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Drug Class Update with New Drug Evaluation: Vascular Endothelial Growth Factor (VEGF) Inhibitors

Date of Review: April 2024

Date of Last Review: August 2020
Dates of Literature Search: 01/01/2020 - 02/01/2024
Brand Name (Manufacturer): Vabysmo (Genentech, Inc)
Dossier Received: yes

Generic Name: faricimab-svoa

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose for this class update is to evaluate new comparative evidence for vascular endothelial growth factor (VEGF) inhibitors and place in therapy for faricimab which was approved by the Food and Drug Administration (FDA) in 2022.

Plain Language Summary:

- VEGF is a protein produced by cells in the body that helps create new blood vessels. When cells produce too much VEGF, abnormal blood vessels can grow in the eye. These new blood vessels cause fluid accumulation (called macular edema) and damage to the retina of the eye leading to reduced vision and blindness.
- VEGF inhibitors are medicines injected into the eye that slow growth of blood vessels. VEGF inhibitors improve vision when macular edema or growth of new blood vessels is related to:
    - advanced age (called age-related macular degeneration)
    - diabetes or high blood sugar levels (called diabetic macular edema or diabetic retinopathy)
    - blocked blood vessels in the eye (called retinal vein occlusion)
    - changes in the shape of the eye (called myopic choroidal neovascularization)
    - premature birth in very small infants (called retinopathy of prematurity)
- There is no evidence that one specific VEGF inhibitor improves vision better than another. Studies usually evaluate vision over 1-2 years, but some have studied VEGF inhibitors up to 4 years.
- OHP will pay for VEGF inhibitors when prescribed and injected by a healthcare professional. We do not recommend any changes to the current policy.

Research Questions:

1. What is the comparative efficacy or effectiveness of VEGF inhibitors in people with macular edema related to ocular conditions?
2. What is the comparative safety of VEGF inhibitors in people with ocular conditions?

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3. Is there evidence to show that individual VEGF inhibitors are more effective or safe in certain populations of people (based on diagnoses, disease characteristics, or baseline visual acuity)?

Conclusions:

- Updated systematic reviews in neovascular age-related macular degeneration (AMD) and diabetic macular edema (DME) continue to demonstrate no clinical differences in best corrected visual acuity (BCVA) between VEGF inhibitors after 1 to 2 years.[1,2] Certainty in evidence ranged from moderate to low quality depending on the comparison and population.
- Faricimab is a new VEGF inhibitor approved in neovascular AMD, DME, and macular edema due to retinal vein occlusion. Faricimab was non-inferior to aflibercept for changes in BCVA based on results of 2 trials in each condition (moderate certainty evidence for retinal vein occlusion and low certainty evidence for AMD and DME). All trials evaluated efficacy within 1 year; and long-term data evaluating durability of response is currently lacking. Data was supported by phase 2 dose-finding studies evaluating faricimab to ranibizumab, which generally showed no difference in BCVA between therapies (insufficient evidence).
- Aflibercept was approved by the Food and Drug Administration (FDA) for retinopathy of prematurity (ROP) based on 2 open-label, non-inferiority RCTs comparing aflibercept to laser photocoagulation therapy.[3] Laser photocoagulation to cauterize and destroy abnormal blood vessels is one of the currently available treatment strategies in infants with retinopathy of prematurity and is preferred over cryotherapy because of better visual outcomes.[4] Compared to laser photocoagulation therapy, there was no difference in the proportion of infants without active retinopathy of prematurity at 1 year in either study (79.6% vs. 77.8%; mean difference [MD] 1.81% [95% confidence interval [CI] -15.7 to 19.3] and 78.7% vs. 81.6%; MD -1.88% [95% CI -17.0 to 13.2]; low certainty evidence).[3] However, confidence intervals were wide, and the analysis failed to meet pre-established criteria for non-inferiority of aflibercept (pre-specified as a difference of 5%). Neither trial demonstrated that aflibercept was superior or inferior to laser photocoagulation therapy.
- New formulations approved by the FDA include a ranibizumab port delivery system with administration every 6 months,[5] high-dose (8 mg) aflibercept administered every 8 to 16 weeks,[6] and 2 biosimilars of ranibizumab.[7,8]
- Evidence for safety outcomes related to use of VEGF inhibitors (including all-cause mortality, arterial thromboembolic events, and serious ocular events) was graded as low certainty. For people with DME, there was no difference in all-cause mortality or thromboembolic events compared to control therapies, but clinically relevant increases in safety outcomes could not be ruled out.[2] Evidence was limited by inconsistency and imprecision. In people with AMD, serious events and mortality was rare with no differences between VEGF inhibitors (low to very low certainty evidence).[1]
- FDA labeling for brolucizumab was updated to include risk for retinal vasculitis and retinal vascular occlusion.[9] Because of this risk, brolucizumab should not be administered more frequently than every 8 weeks.[9] Events appear to be immune mediated and correlate with increased intraocular inflammation. Compared to aflibercept, patients treated with brolucizumab every 8 to 12 weeks had a higher rate of intraocular inflammation (4% vs. 1%).[9] Trials evaluating every 4-week dosing of brolucizumab were discontinued early due to increased incidence of these serious adverse events.[10] Compared to aflibercept, patients with neovascular AMD treated with brolucizumab every 4 weeks had higher rates of inflammation (9.3% vs. 4.5%), retinal vasculitis (0.8% vs. 0%), and retinal occlusion (2% vs. 0%), and all-cause mortality (n=6, 1.7% vs. 0%).[10]

Recommendations:

- No PDL recommendations based on clinical evidence. After review of comparative costs in executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy

- Current evidence indicates that there is no clinically meaningful difference in BCVA between ranibizumab, bevacizumab, or aflibercept in patients treated for DME, neovascular AMD, or macular edema associated with retinal vein occlusion based on moderate to high quality evidence. There is moderate quality evidence that brolucizumab is non-inferior to aflibercept at 48 weeks based on BCVA in patients with neovascular AMD with limited long-term evidence beyond 2 years.
- There is low quality evidence of no difference in visual acuity between ranibizumab and bevacizumab for the treatment of myopic choroidal neovascularization.
- There is no difference in serious ocular events between ranibizumab, bevacizumab or aflibercept (low quality evidence). Evidence regarding comparative risk of thrombotic events and serious adverse effects with anti-VEGF agents is mixed, though higher quality observational studies and systematic reviews of RCTs failed to demonstrate any difference in cardiovascular events between agents. Overall, differences in rate of cardiovascular events or mortality between agents is likely small (moderate quality evidence).
- Bevacizumab is the current preferred product. All other VEGF inhibitors are non-preferred. The majority of claims are billed via medical claims and administered in a provider setting.

Background:

Vascular endothelial growth factor (VEGF) inhibitors are indicated for a wide variety of ocular conditions. FDA-approved indications differ between agents, but commonly include macular edema associated with diabetic retinopathy or retinal vein occlusion, neovascular AMD, and myopic choroidal neovascularization. In these diseases, vascular damage can trigger inflammatory responses, expression of VEGF, and formation of new blood vessels in the choroid layer of the eye located between the retina and sclera.[11,12] Accompanying features of choroidal neovascularization include sub-retinal exudation and hemorrhage, lipid deposits, retinal pigment epithelium detachment, and fibrotic scarring which cause progressive vision impairment and blindness.[11,12] Intraocular injections of VEGF inhibitors work to prevent vascular endothelial growth factor expression in late stage disease, thereby preventing further choroidal neovascularization and preserving vision in these populations.[11,12]

These ocular conditions are often categorized according to the type of retinal abnormalities present including presence or absence of neovascularization or macular edema. Macular edema is usually evaluated via optical coherence tomography. A larger central subfield thickness upon optical coherence tomography represents presence of macular edema and decreases in the central subfield thickness have been correlated with improvements in macular edema.

With presence of neovascularization or macular edema, VEGF inhibitors are typically indicated as a first-line treatment option. Guidelines from the American Academy of Ophthalmology (AAO) recommend VEGF inhibitors as first-line therapy for macular edema associated with branched or central retinal vein occlusion, neovascular AMD, and clinically significant DME associated with vision loss.[13] No recommendations are made for any specific agent. Similar guidelines are available from National Institute for Health and Care Excellence (NICE) which recommend VEGF inhibitors as first-line therapy for neovascular AMD, myopic choroidal neovascularization, and macular edema due to retinal vein occlusion or diabetes.[14-17] Alternative treatment options vary by condition and disease characteristics, but can include intraocular steroids, laser photocoagulation, and panretinal photocoagulation. In patients with other associated complications of diabetic retinopathy, these non-pharmacological options may be preferred or used in combination with VEGF inhibitors.[12,18] For example, panretinal photocoagulation is a laser treatment usually recommended for people with proliferative diabetic retinopathy or severe non-proliferative diabetic retinopathy to slow growth of new blood vessels.[12]

Recently, VEGF inhibitors have also been studied for treatment of retinopathy of prematurity (ROP). In premature infants, birth interrupts the normal development of vasculature in the eye.[4] As a result, VEGF is upregulated which can result in growth of new blood vessels, macular edema, and damage to the

eye.[4] Retinopathy of prematurity is most common in infants born at less than or equal to 30 weeks gestational age, infants with very low birth weight (<1500 g or about 3.3 lbs), or infants who need supplemental oxygen.[4] Disease is categorized based on location (zone 1 to 3 from the central to peripheral retina), pathologic changes (stage 0 to 5 with higher numbers indicating worsening involvement), and presence of abnormal (e.g., dilated or twisted) blood vessels in the posterior pole of the eye in at least 2 quadrants (plus [+] disease).[4] In about 90% of infants, retinopathy of prematurity is classified as mild disease which does not require treatment.[4] Prompt ablative treatment (usually laser photocoagulation within 72 hours) to destroy abnormal blood vessels is recommended by the American Academy of Pediatrics for the following groups:[4]

- Zone 1: stage 0-5+ disease
- Zone 1: stage 3 disease
- Zone 2: stage 2+ or 3+ disease

VEGF inhibitors used most commonly in practice in the United States (US) include bevacizumab, ranibizumab and aflibercept. Newer agents include brolucizumab and faricimab which were FDA approved in 2019 and 2022, respectively. See **Table 1** for a list of common ocular indications. While bevacizumab is not FDA-approved for any ophthalmic indications, there is a substantial body of evidence supporting off-label use.

