reasons other than lack of efficacy or any safety event	1 (1.6)	1 (2.2)	2 (1.9)
Patients with ≥ 1 missing assessment, n (%)	3 (4.8)	2 (4.4)	5 (4.7)
Early treatment discontinuation due to lack of efficacy	1 (1.6)	0	1 (0.9)
Missed active treatment for reasons other than lack of efficacy or related safety event or protocol deviation	2 (3.2)	2 (4.4)	4 (3.7)

[a] Brolucizumab 3 mg – 6 mg refers to patients who received brolucizumab 3 mg injections in the HAWK study and 6 mg injections in the extension study. Brolucizumab 6 mg – 6 mg refers to patients who received brolucizumab 6 mg injections in the HAWK study.

Source: Clinical Study Report for HAWK extension study.

Exposure to Study Treatments

In the brolucizumab group, 93.5% of patients received three injections of brolucizumab, with all 107 enrolled patients receiving an injection at baseline, 102 patients (95.3%) receiving an injection at week 8, 31 patients (29.0%) receiving an injection at week 16, and 72 patients (67.3%) receiving an injection at week 20. Of the 31 patients who received a brolucizumab injection at week 16, nine did not have a positive disease activity assessment, and should have had their brolucizumab injection at week 20 instead. In total, 100 patients received the three planned brolucizumab injections (with 70 patients receiving the third injection at week 20 and 30 patients receiving it at week 16).

There were two patients (1.9%) who received one injection (these were the patients who discontinued study treatment) and five patients (4.7%) who received two injections (two patients missed the scheduled visit and three had an AE leading to treatment interruption).

Efficacy

Results for BCVA, as measured using the ETDRS chart, are presented in Table 24. In patients who received brolucizumab, there was no notable change in mean BCVA from baseline to week 24, regardless of the dosage received in the core study (overall change of –1.0 letters; SE of 7.67 letters). The percentages of patients who gained and lost five letters (16.8% and 18.7%), 10 letters (5.6% and 11.2%), and 15 letters (2.8% for both) were similar. One patient experienced a loss of at least 30 letters; no patients experienced a gain of at least 30 letters. Sensitivity analyses for mean BCVA using observed values only were consistent with the main analyses.

Table 24: Best-Corrected Visual Acuity, HAWK Extension Study

	Brolucizumab 3 mg – 6 mg[a] N = 62	Brolucizumab 6 mg – 6 mg[a] N = 45	Brolucizumab combined N = 107
Mean BCVA, letters read (SD)			
Baseline	64.7 (17.36)	65.8 (18.82)	65.2 (17.91)
Week 24	62.7 (19.82)	66.1 (19.05)	64.2 (19.48)
Mean change in BCVA, letters read (SE)	–2.0 (1.04)	0.3 (1.01)	–1.0 (0.74)
Patients with gain of letters from baseline to week 24, n (%)			
≥ 5 letters	10 (16.1)	8 (17.8)	18 (16.8)
≥ 10 letters	1 (1.6)	5 (11.1)	6 (5.6)
≥ 15 letters	1 (1.6)	2 (4.4)	3 (2.8)
Patients with loss of letters from baseline to week 24, n (%)			
≥ 5 letters	13 (21.0)	7 (15.6)	20 (18.7)
≥ 10 letters	8 (12.9)	4 (8.9)	12 (11.2)
≥ 15 letters	3 (4.8)	0	3 (2.8)
≥ 30 letters	1 (1.6)	0	1 (0.9)

BCVA = best-corrected visual acuity; SD = standard deviation; SE = standard error.

Note: LOCF used for missing observations.

[a] Brolucizumab 3 mg to 6 mg refers to patients who received brolucizumab 3 mg injections in the HAWK study and 6 mg injections in the extension study. Brolucizumab 6 mg to 6 mg refers to patients who received brolucizumab 6 mg injections in the HAWK study.

Source: Clinical Study Report for the HAWK extension study.

Results for CSFT, as measured using OCT, are presented in Table 25. In patients who received brolucizumab, there was a numeric decrease in mean CSFT from baseline to week 24 (overall change of –21.8 µm; SE of 3.82 µm). Sensitivity analyses using observed values only were consistent with the main analyses.

Table 25: Central Subfield Thickness, HAWK Extension Study

	Brolucizumab 3 mg – 6 mg N = 62	Brolucizumab 6 mg – 6 mg N = 45	Brolucizumab combined N = 107
Mean CSFT, µm (SD)			
Baseline	274.5 (70.41)	296.8 (91.85)	283.9 (80.48)
Week 24	254.8 (63.90)	272.2 (71.93)	262.1 (67.62)
Mean change in CSFT, µm (SE)	–19.8 (4.78)	–24.6 (6.28)	–21.8 (3.82)

CSFT = central subfield thickness; SD = standard deviation; SE = standard error.

Note: LOCF used for missing observations.

[a] Brolucizumab 3 mg to 6 mg refers to patients who received brolucizumab 3 mg injections in the HAWK study and 6 mg injections in the extension study. Brolucizumab 6 mg to 6 mg refers to patients who received brolucizumab 6 mg injections in the HAWK study.

Source: Clinical Study Report for the HAWK extension study.

Harms

AEs, SAEs, treatment discontinuations, and deaths are presented in Table 26. In patients receiving brolucizumab, 18.7% had at least one ocular AE in the study eye, with cataract, nAMD, and retinal hemorrhage each occurring in 2.8% of patients (with other ocular AEs

reported by less than 2% of patients). The percentage of patients with an ocular SAE in the study eye was 0.9%, with one patient experiencing both retinal artery occlusion (a notable harm, according to the systematic review protocol) and retinal vein occlusion. In terms of non-ocular AEs, 47.7% of brolucizumab patients reported at least one AE and 5.6% reported at least one SAE.

Two patients (1.9%) discontinued treatment due to AE, one due to worsening of nAMD and one due to hospitalization for congestive heart failure. Seven patients (6.5%) temporarily interrupted study treatment due to AE, including one patient with an ocular AE in the study eye (vitritis, a notable harm). Other notable harms in the study eye were conjunctival hemorrhage experienced by two patients (1.9%) and eye inflammation, retinoschisis, and increased intraocular pressure experienced by one patient each (0.9%).

One patient died after experiencing congestive heart failure and subsequent multiple organ dysfunction syndrome.

