Reimbursement Recommendation

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(Draft)

Faricimab (Vabysmo)

Indication: For the treatment of macular edema secondary to retinal vein occlusion.

Sponsor: Hoffmann-La Roche Limited

Recommendation: Reimburse with Conditions

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Recommendation

The CDA-AMC Canadian Drug Expert Committee (CDEC) recommends that faricimab be reimbursed for the treatment of macular edema secondary to retinal vein occlusion (RVO) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 2 phase III, multicentre, randomized, double-masked, active comparator-controlled studies, BALATON and COMINO, demonstrated that treatment with faricimab 6 mg administered every 4 weeks for 24 weeks resulted in similar clinical benefit for patients with macular edema secondary to branch retinal vein occlusion (BRVO) in BALATON (N = 553) and macular edema secondary to central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO) in COMINO (N = 729) when compared to aflibercept 2 mg administered every 4 weeks in terms of visual acuity. More specifically, based on a test for non-inferiority followed by a test for superiority on the change from baseline to week 24 in BCVA in the study eye, faricimab results in little to no difference in BCVA when compared with aflibercept 2 mg. Observations from these trials additionally suggest that compared to aflibercept 2 mg, faricimab likely results in little to no difference in anatomical outcomes and vision-related health-related quality of life (HRQoL). Indirect evidence submitted by the sponsor suggests that there may be little to no difference in BCVA with faricimab every 4 weeks compared to other anti-VEGFs administered using a flexible injection schedule. However, there is uncertainty in these findings owing to limitations with the sponsor-submitted indirect evidence.

Patient input received for this review indicated that there is an unmet need for a treatment that prevents, slows, or reverses vision loss; a treatment that has fewer treatment-related side-effects; and a treatment that has a less frequent injection schedule. Patients also want a treatment that improves their HRQoL. CDEC concluded that faricimab does not meet the unmet needs identified by patients when compared to other available anti-VEGFs; however, the evidence is supportive of faricimab as an additional treatment option for patients living with macular edema secondary to RVO.

At the sponsor submitted price for faricimab and publicly listed prices for all comparators, faricimab was less costly than aflibercept 2 mg and ranibizumab and more costly than bevacizumab and ranibizumab biosimilars. As there is insufficient evidence to suggest that faricimab is more effective than its comparators, the total drug cost of faricimab should not exceed the total drug cost of the lowest-cost anti-VEGFs used in the treatment of RVO.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, renewal, discontinuation, and prescribing		
1. Reimbursement of faricimab should be based on the criteria used by each of the public drug plans for initiation, renewal, discontinuation, and prescribing of anti-VEGFs for the treatment of macular edema secondary to RVO.	Based on the results of the BALATON and COMINO trials, treatment with faricimab results in little to no difference in visual acuity, anatomical outcomes, or vision-related HRQoL, compared to aflibercept 2 mg. Therefore, there is insufficient evidence to suggest that faricimab should be held to a different standard than other options currently reimbursed for the treatment of macular edema secondary to RVO.	—
Pricing		
2. Faricimab should be negotiated so that it does not exceed the drug cost for treatment with the least costly anti-VEGFs reimbursed for the treatment of macular edema secondary to RVO.	There is insufficient evidence to justify a cost premium for faricimab over the least expensive anti-VEGF reimbursed for macular edema secondary to RVO.	—
Feasibility of adoption		
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.	—

BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; HRQoL = health-related quality of life; RVO = retinal vein occlusion; anti-VEGF = antivascular endothelial growth factor.

Discussion Points

- **Assessment of clinical benefit**: CDEC discussed the BALATON and COMINO trials that included direct comparative evidence for faricimab and aflibercept 2 mg. CDEC noted that while there was little to no difference between faricimab and aflibercept 2 mg based on the GRADE assessment and results of the primary endpoint, change from baseline in BCVA; there is insufficient clinical evidence to support clinical superiority of faricimab compared to aflibercept 2 mg. Overall, the committee concluded that the evidence is supportive of faricimab as an alternative treatment option for macular edema secondary to RVO.
- **Injection frequency**: Both patients and clinicians identified a reduction in the frequency of injections as an outcome of interest for new treatments for macular edema secondary to RVO. CDEC considered the evidence from the BALATON and COMINO trials to be very uncertain due to the absence of a comparison group and therefore insufficient to ascertain the relative injection frequency for faricimab versus other anti-VEGFs. In the economic model, the sponsor incorporated the injection frequency for each anti-VEGF directly from clinical trials, without adjustment or accounting for differences in patient characteristics. Owing to the direct use of clinical trial data, it is not possible to determine if any observed differences are due to the treatment. In clinical practice, the injection frequency is guided by treatment response.
- **Lack of evidence on switching and treatment-experienced/refractory patients:** The BALATON and COMINO studies excluded patients with a history of previous episodes of macular edema due to RVO or persistent macular edema due to RVO diagnosed greater than 4 months prior to screening, as well as any prior or current treatment for macular edema due to RVO, including anti-VEGF intravitreal injections, in the study eye. However, the clinical expert suggested that from a clinical perspective, it is likely that these patients would not be excluded from treatment with faricimab.

- **Clinical outcomes due to Ang-2 inhibition:** CDEC noted that faricimab has a distinct mechanism of action compared to other anti-VEGFs for the treatment of RVO through the inhibition of Ang-2; however, the committee indicated that there is no evidence to support whether this correlates clinically with any differences in safety or efficacy for faricimab relative to other anti-VEGF treatments.
- **Patients with HRVO:** CDEC noted that in the COMINO trial, 17.0% (62 patients) of patients randomized to receive faricimab and 18.1% (65 patients) of patients randomized to receive aflibercept were reported as living with macular edema secondary to HRVO. However, the clinical expert advised that the difference between subtypes of RVO is not a major factor for consideration because macular edema secondary to HRVO is expected to respond to treatment similarly to macular edema secondary to CRVO. As such, CDEC noted that jurisdictions may wish to implement reimbursement of HRVO similarly to CRVO and BRVO.
- **Cost-effectiveness:** CDEC discussed the uncertainty in the economic analysis, notably that the incremental gain in QALYs predicted by the sponsor's model for faricimab compared to other anti-VEGFs is not supported by the submitted indirect evidence. Particularly, the committee noted that, although there are limitations to the submitted indirect evidence such as uncertainty related to potential heterogeneity and wide credible intervals, overall the indirect evidence suggests that there may be little to no difference in BCVA with faricimab compared to other anti-VEGFs administered using a flexible injection schedule. As such, whether the use of faricimab will result in improved health outcomes (and hence QALYs) among patients with RVO is highly uncertain.
- **Biosimilar availability:** Biosimilars for aflibercept are currently under review by Health Canada. The introduction of such biosimilars may affect the cost-effectiveness of faricimab versus aflibercept depending on the negotiated price. CDEC discussed that, at the time of this review, the comparative efficacy and cost-effectiveness of faricimab relative to biosimilar aflibercept is unknown.
- **Anti-VEGF pricing:** The committee discussed that faricimab has successfully undergone price negotiations for the treatment of neovascular (wet) age-related macular edema and diabetic macular edema, and it is likely that the unit cost paid by public drug plans is lower than the price submitted in the current review. Similarly, the prices of other anti-VEGFs in the sponsor's model do not reflect existing confidential prices negotiated by public plans.
- **Budget impact:** The committee discussed uncertainty in the estimated budget impact of reimbursing faricimab for the treatment of RVO. The sponsor's estimate suggests that reimbursing faricimab for the treatment of macular edema secondary to RVO will be cost-saving for the public drug plans; however, whether there will be cost savings and the extent of any savings realized is highly uncertain and will depend on which anti-VEGFs are displaced by faricimab, as well as the injection frequency and the confidentially negotiated price of each anti-VEGF.

Background

Retinal vein occlusion (RVO) develops when a thrombus blocks the venous outflow of the retina, resulting in macular edema (fluid accumulation at the back of the eye). Macular edema can lead to significant retinal thickening, hemorrhage, and leakage. Patients with RVO usually experience acute, painless visual symptoms, including visual loss or varying degrees of visual alteration due to the edema. There are 3 subtypes of RVO that are classified according to the location of the occlusion: branch (involving a complete or partial obstruction at a branch or tributary of the central retinal vein), central (involving obstruction of the retinal vein at or posterior to the optic nerve head), and hemi-central (involving occlusion occurring at the disc that commonly involves half of the neurosensory retinal venous drainage, either the superior or inferior hemifield).

