Canadian Journal of Health Technologies

CADTH

October 2022 Volume 2 Issue 10

CADTH Reimbursement Recommendation

Faricimab (Vabysmo)

Indication: For the treatment of diabetic macular edema

Sponsor: Hoffmann-La Roche Canada

Final recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

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 Vabysmo?

CADTH recommends that Vabysmo 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?

Vabysmo should be covered to treat patients with DME provided that it 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?

Vabysmo should only be reimbursed if prescribed by an ophthalmologist with experience managing DME and if the cost of Vabysmo 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 Vabysmo 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 Vabysmo can be given at an interval of up to every 16 weeks, approximately 62% of patients received Vabysmo every 16 weeks at week 96 in the trials.
- Based on CADTH's assessment of the health economic evidence, Vabysmo does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Vabysmo compared with other anti-VEGF drugs covered by the public drug plans for patients with DME.
- Based on public list prices, Vabysmo 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 Vabysmo.

Additional Information

What Is DME?

DME is an eye disease that can occur in people living with diabetes. It is 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 requiring treatment.

Unmet Needs in DME

Patients with DME expressed a need for new treatments that are effective, safe, and require fewer injections.

How Much Does Vabysmo Cost?

Treatment with Vabysmo is expected to cost between $8,100 and $18,900 per patient in the first year of use depending on how many injections are required (between 6 and 14). In subsequent years, the annual cost per patient is expected to be between $4,050 and $17,550 (based on 3 to 13 injections per year).

Recommendation

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

Rationale for the Recommendation

Two randomized, double-blind, active-controlled, phase III trials (YOSEMITE, N = 940, and RHINE, N = 951) demonstrated that faricimab administered at every 8 weeks or personalized treatment interval (PTI) dosing was noninferior to aflibercept every 8 weeks in the change in best corrected visual acuity (BCVA) from baseline averaged over weeks 48, 52, and 56 of treatment in adult patients with DME. In the YOSEMITE trial, the mean difference between the faricimab and aflibercept arms was −0.2 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (97.5% confidence interval [CI], −2.0 to 1.6) and 0.7 ETDRS letters (97.5% CI, −1.1 to 2.5) for the faricimab every 8 weeks and faricimab PTI arms, respectively. In the RHINE trial, the mean difference of change was 1.5 ETDRS letters (97.5% CI, −0.1 to 3.2) and 0.5 ETDRS letters (97.5% CI, −1.1 to 2.1) for faricimab every 8 weeks and faricimab PTI arms, respectively, compared to aflibercept. While most patients reported satisfaction with current intravitreal treatments for DME, they expressed a need for new treatments for DME that are effective, safe, and will result in fewer injections. The majority (78.1%) of patients randomized to the faricimab PTI arm received faricimab at an extended interval of every 12 weeks or every 16 weeks at week 96 in the YOSEMITE and RHINE trials.

Using the sponsor-submitted price for faricimab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for faricimab was $164,743 per quality-adjusted life-year compared with bevacizumab; all other comparators were associated with fewer quality-adjusted life-years and greater costs relative to faricimab. This analysis assumes that faricimab is associated with lower administration frequency and similar clinical efficacy relative to all comparators. Given that there is uncertainty regarding the frequency of injections and the comparative effectiveness data, there is insufficient evidence to justify a higher cost for faricimab relative to other comparators. Faricimab 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 faricimab should be based on the criteria used by each of the public drug plans for reimbursement of other anti-VEGF drugs for the treatment of adult patients with DME.	There is no direct evidence that faricimab is clinically superior or inferior to other anti-VEGF treatments currently reimbursed for the treatment of adult patients with DME. The YOSEMITE and RHINE studies demonstrated that faricimab administered at q.8.w. or PTI dosing was noninferior to aflibercept q.8.w. in the change in BCVA	The clinical expert noted to CDEC that 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). The clinician group noted in their input that those without centre-involved DME should not be treated with faricimab.

Reimbursement condition	Reason	Implementation guidance
	from baseline averaged over weeks 48, 52, and 56.	
Renewal		
2. Faricimab should be renewed in a similar manner to other anti-VEGF therapies currently reimbursed for the treatment of adult patients with DME.	There is no evidence that faricimab should be held to a different standard than other anti-VEGF treatments currently reimbursed when considering renewal.	—
Discontinuation		
3. Faricimab should be discontinued in a similar manner to other anti-VEGF drugs currently reimbursed for the treatment of adult patients with DME.	There is no evidence that faricimab 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 managing DME.	To ensure that faricimab is prescribed for appropriate patients and administered by a trained ophthalmologist.	—
Pricing		
5. Faricimab 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.	Faricimab demonstrated noninferiority compared to aflibercept in the clinical trials. Uncertainty in the indirect evidence precluded CDEC from drawing conclusions about the clinical benefit and frequency of injections of faricimab compared to other anti-VEGF drugs in patients with DME. As such, there is insufficient evidence to justify a cost premium for faricimab over the least expensive anti-VEGF reimbursed for DME.	—

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

Discussion Points

- CDEC discussed that although faricimab was noninferior to aflibercept in the YOSEMITE and RHINE trials, there is limited direct evidence comparing faricimab to other treatments currently available for DME. CDEC discussed the results of 1 network meta-analysis (NMA) that was conducted to estimate the efficacy and frequency of faricimab injection in patients with DME against other anti-VEGF drugs. The limitations in the indirect evidence have led to inconclusive results regarding faricimab's efficacy and frequency of injection when compared to other anti-VEGF drugs.
- CDEC noted that frequency of injection is considered to be an important outcome of interest by both patient and clinician groups as it has implications on the frequency of

adverse events (AEs), health-related quality of life (HRQoL), and burden of treatment. CDEC discussed that based on the direct and indirect evidence available, the actual magnitude and clinical significance of any reduction in the frequency of injection compared to existing therapies in clinical practice is uncertain. In addition, in the YOSEMITE and RHINE trials, aflibercept was given at a fixed dosing interval in the maintenance phase, which does not align with the "treat-and-extend" protocol commonly used in clinical practice, thus limiting the generalizability of the results.

