CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Report

Brolucizumab (BEOVU)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Treatment of neovascular (wet) age-related macular degeneration (AMD)

Service Line: CADTH Common Drug Review
Version: Final
Publication Date: July 2020
Report Length: 32 Pages

CADTH

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.

CADTH

Table of Contents

Tables

Figure

CADTH

Abbreviations

AE	adverse event
AMD	age-related macular degeneration
BCVA	best-corrected visual acuity
CI	confidence interval
ETDRS	Early Treatment Diabetic Retinopathy Study
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
nAMD	neovascular age-related macular degeneration
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
PRN	as needed
QALY	quality-adjusted life-year
QoL	quality of life
VEGF	vascular endothelial growth factor
WTP	willingness-to-pay

Executive Summary

The executive summary is composed of two tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Brolucizumab (BEOVU), 120 mg/mL, single-use, pre-filled syringe
Submitted price	Brolucizumab, 120 mg/mL, single-use, pre-filled syringe: $1,418.00
Health Canada–approved indication	Proposed: treatment of neovascular (wet) age-related macular degeneration
Health Canada review pathway	Standard review
NOC date	March 12, 2020
Reimbursement request	As per indication

NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov Model
Target population	Patients with nAMD; aligned with reimbursement request
Treatment	Brolucizumab
Comparators	Aflibercept Ranibizumab Bevacizumab (separate analysis provided)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (maximum 100 years of age)
Key data sources	Sponsor-submitted NMA reporting mean change in BCVA (ETDRS chart letters) and arm-based pooling for adverse events, treatment discontinuation, and injection frequencies from the corresponding clinical trials. The network included three trials studying brolucizumab (HAWK, HARRIER, and Dugel et al. [2017]).
Submitted results for base case	Brolucizumab dominated both aflibercept and ranibizumab (i.e., brolucizumab is less costly and produces more QALYs).
Key limitations	• Bevacizumab was excluded from the sponsor's base-case economic model. However, given that multiple public drug programs reimburse treatment with bevacizumab for nAMD, CADTH considered this to be a relevant comparator. • Discontinuation rates differed between anti-VEGF inhibitors based on outputs from an NMA. However, CADTH considered equal discontinuation to be more appropriate based on clinical expert input. • Costs associated with vision loss were overestimated because it was uncertain if these costs represented only costs to the health system and adequately captured costs specific to nAMD. • The treatment effect was assumed to be maintained after year 3. CADTH considered this assumption to be overly optimistic and was associated with uncertainty, given the lack of long-term data. • The sponsor included vision loss-adjusted mortality. However, this was not appropriately implemented in the economic model, and the study results used to generate mortality estimates

Component	Description
	may not be applicable to the HAWK/HARRIER trial population, adding uncertainty to the cost-effectiveness results. • Treatment switching and discontinuation criteria were not included in the economic model, limiting generalizability for reimbursement decisions and clinical practice.
CADTH reanalysis results	CADTH undertook reanalyses to address the identified limitations by including bevacizumab, applying equal discontinuation rates, adjusting costs of vision loss, and applying a pooled treatment effect for the long-term extrapolation. Based on sequential analyses, brolucizumab is not cost effective at a WTP threshold of $50,000 per QALY with an ICER of $250,575 per QALY. A price reduction of 85% for brolucizumab is required to achieve an ICER of $50,000 per QALY gained.

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; ICER = incremental cost-effectiveness ratio; LY = life-year; nAMD = neovascular age-related macular degeneration; NMA = network meta-analysis; QALY= quality-adjusted life-year; VEGF = vascular endothelial growth factor; WTP = willingness-to-pay.

Conclusions

CADTH undertook reanalyses to address limitations that included bevacizumab as a relevant comparator, applying equal treatment discontinuation, adjusting vision impairment costs, and applying a pooled, long-term treatment effect.

Using the CADTH base-case reanalyses, brolucizumab would not be considered cost-effective treatment at a willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life-year (QALY). The probability of brolucizumab being considered the most cost-effective intervention was 0% at a threshold of $50,000 per QALY (and even at a threshold of $100,000 per QALY). Price reductions can improve the cost-effectiveness of brolucizumab in patients with neovascular age-related macular degeneration (nAMD). At a WTP threshold of $50,000 per QALY, a respective price reduction of 85% is required for brolucizumab to be considered cost-effective compared to bevacizumab. No price reduction would be required for brolucizumab if bevacizumab was unavailable as a treatment option.

While some uncertainties remain in the model, it is highly unlikely that brolucizumab would be considered a cost-effective intervention relative to bevacizumab based on the efficacy estimates and price submitted by the sponsor.

Stakeholder Input Relevant to the Economic Review

This section summarizes the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process (specifically, information that pertains to the economic submission).

A joint patient group submission was prepared by Fighting Blindness Canada, the Canadian Council of the Blind, the Canadian National Institute for the Blind Foundation, and Vision Loss Rehabilitation Canada. The online survey included input from 157 patients living with age-related macular degeneration (AMD), with 97 respondents reporting having nAMD. The most frequent challenges reported by patients with nAMD include concerns over deterioration of sight (80% of respondents), 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%). Quality of life (QoL) was affected in 37% of patients due to medication or treatment routine, specifically related to limited vision or pain for one to three days following injection as well as inconvenience, disruption, and expense associated with transportation to and/or from treatments. Only a small proportion of patients were unsatisfied with current treatments; however, 64% of respondents indicated that they would prefer a treatment that could be taken less frequently.

Several of these concerns were addressed in the sponsor's model:

- Treatment efficacy (change in best-corrected visual acuity [BCVA]) was incorporated using results from the sponsor-submitted network meta-analysis (NMA).
- Treatment-specific dosing schedules were included in the economic model, with only the most common dosing used in clinical practice (based on sponsor clinical expert opinion) applied in the base-case analyses.
- QoL was captured according to each health state; however, no utility decrement for treatment injection was applied as part of the base-case analyses (explored in the scenario analyses).
- Adverse events (AEs) were included (costs and QoL decrements). However, anxiety and depression were not included.
- A societal perspective was explored in scenario analyses to assess the impact of indirect costs associated with nAMD.

In addition, CADTH addressed the inclusion of an injection utility decrement as part of scenario analyses to assess the impact on QoL.

Economic Review

The current review is for brolucizumab (Beovu) for the treatment of nAMD.[1]

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis assessing brolucizumab (an anti–vascular endothelial growth factor [anti-VEGF]) in patients with nAMD. The modelled population was consistent with the HAWK and HARRIER phase III clinical trials for brolucizumab and aligned with the funding request.[2] No analyses were conducted for patient subgroups.

The recommended dose of brolucizumab is 6 mg (0.05 mL) administered by intravitreal injection every four weeks (monthly) for the first three doses (loading phase). Thereafter, brolucizumab is administered every 12 weeks (three months).[3] The comparators included aflibercept (2 mg [0.05 mL] every four weeks for the first three months, followed by 2 mg [0.05 mL] every eight weeks) and ranibizumab (0.5 mg [0.05 mL] every four weeks, possibly reduced to one injection every three months).[4,5] In the economic model, the sponsor applied a treat-and-extend injection regimen for ranibizumab, where each visit was combined with an injection and time between visits could be progressively lengthened or shortened (in increments of two weeks). Treatment administration costs were applied to all treatments; treatments were assumed to be performed by an ophthalmologist or retinal specialist with nurse or technician assistance. Patients discontinuing treatment transitioned to the "off treatment" health states. It was assumed that patients would follow the disease progression associated with untreated nAMD. The same model structure was applied to the sponsor-submitted reanalysis that included the off-label use of bevacizumab, which CADTH considered as a relevant comparator.

The clinical outcomes of interest were QALYs and life-years. The economic evaluation was undertaken over a lifetime time horizon (maximum 100 years) using one-year cycle lengths (half-cycle correction applied) from the perspective of the public health care payer. Discounting (1.5% per annum) was applied to both costs and outcomes.

The total annual drug acquisition cost of brolucizumab is $8,508 in year 1 and $5,672 in subsequent years, based on a unit price of $1,418.00 per 120 mg/mL pre-filled syringe.

