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CADTH Reimbursement Recommendation

Brolucizumab (Beovu)

Indication: For the treatment of diabetic macular edema

Sponsor: Novartis Pharmaceuticals Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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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.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Beovu?

CADTH recommends that Beovu be reimbursed by public drug plans for the treatment of diabetic macular edema (DME) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Beovu should be covered to treat patients with DME provided that Beovu is covered for a similar patient population and in a similar way to other anti–vascular endothelial growth factor (VEGF) drugs currently reimbursed by public drug plans for the treatment of adult patients with DME.

What Are the Conditions for Reimbursement?

Beovu should only be reimbursed if prescribed by an ophthalmologist with experience in managing DME and if its cost is not more than the least costly anti-VEGF drug covered by the public drug plans for the treatment of DME.

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that Beovu is no worse than Eylea in maintaining or improving clearness or sharpness of vision in patients with DME.
- Patients with DME identified a need for new treatments that require fewer injections. Although there was not enough evidence that injections are less frequent with Beovu, approximately half of the patients treated with Beovu received it every 12 weeks (versus Eylea at every 8 weeks) after 52 weeks of treatment in both trials.
- Based on CADTH's assessment of the health economic evidence, Beovu does not represent good value to the health care system at the public list price. There is not enough evidence to justify a greater cost for Beovu compared with other anti-VEGFs covered by the public drug plans for patients with DME.
- Based on public list prices, Beovu may decrease costs for the public drug plans; however, the actual budget impact is uncertain and will depend on the treatment frequency and which anti-VEGF drugs are displaced by Beovu.

Additional Information

What Is DME?

DME is an eye disease caused by blood vessels leaking fluid into a part of the eye called the macula, which is responsible for sharp central vision and seeing fine detail. Untreated DME is a leading cause of visual loss, visual disability, and legal blindness in people with diabetes. It is estimated that 60,000 adults with DME in Canada experience vision impairment that requires treatment.

Unmet Needs in DME

Patients with DME expressed a need for new treatments that are effective, less invasive, and require fewer administrations.

How Much Does Beovu Cost?

Treatment with Beovu is expected to cost between $9,730 and $11,120 per patient in the first year of use (based on 7 to 8 injections) depending on how many injections are required. In subsequent years, the annual cost per patient is expected to be between $5,560 and $9,730 (based on 4 to 7 injections per year).

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that brolucizumab be reimbursed for the treatment of DME only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two randomized, double-masked, active-controlled, phase III trials (KESTREL, N = 566; KITE, N = 360) demonstrated that brolucizumab 6 mg administered at a personalized treatment interval (every 8 or 12 weeks, depending on disease activity) was noninferior to aflibercept 2 mg every 8 weeks in the change in best corrected visual acuity (BCVA) from baseline to week 52 in patients with DME who are anti-VEGF naive. The between-group least squares (LS) mean difference for brolucizumab versus aflibercept in KESTREL was −1.3 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (95% confidence interval [CI], −2.9 to 0.3); the between-group LS mean difference in the KITE trial was 1.2 ETDRS letters (95% CI, −0.6 to 3.1). A noninferiority margin of 4 ETDRS letters was used in both studies. Results for retinal thickness and presence of intraretinal fluid (IRF) and/or subretinal fluid (SRF) were generally supportive of noninferiority of brolucizumab versus aflibercept.

Patient input indicated a need for treatments that can be given at longer intervals without recurrence of disease to reduce the burden on patients and caregivers associated with frequent treatment visits, and to improve treatment adherence. Approximately half of patients who received treatment with brolucizumab maintained a treatment interval of 12 weeks at week 52 in both studies. However, conclusions on the comparative efficacy of brolucizumab versus other anti-VEGFs for injection frequency could not be drawn.

At the sponsor-submitted price for brolucizumab and publicly listed price for all other drug costs, brolucizumab was more costly than bevacizumab but less costly than aflibercept and ranibizumab. As brolucizumab is considered similarly effective to other anti-VEGF drugs and it is uncertain whether brolucizumab will be associated with fewer annual injections, there is insufficient evidence to justify a higher cost for brolucizumab relative to other comparators. The cost of brolucizumab should therefore be negotiated so that it does not exceed the drug program cost for the least costly anti-VEGF drug reimbursed for the treatment of DME.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Eligibility for reimbursement of brolucizumab should be based on the criteria used by each of the public drug plans for reimbursement of other anti-VEGFs for the treatment of adult patients with DME.	The KESTREL and KITE studies demonstrated that brolucizumab 6 mg administered at q.8.w. or q.12.w. dosing was noninferior to aflibercept q.8.w. in the change in BCVA from baseline to week 52. There is no direct evidence that brolucizumab is clinically superior or inferior to any other anti-VEGF treatments	—

Reimbursement condition	Reason	Implementation guidance
	currently reimbursed for the treatment of adult patients with DME.	
Renewal		
2. Brolucizumab should be renewed in a similar manner to other anti-VEGFs currently reimbursed for the treatment of adult patients with DME.	There is no evidence that brolucizumab should be held to a different standard than other anti-VEGF treatments currently reimbursed when considering renewal.	—
Discontinuation		
3. Brolucizumab should be discontinued in a similar manner to other anti-VEGFs currently reimbursed for the treatment of adult patients with DME.	There is no evidence that brolucizumab should be held to a different standard than other anti-VEGF treatments currently reimbursed when considering discontinuation.	—
Prescribing		
4. The patient should be under the care of an ophthalmologist with experience in managing DME.	This will ensure that brolucizumab is prescribed for appropriate patients and administered by a trained ophthalmologist.	—
Pricing		
5. Brolucizumab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly anti-VEGF drug reimbursed for the treatment of DME.	Brolucizumab demonstrated noninferiority compared to aflibercept in terms of improving visual acuity in the clinical trials. Uncertainty in the indirect evidence precluded CDEC from drawing conclusions about the clinical benefit and frequency of injections of brolucizumab compared to other anti-VEGF drugs in patients with DME. As such, there is insufficient evidence to justify a cost premium for brolucizumab over the least expensive anti-VEGF reimbursed for DME.	—

BCVA = best corrected visual acuity; CDEC = CADTH Canadian Drug Expert Committee; DME = diabetic macular edema; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; VEGF = vascular endothelial growth factor.