Table 26: Summary of Harms, HAWK Extension Study

	Brolucizumab combined N = 107
Patients with ≥ 1 ocular AE in the study eye	
n (%)	20 (18.7)
Most common events [a]	
Cataract	3 (2.8)
Neovascular age-related macular degeneration	3 (2.8)
Retinal hemorrhage	3 (2.8)
Patients with ≥ 1 non-ocular AE	
n (%)	51 (47.7)
Most common events[a]	
Nasopharyngitis	5 (4.7)
Hypertension	4 (3.7)
Urinary tract infection	4 (3.7)
Bronchitis	3 (2.8)
Dehydration	3 (2.8)
Pneumonia	3 (2.8)
Sinusitis	3 (2.8)
Patients with ≥ 1 ocular SAE in the study eye	
n (%)	1 (0.9)
Retinal artery occlusion[b]	1 (0.9)
Retinal vein occlusion	1 (0.9)
Patients with ≥ 1 non-ocular SAE[c]	
n (%)	6 (5.6)
Patients who discontinued treatment due to AE[d]	
n (%)	2 (1.9)
Patients who interrupted treatment temporarily due to AE	
n (%)	7 (6.5)

	Brolucizumab combined N = 107
Vitritis[b] (ocular AE)	1 (0.9)
Non-ocular AE[e]	6 (5.6)
Deaths	
n (%)	1 (0.9)
Multiple organ dysfunction syndrome assessed as septic shock	1 (0.9)
Other notable harms (study eye), n (%)	
Conjunctival hemorrhage	2 (1.9)
Eye inflammation	1 (0.9)
Retinoschisis	1 (0.9)
Intraocular pressure increased	1 (0.9)

AE = adverse event; SAE = serious adverse event.

Note: AEs that started on or after the first study treatment administration in the extension study were included.

[a] Frequency ≥ 2%.

[b] Identified as a notable harm in the systematic review protocol.

[c] Non-ocular SAEs were bile duct stone, congestive cardiac failure, acute cholecystitis, femur fracture, intracranial hemorrhage, hypertension, multiple organ dysfunction syndrome, pneumonia, and respiratory failure (each SAE was reported by one patient).

[d] One patient experienced worsening of neovascular age-related macular degeneration in the study eye and one patient experienced hospitalization for congestive cardiac failure followed by multiple organ dysfunction syndrome and death.

[e] Non-ocular AEs were pneumonia, sinusitis, hypertension, asthma, congestive cardiac failure, fractured femur, joint dislocation, and depression (each AE was reported by one patient).

Source: Clinical Study Report for the HAWK extension study.

Critical Appraisal

Internal Validity

Major limitations of the extension study were the lack of a comparison between the brolucizumab and aflibercept treatment groups and the lack of planned hypothesis testing (and lack of sample-size considerations related to hypothesis testing). These limitations meant that conclusions could not be drawn concerning the comparative efficacy of the brolucizumab product intended for commercialization versus aflibercept.

The timing of brolucizumab injections in the extension study was not strictly a continuation of the brolucizumab treatment regimens in the core study because the duration between the last active treatment in the core study and the first treatment in the extension study exceeded the treatment interval established in the core study by four weeks in about 30% of patients. The clinical expert consulted for this review did not consider this extension in treatment interval to be detrimental to the patients, as they had already been on active treatment for the duration of the core study. Also, 8% of patients being treated with brolucizumab in the extension study received active treatment at week 16 when they should have received it at week 20 based on absence of disease activity.

OCT-measured CSFT may not have had the same inter-rater reliability in the extension study as in the core study, because exams were assessed by investigators at each centre as opposed to at a central reading centre.

External Validity

Compared with the HAWK core study population, patients in the extension study had a greater mean age. The study also included a greater proportion of females and a greater proportion of patients diagnosed with nAMD within one month of the core study baseline. Also, only US patients were eligible for the extension study. Otherwise, the extension study population was similar to the population in the HAWK core study.

Discussion

Summary of Available Evidence

In this review, we have included two RCTs, one ITC, and one extension study.

Two studies met the inclusion criteria for this systematic review: HAWK and HARRIER. Both studies were phase III, noninferiority, multi-centre, double-masked, active-controlled, parallel, randomized trials. Both studies lasted for a total of 96 weeks. In HAWK, a total of 1,082 patients with nAMD were randomized in a 1:1:1 ratio to a brolucizumab 3 mg arm, a brolucizumab 6 mg arm, or an aflibercept 2 mg arm. Given that only the brolucizumab 6 mg dose is recommended by Health Canada, we only reported information relevant to the brolucizumab 6 mg arm. In HARRIER, a total of 743 patients with nAMD were randomized in a 1:1 ratio to a brolucizumab 6 mg arm or an aflibercept 2 mg arm. All patients received three monthly loading IVT injections followed by treatment every 12 weeks for brolucizumab and every eight weeks for aflibercept. Patients on the brolucizumab 12-week regimen could be permanently switched to the eight-week regimen if an investigator determined the presence of continuous disease activity based on certain criteria.

Both studies aimed to establish the noninferiority of brolucizumab 6 mg to aflibercept 2 mg through the primary outcome of change in BCVA from baseline to week 48. The noninferiority margin was determined to be four ETDRS chart letters; the end point was analyzed using a pairwise ANOVA model, including treatment, baseline BCVA categories (≤ 55 letters, 56 letters to 70 letters, or ≥ 71 letters), and age categories (< 75 years or ≥ 75 years) as factors. In addition, HAWK included a statistical hierarchy and an alpha spending method to control for multiple testing and allow for additional secondary outcomes testing.

Overall, patients randomized into the treatment arms had similar baseline characters within each study and across studies in terms of age, gender, number of eyes affected, BCVA, and CSFT. HARRIER had a higher proportion of white patients compared to HAWK, as well as a greater proportion of patients with a disease duration of longer than three months. Within the HARRIER study, there was a higher proportion of patients with SRF in the aflibercept arm compared to the brolucizumab arm (72.6% versus 67.8%).

The treatment group differences in both studies were within the noninferiority margin. In HAWK, the mean difference between the brolucizumab 6 mg group and the aflibercept 2 mg group was –0.2 (95% CI, –2.1 to 1.8); in HARRIER, it was –0.7 (95% CI, –2.4 to 1.0). Sensitivity analyses reported by the sponsor showed similar results to the base case. Results at week 96 indicate that the improvements reported at week 48 were maintained. The assessment of the proportion of patients at week 48 who gained greater than or equal to 15 letters from baseline or had a BCVA of greater than or equal to 84 letters at week 48 found a higher numerical proportion in the brolucizumab 6 mg group (33.6%) than in the aflibercept 2 mg group (25.4%) in HAWK. However, these results are numerically similar in

HARRIER, with 29.3% for the brolucizumab 6 mg group and 29.9% for the aflibercept 2 mg group. On the other hand, the proportion of patients with a loss of greater than or equal to 15 letters from baseline at week 48 was similar within and across trials, with 6.4% and 3.8% in in the brolucizumab 6 mg groups in HAWK and HARRIER, respectively, and 5.5% and 4.8% in the aflibercept groups in HAWK and HARRIER, respectively.

There were statistically significant improvements in anatomical-related outcomes related to retinal thickness and the proportion of patients with SRF or IRF in patients treated with brolucizumab 6 mg compared to those treated with aflibercept in the HAWK study at week 48. These findings are supported numerically by the results in the HARRIER study. Other outcomes show numerically similar results within and across studies, including the reported HRQoL measure, the NEI VFQ-25 composite score.