In Canada, the annual estimated incidence rate of visual impairment due to macular edema secondary to branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) was 0.056% and 0.021%, respectively (56 and 21 per 100,000). Based on pooled data from 11 population-based studies from the US, Europe, Asia, and Australia, the estimated prevalence rates of RVO, BRVO, and CRVO were 0.52%, 0.44%, and 0.08%, respectively (520, 440, and 80 people per 100,000, respectively).

The Canadian Expert Consensus on Optimal Treatment of Retinal Vein Occlusion (published in 2015) advises on the following:

BRVO with OCT evidence of macular edema — If visual acuity is greater than 20/40, then observation and close follow-up are suggested. Alternatively, anti-VEGF therapy can be considered in patients with relatively good functional vision and optical coherence tomography (OCT) evidence of minimal subclinical macular edema (i.e., 1 to 2 small intraretinal cysts). If there is no foveal involvement, then focal laser is also an option. If visual acuity is less than 20/40 with sub-foveal involvement, then treatment with anti-vascular endothelial growth factor (VEGF) monotherapy is advised. According to Canadian Expert Consensus, most clinicians manage macular edema secondary to hemiretinal vein occlusion (HRVO) similarly to BRVO.

CRVO with OCT evidence of macular edema — If visual acuity is greater than 20/40, then observation and close follow-up are suggested. Otherwise, treatment with anti-VEGF monotherapy is advised.

Faricimab injection has been approved by Health Canada for the treatment of macular edema secondary to RVO. Faricimab injection is an ophthalmological anti-vascular endothelial growth factor and anti-angiopoietin-2 drug (a humanized bispecific immunoglobulin G1 [IgG1] antibody). It is available as a solution for intravitreal injection and the dosage recommended in the product monograph is 6 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 plus or minus 7 days) for 6 months.

Sources of Information Used by the Committee

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

- a review of two phase III, randomized, double-masked, active comparator-controlled, parallel group, 2-part studies in patients with macular edema secondary to BRVO, CRVO or HRVO; one indirect treatment comparison
- patients' perspectives gathered by 3 patient groups, Fighting Blindness Canada, the Canadian Council of the Blind, and Vision Loss Rehabilitation Canada
- input from public drug plans that participate in the reimbursement review process
- one clinical specialist with expertise diagnosing and treating patients with retinal vein occlusion
- input from 4 clinician groups, Toronto Retina Institute, Southeastern Ontario Community Ophthalmologists, Southwestern Ontario Community Ophthalmologists, and Northeastern Ontario Community Ophthalmologists
- a review of the pharmacoeconomic model and report submitted by the sponsor

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to the call for input and from the clinical expert consulted for this review.

Patient Input

Input from one joint patient advocacy group (Fighting Blindness Canada [FBC], the Canadian Council of the Blind, and Vision Loss Rehabilitation Canada) was summarized for this report. The patient input submission included a summary of an online survey made available to Canadians living with RVO from March and April 2024, supplemented with qualitative interviews held in March and April 2024 with 3 patients diagnosed with RVO. The joint survey gathered information about patient-lived experiences, associated vision loss and current treatments for RVO. In total, 32 patients living in Canada (62.5% of respondents with central RVO, 21.9% with branch RVO, and 15.6% who did not know what type of RVO they were diagnosed with) responded to the survey. Most respondents worried about vision worsening (53%). Respondents in the survey revealed that RVO significantly impacted their day-to-day lives and psychological well-being. Some respondents expressed being anxious about their RVO diagnosis, while others expressed fear, isolation, anger and or loss of confidence/self-worth. Due to the sudden nature of RVO and severity, respondents expressed ongoing fear of progression or that the unaffected eye may one day be affected. Overall, 60.0% of respondents indicated they had received anti-VEGF injections for their condition.

When patients were asked how they felt about their current ongoing treatments, the main reasons for stress were anxiety about injections (83%), symptoms from the injections (50%) and travel to appointments (33%). Respondents primarily expressed that treatment improved their vision or that treatment made their vision stable. Respondents in the survey highlighted the need for new treatments that prevent or slow down further vision loss and restore vision. Patients also expressed that they would like treatments that lower out-of-pocket costs, lower side effects, require fewer injections, and are effective.

The joint patient group noted that RVO leads to visual complications that render certain daily activities – such as reading or driving – either problematic or impossible. The joint input noted that while the current anti-VEGF treatments on the market have shown high levels of effectiveness in slowing or halting vision loss, they also come with the highly burdensome regular intravitreal injections, creating challenges for many patients, such as painfulness of the injection, both during and after the procedure, and their difficulties managing their bidirectional commute for their appointments. Patients expressed that they preferred treatment options that could be administered less frequently and supported treatments that could be made available to patients regardless of their province.

Clinician Input

Input From Clinical Expert Consulted

The unmet needs identified by the clinical expert include not all patients respond to available treatments; patients become refractory to current treatment options; no treatments are available to reverse the course of disease and address key outcomes; and treatments that are better tolerated, improve adherence and convenience are needed. Additionally, the clinical expert indicated that treatments that address treatment frequency and associated socioeconomic burden (i.e., treatment burden for clinicians and associated cost for patients and family, such as transportation and missed workdays) are needed. The clinical expert indicated that the anticipated place in therapy of faricimab is as an alternative to other currently available anti-VEGF therapies (i.e., the clinical expert does not expect a shift in the current treatment paradigm for macular edema secondary to RVO). The clinical expert noted that clinical practice, treatment history (suboptimal response with other treatments), access and drug costs can influence treatment decisions. The clinical expert indicated that the anticipated target population for faricimab includes all patients with RVO, regardless of subtype, severity, symptoms, etc. Additionally, the clinical expert indicated that patients currently being treated with an anti-VEGF therapy may also be considered as candidates for treatment with faricimab.

Based on clinical expert input, the diagnosis of RVO and treatment with faricimab should ideally be performed by a retina specialist. In situations where a retina specialist is not available, such as in remote areas, the clinical expert advised that the diagnosis of RVO and treatment with faricimab should ideally be performed by a well-trained general ophthalmologist. The clinical expert further advised that an outpatient setting that is well equipped with ophthalmic examination and OCT is an appropriate setting for treatment with faricimab.

The clinical expert acknowledged the goal of treatment is to improve visual acuity; however, in practice, the clinical expert indicated that OCT quantitative measurement of macular edema (CST measurement) is the most important outcome used to assess response to treatment. The clinical expert noted that some clinicians also use qualitative parameters to assess treatment response, such as presence and size of cystoid spaces. For visual acuity, the clinical expert indicated that a difference of more than 1 Snellen line of

acuity is typically considered clinically meaningful (in the context of a comparison with a similar treatment). However, depending on variability in light conditions, technician factors, and patient concentration, the clinical expert indicated that a difference of at least 2 Snellen lines can be considered clinically meaningful. For macular edema measured by OCT, the clinical expert indicated that a difference of 10% is typically considered clinically meaningful. The clinical expert indicated that assessment of treatment response usually coincides with treatment schedule (i.e., initially once per month). When the condition is stabilized and the patient enters into the treat and extend phase, the clinical expert indicated that both treatment and response assessment are extended accordingly.

The clinical expert suggested the following scenarios in which discontinuation of faricimab could be considered: when the underlying pathology has resolved; when presence or absence of macular edema show no difference in acuity; when the treat and extend protocol allows extension to more than 4 to 6 months between injections.

Clinician Group Input

Inputs from 4 clinician groups were summarized for this review: Toronto Retina Institute, Southeastern Ontario Community Ophthalmologists, Southwestern Ontario Community Ophthalmologists, and Northeastern Ontario Community Ophthalmologists. In total, 19 ophthalmologists contributed to the clinician input submission. Treatment goals highlighted by the groups included extending treatment intervals, reducing macular edema, preserving visual acuity, improving visual acuity, reducing VEGF levels, and preventing neovascularization and neovascular glaucoma in RVO patients. According to the groups, an ideal treatment is one with demonstrated efficacy in sustaining improvements in visual acuity over the long term and durable in reducing the treatment burden associated with repetitive intravitreal therapy (i.e. requiring fewer injections, reducing the frequency of patient visits, cost, and burden on the healthcare system). There is an unmet need for patients who do not achieve durable responses to existing treatment options. Therefore, there is a need for efficacious, durable and long-lasting treatments that can minimize treatment burden compared to existing ones and extend treatment intervals while maintaining efficacy. The clinician groups anticipate that faricimab will be used as a first-line option for newly diagnosed patients with RVO based on its bispecific action mechanism and anticipate generating a greater response. According to the clinician groups, faricimab would be suited for any patient with RVO, particularly those who have failed to respond to other treatment options, although caution will be exercised for patients who have inflammation from other pre-existing conditions. The clinician groups did not anticipate misdiagnosis. Any improvement in swelling determined with an OCT scan was considered a clinically meaningful improvement. The groups noted the following outcomes to assess whether a patient responds to treatment: stable or improved visual acuity (improved vision), reduced presence of fluid via optical coherence tomography (OCT), improved clinical exam measures of retinal hemorrhages, ischemia, neovascularization, and fewer injections required and or increased interval between injections. The clinician groups highlighted that factors considered for treatment discontinuation would be similar to currently approved therapies. These included no response or the presence of irreversible macular damage. One group highlighted that if a patient responds well and treatment extension has increased to 4 months or more, it would be assessed whether to stop treatment and undergo reasonably close observation. Faricimab can be administered in any outpatient setting and should preferably be administered by trained retinal specialists.