Table 1. FDA-approved and compendia-supported ophthalmic indications for VEGF inhibitors

Generic Drug Name (Brand)	Neovascular AMD	Macular Edema Following RVO	Diabetic Retinopathy	DME	ROP	Myopic Choroidal Neovascularization
Aflibercept (Eylea®)	**FDA**	**FDA**	**FDA**	**FDA**	**FDA**	
Bevacizumab (Avastin®)	**compendia**	**compendia**	**compendia**	**compendia**	**compendia**	**compendia**
Brolucizumab (Beovu®)	**FDA**			**FDA**		
Faricimab (Vabysmo®)	**FDA**	**FDA**		**FDA**		
Ranibizumab (Lucentis®) and biosimilars (Cimerli®, Byooviz®)	**FDA**	**FDA**	**FDA***	**FDA***	**compendia**	**FDA**

Abbreviations: AMD = age related macular degeneration; DME = diabetic macular edema; FDA = Food and Drug Administration; RVO = retinal vein occlusion; ROP = retinopathy of prematurity

*Not FDA-approved for Byooviz®

In clinical trials, visual acuity changes are often evaluated using the Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR chart. The minimal clinically important difference referenced in the literature can vary, but a change of 5 letters (corresponding to 1 line on the chart or 0.1 logMAR) is typically considered to be the minimum clinically detectable change.[14] For many conditions, moderate visual gains or losses are defined as changes of at least 10 to 15 letters (corresponding to approximately 2-3 lines).[14] Many trials also report improvements in central subfield thickness or central retinal thickness as a secondary surrogate outcome. However, in changes in central retinal thickness may not correlate with changes in visual acuity.[19]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high

quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Age-related Macular Degeneration (AMD)

A 2022 AHRQ review evaluated the efficacy and safety of screening and treatments for impaired visual acuity in older adults.[1] The review was used to inform vision screening recommendations for the US Preventative Services Task Force. The review focused on uncorrected refractive errors, cataracts, and AMD and did not include screening for diabetic retinopathy.[1] RCTs comparing VEGF inhibitors to placebo, sham injection (use of a syringe without a needle pressed against the anesthetized eye) or active treatment with an alternative VEGF inhibitor were included. BCVA was the primary efficacy outcome evaluated by gain or loss of at least 15 ETDRS letters or having vision 20/200 or better (the current legal threshold for blindness in the US). Four RCTs (n=2086) compared a VEGF inhibitor (ranibizumab or pegaptanib) to sham injection over 1-2 years. After 1 year of treatment, use of VEGF inhibitors was associated with improved BCVA for the following outcomes:[1]

- gain in visual acuity of at least 15 letters (RR, 2.92, 95% CI 1.20 to 7.12, I2=76%; absolute risk difference [ARD] 10%),
- less than 15 letters of visual acuity loss (RR, 1.46, 95% CI 1.22 to 1.75, I2=80%; ARD 27%), and
- having vision 20/200 or better (RR, 1.47, 95% CI 1.30 to 1.66, I2=42%; ARD 24%).[1]

Results were comparable when evaluating ranibizumab or pegaptanib separately. Mean age in these trials ranged from 75 to 78 years and 54-68% of patients were female.[1] Mean baseline visual acuity was about 20/80 in 3 trials and most patients enrolled in the fourth study had a visual acuity between 20/40 and 20/200. Only one trial evaluated functional outcomes with ranibizumab at 2 years. Vision-related function and quality of life measures at 1 and 2 years had a small, but clinically significant, improvement with VEGF inhibitors compared to sham injection (8 points on a 0-100 point scale; published MCID of 4-6 points).[1] In a subgroup of people who were driving at baseline, there was also an increased likelihood that patients treated with ranibizumab 0.3 or 0.5 mg would continue to be driving after 2 years compared to sham injection (78-81% vs. 67%), though there was no difference in the subgroup of patients who were not driving at baseline.[1] Deaths and serious ocular adverse events were infrequently reported in these trials and were comparable between groups.[1] There was no difference compared to sham injection in the number of patients who withdrew due to adverse events.

This systematic review also evaluated evidence of newer VEGF inhibitors (aflibercept and brolucizumab) compared to older agents (ranibizumab or bevacizumab). Trials which compared brolucizumab and aflibercept did not meet prespecified inclusion criteria for the review and were excluded. Three trials were identified which compared aflibercept and ranibizumab.[1] Included patients were on average 73 to 79 years of age and 53-57% were female. Average baseline visual acuity was 20/80 for 2 studies and 20/50 in the third trial.[1] Patients were followed for 1-4 years. Dosing frequency varied among trials and included fixed monthly dosing, dosing every 8 weeks, or dosing at least every 12 weeks with frequency based on disease activity. After one year of treatment, aflibercept and ranibizumab had comparable improvement in BCVA outcomes:[1]

- gain in visual acuity of at least 15 letters (31.4% vs. 32%)
- less than 15 letters of visual acuity loss (94.9% vs. 94.3%)
- having vision 20/40 or better (35.2% vs. 35.1%).[1]

Both drugs also had comparable improvement in vision-related functional scores with an average improvement from baseline of 4.5 to 6.7 points (range 0-100) at 1 year. Change in BCVA remained similar between groups at 2 years. Deaths and serious adverse events were infrequently reported and comparable between groups.[1]

Diabetic Macular Edema (DME)

A 2023 update of a Cochrane review evaluated use of VEGF inhibitors for DME.[2] Previous Cochrane reviews on this topic have identified only small differences between VEGF inhibitors which did not achieve thresholds for clinically important differences in visual acuity.[2] The primary outcome for this review was BCVA between VEGF inhibitors at 24 months. Secondary outcomes of interest included BCVA at 12 months, gain of at least 3 ETDRS lines from baseline to 24 months, and change in central retinal thickness at 24 months. Safety outcomes included all-cause mortality, and arterial thromboembolic events and serious ocular adverse events at the longest available follow-up. Laser therapy, observation, sham procedures were used as control groups for safety outcomes. A systematic review of the literature through July 2022 identified 23 RCTs (n=3513) which met inclusion criteria.[2] Nine studies were industry sponsored, 7 were independent RCTs, and 2 were publicly funded. Only 9 RCTs maintained randomization at 2 years.[2] People included in these trials had DME with a mean central thickness of 460 microns and an average BCVA of 0.48 logMAR (Snellen equivalent of about 20/60) corresponding to moderate vision loss.[2] Most studies excluded participants with a central subfield thickness (CST) below 400 microns.[2] A difference of 0.1 logMAR (corresponding to one ETDRS line or 5 letters) was used for the minimum clinically important difference for non-inferiority trials.[2] On average, patients enrolled in trials received 7 to 10 injections per year (which is higher than many clinical settings).[2] In practice, many VEGF inhibitors are administered at longer dosing intervals for people with stable disease under a "treat and extend" protocol in which injections are given at increasingly extended intervals in people whose disease has remained stable.[20-23] VEGF inhibitors evaluated in RCTs included ranibizumab (n=13 RCTs), bevacizumab (n=5), aflibercept (n=6), brolucizumab (n=2) and faricimab (n=2). There was high or unclear risk of bias for random sequence generation (5 RCTs), allocation concealment (8 RCTs), blinding of patients and personnel (9 RCTs) or outcome assessment (9 RCTs), attrition bias (8 RCTs), and selective reporting (5 RCTs).[2] A network meta-analysis was conducted for efficacy outcomes. Statistical analyses demonstrated inconsistency (with difference in treatment effects for direct and indirect analyses) for the following comparisons: bevacizumab vs. ranibizumab for the outcome of BCVA at 24 months; aflibercept versus control for the outcome of all-cause mortality; for aflibercept and ranibizumab versus control and each other for arterial thromboembolic events.[2] No inconsistency was identified for other comparisons or outcomes.

- The median change in BCVA at 24 months was improved by -0.19 logMAR (8 RCTs) with no difference when comparing ranibizumab to aflibercept (moderate quality evidence), brolucizumab (low quality evidence), or bevacizumab (low quality evidence). A change of 0.1 logMAR typically corresponds to a change of 5 letters or 1 line on the ETDRS chart.[14] At 12 months compared to ranibizumab (20 RCTs), there were small differences in BCVA favoring faricimab (MD −0.08 logMAR, 95% CI −0.12 to −0.05), aflibercept (MD −0.07 logMAR, 95% CI −0.10 to −0.04), and brolucizumab (MD −0.07, 95% CI −0.10 to −0.03), but the average difference did not reach thresholds for minimum clinically important changes (moderate quality evidence).[2]
- Thirty-four percent of people treated with ranibizumab gained 3 or more ETDRS lines at 24 months with no difference compared to aflibercept (moderate quality evidence) or bevacizumab (low or very low quality evidence).[2] There was no data for comparisons of brolucizumab or faricimab at 24 months.
- Compared to control (e.g., laser therapy, observation, or sham procedures), there was no statistical differences in all-cause mortality with any VEGF inhibitor (20 RCTs; low quality evidence).[2] The average mortality in control groups was 1.8% at the longest available follow-up.[2] However, all trials of VEGF inhibitors demonstrated a trend toward increased mortality. While statistical analyses did not demonstrate increases in mortality, clinically relevant increases in mortality could also not be ruled out. Similarly, there was no difference in arterial thromboembolic events with VEGF inhibitors compared to control, but analyses were limited by inconsistency and imprecision (low to very low quality evidence for all VEGF inhibitors).[2] Serious ocular events were rare and definitions varied across trials. Endophthalmitis (related to intraocular injections) occurred in 0.24% to 0.8% of participants; vascular disorders, retinal vein occlusion, and retinal artery occlusion occurred on 0% to 0.54% of participants treated with VEGF inhibitors, and intraocular inflammation occurred in 0.12% to 2.72% of participants.[2] Overall, authors highlighted the need for additional long-term safety data.

