

## CADTH Reimbursement Recommendation

# Faricimab (Vabysmo)

**Indication:** For the treatment of neovascular (wet) age-related macular degeneration

**Sponsor:** Hoffmann-La Roche Ltd.

**Final recommendation:** Reimburse with conditions

**ISSN:** 2563-6596

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

## What Is the CADTH Reimbursement Recommendation for Vabysmo?

CADTH recommends that Vabysmo be reimbursed by public drug plans for the treatment of neovascular (wet) age-related macular degeneration (nAMD) if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Vabysmo should only be covered to treat patients with nAMD, as per the approved Health Canada indication.

### What Are the Conditions for Reimbursement?

Vabysmo should only be reimbursed if prescribed by an ophthalmologist with experience managing nAMD and if the cost per administration is not more than the least costly drug covered by the public drug plans for the treatment of nAMD.

### 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 nAMD.
- Patients with nAMD identified a need for new treatments that require fewer injections. Although Vabysmo can be given at an interval of up to every 16 weeks, there is not enough evidence to prove that treatment with Vabysmo results in fewer injections than other treatments for nAMD.
- There is not enough evidence to suggest Vabysmo works better than other drugs that are covered by the public drug plans for patients with nAMD. Therefore, the price of Vabysmo should not be more than the lowest-cost drug covered by the public drug plans to ensure that coverage does not increase drug plan budgets.
- Vabysmo may decrease costs for the public drug plans, but for this to occur, the price must be less than the lowest-cost drug covered by the plans.

## Additional Information

### What is nAMD?

nAMD is an eye disease in which there is a leakage of blood and fluids from abnormal blood vessels formed under the central retina, which causes damage to the retina and irreversible loss of central vision. It is estimated that nAMD affects more than 150,000 people in Canada.

### Unmet Needs in nAMD

Patients with nAMD expressed a need for new treatments for nAMD that 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 as the number of injections required falls to between 3 and 13.

# Recommendation

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

# Rationale for the Recommendation

Two randomized, double-blind, active-controlled, phase III trials (TENAYA, N = 671, and LUCERNE, N = 658) demonstrated that faricimab was noninferior to aflibercept in the change in best corrected visual acuity (BCVA) from baseline over weeks 40, 44, and 48 of treatment in treatment-naïve adult patients with nAMD. The mean difference between the faricimab and aflibercept arms was 0.7 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (95% confidence interval [CI], -1.1 to 2.5) in the TENAYA trial and 0.0 ETDRS letter (95% CI, -1.7 to 1.8) in the LUCERNE trial. Patients expressed a need for new treatments for nAMD that have fewer injections. Most patients received faricimab at an extended interval of every 12 weeks or every 16 weeks at week 48 in the TENAYA and LUCERNE trials. However, results from a network meta-analysis (NMA) found that faricimab was not associated with fewer injections than other anti-vascular endothelial growth factor (VEGF) drugs at 12 months, except for regimens that were administered every 4 or 6 weeks per protocol, but there were important limitations associated with the indirect evidence that created uncertainty in the results.

Using the sponsor-submitted price for faricimab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for faricimab was \$695,839 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 better clinical efficacy relative to all comparators. Given that there is substantial uncertainty regarding these conclusions, there is not sufficient 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 with the least costly anti-VEGF therapy reimbursed for the treatment of nAMD.

**Table 1: Reimbursement Conditions and Reasons**

Reimbursement condition	Reason	Implementation guidance
<b>Prescribing</b>		
1. The patient should be under the care of an ophthalmologist with experience in managing nAMD.	To ensure that faricimab is prescribed for appropriate patients and administered by a trained ophthalmologist.	—
<b>Pricing</b>		
2. 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 nAMD.	Faricimab demonstrated noninferiority compared to aflibercept in clinical trials. Uncertainty in the indirect and phase II evidence precluded CDEC from drawing conclusions regarding comparative efficacy from these studies. Additionally,	—

Reimbursement condition	Reason	Implementation guidance
	no definitive conclusion could be reached regarding whether faricimab is associated with fewer injections compared to other anti-VEGF drugs. Therefore, to ensure cost-effectiveness, faricimab should be priced such that the cost per administration does not exceed that of the least costly drug reimbursed for the treatment of nAMD. This would need to account for vial cost as well as number of administrations per vial.	
<b>Feasibility of adoption</b>		
3. The feasibility of adoption of faricimab must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—

CDEC = Canadian Drug Expert Committee; nAMD = neovascular age-related macular degeneration; VEGF = vascular endothelial growth factor.