Drug Program Input

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

- Relevant comparators
- Initiation of therapy
- Continuation or renewal of therapy
- Discontinuation of therapy
- Prescribing of therapy
- System and economic issues

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

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
In BALATON and COMINO, faricimab 6.0 mg every 4 weeks was compared to aflibercept 2.0 mg every 4 weeks through week 20. Active control is considered appropriate as the dose for aflibercept is the monograph dose.	This is a comment from the drug plans to inform CDEC deliberations.
Different programs for anti-VEGF access exist across drug plans. • Criteria for anti-VEGF therapy for RVO varies across jurisdictions. • Bevacizumab may or may not be considered a relevant comparator for some jurisdictions; this was considered in the economic analysis. • Ranibizumab biosimilar may or may not be listed in different jurisdictions; may or may not be subject to biosimilar policies relating to switching. • Aflibercept biosimilars on the horizon. • Aflibercept (8 mg) was not considered as a comparator as it is not indicated for RVO at the time of review.	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for initiation of therapy	
Is RVO similar to macular edema secondary to BRVO (i.e., same indication)? Note that aflibercept was initially reviewed for the latter.	The clinical expert indicated that the subtypes of RVO are similar but also have important clinical differences. However, when considering treatment response, there may be less to differentiate between the subtypes. The clinical expert advised that the mainstay of treatment for macular edema associated with RVO is anti-VEGF therapy. The clinical expert noted some differences in the treatment approach between the subtypes of RVO. For example, in certain cases of BRVO, laser treatment may be started to avoid anti-VEGF treatment. In other cases of BRVO, intravitreal injections may be supplemented with laser treatment to reduce the number of injections. In contrast to BRVO, CRVO generally do not respond to laser treatment. CDEC agreed with the clinical expert.
Switching between anti-VEGF treatments is a consideration.	This is a comment from the drug plans to inform CDEC deliberations.
Given differences in reimbursement landscape across drug plans, consider implementation guidance to note that faricimab could be **initiated, renewed, discontinued, and prescribed** in a similar manner to other anti-VEGF drugs for RVO as per the reimbursement criteria for each public drug plan if determined to be therapeutically equivalent.	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for continuation or renewal of therapy	

Implementation issues	Response
Treat and extend is an important consideration for drug plans and may be beneficial from a health system perspective. By week 72 of the trials, a portion of patients transitioned to extended dosing intervals with faricimab (i.e., Q12W and Q16W).	This is a comment from the drug plans to inform CDEC deliberations.
What is the importance of the extended intervals? Are the extended intervals maintained over time? In practice, how many patients can be treated with an extended interval?	The clinical expert suggested that the advantage of extended treatment intervals is reduced patient and clinician burden of treatment, as well as reduced socioeconomic burden. The clinical expert indicated that in most cases, the extended interval is maintained over time but also highlighted the fact that treatment intervals can be reduced, maintained, and extended in practice (i.e., there is greater flexibility compared to the personalized treatment interval dosing regimen criteria used in the pivotal trials). The clinical expert estimated 40% to 50% of patients (as the upper limit) can be treated with an extended interval (i.e., every 4 months). CDEC agreed with the clinical expert.
Considerations for discontinuation of therapy	
Is there a role for faricimab in patients who have failed previous anti-VEGF therapies?	The clinical expert indicated there is presently no evidence to support this approach. CDEC agreed with the clinical expert.
Considerations for prescribing of therapy	
Is there potential to extend intervals for other anti-VEGF therapies for RVO? If yes, what intervals are seen with the different anti-VEGF treatments for RVO (i.e., ranibizumab, aflibercept)? Is the effect from extended intervals maintained over time?	The clinical expert indicated that extending treatment intervals to every 4 months or beyond and stopping therapy for other anti-VEGF therapies are possible in patients with RVO. As above, the clinical expert indicated that in most cases, the extended interval is maintained over time but also highlighted the fact that treatment intervals can be reduced, maintained, and extended in practice. The clinical expert further advised that this also depends on systemic factors (i.e., whether diabetes, hypertension, or other cardiovascular disease is controlled). CDEC agreed with the clinical expert.
Intraocular injection requires administration by a retinal specialist. Is access to specialists appropriate to support patient populations and ongoing treatment regimens?	The clinical expert agreed that ideally, treatment should be performed by a retinal specialist. The expert also noted that in situations where a retina specialist is not available, such as in remote areas, the diagnosis of RVO and treatment with faricimab could be performed by a well-trained general ophthalmologist; however, they noted that the definition of a well-trained individual may differ between jurisdictions. CDEC agreed with the clinical expert.

Implementation issues	Response
Is the treat and extend an important consideration to help support ongoing access to treatment and support the growing patient population?	Please refer to the second question and response in Considerations for continuation or renewal of therapy category. CDEC agreed with the clinical expert.
Is there potential for combination use of different anti-VEGF therapies?	The clinical expert did not anticipate combination use of different anti-VEGF therapies. CDEC agreed with the clinical expert and noted that there is presently no evidence support this approach.
System and economic issues	
• Vabysmo has completed pCPA negotiations for AMD and DME. • Byooviz and Ranopto have been negotiated through pCPA for AMD, DME, RVO, choroidal neovascularization secondary to ocular conditions other than AMD or PM. • Eylea was negotiated through pCPA for BRVO and AMD • Eylea HD is under active negotiations through pCPA for the indications of AMD and DME.	This is a comment from the drug plans to inform CDEC deliberations.
Certain programs in place within jurisdictions may affect the economic impact of faricimab. Anti-VEGFs are administered via intravitreal injection either at a hospital, ophthalmology clinic, or in a private ophthalmology clinic and this varies across provinces and jurisdictions in Canada.	This is a comment from the drug plans to inform CDEC deliberations.

AMD = age-related macular degeneration; BRVO = branch retinal vein occlusion; DME = diabetic macular edema; pCPA = pan-Canadian Pharmaceutical Alliance; PM = pathologic myopia; Q12W = every 12 weeks; Q16W = every 16 weeks; RVO = retinal vein occlusion; VEGF = anti-vascular endothelial growth factor.

Clinical Evidence

Systematic Review

Description of Studies

BALATON and COMINO were phase III, multicentre, randomized, double-masked, active comparator-controlled, parallel-group, two-part studies. Part 1 evaluated the efficacy, safety, and pharmacokinetics of intravitreal faricimab 6 mg every 4 weeks compared with intravitreal aflibercept 2 mg every 4 weeks in patients with macular edema secondary to BRVO (in BALATON), CRVO or HRVO (in COMINO) from day 1 through week 24 (24 weeks of treatment). Part 2 evaluated the efficacy, durability, safety, and pharmacokinetics of faricimab administered at masked treatment intervals between every 4 weeks and every 16 weeks based on personalized treatment interval dosing criteria, without an active control from week 24 through week 72 (48 weeks of treatment). Of note, there was no comparator in part 2 of the studies as all patients from part 1 received faricimab intravitreal injections according to a personalized treatment interval dosing regimen and sham procedure to maintain masking of the treatment intervals.

The studies included patients with foveal center-involved macular edema in the study eye due to BRVO (BALATON), or CRVO or HRVO (COMINO), diagnosed no longer than 4 months prior to screening and confirmed by the central reading center based on spectral-domain optical coherence tomography (SD-OCT) (or swept-source optical coherence tomography [SS-OCT]) images. The studies excluded patients with history of previous episodes of macular edema due to RVO or persistent macular edema due to RVO

diagnosed greater than 4 months prior to screening, as well as any prior or current treatment for macular edema due to RVO, including anti-VEGF intravitreal injections, in the study eye.