Proliferative Diabetic Retinopathy

A 2023 Cochrane systematic review evaluated evidence of efficacy and safety of VEGF inhibitors for proliferative diabetic retinopathy.[24] The review evaluated literature through June 2022 and included RCTs of VEGF inhibitors compared to other active therapy (e.g., panretinal photocoagulation), sham treatment, or no treatment.[24] The review identified 23 RCTs (12 evaluating bevacizumab, 7 evaluating ranibizumab, and 1 evaluating aflibercept). [24] Most included studies had high or unclear risk of performance and detection bias due to blinding of participants and outcome assessors. Most trials also had unclear risk for selection bias from random sequence generation and allocation concealment.[24] Seven studies were industry funded and 11 did not report a funding source. The average age of participants was 56 years (range 48 to 77 years) and average HbA1c was 8.25 to 8.45%.[24] About half of studies enrolled participants with proliferative diabetic retinopathy and half included people with high-risk proliferative diabetic retinopathy.[24] The average follow-up period was 8 months, and all except 2 RCTs evaluated VEGF inhibitors in combination with panretinal photocoagulation compared to panretinal photocoagulation alone. Panretinal photocoagulation is a laser treatment recommended by the American Academy of Opthamology as a preferred option in people with high-risk proliferative diabetic retinopathy.[12,18] VEGF inhibitors with or without panretinal photocoagulation improved visual acuity compared to panretinal photocoagulation alone (MD -0.08 logMAR; 95% CI -0.12 to -0.04; moderate quality evidence), but differences were generally small corresponding to an average difference of 4 letters (95% CI 2.5 to 5 letters).[24] There was also moderate quality evidence that VEGF inhibitors reduced the need for additional laser photocoagulation (RR 0.18, 95% CI 0.11 to 0.28; I2=0%; 2 RCTs, 464 eyes; moderate-certainty evidence) or vitrectomy (RR 0.67, 95% CI 0.49 to 0.93; I2= 43%; 8 RCTs, 1248 eyes; low-certainty evidence) compared to panretinal photocoagulation.[24] Comparisons between VEGF inhibitors were not reported. All safety outcomes were graded as very low quality indicating substantial uncertainty in the treatment effect.[24]

Neovascular glaucoma

A 2020 Cochrane systematic review evaluated VEGF inhibitors for treatment of neovascular glaucoma.[25] Four RCTs (n=263) published prior to March 2019 were included in the review.[25] Trials compared bevacizumab, aflibercept, or ranibizumab as monotherapy in one study or combined with Ahmed valve implantation or panretinal photocoagulation in 3 studies. All studies used anti-glaucoma medications to control intraocular pressure. The primary outcome was control of intraocular pressure reported as the proportion of patients with intraocular pressure less than or equal to 21 mmHg.[25] No study reported changes in visual acuity. Trials were conducted in China, Brazil, Egypt and Japan. Two studies included participants with central retinal vein occlusion or proliferative diabetic retinopathy as the underlying cause of the neovascular glaucoma.[25] Heterogeneity in study designs precluded combination of results in a meta-analysis. Efficacy outcomes were graded with low certainty of evidence due to unclear risk of bias for most categories, inconsistency in treatment effects between studies, and imprecision.[25] Overall authors concluded that there is not enough evidence to determine whether adjunct use of VEGF inhibitors improve intraocular pressure in people with neovascular glaucoma compared to conventional glaucoma treatments.[25]

After review, 42 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., non-VEGF inhibitor), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

Since the last review, NICE has evaluated evidence and made recommendations for faricimab and brolucizumab for treatment of neovascular AMD and DME in 2020 and 2022.

- Brolucizumab and faricimab are recommended as treatment options for DME in adults when the eye has a central retinal thickness of 400 micrometers or more prior to treatment.[26,27] A review of available evidence demonstrated similar efficacy when compared to aflibercept. Indirect comparisons of these agents to ranibizumab also showed similar clinical effectiveness, although these results are less certain.[26,27]

- Brolucizumab and faricimab are recommended as treatment options for neovascular AMD when the patient meets the following criteria:[28,29]
    - The eye has a BCVA between 6/12 and 6/96 prior to treatment,
    - There is no permanent structural damage to the central fovea,
    - Lesion size is 12 disc areas or less, AND
    - There are recent signs of disease progression (e.g., visual acuity changes or blood vessel growth)
- Brolucizumab and faricimab should only be continued for patients with neovascular AMD if they maintain adequate response to therapy.[28,29] Discontinuation is recommended if there are persistent visual acuity changes or anatomical changes to the retina despite treatment which would indicate inadequate response. Recommendations were based on clinical trial evidence and network meta-analyses which demonstrated comparable net health benefits with these drugs versus aflibercept and ranibizumab.[28,29]

CADTH evaluated evidence and made recommendations for faricimab for treatment of neovascular AMD and DME in 2022.[30,31]

- Faricimab was recommended as an option for the treatment of neovascular AMD or DME when the patient is under the care of an ophthalmologist experienced in managing neovascular AMD or DME and when the cost does not exceed alternative VEGF inhibitors.[30,31] This recommendation was based on clinical trials which demonstrated non-inferiority to aflibercept in people with neovascular AMD (2 RCTs) and DME (2 RCTs). Phase 2 trials compared faricimab to ranibizumab in neovascular AMD, but study designs prevented definitive conclusions regarding comparative efficacy. Based on available evidence, it is unknown whether faricimab is associated with fewer injections than other VEGF inhibitors.[30,31]

New Formulations or Indications:

<u>New Formulations</u>

A new formulation of ranibizumab (SUSVIMO) was FDA approved in October 2021. This formulation is administered via a port delivery system in which a surgically planted, permanent, refillable ocular implant is used to deliver intraocular ranibizumab over 24 weeks. Approval was primarily based on a single, open-label, study comparing ranibizumab monthly injections to the port delivery system in patients with neovascular AMD who were previously responsive to a VEGF inhibitor (**Table 3**). Outcomes were evaluated at 36-40 weeks after at least one refill of the port delivery system (at 24 weeks). Subsequent results were published with about 2 years of follow-up, and results were supported by a smaller phase 2, dose-finding, study. The port delivery system met prespecified margins for non-inferiority and equivalence compared to ranibizumab monthly injections.[32] In November 2022, a voluntary recall was issued for SUSVIMO due to manufacturing issues associated with the port delivery system resulting in leaking of the drug after injection and/or repeated dosing (**Table 2**). The timeframe for resolution of these manufacturing issues is unknown at this time.

Since the last review, 2 biosimilars have been approved for ranibizumab. BYOOVIZ (ranibizumab-nuna) was approved by the FDA in September 2021 and has indications for treatment of neovascular AMD, macular edema associated with retinal vein occlusion and myopic choroidal neovascularization. CIMERLI (ranibizumab-eqrn) was approved by the FDA in August 2022 for neovascular AMD, DME, diabetic retinopathy, macular edema associated with retinal vein occlusion and myopic choroidal neovascularization. CIMERLI is interchangeable with the originator product (LUCENTIS).[7]

A new dosage form of aflibercept (EYLEA HD®) was FDA approved in August 2023 for indications of AMD, DME, and diabetic retinopathy.[6] The recommended dosing regimen is 8 mg intravitreal injection every 4 weeks for the first 3 weeks followed by maintenance injections once every 8 to 16 weeks in people with AMD or DME and every 8 to 12 weeks for people with diabetic retinopathy.[6] Approval was based 2 multi-center, double-blind non-inferiority RCT in patients with AMD and DME (PULSAR and PHOTON) which evaluated 3 maintenance regimens of aflibercept: 8 mg every 12 weeks, 8 mg every 16 weeks, and 2 mg every 8 weeks. In patients receiving treatment every 12 or 16 weeks, dose interval could be increased to every 8 weeks based on pre-specified visual and anatomic

criteria. In people with AMD, the average number of doses administered was 5.2 for patients randomized to treatment every 16 week group, 6.1 injections for patients in the 12 week group, and 6.9 injections for patients in the 8 week group.[6] At 48 weeks, both groups randomized to 8 mg doses met non-inferiority criteria for BCVA (4 ETDRS letters) compared to patients given 2 mg every 8 weeks (MD of -1.0 letters, 95% CI -2.9 to 0.9 for 8 mg every 12 weeks and MD of -1.1 letters, 95% CI -3.0 to 0.7 for 8 mg every 16 weeks.[6] The chosen non-inferiority margin was within the minimum clinically important difference referenced in the literature (5 ETDRS letters). Non-inferiority was also achieved in people with DME. Compared to aflibercept 2 mg every 8 weeks, aflibercept 8 mg every 12 weeks (MD -0.6, 95% CI -2.3 to 1.1) and aflibercept 8 mg every 16 weeks (MD -1.4, 95% CI -3.3 to 0.4) had similar changes in visual acuity at 48 weeks.[6]A key secondary outcome for people with DME was the proportion of patients with at least a 2 step improvement in DRSS score at 48 weeks (with a non-inferiority margin of 10%). The proportion of people with a 2 step improvement in DDRS score was similar for people treated with aflibercept 2 mg every 8 weeks (27%) and aflibercept 8 mg every 12 weeks (29%; MD 2%, 95% CI -6.6 to 10.6) but not aflibercept 8 mg every 16 weeks (20%; MD -8%, 95% CI -16.9 to 1.8).[6] Thus, for people with diabetic retinopathy, maintenance dosing every 16 weeks is not included in the FDA label.