Model Structure

A cohort-level Markov model was developed in Microsoft Excel and included a total of 13 mutually exclusive health states. Six health states were divided according to the level of BCVA in a single eye for both "on treatment" and "off treatment" patients. BCVA was measured using the number of Early Treatment Diabetic Retinopathy Study (ETDRS) chart letters, with the best state being greater than 85 letters and the worst state being less than or equal to 25 letters. All patients entered the model in "on treatment" health states (distribution informed by the HAWK and HARRIER trials) and could experience one of five scenarios annually: maintain their current BCVA health state; transition by one BCVA health state (i.e., lower or higher number of ETDRS chart letters); transition by two BCVA health states; discontinue treatment and transition to "off treatment;" or enter death from any health state (Appendix 3, Figure 1). Clinical trials typically report the proportion of patients gaining

or losing greater than or equal to 15 letters or 30 letters. However, some patients may need only a few letters to transition between health states, and clinical trial measures are unlikely to capture these patient transitions accurately. Therefore, the sponsor assumed patients would have a midpoint BCVA for each health-state range. This means patients need to gain or lose 7.5 letters to transition by one health state and gain or lose 22.5 letters to transition between two health states. The relative treatment effects (i.e., mean change in BCVA) of all included therapies were derived from the sponsor-submitted NMA using aflibercept as the reference arm. Patients in the "on treatment" health states presenting with bilateral disease, or who developed nAMD in the other eye in subsequent years, incurred additional treatment costs to treat the other eye. However, this had no impact on BCVA. Treatment discontinuation was assumed to occur simultaneously in both eyes.

Model Inputs

The baseline characteristics in the model were aligned with those in the HAWK and HARRIER trials' patient populations. Both trials were phase III, multi-centre, randomized, active-controlled trials involving adult patients with nAMD.[2] The clinical efficacy of brolucizumab and the comparators of interest (measured in terms of change in BCVA) were obtained from an unpublished NMA commissioned by the sponsor, and estimates from baseline to year 1 and year 1 to 2 were calculated. Long-term treatment effectiveness was extrapolated in year 3 and onwards, where it was assumed that the change in BCVA in year 2 would continue to occur each year for the remainder of the time horizon. Over time, a treatment waning effect of –0.5 ETDRS chart letters per year was applied equally to each treatment based on the results of the observational study by Eleftheriadou et al. (2018).[6] Patients discontinuing treatment were assumed to follow a progression similar to that of untreated nAMD patients, as represented by placebo arms included in the sponsor-submitted NMA.

Transition probabilities for change in mean BCVA were estimated using the HAWK and HARRIER trial data, with the assumption that patients would have a higher probability of transitioning by one health state (i.e., gain or loss of 7.5 letters) compared to two health states (i.e., gain or loss of 22.5 letters) based on the methodology used in the 2018 National Institute for Health and Care Excellence (NICE) AMD Guidelines (NG82).[7] The sponsor also adjusted the change in BCVA over the initial two years of treatment by applying an odds ratio for the probability of gaining or losing 7.5 ETDRS chart letters based on the current BCVA health state using the study by Buckle et al. (2016).[8] When applying the health-state adjustment, patients in a worse BCVA health-state (e.g., ≤ 25 letters) were less likely to deteriorate and more likely to improve when receiving treatment, whereas patients in a better BCVA health state (e.g., > 85 letters) were less likely to improve (Table 12). Annual probabilities for treatment discontinuation were derived from an NMA using arm-based pooling; the sponsor assumed that treatment-specific discontinuations (7.78% ranibizumab; 8.65% aflibercept; 7.86% brolucizumab) would be constant over time. To model the development of bilateral disease, an annual probability of 16.6% for developing nAMD in the other eye was obtained from Zarranz-Ventura et al. (2014)[9] and applied to all treatments. Serious ocular AEs (i.e., cataract, endophthalmitis, retinal detachment, retinal tear), gastrointestinal events, and stroke were also included using results from Solomon et al. (2014),[10] with the assumption that all treatments would have similar safety profiles. The sponsor adjusted mortality for patients with visual impairment (< 35 ETDRS chart letters in either eye; hazard ratio [HR]: 1.23 [95% CI, 1.16 to 1.31]) or defined as blind (≤ 25 ETDRS chart letters in either eye; HR: 1.54 [95% CI, 1.28 to 1.86]).[11]

Health-state utility values were derived for each BCVA health state using regression models outlined by Hodgson et al. (2017).[12] The resulting EuroQol 5-Dimensions estimates are presented in Table 13. Utility decrements for serious ocular AEs, gastrointestinal events, and stroke (expressed as a multiplier) were included as part of the base case (Table 14). The sponsor assumed a retinal tear would not affect QoL.

Costs included drug costs, treatment administration costs, monitoring visits, vision impairment and blindness management costs, and AE costs. The drug price of brolucizumab was obtained from the sponsor. Prices for all other treatments were sourced from publicly available sources, including the Ontario Drug Benefit Formulary.[13] Administration costs included a retinal specialist visit ($82.30; A235), nursing visit (15 minutes),[14] and an injection fee ($90.00; E147).[15] Injection frequencies were assumed to vary by regimen; an overview is provided in Table 15. The sponsor assumed continuous treatment regimens; no additional monitoring visits would be required, as these are captured in the visits for injections. As needed (PRN) and PRN extension regimens would require 12.69 and 10.10 visits in years 1 and 2 respectively.[16] In year 3 and onwards, a total of 8.20 visits based on NICE guidance for AMD was applied.[7] Monitoring costs included a one-time IV fluorescein angiography ($66.35; G853, G425)[15] for diagnosis and a continual cost for optical coherence tomography ($30.67; G821, G822)[15] based on an average of 7.01 visits per year. The cost of low vision (≤ 35 ETDRS chart letters) was applied annually in the model using a Canadian-based observational study that found the annual total cost of vision loss was $19,370 (2007) per patient.[17] It was estimated that 55.3% of the costs would be incurred by the provincial and federal governments, with costs inflated to 2019 Canadian Dollars ($13,047). Additionally, the cost of blindness registration (≤ 25 ETDRS chart letters in either eye) with the Canadian National Institute for the Blind Foundation was applied as a one-time cost ($10).[18] For patients with bilateral nAMD, drug acquisition costs were doubled and an administration cost multiplier (1.49) was applied, with the assumption that an injection fee would be billed twice. Costs for AEs were applied on a one-off basis using publicly available sources and clinical expert opinion, with the exception of stroke, which would require ongoing costs (Table 16).

Summary of Sponsor's Economic Evaluation Results

The sponsor presented probabilistic analyses (5,000 iterations for the base-case and scenario analyses).

Base-Case Results

In the sponsor's base-case analysis, brolucizumab was associated with an expected cost of $115,560 and 6.84 QALYs over a lifetime time horizon (until cohort reaches 100 years of age). Based on a full sequential analysis, treatment with brolucizumab was less costly and produced more QALYs than both aflibercept and ranibizumab (Table 3). At a WTP threshold of $50,000 per QALY, brolucizumab has an 87.2% probability of being cost-effective, while aflibercept has a 12.8% probability of being cost-effective.

Table 3: Disaggregated Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental cost	Total QALYs	Incremental QALYs	ICER ($/QALY) versus brolucizumab	Sequential ICER ($/QALY)
Brolucizumab	115,560	Reference	6.84	Reference	Reference	–
Aflibercept	123,242	7,682	6.76	–0.08	Dominated	Dominated
Ranibizumab	198,660	83,100	6.17	–0.67	Dominated	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: The submitted analysis is based on publicly available prices of the comparator treatments.

Source: Adapted from sponsor's pharmacoeconomic submisstion.[1]

At CADTH's request to include bevacizumab as part of the base-case analyses, the sponsor provided a revised model that permitted the comparison of bevacizumab with brolucizumab, ranibizumab, and aflibercept. However, no report was submitted with this model. Based on the revised economic model, the incremental cost-effectiveness ratio (ICER) for brolucizumab versus bevacizumab was $250,575 per QALY, with a 0% chance of brolucizumab being considered cost-effective at a WTP threshold of $50,000. Additional details are provided in the CADTH Appraisal of the Sponsor's Economic Evaluation.

Sensitivity and Scenario Analysis Results

The sponsor undertook scenario analyses that varied several parameters, including the time horizon (five years), discount rate, adoption of a societal perspective, proportion of patients with bilateral nAMD at baseline, application of an average discontinuation, inclusion of injection-related utility decrement, assessment of head-to-head data with aflibercept, inclusion of ranibizumab PRN for efficacy, and removal of adjusted mortality rates. In all scenarios, brolucizumab was less costly and produced more QALYs, dominating both aflibercept and ranibizumab.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis.