In BALATON, the mean age of patients was 64.3 years (SD = 10.7 years; range = 35 to 93 years) in the faricimab group and 63.8 years (SD = 10.6 years; range = 28 to 88 years) in the aflibercept group. The mean BCVA in the study eye was 57.50 letters (SD = 13.04 letters; range = 19.0 to 76.0 letters) in the faricimab group and 57.64 letters (SD = 12.15 letters; range = 21.0 to 73.0 letters) in the aflibercept group. The mean CST in the study eye was 558.32 microns (SD = 177.03 microns; range = 281.0 to 1,154.0 microns) in the faricimab group and 558.12 microns (SD = 180.26 microns; range = 290.0 to 1,208.0 microns) in the aflibercept group. A total of 2.9% of patients (8 of 276 patients) in the faricimab group and 5.8% of patients (16 of 277 patients) in the aflibercept group had experience with at least 1 prior targeted ocular therapy or treatment in the study eye. A total of 17.4% of patients (48 of 276 patients) in the faricimab group and 16.6% of patients (46 of 277 patients) in the aflibercept group had at least 1 prior ocular surgery or procedure in the study eye, with the most common being cataract surgery.

In COMINO, the mean age of patients was 65.6 years (SD = 13.1 years; range = 22 to 100 years) in the faricimab group and 64.7 years (SD = 13.3 years; range = 27 to 95 years) in the aflibercept group. A total of 83.0% (303 of 366 patients) of patients randomized to receive faricimab and 81.9% (294 of 363 patients) of patients randomized to receive aflibercept were reported with CRVO. A total of 17.0% (62 patients) of patients randomized to receive faricimab and 18.1% (65 patients) of patients randomized to receive aflibercept were reported with HRVO. The mean BCVA in the study eye was 50.25 letters (SD = 16.25 letters; range = 19.0 to 87.0 letters) in the faricimab group and 50.71 letters (SD = 16.34 letters; range = 19.0 to 73.0 letters) in the aflibercept group. The mean CST in the study eye was 702.21 microns (SD = 244.00 microns; range = 266.0 to 1,500.0 microns) in the faricimab group and 721.07 microns (SD = 242.86 microns; range = 281.0 to 1,419.0 microns) in the aflibercept group. A total of 5.7% of patients (21 patients) in the faricimab group and 5.0% of patients (18 patients) in the aflibercept group had experience with at least 1 prior targeted ocular therapy or treatment in the study eye. A total of 17.5% of patients (64 patients) in the faricimab group and 15.2% of patients (55 patients) in the aflibercept group had at least 1 prior ocular surgery or procedure in the study eye, with the most common being cataract surgery.

The BALATON and COMINO studies were ongoing at the time of the primary analysis — this report reflected a data cut-off date of July 6, 2022, and August 9, 2022, respectively, when all patients from the global enrolment phase had either completed the study through week 24 or had discontinued from the study prior to week 24. This report also presented data from the final analysis through week 72, corresponding to the last patient last visit date of June 12, 2023, in BALATON and July 12, 2023, in COMINO (global enrolment phase only).

Note that efficacy and safety data from the BALATON and COMINO studies was available up to week 68; however, it was not summarized in this report because results at week 24 (with the exception of treatment interval) were considered as most relevant for the purpose of this review to inform expert committee deliberations.

Efficacy Results

Visual Acuity Outcomes

The most relevant assessments of visual acuity determined for this review were change in BCVA and the proportion of patients with an improvement in BCVA. These outcomes provide information on the degree of improvement in visual acuity and the proportion of patients with an improvement in visual acuity, respectively. Scores are based on the number of letters read correctly on the ETDRS chart, with higher letter scores indicating better visual acuity (the maximum score is 100).

The primary end point in both studies was change from baseline in BCVA at week 24. If statistical significance was achieved on the non-inferiority test, then the test for superiority could proceed; the non-inferiority margin was 4 letters.

BALATON — The treatment difference in the mean change from baseline in BCVA in the study eye at week 24 between faricimab every 4 weeks versus aflibercept every 4 weeks was −0.6 letters (95% CI, −2.2 to 1.1 letters; P value for superiority test = 0.4978). A sensitivity analysis using multiple imputation to handle missing data differently and supplementary analyses in the PP analysis population and using hypothetical strategy for all intercurrent events were performed for this outcome. The results of the sensitivity and supplementary analyses were generally supportive of the primary analysis results.

The treatment difference in the estimated proportion of patients with a gain of 15 letters and greater in BCVA in the study eye from baseline at week 24 between faricimab every 4 weeks versus aflibercept every 4 weeks was −4.3% (95% CI, −12.3% to 3.8%; P value = 0.3023). The supplementary analysis result was generally supportive of the primary analysis result.

COMINO — The treatment difference in the mean change from baseline in BCVA in the study eye at week 24 between faricimab every 4 weeks versus aflibercept every 4 weeks was −0.4 letters (−2.5 to 1.6 letters; P value for superiority test = 0.6715). The sensitivity and supplementary analysis results were generally supportive of the primary analysis results.

A subgroup analysis based on baseline RVO status (CRVO and HRVO) was performed for the change from baseline in BCVA in the study eye at week 24. In the subgroup of patients with CRVO, the treatment difference in the mean change from baseline in BCVA in the study eye at week 24 between faricimab every 4 weeks versus aflibercept every 4 weeks was 0.2 letters (95% CI, −2.1 to 2.6 letters). In the subgroup of patients with HRVO, the treatment difference in the mean change from baseline in BCVA in the study eye at week 24 between faricimab every 4 weeks versus aflibercept every 4 weeks was −3.8 letters (95% CI, −7.3 to −0.4 letters).

The treatment difference in the estimated proportion of patients with a gain of 15 letters and greater in BCVA in the study eye from baseline at week 24 between faricimab every 4 weeks versus aflibercept every 4 weeks was −1.5% (95% CI, −8.4% to 5.3%; P value = 0.6661). The supplementary analysis result was generally supportive of the primary analysis result.

Anatomical Outcomes

The most relevant assessments of the anatomy of the study eye determined for this review were change in CST and the proportion of patients with absence of macular edema and fluid. Based on clinical expert input, these outcomes provide information on the extent of improvement in tissue swelling or edema, the physiological environment (i.e., reestablishment of the blood retina barrier), and the presence or absence of cystoid spaces, respectively.

In both studies, CST was defined as the distance measured between internal limiting membrane and Bruch's membrane, standardized to Spectralis SD-OCT; absence of macular edema was defined as CST less than 325 µm; and absence of both intraretinal fluid and subretinal fluid was measured in the central subfield (center 1 mm).

BALATON — The treatment difference in the mean change from baseline in CST in the study eye at week 24 between faricimab every 4 weeks versus aflibercept every 4 weeks was −7.0 microns (95% CI, −14.1 to 0.0 microns; P value for superiority test = 0.0495).

The treatment difference in the estimated proportion of patients with absence of macular edema at week 24 between faricimab every 4 weeks versus aflibercept every 4 weeks was 1.4% (95% CI, −2.3% to 5.0%; P value for superiority test = 0.4742).

The treatment difference in the estimated proportion of patients with absence of both intraretinal fluid and subretinal fluid at week 24 between faricimab every 4 weeks versus aflibercept every 4 weeks was 5.3% (95% CI, −2.7% to 13.3%; P value for superiority test = 0.1967).

COMINO — The treatment difference in the mean change from baseline in CST in the study eye at week 24 between faricimab every 4 weeks versus aflibercept every 4 weeks was −12.8 microns (95% CI, −26.7 to 1.0 microns; P value for superiority test = 0.0684).

The treatment difference in the estimated proportion of patients with absence of macular edema at week 24 between faricimab every 4 weeks versus aflibercept every 4 weeks was 1.7% (95% CI, −2.0% to 5.4%; P value for superiority test = 0.3589).

The treatment difference in the estimated proportion of patients with absence of both intraretinal fluid and subretinal fluid at week 24 between faricimab every 4 weeks versus aflibercept every 4 weeks was 6.5% (95% CI, 0.1% to 13.0%; P value for superiority test = 0.0489).

Vision-related Functioning and Health-related Quality of Life Outcome

The most relevant assessment of vision-related functioning and HRQoL determined for this review was change in the NEI VFQ-25 composite score. This outcome provides information on the degree of improvement in vision-related functioning and HRQoL from the patient's perspective. Specifically, subscales include general vision, ocular pain, near activities, distance activities, social functioning,

mental health, role difficulties, dependency, driving, color vision, and peripheral vision. The composite score ranges from 0 to 100, with higher scores indicating better vision-related functioning and HRQoL.