New Indications

Brolucizumab for DME

In May 2022, brolucizumab was FDA approved for the treatment of DME based on results from 2, phase 3 trials which compared treatment to aflibercept (KITE and KESTREL).[33] Brolucizumab was previously approved for AMD. Loading doses of brolucizumab were studied every 6 weeks for 5 doses (compared to 3 doses studied for AMD) before switching to maintenance administration every 8-12 weeks.[33] Aflibercept loading doses were given every 4 weeks for 5 doses, then every 8 weeks. The primary outcome was BCVA at 52 weeks. Enrolled patients had an HbA1c of less than or equal to 10%, BCVA between 78 and 23 ETDRS letters (~20/32 to 20/320 Snellen equivalent), and central-involved DME based on a central subfield thickness of at least 320 µm at screening.[33] Patients were excluded if they had active proliferative diabetic retinopathy, had recent intraocular steroid treatment or any prior VEGF treatment.[33]

Multiple methodological limitations limit interpretation of results in these studies. Sham injections were used to mask treatment groups when study treatments were administered at different times.[33] However, patients can often determine when they are receiving a sham injection which may lead to unmasking of treatment groups and increase risk of performance bias, particularly for outcomes like BCVA which are dependent on patient effort. A different masked investigator administered outcome and disease activity assessment. Missing or censored data was imputed using a last observation carried forward methodology and slightly more patients discontinued treatment in brolucizumab 6 mg groups compared to aflibercept in each study (18.5% vs. 13.4% and 19% vs. 16%).[33] This could result in an overestimation of the treatment effect. Non-inferiority analysis was performed using all enrolled patients which may bias groups toward no difference.[33] There were slight imbalances in baseline characteristics which increases risk of selection bias. In KITE, mean BCVA at baseline was slightly lower in aflibercept treatment group (63.7 vs. 66 ETDRS letters).[33] Patients randomized to brolucizumab were also more commonly male (67% vs. 63.5%), had an HbA1c over 7.5% (54.2% vs. 47%), and had a lower incidence of subretinal fluid (31.3% vs. 37%). In KESTREL, patients randomized to brolucizumab 6 mg were slightly younger (mean 62 vs. 64 years), less commonly male (58% vs. 67%), had a HbA1c of at least 7.5% (60% vs. 43%), and had a lower average central subfield thickness at baseline (453 vs. 476 µm).[33]

Brolucizumab 6mg was non-inferior to aflibercept for mean BCVA at 52 weeks in both studies (9.2 vs. 10.5 ETDRS letters; MD-1.3 [95% CI -2.9 to 0.3] and 10.6 vs. 9.4 ETDRS letters; MD 1.2 [95% CI -0.6 to 3.1]).[33] The non-inferiority margin (4 ETDRS letters) was also achieved for the key secondary endpoint which evaluated average change in BCVA over 40-52 weeks.[33] The proportion of patients who gained at least 15 letters or reached a BCVA of 84 letters was comparable in one study (37% vs. 39%) and improved with brolucizumab treatment in KITE compared to aflibercept (46.4% vs. 37.6%).[33] However, results in KITE may have been influenced by imbalances in baseline characteristics as there were a greater proportion of patients randomized to brolucizumab with a higher visual acuity compared to the aflibercept group (45.8% in brolucizumab group with a BCVA ≥ 70 letters at baseline vs. 32% with aflibercept).[33] Overall rates of serious ocular

adverse events were infrequent and similar between groups (1.1 to 2.2%).[33] Rates of intraocular inflammation occurred more frequently with brolucizumab compared to aflibercept in KESTREL (3.7% vs. 0.5%) and at similar rates in KITE (1.7% in each group).[33] Retinal artery occlusion and endophthalmitis were infrequent and occurred at similar rates between groups.

Aflibercept for Retinopathy of Prematurity (ROP)

In February 2023, aflibercept was FDA approved for retinopathy of prematurity.[3] FDA approval was based on 2, open-label, non-inferiority RCTs comparing aflibercept to laser photocoagulation therapy (BUTTERFLEYE [n=120] and FIREFLEYE [n=113]). FIREFLEYE enrolled participants in Europe, Asia, and South America.[34] BUTTERFLEYE was completed in 2022 and enrolled participants in the United States, South America, Europe, and Asia but remains unpublished.[35] Aflibercept 0.4 mg was administered up to three times in each eye with at least 28 days between injections.[3] Rescue therapy could be provided based on pre-specified criteria. In BUTTERFLEYE, 18.5% of infants randomized to laser photocoagulation and 15.1% of participants randomized to aflibercept received rescue therapy from baseline to 52 weeks.[35] In FIREFLEYE, rescue therapy was administered for 12.5 % and 8.2% of infants randomized to laser photocoagulation and aflibercept, respectively.[34] In people treated with aflibercept, 92% received injections in both eyes.[3] Pre-term infants enrolled in the study had a max gestational birth of 32 weeks, max birth weight of 1500 g (about 3.3 lbs) and weighed at least 800 g on the day of treatment.[3] Retinopathy of prematurity was defined according to international guidelines and could include zone 1 (stage 1+, 2+, 3, or 3+), zone 2 (stage 2+ or 3+), or aggressive posterior retinopathy of prematurity.[3] Zone 1 is defined as the innermost zone of the retina around the optic disc and is more likely to progress and become more severe than retinopathy of prematurity in zone 2 (which is a more peripheral retinal zone).[34] Advanced stages of retinopathy of prematurity with complete or partial retinal detachment were excluded (stage 4 and 5) and retinopathy of prematurity only involving zone 3 were excluded.[35] Participants were on average 10 weeks old at enrollment. In BUTTERFLEYE, 26% had zone 1 involvement.[35] In FIREFLEYE, 20% had zone 1 involvement, and aggressive posterior retinopathy of prematurity was present in 13 and 19% of members in the aflibercept and laser groups, respectively.[34]

The primary outcome was absence of active retinopathy of prematurity or unfavorable structural ocular outcomes (such as retinal detachment, macular dragging, macular fold, or retrolental opacity) at 1 year.[3] The non-inferiority margin was pre-specified at 5%.[34] For infants who received bilateral treatment, both eyes were required to meet the primary endpoint. Compared to laser photocoagulation therapy, there was no difference in the proportion of people without active retinopathy of prematurity at 1 year in either study (79.6% vs. 77.8%; MD 1.81% [95% CI -15.7 to 19.3] and 78.7% vs. 81.6%; MD -1.88% [95% CI -17.0 to 13.2]).[3] However, the analysis failed to meet pre-established criteria for non-inferiority of aflibercept compared to laser photocoagulation therapy. Neither trial demonstrated that aflibercept was superior or inferior to laser photocoagulation therapy.[3]

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Ranibizumab[5]	SUSVIMO	April 2022	Warnings/ Precautions	Septum dislodgement, implant damage where the septum has dislodged into the implant body, has been reported in clinical trials. During administration, avoid twisting and/or rotating the refill in order to minimize risk of septum dislodgement. Manufacturer labeling recommends evaluation by dilated slit lamp exam and/or dilated indirect ophthalmoscopy to evaluate whether septum dislodgement has occurred.

				Voluntary recall issued November 2022 related to manufacturing of the seal on the port delivery system which could result in leaking after injection and/or repeated dosing.
Brolucizumab-dbbl[9]	BEOVU	2020-2022	Warnings/ Precautions	Retinal Vasculitis and/or Retinal Vascular Occlusion have occurred in post-marketing studies and subsequent phase 3 clinical trials following administration of brolucizumab. These events are immune-mediated, have typically occurred in the presence of intraocular inflammation, and can occur after the first injection. Patients with intraocular inflammation should be closely monitored and treatment discontinuation is recommended if retinal vasculitis or vascular occlusion occurs.[9] In clinical trials of patients treated with brolucizumab every 8-12 weeks, intraocular inflammation occurred in 4% of patients with AMD and 2% of patients with DME compared to 1% with aflibercept.[9] Compared to aflibercept, patients with neovascular AMD treated with brolucizumab every 4 weeks had higher rates of inflammation (9.3% vs. 4.5%), retinal vasculitis (0.8% vs. 0%), and retinal occlusion (2% vs. 0%).[10] Trials evaluating every 4 week dosing were discontinued early due to increased incidence of these serious adverse events (see **Table 3**). Overall incidence of events for patients treated every 4 weeks was more common than studies of patients treated every 8 or 12 weeks. Based on these trials labeling was updated to specify that doses for maintenance treatment should not occur more frequently than every 8 weeks.[9]

Randomized Controlled Trials:

A total of 427 citations were manually reviewed from the initial literature search. After further review, 421 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., non-VEGF inhibitor), or outcome studied (e.g., non-clinical). The remaining 6 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr><td>1. Khanani, et al. 2022.[10]

MERLIN NCT03710564

MC, DB, NI, phase 3 RCT</td><td>1. Brolucizumab 6 mg every 4 weeks (n=356)
2. Aflibercept 2 mg every 4 weeks (n=179)

*Intensive dose regimen (FDA labeled dose is brolucizumab 6 mg every 6 weeks for 5 doses then</td><td>Patients ≥50 years of age who had active CNV secondary to neovascular AMD and persistent fluid affecting the central subfield despite prior treatment with VEGF inhibitors. Patients</td><td>Mean change in BCVA at 52 weeks (non-inferiority margin 4 ETDRS letters)</td><td>Change in BCVA from baseline to week 52
1. 0.3 letters (SE 0.44)
2. 0.9 letters (SE 0.62)
MD -0.6 ETDRS letters (95% CI -2.1 to 0.9); non-inferiority margin met

BCVA gain or loss from baseline to week 52
<table>
<tr><th></th><th>Gain ≥ 15 letters</th><th>Loss ≥ 15 letters</th></tr>
<tr><td>1.</td><td>16.9%</td><td>4.8%</td></tr>
<tr><td>2.</td><td>17.4%</td><td>1.7%</td></tr>
</table>
</td></tr>
</table>

<table>
<tr>
<td>Duration: 104 weeks

Early study termination after 52 weeks</td>
<td>every 8-12 weeks and aflibercept 2 mg every 4 weeks for 5 doses then every 8 weeks)</td>
<td>had BCVA of ≥ 55 letters (about ≥ 20/80).