By the end of the first year, almost half of the patients randomized to brolucizumab had been switched to a regimen of treatment every eight weeks. The majority who were switched to this regimen were identified at week 16 and week 20.

Limitations of the HAWK and HARRIER studies include lack of stratification for geographic region, lack of adjustment for multiplicity in HARRIER, and potential risk of unmasking treatment assignment through the use of sham injection and an unmasked injection physician. In addition, the generalizability of the results is limited to the treatment-naive population. Also, given the lack of information regarding development, validation, and the extent of use by investigator of the criteria described in the two studies to determine disease activity, the applicability of the injection regimen results may be uncertain. Finally, no direct evidence comparing brolucizumab to ranibizumab or bevacizumab is available.

Due to the lack of direct evidence comparing brolucizumab with anti-VEGFs other than aflibercept, the sponsor performed an NMA to estimate the efficacy of brolucizumab versus other anti-VEGFs in patients with nAMD. The authors of the sponsor-submitted ITC used a Bayesian approach through Markov chain Monte Carlo methods . Non-informative priors were chosen for the analysis. For the outcome of BCVA at one year, the authors analyzed 21 trials using a fixed-effects model.

In the ITCs, brolucizumab 6 mg every 12 weeks or every eight weeks was significantly better than sham. All other comparisons included zero in the 95% CrI. Also, wide CrIs were noted in several comparisons. At two years, the network for the BCVA outcome was much sparser it was at one year, including only nine trials. Similar to the one-year results, brolucizumab was significantly better than sham, but wide CrIs were more prominent at the two-year outcome than at the one-year outcome. For the outcome of retinal thickness, at one year, the authors analyzed 18 RCTs using a fixed-effects model. The results showed brolucizumab to be significantly better than almost all comparators. The exceptions were ranibizumab 0.5 mg as needed after a loading phase and extension, and brolucizumab 3 mg every 12 weeks or every eight weeks after a loading phase. However, the CrIs in these results are notably large. At two years, the authors analyzed eight trials, with the results showing larger CrIs than were observed for the one-year results and the null included in comparisons that were significant in the one-year analysis (versus loading phase -> ranibizumab 0.5 mg treat-and-extend, bevacizumab 1.25 mg treat-and-extend, and bevacizumab 1.25 mg every six weeks).

Limitations in the sponsor's ITC include: lack of reporting on informative items (e.g., DIC values, graphic representation of the baseline characteristics across trials, and results of the random-effects model); considerable heterogeneity in some baseline characteristics (most notably, the variation in retinal thickness values and in the method of assessing

retinal thickness); lack of inconsistency assessment; and weak connections between brolucizumab and the rest of the network (as evidenced by the wide CrIs). These limitations pose considerable challenges in terms of making a conclusive decision about the validity of the results to inform clinical practice.

Because the HAWK and HARRIER studies delivered brolucizumab in a formulation that differed from the product intended for commercialization, the FDA recommended collecting clinical data from at least 50 patients originally enrolled in the pivotal trials and studying them for an additional six months while treating them with the brolucizumab 6 mg product intended for commercialization. Compared with patients in the core study, patients in the extension study had a greater mean age. The extension study also had a greater proportion of females and a greater proportion of patients diagnosed with nAMD within one month of core study baseline. Disease activity was assessed at week 16 and week 20; investigators determined disease activity status based on their own expert judgment and guidance from disease activity criteria. Descriptive statistics were reported for patients with a loss in BCVA in the study eye from baseline to each study visit of at least five letters, 10 letters, 15 letters, and 30 letters, as well as a gain in BCVA for the same time points and thresholds. Mean change in BCVA from baseline to each study visit was also reported.

In patients who received brolucizumab, there was no notable change in mean BCVA from baseline to week 24, regardless of dosage received in the core study (overall change of –1.0 letters; SE of 7.67 letters). The percentages of patients who gained and lost five letters (16.8% and 18.7%), 10 letters (5.6% and 11.2%), and 15 letters (2.8% for both) were similar. One patient experienced a loss of at least 30 letters; no patients experienced a gain of at least 30 letters. Sensitivity analyses for mean BCVA using observed values only were consistent with the main analyses.

The extension study provided descriptive results that lacked control and randomization. It serves as a supporting information for the lack of a severe loss of improvements gained from the core studies.

Interpretation of Results

Efficacy

The evidence included in this systematic review showed that brolucizumab 6 mg is noninferior to aflibercept 2 mg every eight weeks for mean change in BCVA at week 48 in treatment-naive patients with nAMD. Results in the HAWK study also showed statistically significant improvements in retinal thickness and in the proportion of patients free from IRF or SRF in patients treated with brolucizumab 6 mg compared with those treated with aflibercept 2 mg. However, the clinical value of these results and how they reflect the overall prognosis of patients remains unclear.

The applicability to clinical practice of the assessment of the need to switch to a regimen of treatment every eight weeks is limited. This is due to lack of information about development, validation, and the extent of use by investigator of the criteria described in the two studies to determine disease activity. In addition, in clinical practice, it would not be unlikely for patients to switch back to an every-12-weeks regimen if improvements and/or stabilization were observed. Finally, the results are descriptive, with no comparison or assessment through statistical testing.

The results at week 96 are supportive information that may demonstrate that the improvements gained by week 48 are not lost and that no clear sign of loss of efficacy over

time has occurred. Further, the extension study also provides supportive, uncontrolled information regarding the lack of clear deterioration of visual acuity in enrolled patients.

With the inclusion of up to 21 trials in an NMA, the sponsor's ITC demonstrated results that indicate brolucizumab 6 mg every 12 weeks or every eight weeks is significantly better than sham in terms of BCVA outcomes, and significantly better than most other comparators in terms of retinal thickness outcomes. However, due to the high heterogeneity in the retinal thickness baseline values and definition, and because of the low statistical robustness of the model (as evidenced by the wide CrIs in most outcomes), no confident conclusion can be drawn regarding the similarity or superiority of brolucizumab versus other anti-VEGFs.

Harms

The clinical expert involved in this review noted that most of the ocular harms reported for the HAWK and HARRIER studies appeared to be related to the mode of administration (IVT injection) rather than to the introduction of anti-VEGF molecules. Traumatic cataract, conjunctival hemorrhage, eye pain, and eye irritation can all be directly associated with the manipulation and penetration of the eye while performing IVT injection.

A concern with all anti-VEGF treatments is the theoretical increased risk of cardiovascular events due to systemic inhibition of angiogenesis as a result of the potential diffusion of anti-VEGF molecules through the retina into the systemic circulation. The risk of endophthalmitis, a serious complication, is another concern. Both studies are unlikely to have sufficient power to capture and statistically detect any true differences in the risk of cardiovascular events or endophthalmitis between the two interventions. Nevertheless, the data that are available do not reveal any notable differences between brolucizumab and aflibercept with respect to cardiovascular harms. However, there was a numerically higher proportion of patients with overall eye inflammation–related AEs in the brolucizumab group compared to the aflibercept group. Specifically, among patients who received brolucizumab 6 mg, 5.8% and 3.0% experienced at least one eye infection event in HAWK and HARRIER, respectively, while among patients who received aflibercept, 0.6% and 1.4% experienced at least one eye infection event in HAWK and HARRIER, respectively.