Discussion Points

- CDEC discussed the limited direct evidence comparing brolucizumab to treatments currently available for DME (aside from aflibercept). CDEC discussed the results of 1 network meta-analysis (NMA) that was conducted to estimate the efficacy and safety of brolucizumab in patients with DME versus other anti-VEGFs for DME (ranibizumab, aflibercept, and bevacizumab). The limitations in the indirect evidence, including significant heterogeneity in patient characteristics and study design across the included randomized controlled trials (RCTs) and imprecision around the effect estimates, meant that firm

conclusions could not be drawn regarding brolucizumab's efficacy and safety compared to other anti-VEGFs.

- While the clinical evidence suggests there may be a benefit of brolucizumab in reducing treatment frequency while maintaining similar efficacy versus ranibizumab, aflibercept, and bevacizumab, there is insufficient evidence to confirm this benefit. Brolucizumab was compared with aflibercept at a fixed treatment interval in KESTREL and KITE, which does not reflect clinical practice as the treatment interval for aflibercept can be extended beyond 8 weeks. Injection frequency was compared between brolucizumab and other anti-VEGF therapies in naive pooled comparisons, which were associated with even greater uncertainty than the NMA.
- A biosimilar for ranibizumab was recently approved by Health Canada and a biosimilar for aflibercept is currently under review by Health Canada. CDEC discussed that, at the time of this review, the comparative efficacy and cost-effectiveness of brolucizumab relative to biosimilars of anti-VEGF drugs is unknown. CDEC considered that there is the potential that brolucizumab is not cost-effective when compared to other biosimilars of anti-VEGFs used to treat DME.

Background

DME is a vision-threatening complication of diabetes mellitus (both type 1 and type 2). Untreated DME is considered to be the leading cause of visual loss, visual disability, and legal blindness in people with diabetic retinopathy (DR). Patients' health-related quality of life (HRQoL) and their daily functioning will be significantly affected, and indirect costs due to lost productivity are high if patients are left untreated. It was estimated that there are approximately 60,000 adults with DME in Canada who experience vision impairment requiring treatment.

Current therapies for DME in Canada include nonpharmacological interventions (laser therapy and vitrectomy) and pharmacological interventions (intravitreal anti-VEGF drugs and intravitreal steroids). Health Canada–approved anti-VEGF drugs for DME treatment include ranibizumab and aflibercept (with bevacizumab used off-label), while approved intravitreal steroids include dexamethasone.

Brolucizumab is a humanized VEGF inhibitor that suppresses endothelial cell proliferation in vitro and reduces neovascularization and vascular permeability. It is indicated for the treatment of DME and the sponsor's reimbursement request is identical to the Health Canada indication.

The recommended dosage for brolucizumab for DME is 6 mg administered by intravitreal injection every 6 weeks for the first 5 doses. Thereafter, the physician may modify treatment intervals based on disease activity as assessed by visual acuity and/or anatomic parameters. In patients without disease activity, treatment up to every 12 weeks (3 months) could be considered. In patients with disease activity, treatment every 8 weeks (2 months) could be considered; however, the interval between 2 doses should not be less than every 8 weeks (2 months).

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 2 RCTs in adult patients with DME (the KESTREL and KITE studies)
- a review of 1 sponsor-submitted indirect treatment comparison (ITC)
- a review of safety data from 1 RCT in which brolucizumab was administered at a non–Health Canada–recommended dosage (the KINGFISHER trial)
- patients' perspectives gathered by 5 patient groups: Fighting Blindness Canada, The Canadian Council of the Blind (CCB), the CNIB Foundation, Vision Loss Rehabilitation Canada, and Diabetes Canada
- input from public drug plans that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with DME
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups that responded to CADTH's call for patient input and from a clinical expert consulted by CADTH for the purpose of this review.

Patient Input

Patient input was provided as a joint submission by 5 groups: Fighting Blindness Canada, the CCB, the CNIB Foundation, Vision Loss Rehabilitation Canada, and Diabetes Canada. The information used to inform the submission was based on an online survey of people in Canada living with DR or DME conducted in the first months of 2020 by the submitting organizations. A total of 67 people living in Canada responded to the survey, many (44.4%) were aged between 61 and 80 years (n = 54) and the majority (76.1%) of respondents reported DME and/or DR in both eyes. Most respondents were either working full-time (38.9%) or retired (33.3%) (n = 54). A separate survey conducted by CCB in April 2020 further supported the submission by providing data on the impact of the COVID-19 pandemic on Canadians who have blindness, deafblindness, or partial vision (n = 572).

Survey respondents had emphasized that DR and DME have substantial and life-altering impacts on daily life, including reading, driving, and using a phone. In addition to the concern for worsening of their eyesight, coping with everyday life and general safety when outside of home were identified as notable concerns in the past month by respondents. The results of the CCB survey showed that fear, anxiety, loneliness, and other psychosocial impacts were intensified for patients with age-related macular edema and DR during the pandemic.

The majority (56.4%) of respondents indicated that they were currently receiving injections for DR or DME; the most common therapeutic options were ranibizumab (29.4%), aflibercept (24.6%), bevacizumab (20.2%), and dexamethasone implant (13.5%). Most (54.5%) respondents indicated that they were satisfied with their injections and 63.6% indicated the injections have helped them avoid losing more of their eyesight (n = 22). Of note, 31.8% of respondents reported missing injections in the last year. According to respondents (n = 6),

reasons for cancelled or delayed appointments in the past included being too busy (50.0%), feeling unwell (33.3%), not being able to find someone to take them to the appointment (16.7%), and fear of injections (16.7%). According to respondents (n = 22), the most difficult part of eye injection appointments was the long wait times (50.0%), finding someone to take them to and from the appointment (31.8%), anxiety or fear about the injection (27.3%), and taking time off work (27.3%). No survey respondents reported experience with brolucizumab.