- **Exclusion of bevacizumab as a comparator:** Based on clinical guidelines and feedback from the public payers as per the CADTH therapeutic review for anti-VEGF inhibitors, off-label use of bevacizumab was considered a relevant comparator and should be included in the economic model.[19,20] Currently, five provinces reimburse the cost of bevacizumab for nAMD (Alberta, British Columbia, Manitoba, Newfoundland and Labrador, and Nova Scotia), with Newfoundland and Labrador recommending bevacizumab as initial treatment.[21-25] Based on feedback from the clinical expert consulted by CADTH, the use of bevacizumab is expected to vary among clinicians due to perceived uncertainty regarding its efficacy and safety in treating nAMD.

  Further, a recent Cochrane Review illustrated that bevacizumab was noninferior to ranibizumab with respect to gain and maintenance of visual acuity, and that serious systemic AEs were comparable across anti-VEGF treatments, with the exception of gastrointestinal disorders, which were elevated in bevacizumab compared with ranibizumab.[26] Similar conclusions for ocular AEs were also found in the sponsor-submitted NMA.

Therefore, CADTH requested that the economic model include a comparison with bevacizumab and that all associated inputs from the sponsor-submitted NMA be updated with this comparator. The sponsor disagreed with CADTH's request to include bevacizumab, based on patient safety concerns. However, an updated model was provided (without a written report).[27] When using the revised economic model, bevacizumab every four weeks was the least costly treatment ($57,539) and produced 6.61 QALYs (Table 4). Based on sequential analyses, brolucizumab is not cost effective at a WTP threshold of $50,000 per QALY with an ICER of $250,575 per QALY.

- CADTH included bevacizumab (on an as-needed basis, based on clinical expert feedback) as part of the base-case reanalyses. Based on the CADTH therapeutic review for anti-VEGF inhibitors, it was assumed that 15 doses could be obtained per 100 mg (4 mL) vial.[20]

Table 4: Summary Results of the Sponsor's Analysis With Bevacizumab Included

Drug	Total costs ($)	Total QALYs	ICER vs. bevacizumab ($/QALY)	Sequential ICER ($/QALY)
Bevacizumab[a]	57,539	6.61	Reference	Reference
Brolucizumab	115,265	6.84	250,575	250,575
Aflibercept	122,744	6.77	424,421	Dominated by brolucizumab
Ranibizumab	194,480	6.17	Dominated	Dominated by bevacizumab, aflibercept, and brolucizumab

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; vs. = versus.

Note: The submitted analysis is based on publicly available prices of the comparator treatments. Results were presented probabilistically.

[a] Reference product is least costly alternative.

Source: Based on the revised economic model submitted to CADTH on November 28th, 2019.[27]

- **Limited modelling of treatment initiation, discontinuation, and switching:** The sponsor included discontinuation estimates based on its NMA results. However, differences between treatments were not statistically significant, and the clinical expert consulted by CADTH highlighted that discontinuation rates would likely be similar. Further, the clinical expert indicated that a proportion of patients receiving treatments that require frequent injections (i.e., ranibizumab) may discontinue treatment and switch to therapies that require less frequent injections (i.e., aflibercept). However, this was not explored in the sponsor's economic model.
- Six public drug programs have implemented initiation criteria for both aflibercept and ranibizumab where patients must have a BCVA between 6/12 (20/40) and 6/96 (20/320); i.e., approximately 70 letters and 25 letters, respectively. However, this was not considered by the sponsor, given that 27.96% of patients with greater than 70 letters and fewer than 25 letters were included in the initial distribution.[28-33] Five public drug programs also included discontinuation criteria where patients are discontinued from treatment if a reduction in BCVA to fewer than 15 letters on two consecutive visits or a reduction of 30 letters from baseline or best recorded level occurs. This was also not explored by the sponsor.[28,30-33] It is unlikely that the treatment discontinuation rates implemented by the sponsor incorporated the cited reimbursement criteria, and the model structure limits a decision-maker's ability to assess the cost-effectiveness of brolucizumab within this context.

- CADTH applied an average discontinuation rate of 8.84% to all treatments as part of the base-case reanalyses. In scenario analyses, CADTH applied a higher discontinuation rate to all treatments based on bevacizumab (11.06%) and explored the exclusion of patients failing to meet the public drug program initiation criteria. Due to structural limitations of the economic model, CADTH was unable to explore the impact of public drug program discontinuation criteria, although the impact on the cost-effectiveness results may be limited.

- **Uncertainty of long-term treatment effect:** Due to the short follow-ups in the HAWK and HARRIER trials, the sponsor extrapolated the treatment effect from year 2 as obtained from the NMA for both brolucizumab and the comparators over the remainder of the analysis time horizon. CADTH considered this approach to be severely limited, given the lack of data to support a continued treatment effect beyond two years. The approach substantially favoured brolucizumab, because the treatment effect for brolucizumab was associated with a BCVA gain in year 2 (+ 0.41) compared to ranibizumab treat-and-extend (–4.42), aflibercept treat-and-extend (0.00), and bevacizumab PRN (–1.17). This translated to an annual BCVA decrease of 0.09 letters (includes disease progression of –0.5 letters) for patients receiving brolucizumab until treatment discontinuation, whereas BCVA would decrease annually by 0.5 to 4.92 letters for patients on comparator treatments. The assumption that anti-VEGF treatment effect is maintained for the remaining duration of the time horizon was also not considered realistic in clinical practice, based on feedback from the clinical expert consulted by CADTH.

  Based on the sponsor-submitted NMA, the only comparison where the 95% confidence interval (CI) around the mean change in BCVA was greater than zero was between sham (placebo) intravitreal injection and all other anti-VEGFs. This highlights the uncertainty of applying individual treatment effects in the long term, considering that an assumption of equal efficacy may be more appropriate. The CADTH Common Drug Review clinical report also cited numerous limitations associated with the analysis, including the choice of fixed-effects models and missing results for random-effects models, considerable heterogeneity in baseline characteristics, and weak connections between brolucizumab and the overall network, which affected the reliability of the NMA findings.

  - CADTH applied a pooled treatment effect (i.e., the pooled mean of brolucizumab 6 mg every 12 or eight weeks, bevacizumab PRN, aflibercept every eight weeks, and ranibizumab treat-and-extend regimens) to all treatments from year 3 and beyond. As part of scenario analyses, individual treatment effects from year 2 were extended for years 3 to 5, and then a pooled treatment effect was applied to all treatments for year 6 and beyond. Finally, a scenario where no treatment effect was applied beyond year 2 was explored.

- **Overestimation of vision loss costs:** The sponsor included costs associated with vision loss for patients with a BCVA less than or equal to 35 ETDRS chart letters using the publication by Cruess et al. (2011);[17] however, multiple limitations were associated with using this data source. The estimated per capita costs are based on the top five major causes of visual impairment costs in Canada (i.e., AMD, cataract, diabetic retinopathy, glaucoma, and refractive error), with AMD representing only approximately 12.8% of health system expenditures. There were also various health system expenditures included that are not covered as part of the health care payer perspective, such as research. Likewise, it was uncertain which costs were already captured as part of the economic model (i.e., treatment costs, hospitalizations, physician or health care services), and there is a potential risk of double counting.

An international observational study conducted by Cruess et al. (2007)[34] reported on the economic burden of nAMD in Canada based on the level of visual acuity. The publication also presented individual cost components as a proportion of the total health care system expenditure, which CADTH considered to be more transparent, to confirm if these costs are already captured in the economic model. Based on this study, mean direct vision-related costs and non–vison-related medical costs (in 2005 Canadian Dollars) for patients with severe vision loss or patients who were nearly blind (i.e., ≤ 35 ETDRS chart letters) were $4,240 and $2,843, respectively. Given that specific elements of the reported costs are already captured in the economic model (i.e., retina specialist visits, diagnostic tests, treatment of nAMD), direct vision-related costs were modified by removing these elements. This resulted in direct vision-related costs of $169 and direct non–vision-related costs of $2,843, for a total cost due to vision loss of $3,012 ($3,815 in 2019 Canadian Dollars) annually.[35]

  - CADTH included treatment costs from Cruess et al. (2007) for patients with severe vision loss or who were nearly blind (i.e., ≤ 35 ETDRS chart letters) as part of its base-case reanalyses.

- **Uncertain treatment impact on mortality:** The sponsor applied an HR for both severe vision impairment (≤ 25 letters; 1.54 [95% CI, 1.28 to.86]) and some visual impairment (< 35 letters; 1.23 [95% CI, 1.16 to 1.31]) from the publication by Christ et al. (2008).[11] It was unclear from the publication if severe or some visual impairment was reflective of the BCVA cut-offs used in the sponsor's economic model. Using WHO's definition of low vision (< 6/18 to ≥ 3/60, or approximately < 61 to ≥ 20 letters), the application of the HR for some visual impairment may better apply to these BCVA health states.[36] Further, the patient population included in the study is not likely representative of the HAWK/HARRIER trials, given that patients were younger (44 years versus 75.8 years) and that current patient management and care may have improved mortality since the survey was conducted (1986 to 1996).
  - As part of scenario analyses, CADTH removed the impact of mortality adjustments.