- A biosimilar for ranibizumab was recently approved by Health Canada. CDEC discussed that, at the time of this review, the comparative efficacy and cost-effectiveness of faricimab relative to biosimilars of anti-VEGF drugs is unknown. CDEC considered that there is potential for faricimab not to be cost-effective versus a biosimilar of an anti-VEGF used to treat DME.

Background

DME is a vision-threatening complication of diabetic retinopathy that occurs when damaged capillaries in the eye leak fluid into the centre of the retina (the macula), causing it to thicken. Generally, DME manifests as a slowly progressive vision loss in people with either type 1 or type 2 diabetes mellitus. Untreated DME is a leading cause of visual loss, visual disability, and legal blindness in people with diabetes. An estimated 60,000 adults with DME in Canada experience vision impairment requiring treatment.

In Canada, the current first-line standard of care for patients with DME with central macular thickening is anti-VEGF drugs, which include ranibizumab, aflibercept, and bevacizumab (off-label). These drugs can delay and, in some cases, reverse disease progression of DME, as well as improve vision-related and general HRQoL. Anti-VEGF drugs are administered as intravitreal injections on an ongoing basis and, after completion of loading doses, the interval between injections ranges from every 1 to 3 months. As adjunctive therapies, patients may receive focal laser therapy or vitrectomy (for eyes with vitreomacular traction). For patients who have had cataract extraction with lens implants (i.e., pseudophakic), intravitreal steroids may be used as a second-line adjunctive treatment.

Faricimab has been approved by Health Canada for the treatment with DME in adults (18 years or older). Faricimab is a humanized bispecific immunoglobulin G1 directed against human vascular endothelial growth factor-A (VEGF-A) and Angiopoietin-2 (Ang-2). It is available as a single-use vial for intravitreal injection and the Health Canada–approved dose is 6 mg (0.05 mL) administered by intravitreal injection for 6 loading doses every 4 weeks, followed by injections every 8 weeks; or 6 mg (0.05 mL) administered intravitreally every 4 weeks for at least the first 4 doses, followed by dosing via a treat-and-extend approach, with dosing intervals of up to every 16 weeks based on patient outcomes.

Sources of Information Used by the Committee

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

- a systematic review that included 2 phase III randomized controlled trials (RCTs) in patients with DME
- patients' perspectives gathered through a joint patient input from the following patient groups: Fighting Blindness Canada, the Canadian Council of the Blind, 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
- input from 1 clinician group, the Canadian Retina Society
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

CADTH received 1 joint patient input from the following patient groups: Fighting Blindness Canada, the Canadian Council of the Blind, the CNIB Foundation, Vision Loss Rehabilitation Canada, and Diabetes Canada. Canadians with DME indicated that the condition had a "substantial and life-altering" impact on their lives, as the condition causes vision loss that can affect daily activities such as reading, using a phone, and driving. Patients also mentioned experiencing emotional, psychological, and social impacts from the condition; for example, having worries about the condition worsening in the future and requiring help with everyday tasks and to get to appointments. Furthermore, patients must still cope with the common symptoms of diabetes, including extreme fatigue, weight changes, and frequent urination, and their associated management. Patients indicated a need for a treatment that reduces the physical (e.g., pain from injection), psychological (e.g., anxiety or fear about the injection), and logistical burden (e.g., frequency of appointments) of current treatments. Patients expressed interest in a treatment that is less invasive or similarly invasive but administered less frequently, thus requiring less travel for appointments and less dependency on caregivers. Patients living outside of Canada's urban centres and those from equity-deserving populations may experience greater burdens (e.g., increased challenges attending appointments).

Clinician Input

Input From the Clinical Experts 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 diabetic retinopathy, as well as to improve vision-related and general HRQoL. Considering 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 regimes.

The clinical expert noted that faricimab is expected to have a similar place in therapy as other anti-VEGF therapies, as a first-line or as a later line of treatment in patients with DME. The clinical expert indicated that if faricimab is reimbursed, a shift in the treatment paradigm will be likely given that faricimab is the first anti-VEGF treatment approved for an extended

interval of up to 16 weeks, which could potentially address the unmet need related to frequent treatment visits. The clinical expert noted the dual mechanism of faricimab, which targets both the VEGF-A and Ang-2 pathways, as being relevant for diabetic retinopathy.

The clinical expert identified that patients with diabetic retinopathy associated with vision loss secondary to centre-involving DME are suitable candidates for faricimab. The clinical expert indicated that faricimab 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 (OCT) should be performed for prognosis and follow-up at dosing visits. Key assessment outcomes include change in visual acuity, retinal thickness, and the presence of retinal fluid. According to the expert, optimal response to anti-VEGF therapies is generally achieved at least 6 to 12 months after initiation of therapy.

The clinical expert indicated that faricimab 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 faricimab in urban areas and trained comprehensive ophthalmologists with experience and expertise managing DME as sufficient in rural settings.

Clinician Group Input

CADTH received input from 1 clinician group, the Canadian Retina Society.