The submitting organizations indicated that any treatment that reduces the physical, psychological, and logistical strain on patients would be preferred. The submitting organizations suggested that this may be addressed by a treatment that is less invasive, or similarly invasive but administered less frequently. Furthermore, the submitting organizations suggested that any treatment that can extend the interval between injections would be considered advantageous for patients living with vision loss, particularly in the context of the COVID-19 pandemic, thereby minimizing vision loss.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

The clinical expert consulted by CADTH indicated that the treatment goals of DME are to delay and, in some cases, reverse disease progression of DME and/or DR, as well as to improve vision-related and general quality of life. Considering that most patients are currently required to attend treatment visits once every 1 to 3 months, the clinical expert noted that there is an unmet need for treatments that can be given at longer treatment intervals, without recurrence of disease, to reduce the burden on patients and caregivers associated with frequent treatment visits and to increase adherence with treatment regimens.

The clinical expert noted that brolucizumab is expected to have a similar place in therapy to other anti-VEGFs, as a first line or as a later line of treatment in patients with DME. Treatment with brolucizumab is anticipated to reduce the burden of care by increasing the intervals between treatments but still maintain therapeutic benefit, when compared to other anti-VEGFs, which could potentially address the unmet need related to frequent treatment visits.

The clinical expert identified that patients with vision loss–associated DR secondary to centre-involving DME are suitable candidates for brolucizumab. The clinical expert indicated that brolucizumab can be used in patients who are treatment naive or those who require a change in therapy due to inadequate response to other anti-VEGF drugs. Patients who may not be suitable for treatment include those who present with major structural damage to the macular retina (e.g., macular atrophy or fibrosis), according to the expert.

The clinical expert noted that clinical evaluation and optical coherence tomography should be performed for prognosis and follow-up at dosing visits. Key assessment outcomes include change in visual acuity and retinal thickness, and the presence of retinal fluid. According to the expert, optimal response to anti-VEGFs is generally achieved at least 6 to 12 months after initiation of therapy.

The clinical expert indicated that brolucizumab should be discontinued in patients with treatment futility with proof of irreversible anatomic or functional damage, such as macular atrophy (schema) and fibrosis.

Regarding prescribing conditions, the clinical expert recommended retina subspecialty care as the most appropriate treatment setting for prescription and administration of

brolucizumab in urban areas and trained comprehensive ophthalmologists with experience and expertise in managing DME as sufficient in rural settings.

Drug Program Input

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
There were 3 phase III, double-masked RCTs submitted: • **KITE and KESTREL:** evaluated efficacy and safety of brolucizumab in treatment-naive patients • **KINGFISHER:** evaluated efficacy and safety of once-monthly brolucizumab in both treatment-naive and previously treated patients Aflibercept was the comparator in these trials. Ranibizumab is also a relevant comparator. There were no trials comparing brolucizumab with ranibizumab for DME. Intravitreal bevacizumab could also be considered a relevant comparator.	This was a comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
The inclusion criteria for the pivotal trials (KESTREL and KITE) included: • type 1 and 2 diabetes mellitus and hemoglobin A1C ≤ 10% at screening • visual impairment due to DME with BCVA score between 23 to 78 letters • DME involving the centre of the macula with CSFT ≥ 320 µm on SD-OCT. However, this is not consistent with the drug plan coverage criteria for currently listed anti-VEGFs (for example, the reimbursement criteria for Eylea in Ontario require an hemoglobin A1C value of less than 12%, while in PEI, an hemoglobin A1C value of less than or equal to 11% plus the central retinal thickness greater than or equal to 250 µm are required for the initial coverage) and may raise issues if the recommendation is to "list in a similar manner." **Question 1**: Are the ophthalmologic measures in the inclusion criteria of the KESTREL and KITE trials generally used in Canadian clinical practice? **Question 2**: The hemoglobin A1C criterion has resulted in pushback from prescribers, who feel that it's inappropriate to require control of metabolic parameters before starting treatment (i.e., it would have no effect on treatment). In your opinion, is there a role for the hemoglobin A1C criterion in the initiation of treatment with anti-VEGFs? How often would the patients require treatment with anti-VEGFs for DME when they do not meet the hemoglobin A1C requirement?	**Question 1:** The clinical expert noted that the retinal eligibility criteria in the pivotal trials are consistent and realistic with respect to clinical practice. However, the expert did not support using the hemoglobin A1C criterion for reimbursement of treatment with brolucizumab. The reasons included the following: • In clinical practice, patients with poor glycemic control would still benefit from treatment with brolucizumab. In the clinical trials, the purpose of excluding these patients is to reduce the potential confounding effect from higher levels of hemoglobin A1C on the study drug effect. • Many patients who require management of their diabetes or other comorbid conditions are currently without a family physician. In this situation, the patients would be referred to their endocrinology unit and the treatment of DME would be delayed until hemoglobin A1C can be examined. • Testing of hemoglobin A1C is not always available for the patients, especially when the laboratories were overwhelmed with COVID-19 testing in recent years. **Question 2:** Patients with a hemoglobin A1C value consistently higher than 12% are less likely to benefit from anti-VEGF therapy in general. The expert indicated that they would not withhold treatment in these cases; however, the expert emphasized blood sugar control, hypertension control, and cholesterol lowering as important strategies for long-term preservation of vision in patients with diabetic retinopathy, especially DME.