Conclusions

The results of the two double-blind, multinational, randomized, active-controlled trials (HAWK and HARRIER) indicate that, at week 48, three monthly loading IVT injections of brolucizumab 6 mg followed by IVT injections every 12 weeks or every eight weeks is noninferior to three monthly loading IVT injections of aflibercept 2 mg followed by IVT injections every eight weeks in terms of mean change from baseline in BCVA in treatment-naive patients with nAMD. Almost half of the patients treated with brolucizumab 6 mg required a regimen of treatment every eight weeks by the end of the first year. The sponsor's ITC demonstrated results that suggest brolucizumab 6 mg every 12 weeks or every eight weeks is significantly better than sham in BCVA outcomes, and significantly better than most other comparators in retinal thickness outcomes. However, due to the high heterogeneity in the retinal thickness baseline values and definition, and because of the low statistical robustness of the model (as evidenced by the wide CrI in most outcomes), no confident conclusion can be drawn regarding the similarity or superiority of brolucizumab versus other anti-VEGFs. Safety data from the two studies indicate that the most common ocular SAEs in the brolucizumab arms were endophthalmitis, uveitis, retinal tear, and retinal pigment epithelial tear.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	December 12, 2019
Alerts:	Weekly search updates until project completion
Study Types:	No study filters applied.
Limits:	Conference abstracts: excluded

SYNTAX GUIDE	
/	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 terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
.jw	Journal word title
freq=#	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATGY	
#	**Searches**
1	(brolucizumab* or beovu* or dlx 1008 or dlx1008 or esba 1008 or esba1008 or rth 258 or rth258 or XSZ53G39H5).ti,ab,kf,ot,hw,rn,nm.
2	1 use medall
3	*Brolucizumab/
4	(brolucizumab* or beovu* or dlx 1008 or dlx1008 or esba 1008 or esba1008 or rth 258 or rth258).ti,ab,kw,dq.
5	3 or 4
6	5 use oemezd
7	6 not (conference abstract or conference review).pt.
8	2 or 7
9	remove duplicates from 8

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. (Search terms — brolucizumab OR beovu OR rth258 OR esba1008 OR dlx1008)	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms — brolucizumab OR beovu OR rth258 OR esba1008 OR dlx1008	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

Dates for Search:	December 5, 2019 – December 9, 2019
Keywords:	brolucizumab OR beovu OR rth258 OR esba1008 OR dlx1008
Limits:	Publication years: None

Relevant websites from the following sections of the CADTH checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

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

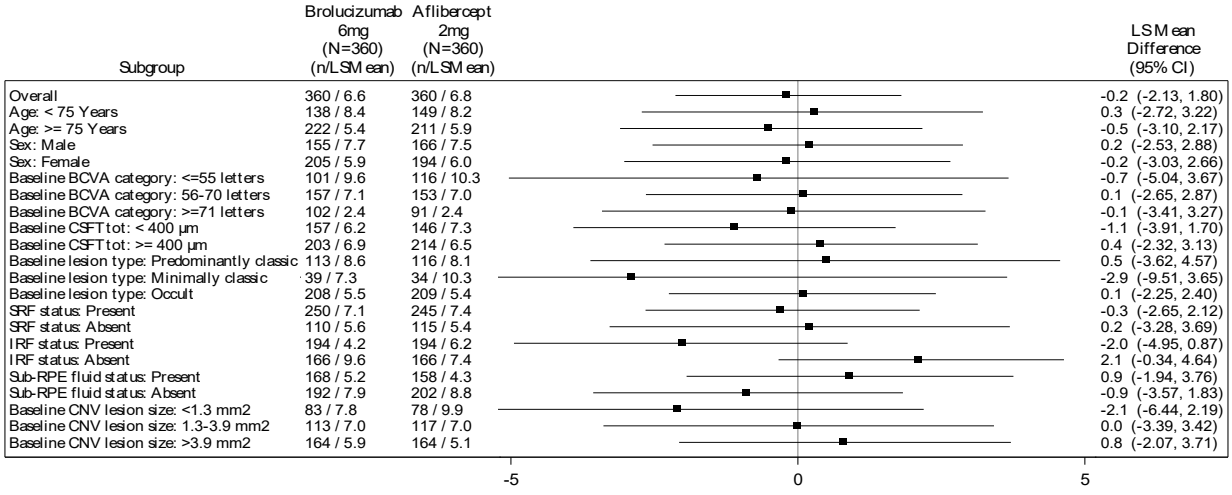
Appendix 2: Excluded Studies

Table 27: Excluded Studies

Reference	Reason for exclusion
Dugel PU, Jaffe GJ, Sallstig P, et al. Brolucizumab Versus Aflibercept in Participants with Neovascular Age-Related Macular Degeneration: A Randomized Trial. Ophthalmology. 2017;124(9):1296-304. Epub 2017/05/30. doi: 10.1016/j.ophtha.2017.03.057	Study design
Holz FG, Dugel PU, Weissgerber G, et al. Single-Chain Antibody Fragment VEGF Inhibitor RTH258 for Neovascular Age-Related Macular Degeneration: A Randomized Controlled Study. Ophthalmology. 2016;123(5):1080-9. doi: 10.1016/j.ophtha.2015.12.030	Study design

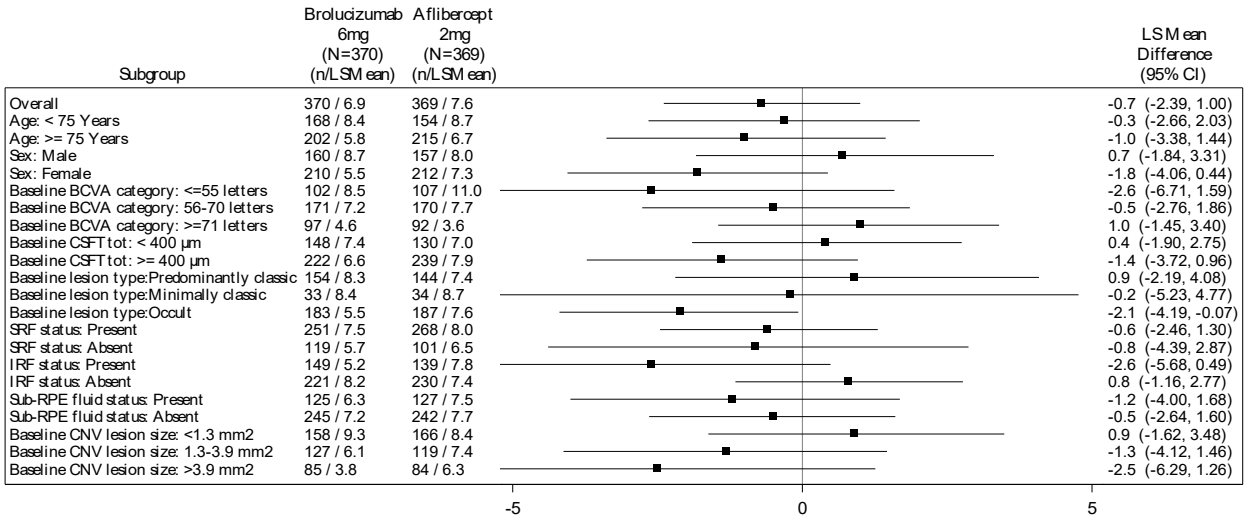
Appendix 3: Detailed Outcome Data

Figure 5: HAWK Best-Corrected Visual Acuity (Letters): Forest Plot of ANOVA Estimates for Change From Baseline at Week 48 by Subgroups of Interest (FAS – LOCF)