## Discussion Points

- CDEC noted that the TENAYA and LUCERNE trials enrolled treatment-naïve patients with nAMD. CDEC discussed the available evidence supporting the efficacy and safety of faricimab in patients with previous anti-VEGF experience. One phase II study (AVENUE) provided evidence on the use of faricimab in a treatment-experienced population from a subgroup that switched from ranibizumab to faricimab in the study after incomplete response. Overall, superiority of faricimab over ranibizumab was not demonstrated based on the results of the primary outcome.
- CDEC discussed that although faricimab was noninferior to aflibercept in the TENAYA and LUCERNE trials, there is limited direct comparative evidence between faricimab and other currently available nAMD treatments. The phase II STAIRWAY and AVENUE trials provided direct evidence comparing faricimab to ranibizumab, but limitations of the study designs and analyses precluded CDEC from drawing conclusions regarding comparative efficacy from these studies. CDEC discussed the results of 1 NMA that was conducted to estimate the efficacy of faricimab in patients with nAMD against other anti-VEGFs. The limitations in the indirect evidence have also led to inconclusive results regarding faricimab's efficacy versus other anti-VEGFs.
- It is possible that anti-VEGFs biosimilars used to treat nAMD will enter the market in the future, though at the time of this review, the comparative efficacy or cost-effectiveness of such biosimilars versus faricimab is unknown. CDEC considered that faricimab may not be cost-effective versus an anti-VEGF biosimilar used to treat nAMD should such a product enter the market.

## Background

Faricimab has been approved by Health Canada for the treatment of nAMD. 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 every 4 weeks (approximately every  $28 \pm 7$  days) for the first 4 doses, followed by anatomic and visual acuity evaluations at week 20 and week 24 to inform dosing of faricimab at intervals of 8, 12, or 16 weeks through week 60.

## 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 in patients with nAMD
- patients' perspectives gathered by patient groups, including Fighting Blindness Canada, the Canadian Council of the Blind, CNIB, and Vision Loss Rehabilitation 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 nAMD
- 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 input from Fighting Blindness Canada, the Canadian Council of the Blind, CNIB, and Vision Rehabilitation Canada. Canadians with age-related macular degeneration (wet or dry) indicated that age-related macular degeneration had physical, psychological, and social impacts on their daily lives. Patients indicated that vision loss could affect daily activities such as using electronic devices, reading, self-care, recognizing or meeting people, and driving. The patients reported that having to think about their disease frequently and worry about their condition worsening in the future created psychological stress. Patients indicated that the need for assistance and feelings of isolation and loneliness also had social impacts.

Most patients receiving anti-VEGF injections indicated that the treatment had helped them avoid losing more eyesight, though some noted no beneficial effect or were unsure if there was an effect from the treatments. Attending injection appointments was reported to be a challenge by some patients, most commonly due to the lack of assistance to attend appointments. Anxiety and fear about the injection was noted by patients to be the most difficult part of the appointment. Most patients reported experiencing some pain into the

evening after the appointment. Post-injection visual complications (e.g., blurry vision) and the resulting need for more frequent assistance were also reported.

Most patients expressed a preference for new treatments that can be taken less frequently.

## Clinician Input

### Input From the Clinical Expert Consulted by CADTH

The clinical expert consulted by CADTH indicated the treatment goals of nAMD are to delay and/or reverse disease progression, reduce symptom severity, minimize adverse events (AEs), preserve and/or enhance health-related quality of life, and maintain patient independence. 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 of care associated with frequent treatment visits. This must be balanced with a promising safety profile.

The clinical expert noted that faricimab is expected to have a similar place of therapy as other anti-VEGF drugs — as a first-line treatment in patients with nAMD. The clinical expert expressed that if faricimab is reimbursed, a shift in the treatment paradigm will be likely considering that faricimab is the first anti-VEGF therapy approved for an extended interval of every 16 weeks, which could potentially address the unmet need related to frequent treatment visits.

The clinical expert identified that the patients with nAMD who have early and small (in size) neovascular lesions and sign(s) of active choroidal neovascularization are suitable candidates for faricimab. The clinical expert indicated that faricimab can be used in patients who are treatment-naïve or require a change in therapy due to inadequate response to other anti-VEGF drugs. The clinical expert indicated that patients with extensive subretinal fibrosis and macular tissue damage, very poor baseline visual acuity, long disease duration, or unsuccessful therapy with an anti-VEGF drug for more than 2 years may not be suitable for treatment with faricimab.