Implementation issues	Response
	CDEC discussed the difficulty with generalizing the evidence beyond the studied patient population. However, as there is no evidence that brolucizumab should be held to a different standard than other anti-VEGF therapies for DME, CDEC considered it appropriate for reimbursement of brolucizumab to be based on existing drug plan criteria for the other anti-VEGF therapies.
Current CADTH reimbursement criteria (and drug plan coverage criteria) for aflibercept and ranibizumab include "for whom laser photocoagulation is also indicated." If the recommendation is to "list in a similar manner," would the criterion "for whom laser photocoagulation is also indicated" also apply to brolucizumab?	CDEC noted that the criterion "for whom laser photocoagulation is also indicated" would apply for a recommendation to reimburse based on existing criteria for anti-VEGFs for DME.
The reimbursement criteria for anti-VEGFs in at least 2 jurisdictions indicate that coverage of an alternative anti-VEGF will not be provided for the patients who have failed to respond to a previous anti-VEGF therapy. Should patients with DME who have not responded or adhered to a previous anti-VEGF be eligible for coverage if they switch to brolucizumab?	The expert disagreed with this condition and indicated that patients should be eligible for reimbursement of brolucizumab therapy even if they fail on other anti-VEGFs. CDEC noted that there are no data to provide guidance for the use of brolucizumab in patients with DME who have not responded or adhered to a previous anti-VEGF therapy. However, CDEC considered it appropriate to base reimbursement conditions for brolucizumab on existing drug plan criteria for other anti-VEGF therapies for DME.
The CADTH recommendation for aflibercept for DME (2015) was to list in a similar manner to ranibizumab for DME (2011). If the recommendation is to list in a similar manner, it's important to consider that the CADTH recommendations for aflibercept and ranibizumab for DME are older recommendations. For the most part, current drug plan coverage criteria for anti-VEGFs don't align with the CADTH recommendations. The criteria for initiation, renewal, discontinuation, and prescribing for anti-VEGFs tend to be consistent within a jurisdiction, but not between jurisdictions.	CDEC considered it appropriate for the reimbursement conditions for brolucizumab to be based on the existing drug plan criteria given the lack of alignment between past CADTH recommendations and existing criteria.
System and economic issues	
The sponsor noted that bevacizumab is not funded in all CADTH-participating jurisdictions. As such, their pharmacoeconomic analysis was only against treatments indicated for DME. The results suggest that at the submitted price ($1,390.00 per prefilled syringe), brolucizumab is a cost-saving option. Note that "cost-saving" will depend on the frequency of administration. Should bevacizumab also be considered in the pharmacoeconomic evaluation?	The clinical expert indicated that bevacizumab is used off-label in the treatment of DME and should be included in the pharmacoeconomic evaluation and budget impact analysis. CDEC noted that including bevacizumab in the sponsor's pharmacoeconomic evaluation is consistent with current CADTH Reimbursement Review procedures given its reimbursement in several jurisdictions. However, it was assumed to have no market share in the sponsor's budget impact analysis and this assumption is a notable source of uncertainty in the budget impact of brolucizumab.
Brolucizumab is not likely to remain cost-saving once biosimilars for the alternative anti-VEGFs become available. Note that biosimilar ranibizumab (brand name Byooviz) was	This was a comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
approved by Health Canada (March 2022) and a biosimilar of aflibercept is currently under Health Canada review.	

BCVA = best corrected visual acuity; CDEC = CADTH Canadian Drug Expert Committee; CSFT = central subfield thickness; DME = diabetic macular edema; PEI = Prince Edward Island; RCT = randomized controlled trial; SD-OCT = spectral domain optical coherence tomography; VEGF = vascular endothelial growth factor.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two studies, KESTREL (N = 566) and KITE (N = 360), met the inclusion criteria for the systematic review section. They were similarly designed phase III RCTs that evaluated the noninferiority (based on an a priori noninferiority margin of −4 ETDRS letters) of brolucizumab (6 mg every 8 weeks or every 12 weeks during maintenance with every 16 weeks as an option after week 72 in the KITE trial) to aflibercept (2 mg every 8 weeks during maintenance) through the change from baseline in BCVA using ETDRS letters at week 52 in the full analysis set population as a primary end point. The dose frequency for brolucizumab was determined by disease activity as assessed by visual acuity and/or anatomic parameters. Patient demographic and disease characteristics were generally well balanced across the arms in both trials at baseline. The mean age of enrolled patients at baseline in these studies ranged from 62.2 years to 64.4 years, and the majority of patients were male (greater than 58%) and white (greater than 73%). The mean time since the diagnosis of DME was 9.4 months to 12.5 months in the KESTREL study and 9.9 months to 10.4 months in the KITE study; mean baseline retinal thickness in these 2 studies ranged from 453 µm to 484 µm; and the mean baseline BCVA score ranged from 63.7 letters to 66.6 letters in both studies, although in the KITE trial, there was an imbalance in the number of ETDRS letters (66.0 [standard deviation (SD) = 10.8] in the brolucizumab group and 63.7 [SD = 11.7] in the aflibercept group). All enrolled patients were anti-VEGF-naive. Outcomes included changes in BCVA, anatomic outcomes, DR severity, vision-related function, injection frequency, and safety, with a primary analysis at week 52, and data up to 100 weeks.

Efficacy Results

The results of KESTREL and KITE trials support the noninferiority of brolucizumab 6 mg (5 every 6 weeks loading doses followed by maintenance injections every 8 weeks or every 12 weeks) versus aflibercept 2 mg (5 monthly loading doses followed by maintenance injections every 8 weeks) for the change in BCVA. Noninferiority of brolucizumab 6 mg to aflibercept 2 mg was demonstrated for the primary end point (change from baseline in BCVA at week 52 for the study eye) using a noninferiority margin of 4 letters ($P < 0.001$ for noninferiority). The between-group LS mean difference for brolucizumab 6 mg versus aflibercept 2 mg in the KESTREL trial was −1.3 letters (95% CI, −2.9 to 0.3); the between-group LS mean difference in the KITE trial was 1.2 letters (95% CI, −0.6 to 3.1). In addition, several sensitivity analyses by the sponsor, as well as a supportive analysis using the per-protocol population, were consistent with the findings of the primary analyses. Results were consistent for change from baseline to week 100. Results of prespecified subgroup analyses (i.e., baseline BCVA categories and central subfield thickness [CSFT] categories) were generally consistent with the overall population at week 52; however, the study was not powered to detect

subgroup differences. Noninferiority of brolucizumab 6 mg to aflibercept 2 mg was also demonstrated for the mean change from baseline in BCVA averaged over the period of week 40 through week 52.