BALATON — The treatment difference in the mean change from baseline in NEI VFQ-25 composite score at week 24 between faricimab every 4 weeks versus aflibercept every 4 weeks was −0.4 (95% CI, −1.9 to 1.1; P value for superiority test = 0.6370).

COMINO — The treatment difference in the mean change from baseline in NEI VFQ-25 composite score at week 24 between faricimab every 4 weeks versus aflibercept every 4 weeks was −1.2 (95% CI, −2.7 to 0.3; P value for superiority test = 0.1088).

Treatment Interval Outcomes

Treatment interval was identified as a relevant outcome for this review because the clinician groups indicated that an ideal treatment demonstrates a durable effect (i.e., demonstrates efficacy in sustaining improvement in visual acuity over the long term) measured by a reduction in the treatment burden associated with repetitive intravitreal injections.

Treatment intervals at week 68 were defined as the treatment interval decision followed at week 68.

BALATON — The proportion of patients on an extended treatment interval at week 68 were as follows (patients randomized to receive faricimab every 4 weeks in part 1 and patients randomized to receive aflibercept every 4 weeks in part 1):

- Faricimab every 8 weeks: 13.3% (95% CI, 9.1% to 17.5%) and 18.0% (95% CI, 13.2% to 22.9%), respectively
- Faricimab every 12 weeks: 11.7% (95% CI, 7.7% to 15.7%) and 9.4% (95% CI, 5.8% to 13.1%), respectively
- Faricimab every 16 weeks: 52.4% (95% CI, 46.2% to 58.6%) and 47.5% (95% CI, 41.3% to 53.8%), respectively.

COMINO — The proportion of patients on an extended treatment interval at week 68 were as follows (patients randomized to receive faricimab every 4 weeks in part 1 and patients randomized to receive aflibercept every 4 weeks in part 1):

- Faricimab every 8 weeks: 20.0% (95% CI, 15.7% to 24.3%) and 17.5% (95% CI, 13.3% to 21.7%), respectively
- Faricimab every 12 weeks: 8.5% (95% CI, 5.5% to 11.5%) and 11.1% (95% CI, 7.6% to 14.6%), respectively
- Faricimab every 16 weeks: 37.0% (95% CI, 31.8% to 42.2%) and 39.0% (95% CI, 33.7% to 44.4%), respectively.

Harms Results

At the primary analysis, safety was assessed through descriptive summary based on data through week 24. At the final analysis, safety was also assessed through descriptive summary based on data through week 72 according to the various predefined groups (due to the crossover) (detailed results are included in the full clinical review report).

Adverse Events Through Week 24

BALATON — Of patients who received at least 1 injection of active study drug in the study eye, 16.3% (45 of 276 patients) randomized to receive faricimab and 20.4% (56 of 274 patients) randomized to receive aflibercept were reported with at least 1 ocular AE in the study eye. Each ocular AE in the study eye was reported in less than 4.0% of patients in each group.

An independent Clinical Events Coding Committee adjudicated thromboembolic events reported during the study. Anti-Platelet Trialist's Collaboration (APTC) events were defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause). Of patients who received at least 1 injection of active study drug in the study eye, 1.1% (3 patients) randomized to receive faricimab and 1.5% (4 patients) randomized to receive aflibercept were reported with at least 1 adjudicated APTC-defined AE. Each adjudicated APTC-defined AE was reported in less than 1.0% of patients in each group.

COMINO — Of patients who received at least 1 injection of active study drug in the study eye, 23.0% (84 of 365 patients) randomized to receive faricimab and 27.7% (100 of 361 patients) randomized to receive aflibercept were reported with at least 1 ocular AE in the study eye. Each ocular AE in the study eye was reported in less than 4.0% of patients in each group.

Of patients who received at least 1 injection of active study drug in the study eye, 1.1% (4 patients) randomized to receive faricimab and 1.4% (5 patients) randomized to receive aflibercept were reported with at least 1 adjudicated APTC-defined AE. Each adjudicated APTC-defined AE was reported in less than 1.0% of patients in each group.

Serious Adverse Events Through Week 24

BALATON — Of patients who received at least 1 injection of active study drug in the study eye, 1.1% (3 patients) randomized to receive faricimab and 0.7% (2 patients) randomized to receive aflibercept were reported with at least 1 serious ocular AE in the study eye. Each serious ocular AE in the study eye was reported in less than 1.0% of patients in each group.

COMINO — Of patients who received at least 1 injection of active study drug in the study eye, 2.5% (9 patients) randomized to receive faricimab and 3.3% (12 patients) randomized to receive aflibercept were reported with at least 1 serious ocular AE in the study eye. Each serious ocular AE in the study eye was reported in less than 1.0% of patients in each group.

Withdrawals Due to Adverse Events Through Week 24

BALATON — Of patients who received at least 1 injection of active study drug in the study eye, no patients stopped study treatment due to ocular AEs.

COMINO — Of patients who received at least 1 injection of active study drug in the study eye, 0.8% (3 patients) randomized to receive faricimab and 0.6% (2 patients) randomized to receive aflibercept stopped study treatment due to ocular AEs. Each ocular AE that led to a patient stopping their study treatment was reported in less than 1.0% of patients in each group.

Mortality Through Week 24

BALATON — Of patients who received at least 1 injection of active study drug in the study eye, 0.4% (1 patient due to cerebrovascular accident) randomized to receive faricimab and no patients randomized to receive aflibercept died during the study through week 24.

COMINO — Of patients who received at least 1 injection of active study drug in the study eye, 0.3% (1 patient due to pneumonia) randomized to receive faricimab and 0.6% (2 patients due to myocardial infarction) randomized to receive aflibercept died during the study through week 24.

Notable Harms Through Week 24

BALATON — Of patients who received at least 1 injection of active study drug in the study eye, no patients were reported with endophthalmitis in the study eye.

COMINO — Of patients who received at least 1 injection of active study drug in the study eye, no patients randomized to receive faricimab and 0.3% (1 patient) randomized to receive aflibercept were reported with endophthalmitis in the study eye.

Critical Appraisal

Internal Validity

Part 1 of the BALATON and COMINO studies were appropriately designed and powered to evaluate the efficacy of faricimab relative to aflibercept. Methods for randomization and allocation concealment were appropriate and the review team judged that risk of bias arising from the randomization process is unlikely. Part 2 of the studies did not have a relevant comparison group; therefore, conclusions about the number of injections relative to aflibercept or any other active comparator cannot be drawn.

There is a lack of evidence in the literature to inform the measurement properties of BCVA as measured by ETDRS charts, CST as measured by OCT, and vision-related functioning and HRQoL as measured by NEI VFQ-25 in patients with RVO. However, there was also no evidence in the literature to suggest that there are concerns with these tools. As the studies were masked, the risk of bias in the measurement of the outcomes is likely low.

As noted in guidance by the FDA, there was no impact on the type I error rate for the superiority test following the non-inferiority test. The review team judged that the methods for deciding the 4-letter non-inferiority margin were appropriate. Further, the clinical expert

agreed that a difference of 5 letters or 1 Snellen line can be considered clinically meaningful in the context of comparisons with a similar treatment. Since no formal superiority tests were performed for the secondary end points and the subgroup analysis of the primary end point, these results are considered as supportive evidence only. For statistically significant results, there is an increased risk that the null hypothesis was erroneously rejected.

The number of patients with HRVO available for the subgroup analysis was relatively low (< 20%) and as such, the small sample size introduced uncertainty in the results (i.e., whether they would be replicated in a larger sample). There was no formal statistical approach for testing subgroup differences by RVO type. Although the estimated effect was statistically significant in the HRVO subgroup (and not in the CRVO subgroup), this contrast is not sufficient for inferring effect modification.

Although major protocol deviation rates through week 24 were approximately 30% for each group from each study, the rates were generally balanced between groups. The most frequent type of major protocol deviation in both studies was procedural-related; however, each procedural-related protocol deviation was reported in less than 10% of patients in each group from both studies. As such, it was concluded that the risk of bias due to deviations from the intended intervention in part 1 of the studies is low. However, more than 50% of patients in each group from both studies were reported with at least 1 major protocol deviation through week 72, with more than 40% related to procedures. As such, it was concluded that the risk of bias (unknown direction and magnitude) due to deviations from the intended interventions in part 2 of the studies is high.