The clinical expert noted that clinical evaluation and optical coherence tomography should be performed every 6 to 8 weeks at follow-up visits after the completion of loading doses to assess treatment response. Key assessment outcomes include change in visual acuity and presence of intraretinal fluid (IRF) or subretinal fluid (SRF), and blood accumulation in the macular. The clinical expert reported that optimal response to anti-VEGF therapies is generally achieved at least 4 to 6 months after initiation of therapy.

The clinical expert indicated that faricimab should be discontinued if extensive subretinal fibrosis (disciform scarring) has occurred with vision loss to counting fingers or worse, disease progression could not be modified with faricimab therapy, or disease is end stage.

### Clinician Group Input

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

The clinician group noted that there have been limitations with the current intravitreal anti-VEGF therapies used to treat nAMD. The clinician group indicated that there has been an efficacy gap in real-world treatment outcomes compared to the outcomes observed in clinical trials due to the intense treatment burden associated with anti-VEGF therapy. The clinician

group reported that in real-world practice, the visual outcomes are suboptimal, and the recent COVID-19 pandemic and other limitations to health care delivery have made it more difficult for patients to get regular, intense treatment.

The clinician group identified durability and reduced treatment frequency as the most important unmet needs in nAMD treatment. Patients need to be treated with a current anti-VEGF therapy every 7 to 8 weeks after an intensive monthly loading treatment cycle, and the clinician group reported that this puts a high burden on patients and their caregivers related to time off work to attend appointments. The clinician group indicated that new treatments that require less frequent injections would help reduce treatment burden for these patients. Another unmet need for nAMD treatment identified by the clinician group is the development of fibrosis and atrophy due to poor disease control in the long term, which eventually can result in vision loss. To improve the long-term visual outcomes, the clinician group mentioned the need for drugs that could effectively dry the retina for a longer period and reduce the nAMD treatment burden. Lastly, the clinician group mentioned the need for drugs that could also maintain a high safety profile to minimize the risk of ocular complications.

The clinician group mentioned that the dual mechanism of faricimab, which targets both the VEGF-A and Ang-2 pathways that are critical in the development of retinal and choroidal vascular disease, is different from other available drugs. The clinician group agreed that this drug can be considered as first-line treatment or as rescue therapy for patients not responding to current nAMD treatments, while potentially reducing treatment burden with the option to use longer treatment intervals than existing drugs.

## Drug Program Input

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

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

The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

**Table 2: Responses to Questions From the Drug Programs**

Implementation issues	Response
<b>Relevant comparators</b>	
Aflibercept appears to be an appropriate comparator, but do clinical experts believe a more appropriate comparator could have been selected?	The clinical expert commented that aflibercept was likely the most appropriate comparator among the anti-VEGF drugs available at the time of the study's conduct, considering that aflibercept was the most commonly prescribed drug.



Implementation issues	Response
The study protocol mentions the administration of a sham treatment to maintain masking among arms. Given the titration schedule for faricimab, is it realistic to expect that masking was successful?	The clinical expert noted that, based on their experience in conducting clinical trials, it is unlikely that patients would differentiate between a sham injection and an actual intravitreal injection given the study eye is anesthetized.
Should aflibercept have been dosed according to the “treat-and-extend” regimen?	The clinical expert commented that the use of a fixed q.8.w. interval for aflibercept in the maintenance phase was reasonable considering the study objective was to demonstrate durability of faricimab when given at longer intervals than aflibercept. The clinical expert further noted that, in their clinical experience, q.8.w. to q.10.w. is the most commonly prescribed maintenance regimen for aflibercept in patients who are in the first few years of treatment.
What percentage of patients treated with ranibizumab, bevacizumab, aflibercept, and brolucizumab dosed according to the “treat-and-extend” regimen receive therapy q.12.w. or q.16.w.?	The clinical expert noted that the percentage of patients on extended treatment interval varies by drug and is affected by many factors. The duration of follow-up, for example, may have more influence on certain drugs (patients on ranibizumab or aflibercept tend to withstand longer intervals over time), and less so on others. As such, it is challenging to ascertain the percentage for each drug.
Is there any discussion or experience with administering faricimab longer than q.16.w.?	The clinical expert indicated there is generally hesitancy to extend the treatment interval of existing anti-VEGF drugs beyond 16 weeks due to concerns with hemorrhagic recurrence, which can result in severe vision loss. There is no experience with administering faricimab beyond q.16.w. intervals.
<b>Considerations for initiation of therapy</b>	
Is there any inclusion or exclusion criteria that seems inappropriate?	The clinical expert and CDEC commented that the inclusion and exclusion criteria were appropriate.
Is there any inclusion or exclusion criteria that needs to be specified in the initiation criteria (if the drug receives a positive recommendation)?	CDEC acknowledged that given the potential for some patients who receive faricimab to have maintenance dosing intervals of q.16.w., which is longer than most of the comparator anti-VEGF drugs, there may be interest in treatment-experienced patients switching from a comparator anti-VEGF drug to faricimab after treatment failure or for convenience. CDEC noted that there is limited data on the use of faricimab in treatment-experienced patients. The only data available to support the use of faricimab in a treatment-experienced population is a subgroup in the AVENUE trial.
One inclusion criterion for the study was to be treatment naive. Is there any hesitancy in switching patients from another anti-VEGF therapy to faricimab?	The clinical expert expressed that they have no hesitancy in switching patients from another anti-VEGF therapy to faricimab if a switch is deemed medically necessary.
What criteria for therapy initiation would be ideal for clinical practice?	The clinical expert noted that it would be appropriate to align the criteria for therapy initiation with the inclusion and exclusion criteria of the pivotal trials.
<b>Considerations for discontinuation of therapy</b>	
What criteria for discontinuation of faricimab therapy would be ideal for clinical practice?	The clinical expert noted that faricimab should be discontinued if severe structural macular damage (e.g., fibrosis) has occurred with vision loss to counting fingers or worse, disease progression