The change in retinal thickness (measured with CSFT) from baseline and patients with CSFT lower than 280 µm were secondary outcomes in the studies. According to the expert, the reduction in retinal thickness correlates well to the improvement in visual acuity. In the KESTREL trial, the LS mean difference in the change from baseline in CSFT between the brolucizumab 6 mg arm and the aflibercept 2 mg arm was −5.1 µm (95% CI, −22.3 µm to 12.2 µm). Over the period of week 40 through week 52, the average LS mean of the change from baseline in CSFT between brolucizumab 6 mg and aflibercept 2 mg was −1.4 µm (95% CI, −17.9 µm to 15.0 µm). In the KITE trial, the LS mean difference in the change from baseline in CSFT to week 52 between the brolucizumab 6 mg arm and the aflibercept 2 mg arm was −32.8 µm (95% CI, −52.5 µm to −13.0 µm). Over the period of week 40 through week 52, the average LS mean of the change from baseline in CSFT between brolucizumab 6 mg and aflibercept 2 mg was −29.4 µm (95% CI, −48.6 µm to −10.2 µm; P = 0.001) in favour of brolucizumab. These differences between brolucizumab and aflibercept were similar at year 2.

The change from baseline in National Eye Institute Visual Functioning Questionnaire–25 (NEI-VFQ-25) composite score, which measures vision-related functions and some aspects of HRQoL, was a secondary outcome in the KESTREL and KITE trials, but not included in the statistical hierarchy. In the KESTREL study, the between-group LS mean differences for the change from baseline were −1.0 (95% CI, −3.4 to 1.4) at week 52 and −0.2 (95% CI, −2.9 to 2.6) at week 100. In the KITE study, the between-group LS mean differences for the change from baseline were 2.5 (95% CI, 0.2 to 4.8) at week 52 and 3.4 (95% CI, 0.8 to 6.1) at week 100.

ETDRS Diabetic Retinopathy Severity Scale score was used to measure disease activity in patients with DME. Regression of Diabetic Retinopathy Severity Scale score is another clinically meaningful outcome in this study population; however, this outcome was not included in the statistical hierarchy. For most of the results for this outcome at week 52 and week 100, there was no evidence to suggest a difference between brolucizumab and aflibercept. Given the uncertainty in the analysis due to lack of statistical testing and imprecision in the between-group differences, no definite conclusions on the change in disease severity can be drawn.

The pivotal trials measured the proportions of patients with presence of IRF and SRF as secondary outcomes. IRF and SRF are indicators of active disease noted with care by clinicians on the qualitative assessment of the optical coherence tomography. According to the clinical expert consulted by CADTH, IRF is a more relevant outcome than SRF in patients with DME as SRF is uncommon in DME and is a marker for more severe DME. This outcome was not tested statistically due to a previous failure of the hierarchical testing procedure. A numerically lower proportion of patients treated with brolucizumab had the presence of IRF and/or SRF compared to the aflibercept group in both studies at week 52 and week 100.

Frequency of injection was noted to be an important outcome of interest by both patients and the clinical expert as it may have implications on frequency of adverse events (AEs), HRQoL, burden of treatment, and patient adherence, and subsequently can have an impact on the treatment effect. The proportion of patients treated with brolucizumab maintained on an every 12 weeks schedule was reported descriptively in the studies. At

week 52, approximately half of this subgroup of patients maintained the every 12 weeks regimen [redacted] in the KESTREL and KITE trials, respectively. Among patients who completed treatment with brolucizumab at week 100, the majority of them were on an every 8 weeks regimen (67.1% in the KESTREL trial; 52.5% in the KITE trial).

Harms Results

The safety profile of brolucizumab 6 mg, was generally consistent with that of aflibercept 2 mg in the KESTREL and KITE trials. The proportion of patients reporting at least 1 ocular AE in the study eye up to week 100 was comparable across treatment arms in both studies (the KESTREL study = 48.7% and 50.3% in the brolucizumab 6 mg and aflibercept 2 mg group, respectively; the KITE study = 40.8% and 40.9% in the brolucizumab 6 mg and aflibercept 2 mg group, respectively). Overall, the most frequently reported ocular AEs related to brolucizumab in both studies were cataract, conjunctival hemorrhage, vitreous detachment, vitreous floaters, increased intraocular pressure, diabetic retinal edema, dry eye, eye pain, posterior capsule opacification, conjunctivitis, and reduced visual acuity. Cataract was reported as the most commonly reported ocular AE, which was anticipated because of the age of the study populations. Ocular serious AEs were reported with low frequency and similar between the 2 treatment groups in both studies (3.7% and 2.7% of patients in the KESTREL trial and 2.8% and 1.7% of patients in the KITE trial in the brolucizumab 6 mg group and aflibercept 2 mg group, respectively). The incidence of withdrawals due to AEs was also similar between the 2 treatment groups: (1.6% and 1.1% of patients in the KESTREL trial and 2.8% and 2.2% of patients in the KITE trial in the brolucizumab group compared with the aflibercept group, respectively). There were 15 deaths in the KESTREL study, 8 (4.2%) in the brolucizumab group and 7 (3.7%) in the aflibercept group. In the KITE study, 13 (7.3%) deaths occurred in the brolucizumab group and 9 (5.0%) in the aflibercept group. According to the sponsor, none of the deaths were related to the study treatment.

Critical Appraisal

KESTREL and KITE were similarly designed randomized, double-masked, active-controlled, noninferiority phase III trials comparing brolucizumab (6 mg in both studies, 3 mg in the KESTREL trial only) to aflibercept (2 mg). The overall designs of the KESTREL and KITE trials were appropriate for the objectives of the studies. There were no major concerns with regards to the method of randomization, stratification, allocation concealment, and masking for randomized assignment. The baseline characteristics of the study population were generally well balanced between treatment arms and across studies, with the exception that patients in the KITE study had a relatively large imbalance in the number of ETDRS letters between the 2 treatment arms, somewhat thicker retina at baseline, and were more likely to receive prior ocular medications compared to those enrolled in the KESTREL study. However, the clinical expert thought that these differences were unlikely to impact the results between the studies.