The clinician group input was consistent with the clinical expert CADTH consulted with respect to the unmet need for a more durable treatment with fewer injections to reduce treatment burden while maintaining maximal vision gain. The clinical group also noted minimizing side effects as an important consideration; for example, injection-related complications such as inflammation, infection, bleeding, retinal detachment, cataract, and glaucoma.

Clinician group input was consistent with the clinical expert input regarding potential place in therapy and suitable patient population for faricimab. The group also noted that patients without centre-involved DME should not be treated with faricimab and those without vision loss secondary to DME (i.e., patients who are “pre-symptomatic”) should be monitored as long as very close follow-up can be maintained.

Clinician group input generally aligned with the clinical expert input on assessing response to treatment and discontinuation of treatment. The clinician group highlighted improvement in vision, reduction or resolution of macular edema, regression in diabetic retinopathy severity scale (DRSS), and reduction in frequency of treatment (4 months or longer interval between treatments) as clinically meaningful outcomes.

The clinician group’s suggested setting for treatment administration was more broadly identified as ophthalmology offices in the community setting and/or hospital setting.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified by the drug programs as key factors that could potentially impact the implementation of a CADTH recommendation for faricimab:

- relevant comparators
- considerations for initiation of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- system and economic issues.

The clinical experts consulted by CADTH provided advice on these potential implementation issues (refer to Table 2).

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The active comparator in the pivotal trials of faricimab (YOSEMITE and RHINE) was aflibercept, which is appropriate; however, would it have been helpful to have a different active comparator or more than 1 active comparator?	The clinical expert noted to CDEC that although it would be ideal to have direct comparative evidence for ranibizumab and bevacizumab, as well, including only aflibercept was a reasonable choice for the trial design and it was likely the most appropriate comparator among the anti-VEGF drugs available at the time of study conduct.
Intravitreal bevacizumab could be considered a comparator in this population; however, its use is off-label. It was considered in the ITC, which looked at ranibizumab, aflibercept, brolucizumab, and bevacizumab. The NMA demonstrated [redacted] than these current options available in Canada. Was the ITC sufficient or adequate?	CDEC noted that there may be important sources of bias related to different study or patient characteristics that may impact conclusions that can be drawn about this ITC. These limitations may pose a considerable challenge to take a conclusive decision regarding the validity of the results to inform clinical practice.
Considerations for initiation of therapy	
The Health Canada indication is for treatment of DME. The inclusion criteria in the pivotal trials of faricimab (YOSEMITE and RHINE) considered participants with HbA1c ≤ 10%, a BCVA of 73 to 25 letters inclusive (Snellen equivalent of 20/40 to 20/320), and a CST ≥ 325 mm (Spectralis SD-OCT) or ≥ 315 mm (on Cirrus SD-OCT or Topcon SD-OCT). If CDEC recommended to reimburse faricimab, should the initiation criteria specify these characteristics? As current public drug plan criteria for ranibizumab and aflibercept commonly outline such characteristics, it would be helpful to drug plans if this type of information is specified in the criteria.	The clinical expert noted to CDEC that it would be reasonable to align the criteria for therapy initiation with the inclusion criteria of the pivotal trials but would not recommend using HbA1c as a criterion to restrict access to potential treatment. CDEC recommended that the initiation, renewal, and discontinuation criteria for faricimab be similar to other anti-VEGF therapies currently reimbursed for the treatment of adult patients with DME.
How likely is it that patients will require treatment in 2 eyes vs. in 1 eye?	The clinical expert noted to CDEC that it is quite common for patients to require treatment in both eyes, about 40% to 50% of patients with DME seen in the expert's practice receive bilateral

Implementation issues	Response
	therapy. In some cases, one of the eyes will respond better to treatment than the other and after a period of bilateral treatment continued treatment may only be needed unilaterally, in the eye that is responding poorly.
The 2 pivotal trials of faricimab (YOSEMITE and RHINE) included participants who were either treatment-naive or had previously been treated with an anti-VEGF therapy. Would consideration be given to a criteria requirement of failure or intolerance to an anti-VEGF drug before initiation of faricimab? How likely is it that patients would be prescribed faricimab as first-line treatment for DME?	The clinical expert noted to CDEC that faricimab would not be reserved for treatment failures or intolerance to an anti-VEGF drug before initiation, but would, if it proves to be safe as well as efficacious, offer it to treatment-naive patients, especially those with < 6/15 visual acuity. The clinical expert thought it would be very likely that patients would be prescribed faricimab as a first-line treatment for DME.
The CADTH recommendations for treatment of DME with Lucentis and Eylea were finalized in 2012 and 2015, respectively. For the most part, drug plan coverage criteria for both anti-VEGF drugs do not align with the CADTH recommendations. In the case of a positive recommendation outlining specific criteria (such as HbA1c, BCVA, CST), it would be helpful if the recommendation references the tools used in Canadian clinical practice. Some drug plans may have issues aligning criteria with currently listed anti-VEGF drugs. The CADTH recommendation for Eylea was to list in a similar manner as Lucentis. Some of the criteria (e.g., HbA1c) faced pushback from prescribers. The prescribers commented that it was inappropriate to control metabolic parameters before starting therapy and that it would have no effect on treatment. The drug plans are wondering if CDEC could take into consideration the clinical expert's opinion on some of these issues (note that the criteria for Lucentis may be quite old now).	CDEC noted that clinicians in different jurisdiction may use different types of anti-VEGF drugs, so tailoring recommendations based on current clinical practice in Canada may miss an opportunity for changes in the future.
Considerations for discontinuation of therapy	
Are there are any points at which treatment would be discontinued?	The clinical expert noted to CDEC that treatment would be discontinued in cases of extensive retinal atrophy (ischemia) and/or retinal fibrosis in the macula that makes treatment improvement of vision impossible, or traction retinal detachment.
Considerations for prescribing of therapy	
Dosing of faricimab for DME is 6 mg administered by intravitreal injection every 4 weeks for the first 4 doses, then the dosing interval may be extended up to every 16 weeks, in increments of 4 weeks, depending on physician's judgment (PTI). What is the expected percentage of patients receiving treatment with faricimab who would be on a PTI of every 16 weeks? Every 12 weeks? Every 8 weeks?	The clinical expert anticipated the percentage of patients receiving faricimab at various intervals in practice to align with the results of the pivotal trials. Percentages from YOSEMITE and RHINE: • q.4.w.: 11% to 13% (year 1); 7% to 10% (year 2) • q.8.w.: 15% to 16% (year 1); 12% to 14% (year 2) • q.12.w.: 20% to 21.0% (year 1); 14% to 18% (year 2) • q.16.w.: 51% to 53% (year 1); 60% to 65% (year 2)