Missing data were implicitly imputed by the MMRM model assuming missing at random for both the primary end point of change from baseline in BCVA and secondary end point of change from baseline in CST at week 24. A sensitivity analysis (in which missing data were assumed to be missing not at random and were assumed to have worse outcomes compared to the rest of the study population) was performed for the primary end point only. As the results were consistent with the main analysis, the review team judged that the risk of bias due to missing outcomes data for this end point was low.

The assumptions for missing outcomes data (missing at random for change from baseline in CST at week 24 and LOCF for categorical secondary outcomes at week 24) are likely not plausible and for change from baseline in NEI VFQ-25 composite score at week 24 and treatment intervals at week 68, missing data were not imputed. Nonetheless, the amounts of missing outcomes data were generally low and balanced between groups in both studies so risk of bias due to missing outcomes data was considered low. The exception was for the proportion of patients with absence of both intraretinal fluid and subretinal fluid in BALATON, where missing outcome data was relatively high (13% to 16%). The clinical expert informed that the assumption that fluid status would stay constant over time is likely not plausible, so there is a potential for risk of bias due to missing outcomes data for this end point.

External Validity

The inclusion criteria in the BALATON and COMINO studies included the population of interest identified in the indication for faricimab, which is for the treatment of macular edema secondary to RVO. Notably, less than 20% of patients in COMINO had HRVO; therefore, the generalizability of the study results to patients with HRVO is less certain.

The clinical expert indicated that the inclusion criteria adequately captured all patients who would be considered candidates for faricimab in practice. Further, the clinical expert indicated that the study population was generally representative of the patients typically seen in practice who would be candidates for treatment with faricimab. Of note, the clinical expert noted that patients with RVO generally present with uncontrolled blood pressure, cardiovascular disease including stroke and myocardial infarction, diabetic retinopathy, and complications of cataract surgery. The clinical expert advised that these patients would be considered candidates for treatment with faricimab in practice.

In general, the Canadian Expert Consensus on Optimal Treatment of Retinal Vein Occlusion (published in 2015)[7] advises on the use of anti-VEGF therapy in patients with RVO with OCT evidence of macular edema. This is aligned with input from the clinician groups and clinical expert regarding current treatment options available in practice. Therefore, the comparator in the studies (aflibercept) is relevant for the purpose of the present review; however, direct evidence for the effect of faricimab versus other anti-VEGF treatments (e.g., ranibizumab and bevacizumab) in the treatment of patients with macular edema secondary to RVO is lacking.

In consultation with the clinical expert, it was concluded that the outcome measures are generally reflective of assessments of treatment response in practice. Since the goal of treatment is to improve visual acuity, the clinical expert advised that if treatment

response is demonstrated on imaging (CST measure) but there is no change in visual acuity, then the clinician will consider discontinuing treatment. However, if treatment response is demonstrated in visual acuity with change in macular edema status, then the clinician will likely use the imaging results (CST as assessed by OCT) as an objective approach to determine whether to extend, maintain, or reduce treatment interval in practice.

The clinical expert indicated that the common practice in Canada is to treat and extend, but it can also be a fixed treatment interval if extending is not possible. However, the clinical expert noted that the criteria used to determine a personalized treatment interval dosing regimen are not used uniformly by clinicians in practice.

In consultation with the clinical expert, it was concluded that the assessment timepoint at week 24 are considered appropriate for evaluating treatment effect in the therapeutic area of macular edema secondary to RVO. The exception is the outcome measure of treatment interval (proportion of patients on extended treatment intervals), for which the clinical expert suggested an assessment timepoint at month 24 (versus week 68 in the studies).

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group:

- **For RCTs**: Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.
- **For single-arm trials**: Although GRADE guidance is not available for noncomparative studies, the review team assessed pivotal single-arm trials for study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias to present these important considerations. Because the lack of a comparator arm does not allow for a conclusion to be drawn on the effect of the intervention versus any comparator, the certainty of evidence for single-arm trials started at very low certainty with no opportunity for rating up. In the current review, 68-week data from both trials were appraised as single-arm given the lack of relevant comparator at this time point.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of an important effect based on thresholds informed by the clinical expert consulted for this review. For the primary outcome of change from baseline in BCVA at week 24, the non-inferiority margin used in the trials was the threshold.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with the clinical expert, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Visual acuity (BCVA)
- Anatomical outcomes (CST, absence of macular edema, absence of both intraretinal and subretinal fluid)
- Vision-related functioning and HRQoL (NEI VFQ-25)
- Extended treatment interval (every 8 to 16 weeks)
- Notable harms (endophthalmitis)

For the GRADE assessments, the BALATON and COMINO studies were assessed individually because the BALATON study had a patient population with macular edema secondary to BRVO and the COMINO study had a patient population with macular edema secondary to CRVO or HRVO.

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for faricimab versus aflibercept in patients with macular edema secondary to BRVO.

Table 4 presents the GRADE summary of findings for faricimab versus aflibercept in patients with macular edema secondary to CRVO or HRVO.

Table 3: Summary of Findings for Faricimab Versus Aflibercept for Patients With Macular Edema Secondary to Branch Retinal Vein Occlusion

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Aflibercept	Faricimab	Difference		
Visual Acuity							
Change from baseline in BCVA in study eye (ETDRS letter score), adjusted mean Follow-up: Week 24	553 (1 RCT)	NA	17.5	16.9 (15.7 to 18.1)	−0.6 (−2.2 to 1.1)	High[a]	Faricimab results in little to no difference in BCVA when compared with aflibercept.
Proportion of patients gaining ≥ 15 letters in BCVA in the study eye from baseline, weighted estimate Follow-up: Week 24	553 (1 RCT)	NR	60 per 100	56 per 100 (50 to 62 per 100)	4 less per 100 (12 less to 4 more per 100)	Moderate[b]	Faricimab likely results in little to no difference in the proportion of patients gaining ≥ 15 letters in BCVA when compared with aflibercept.
Anatomical							
Change from baseline in CST in study eye (microns), adjusted mean Follow-up: Week 24	553 (1 RCT)	NA	−304.4	−311.4 (−316.4 to −306.4)	−7.0 (−14.1 to 0)	High[c]	Faricimab results in little to no difference in CST when compared with aflibercept.
Proportion of patients with absence of macular edema defined as CST < 325 µm, weighted estimate Follow-up: Week 24	553 (1 RCT)	NR	94 per 100	95 per 100 (93 to 98 per 100)	1 more per 100 (2 less to 5 more per 100)	High[c]	Faricimab results in little to no difference in the proportion of patients with absence of macular edema when compared with aflibercept.
Proportion of patients with absence of both intraretinal fluid and subretinal fluid, weighted estimate Follow-up: Week 24	553 (1 RCT)	NR	61 per 100	66 per 100 (61 to 72 per 100)	5 more per 100 (3 less to 13 more per 100)	Low[d]	Faricimab may result in little to no difference in the proportion of patients with absence of both intraretinal fluid and subretinal fluid when compared with aflibercept.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Aflibercept	Faricimab	Difference		
Vision-related Functioning and HRQoL							
Change from baseline in NEI VFQ-25 composite score, adjusted mean Follow-up: Week 24	497 (1 RCT)	NA	5.9	5.6 (4.5 to 6.7)	−0.4 (−1.9 to 1.1)	High[c]	Faricimab results in little to no difference in vision-related functioning and HRQoL as assessed by NEI VFQ-25 when compared with aflibercept.
Treatment Interval							
Proportion of patients on an extended treatment interval with faricimab Follow-up: Week 68	492 (1 RCT)	**Q8W treatment interval:** • Faricimab Q4W to faricimab PTI: 13 per 100 (9 to 17 per 100) **Q12W treatment interval:** • Faricimab Q4W to faricimab PTI: 12 per 100 (8 to 16 per 100) **Q16W treatment interval:** • Faricimab Q4W to faricimab PTI: 52 per 100 (46 to 59 per 100)				Very low[e]	The evidence is very uncertain about the effect of faricimab on extended treatment interval when compared with aflibercept.
Harms							
Patients with an AE of endophthalmitis in study eye Follow-up: Week 24	550 (1 RCT)	NR	0 per 100	0 per 100 (NR)	NR	Low[f]	Faricimab may result in little to no difference in endophthalmitis when compared with aflibercept.