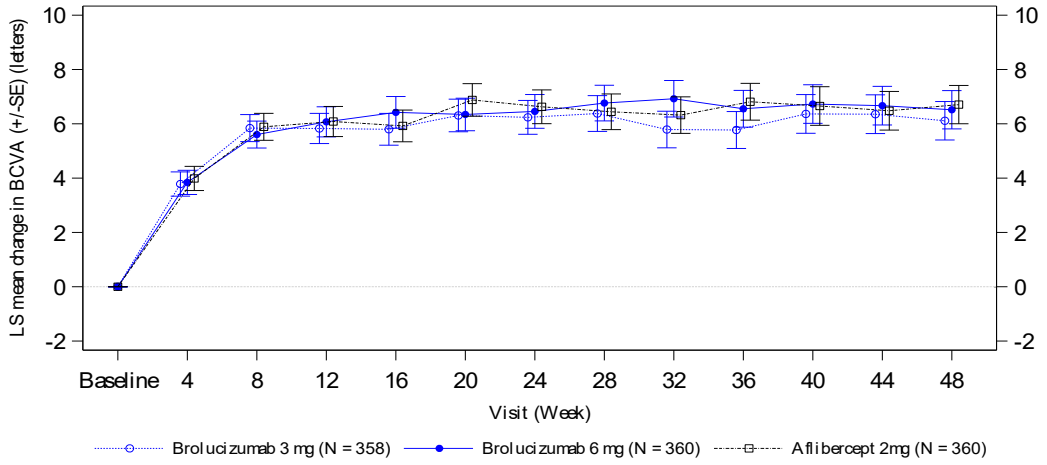
BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; CSFTtot = central subfield thickness total; FAS = full analysis set; IRF = intraretinal fluid; LOCF = last observation carried forward; LSM = least squares mean; RPE = retinal pigment epithelium; SRF = subretinal fluid.

Figure 6: HARRIER Best-Corrected Visual Acuity (Letters) for Change From Baseline at Week 48 by Subgroups of Interest (FAS – LOCF)



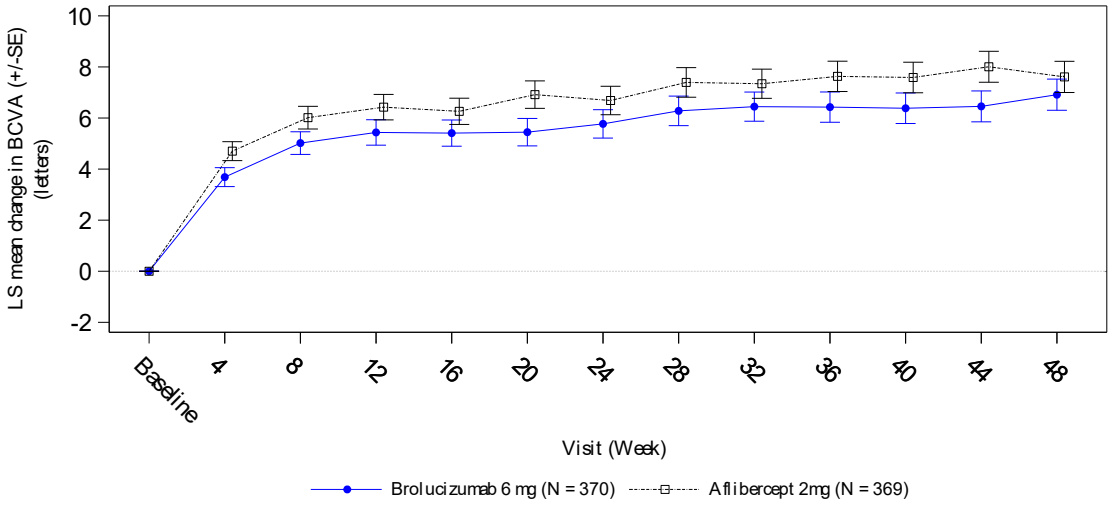
BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; CSFTtot = central subfield thickness total; FAS = full analysis set; IRF = intraretinal fluid; LOCF = last observation carried forward; LSM = least squares mean; RPE = retinal pigment epithelium; SRF = subretinal fluid.

Figure 7: HAWK Best-Corrected Visual Acuity (Letters): LSM Change (Plus/Minus SE) From Baseline by Visit (FAS – LOCF)



BCVA = best-corrected visual acuity; FAS = full analysis set; LOCF = last observation carried forward; LSM = least squares mean; SE = standard error.

Figure 8: HARRIER Best-Corrected Visual Acuity (Letters): LSM change (Plus/Minus SE) From Baseline by Visit (FAS – LOCF)



BCVA = best-corrected visual acuity; FAS = full analysis set; LOCF = last observation carried forward; LSM = least squares mean; SE = standard error.

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the outcome measures in Table 28 and review their measurement properties (validity, reliability, responsiveness to change, and MCID).

Table 28: Outcome Measures Included in Each Study

Outcome measure	HAWK/HARRIER
BCVA using ETDRS chart	Primary
CSFT using SD-OCT	Secondary
NEI VFQ-25	Secondary
Presence of SRF and/or IRF	Secondary

BCVA = best-corrected visual acuity; CSFT = central subfield thickness; ETDRS = Early Treatment of Diabetic Retinopathy Scale; IRF = intraretinal fluid; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire–25; SD-OCT = spectral-domain optical coherence tomography; SRF = subretinal fluid.