Implementation issues	Response
Presuming progression of the disease over time, would it be likely that a patient be switched from faricimab to a different anti-VEGF therapy should the PTI increase to q.8.w. or q.4.w.? Or would it be more likely that faricimab be continued?	The clinical expert noted to CDEC that a switch might be made if a patient was on a q.4.w. interval; but, if a patient was on a q.8.w. interval, the patient would most likely continue on treatment with faricimab.
System and economic issues	
For Eylea and Lucentis: Some jurisdictions provide these treatments through centralized service (provincial eye centres) What is the appropriate setting to receive faricimab?	The clinical expert noted to CDEC that retina subspecialist offices or hospital clinics, where available, are the most appropriate setting for faricimab treatment. In rural settings, trained comprehensive ophthalmologists with experience and expertise managing DME may suffice.

BCVA = best corrected visual acuity; CDEC = Canadian Drug Expert Committee; CST = central subfield thickness; DME = diabetic macular edema; HbA1c = hemoglobin A1C; ITC = indirect treatment comparison; NMA = network meta-analysis; PTI = personalized treatment interval; q.4.w. = every 4 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; q.16.w. = every 16 weeks; SD-OCT = Spectral Domain Optical Coherence Tomography; VEGF = vascular endothelial growth factor.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

The YOSEMITE and RHINE studies met the inclusion criteria for the systematic review. They were identically designed, phase III, multicenter, randomized, double-blind, active-controlled, noninferiority trials that evaluated the use of faricimab in comparison with aflibercept in patients with DME (YOSEMITE, n = 940, and RHINE, n = 951) over 100 weeks. Patients were randomized on a 1:1:1 ratio into 1 of 3 arms: fixed-dose faricimab every 8 weeks; faricimab dosing on a PTI faricimab, or fixed-dose aflibercept every 8 weeks. Patients in the faricimab every 8 weeks arm were given faricimab 6 mg intravitreally every 4 weeks for 6 loading doses followed by maintenance doses every 8 weeks. Patients in the faricimab PTI arm were given faricimab 6 mg intravitreally every 4 weeks for 4 loading doses, after which maintenance doses could be every 4 weeks, every 8 weeks, every 12 weeks, or every 16 weeks depending on patient outcomes as determined by a predefined algorithm. Patients in the aflibercept arm received aflibercept 2 mg intravitreally every 4 weeks for 5 loading doses then at a fixed maintenance interval of every 8 weeks.

Both studies aimed to establish the noninferiority of faricimab to aflibercept through the primary outcome, which was the change from baseline in BCVA (measured using the ETDRS chart) averaged over weeks 48, 52, and 56 in the intention-to-treat (ITT) population. The noninferiority margin was specified as 4 letters on ETDRS chart. The proportion of patients with a 2-step or higher diabetic retinopathy severity improvement from baseline on the ETDRS DRSS at week 52 was a key secondary end point. The noninferiority margin for this outcome was specified as a difference of 10% between treatment arms. Other secondary outcomes included frequency of administration for faricimab PTI, retinal thickness, presence of retinal fluids, and measures of HRQoL and vision-related function, all of which were analyzed without control for multiplicity. The primary analysis was conducted at week 56 and secondary analysis data were available up to week 100.

The baseline demographic and ocular characteristics of patients were overall balanced between the treatment arms within each study. The baseline characteristics were generally similar across the studies, except for median months since DME diagnosis, which was shorter for patients in the YOSEMITE trial than in the RHINE trial (3.1 months versus 6.6 months, respectively), and mean baseline central subfield thickness (CST), which was slightly higher for patients in the YOSEMITE trial than in the RHINE trial (487.5 µm versus 471.6 µm, respectively). In both studies, the median age of patients at baseline was between 62 to 64 years, and the majority were male (> 57%), and White (> 76%). At the start of the studies, most patients (around 70% to 75%) had a diabetic retinopathy severity level of 35 to 47 (from mild to moderately severe non-proliferative diabetic retinopathy [PDR]), with mean baseline BCVA scores of around 62 letters. Approximately 20% to 23% of patients had been previously treated with an anti-VEGF therapy.