AE = adverse event; BCVA = best-corrected visual acuity; CI = confidence interval; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; NA = not applicable; NEI VFQ-25 = National Eye Institute 25-Item Visual Functioning Questionnaire; NR = not reported; PTI = personalized treatment interval; Q4W = every 4 weeks; Q12W = every 12 weeks; Q16W = every 16 weeks; RCT = randomized controlled trial.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

The primary end point was change from baseline in BCVA at week 24; if statistical significance was achieved on the non-inferiority test, then the test for superiority can proceed. No formal superiority tests were performed for the secondary end points; therefore, these results were considered as supportive evidence only.

[a] The non-inferiority margin of 4 letters was used as the threshold of importance for assessing imprecision.

[b] Rated down 1 level for serious imprecision. There was no known threshold for a clinically important effect, and the clinical expert consulted for this review could not estimate the threshold of a clinically important difference. The review team considered the 95% CI to include the potential for both little to no difference and clinically relevant comparative harm.

[c] There was no known threshold for a clinically important effect, and the clinical expert consulted for this review could not estimate the threshold of a clinically important difference. The review team considered the 95% CI to include the potential for little to no difference only.

[d] Rated down 1 level for serious study limitations. Missing outcome data was relatively high (13% to 16%), and it is unclear whether the reasons for missingness are balanced between groups. In consultation with the clinical expert, it was concluded that the assumption that fluid status would stay constant over time is likely not plausible. Therefore, it was concluded that there are some concerns for risk of bias due to missing outcome data. Rated down 1 level for serious imprecision. There was no known threshold for a clinically important effect, and the clinical expert consulted for this review could not estimate the threshold of a clinically important difference. The review team considered the 95% CI to include the potential for both little to no difference and clinically relevant comparative benefit.

[e] In the absence of a relevant comparison group, conclusions about the number of injections relative to aflibercept or any other active comparator cannot be drawn and the certainty of evidence started at very low. Rated down 1 level for serious study limitation. A relatively large proportion of patients (> 50%) were reported with at least 1 major protocol deviation through week 72, with the majority of the major protocol deviations (> 40%) related to procedures. Therefore, it was concluded that the risk of bias (unknown direction and magnitude) due to deviations from the intended intervention in part 2 of the studies is high. Rated down 1 level for serious indirectness. Per the clinical expert consulted for this review, the criteria for extending the treatment interval in the trials were not reflective of clinical practice in Canada.

[f] Rated down 2 levels for very serious imprecision. No events were observed; therefore, there were inadequate events to inform a higher certainty judgement.

Sources: Primary Clinical Study Report of Study GR41984 (BALATON) and Final Clinical Study Report of Study GR41984 (BALATON). Details included in the table are from the sponsor's Summary of Clinical Evidence.

Table 4: Summary of Findings for Faricimab Versus Aflibercept for Patients With Macular Edema Secondary to Hemiretinal and Central Retinal Vein Occlusion

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Aflibercept	Faricimab	Difference		
Visual Acuity							
Change from baseline in BCVA in study eye (ETDRS letter score), adjusted mean Follow-up: Week 24	729 (1 RCT)	NA	17.3	16.9 (15.4 to 18.3)	−0.4 (−2.5 to 1.6)	High[a]	Faricimab results in little to no difference in BCVA when compared with aflibercept.
Proportion of patients gaining ≥ 15 letters in BCVA in the study eye from baseline, weighted estimate Follow-up: Week 24	729 (1 RCT)	NR	58 per 100	57 per 100 (52 to 61 per 100)	1 less per 100 (8 less to 5 more per 100)	High[b]	Faricimab results in little to no difference in the proportion of patients gaining ≥ 15 letters in BCVA when compared with aflibercept.
Anatomical							
Change from baseline in CST in study eye (microns), adjusted mean Follow-up: Week 24	729 (1 RCT)	NA	−448.8	−461.6 (−471.4 to −451.9)	−12.8 (−26.7 to 1.0)	High[b]	Faricimab results in little to no difference in CST when compared with aflibercept.
Proportion of patients with absence of macular edema defined as CST < 325 µm, weighted estimate Follow-up: Week 24	729 (1 RCT)	NR	92 per 100	94 per 100 (91 to 96 per 100)	2 more per 100 (2 less to 5 more per 100)	High[b]	Faricimab results in little to no difference in the proportion of patients with absence of macular edema when compared with aflibercept.
Proportion of patients with absence of both intraretinal fluid and subretinal fluid, weighted estimate Follow-up: Week 24	729 (1 RCT)	NR	69 per 100	75 per 100 (71 to 79 per 100)	6 more per 100 (0 to 13 more per 100)	Moderate[c]	Faricimab likely results in little to no difference in the proportion of patients with absence of both intraretinal fluid and subretinal fluid when compared with aflibercept.
Vision-related Functioning and HRQoL							
Change from baseline in NEI VFQ-25 composite score, adjusted mean Follow-up: Week 24	669 (1 RCT)	NA	8.1	6.9 (5.8 to 8.0)	−1.2 (−2.7 to 0.3)	High[b]	Faricimab results in little to no difference in vision-related functioning and HRQoL as assessed by NEI VFQ-25 when compared with aflibercept.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Aflibercept	Faricimab	Difference		
Treatment Interval							
Proportion of patients on an extended treatment interval with faricimab Follow-up: Week 68	645 (1 RCT)	**Q8W treatment interval:** • Faricimab Q4W to faricimab PTI: 20 per 100 (16 to 24 per 100) **Q12W treatment interval:** • Faricimab Q4W to faricimab PTI: 8 per 100 (5 to 11 per 100) **Q16W treatment interval:** • Faricimab Q4W to faricimab PTI: 37 per 100 (32 to 42 per 100)				Very low[d]	The evidence is very uncertain about the effect of faricimab on extended treatment interval when compared with aflibercept.
Harms							
Patients with an AE of endophthalmitis in study eye Follow-up: Week 24	726 (1 RCT)	NR	3 per 1,000	0 per 1,000 (NR)	NR	Low[e]	Faricimab may result in little to no difference in endophthalmitis when compared with aflibercept.

AE = adverse event; BCVA = best-corrected visual acuity; CI = confidence interval; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; NA = not applicable; NEI VFQ-25 = National Eye Institute 25-Item Visual Functioning Questionnaire; NR = not reported; PTI = personalized treatment interval; Q4W = every 4 weeks; Q12W = every 12 weeks; Q16W = every 16 weeks; RCT = randomized controlled trial.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

The primary end point was change from baseline in BCVA at week 24; if statistical significance was achieved on the non-inferiority test, then the test for superiority can proceed. No formal superiority tests were performed for the secondary end points; therefore, these results were considered as supportive evidence only.

[a] The non-inferiority margin of 4 letters was used as the threshold of importance for assessing imprecision.

[b] There was no known threshold for a clinically important effect, and the clinical expert consulted for this review could not estimate the threshold of a clinically important difference. The review team considered the 95% CI to include the potential for little to no difference only.

[c] Rated down 1 level for serious imprecision. There was no known threshold for a clinically important effect, and the clinical expert consulted for this review could not estimate the threshold of a clinically important difference. The review team considered the 95% CI to include the potential for both little to no difference and clinically relevant comparative benefit.

[d] In the absence of a relevant comparison group, conclusions about the number of injections relative to aflibercept or any other active comparator cannot be drawn and the certainty of evidence started at very low. Rated down 1 level for serious study limitation. A relatively large proportion of patients (> 50%) were reported with at least 1 major protocol deviation through week 72, with the majority of the major protocol deviations (> 40%) related to procedures. Therefore, it was concluded that the risk of bias (unknown direction and magnitude) due to deviations from the intended intervention in part 2 of the studies is high. Rated down 1 level for serious indirectness. Per the clinical expert consulted for this review, the criteria for extending the treatment interval in the trials were not reflective of clinical practice in Canada.

[e] Rated down 2 levels for very serious imprecision. Few to no events were observed; therefore, there were inadequate events to inform a higher certainty judgement.

Sources: Primary Clinical Study Report of Study GR41986 (COMINO) and Update Clinical Study Report of Study GR41986 (COMINO). Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

The sponsor did not submit long-term extension studies.

Indirect Comparisons

Description of Studies

One sponsor-conducted indirect treatment comparison (ITC) compared faricimab (6mg Q4W) to other anti-VEGF treatments, dexamethasone, and laser for the treatment of RVO. The main comparators of interest identified in the systematic literature review (SLR) were anti-VEGF treatments (aflibercept 2mg, ranibizumab, and bevacizumab), specifically those given in flexible regimens such as pro re nata (PRN), which are typically used in clinical practice. A Bayesian approach under the random effect (RE) model as the principal analysis and fixed effects (FE) model for sensitivity was implemented. Outcomes assessed included the mean change from baseline in BCVA, proportion of patients gaining 15+ letters, CST, and mean number of injections. The difference in the proportion of patients with any and serious adverse events as well as all-cause discontinuations was also assessed. Treat and extend regimens could not be investigated due to a lack of connected studies.