Implementation issues	Response
	could not be modified with faricimab therapy, or disease is end stage.
<b>Considerations for prescribing of therapy</b>	
How frequently should faricimab be administered?	In the clinical expert's opinion, most patients will receive faricimab q.8.w. to q.16.w. interval following completion of loading doses.
<b>System and economic issues</b>	
What is the percentage price reduction to meet a \$50,000 per QALY threshold?	Using the sponsor-submitted price for faricimab and publicly listed prices for all other drug costs, the ICER for faricimab was \$695,839 per QALY compared with bevacizumab; all other comparators were associated with fewer QALYs and greater costs relative to faricimab. This analysis assumes that faricimab is associated with lower administration frequency and better clinical efficacy relative to all comparators. Given that there is substantial uncertainty regarding these conclusions, there is not sufficient 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 with the least costly anti-VEGF drug reimbursed for the treatment of nAMD.

anti-VEGF = anti-vascular endothelial growth factor; CDEC = Canadian Drug Expert Committee; ICER = incremental cost-effectiveness ratio; nAMD = neovascular age-related macular degeneration; q.8.w. = every 8 weeks; q.10.w. = every 10 weeks; q.12.w. = every 12 weeks; q.16.w. = every 16 weeks; QALY = quality-adjusted life-year.

## Clinical Evidence

### Pivotal Studies and Protocol Selected Studies

#### Description of Studies

The TENAYA and LUCERNE studies met the inclusion criteria for the systematic review. They were identically designed phase III, multicentre, randomized, double-blind, active-controlled, noninferiority trials that evaluated the use of faricimab in comparison with aflibercept in treatment-naïve patients with nAMD (TENAYA, n = 671, and LUCERNE, n = 658) for 112 weeks. Patients were randomized to either the faricimab or aflibercept arm on a 1:1 ratio. Patients in the faricimab arm were given faricimab 6 mg intravitreally every 4 weeks for 4 loading doses followed by maintenance doses either every 8 weeks, every 12 weeks, or every 16 weeks. Patients in the aflibercept arm received aflibercept 2 mg intravitreally every 4 weeks for 3 doses then at a fixed maintenance interval of every 8 weeks.

Both pivotal 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 40, 44, and 48 in the intention-to-treat (ITT) population. The noninferiority margin was specified as 4 letters on the ETDRS chart. Secondary outcomes included measures for frequency of administration for faricimab, measures for retinal thickness, retinal fluids, pigment epithelial detachment, and vision-related function, all of which were measured without control for multiplicity. At the time of this review, the studies were ongoing and data from the primary analysis at week 48 was available.

In both studies, the mean age of patients at baseline was between 74 and 77 years, and the majority were female (between 57.2% and 62.6%) and White (between 82.6% and 90.7%). The mean time since the diagnosis of nAMD was between 1.5 months and 3.2 months and the majority has a baseline BCVA of 73 to 55 letters on the ETDRS chart.