Findings

Table 29: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MCID
BCVA using ETDRS charts	The ETDRS charts were developed to measure visual acuity in clinical trials. Patients are presented with a series of 5 letters of equal difficulty on each row, with standardized spacing between letters and rows (total of 14 lines and 70 letters).	**Validity** While the ETDRS charts are commonly used in clinical trials to measure visual acuity, overall visual function also depends upon variables such as contrast sensitivity, near vision, colour vision, and sensitivity to glare. The various components of visual function will affect the performance of different vision-related tasks by varying degrees. **Reliability** ETDRS charts may reliably identify changes in visual acuity of 2 lines (10 letters) or more, but not changes of 1 line (5 letters) or fewer. **Responsiveness** A loss or gain of 3 lines (15 letters) is considered a moderate degree of change and is commonly used as an outcome in clinical trials.	A loss or gain of 3 lines (15 letters) is considered a moderate degree of change and is commonly used as an outcome in clinical trials. Clinical trials supporting regulatory approval of previous anti-VEGF treatments for nAMD (ranibizumab and aflibercept) had as the primary end point the proportion of patients with a loss of less than 15 letters on the ETDRS charts (considered to be vision maintenance).
CSFT using SD-OCT	A technique used to create cross-sectional maps of the retinal structures and quantify retinal thickness. CSFT is the average retinal thickness within a 1 mm diameter centred on the fovea.	**Validity** The evidence in nAMD patients for a linear relationship between OCT-measured CSFT and visual acuity, as well as between changes over time in the 2 measures, is inconsistent. In pooled data taken 4 weeks, 12 weeks, and 24 weeks after initiation of anti-VEGF treatment for nAMD, eyes with a CSFT of < 120 µm or > 212 µm had worse visual acuity than eyes with a CSFT in the range of 120 µm to 212 µm.	Unknown

Outcome measure	Type	Conclusions about measurement properties	MCID
		Reliability With manual correction or exclusion of exams with automatic segmentation errors, values of 12 µm to 18 µm have been reported for the coefficient of repeatability (1.96 × square root of the within-patient variance of the differences between each pair of measurements) for intra-session repeatability. For inter-session reproducibility, a coefficient of repeatability of 26 µm was reported for separate imaging sessions conducted on the same day; and a coefficient of repeatability of 44 µm to 47 µm was reported for separate sessions on different days when automatic segmentation errors were excluded or manually corrected.	
NEI VFQ-25	Developed as a means to measure vision-targeted quality of life. It includes 25 items relevant to 11 vision-related constructs in addition to a single-item, general-health component.	**Validity** The original 51-item NEI VFQ was developed based on focus groups composed of people with a number of common eye conditions (including AMD); thus, the questionnaire may be used to assess quality of life for a broad range of eye conditions. Aside from expectations for future vision, all the original constructs were retained in the shortened version, the NEI VFQ-25. There is evidence for convergent validity of the NEI VFQ-25 composite score and most of the subscale scores, as demonstrated by correlations with visual acuity in patients with various chronic eye diseases, including AMD. The composite score has also shown correlations with the SF-36 (a generic HRQoL instrument) component summary scores. Correlations of subscale and composite scores with visual acuity were weaker overall in the worse-seeing eye than in the better-seeing eye. Rasch and component analysis have shown issues with multi-dimensionality (measurement of more than one construct) and poor performance of the subscales. **Reliability** While acceptable internal consistency has been demonstrated for the composite score and most subscale scores in patients with AMD, evidence for test-retest reliability was not found. **Responsiveness** A change of 9.61 to 10.57 points in the composite score corresponded to a medium effect size in patients with nAMD.	In patients with nAMD, a 15-letter change in visual acuity in the worse- and better-seeing eye corresponded to a 4-point and 7- to 8-point change in the composite score, respectively.

Outcome measure	Type	Conclusions about measurement properties	MCID
Presence of IRF and/or SRF on SD-OCT	The presence of IRF or SRF is detected on OCT exam. IRF appears as diffuse retinal thickening or as hyporeflective cystoid spaces (also referred to as intraretinal cysts). SRF appears as hyporeflective areas between the retina and retinal pigment epithelium.	**Validity** The presence of IRF has been shown to have an association with worse visual acuity in eyes with nAMD, both at baseline (treatment-naive) and following anti-VEGF treatment. In addition, it has been shown to be a prognostic factor for worsening visual acuity. The presence of SRF appears to have no association with visual acuity in treatment-naive eyes and a potential association with better visual acuity at two years following anti-VEGF treatment (with no association at one-year and five-year follow-ups). SRF was not found to be a prognostic factor for visual acuity. Due to the potentially conflicting associations of IRF and SRF with visual acuity, the association of a combined IRF and SRF status with visual acuity is unclear. In a post hoc analysis of the VIEW studies comparing aflibercept and ranibizumab treatment for nAMD, visual acuity outcomes at week 52 were no different between eyes with IRF, IRC, and/or SRF and eyes with no retinal fluid at week 12. **Reliability** Studies of inter-rater reliability have found almost perfect agreement in identifying IRF presence using SD-OCT and good agreement using TD-OCT. For identifying the presence of SRF, there was substantial agreement using both SD-OCT and TD-OCT.	Not applicable

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CSFT = central subfield thickness; ETDRS = Early Treatment of Diabetic Retinopathy Study; HRQoL = health-related quality of life; IRC = intraretinal cyst; IRF = intraretinal fluid; MCID = minimal clinically important difference; nAMD = neovascular age-related macular degeneration; SD-OCT = spectral-domain optical coherence tomography; SF-36 = Short Form (36) Health Survey; SRF = subretinal fluid; TD-OCT = time-domain optical coherence tomography; VEGF = vascular endothelial growth factor; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire–25.

Early Treatment Diabetic Retinopathy Study Charts

ETDRS charts are based on a design by Bailey and Lovie and are commonly used in clinical research.[23-27] 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 when 20 or more letters are read correctly from a distance of 4.0 metres; the visual acuity letter score is equal to the total number of letters read correctly at 4.0 metres plus 30. If fewer than 20 letters are read correctly at 4.0 metres, the visual acuity letter score is equal to the total number of letters read correctly at 4.0 metres (number of letters recorded on line 1.0) plus the total number of letters in the first six lines read correctly at 1.0 metre. Therefore, the ETDRS letter score could result in a maximum score of 100.[28,29]

Charts are used in a standard light box with a background illumination of approximately 150 cd/m^2. The standard chart testing distance is 4.0 metres; however, shorter distances may be used when vision is severely impaired.[25,30] ETDRS results can be converted to

Snellen fractions, another common measure of visual acuity in which the numerator indicates the distance at which the chart was read and the denominator indicates the distance at which a person may discern letters of a particular size. A larger denominator indicates worsening vision. ETDRS chart letters range from 58.18 mm to 2.92 mm in height, corresponding to Snellen visual acuity fractions of 20/200 to 20/10, respectively. Further, letter size increases geometrically and equivalently in every line by a factor of 1.2589 (or 0.1 log unit), moving up the chart. Scoring for ETDRS charts is designed to produce a logarithmic score (in logarithmic minimal angle of resolution units) suitable for statistical analysis in which individual letters score 0.02 log units.