Efficacy Results

Mean change from baseline in BCVA

Compared with other anti-VEGFs, point estimates for the difference in mean change from baseline BCVA at 6 months mostly suggested little to no difference as compared with faricimab 6 mg every 4 weeks. The point estimate for the comparison to bevacizumab 1.25 mg PRN favoured faricimab 6 mg every 4 weeks. In most comparisons, the 95% credible intervals (CrIs) were wide and included the possibility of clinically important effects favouring either treatment being compared. Mean change and 95% CrIs for faricimab against anti-VEGFs administered PRN were as follows: aflibercept 2mg PRN: 1.87 (95% CrI, -7.43 to 11.16), ranibizumab PRN: 3.59 (95% CrI, -2.94 to 10.17), and bevacizumab PRN 5.22 (95% CrI, -3.35 to 13.80). The between-study heterogeneity estimate (tau) assessed reported a median of 2.85 (95% CrI, 1.397 to 3.911), indicating a small heterogeneity.

Mean change from baseline in CST

For change from baseline in CST at 6 months, faricimab 6 mg every 4 weeks was favoured over bevacizumab 1.25 mg PRN; however, the 95% CrI for the between-group difference included the possibility of little to no difference between the 2 treatments. In the comparisons with all other anti-VEGFs, point estimates for between-group differences favoured faricimab 6 mg every 4 weeks; however, the 95% CrI included the possibility that either treatment could be favoured. Mean change and 95% CrIs for faricimab against anti-VEGFs administered PRN were as follows: aflibercept 2mg PRN: -37.3 (95% CrI, -107.99 to 35.72), ranibizumab PRN: -20.08 (95% CrI, -70.53 to 32.35), and bevacizumab PRN -68.95 (95% CrI, -133.02 to -1.48). The between study heterogeneity estimate (tau) had a median of 9.518 (95% CrI: 0.334, 23.977) indicating a small heterogeneity.

Proportion of patients gaining at least 15 ETDRS letters

Results specific to the proportion of patients gaining at least 15 ETDRS were not reported in the sponsor-submitted ITC.

Mean number of injections

The network of studies for faricimab and anti-VEGF treatments allowing for a flexible treatment regimen (PRN) were connected with Sham injections only, therefore, no treatment effect with regards to flexible regimens could be estimated.

Harms Results

Ocular adverse events

For ocular adverse events, for comparisons with all anti-VEGFs, the 95% CrIs for the odds ratios were too wide to inform about which treatment may be favoured. The between-study heterogeneity estimate (tau) reported a median of 0.351 (95% CrI, 0.025 to 1.350). Odds ratios and 95% CrIs for faricimab against anti-VEGFs administered PRN were as follows: ranibizumab PRN: 0.64 (95% CrI, 0.14 to 2.80).

Serious ocular AEs

For serious ocular adverse events, for comparisons with all anti-VEGFs, the 95% CrIs for the odds ratios were too wide to inform about which treatment may be favoured. Odds ratios and 95% CrIs for faricimab against anti-VEGFs administered PRN were as follows: ranibizumab PRN 0.53 (95% CrI, 0.03 to 10.5).

All cause discontinuation

For comparisons with all other anti-VEGFs, the 95% CrIs for the odds ratios were too wide to inform about which treatment may be favoured. The between study heterogeneity estimate (tau) had a median of 0.632 (95% CrI, 0.160 to 1.377). Odds ratios and 95% CrIs for faricimab against anti-VEGFs were as follows: aflibercept 2mg, Q4W: 1.28 (95% CrI, 0.39 to 5.14), ranibizumab PRN: 1.00 (95% CrI, 0.16 to 6.53), and bevacizumab Q4W 0.79 (95% CrI, 0.11 to 6.20).

Critical Appraisal

There was variability in baseline characteristics (age, baseline BCVA, retinal thickness measurements, treatment patterns, number of injections administered, prior therapy, concomitant or background medications, intraocular pressure) across studies included in the NMA feasibility assessment. There was also a lack of reporting on several key study characteristics of interest for RVO (e.g. blood pressure, diabetes, concurrent diabetic retinopathy, coagulability, blood viscosity, and anemia), which could be potential effect modifiers. As such, there is uncertainty as to whether the assumptions related to homogeneity were met for the NMA. There was also a lack of clarity on the number of studies included in the network that enrolled treatment-experienced or treatment naïve RVO patients. Prior treatment for macula edema with anti-VEGFs potentially negatively impacts treatment response. This adds uncertainty to the results and limits conclusions on the relative effect of faricimab against anti-VEGFs commonly as PRN regimens in practice. In addition, the credible intervals for between-group comparisons were wide, often including the potential that either treatment being compared could be favoured.

Studies Addressing Gaps in the Evidence From the Systematic Review

Sixteen studies were submitted by the sponsor to address gaps in the RCTs submitted for faricimab for the treatment of RVO. These studies were excluded from the report because patients enrolled across studies included nAMD and DME populations, which differ from the sponsor-submitted reimbursement population. One matched cohort study, which matched RVO patients from 2 registries (Vestrum and Medisoft) with baseline characteristics of patients enrolled in the 2 pivotal trials submitted for this review (BALATON and COMINO trials) was also submitted by the sponsor. However, given that the therapies evaluated, in association with the outcomes of interest did not include faricimab, the study was excluded from the report.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients with retinal vein occlusion
Treatment	Faricimab administered by intravitreal injection every 4 weeks for 6 months[a]
Dose regimen	6 mg every 4 weeks for first 6 doses followed by 6 mg at a dosing interval of 8 to 16 weeks.
Submitted price	Faricimab, 6 mg per 0.05 mL, single-use vial: $1,350.00
Treatment cost	$9,450 to $13,500 in the first year, based on 7 to 10 injections $5,400 to $9,450 in subsequent years, based on 4 to 7 injections
Comparators	• Aflibercept 2 mg • Bevacizumab • Ranibizumab
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs

Component	Description
Time horizon	Lifetime (25 years)
Key data source	• Clinical efficacy and injection frequency for faricimab was informed by observations from the BALATON and COMINO trials • Clinical efficacy of comparators was derived from a sponsor-submitted NMA; injection frequency based on naïve comparison.
Key limitations	• The comparative efficacy and safety of faricimab relative to other anti-VEGFs (i.e., aflibercept 2 mg, bevacizumab, ranibizumab) is uncertain owing to a lack of head-to-head trials and limitations with the sponsor's NMA. Indirect evidence submitted by the sponsor suggests that there may be little to no difference in best corrected visual acuity with faricimab compared to other anti-VEGFs administered using a flexible injection schedule. • The relative frequency of injections for faricimab and comparators is highly uncertain. Injection frequencies for faricimab and comparators in the sponsor's model were incorporated directly from clinical trials, without adjustment or accounting for differences in patient characteristics.
CADTH reanalysis results	There is insufficient clinical evidence to justify a price premium for faricimab relative to other currently available treatments for retinal vein occlusion.

ICER = incremental cost-effectiveness ratio; LY = life-year; NMA = network meta-analysis; QALY= quality-adjusted life-year; VEGF = vascular endothelial growth factor.

[a] Injection schedule beyond 6 months not specified in the Health Canada monograph.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the frequency of injections for faricimab and other anti-VEGFs is uncertain, the displacement of other anti-VEGFs by faricimab is uncertain, and the price of faricimab and other anti-VEGFs paid by the public drug plans is uncertain. In the absence of more reliable input values to estimate the key parameters of the BIA, the sponsor's base case was maintained. The sponsor estimates that reimbursing faricimab for the treatment of macular edema secondary to RVO will be cost-saving for the public drug plans; however, this result is highly sensitive to the relative injection frequency of faricimab and other anti-VEGFs as well as the prices paid by the public drug plans for each anti-VEGF. Whether there will be cost savings and the extent of any savings realized by the drug plans is highly uncertain, and will depend on which anti-VEGFs are displaced by faricimab, as well as the injection frequency and the confidentially negotiated price of each anti-VEGF.

CDEC Information

Members of the Committee:

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: December 18, 2024

Regrets:

1 expert committee member did not attend.

Conflicts of interest:

None