## **Efficacy Results**

### ***Change in Visual Acuity***

The primary outcome of both studies was the change from baseline in BCVA (ETDRS letters) averaged over weeks 40, 44, and 48 in the ITT population. The mean difference between the faricimab and aflibercept arms was 0.7 ETDRS letters (95% CI, -1.1 to 2.5) in the TENAYA trial, and 0.0 ETDRS letter (95% CI, -1.7 to 1.8) in the LUCERNE trial in the ITT populations, both of which fell within the noninferiority margin.

The proportion of patients gaining greater than or equal to 15 ETDRS letters in BCVA from baseline averaged over weeks 40, 44, and 48 was a secondary outcome. The proportion was 20.0% and 15.7% in the faricimab arm and aflibercept arm, respectively, in the TENAYA trial, and 20.2% and 22.2% in the LUCERNE trial, respectively. In the TENAYA trial, the proportion of patients avoiding loss of greater than or equal to 15 ETDRS letters in BCVA from baseline averaged over weeks 40, 44, and 48 was 95.4% and 94.1% in the faricimab and aflibercept arms, respectively, while in the LUCERNE trial, the proportion was 95.8% and 97.3%, respectively.

### ***Frequency of Faricimab Injections***

In the TENAYA trial, the mean number of study treatment injections given through week 48, a secondary outcome, was 6.9 (standard deviation [SD] = 0.63) in the faricimab arm and 7.8 (SD = 0.45) in the aflibercept arm. In the LUCERNE trial, the mean number of study treatment injections given through week 48 was 7.0 (SD = 0.53) in the faricimab arm and 7.9 (SD = 0.32) in the aflibercept arm.

The studies measured the proportion of patients in the faricimab arm on an every 8 weeks, every 12 weeks, and every 16 weeks injection interval as a secondary outcome. The proportion of patients who received faricimab every 8 weeks, every 12 weeks, and every 16 weeks at week 48 was 20.3%, 34.0%, and 45.7%, respectively, in the TENAYA trial, and 22.2%, 32.9%, and 44.9%, respectively, in the LUCERNE trial.

### ***Vision-Related Function***

In the TENAYA study, the change from baseline in National Eye Institute Visual Functioning Questionnaire 25 composite score at week 48 (exploratory outcome), was 4.82 points (SD = 10.81) and 2.54 points (SD = 10.93) in the faricimab and aflibercept arms, respectively. In the LUCERNE trial, the composite score increased from baseline at week 48 by 4.35 points (SD = 10.65) and 5.55 points (SD = 11.17) in the faricimab and aflibercept arms, respectively.

### ***Legal Blindness***

The proportion of patients with legal blindness averaged over weeks 40, 44, and 48 (secondary outcome) was 6.4% and 7.0% in the faricimab and aflibercept arms, respectively, in the TENAYA trial, while in the LUCERNE trial, the proportion was 7.9% and 7.5%, respectively.

### **Anatomic Outcomes**

The change from baseline in central subfield thickness (CST) (measuring distance between internal limiting membrane and retinal pigment epithelium) was a secondary end point. A reduction in CST was observed in both treatment arms in both trials.

The proportions of patients with absence of IRF, SRF, and pigment epithelial detachment (secondary outcomes) at week 48 were in the range of 74.4% to 84.1%, 62.1% to 75.7%, and 3.0% to 7.7%, respectively, in the studies.

### **Harms Results**

As of the primary analysis (follow-up until week 48), ocular AEs were reported in 36.2% and 38.1% of patients who received faricimab and aflibercept, respectively, in the TENAYA trial. In the LUCERNE trial, 40.2% of patients who received faricimab and 36.2% of patients who received aflibercept reported at least 1 ocular AE. The most common ocular AE was conjunctival hemorrhage (5.7% to 8.9%). The frequency of ocular serious adverse event (SAE) was 1.2% and 1.8% in the faricimab and aflibercept arms, respectively, in the TENAYA trial, and 2.1% in both arms in the LUCERNE trial. The most common ocular SAE was worsening of nAMD (up to 0.9%). In both studies, about half of the study populations reported a non-ocular AE. Nasopharyngitis (4.9% to 8.3%) was the most frequently reported non-ocular AE. The frequency of non-ocular SAEs in either arm of the studies was within the range of 9.0% to 14.7%, with cardiac failure being the most frequently reported. The frequency of treatment discontinuation due to AE(s) was 2.4% in the faricimab arm and 0.3% in the aflibercept arm in the LUCERNE trial, and 0.9% in both treatment arms in the TENAYA trial. Death was reported in 0.3% to 2.1% of patients across treatment arms in the studies.