Patients with active intraocular inflammation or infection were excluded.</td>
<td></td>
<td>
<table>
<tr><td>MD</td><td>-0.5% (95% CI -9.5 to 8.4)</td><td>3.1% (95% CI -5.9 to 12.1)</td></tr>
</table>
Intraocular inflammation
1. 33 (9.3%)
2. 8 (4.5%)

Study terminated early due to increased incidence of adverse events with brolucizumab including serious ocular events, intraocular inflammation, retinal vasculitis and retinal vascular occlusion. All-cause mortality also occurred in more patients receiving brolucizumab compared to aflibercept (n=6, 1.7% vs. 0%).
</td>
</tr>
<tr>
<td>Vader, et al. 2020.[36]

BRDME Study NCT01635790

MC, DB, NI, RCT

Duration: 26 weeks</td>
<td>1. Bevacizumab 1.25 mg (n=86) every 4 weeks
2. Ranibizumab 0.5 mg (n=84) every 4 weeks

N=170</td>
<td>Adults with DME with HbA1c ≤12%, CST ≥ 325 µm and BCVA of 24-78 ETDRS letters

Location: Netherlands from June 2012 to February 2018</td>
<td>Change in BCVA at 6 months (non-inferiority margin of -3.5 ETDRS letters)</td>
<td>Change in BCVA at 6 months
1. 4.9 (SD 6.7)
2. 6.7 (SD 8.7)
Lower bound of 90% CI was -3.626. Non-inferiority was not achieved.</td>
</tr>
<tr>
<td>Singh, et al. 2023.[37]

KINGFISHER; NCT03917472

MC, DB, NI, phase 3 RCT

Duration: 52 weeks</td>
<td>1. Brolucizumab 6 mg every 4 weeks*
2. Aflibercept 2 mg every 4 weeks*

N = 517

*Intensive dose regimen (FDA labeled dose is brolucizumab 6 mg every 6 weeks for 5 doses then every 8-12 weeks and aflibercept 2mg every 4 weeks for 5 doses then every 8 weeks)</td>
<td>Adults with DME with HbA1c ≤12% and not treated with a VEGF inhibitor within 3 months. Participants excluded if they had stroke or myocardial infarction in the prior 6 months, ocular disorders, or uncontrolled glaucoma

Location: Hungary, Israel, Slovakia, and the US from September 2019 to March 2020.</td>
<td>Change in BCVA at 52 weeks (NI margin of -4 ETDRS letters)</td>
<td>Change in BCVA at 6 months
1. 12.2 letters
2. 11.0 letters
MD 1.1 letters; 95% CI,−0.6 to 2.9
p < 0.001 for non-inferiority; p = 0.10 for superiority
Brolucizumab 6 mg every 4 weeks was non-inferior but not superior to aflibercept 2 mg every 4 weeks.

BCVA gain or loss from baseline to week 52
<table>
<tr><td></td><td>Gain ≥15 letters or BCVA ≥84 letters</td><td>Loss ≥15 letters (at any visit)</td></tr>
<tr><td>1.</td><td>43.6%</td><td>3.2%</td></tr>
<tr><td>2.</td><td>40.4%</td><td>2.9%</td></tr>
<tr><td>MD</td><td>5.5% (95% CI -2.7 to 14.3)</td><td>NR</td></tr>
</table>
Safety
<table>
<tr><td></td><td>Serious Ocular AEs</td><td>Intraocular inflammation</td></tr>
<tr><td>1.</td><td>0.9%</td><td>14 (4.0%)</td></tr>
<tr><td>2.</td><td>0%</td><td>5 (2.9%)</td></tr>
</table>
</td>
</tr>
</table>

				All 13 injections were given for 55% of the brolucizumab group and 55% of the aflibercept group. Protocol deviations due to COVID-19 pandemic (primarily missed visits) were noted for ~25% of people in each group.
Jhaveri, et al. 2022.[38] PROTOCOL AC NCT03321513 MC, DB, NI, RCT Duration: 2 years	1. Aflibercept 2mg every 4 weeks for 1 year then every 4-16 weeks as needed 2. Bevacizumab 1.25 mg every 4 weeks for 1 year then every 4-16 weeks as needed After 12 weeks patients in the bevacizumab group could switch to aflibercept based on pre-specified criteria including persistent DME, visual acuity change of <5 letters, change in central subfield thickness of <10%, and visual acuity below 20/50 at 24 weeks or later N = 270 (312 eyes)	Adults with DME and visual acuity of 20/320 to 20/50 Location: 54 sites in the US between December 2017 and November 2019	Change in BCVA (time-averaged over 2 years); NI margin 3.5 letters	BCVA at 2 years 1. 15.0 (SD 8.5) letters 2. 14.0 (SD 8.8) letters MD 0.8 letters, 95% CI -0.9 to 2.5, p=0.37 70% of people who started bevacizumab met pre-defined criteria and switched to aflibercept over 2 years. 30% of people prescribed aflibercept met pre-defined criteria and continued treatment. Serious AE 1. 52% 2. 36% Hospitalization for AE 1. 48% 2. 32%
Regillo, et al. 2023.[39] Holekamp, et al. 2022.[40] ARCHWAY NCT03677934 MC, NI, OL, phase 3, RCT Duration: 2 years	1. Ranibizumab port delivery system, filled every 24 weeks (n=248) 2. Ranibizumab 0.5 mg injections every 4 weeks (n=167) N=415	Adults with neovascular AMD diagnosed within 9 months and with prior treatment response to VEGF inhibitors Location: 78 sites in the US from September 2018 to June 2021	Change in BCVA at 36-40 weeks (9 months) and 88 to 92 weeks (1.7 years); NI margin of 3.9 ETDRS letters	BCVA at 36-40 weeks 1. 0.2 (SE 0.5) ETDRS letters 2. 0.5 (SE 0.6) ERDRS letters MD -0.3 ETDRS letters (95% CI -1.7 to 1.1) BCVA at 88 to 92 weeks 1. -1.1 (SE 0.61) ETDRS letters 2. -0.5 (SE 0.75) ETDRS letters MD -0.6 ETDRS letters (95% CI -2.5 to 1.3)

Vader, et al. 2020.[41] NCT01635803 DB, NI, MC, RCT Duration: 6 months	1. Bevacizumab 1.25 mg every 4 weeks (n=139) 2. Ranibizumab 0.5 mg every 4 weeks (n=138)	Adults with macular edema secondary to branch, hemi or central RVO Location: The Netherlands from June 2012 to February 2018	Change in BCVA at 6 months (NI margin of 4 letters)	Change in BCVA 1. 15.3 (SD 13.0) ETDRS letters 2. 15.5 (SD 13.3) ETDRS letters Lower bound of 90% CI was -1.724. Non-inferiority criteria were met.

Abbreviations: AE = adverse events; AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CI = confidence interval; CNV = choroidal neovascularization; CST = central subfield thickness; DB = double blind; DME = diabetic macular edema; ETDRS = early treatment diabetic retinopathy study; FDA = Food and Drug Administration; HbA1c = hemoglobin A1c; MC = multicenter, MD = mean difference; NI = non-inferiority; OL = open label; RCT = randomized controlled trial; RVO = retinal vein occlusion; SD = standard deviation; SE = standard error; US = United States; VEGF = vascular endothelial growth factor

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Faricimab was approved by the FDA in 2022 for the treatment of neovascular AMD, DME, and macular edema following retinal vein occlusion. Approval for each condition was based on 2 identically designed, phase 3 trials comparing faricimab to aflibercept with supporting data from phase 2 trials comparing faricimab to ranibizumab in AMD[42,43] and DME.[44] Clinical outcomes focused on improvements in BCVA after about 1 year of treatment for AMD and DME and after 6 months for people with retinal vein occlusion.