ETDRS charts may reliably identify changes in visual acuity of two lines (10 letters) or more, but not changes of one line (five letters) or fewer.[31] ETDRS chart reliability depends on baseline visual acuity. For eyes with acuity better than 20/100, a change in visual acuity of five or more letters has a greater than 90% probability of being a real change, while for eyes worse than 20/100, a change of 10 or more letters is required for the same reliability.[32] A loss or gain of three lines (15 letters) is considered a moderate degree of change and is commonly used as an outcome in clinical trials.[33] For macular edema, the FDA recommends a mean change of 15 letters or more on an ETDRS chart, or a statistically significant difference in the proportion of patients with a 15-letter change in visual acuity greater than or equal to clinically relevant outcome measures in trials of interventions.[34] Pivotal trials of previous anti-VEGF treatments for nAMD (ranibizumab and aflibercept) had as the primary end point the proportion of patients with a loss of less than 15 letters on the ETDRS charts (considered to be vision maintenance).[35]

With regard to the relationship between visual acuity measurement and visual function, a loss of three or more lines (greater than or equal to 15 letters) on an ETDRS chart corresponds to a doubling of the visual angle and is considered moderate visual loss, while a loss of six or more lines (greater than or equal to 30 letters) corresponds to a quadrupling of the visual angle and is considered severe. However, visual acuity is only one component contributing to overall visual function and the ability to perform everyday visual tasks (e.g., reading, recognizing faces, driving, and using the telephone). Overall visual function also depends upon variables such as contrast sensitivity, near vision, colour vision, and sensitivity to glare.[36] The various components of visual function will affect the performance of different vision-related tasks by varying degrees. For example, the use of distance acuity to measure the success of treatments for AMD is not optimal, given that distance vision is usually two ETDRS chart lines better than reading vision,[33] and difficulty with reading is a common complaint among people with eye disease.[37] Rather, contrast sensitivity is a more important contributor to reading performance.[33,38]

Central Subfield Thickness Using Spectral-Domain Optical Coherence Tomography

OCT is a fast, non-invasive imaging technique that can be used to create cross-sectional maps of the retinal structures and to quantify retinal thickness in patients with retinal disease.[39] OCT uses lasers centred on infrared wavelengths to record light reflected from interfaces between materials with different refractive indices, and from materials that scatter light. A recent advancement in OCT device technology has been the shift from time-domain (TD-OCT) to spectral-domain OCT (SD-OCT), as the latter can acquire data at a higher speed with better image resolution and reduced motion artifact.[40] While TD-OCT systems typically acquire two-dimensional images in a radial pattern, retinal scanning protocols in SD-OCT systems tend to acquire a stack of two-dimensional images in a raster pattern.[41]

OCT systems have segmentation algorithms that automatically delineate the boundaries of the retina and calculate retinal thickness parameters.[41]

In the HAWK and HARRIER studies, CSFT was measured on SD-OCT images at central reading centres. CSFT was defined in the studies as the average thickness of the retina between the inner limiting membrane and Bruch's membrane within a 1 mm diameter centred on the fovea. This measurement is often referred to as CRT in the literature. The tissue layer used as the outer boundary for retinal thickness can vary.[41,42]

The evidence in nAMD patients for a linear relationship between OCT-measured CRT and visual acuity, as well as between changes over time in the two measures, is inconsistent. In one study that pooled two trials of anti-VEGF treatment in patients with nAMD (N = 149 at baseline and N = 134 at month 12), there was a weak, negative correlation[43] (Pearson correlation coefficient of –0.24) between BCVA measured as a letter score and CRT at baseline; there was no correlation between changes in BCVA and CRT from baseline to month 12.[44] CRT was measured on SD-OCT images using automatic segmentation and manual error correction; P values were adjusted to control for type I error. In a study involving Chinese patients with nAMD who were receiving anti-VEGF treatment (N = 113), there was a moderate correlation[43] between change from baseline to month 9 in CRT measured with SD-OCT and BCVA measured in logarithmic minimal angle of resolution units (Pearson correlation coefficient of 0.34).[45] In a prospective cohort study (N = 1,142) within the Comparison of AMD Treatments Trials (CATT), a non-linear relationship was observed between CRT measured using TD-OCT and visual acuity assessed with a computerized version of the ETDRS chart.[46] In pooled data taken four weeks, 12 weeks, and 24 weeks after initiation of treatment, eyes with CRTs of less than 120 µm or greater than 212 µm had worse visual acuity than eyes with CRTs in the range of 120 µm to 212 µm (i.e., the range of values within two standard deviations of the mean measured for healthy eyes). This non-linear relationship was confirmed with follow-up results from five years after baseline.[47]

Intra-session repeatability and inter-session reproducibility of CRT measured using SD-OCT in patients with nAMD depends on whether segmentation errors by the system's automated segmentation software are corrected manually by readers. Segmentation errors can arise from the software's misplacement of the foveal centre[48] or inaccurate delineation of the retinal layer boundaries.[49,50] The percentage of cross-sectional, two-dimensional images acquired with SD-OCT with boundary delineation errors (in the central 1 mm diameter portion of the retina) in eyes with nAMD has been reported to range from 18% to 32%.[49,50] Manual correction of these errors[48] or exclusion of exams with segmentation errors[51,52] has been shown to improve intra-session repeatability (between two consecutive exams in the same session, performed and analyzed by a single reader)[48,51] and test-retest reproducibility (between two exams performed in different sessions, performed and analyzed by a single reader).[48,52] With manual correction or exclusion of exams with automatic segmentation errors, values of 12 µm to 18 µm have been reported for the coefficient of repeatability (1.96 × square root of the within-patient variance of the differences between each pair of measurements) for intra-session repeatability.[48,51] For inter-session reproducibility, a coefficient of repeatability of 26 µm was reported for separate imaging sessions conducted on the same day,[52] and a coefficient of repeatability of 44 µm to 47 µm was reported for separate sessions on different days[48] when automatic segmentation errors were excluded or manually corrected.

An MCID was not identified for CSFT measured by SD-OCT in nAMD.

National Eye Institute 25-Item Visual Function Questionnaire

The NEI VFQ-25 was developed to measure vision-targeted QoL. The original 51-item questionnaire was developed based on focus groups composed of people with a number of common eye conditions (e.g., age-related cataracts, AMD, and diabetic retinopathy); thus, the questionnaire may be used to assess QoL for a broad range of eye conditions.[37] The original 51-item questionnaire comprises 12 subscales related to general vision, ocular pain, near vision, distance vision, social functioning, mental health, role functioning, dependency, driving, peripheral vision, colour vision, and expectations for future vision. In addition, the questionnaire includes one general-health subscale.[53] A shorter version of the original instrument, the NEI VFQ-25, was subsequently developed. It retains the multi-dimensional nature of the original, but is more practical and efficient to administer.[54] With the exception of the expectations for future vision, all the constructs listed previously were retained in the shortened version, with a reduced number of items within each subscale. 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; averaging of the subscale scores produces the overall composite score. Alternative scoring approaches for the NEI VFQ-25 have been proposed.[55] Rasch modelling is used to obtain measurements from categorical data. When comparing standard scoring with Rasch analysis and using an algorithm to approximate Rasch scores, all methods were highly correlated.[55] 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.[55]