Efficacy Results

Change in Visual Acuity

The primary outcome of both studies was the change from baseline in BCVA (ETDRS letters) averaged over weeks 48, 52, and 56 in the ITT population. In the YOSEMITE trial, the mean difference of change between the faricimab treatment arms and aflibercept was −0.2 letters (97.5% CI, −2.0 to 1.6) and 0.7 letters (97.5% CI, −1.1 to 2.5) for the faricimab every 8 weeks and faricimab PTI arms, respectively. In the RHINE trial, the mean difference of change was 1.5 letters (97.5% CI, −0.1 to 3.2) and 0.5 letters (97.5% CI, −1.1 to 2.1) for the faricimab every 8 weeks and faricimab PTI arms respectively, compared to aflibercept. The CI for all these estimates did not cross the preestablished noninferiority margin of 4 letters. All the confidence intervals in these comparisons crossed the line of no effect and therefore neither faricimab arm was superior to aflibercept for change in BCVA. Results of the sensitivity analyses, the supplemental analyses, and the per-protocol population were congruent with the primary analysis.

The proportion of patients gaining greater than or equal to 15 ETDRS letters in BCVA from baseline averaged over weeks 48, 52, and 56 (a secondary outcome) was comparable across treatment arms and studies: 29.2%, 35.5%, and 31.9% in the faricimab every 8 weeks, faricimab PTI, and aflibercept every 8 weeks arms, respectively, in the YOSEMITE trial, and 33.6%, 28.3%, and 30.5%, respectively, in the RHINE trial. Most patients (> 95% across treatment arms) avoided a loss of 15 or more ETDRS letters in BCVA from baseline throughout the studies. Comparable results were also seen across all 3 treatment arms for patients gaining at least 10, 5, or 0 letters, or avoiding a loss of at least 10 or 5 letters in BCVA from baseline in both studies, which were assessed as other secondary outcomes in the trials.

Results at year 2 were mostly congruent with year 1 for the previously mentioned BCVA outcomes, except for the faricimab PTI arm in the RHINE study, in which a numerically lower adjusted proportion of patients gained greater than or equal to 15 ETDRS letters in BCVA from baseline averaged over weeks 92, 96, and 100 compared with the aflibercept every 8 weeks arm.

Change in CST

In both the YOSEMITE and RHINE trials, patients in the faricimab arms (every 8 weeks and PTI) had numerically greater reductions in CST from baseline to weeks 48, 52, and 56, compared to the aflibercept every 8 weeks arm (a secondary outcome), with a difference in mean adjusted change of −36.2 µm (95% CI, −47.8 to −24.7) and −26.2 µm (95% CI, −37.7 to

−14.7) in YOSEMITE, and −25.7 µm (95% CI, −37.4 to −14.0) and −17.6 µm (95% CI, −29.2 to −6.0) for the faricimab every 8 weeks and faricimab PTI arms, respectively.

A numerically higher proportion of patients treated with faricimab every 8 weeks or PTI had an absence of DME (CST < 325 µm for Spectralis SD-OCT) averaged over weeks 48, 52, and 56 compared with patients treated with aflibercept every 8 weeks, with a difference in the adjusted proportion of 16.0% (95% CI, 8.9% to 23.1%); 12.7% (95% CI, 5.4% to 20.0%) in YOSEMITE and 12.3% (95% CI, 5.7% to 18.9%); 8.2% (95% CI, 1.5% to 14.9%) in RHINE between the faricimab every 8 weeks and PTI dosing arms, respectively, when compared with the aflibercept every 8 weeks arm.

The differences between faricimab treatment arms and the aflibercept arm for both of the previously mentioned CST-related outcomes were less pronounced at year 2 of the studies.

Frequency of Faricimab Injections

The studies measured the proportion of patients in the faricimab PTI arm on an every 4 weeks, every 8 weeks, every 12 weeks, and every 16 weeks injection interval as a secondary outcome. At week 52, the proportion of patients who received faricimab every 4 weeks, every 8 weeks, every 12 weeks, and every 16 weeks in the YOSEMITE trial was 10.8%, 15.4%, 21.0%, and 52.8%, respectively, while in the RHINE trial, the proportions were 13.3%, 15.6%, 20.1%, and 51.0%, respectively. At week 96, the proportion of patients in the faricimab PTI arm on an every 4 weeks, every 8 weeks, every 12 weeks, and every 16 weeks treatment interval, a secondary outcome, was 7.0%, 14.8%, 18.1%, and 60.0% respectively, in the YOSEMITE trial, while in the RHINE trial, the proportions were 10.1%, 11.8%, 13.6%, and 64.5%, respectively.

HRQoL and Vision-Related Function

Patients treated with faricimab every 8 weeks or PTI had comparable mean changes from baseline in the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) composite score at week 24, week 52, and week 100 compared with patients treated with aflibercept every 8 weeks in both studies (a secondary outcome). At week 52, the difference in the adjusted mean change from baseline in NEI VFQ-25 composite score was −0.2 points (95% CI, −2.1 to 1.7) and 0.5 points (95% CI, −1.5 to 2.4) in the YOSEMITE trial, and −0.8 points (95% CI, −2.7 to 1.1) and −1.0 points (95% CI, −2.9 to 0.8) between the faricimab every 8 weeks and PTI dosing arms when compared to the aflibercept every 8 weeks arm, respectively. Around half of patients (46.0% to 52.5%) in all treatment arms had a 4-point or more improvement from baseline in NEI VFQ-25 composite score (an exploratory outcome) in both studies at week 24.

A comparable proportion of patients, around two-thirds of patients (68.8% to 77.2% across all treatment arms) in both studies, had a BCVA Snellen equivalent of 20/40 or better averaged over weeks 48, 52, and 56 (a secondary outcome and a common visual acuity standard used for obtaining a driver's licence in the US), with consistent results at year 2 of the studies.