In the KESTREL and KITE trials, the results of change from baseline in BCVA at week 52 using the per-protocol population were consistent with those in the full analysis set. In both studies, sensitivity analyses were conducted to assess the robustness of the hypothesis testing that resulted from the primary analysis. Various methods were used to account for missing data, such as the mixed models for repeated measures modelling assuming a missing at random mechanism, or the last observation carried forward approach. The missing at random assumption may be a concern, given that the primary reasons for discontinuation from the study included patient decision, death, and AEs. Furthermore, the last observation carried forward method assumes that patient outcomes do not change after they drop out, which may not hold true in practice. Therefore, additional sensitivity analyses that did not assume

that missing data were missing at random could be useful. However, the results of the sensitivity analyses confirmed those of the primary analysis, suggesting these approaches in handling missing data were unlikely to introduce bias in the primary end point. Risk of attrition bias due to missing data was of particular concern for the NEI-VFQ-25 as there was more than 20% missing data for some treatment groups.

A statistical hierarchy was used for multiplicity adjustment for selected outcomes. Some important outcomes were not included in the hierarchy, such as vision-related HRQoL assessed by NEI-VFQ-25, change in retinal thickness, or change in DR severity. In addition, the statistical hierarchy failed relatively early on at some points. In the KESTREL trial, noninferiority of brolucizumab 3 mg to aflibercept 2 mg was not achieved at week 52. As per the study protocol, confirmatory testing did not proceed to assess the superiority of brolucizumab versus aflibercept for the outcomes that followed in the hierarchical testing procedure, which limits drawing definite conclusions on these outcomes.

Based on the patient's baseline characteristics, the study population in the KESTREL and KITE trials may not fully represent the typical population of patients with DME in Canada who would be receiving anti-VEGF therapy. The clinical expert consulted by CADTH indicated that the inclusion criteria of the KESTREL and KITE trials were reasonable and reflective of the eligibility criteria for anti-VEGF treatment in clinical practice. Although all patients enrolled in the KESTREL and KITE trials were anti-VEGF naive, and exhaustive exclusion criteria were used in the 2 studies, the clinical expert indicated that brolucizumab can be used in a broader population, such as for those with poor glycemic control or those who have received a previous anti-VEGF therapy.

In the 2 pivotal studies, patients in the brolucizumab group could have their dosing interval extended, reduced, or maintained postrandomization based on the assessments of disease activity. Once patients on brolucizumab dropped back to every 8 weeks because of disease activity, they could not extend the treatment interval for the rest of the study, which may contradict clinical practice. Changes in treatment interval and dosage were not allowed for treatment with aflibercept, and these patients remained on a fixed every 8 weeks interval during the maintenance phase; this is contrary to clinical practice as the product monograph of aflibercept states that the treatment interval can be extended after the first year of treatment. According to the clinical expert, patients in the real world may not receive as many loading doses as in the clinical trial and it is possible that the outcomes observed in practice could differ from those shown in the clinical trials.

Indirect Comparisons

Description of Studies

The sponsor-submitted ITC provided indirect evidence on the efficacy and safety of brolucizumab relative to other anti-VEGFs for adult patients with DME. The active comparators for brolucizumab included aflibercept, ranibizumab, and bevacizumab. Relevant RCTs were identified through a systematic literature search, and 43 RCTs were included in the NMA. Outcomes of change in BCVA, retinal thickness, change in disease activity, study discontinuation, and safety were evaluated in the study population. A Bayesian NMA approach was taken for data synthesis.

Efficacy Results

The sponsor-submitted NMA provided indirect comparative evidence for brolucizumab versus other anti-VEGF drugs. After including 43 trials in an NMA, none of the treatments was favoured when brolucizumab was compared with other active treatments, such as aflibercept, ranibizumab or bevacizumab for the treatment of DME, in improving visual acuity and lessening disease severity. For most comparisons, the effect estimate was too imprecise (i.e., wide 95% credible interval [CrI]) to draw a conclusion about the comparative effects. Treatment with brolucizumab was associated with more reduction in retinal thickness than bevacizumab or ranibizumab. In addition, the ITC results suggested that patients treated with brolucizumab may receive fewer injections compared to those treated with other anti-VEGFs, though these results were derived from a naive comparison rather than an NMA and should be particularly interpreted with caution. The key limitations for the ITC are significant heterogeneity across the included RCTs (in study design and patient characteristics) and imprecision around the effect estimates (i.e., wide 95% CrIs), which precluded drawing a conclusion for most outcome comparisons. This limits the conclusions that can be drawn from this ITC.

Harms Results

The risks of ocular AEs, nonocular AEs, and study discontinuation were evaluated in the NMA. The results suggested that none of the treatments was favoured for reduction in the risk of ocular or nonocular-ocular AEs. For all comparisons, the effect estimate was too imprecise (i.e., wide 95% CrIs) to draw a conclusion about the comparative effects. Limitations to the NMA preclude making firm conclusions about relative risks of harm for brolucizumab compared to other anti-VEGFs.

Critical Appraisal

In the sponsor-provided ITC, the degree of heterogeneity between the included studies was difficult to assess because of incomplete reporting of study characteristics (such as patients' disease characteristics at baseline). Description of trial design, sample size, and disease duration were reported; however, the ITC failed to report information related to the methods used for handling missing data. There was considerable variability in study design, year of conduct, sample size, and treatment regimen. The risk of bias in the included trials was assessed using a checklist from the National Institute for Health and Care Excellence (NICE), but further details on how risk of bias assessment was carried out were not provided.

Similarly, inadequate information about baseline patient characteristics as well as variability in baseline patient characteristics contribute to heterogeneity in the studies included in the ITC. Clinical trial eligibility criteria were described for the trials ultimately included in the NMA; however, many individual studies failed to report or inadequately reported patient characteristics, resulting in gaps in the extracted ITC data. There was a lack of information about key baseline characteristic such as the presence of significant diabetic macular ischemia, previous treatment and patient's response, IRF, and systemic comorbidities, including hypertension, chronic kidney disease, obesity, or cardiac conditions.