Additional limitations were identified, but were not considered to be key limitations.

- **Inappropriate cycle length and conversion of trial data:** Due to structural limitations of the model, the sponsor annualized change in BCVA from weeks 53 to 96 to obtain 104-week data that corresponded with time points in the sponsor-submitted NMA. This assumes the treatment effect is maintained over an eight-week period despite an observed decrease in mean change of BCVA between weeks 48 to 96 for all treatment arms in the HAWK/HARRIER trials,[37] which artificially stabilizes the treatment effect. Further, the cycle length of one year was considered excessive by CADTH, given that changes in treatment benefit or the emergence of AEs are likely to occur over a shorter duration (i.e., between treatment injections). A shorter cycle length would have been more appropriate to accommodate data from the HAWK and HARRIER trials. Further, previous reviews of ranibizumab and aflibercept for nAMD by CADTH and NICE included shorter cycles (i.e., four weeks, six weeks, and 12 weeks) to align with treatment administration schedules.
  - Due to structural limitations, CADTH was unable to address cycle length or annualization of trial data.

Additionally, a number of key assumptions were made by the sponsor and appraised by CADTH (see Table 5).

Table 5: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Individual treatment regimens and associated attributes (i.e., loading phase or treatment frequency) have independent treatment effects.	Reasonable, given that differences in efficacy and safety may arise based on treatment frequency.
Aflibercept 2 mg LP -> every 8 weeks is an appropriate reference arm to calculate the relative treatment effect for other comparators.	Reasonable
100% of study eyes are the worst-seeing eyes.	Reasonable, based on clinical expert feedback. Alternate proportions of patients receiving treatment in the worst-seeing eye were explored by CADTH; however, the impact on cost-effectiveness was minimal.
Disease progression is representative of the untreated nAMD population (i.e., sham IVT).	Reasonable
Treatments would have the same safety profile regardless of dosing regimen or molecule.	Uncertain. Although a recent Cochrane Review observed similar rates of AEs between anti-VEGF inhibitors, clinical trials are typically insufficiently powered to capture AEs, and additional long-term data are needed.[26] There was a minimal impact on cost-effectiveness results when adjusting AE probabilities specific to each treatment.

AE = adverse event; IVT = intravitreal; LP = loading phase; nAMD = neovascular age-related macular degeneration; VEGF = vascular endothelial growth factor.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH reanalyses addressed several limitations within the economic model. These are summarized in Table 6. Due to structural limitations, CADTH was unable to address the cycle length, annualization of trial data, treatment switching, or reimbursement discontinuation criteria.

Table 6: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Correction of time horizon used in the model so the cohort could reach a maximum of 100 years in age[a]	75 years	25 years
2. Utility decrement for AEs not input probabilistically	Not included probabilistically	Included probabilistically
Changes to derive the CADTH base case		
1. Considered bevacizumab as a relevant comparator and updated unit costs	Excluded	Included (PRN); $385.94 per 100 mg vial
2. Equal treatment discontinuation	Brolucizumab: 7.86% Aflibercept: 8.65% Ranibizumab: 7.78% Bevacizumab: 11.06%	All treatments: 8.84%
3. Revised costs for vision loss	$13,047	$3,815

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
4. Long-term treatment effect year 3 and beyond	Applied individual treatment effects with an annual deterioration due to disease progression of –0.5 letters	Applied individual treatment effects year 1 and 2 and a pooled treatment effect for both the intervention and comparators year 3 and beyond, with an annual deterioration due to disease progression of –0.5 letters
CADTH base case	-	Reanalyses 1 to 4

AE = adverse event; PRN = as needed.

[a] Based on the sponsor's model, the application of a 75-year time horizon combined with the mean patient age (75.80 years) would extend the maximum time horizon to over 150 years.

CADTH's base-case results are presented in Table 7. Additional reanalyses and results are presented in Table 17 and Table 18.

In CADTH's base case, bevacizumab is the least costly option ($24,024) and provides 6.55 QALYs over a lifetime time horizon. Based on a full sequential analysis, bevacizumab is the most cost-effective option at a WTP threshold of $50,000 per QALY (Table 7). Ranibizumab was dominated (i.e., more costs and fewer QALYs) by bevacizumab, brolucizumab, and aflibercept. At a WTP threshold of $50,000 per QALY, 0% of simulations resulted in brolucizumab being cost-effective.

Table 7: Summary of the CADTH Reanalysis Results

Drug	Total costs ($)	Total QALYs	ICER vs. bevacizumab ($/QALY)	Sequential ICER ($/QALY)
Sponsor-corrected base case (bevacizumab included)				
Bevacizumab[a]	57,489	6.61	Reference	Reference
Brolucizumab	114,881	6.84	256,064	256,064
Aflibercept	122,859	6.76	Dominated by brolucizumab	Dominated by brolucizumab
Ranibizumab	194,818	6.16	Dominated by bevacizumab, brolucizumab, and aflibercept	Dominated by bevacizumab, brolucizumab, and aflibercept
CADTH base case				
Bevacizumab[a]	24,024	6.55	Reference	Reference
Brolucizumab	88,047	6.66	583,404	583,404
Aflibercept	98,318	6.66	655,564	2,862,068
Ranibizumab	156,316	6.49	Dominated by bevacizumab	Dominated by bevacizumab, brolucizumab, aflibercept

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; vs. = versus.

Note: The submitted analysis is based on publicly available prices of the comparator treatments.

[a] Reference product is least costly alternative.

Scenario Analysis Results

CADTH Exploratory Analyses

Exploratory analyses were conducted using the CADTH base case to investigate the impact of mortality adjustments, BCVA health-state initiation, injection utility decrements, treatment efficacy, treatment discontinuation, and bevacizumab or brolucizumab regimen used (Table 8).

Table 8: CADTH Scenario Analyses

	CADTH base case	CADTH scenario
Scenario analyses		
1. Mortality adjustments according to BCVA health states	Included	Excluded
2. BCVA starting distribution	86 to 100: 0.00% 71 to 85: 26.18% 56 to 70: 44.62% 41 to 55: 18.57% 26 to 40: 8.84% 0 to 25: 1.78%	• 100% for each health state • Exclusion of patients not meeting reimbursement criteria related to current anti-VEGFs outlined by some provinces
3. Injection utility decrement	Excluded	Included
4. Treatment efficacy	Pooled treatment effect year 3 and beyond	• No treatment effect year 3 and beyond • Individual treatment effect years 2 to 5 and pooled treatment effect year 6 and beyond
5. Treatment discontinuation	8.84%	11.06%
6. Bevacizumab regimen for treatment effect and resource use	Bevacizumab 1.25 mg PRN	• Bevacizumab 1.25 mg q.4.w. • Bevacizumab 1.25 mg q.6.w.
7. Brolucizumab regimen for treatment effect and resource use	Brolucizumab 6 mg q.12.w./q.8.w.	• Brolucizumab 6 mg q.8.w. -> q.12.w. • Brolucizumab 3 mg q.12.w./q.8.w.

BCVA = best-corrected visual acuity; PRN = as needed; q.4.w. = every 4 weeks; q.6.w. = every 6 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; VEGF = vascular endothelial growth factor.

Note: Reanalyses are based on publicly available prices of the comparator treatments.

Based on CADTH scenario analyses, the use of bevacizumab every four weeks had the largest impact on brolucizumab results, making it less cost-effective, with a higher sequential ICER of $1,998,255 per QALY (Table 19). When exploring subgroup analyses for the initial BCVA distribution, the ICER for brolucizumab, when compared to bevacizumab, ranged from $502,929 to $1,378,075 per QALY, with lower ICERs attributed to more people starting in states with lower BCVA scores (except ≤ 25 letters). When brolucizumab 6 mg was administered every eight weeks followed by every 12 weeks, brolucizumab was extendedly dominated (i.e., the ICER for brolucizumab was higher than the next more-effective treatment [aflibercept] despite lower incremental costs); however, these results were based on a small number of patients, and the trial was of limited duration (56 weeks).