The number of patients progressing to legal blindness (a secondary outcome, defined as BCVA Snellen equivalent of 20/200 or worse) was small across all treatment arms in both studies during the entire study period (1.5% to 2.1% per arm).

Absence of Retinal Fluids

Over the course of both studies, a numerically higher proportion of patients treated in the faricimab every 8 weeks arm had an absence of intraretinal fluid at week 52 (a secondary

outcome) compared to the aflibercept every 8 weeks arm, with a difference in the adjusted proportion of 16.6% (95% CI, 8.7% to 24.5%) in the YOSEMITE trial; and 10.7% (95% CI, 2.8% to 18.6%) in the RHINE trial. The difference in adjusted proportions of patients with an absence of intraretinal fluid between the faricimab PTI and aflibercept every 8 weeks treatment arms at week 52 were less pronounced: 13.4% (95% CI, 5.4% to 21.3%) in the YOSEMITE trial; and 7.2% (95% CI, −0.5% to 14.9%) in the RHINE trial. After week 48, the vast majority of patients (> 94% across treatment arms) in both studies had an absence of subretinal fluid (a secondary outcome).

Improvement From Baseline on the ETDRS DRSS

There were conflicting results between the YOSEMITE and RHINE trials for the proportion of patients with a 2-step or greater change on the ETDRS DRSS from baseline at week 52, the key secondary end point in the studies. In the YOSEMITE trial, noninferiority for this end point was met, with differences in the adjusted proportion between the faricimab (every 8 weeks and PTI) arms compared to aflibercept every 8 weeks of 10.2% (97.5% CI, 0.3% to 20.0%) and 6.1% (97.5% CI, −3.6% to 15.8%), respectively. However, in the RHINE study, noninferiority was not met for this outcome as the lower bound of the 97.5% CI for the difference in the adjusted proportion between the faricimab and aflibercept arms was less than −10% for both the faricimab every 8 weeks and faricimab PTI arms at week 52: −2.6% (97.5% CI, −12.6% to 7.4%) and −3.5% (97.5% CI, −13.4% to 6.3%), respectively. At week 96, there was a generally comparable proportion of patients in the faricimab (every 8 weeks and PTI) and aflibercept arms of both studies who achieved at least 2-step improvement on the ETDRS DRSS from baseline in both studies.

A comparable proportion of patients in the faricimab (every 8 weeks and PTI) arms versus the aflibercept arm achieved a 3 or greater step improvement on the ETDRS DRSS from baseline at week 52, a secondary outcome (14.8% to 19.5% across treatment arms in both studies). Few patients developed new PDR in the study eye over time (a secondary outcome) (< 3% in any treatment arm up to week 96 in both studies). Similarly, few patients in any treatment arm in their study had at least 2-step or 3-step worsening at week 52, received vitrectomy, or received panretinal photocoagulation (< 1.5% per arm for each individual outcome; all were exploratory outcomes).

Harms Results

Over 100 weeks in the safety evaluable population, the proportion of patients reporting at least 1 ocular AE in the study eye was comparable across treatment arms in the YOSEMITE trial (47.0% in the faricimab every 8 weeks arm, 46.6% in the faricimab PTI arm, and 46.3% in the aflibercept every 8 weeks arm). In the RHINE study, a higher proportion in the faricimab every 8 weeks and faricimab PTI arms reported an ocular AE compared with the aflibercept every 8 weeks arm (52.4% in the faricimab every 8 weeks arm, 51.7% in the faricimab PTI arm, and 44.6% in the aflibercept every 8 weeks arm). The AEs likely contributing to the higher incidence of ocular AEs in both the faricimab arms compared with aflibercept in the RHINE study include cataract, dry eye, and blepharitis, while occurrence of conjunctival hemorrhage, intraocular pressure increased, vitreous floaters, cataract subcapsular, posterior capsule opacification, eye pruritis, and conjunctivitis allergic were numerically higher in the faricimab every 8 weeks arm compared with the aflibercept every 8 weeks arm. The most common ocular AEs in both studies were cataract (9.9% to 17.6% per arm) and conjunctival hemorrhage (5.6% to 9.8% per arm).

Ocular SAEs were reported with low frequency in both trials; however, in both the YOSEMITE and RHINE trials, there was a slightly higher frequency of ocular SAEs in the faricimab PTI arm compared with aflibercept every 8 weeks, and both faricimab arms were somewhat higher compared with the aflibercept every 8 weeks arm in the YOSEMITE trial (YOSEMITE = 3.8%, 4.5%, and 2.3%; RHINE = 4.4%, 6.3%, and 4.1% patients in the faricimab every 8 weeks, faricimab PTI, and aflibercept every 8 weeks arms, respectively). The most common ocular serious adverse event (SAE) reported during both studies was cataract (0.6% to 2.2% across treatment arms). The frequency of non-ocular SAEs in any arm of the studies was in the range of 20.1% to 31.6%, with COVID-19 (1.3% to 3.2%) and pneumonia (1.3% to 2.6%) being the most frequently reported non-ocular SAEs across treatment arms in both studies.

In both studies, a small proportion of patients in all arms discontinued treatment due to AEs (1.6% to 2.9% per arm). The most common AE (≥ 1% in any arm) related to discontinuing treatment was uveitis (3 patients in the YOSEMITE trial's faricimab PTI arm). A higher proportion of patients in all arms discontinued the study due to AEs (4.4% to 8.6% across treatment arms). The most common reason for discontinuing the study was death (9 patients across faricimab arms; 1 patient in aflibercept arm) and COVID-19 (8 patients across faricimab arms; 1 patient in the aflibercept arm).