Most of the patients' baseline characteristics were presented graphically. Even though some of the patients' baseline characteristics were comparable, for example age (ranged from 58 to 66 years) and hemoglobin A1C level (ranged from 7.3 to 8.7), heterogeneity still exists. The mean time since diagnosis of DME ranged from 1.2 to 3.4 years. The duration of diabetes ranged from 10 to 18 years in the included studies. Based on data from 26 trials, the mean BCVA scores ranged from 33 to 71 letters. Based on data from 25 trials, the mean retinal

thickness at baseline ranged from 321 µm to 596 µm, and the majority of studies included patients with a retinal thickness of more than 400 µm. There was also heterogeneity in the reporting of methods for measuring and in results of changes in retinal thickness. Based on heterogeneity in the factors that were reported and the inability to assess those that were not reported, there is considerable uncertainty whether the assumptions related to homogeneity were met. The treatment effect of the study drug could differ by patient characteristics at baseline. Despite acknowledging the degree of heterogeneity, the technical report did not provide sufficient information of assessments of heterogeneity (e.g., graphic representation of baseline characteristics, statistical tests) to fully understand the sources of heterogeneity. Therefore, the potential for heterogeneity to have influenced the comparative efficacy and safety estimates is plausible, and it is not possible to quantify or identify the direction of the bias. Several assumptions were made when defining treatment node assignment; for example, the different dose does not impact the outcomes, and similar efficacy was assumed between the ranibizumab 0.3 mg and 0.5 mg doses, or there were no significant differences in the effect of different regimens (aflibercept every 4 weeks, every 8 weeks, or as needed). It is uncertain if these assumptions are valid.

For injection frequency, brolucizumab every 8 weeks and every 12 weeks were examined in the ITC. Data were pooled without conducting an NMA. Although drug administration with fixed treatment intervals according to the protocol are commonly observed in clinical trials, the clinical expert consulted by CADTH indicated that in the real world, treatment regimens could be more flexible based on a patient's response. Therefore, the findings from clinical trials may not reflect the clinical practice.

Other Relevant Evidence

This section includes a summary of 1 additional relevant study, KINGFISHER, which was included in the sponsor's submission to CADTH and was considered to provide further information on the safety of brolucizumab in patients with DME. The study compared the efficacy and safety of brolucizumab versus aflibercept in patients with DME, but the treatment intervals beyond the loading phase used for both drugs were shorter than the recommended intervals in the drugs' respective Health Canada–approved monographs.

The frequency of dosing for brolucizumab was selected based on previous studies that have suggested that for some patients with DME, frequent dosing (i.e., every 4 weeks) with an anti-VEGF therapy may be required to improve and maintain functional and anatomic outcomes. The clinical expert consulted by CADTH did not consider the efficacy results with the treatment intervals used in the KINGFISHER trial to be relevant or generalizable to clinical practice; therefore, they are not included in this summary. However, given the frequency of administration, the clinical expert suggested that the safety data may provide information on whether intraocular inflammation and retinal vasculitis are idiosyncratic AEs related to brolucizumab itself rather than the frequency of intravitreal injections.

Description of Study

One multicentre, randomized, double-masked, active-controlled, parallel group, prospective, phase III study (KINGFISHER) was conducted to evaluate the efficacy and safety of brolucizumab versus aflibercept in the treatment of adult patients with visual impairment due to DME. The primary objective was to demonstrate that brolucizumab was noninferior to aflibercept with respect to change in visual acuity from baseline up to week 52.

A total of 346 and 171 patients were randomized to brolucizumab 6 mg administered every 4 weeks and aflibercept 2 mg administered every 4 weeks, respectively. The 48-week double-masked treatment period was followed by a 4-week follow-up period of up to week 52. Patients were evaluated every 4 weeks for the duration of the study. Only 1 eye was selected as the study eye and treated with the study drug. Study discontinuation rates were 10.1% and 8.8% in the brolucizumab and aflibercept arms, respectively. A total of 189 patients (54.6%) in the brolucizumab arm and 94 patients (55.0%) in the aflibercept arm received all 13 injections following the every 4 weeks regimen.

The inclusion and exclusion criteria used in the KINGFISHER study were generally consistent with the eligibility criteria used in the pivotal KESTREL and KITE studies. The KINGFISHER trial included adult patients with diabetes mellitus type 1 or type 2 who were diagnosed with visual impairment due to DME. Of note, patients could either be treatment naive or have previously received an anti-VEGF therapy but could not have received any injections within the 3-month period before baseline.

The mean age of patients was 60.9 years (SD = 10.59) in the brolucizumab arm and 60.2 years (SD = 9.31) in the aflibercept arm. There was a higher proportion of males than females in both arms (56.1% in the brolucizumab arm and 61.4% in the aflibercept arm). The mean duration of diagnosis with DME was 20.6 months (SD = 29.94) and 18.2 months (SD = 25.60) in the brolucizumab and aflibercept arms, respectively. The mean BCVA letters score was 61.3 (SD = 10.14) and 60.5 (SD = 11.27) in the brolucizumab and aflibercept arms, respectively. The mean CSFT was 514.1 µm (SD = 138.94 µm) and 511.2 µm (SD = 156.29 µm) in the brolucizumab and aflibercept arms, respectively. Most patients in both treatment arms had mild to moderately severe nonproliferative DR (75.6% [n = 167] and 76.3% [n = 90] in the brolucizumab and aflibercept arms, respectively). Prior anti-VEGF treatment in the study eye was reported in 95 patients (27.5%) and 52 patients (30.4%) in the brolucizumab and aflibercept arms, respectively.

Harms Results

A total of 105 patients (30.3%) in the brolucizumab arm and 59 patients (34.5%) in the aflibercept arm reported at least 1 ocular AE. The most common ocular AE reported in the brolucizumab arm was vitreous detachment in 10 patients (2.9%). A total of 3 patients (0.9%) in the brolucizumab arm reported at least 1 serious ocular AE; vitreous hemorrhage in 2 patients (0.6%), and cataract subcapsular and retinal vasculitis in 1 patient (0.3%) each. No patients in the aflibercept arm reported any serious ocular AE. A total of 7 patients (2.0%) and 3 patients (1.8%) withdrew from study treatment in the brolucizumab and aflibercept arms, respectively, due to an ocular AE, with the most common ocular event documented as related to an eye disorder (6 patients [1.7%] and 3 patients [1.8%], respectively).