Price Reduction Analyses

Price reduction analyses were conducted using the CADTH base case (Table 9). Based on the sponsor's base case (bevacizumab included), a respective price reduction of 60% to 65% would be required for a WTP threshold of $50,000 per QALY. When using the CADTH base case, at a WTP threshold of $50,000 per QALY, brolucizumab would require a respective price reduction of 85% to be considered cost-effective versus bevacizumab.

Table 9: CADTH Price Reduction Analyses

	ICER ($/QALY) for brolucizumab versus bevacizumab	
Price reduction	**Sponsor base case (bevacizumab included)**	**CADTH reanalysis**
No price reduction	250,575	583,404
45%	106,165	296,929
50%	**91,981**	265,520
55%	75,006	238,035
60%	57,002	202,473
65%	**41,352**	173,219
70%	26,534	144,188
75%	9,133	112,870
80%	Dominant	**81,158**
85%	Dominant	**49,157**

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years.

Note: The submitted analysis is based on publicly available prices of the comparator treatments.

Issues for Consideration

- **Included dosing:** The HAWK and HARRIER clinical trials included a 3 mg dose for brolucizumab, which is neither currently available in Canada nor expected to become available. However, based on the economic model, cost-effectiveness was not expected to be extensively affected.
- **Availability of ranibizumab biosimilar:** A phase III clinical trial comparing the proposed ranibizumab biosimilar with the reference drug (Lucentis) was recently completed (December 9, 2019) for patients with nAMD.[38] Given potential price reductions associated with the introduction of a ranibizumab biosimilar, the current list price of ranibizumab may not be reflective of the future treatment costs for nAMD.

Overall Conclusions

CADTH undertook reanalyses to address limitations that included bevacizumab as a relevant comparator, applying equal treatment discontinuation, adjusting vision impairment costs, and applying a pooled long-term treatment effect.

Using the CADTH base-case reanalyses, brolucizumab would not be considered cost-effective treatment at a WTP threshold of $50,000 per QALY. The probability of brolucizumab being considered the most cost-effective intervention was 0% at a $50,000 per QALY threshold (and even at $100,000 per QALY). Price reductions can improve the cost-effectiveness of brolucizumab in patients with nAMD. At a WTP threshold of $50,000 per QALY, a respective price reduction of 85% is required for brolucizumab to be considered cost-effective when compared to bevacizumab. No price reduction would be required for brolucizumab if bevacizumab is unavailable as a treatment option.

While some uncertainties remain in the model, it is highly unlikely that brolucizumab would be considered a cost-effective intervention, relative to bevacizumab, based on the efficacy estimates and price submitted by the sponsor.

Appendix 1: Cost Comparison Table

The comparators presented in the Table 10 have been deemed appropriate based on feedback from clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table. As such, the table may not represent the actual costs to public drug plans.

Table 10: CADTH Cost Comparison Table for Neovascular (Wet) Age-Related Macular Degeneration

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily average cost ($)	Annual average cost ($)
Brolucizumab (Beovu)	120 mg/mL	0.05 mL vial	1,418.0000	6 mg administered by intravitreal injection every 4 weeks for the first three doses followed by 6 mg every 12 weeks thereafter	**Year 1:** 23.31 **Subsequent:** 15.54	**Year 1:** 8,508 (6 inj.) **Subsequent:** 5,672 (4 inj.)
Anti-VEGF inhibitors						
Aflibercept (Eylea)	40 mg/mL	0.05 mL vial	1,418.0000	2 mg administered by intravitreal injection every 4 weeks for the first three doses, followed by 2 mg every 8 weeks thereafter; treatment intervals may be extended to 12 weeks if visual outcomes remain stable	**Year 1:** 27.19 **Subsequent:** 15.54 to 23.31	**Year 1:** 9,926 (7 inj.) **Subsequent:** 5,672 to 8,508 (4 to 6 inj.)
Bevacizumab (Avastin)	25 mg/mL	4 mL vial 16 mL vial	519.1800[a] 2,076.7104[a]	1.25 mg administered by intravitreal injection every 4 weeks for the first three doses, followed by 0.5 mg every 4 weeks thereafter; the treatment interval may be extended to 12 weeks[b]	**Year 1:** 1.14[c] **Subsequent:** 0.38 to 1.14[c]	**Year 1:** 415 (12 inj.)[c] **Subsequent:** 138 to 415[c] (4 to 12 inj.)
Bevacizumab (Mvasi)	25 mg/mL	4 mL vial 16 mL vial	385.9424[a] 1,543.7600[a]		**Year 1:** 0.85[c] **Subsequent:** 0.28 to 0.85[c]	**Year 1:** 309 (12 inj.)[c] **Subsequent:** 103 to 309[c] (4 to 12 inj.)
Bevacizumab (Zirabev)	25 mg/mL	4 mL vial 16 mL vial	385.9400[a] 1,543.7696[a]		**Year 1:** 0.85[c] **Subsequent:** 0.28 to 0.85[c]	**Year 1:** 309 (12 inj.)[c] **Subsequent:** 103 to 309[c] (4 to 12 inj.)
Ranibizumab (Lucentis)	10 mg/mL	0.165 mL vial 0.230 mL vial	1,575.0000	0.5 mg administered by intravitreal injection every 4 weeks for the first three doses, followed by 0.5 mg every 4 weeks	**Year 1:** 51.78 **Subsequent:** 17.26 to 51.78	**Year 1:** 18,900 (12 inj.) **Subsequent:** 6,300 to 18,900 (4 to 12 inj.)

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily average cost ($)	Annual average cost ($)
				thereafter; the treatment interval may be extended to 12 weeks (however, this will lead to a 5-letter loss of visual acuity benefit over the following 9 months)		

Inj. = injection; VEGF = vascular endothelial growth factor.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed December 2019), unless otherwise indicated, and do not include dispensing fees. Daily and annual costs reflect treatment for one eye only. Daily cost calculations based on 365 days per year.

[a] Wholesale price reported by IQVIA DeltaPA, December 2019.[39]

[b] The bevacizumab recommended dosage was assumed to reflect the ranibizumab product monograph, as aligned with the CADTH Therapeutic Review of Anti-VEGF Drugs for the Treatment of Retinal Conditions.[20,40]

[c] Costs calculated based on the assumption that 15 doses could be obtained per 100 mg (4 mL) vial.[20]

Appendix 2: Submission Quality

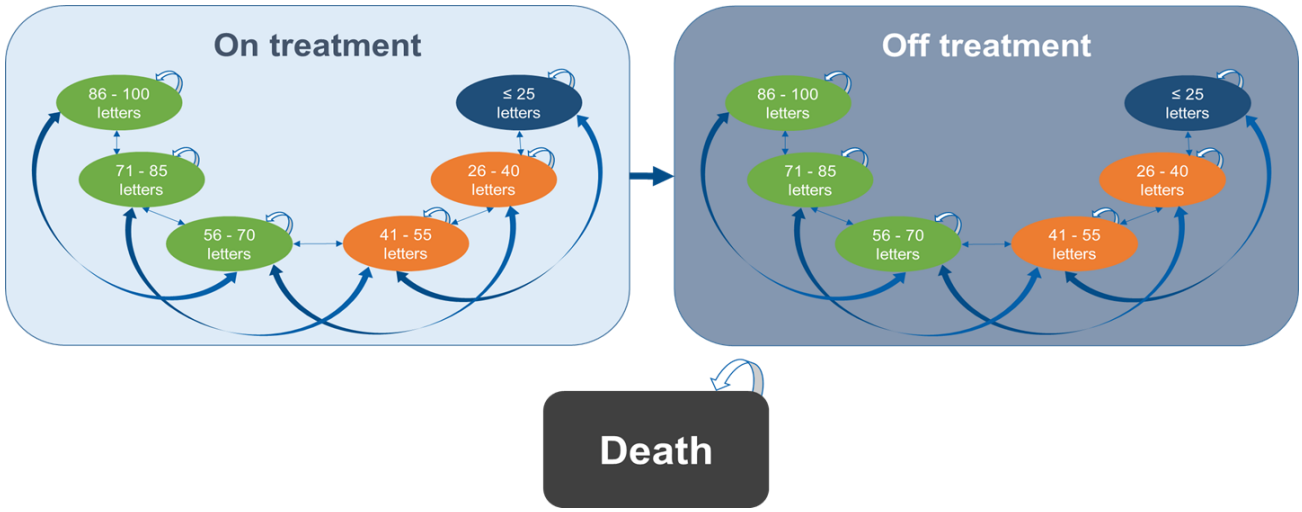
Table 11: Submission Quality

	Yes	No	Comments
Population is relevant, with no critical intervention missing and no relevant outcome missing.	☐	☒	Bevacizumab was excluded from the sponsor's base case. However, CADTH considered bevacizumab to be a relevant comparator, given its frequent use in clinical practice. See CADTH Appraisal of the Sponsor's Economic Evaluation.
The model has been adequately programmed and has sufficient face validity.	☒	☐	NA
The model structure is adequate for the decision problem.	☒	☐	NA
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis).	☐	☒	Parameters for utility decrements due to AEs were not incorporated probabilistically.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem.	☒	☐	NA
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in sufficient detail).	☒	☐	NA

AE = adverse event; NA = not applicable.