Faricimab is a monoclonal antibody with a dual mechanism of action. It inhibits both VEGF and Ang-2. The effect of Ang-2 inhibition on macular edema has yet to be established. In AMD and DME, trials evaluated dosing as needed based on disease activity for faricimab, but the comparator, aflibercept, was only evaluated at fixed dosing every 8 weeks. Studies were not designed to compare faricimab to treat-and-extend dosing for aflibercept, and conclusions regarding less frequent dosing of faricimab compared to aflibercept cannot be made.[45] Because currently available studies were not designed to evaluate dosing frequency compared to an appropriate comparison regimen, it is not clear if Ang-2 inhibition has any effect on the durability of therapy in these conditions.[45] Fixed monthly dosing was evaluated in people with macular edema due to retinal vein occlusion. In AMD and DME, the FDA approved dose for faricimab is 6 mg given every 4 weeks for at least the first 4 doses then frequency of injections is determined based on treatment response.[46] In patients with AMD, dose frequency could be adjusted every 8, 12, or 16 weeks based on optical coherence tomography and visual acuity evaluations.[46] In patients with DME, dose could be adjusted as needed to regimens every 4, 8, 12, or 16 weeks based central subfield thickness (CST) and visual acuity evaluations. Some patients with active disease may need more frequent dosing every 4 weeks.[46] Fixed monthly dosing for up to 6 months is recommended in people with macular edema due to retinal vein occlusion as there is no comparative data for treat-and-extend regimens.[46]

In both phase 3 trials, patients were randomized with adequate methods and allocation concealment with baseline characteristics generally well balanced between groups. Risk of performance and detection bias was high in trials for AMD and DME due to unblinding. Because frequency of administration differed between groups, patients and providers were blinded with use of sham injections (use of a syringe without a needle pressed against the anesthetized eye). However, often patients can identify if they are receiving a sham injection, which likely led to unblinding of groups at 16 to 24 weeks. Unblinded groups is of particular concern for outcomes such as BCVA where patient effort may significantly impact results. The method of blinding was not reported in clinical trials evaluating retinal vein occlusion leading to unclear risk for performance bias.

Major limitations in the evidence include lack on long-term data to evaluate durability of response or safety beyond one year. There is limited data comparing faricimab to other VEGF inhibitors or comparing faricimab to other treatment regimens of aflibercept. Phase 2 studies comparing faricimab to ranibizumab had small sample sizes with generally high or unclear risk of bias which limits ability to draw conclusions in efficacy or safety.

Diabetic Macular Edema

In phase 3 trials for DME, patients were required to have center-involving DME with central subfield thickness of at least 325 µm and BCVA 25-73 ETDRS letters (approximate Snellen equivalent of 20/320 to 20/40).[47] Patients were excluded if they had an A1C greater than 10%, were recently initiated on DM treatment, had blood pressure over 180/100 mmHg, or had a stroke or MI in the previous 6 months. Patients with a variety of other ocular conditions were also excluded. About 38% and 44% of patients screened for these trials were excluded.[47] Some of the most common reasons for exclusion were retinal complications (such as presence of tractional retinal detachment, pre-retinal fibrosis and epiretinal membrane; 6-8%), failure to meet BCVA criteria (7-8%), and failure to meet central subfield thickness criteria for macular thickening of the central fovea (7-8%).[47] The majority of patients enrolled were White (77-81%), had DM that was reasonably well-controlled (average HbA1c 7.6 to 7.7%), and were treatment naïve (76-80%).[47] A little more than half of patients did not have diabetic retinopathy or had diabetic retinopathy that was questionable upon exam. Average BCVA at baseline was 62 letters, and average central subfield thickness was 466-492 µm.[47]

Average improvement in BCVA In patients with DME after 1 year was similar upon comparison of aflibercept and faricimab (average gain of 10-12 letters).[47] About one-third of patients (29-35%) had a gain of 15 or more ETDRS letters which was comparable between groups.[47] In the group of patients with faricimab dose adjusted based on disease activity, a little over 50% of patients were receiving treatment every 16 weeks, 20% had dosing every 12 weeks, and 15% were on faricimab every 8 weeks.[47] A smaller, phase 2 trial comparing faricimab and ranibizumab in treatment-naïve patients demonstrated similar magnitude of benefit with an average gain of 13.9 ETDRS letters (80% CI 12.2 to 15.6) at 24 weeks with faricimab 6 mg monthly compared to 10.3 ETDRS letters (80% CI 8.8 to 11.9) with ranibizumab monthly (MD 3.6 letters; 80% CI 1.5 to 5.6).[44] Difference in BCVA did not achieve MCIDs referenced in the literature (5 ETDRS letters or approximately 1 line on the Snellen chart), and data were limited by imbalances in baseline characteristics and lack of methodological reporting for masking treatment groups. Results from these trials are generally applicable to patients with early disease and diabetes that is relatively well-controlled. The majority of patients had never received treatment for DME and had an average BCVA of 62 letters. Patients with retinal complications or DME which didn't involve the central fovea were excluded. Despite the fact that diabetes affects a large number of populations and communities that have been most impacted by historic and contemporary injustices and health inequities, people who identified as races other than white were underrepresented in these trials. Of patients with diabetes, population studies show that diabetic retinopathy is more prevalent in people of African or Asian or descent compared to patients identifying as White.[48] However, in these trials, only 8-11% identified as Asian and 4-8% identified as black.[47]

Age-related Macular Degeneration

In phase 3 trials for AMD, enrolled patients were at least 50 years of age and had treatment-naïve neovascular AMD with active choroidal neovascularization with a subfoveal component (involving the central portion of the macula).[49] Lesion size was required to be less than 9 disc areas, and choroidal

neovascularization component area had to be less than 50% of the total session size.[49] Patients were excluded if they had uncontrolled blood pressure greater than 180/100 mmHg or uncontrolled glaucoma, or other eye conditions related to choroidal neovascularization or macular pathology. Patients with recent stroke, cancer, cataract surgery, or a history of uveitis were also excluded. The most common reasons for exclusion were lack of subfoveal involvement, inability to meet choroidal neovascularization lesion characteristics, BCVA outside of specified range (24-78 ETDRS letters), or the patient met other ocular exclusion criteria.[49]

Patients enrolled in the phase 3 trials were on average 75-76 years of age.[49] Most patients identified as White (83-90%); 8-11% identified as Asian and 8-14% identified Hispanic.[49] AMD is generally more common in patients who are White. This is generally representative of disease prevalence estimates. More than half of patients and average BCVA was 59-61 letters were within 1 month of diagnosis. Most patients had presence of intra-retinal (43-47%) or subretinal fluid (65-68%). After 40-48 weeks, about 45-46% of patients in the faricimab group were receiving treatment every 16 weeks. About 33-34% of patients received faricimab every 12 weeks.[49]

There was no difference between faricimab and aflibercept for the primary outcome (change in BCVA) at 40 to 48 weeks in both trials.[49] Average improvement from baseline was 5-7 ETDRS letters for both groups.[49] Similarly there was no difference in the proportion of patients gaining 15 or more ETDRS letters. The proportion of patients with a gain of 15 or more ETDRS letters was 20% for faricimab and 15.7% for aflibercept (MD 4.3% [95% CI −1.6 to 10.1]) in the first trial and 20% for faricimab and 22% for aflibercept (MD −2.0% [95% CI −8.3 to 4.3]) in the second trial.[49] Two phase 2 trials evaluated faricimab every 4, 12, or 16 weeks compared to ranibizumab 0.5 mg every 4 weeks.[42,43] Both trials recruited similar patients as phase 3 trials. Data from phase 2 trials were limited by small sample sizes, imbalances in baseline characteristics, and unclear reporting of trial methods. However, results are generally supportive of magnitude of benefit observed in phase 3 trials. In both trials, the average change in BCVA from baseline to 36 or 40 weeks was similar upon comparison of ranibizumab and faricimab at FDA approved doses (about 6-8 ETDRS letters in one trial and 9-12 letters in the second trial).[42,43]

<u>Macular edema due to retinal vein occlusion</u>

Phase 3 RCTs evaluating retinal vein occlusion enrolled participants with center-involved macular edema due to branched, central or hemi-retinal vein occlusion.[50] Participants were newly diagnosed with macular edema (within the past 4 months) and were excluded if they had prior treatment for macular edema. Other exclusion criteria included uncontrolled blood pressure, history of other systemic or ocular disease, macular neovascularization, or vitreomacular-interface abnormalities.[50] Participants were on average 65 years of age and primarily identified as white, Asian or Hispanic; other races were under-represented. The average BCVA at baseline was 50 and 57 ETDRS letters in each trial and participants were required to have a central subfield thickness of at least 325 µm.[50]

A 6 months, BCVA was improved by an average of 17 ETDRS letters with no difference between aflibercept 2 mg or faricimab 6 mg every 4 weeks in both RCTs.[50] Faricimab met the pre-specified non-inferiority margin of 4 ETDRS letters.[50] Similarly there was no difference between groups in the proportion of patients gaining 15 or more ETDRS letters. In each trial, 56.1% and 56.6% of patients treated with faricimab gained at least 15 ETDRS letters compared to 60.4% and 58.1% of patients treated with aflibercept.[50] In people with retinal vein occlusion, there is no comparative data on treat-and-extend dosing intervals with faricimab or comparative data beyond 6 months.