In terms of notable harms, 1 patient reported endophthalmitis in the aflibercept arm in the LUCERNE trial, while none reported this AE in the faricimab arms in either trial. No incidence of retinal vasculitis was reported. Intraocular inflammation was reported in 0.6% to 2.4% of patients, and vitreous floaters were reported in 1.2% to 3.9% of patients. Arterial thromboembolic events were reported in 0.9% to 1.2% of patients in both arms of the studies.

### **Critical Appraisal**

The overall study designs of the TENAYA and LUCERNE trials were appropriate for the objectives of the studies. There was no particular concern with the methods of randomization, allocation concealment, and blinding. While imbalances were identified in 2 baseline characteristics in the LUCERNE trial, including time since diagnosis of nAMD and proportion of patients with occult choroidal neovascularization lesions, these imbalances were unlikely to cause bias in favour of the faricimab arm, according to the clinical expert consulted by CADTH. The conclusion of noninferiority of faricimab to aflibercept was drawn based on an ITT analysis of the primary outcome, though 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. The noninferiority margin of 4 ETDRS letters was justified, and the clinical rationale was considered reasonable by the clinical expert. The studies were adequately powered for the assessment of the primary outcome. Per the clinical expert, the dropout rate was acceptable at 4.3% in both studies. Intercurrent events, mostly COVID-19-related, were reported in approximately 10% of patients in both studies, and the approach in handling intercurrent events was considered appropriate by the CADTH review team. A key

limitation in the statistical analysis was the lack of adjustment for multiplicity for secondary outcomes and subgroup analyses; as such, the findings were considered exploratory.

In terms of generalizability, a limitation to note is that the studies included treatment-naïve patients only; therefore, the applicability of trials results to treatment-experienced patients 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 uncertainty on the outcome of frequency of faricimab injections considering the method of interval assignment for faricimab in the maintenance phase up until the conduct of primary analysis (week 48) is more rigid than in clinical practice, though by keeping the dosing consistent, it might have helped reduce internal validity issues in the studies. It is anticipated by the clinical expert consulted by CADTH that later analysis may have more generalizability value as a result of the implementation of a personalized treatment interval algorithm from week 60 and onwards, which involves routine adjustment of intervals based on disease activity. Furthermore, while, according to the clinical expert, 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, it is expected that at least 2 to 3 years of clinical data are required to assess the durability of faricimab. Finally, there is no direct evidence comparing faricimab to brolucizumab 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 nAMD against other anti-VEGF therapies.

### Efficacy Results

For the outcome of BCVA at 1 year, 35 trials were analyzed under a random-effects model. In the ITC, faricimab 6 mg intravitreal every 8 to 16 weeks was not different (95% credible intervals [CrIs] include the null) to comparators for BCVA. For the outcome of number of injections at 1 year, 27 trials were analyzed under a random-effects model. The ITC suggests that faricimab does not demonstrate (95% CrIs include the null) fewer injections in a 12-month period than comparators, except for those regimens that were administered every 4 or 6 weeks. For the outcome of retinal thickness at 1 year, 25 randomized controlled trials were analyzed under a random-effects model. The ITC suggests that faricimab may be favourable (95% CrIs exclude the null) to bevacizumab regimens and ranibizumab 0.5 mg intravitreal every 8 weeks for the outcome of mean change in retinal thickness (CST). Additionally, brolucizumab 6 mg intravitreal every 8 to 12 weeks may be favourable (95% CrI excludes the null) to faricimab for this outcome. 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 on the effect of faricimab versus comparators for this outcome.

### Harms Results

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

## Critical Appraisal

Limitations of the sponsor's ITC include considerable heterogeneity in the study and some baseline characteristics (most notably is the heterogeneity in the methods to assess retinal thickness and in the method of assessing retinal thickness), and the availability of information around prognostic factors such as presence of SRF or IRF. Additionally, there was a weak connection between faricimab and the rest of the network through aflibercept via the LUCERNE and TENAYA trials, and through ranibizumab in a phase II trial.

The results of the analysis related to number of injections may have been impacted by protocol-driven administration of therapies with fixed intervals in clinical trials. Limitations to the NMA preclude conclusions about the proportions of patients gaining or losing 10 or 15 ETDRS letters and retinal thickness.

There was limited data available for the NMAs that were conducted for ocular adverse effects 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 adverse effects and treatment discontinuation.