Appendix 3: Detailed Information on the Submitted Economic Evaluation

Figure 1: Model Structure



Source: Sponsor's pharmacoeconomic submission.[1]

Detailed Results of the Sponsor's Base Case

Table 12: Probability of Gaining or Losing at Least 15 Letters by Initial BCVA

BCVA health state	BCVA from Buckle et al.	Gaining ≥ 7.5 letters		Losing ≥ 7.5 letters	
		Probability	OR	Probability	OR
86 to 100 letters	> 70 letters	NR	1.00[a]	9.20%	0.95
71 to 85 letters	> 70 letters	NR	1.00[a]	9.20%	0.95
56 to 70 letters	55 to 70 letters	11.00%	1.00[b]	9.60%	1.00[b]
41 to 55 letters	40 to 54 letters	20.60%	2.10	12.10%	1.30
26 to 40 letters	23 to 39 letters	28.80%	3.27	6.70%	0.68
0 to 25 letters	23 to 39 letters	28.80%	3.27	6.70%	0.68

BCVA = best-corrected visual acuity; NR = not reported; OR = odds ratio.

[a] Assumed to be equal to referent BCVA health state.

[b] Referent BCVA health state.

Source: Adapted from sponsor's pharmacoeconomic submisstion.[1]

Table 13: Derived Best-Corrected Visual Acuity Quality of Life (EQ-5D)

BCVA health state	Best-seeing eye	Worst-seeing eye
86 to 100 letters	0.869	0.915
71 to 85 letters	0.772	0.819
56 to 70 letters	0.674	0.723
41 to 55 letters	0.577	0.627
26 to 40 letters	0.480	0.531
0 to 25 letters	0.347	0.400

BCVA = best-corrected visual acuity; EQ-5D = EuroQol 5-Dimensions.

Source: Sponsor's pharmacoeconomic submission.[1]

Table 14: Utility Decrements Due to Adverse Events

Adverse events	Utility decrement/multiplier		Duration		Source
	Estimate	SE	Years	Details	
Decrements					
Cataract	–0.142	0.0071	0.083	1 month	Brown et al. (2007)[41]
Endophthalmitis	–0.300	0.0150	0.300	20% year 1; 80% 1.5 months	Brown et al. (2007)[41]
GI event	–0.044	0.0022	0.083	1 month	Sullivan et al. (2011)[42]
Retinal detachment	–0.270	0.0135	0.250	3 months	Brown et al. (2007)[41]
Multipliers					
Stroke	0.628	0.0314	1.000	Ongoing	CG181 (Table 81)[43]
No effect					
Retinal tear	0.000	–	–	–	Assumption

GI = gastrointestinal; SE = standard error.

Source: Sponsor's pharmacoeconomic submission.[1]

Table 15: Mean Annualized Number of Injection Frequencies Based on Arm-Based Pooling

Dosing regimen	Injections	
	Year 1	Year 2+
Bro 3 mg LP > q.12.w./ q.8.w.	6.60	4.77
Bro 6 mg LP -> q.12.w./ q.8.w.	6.66	4.77
Afli 2 mg q.4.w.	11.90	4.44
Afli 2 LP -> q.8.w.	7.14	5.49
Rani 0.5 LP -> PRN	7.43	5.60
Rani 0.5 LP -> PRNX	5.50	5.50
Rani 0.5 LP -> q.8.w.	8.00	5.44
Rani 0.5 PRN	6.90	5.70
Rani 0.5 T&E	9.53	8.50
Rani 0.5 q.4.w.	11.80	11.19

Afli = aflibercept; Bro = brolucizumab; LP = loading phase; PRN = as needed; PRNX = as needed extended; q.4.w. = every 4 weeks; q.8.w. = every 8 weeks; q.12.w = every 12 weeks; T&E = treat-and-extend.

Source: Sponsor's pharmacoeconomic submission.[1]

Table 16: Costs of Adverse Events

Adverse event	Annual frequency (%)	Cost of adverse event ($)	Source
Cataract	0.16	5,160	OCCI H268; H269[44]
Endophthalmitis	0.47	330	Vitrectomy in 5% patients; tap and inject in 95% patients[15,44]
GI event	0.77	0	Clinical expert opinion
Retinal detachment	0.08	3,279	OCCI H332; H335[44]
Retinal tear	0.33	3,279	OCCI H330; H333[44]
Stroke (occurrence)	0.70	11,547	OCCI I64 (acute inpatient)[44]
Stroke (subsequent)	–	626	OCCI I64 (ambulatory care)[44]

GI = gastrointestinal; OCCI = Ontario Case Costing Initiative.

Note: Costs inflated to 2019.

Source: Adapted from sponsor's pharmacoeconomic submission.[1]

Appendix 4: CADTH Detailed Reanalyses and Sensitivity Analyses of the Economic Evaluation

Detailed Results of CADTH Base Case

Table 17: Stepped Analyses of CADTH's Economic Evaluation Results (Sequential)

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Sponsor's base case (bevacizumab included)	Bevacizumab[a]	57,539	6.61	Reference
	Brolucizumab	115,265	6.85	250,575
	Aflibercept	122,744	6.77	Dominated by brolucizumab
	Ranibizumab	194,480	6.17	Dominated by bevacizumab, brolucizumab, and aflibercept
CADTH reanalysis 1: include bevacizumab (PRN)	Bevacizumab[a]	50,807	6.46	Reference
	Brolucizumab	115,094	6.83	170,717
	Aflibercept	122,625	6.76	Dominated by brolucizumab
	Ranibizumab	194,545	6.16	Dominated by bevacizumab, brolucizumab, and aflibercept
CADTH reanalysis 2: equal treatment discontinuation	Bevacizumab[a]	51,346	6.51	Reference
	Brolucizumab	110,975	6.78	215,916
	Aflibercept	121,964	6.75	Dominated by brolucizumab
	Ranibizumab	189,282	6.14	Dominated by bevacizumab, brolucizumab, and aflibercept
CADTH reanalysis 3: revised vision loss costs	Bevacizumab[a]	23,232	6.46	Reference
	Brolucizumab	92,731	6.83	184,163
	Aflibercept	99,116	6.76	Dominated by brolucizumab
	Ranibizumab	162,006	6.16	Dominated by bevacizumab, brolucizumab, and aflibercept
CADTH reanalysis 4: long-term treatment extrapolation	Bevacizumab[a]	49,942	6.50	Reference
	Brolucizumab	117,423	6.70	330,818
	Aflibercept	124,059	6.68	Dominated by brolucizumab
	Ranibizumab	188,915	6.52	Dominated by brolucizumab and aflibercept
CADTH base case	Bevacizumab[a]	24,024	6.55	Reference
	Brolucizumab	88,047	6.66	583,404
	Aflibercept	98,318	6.66	2,862,068
	Ranibizumab	156,316	6.49	Dominated by bevacizumab, brolucizumab, and aflibercept

ICER = incremental cost-effectiveness ratio; PRN = as needed; QALY = quality-adjusted life-year.

[a] Reference product is least costly alternative.