Intraocular inflammation was reported in 14 patients (4.0%) in the brolucizumab arm versus 5 patients (2.9%) in the aflibercept arm. Retinal vasculitis was reported in 3 patients (0.9%) in the brolucizumab arm versus 1 patient (0.6%) in the aflibercept arm. Retinal vascular occlusion was reported in 1 patient in each arm (0.3% versus 0.6% in brolucizumab and aflibercept arms, respectively). Arterial thromboembolic events were reported in 15 patients (4.3%) in the brolucizumab arm versus 9 patients (5.3%) in the aflibercept arm. Increased transient intraocular pressure was reported in 3 patients (0.3%) in the brolucizumab arm versus 2 patients (1.2%) in the aflibercept arm. No reports of endophthalmitis were recorded.

Critical Appraisal

The trial was at low risk of bias due to randomization; the 2 arms were generally balanced with respect to baseline demographic and disease characteristics. The trial was double masked; however, there was some potential for unmasking because the personnel providing the injections were aware of the assigned treatment. The likelihood of unmasking and potential for bias in the reporting of subjective outcomes (i.e., some harms) is uncertain. The trial was powered for the safety assessment according to FDA recommendations. Attrition was relatively low and balanced across the arms, suggesting a low risk of attrition bias.

The clinical expert consulted by CADTH for this review advised that the results of the KINGFISHER trial would not be generalizable to the patient population in Canada and to Canadian clinical practice because the frequency of administration (i.e., every 4 weeks) is not a relevant treatment interval. Furthermore, aflibercept is rarely administered every 4 weeks in clinical practice.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients with DME
Treatment	Brolucizumab
Dose regimen	6 mg administered by intravitreal injection every 6 weeks for 5 doses, followed by 6 mg at an interval of up to 12 weeks in patients without disease activity, with every 8 weeks considered in patients with disease activity
Submitted price	Brolucizumab 6 mg per 0.05 mL, single-use prefilled syringe: $1,390.00
Treatment cost	Brolucizumab has an annual cost in year 1 ranging from $9,730 to $11,120 (7 to 8 injections) and in subsequent years ranging from $5,560 to $9,730 (4 to 7 injections)
Comparators	Aflibercept Bevacizumab Ranibizumab
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (37 years)
Key data source	• The target population (baseline characteristics) was based on pooled data from the phase III trials of brolucizumab: KITE and KESTREL. • Comparative clinical efficacy data were derived from a sponsor-submitted NMA to inform change in BCVA, treatment discontinuation, and adverse event rates.

Component	Description
	• A combination of data from clinical trials and a retrospective cohort study were used to inform the frequency of administration.
Key limitations	• The comparative clinical efficacy and safety of brolucizumab is uncertain as a result of heterogeneity in the sponsor's NMA. • The survival benefit predicted for brolucizumab is highly uncertain. • The relative frequency of administration of brolucizumab and comparators is uncertain. • Drug acquisition costs for bevacizumab may be overestimated. • Health state utility values are uncertain and likely overestimated. • The sponsor's model did not adhere to best practices, including assuming that the injection frequency of each anti-VEGF drug is fixed and that the anti-VEGF unit prices are variable.
CADTH reanalysis results	• In the CADTH reanalysis, CADTH assumed that each vial of bevacizumab would be used for 30 administrations, that the injection frequency of each anti-VEGF drug is variable, and that drug unit costs are fixed. CADTH was unable to correct for limitations such as the lack of robust comparative data, uncertain survival benefit, uncertain administration frequency, and uncertain health state utility values. • The results of the CADTH reanalysis were consistent with those submitted by the sponsor. The sequential ICER for brolucizumab compared with bevacizumab, which was based on the results of the sponsor's NMA and estimated injection frequency, was $61,621 per QALY gained (incremental costs = $31,899; incremental QALYs = 0.52). Under these assumptions, a 20% price reduction would be required for brolucizumab to be cost-effective compared to bevacizumab at a willingness-to-pay threshold of $50,000 per QALY. Given that these results are predicated on improved efficacy and reduced injection frequency with brolucizumab relative to comparators, these findings are highly uncertain, and a higher price reduction may be required. In scenario analyses that assumed equal efficacy, discontinuations, and injection frequency across treatments, brolucizumab was more costly (incremental costs = $37,413) than bevacizumab. • The absence of robust data means there is no evidence to justify a price premium for brolucizumab over other anti-VEGF drugs for the treatment of DME. To ensure cost-effectiveness, the per administration price of brolucizumab should be no more than the lowest-cost, funded comparator used to treat DME.

BCVA = best corrected visual acuity; DME = diabetic macular edema; ICER = incremental cost-effectiveness ratio; LY = life-year; NMA = network meta-analysis; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the claims-based forecasting was conducted inappropriately for some jurisdictions and was inflexible; no displacement of bevacizumab was assumed, which may not be appropriate; faricimab was not considered as a comparator; the market uptake of brolucizumab is uncertain and may be affected by reimbursement of faricimab; and the administration frequency for brolucizumab and anti-VEGF comparators is uncertain. CADTH reanalysis adjusted the forecasting of aflibercept or ranibizumab claims in some jurisdictions rather than assuming stagnant growth. In the CADTH base case, the estimated cost savings associated with the reimbursement of brolucizumab were $874,107 in year 1, $4,119,735 in year 2, and $8,847,605 in year 3, for a 3-year total cost savings of $13,841,448.

CADTH conducted scenario analyses assuming equal injection frequencies for brolucizumab and comparators, and that 50% of brolucizumab uptake would be among patients switching from maintenance therapy with another anti-VEGF drug. The results of these analyses suggest that the budgetary impact of reimbursing brolucizumab is sensitive to injection

frequency and uptake. CADTH was unable to account for the possibility of faricimab becoming publicly reimbursed during the budget impact analysis horizon.

The cost savings predicted by the sponsor's analysis and CADTH's base case assume that brolucizumab will not displace less expensive treatment options (e.g., bevacizumab and biosimilar anti-VEGF drugs); CADTH was unable to address this in reanalyses. CADTH was also unable to account for confidential prices for comparators, which may reduce the potential cost savings for brolucizumab. As a result, whether there is cost savings and the extent of any savings realized by the drug plans depends on what is displaced.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed

Meeting date: November 23, 2022

Regrets: Two expert committee members did not attend.

Conflicts of interest: None