Convergent validity of the NEI VFQ-25 has been demonstrated in patients with nAMD (N = 1,134[56] and N = 92[57]) and in patients with a variety of chronic eye diseases (N = 597 in total and N = 108 with AMD)[54] using correlations with visual acuity[54,56,57] and the Short Form (36) Health Survey (SF-36) physical and mental component summary scores.[56] In the better-seeing eye, Pearson and Spearman correlation coefficients showed no correlation or weak correlations (± 0.1 to ± 0.3[43]) between the NEI VFQ-25 general-health and ocular pain subscale scores and visual acuity; weak to strong (greater than ± 0.5[43]) correlations between the NEI VFQ-25 colour vision and peripheral vision subscale scores and visual acuity; moderate (± 0.3 to ± 0.5[43]) to strong correlations between the remaining subscale scores and visual acuity; and strong correlations between the composite score and visual acuity. Correlations between subscale and composite scores and visual acuity were weaker overall in the worse-seeing eye than in the better-seeing eye. A weak correlation was found between the NEI VFQ-25 composite score and the SF-36 physical component summary score, while a moderate correlation was found between the NEI VFQ-25 composite score and the SF-36 mental component summary score.[56]

Acceptable internal consistency (Cronbach's alpha of ≥ 0.7[58]) has been demonstrated for all of the NEI VFQ-25 subscale scores (for subscales with more than one item) and for the composite score in a mixed population of patients with eye diseases,[54] as well as for the composite score in patients with nAMD.[56] Internal consistency is acceptable for most subscale scores in patients with nAMD, with values for Cronbach's alpha ranging from 0.62 to 0.92.[56,57] The subscale score for ocular pain did not have acceptable internal consistency.[56,57] Test-retest reliability was not assessed in the previously mentioned studies.

Determination of what constitutes a clinically meaningful change in the NEI VFQ-25 appears to be linked to its correlation with visual acuity. A three-line (15-letter) change in visual acuity has been used as the outcome of interest in clinical trials, and corresponding changes in the NEI VFQ-25 are suggested as clinically meaningful end points. Using results from two trials in patients with nAMD (N = 716 and N = 423), a 15-letter change in visual acuity in the study eye (typically the worse-seeing eye) corresponded to a change in 3.90 to 4.34 points in the composite score.[22] For the better-seeing eye, the clinically relevant difference for the NEI VFQ-25 composite score based on a three-line change was 7.35 to 8.18 points. In terms of responsiveness, a change in 9.61 to 10.57 points corresponded to a medium effect size.[22]

Some assessments of the psychometric validity of the NEI VFQ-25 using Rasch scoring and principal component analysis in patients with various eye conditions have identified issues with multi-dimensionality (measurement of more than one construct) and poor performance of the subscales.[56,59,60] The NEI VFQ-25 subscales were found to have too few items and were unable to discriminate among the population under measurement; thus, they were not valid.[59,60] Re-engineering the NEI VFQ-25 into two constructs (visual functioning and socio-emotional factors) and removing misfit items (e.g., pain around eyes, general health, and driving in difficult conditions) improved the psychometric validity of the scale in individuals with low vision.[59,60] Considering the evidence of multi-dimensionality, the validity of the single composite score of the NEI VFQ-25 may be questioned.

Presence of Intraretinal Fluid and/or Subretinal Fluid

IRF can be detected using OCT. It appears as diffuse retinal thickening or as hyporeflective cystoid spaces (also referred to as intraretinal cysts [IRCs]).[61] In treatment-naive eyes with nAMD, the presence of IRC has shown a tendency to be associated with worse visual acuity.[62] A strong, negative correlation (R^2 = 0.51 from linear regression) was found between the IRC area and BCVA in 38 patients with treatment-naive nAMD.[63] Follow-up data from the CATT has also demonstrated worse visual acuity in eyes with IRF versus no IRF (and worse visual acuity in eyes with foveal IRF versus extrafoveal IRF) at time points ranging from one year to five years following the initiation of anti-VEGF treatment.[47,64] In addition, the presence of IRF and/or IRC has been shown to be a prognostic factor for worsening visual acuity in eyes with nAMD. In follow-up analysis from the CATT, the development or worsening of adverse features (which included foveal IRF) two years to five years after treatment initiation was associated with a three-line worsening of visual acuity in multivariate analysis.[47] In a retrospective study of 447 eyes with nAMD that were switched from ranibizumab to aflibercept treatment, the presence of IRF alone and the presence of combined IRF and SRF at baseline were associated in linear regression over 12 months of treatment with worse visual acuity compared with the absence of IRF and SRF.[65]

In contrast, SRF (fluid between the retina and retinal pigment epithelium) detected using OCT does not appear to be negatively associated with visual acuity in eyes with nAMD. In treatment-naive eyes with nAMD, the presence of SRF or SRF was not associated with visual acuity.[62,63] Follow-up data from the CATT showed an association of foveal SRF presence with better visual acuity two years after treatment initiation, and no independent association between foveal SRF presence and visual acuity after one year or five years of follow-up.[47,64] In terms of predicting visual acuity, the development of foveal SRF in the CATT was not associated with a three-line worsening of visual acuity in multivariate analysis.[47] In the previously mentioned retrospective study in patients switched from ranibizumab to aflibercept treatment, the presence of SRF at baseline was not associated

with visual acuity over 12 months of treatment.[65] In the FLUID randomized controlled trial, visual acuity was compared between two groups following a 24-month treatment period using a treat-and-extend ranibizumab regimen: in the SRF-intolerant treatment group, the presence of IRF and/or SRF in any amount was sufficient to indicate disease activity (and no extension of the treatment interval); in the SRF-tolerant group, SRF of up to 200 µm in height at the sub-foveal centre did not, on its own, preclude treatment interval extension.[66] Visual acuity was found to be noninferior in the SRF-tolerant group compared with the SRF-intolerant group.[66]

In the HAWK and HARRIER studies, the presence or absence of IRF and SRF was reported independently. However, hypothesis testing was only planned for combined fluid status (yes = presence of IRF and/or SRF; no = absence of both types of fluid) in the HAWK study alone. Due to the potentially conflicting associations of IRF and SRF with visual acuity, the association of a combined IRF and SRF status with visual acuity is unclear. In a post hoc analysis of the VIEW studies comparing aflibercept and ranibizumab treatment for nAMD (N = 1,456 eyes), visual acuity outcomes at week 52 were no different between eyes with IRF, IRC, and/or SRF and eyes with no retinal fluid at week 12 following three loading doses.[67]

In the retrospective study of patients with AMD switched from ranibizumab to aflibercept treatment, there was almost perfect agreement[68] between raters for identifying the presence of IRF on SD-OCT exams (Kappa statistic of 0.859), and there was substantial agreement[68] between raters for SRF (Kappa statistic of 0.713).[65] Another study[69] using a sample of 270 TD-OCT exams from the CATT found good agreement[68] between reading teams (with each team composed of two certified readers and one senior reader to reconcile discrepancies) at a reading centre for identifying the presence of IRF (Kappa statistic of 0.48) and substantial agreement for identifying the presence of SRF (Kappa statistic of 0.80).

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