Table 18: Disaggregated Summary of CADTH's Economic Evaluation Results

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)	Percentage of total incremental (sequential)
Discounted LYs					
Bevacizumab	Total	9.95	–	–	–
Brolucizumab		9.98	0.03	0.03	100
Aflibercept		9.98	0.03	0.00	100
Ranibizumab		9.94	–0.02	Dominated	Dominated
Discounted QALYs					
Bevacizumab	VA-related	6.57	–	–	–
	AE-related	–0.02	–	–	–
	Total	6.55	–	–	–
Brolucizumab	VA-related	6.68	0.11	0.11	100
	AE-related	–0.02	0.00	0.00	0
	Total	6.66	0.11	0.11	100
Aflibercept	VA-related	6.69	0.11	0.00	100
	AE-related	–0.02	0.00	0.00	0
	Total	6.66	0.11	0.00	100
Ranibizumab	VA-related	6.52	–0.06	Dominated	Dominated
	AE-related	–0.02	0.00	Dominated	Dominated
	Total	6.49	–0.06	Dominated	Dominated
Discounted costs ($)					
Bevacizumab	Acquisition	1,576	–	–	–
	Administration	9,005	–	–	–
	Monitoring	1,823	–	–	–
	AEs	834	–	–	–
	Visual impairment	10,782	–	–	–
	Cost of blindness	4	–	–	–
	Total	24,024	–	–	–
Brolucizumab	Acquisition	68,836	67,260	67,260	105
	Administration	7,182	–1,823	–1,823	–3
	Monitoring	1,005	–818	–818	–1
	AEs	826	–8	–8	< –1
	Visual impairment	10,193	–589	–589	< –1
	Cost of blindness	4	0	0	0
	Total	88,047	64,023	64,023	100
Aflibercept	Acquisition	78,062	76,245	9,225	90
	Administration	8,128	–2,946	946	9
	Monitoring	1,121	–357	116	1
	AEs	826	–9	0	0
	Visual impairment	10,177	–349	–16	< –1
	Cost of blindness	4	0	0	0

Treatment	Component	Value	Incremental (vs. reference)	Incremental (sequential)	Percentage of total incremental (sequential)
	Total	98,318	72,583	10,272	100
Ranibizumab	Acquisition	130,553	128,977	Dominated	Dominated
	Administration	12,191	3,186	Dominated	Dominated
	Monitoring	1,614	–208	Dominated	Dominated
	AEs	823	–11	Dominated	Dominated
	Visual impairment	11,130	348	Dominated	Dominated
	Cost of blindness	4	0	Dominated	Dominated
	Total	156,316	132,292	Dominated	Dominated
		ICER vs. bevacizumab ($/QALY)		**Sequential ICER ($/QALY)**	
Bevacizumab		Reference		Reference	
Brolucizumab		583,404		583,404	
Aflibercept		655,564		2,862,068	
Ranibizumab		Dominated by bevacizumab		Dominated by bevacizumab, brolucizumab, and aflibercept	

AE = adverse event; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; VA = visual acuity; vs. = versus; LY = life-year.

Scenario Analyses

Table 19: CADTH Scenario Analyses Results

Drug	Total costs ($)	Total QALYs	ICER vs. bevacizumab ($/QALY)	Sequential ICER ($/QALY)
Mortality adjustment excluded				
Bevacizumab[a]	26,028	6.82	Reference	Reference
Brolucizumab	91,259	6.91	676,188	676,188
Aflibercept	101,880	6.92	759,404	3,110,581
Ranibizumab	161,831	6.77	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Everyone starts in BCVA subgroup – 86 to 100 letters				
Bevacizumab[a]	19,855	7.57	Reference	Reference
Brolucizumab	85,026	7.62	1,378,075	1,378,075
Aflibercept	95,499	7.62	1,685,090	Dominated by brolucizumab
Ranibizumab	153,975	7.52	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Everyone starts in BCVA subgroup – 71 to 85 letters				
Bevacizumab[a]	20,912	7.23	Reference	Reference
Brolucizumab	85,805	7.31	749,138	749,138
Aflibercept	96,101	7.32	845,287	4,424,131
Ranibizumab	154,639	7.18	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Everyone starts in BCVA subgroup – 56 to 70 letters				
Bevacizumab[a]	23,289	6.64	Reference	Reference
Brolucizumab	87,488	6.76	532,581	532,581
Aflibercept	97,904	6.76	596,335	2,274,039

Drug	Total costs ($)	Total QALYs	ICER vs. bevacizumab ($/QALY)	Sequential ICER ($/QALY)
Ranibizumab	156,148	6.58	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Everyone starts in BCVA subgroup – 41 to 55 letters				
Bevacizumab[a]	26,291	6.06	Reference	Reference
Brolucizumab	89,793	6.18	502,929	502,929
Aflibercept	99,934	6.19	562,623	2,191,356
Ranibizumab	157,792	6.00	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Everyone starts in BCVA subgroup – 26 to 40 letters				
Bevacizumab[a]	30,521	5.50	Reference	Reference
Brolucizumab	93,110	5.61	586,178	586,178
Aflibercept	103,151	5.61	679,875	182,891,612
Ranibizumab	160,107	5.44	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Everyone starts in BCVA subgroup – 0 to 25 letters				
Bevacizumab[a]	35,111	4.85	Reference	Reference
Brolucizumab	96,178	4.93	775,399	775,399
Aflibercept	106,080	4.93	902,211	Dominated by brolucizumab
Ranibizumab	161,038	4.81	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Initial BCVA subgroup – reimbursement criteria				
Bevacizumab[a]	24,960	6.35	Reference	Reference
Brolucizumab	88,746	6.47	525,174	525,174
Aflibercept	99,139	6.48	587,997	2,211,807
Ranibizumab	156,942	6.30	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Injection utility decrement				
Bevacizumab[a]	24,100	6.51	Reference	Reference
Brolucizumab	88,195	6.63	539,946	539,946
Aflibercept	98,484	6.63	627,307	Dominated by brolucizumab
Ranibizumab	156,494	6.44	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Tx efficacy – no treatment effect year 3 and beyond				
Bevacizumab[a]	23,653	6.63	Reference	Reference
Brolucizumab	87,827	6.74	584,203	584,203
Aflibercept	98,206	6.75	658,077	3,016,645
Ranibizumab	156,419	6.58	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Tx efficacy – pooled Tx effect and AMD progression year 3 and beyond				
Bevacizumab[a]	26,830	6.08	Reference	Reference
Brolucizumab	89,929	6.18	624,468	624,468
Aflibercept	99,989	6.19	698,150	2,685,791
Ranibizumab	156,966	6.03	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Tx efficacy – individual Tx effect years 2 to 5 and pooled Tx effect year 6 and beyond				
Bevacizumab[a]	24,319	6.50	Reference	Reference

Drug	Total costs ($)	Total QALYs	ICER vs. bevacizumab ($/QALY)	Sequential ICER ($/QALY)
Brolucizumab	87,933	6.70	313,344	313,344
Aflibercept	98,298	6.68	400,766	Dominated by brolucizumab
Ranibizumab	156,948	6.26	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Bevacizumab Tx discontinuation				
Bevacizumab[a]	22,999	6.49	Reference	Reference
Brolucizumab	79,818	6.60	525,818	525,818
Aflibercept	88,726	6.60	586,535	2,225,834
Ranibizumab	140,057	6.44	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Bevacizumab q.4.w.				
Bevacizumab[a]	32,437	6.66	Reference	Reference
Brolucizumab	88,221	6.68	1,998,255	1,998,255
Aflibercept	98,437	6.69	2,140,795	3,506,660
Ranibizumab	156,459	6.52	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Bevacizumab q.6.w.				
Bevacizumab[a]	25,926	6.61	Reference	Reference
Brolucizumab	88,205	6.66	1,152,540	1,152,540
Aflibercept	98,498	6.67	1,263,752	3,036,861
Ranibizumab	156,415	6.50	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Brolucizumab 3 mg q.12.w./q.8.w				
Bevacizumab[a]	24,278	6.52	Reference	Reference
Brolucizumab	88,134	6.63	597,879	597,879
Aflibercept	98,503	6.63	652,891	1,506,720
Ranibizumab	156,616	6.46	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept
Brolucizumab 6 mg q.8.w. -> q.12.w.				
Bevacizumab[a]	25,057	6.38	Reference	Reference
Brolucizumab	89,301	6.41	2,076,411	Ext. dominated
Aflibercept	99,022	6.49	659,564	659,564
Ranibizumab	156,639	6.32	Dominated	Dominated by bevacizumab, brolucizumab, and aflibercept

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; Ext. = extendedly; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; q.4.w.; every 4 weeks; q.6.w. = every 6 weeks; Tx = treatment; vs. = versus.

[a] Reference product is least costly alternative.