Clinical Safety:

In clinical trials, the most common adverse effects in patients receiving faricimab were cataracts and conjunctival hemorrhage.[46] Incidence of adverse events varied depending on the population studied (**Table 4**). Like other VEGF inhibitors, warnings and precautions in the labeling for faricimab include risk for

endophthalmitis and retinal detachments, increases in intraocular pressure, thromboembolic events, retinal vasculitis and retinal vascular occlusion.[46] Faricimab is contraindicated in people with periocular infection or intraocular inflammation.[46]

Based on the mechanism of action, faricimab may impact reproductive capacity and embryo-fetal development.[46] Use of an effective contraceptive is recommended for anyone with reproductive potential during therapy and for at least 3 months following the last dose. In animals studies, an increased risk of pregnancy loss was observed with intravenous exposure at 158 times the recommended human dose of 6 mg monthly.[46]

Table 4. Adverse events occurring in more than 1% of patients during phase 3 clinical trials[46]

	Faricimab			Aflibercept		
	AMD N=664	DME N=1262	RVO N=641	AMD N=662	DME N=625	RVO N=635
Cataracts	3%	15%	<1%	2%	12%	1%
Conjunctival hemorrhage	7%	8%	3%	8%	7%	4%
Vitreous detachment	3%	5%	2%	3%	4%	2%
Vitreous floaters	3%	4%	2%	2%	3%	2%
Retinal pigment epithelial tear	3%	0%	0%	1%	0%	0%
Intraocular pressure increased	3%	4%	1%	2%	3%	3%
Eye pain	3%	3%	<1%	3%	3%	<1%
Intraocular inflammation	2%	1%	1%	1%	1%	<1%

Abbreviations: AMD = age-related macular edema; BCVA = best corrected visual acuity; DME = diabetic macular edema; RVO = retinal vein occlusion

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Visual acuity
2) Quality of life
3) Function (e.g., ability to drive, read, perform activities of daily living, etc)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change in best corrected visual acuity (BCVA)

Table 5. Pharmacology and Pharmacokinetic Properties.[46]

Parameter	
Mechanism of Action	Inhibitor of angiopoietin 2 and vascular endothelial growth factor-A which promotes vascular stability, decreases vascular leakage, and prevents inflammation
Oral Bioavailability	Not applicable
Distribution and Protein Binding	C_{max} of about 0.2 mcg/mL in plasma at 2 days post-dose Mean plasma free trough concentrations of 0.02-0.03 mcg/mL for every 4-week dosing
Elimination	Not fully characterized; expected to be renally eliminated

Half-Life	7.5 days
Metabolism	Not fully characterized; expected to be catabolized into small peptides and amino acids which are renally eliminated

Table 6. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Wykoff, et al. 2022.[47] YOSEMITE NCT03622580 Phase 3, DB, NI and superiority RCT	1. faricimab 6mg every 8 weeks (with every 4 week dosing up to week 20; 6 injections) 2. faricimab 6mg every 4 weeks through week 12 (4 injections) and until CST < 325 um. Dose was then adjusted to every 4, 8, 12, or 16 weeks per personalized treatment intervals at 4 week intervals. 3. aflibercept 2mg every 8 weeks (with every 4 week dosing up to week 16; 5 injections)	Demographics: - Female: 37-43% - White 77-81% - Asian 8-10% - Black: 4-7% - BMI: 31 kg/m2 - HbA1c 7.6 (SD 1.1) - T2DM 92-96% - BCVA: 62 letters - CST: 484-492 um - Time since diagnosis: 14-17 months - Treatment-naïve:76-78% - Macular leakage 94-97% - DR absent or questionable: 55-60% - Proliferative DR: 6-7% Key Inclusion Criteria: - Age ≥18 years - T1DM or T2DM on treatment - HbA1c ≤10% - Center-involving DME - CST ≥ 325 um - BCVA 25-73 EDTRS letters (Snellen ~20/320 to 20/40) Key Exclusion Criteria: - VEGF therapy within 3 months - Recent initiation of DM treatment within prior 3 months - Active cancer in past year - Systemic treatment for suspected or active infection - Renal failure - Uncontrolled BP > 180/100 mmHg	ITT: 1. 315 2. 313 3. 312 PP (without major protocol deviations): 1. 251 2. 275 3. 274 Attrition: 1. 31 (9.8%) 2. 30 (9.6%) 3. 26 (8.3%)	Primary Endpoint: Change in BCVA at 1 year (averaged from weeks 48 to 56) 1. 10.7 letters (97.52% CI 9.4 to 12.0) 2. 11.6 letters (97.52% CI 10.3 to 12.9) 3. 10.9 letters (97.52% CI 9.6 to 12.2) 1. vs. 3: -0.2 (97.52% CI -2.0 to 1.6) 2. vs. 3: 0.7 (97.52% CI -1.1 to 2.5) non-inferiority met (margin of 4 letters) superiority criteria not met Secondary Endpoints: Dosing at 1 year (personalized therapy group) Every 4 weeks: 31 (11%) Every 8 weeks: 44 (15%) Every 12 weeks: 60 (21%) Every 16 weeks: 151 (53%) BCVA - gain in ETDRS letters (PP analysis) | | ≥15 | ≥10 | ≥5 | |---|---|---|---| | 1 | 29% | 57% | 79% | | 2 | 35% | 58% | 80% | | 3 | 32% | 58% | 81% | Difference between groups NR BCVA - no loss in ETDRS letters (PP analysis) | | ≥15 | ≥10 | ≥5 | |---|---|---|---| | 1 | 98% | 96% | 95% | | 2 | 99% | 98% | 97% | | 3 | 99% | 98% | 96% | BCVA gain ≥ 15 letters or Snellen ≥ 20/40 1. 32.1% (95% CI 26.6–37.6) 2. 39.1% (95% CI 33.5–44.7) 3. 37.0% (95% CI 31.5–42.5) Snellen ≥ 20/40	NA	Death 1.7 2.9 3.4 Non-fatal MI, stroke or death 1.9 (3%) 2.10 (3%) 3.9 (3%) Serious AEs 1. 171 2. 114 3. 96 Serious ocular AEs 1.6 (2%) 2.9 (3%) 3.2 (1%) Ocular AEs of interest* 1.6 (2%) 2.8 (3%) 3.1 (<1%) DC due to AEs 1. 6 (2%) 2. 8 (3%) 3. 3 (1%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized via IVRS. Slight differences in time since DME diagnosis with a shorter time in faricimab 6 mg every 8 week group (difference of 3 months). Performance Bias: High. Patients, study site personnel, BCVA examiners, study vendors, central reading center personnel, and the sponsor and its agents were blinded via sham injections for non-active dosing visits. Differences in dosing regimens at weeks 16-24 unmasked patients and investigators to treatment groups. Detection Bias: High. BCVA examiners were blinded with use of sham injections. Differences in dosing regimens at weeks 16-24 unmasked patients and investigators to treatment groups.[45] Attrition Bias: Low. Primary analysis based on ITT and included only treatment-naïve patients. Mixed model for repeated measured used. Missing data imputed based on a missing at random mechanism. Data was censored after events due to the COVID pandemic (e.g., use of prohibited medications, missing doses, treatment discontinuation, death). Sensitivity analyses (including a per protocol analysis) conducted with various methods for missing data demonstrated similar results. Type 1 error were controlled for the primary outcome for NI analysis and superiority analyses in the treatment naïve and ITT populations. Reporting Bias: Unclear. Statistical analyses between groups for secondary endpoints were not included. Pre-specified endpoint evaluating visual functioning and quality of life was not reported.

	Screening period of up to 28 days	- Stroke or MI within prior 6 months - Other ocular conditions including tractional retinal detachment, pre-retinal fibrosis, active rubeosis, epiretinal membrane, vitreomacular traction, high-risk proliferative DR, uncontrolled glaucoma, history of retinal detachment or macular hole, other retinal disease-causing macular edema, history of immune-mediated uveitis, active ocular inflammation - Other conditions which could lead to vision loss (foveal atrophy, foveal fibrosis, pigment abnormalities, dense subfoveal hard exudates, or other non-retinal conditions) - Other ocular treatments including PRP, macular laser, anti-VEGF, intraocular surgery in prior 3 months; corticosteroid injections or implants in prior 6 months		1. 71.6 (95% CI 66.5–76.6) 2. 77.1 (95% CI 72.4–81.8) 3. 74.8 (95% CI 69.9–79.6) Patients with ≥ 2 step improvement in ETDRS DRSS 1. 46.0% (97.52% CI 38.8–53.1) 2. 42.5% (97.52% CI 35.5–49.5) 3. 35.8% (97.52% CI 29.1–42.5) NI margin of -10% met				Other Bias: Unclear. F Hoffmann-La Roche participated in the study design, data collection, analysis and interpretation, and report writing. **Applicability**: Patient: Majority of participants identified as White and on average had DM that was controlled. Patients with HbA1c >10% and high-risk proliferative diabetic retinopathy, groups commonly treated in clinical practice, were excluded. Inclusion criteria limited enrollment to a subset of patients. Data is most applicable to patients who have mild vision loss, were treatment naïve, and had well-controlled diabetes without diabetic retinopathy. Intervention: Evaluations every 4 weeks which is likely more frequent than standard practice. Disease activity criteria used to determine dosing frequency is unvalidated.[45] Comparator: Aflibercept at FDA-approved dose and treatment intervals. Study was not designed to compare faricimab to treat-and-extend dosing for aflibercept. Since studies were not designed to evaluate durability of response, conclusions regarding less frequent dosing of faricimab compared to aflibercept cannot be made.[45] Outcomes: BCVA is a well-studied outcome to evaluate visual acuity. A difference of about 5 letters is typically considered clinically significant and corresponds to about one line on the ETDRS chart. Prespecified NI margin established at 4 letters which is reasonable based on prior studies and the MCID. Setting: 179 sites in 16 countries. Enrollment in the US or Canada: 54%

<table>
<tr>
<td>2. Wykoff, et al. 2022.[47]

RHINE

Phase 3, DB, NI and superiority RCT</td>
<td>1. faricimab 6mg every 8 weeks (with every 4 week dosing up to week 20)

2. faricimab 6mg every 4 weeks through week 12 and until CST < 325 um. Dose was then adjusted per personalized treatment intervals at 4 week intervals.