## Other Relevant Evidence

### Description of Studies

The STAIRWAY (N = 76) and AVENUE (N = 273) studies were phase II, multicentre, randomized, double-blind, active-controlled trials that did not meet the inclusion criteria of the systematic review. However, they are the only head-to-head comparisons between faricimab and ranibizumab to date; therefore, these studies were also summarized and critically appraised in this review.

In the STAIRWAY trial, patients were assigned to either faricimab 6 mg (4 monthly loading doses followed by 1 maintenance dose every 12 weeks), faricimab 6 mg (4 monthly loading doses followed by 1 maintenance dose every 16 weeks), or ranibizumab 0.5 mg (every 4 weeks) in a 2:2:1 ratio in a 48-week double-blind period. The primary outcome was the mean change from baseline in BCVA (ETDRS letter) at week 40 in the ITT population. Data were analyzed descriptively.

In the AVENUE trial, patients were assigned to either ranibizumab 0.5 mg (every 4 weeks; arm A), faricimab 1.5 mg (every 4 weeks; arm B), faricimab 6 mg (every 4 weeks; arm C), faricimab 6 mg (4 monthly loading doses followed by 1 maintenance dose every 8 weeks; arm D), or ranibizumab 0.5 mg (3 monthly doses followed by faricimab 6 mg every 4 weeks; arm E), in a 3:2:2:2:3 ratio in a 32-week double-blind period. Arm B does not align with the recommended dose in the product monograph and therefore was not summarized in this review. The primary objective of the AVENUE study was to evaluate the efficacy of faricimab compared to ranibizumab monotherapy in treatment-naïve patients from baseline to week 36, and in treatment-experienced patients (who switched from ranibizumab to faricimab in the study after incomplete response) from week 12 to week 36. The primary outcome was the mean change in BCVA (ETDRS letter) from baseline to week 36 in the comparisons of arms A, C, and D (treatment-naïve population). In the comparison of arms A and E (treatment-experienced population), the primary outcome was the mean change in BCVA (ETDRS letter) from week 12 to week 36 in patients with a BCVA of less than or equal to 68 ETDRS letters at week 12.

## Efficacy Results

### STAIRWAY

In the STAIRWAY trial, the mean differences between the faricimab arms and ranibizumab arm in BCVA were -2.1 ETDRS letters (80% CI, -6.8 to 2.6) (faricimab every 12 weeks) and 1.1 letters (80% CI, -3.4 to 5.5) (faricimab every 16 weeks) at week 40, and 0.5 letters (80% CI, -4.3 to 5.3) (faricimab every 12 weeks) and 1.8 letters (80% CI, -2.7 to 6.4) (faricimab every 16 weeks) at week 52. Since the trial was not designed to test a hypothesis, the results were considered exploratory.

### AVENUE

In the AVENUE trial, the mean differences between the faricimab and ranibizumab arms in the change in BCVA from baseline to week 36 were -1.6 letters (80% CI, -4.9 to 1.7) (Arm C) and -1.5 letters (80% CI, -4.6 to 1.6) (Arm D) in the treatment-naïve population. The mean difference between the faricimab and ranibizumab arms in the change in BCVA from week 12 to week 36 was -1.7 (80% CI, -3.8, 0.4) in the treatment-experienced population in the AVENUE trial. No statistically significant difference between the faricimab treatment arms and ranibizumab were identified for the primary end point in either analysis subpopulation. Overall, superiority of faricimab to ranibizumab was inconclusive based on the results of the primary outcomes.

## Harms Results

The harms and notable harms reported in both phase II trials were generally similar and consistent with the TENAYA and LUCERNE trials. The proportion of patients who experienced at least 1 AE in the STAIRWAY trial was 81.3% in the ranibizumab arm compared to between 74.2% and 75% in the faricimab arms. However, the proportions of patients who experienced SAEs were between 9.7% and 16.7% in the faricimab arm, and the proportions of patients who died were between 4.2% and 6.5% in the faricimab arm, with no deaths occurring in the ranibizumab arm. In the faricimab arms, the SAEs were non-ocular related (cardiac disorders), and the 3 deaths were associated with ischemic stroke, sepsis, and metastatic neoplasm.

In the AVENUE trial, the proportion of patients with AEs was 84.8% and 84.4% in arms D and E, respectively, and 76.1% and 79.5% in arms A and C, respectively. One death occurred (arm E) related to cardio-respiratory arrest.

## Critical Appraisal

In both studies, trial eligibility criteria were appropriate for the indication, and the trial populations were generally representative of the Canadian patient population, based on baseline characteristics. While the dropout rate due to an AE was similar for all arms in the STAIRWAY trial, it was highest (7.8%) in arm E in the AVENUE trial. In terms of harms and notable harms, all these arms had small sample sizes and the number of events were few, making it difficult to draw any conclusions in both trials.