References

1. Pharmacoeconomic evaluation. In: CDR submission: Beovu (Brolucizumab), 120 mg/mL solution for intravitreal injection [CONFIDENTIAL sponsor's submission]. Dorval (QC): Novartis Pharmaceuticals Canada Inc; 2019.
2. Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration. *Ophthalmology.* 2019.
3. BEOVU (Brolucizumab): 120 mg/mL solution for intravitreal injection [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc; 2019 May 27.
4. LUCENTIS (Ranibizumab): 10 mg/mL solution for injection [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2015 May 1: https://www.novartis.ca/sites/www.novartis.ca/files/lucentis_scrip_e.pdf.
5. EYLEA (Aflibercept): 40 mg/mL Solution for Intravitreal Injection [product monograph]. Mississauga (ON): Bayer Inc; 2019 Nov 4: https://www.bayer.ca/omr/online/eylea-pm-en.pdf.
6. Eleftheriadou M, Gemenetzi M, Lukic M, et al. Three-Year Outcomes of Aflibercept Treatment for Neovascular Age-Related Macular Degeneration: Evidence from a Clinical Setting. *Ophthalmology and therapy.* 2018;7(2):361-368.
7. National Institute for Health and Care Excellence. Age-related macular degeneration: NICE Guideline [NG82] - Appendix J: Health Economics. London (UK): NICE; 2018: https://www.nice.org.uk/guidance/ng82. Accessed 2019 Dec 11.
8. Buckle M, Donachie PH, Johnston RL. Long-term outcomes of intravitreal ranibizumab for neovascular age-related macular degeneration in a well defined region of the UK. *The British journal of ophthalmology.* 2016;100(2):240-245.
9. Zarranz-Ventura J, Liew G, Johnston RL, et al. The neovascular age-related macular degeneration database: report 2: incidence, management, and visual outcomes of second treated eyes. *Ophthalmology.* 2014;121(10):1966-1975.
10. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *The Cochrane database of systematic reviews.* 2014(8):Cd005139.
11. Christ SL, Lee DJ, Lam BL, Zheng DD, Arheart KL. Assessment of the effect of visual impairment on mortality through multiple health pathways: structural equation modeling. *Investigative ophthalmology & visual science.* 2008;49(8):3318-3323.
12. Hodgson R, Reason T, Trueman D, et al. Challenges Associated with Estimating Utility in Wet Age-Related Macular Degeneration: A Novel Regression Analysis to Capture the Bilateral Nature of the Disease. *Advances in therapy.* 2017;34(10):2360-2370.
13. Ontario Ministry of Health Long-Term Care. Ontario drug benefit formulary/comparative drug index. 2019; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2019 Dec 11.
14. Ontario Nurses Association. Collective Agreement - Hospital Central Agreement. 2018: https://www.ona.org/wp-content/uploads/ona_hospitalcentralagreement_march312020.pdf. Accessed 2019 Dec 11.
15. Ontario Ministry of Health Long-Term Care. Schedule of benefits for physician services under the Health Insurance Act: effective March 1, 2016. Toronto (ON): The Ministry of Health and Long-Term Care; 2015: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20181115.pdf. Accessed 2019 Dec 11.
16. Eldem BM, Muftuoglu G, Topbas S, et al. A randomized trial to compare the safety and efficacy of two ranibizumab dosing regimens in a Turkish cohort of patients with choroidal neovascularization secondary to AMD. *Acta ophthalmologica.* 2015;93(6):e458-464.
17. Cruess AF, Gordon KD, Bellan L, Mitchell S, Pezzullo ML. The cost of vision loss in Canada. 2. Results. *Canadian journal of ophthalmology Journal canadien d'ophtalmologie.* 2011;46(4):315-318.
18. CNIB Foundation. CNIB Card. 2019; https://cnib.ca/en/programs-and-services/live/cnib-card?region=on_east. Accessed 2019 Dec 12.
19. Guidelines for the Collaborative Management of Persons with Age-Related Macular Degeneration by Health- and Eye-Care Professionals. *Canadian journal of ophthalmology Journal canadien d'ophtalmologie.* 2015;77(1).
20. CADTH Therapeutic Review: Anti–Vascular Endothelial Growth Factor Drugs for the Treatment of Retinal Conditions - Recommendations Report Ottawa (ON): CADTH; 2016: https://www.cadth.ca/sites/default/files/pdf/TR0009_Anti-VEGFs_Recs_Report.pdf. Accessed 2019 Dec 06.
21. Government of Alberta. RAPID Program. 2015; https://www.alberta.ca/specialized-drug-benefits.aspx?utm_source=redirector. Accessed 2019 Dec 18.
22. Government of Newfoundland and Labrador. Provincial Government Lifts the Maximum Dose Caps for Lucentis and Eylea. 2019; https://www.releases.gov.nl.ca/releases/2019/health/1212n04.aspx. Accessed 2019 Dec 18.
23. Misericordia Health Centre. Eye Care Centre of Excellence - Macular Degeneration. 2019; https://misericordia.mb.ca/programs/acute-care/eye-care/macular-degeneration/. Accessed 2019 Dec 18.
24. Province of Nova Scotia. Province to Fund Lucentis Treatment. 2010; https://novascotia.ca/news/release/?id=20101020006. Accessed 2019 Dec 18.
25. Provincial Health Services Authority. Provincial Retinal Diseases Treatment Program. 2009; http://www.phsa.ca/our-services/programs-services/provincial-retinal-disease-treatment. Accessed 2019 Dec 18.

26. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Cochrane Database of Systematic Reviews.* 2019(3).

27. Novartis Beovu - Category 1 Accepted and Initiation Details [**CONFIDENTIAL** additional sponsor's information]. Ottawa (ON): CADTH; 2019 Nov 28.

28. Alberta Health. Interactive drug benefit list. 2019; https://idbl.ab.bluecross.ca/idbl/load.do. Accessed 2020 Jan 6.

29. Government of New Brunswick. New Brunswick Drug Plans Formulary. 2019: https://www2.gnb.ca/content/dam/gnb/Departments/h-s/pdf/en/NBDrugPlan/NewBrunswickDrugPlansFormulary.pdf. Accessed 2020 Jan 06.

30. Health PEI. PEI Pharmacare Formulary. 2019: https://www.princeedwardisland.ca/sites/default/files/publications/pei_pharmacare_formulary.pdf. Accessed 2020 Jan 06.

31. Newfoundland and Labrador Health and Community Services. The Newfoundland and Labrador Prescription Drug Program - Criteria for the coverage of special authorization drugs. 2015: https://www.health.gov.nl.ca/health/prescription/special_auth_drug_products.pdf. Accessed 2020 Jan 06.

32. Non-Insured Health Benefits First Nations and Inuit Health Branch. Drug Benefit List. 2019: https://www.sac-isc.gc.ca/DAM/DAM-ISC-SAC/DAM-HLTH/STAGING/texte-text/nihb_benefits-services_drugs_dbl-index_1573154657223_eng.pdf. Accessed 2020 Jan 06.

33. Saskatchewan Drug Plan and Extended Benefits Branch. Saskatchewan Online Formulary Database. 2019: http://formulary.drugplan.ehealthsask.ca/SearchFormulary/BG/573355. Accessed 2020 Jan 06.

34. Cruess A, Zlateva G, Xu X, Rochon S. Burden of illness of neovascular age-related macular degeneration in Canada. *Canadian Journal of Ophthalmology.* 2007;42(6):836-843.

35. Bank of Canada. Inflation calculator. 2019; https://www.bankofcanada.ca/rates/related/inflation-calculator/. Accessed 2020 Jan 14.

36. World Health Organization. Blindness and vision impairment prevention. 2019; https://www.who.int/blindness/causes/priority/en/index4.html. Accessed 2019 Jan 17.

37. Clinical Study Report: RTH258. 2.7.3 Summary of Clinical Efficacy in neovascular age-related macular degeneration (nAMD) [CONFIDENTIAL internal sponsor's report]. Dorval (QC): Sponsor; 2019.

38. clinicaltrials.gov. A Study to Compare SB11 (Proposed Ranibizumab Biosimilar) to Lucentis in Subjects With Neovascular Age-related Macular Degeneration (AMD). https://clinicaltrials.gov/ct2/show/study/NCT03150589. Accessed 2020 Jan 20.

39. DeltaPA. [Ottawa (ON)]: IQVIA; 2019: https://www.iqvia.com/. Accessed 2019 Dec 06.

40. Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration. *New England Journal of Medicine.* 2011;364(20):1897-1908.

41. Brown GC, Brown MM, Brown HC, Kindermann S, Sharma S. A value-based medicine comparison of interventions for subfoveal neovascular macular degeneration. *Ophthalmology.* 2007;114(6):1170-1178.

42. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Medical decision making : an international journal of the Society for Medical Decision Making.* 2011;31(6):800-804.

43. National Clinical Guideline C. National Institute for Health and Clinical Excellence: Guidance. *Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease*. London: National Institute for Health and Care Excellence (UK); 2014.

44. Ontario Case Costing Initiative (OCCI). Toronto (ON): Ontario Health and Long-Term Care; 2018: https://www.ontario.ca/data/ontario-case-costing-initiative-occi. Accessed 2019 Jul 24.