Across both the YOSEMITE and RHINE trials, death was reported in 81 patients (4.4% in the faricimab every 8 weeks arm, 4.7%, in the faricimab PTI arm, and 3.7% in the aflibercept every 8 weeks arm, pooled for both studies). The most common primary cause of death was the reported term of death, which included gunshot wounds, fall, natural causes, advanced hepatocellular carcinoma with metastasis to bones, head injury, and unexplained deaths (3 patients in the faricimab every 8 weeks arm, 6 patients in the faricimab PTI arm and 1 patient in the aflibercept arm). Study investigators did not consider any of the deaths to be related to study treatment.

Cataract was the most commonly occurring notable harm, occurring in 9.9% to 17.6% of patients across all treatment arms during both studies. Over the course of both studies, 6 patients in the faricimab arms reported endophthalmitis, while 1 patient in the aflibercept arm reported endophthalmitis. Uveitis and iritis were the most commonly reported intraocular inflammation events. Uveitis occurred in 7 patients in the faricimab arms, and no patients in the aflibercept treatments arms. Occurrence of iritis was comparable across treatment arms. Non-ocular arterial thromboembolic events were reported in 6.9% to 10.9% of patients across both studies, with comparable frequency between treatment arms. Vitreous floaters were reported in 1.9% to 5.4% of patients across both studies, and these events were numerically higher in the faricimab every 8 weeks arms than in the aflibercept arms of the studies. Retinal detachment, retinal tear, glaucoma, retinal vascular occlusive disease events, eye irritation, ocular discomfort, and blurred vision occurred infrequently (< 2% for each harm across all treatment arms in both studies). A small number of patients in the faricimab treatment arms reported retinal detachment (6 over both studies) and retinal tear (3 over both studies), while there were 2 retinal detachments in the aflibercept arms and no retinal tears. There were no reports of retinal hemorrhage as an AE in either study.

Critical Appraisal

The overall study designs of YOSEMITE and RHINE were appropriate for the objectives of the studies. There were no major concerns with the methods of randomization, allocation concealment, and blinding. The conclusion of noninferiority of faricimab to aflibercept was drawn based on an ITT analysis of the primary outcome. It is generally preferred if the claim

of noninferiority was based on agreement between both the ITT population and the per-protocol population for a more conservative approach in the context of noninferiority studies. Nonetheless, the results of a supplementary per-protocol analysis in the studies, and several sensitivity analyses conducted by the sponsor and the FDA, were consistent with those of the primary ITT analysis. While there were a large proportion of patients who had at least 1 major protocol deviation (around 50%) in both studies (most frequently missed visits), the sensitivity and supplemental analyses were consistent with the primary estimand. The noninferiority margin of 4 ETDRS letters was considered reasonable by the clinical expert. The studies were adequately powered for the assessment of the primary outcome. Intercurrent events were reported in approximately 9% to 10% of patients in both studies, and most were COVID-19–related. A key limitation in the statistical analysis was the lack of adjustment for multiplicity for secondary outcomes and subgroup analyses, and no sensitivity analyses were conducted to assess the impact of missing data on the secondary outcomes. As such, these findings were considered exploratory. Another limitation is the different dosing schedules used in the treatment arms. In the maintenance phase, the treatment interval could be modified post-randomization for the faricimab PTI arm using prespecified criteria based on a patient's BCVA and CST outcomes to either every 4 weeks, every 8 weeks, every 12 weeks, or every 16 weeks intervals; however, intervals in the aflibercept arm were fixed throughout.

In terms of generalizability, a strength of the trials is that they included patients who had previously received another anti-VEGF drug, as well as patients who were treatment naive. A limitation to note is that the studies excluded some patients who would typically receive treatment in clinical practice: patients with hemoglobin A1C greater than 10% were excluded, as were patients with high-risk PDR. The generalizability of trials results to these patient populations is unclear. In addition, aflibercept was given at a fixed dosing interval in the maintenance phase, which does not align with the treat-and-extend protocol commonly used in clinical practice, thus limiting the generalizability of the results. There is also some uncertainty on the outcome of frequency of faricimab injections considering the method of interval assignment for faricimab PTI in the maintenance phase may be more rigid than what would be used in clinical practice, although the expert thought simplified thresholds for BCVA and OCT from the algorithm could be applied by clinicians in practice. In the trials, patients were monitored monthly; however, according to the clinical expert, in clinical practice, monitoring would typically only occur at treatment visits during the maintenance phase. Furthermore, while the length of assessment in the primary analysis was adequate for assessing the efficacy and safety of faricimab in the context of a noninferiority trial, according to the clinical expert, longer-term data are required to assess the durability and long-term safety of faricimab. Lastly, there is no direct evidence comparing faricimab to ranibizumab (at Health Canada–approved dosages) or bevacizumab, which represents an important evidence gap in the evaluation of anti-VEGF therapies.

Indirect Comparisons

Description of Studies

One indirect treatment comparison (ITC) was submitted by the sponsor and included in this review. No additional ITCs were identified in the literature. The sponsor performed a Bayesian NMA to estimate the efficacy of faricimab in patients with DME against other anti-VEGF drugs.

Efficacy Results

For the outcome of BCVA at 1 year, 23 trials were analyzed using a random-effects model. In the ITC [redacted]. In addition, [redacted]

For the outcome of number of injections at 1 year, 11 trials were analyzed under a random-effects model. The ITC showed that [redacted]. Although [redacted] these data are impacted by administration of therapies with fixed intervals in clinical trials according to protocols within the 1-year time frame of the RCTs.