The study designs and planned analyses were the key limitations to the studies. The phase II designs were not appropriate for testing superiority of faricimab versus ranibizumab. The STAIRWAY trial was designed as an exploratory study that did not test a hypothesis; therefore, no conclusions can be drawn regarding the relative efficacy and safety of faricimab compared to ranibizumab based on this study. The AVENUE study was designed to test an a priori hypothesis that faricimab was superior to ranibizumab. The primary objective of the AVENUE study was not met as no statistically significant difference between the faricimab



treatment arms and ranibizumab were identified for the primary end point in either analysis subpopulation.

## Economic Evidence

**Table 3: Cost and Cost-Effectiveness**

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	People with nAMD
Treatment	Faricimab
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	<ul style="list-style-type: none"> <li>• Aflibercept</li> <li>• Bevacizumab</li> <li>• Brolucizumab</li> <li>• Ranibizumab</li> </ul>
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (25 years)
Key data source	<ul style="list-style-type: none"> <li>• The target population (baseline characteristics and clinical efficacy) was based on the phase III trials of faricimab, TENAYA, and LUCERNE.</li> <li>• 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, AEs, and injection frequency.</li> </ul>
Key limitations	<ul style="list-style-type: none"> <li>• There was some uncertainty with the internal and external validity of the NMA that CADTH was unable to resolve. Estimates of relative effects on BCVA and injection frequency were derived from this NMA; therefore, there is substantial uncertainty regarding incremental differences in effects and costs between faricimab and comparators.</li> <li>• Bevacizumab was assumed to be used for only 1 administration, contrary to clinical expert experience where multiple uses per vial are common in practice.</li> <li>• The absolute number of LYs gained for each comparator was overestimated in the sponsor's base case due to an error in the sponsor's model.</li> <li>• Uncertainty was not accurately characterized and discrepancies remained in the probabilistic analysis results that could not be explained.</li> </ul>
CADTH reanalysis results	<ul style="list-style-type: none"> <li>• The CADTH reanalysis addressed the previously noted limitations by correcting the error in the sponsor's model and assuming multiple administrations of bevacizumab from 1 vial.</li> <li>• The CADTH reanalysis resulted in a deterministic ICER for faricimab vs. bevacizumab of \$695,839 per QALY (incremental costs = \$68,328; incremental QALYs = 0.098). CADTH reanalyses suggest</li> </ul>



Component	Description
	<p>that a price reduction of approximately 79% would be necessary for faricimab to achieve cost-effectiveness at a \$50,000 per QALY threshold.</p> <ul style="list-style-type: none"> <li>• Although aflibercept, brolucizumab, and ranibizumab were dominated in the base case, the probabilistic analysis showed a significant degree of uncertainty associated with this finding, as differences in QALYs were small. This is reflective of the clinical evidence, which showed imprecise confidence intervals that include the null.</li> <li>• A scenario analysis in which equal efficacy and administration frequency were assumed for all comparators suggested a price reduction of greater than 98% would be required to achieve cost parity with bevacizumab.</li> </ul>

AE = adverse events; BCVA = best corrected visual acuity; ICER = incremental cost-effectiveness ratio; LY = life-year; nAMD = neovascular age-related macular degeneration; NMA = network meta-analysis; QALY = quality-adjusted life-year; vs. = versus.

## Budget Impact

CADTH identified the following key limitations with the sponsor's budget impact analysis: the proportion of patients diagnosed was overestimated, the number of administrations of bevacizumab per vial was underestimated, the number of administrations of aflibercept and ranibizumab per vial is uncertain, administration frequency is uncertain, and the market uptake of faricimab is uncertain. CADTH reanalysis decreased the proportion of patients diagnosed and the number of administrations of bevacizumab assumed per vial, resulting in an estimated cost savings of \$90,005,481 over 3 years. However, CADTH conducted a scenario analysis in which multiple administrations per vial were assumed possible for aflibercept and ranibizumab. The budget impact from this analysis was \$61,586,628 in additional costs (i.e., incremental costs) over 3 years, indicating that the budget impact analysis is sensitive to assumptions about vial sharing. Likewise, other scenario analyses demonstrated a high degree of uncertainty regarding potential cost savings if alternate administration frequencies and market share values were assumed.

## CDEC Information

### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, 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:** June 22, 2022

**Regrets:** One

**Conflicts of interest:** None