For the outcome of retinal thickness, at 1 year, 23 RCTs were analyzed using a random-effects model. The results of the NMA showed [redacted]. However, 95% credible intervals are wide and heterogeneity in the methods to assess retinal thickness across studies adds considerable uncertainty to the results for this analysis and limit conclusions about the relative effect of faricimab on central retinal thickness.

The outcome of proportion of patients gaining or losing 10 or 15 ETDRS letters at 1 year was analyzed, but poor model fit precludes conclusions being made on the effect of faricimab versus comparators for this outcome.

Harms Results

There were limited data available for the NMAs that were conducted for ocular AEs and for discontinuation; therefore, fixed-effects models were used for these end points, and there was a high degree of uncertainty in these models. Limitations of the NMA preclude conclusions being made regarding ocular AEs and overall treatment discontinuation.

Critical Appraisal

There may be important sources of bias related to different study or patient characteristics that may impact the conclusions that can be drawn about this ITC. The limitations described may pose a considerable challenge to make a conclusive decision regarding the validity of the results to inform clinical practice. There were many trials with missing information about study and baseline characteristic, and considerable heterogeneity across these characteristics. Most notably, the heterogeneity in the methods of assessing retinal thickness and the availability of information around presence of significant diabetic macular ischemia or systemic comorbidities. Additionally, there was a weak connection between faricimab and the rest of the network through aflibercept.

Although [redacted]. The results of the analysis related to number of injections will have been impacted by administration of therapies with fixed intervals in clinical trials according to study protocols. Limitations to the NMA preclude conclusions about proportion of patients gaining or losing 10 or 15 ETDRS letters and retinal thickness.

There were limited data available for the NMAs that were conducted for ocular AEs and for treatment discontinuation; therefore, fixed-effects models were used for these end points, and there was a high degree of statistical uncertainty in these models. As a result, there are

limited data to draw any conclusions about the effect of faricimab versus comparators on ocular AEs and treatment discontinuation.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	People with DME
Treatment	Faricimab
Dose regimen	6 mg administered by intravitreal injection every 4 weeks for the first 4 doses, followed by 6 mg at a dosing interval of up to every 16 weeks
Submitted price	Faricimab, 28.8 mg per 0.24 mL, single-use vial: $1,350.00
Treatment cost	Faricimab has an annual cost in year 1 ranging from $8,100 to $18,900 (6 to 14 injections) and in subsequent years ranging from $4,050 to $17,550 (3 to 13 injections)
Comparators	• Aflibercept • Bevacizumab • Ranibizumab
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (25 years)
Key data source	• The target population (baseline characteristics and clinical efficacy) was based on the phase III trials of faricimab: YOSEMITE and RHINE • Comparative clinical efficacy data were derived from a sponsor-submitted NMA to inform average annual change in BCVA from baseline, transition matrices (i.e., course of the condition), discontinuation rates, adverse events, and injection frequency
Key limitations	• The comparative effectiveness and safety of faricimab is uncertain owing to heterogeneity in the sponsor's NMA and how the NMA results were used to inform the model. Given that the NMA compared the number of injections during an initial 12-month period, it is unknown how faricimab would compare against relevant comparators beyond 12 months. • The drug acquisition costs of bevacizumab were likely overestimated, given that the sponsor assumed that each vial would be used for only 1 administration. In practice, multiple administrations per vial are common. • Health state utility values are uncertain and likely overestimated. • The sponsor's base-case results were not reproducible, and the ICER varied substantially across model runs because of small differences in QALYs between treatments and an insufficient number of probabilistic model iterations.

Component	Description
CADTH reanalysis results	• In the CADTH base case, CADTH assumed that each vial of bevacizumab would be used for multiple administrations and alternative utility values were adopted. CADTH additionally corrected an error in the sponsor's model and increased the number of probabilistic iterations. • Results of the CADTH base case suggest that: ◦ faricimab is less costly and more effective than aflibercept and ranibizumab ◦ in sequential analysis, faricimab is associated with an ICER of $164,743 per QALY compared with bevacizumab (incremental costs = $58,130; incremental QALYs = 0.353) ◦ there is a 0% probability that faricimab is cost-effective at a willingness-to-pay threshold of $50,000 per QALY, and a 68% price reduction would be necessary for faricimab to be cost-effective at this threshold. • Although aflibercept and ranibizumab were dominated in the base-case probabilistic analysis, there is uncertainty associated with this finding, given that there are small differences in QALYs between treatments (incremental QALYs = 0.150 to 0.320) and the identified limitations with the sponsor's NMA. • A scenario analysis, in which equal efficacy and administration frequency were assumed for all comparators, suggested that a price reduction of greater than 98% for faricimab would be required to achieve cost parity with bevacizumab.

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 limitations with the sponsor's analysis: the proportion of patients with DME who are diagnosed was overestimated, the administration frequency is uncertain, brolucizumab was not included as a comparator, and the number of administrations of bevacizumab per vial was underestimated. CADTH reanalysis reduced the proportion of patients with DME who are diagnosed and increased the number of administrations of bevacizumab per vial. In the CADTH base case, the estimated cost savings of funding faricimab for the treatment of DME were $800,423 in year 1, $3,211,386 in year 2, $6,504,889 in year 3, for a 3-year total cost savings of $10,516,698. A scenario analysis conducted by CADTH that assumed that faricimab would obtain a portion of its market share from bevacizumab resulted in an incremental budget impact of $18,182,088, suggesting that faricimab may ultimately lead to increased costs, depending on which treatments are 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, 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: August 24, 2022

Regrets: Two expert committee members did not attend.

Conflicts of interest: None.