3. aflibercept 2mg every 8 weeks (with every 4 week dosing up to week 16)

See YOSEMITE</td>
<td><u>Demographics</u>:
- Female: 38-41%
- White: 78-80%
- Asian 10-11%
- Black: 6-8%
- BMI: 30 kg/m2
- HbA1c: 7.7%
- T2DM: 94-95%
- BCVA: 62 letters
- CST: 466-477 um
- Time since diagnosis: 19-20 months
- Treatment-naïve:79-80%
- Macular leakage 95-97%
- DR absent or questionable: 56-58%
- Proliferative DR: 6-12%

<u>Key Inclusion Criteria</u>:
- See YOSEMITE

<u>Key Exclusion Criteria</u>:
- See YOSEMITE</td>
<td><u>ITT</u>:
1. 317
2. 319
3. 315

<u>PP:</u>
1. 258
2. 271
3. 273

<u>Attrition</u>:
1. 24 (7.6%)
2. 11 (3.5%)
3. 19 (6.0%)</td>
<td><u>Primary Endpoint</u>:
Change in BCVA at 1 year (averaged from weeks 48 to 56)
1. 11.8 letters (97.52% CI 10.6 to 13.0)
2. 10.8 letters (97.52% CI 9.6 to 11.9)
3. 10.3 letters (97.52% CI 9.1 to 11.4)
1. vs. 3: 1.5 (97.52% CI -0.1 to 3.2)
2. vs. 3: 0.5 (97.52% CI -1.1 to 2.1)
non-inferiority met (margin of 4 letters)
superiority criteria not met

<u>Secondary Endpoints</u>:
Dosing at 1 year (personalized therapy group)
Every 4 weeks: 41 (13%)
Every 8 weeks: 48 (16%)
Every 12 weeks: 62 (20%)
Every 16 weeks: 157 (51%)

BCVA - gain in ETDRS letters (PP analysis)
<table><tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td></tr><tr><td>1</td><td>34%</td><td>59%</td><td>82%</td></tr><tr><td>2</td><td>29%</td><td>53%</td><td>77%</td></tr><tr><td>3</td><td>30%</td><td>54%</td><td>78%</td></tr></table>Difference between groups NR

BCVA - no loss in ETDRS letters (PP analysis)
<table><tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td></tr><tr><td>1</td><td>99%</td><td>98%</td><td>97%</td></tr><tr><td>2</td><td>99%</td><td>98%</td><td>97%</td></tr><tr><td>3</td><td>99%</td><td>98%</td><td>95%</td></tr></table>BCVA gain ≥ 15 letters or Snellen ≥ 20/40
1. 38.3 (95% CI 32.6–44.0)
2. 32.4 (95% CI 27.2–37.6)
3. 33.5 (95% CI 28.1–38.9)

Snellen ≥ 20/40
1. 73.2 (95% CI 68.2–78.3)
2. 71.6 (95% CI 66.7–76.4)
3. 68.5 (95% CI 63.6–73.5)

BCVA ≥ 2 step improvement in ETDRS
1. 44.2% (97.52% CI 37.1–51.4)
2. 43.7% (97.52% CI 36.8–50.7)
3. 46.8% (97.52% CI 39.8–53.8)
NI margin of -10% not met</td>
<td>NA</td>
<td><u>Death</u>
1. 5
2. 0
3. 5

<u>Non-fatal MI, stroke, or death</u>
1. 4 (1%)
2. 2 (1%)
3. 5 (2%)

<u>Serious Non-ocular AEs</u>
1. 101
2. 79
3. 95

<u>Serious ocular AEs</u>
1. 9 (3%)
2. 10 (3%)
3. 6 (2%)

<u>Ocular AEs of interest*</u>
1. 9 (3%)
2. 9 (3%)
3. 5 (2%)

<u>DC due to AEs</u>
1. 4 (1%)
2. 4 (1%)
3. 4 (1%)</td>
<td>NA</td>
<td>Risk of Bias (low/high/unclear):
<u>Selection Bias</u>: Low. See YOSEMITE
<u>Performance Bias</u>: High. See YOSEMITE
<u>Detection Bias</u>: High. See YOSEMITE
<u>Attrition Bias</u>: Low. See YOSEMITE
<u>Reporting Bias</u>: Unclear. See YOSEMITE
<u>Other Bias:</u> Unclear. See YOSEMITE

Applicability:
<u>Patient</u>: See YOSEMITE
<u>Intervention</u>: See YOSEMITE
<u>Comparator</u>: See YOSEMITE
<u>Outcomes</u>: See YOSEMITE
<u>Setting</u>: 174 sites in 24 countries. Enrollment in the US or Canada: 35%.</td>
</tr>
</table>

<table>
<tr>
<td>3. Heier, et al. 2022.[49]

TENAYA
NCT03823287

DB, NI, MC, AC, RCT

Duration: 112 weeks</td>
<td>1. faricimab 6.0 mg every 4 weeks (4 injections) then every 8, 12, or 16 weeks based on disease activity at 20 or 24 weeks

2. Aflibercept 2.0 mg every 4 weeks for 3 injection then every 8 weeks

48 weeks with fixed treatment regimen. After 60 weeks dosing could be adjusted based on disease activity from 8 to 16 weeks.</td>
<td><u>Demographics</u>:
- Age: 76 years
- Female: 57-63%
- White: 90-91%
- Asian: 8%
- Hispanic: 8%
- BCVA 61 letters
- CST: 356-360 µm
- IOP: 15 mmHg
- Time since diagnosis ≤ 1 month: 74%
- Phakic: 55-58%
- Intraretinal fluid: 44-47%
- Subretinal fluid: 67-65%
- CNV location
Subfoveal 55-60%
Juxtafoveal: 26%
Extrafoveal: 12-16%
- CNV lesion type
Occult 52-53%
Classic 22-25%

<u>Key Inclusion Criteria</u>:
- Age ≥ 50 years
- Treatment-naïve
- CNV secondary to neovascular AMD
- Subfoveal CNV or other CNV with subfoveal component
- CNV lesion size ≤ 9 disc areas
- CNV component area ≥50% total lesion area
- Active CNV with exudation (fluid)
- BCVA 78-24 ETDRS letters (~20/32−20/320 Snellen equivalent)

<u>Key Exclusion Criteria</u>:
- Any prior CNV treatment or intraocular surgery
- Uncontrolled blood pressure >180/100 mmHg
- Stroke in prior 6 months
- Uncontrolled glaucoma</td>
<td><u>ITT</u>:
1. 334
2. 337

<u>PP</u> (at least one non-missing BVCA at 40-48 weeks)
1. 292
2. 300

<u>Attrition</u>:
1. 26 (8%)
2. 15 (5%)</td>
<td><u>Primary Endpoint</u>:
Change in BCVA at 40-48 weeks
1. 5.8 letters (95% CI 4.6 to 7.1)
2. 5.1 letters (95% CI 3.9 to 6.4)
MD 0.7 letters (95% CI −1.1 to 2.5)

<u>Secondary Endpoints</u>:
Dosing interval
Every 8 weeks: 64 (20%)
Every 12 weeks: 107 (34%)
Every 16 weeks: 144 (46%)

BCVA - gain in ETDRS letters (PP analysis)
<table><tr><th></th><th>≥15</th><th>≥10</th><th>≥5</th><th>≥0</th></tr><tr><td>1</td><td>20.0</td><td>37.1</td><td>59.2</td><td>75.6</td></tr><tr><td>2</td><td>15.7</td><td>31.7</td><td>58.0</td><td>76.8</td></tr></table>MD ≥15 letters: 4.3 (95% CI −1.6 to 10.1)
MD ≥10 letters: 5.4 (95% CI −2.0 to 12.7)
MD ≥5 letters: 1.2 (95% CI −6.6 to 8.9)
MD ≥0 letters: −1.2 (95% CI −7.9 to 5.4)

BCVA – no loss in ETDRS letters (PP analysis)
<table><tr><th></th><th>≥15</th><th>≥10</th><th>≥5</th></tr><tr><td>1</td><td>95.4</td><td>91.6</td><td>88.0</td></tr><tr><td>2</td><td>94.1</td><td>92.0</td><td>86.8</td></tr></table>MD ≥15 letters: 1.3 (95% CI −2.2 to 4.8)
MD ≥10 letters: −0.4 (95% CI −4.6 to 3.9)
MD ≥5 letters: 1.2 (95% CI −4.0 to 6.4)

BCVA- gain of ≥ 15 ETDRS letters OR BCVA ≥84 ETDRS letters
1. 24.3 (95% CI 19.5, 29.1)
2. 21.3 (95% CI 16.8, 25.7)
MD 3.0 (95% CI −3.6, 9.5)

BCVA Snellen equivalent ≥ 20/40
1. 56.4 (95% CI 51.5, 61.4)
2. 57.0 (95% CI 51.9, 62.1)
MD −0.5 (95% CI −7.7, 6.6)

BCVA Snellen equivalent ≤20/200
1. 6.4 (95% CI 3.7, 9.1)
2. 6.9 (95% CI 4.2, 9.5)
MD −0.5 (95% CI −4.2, 3.3)

Change in CST at 40-48 weeks</td>
<td></td>
<td><u>Serious non-ocular AEs</u>
1. 30 (9%)
2. 34 (10%)

<u>Serious Ocular AEs</u>
1. 4 (1%)
2. 6 (2%)

<u>Intra-ocular inflam-mation</u>
1. 5 (2%)
2. 2 (1%)

<u>Death, Non-fatal MI, stroke</u>
1. 3 (1%)
2. 3 (1%)

<u>DC due to AEs</u>
1. 3 (1%)
2. 3 (1%)</td>
<td></td>
<td>Risk of Bias (low/high/unclear):
<u>Selection Bias</u>: Low. Randomized via interactive voice or web-based response system. Baseline characteristics generally balanced between groups.
<u>Performance Bias</u>: High. Blinded with use of sham injections at non-active dosing visits. Differences in treatment regimen resulted in unmasking of treatment groups at week 12.[45]
<u>Detection Bias</u>: High. BCVA examiners masked to treatment with use of sham injections. Differences in treatment regimen resulted in unmasking of treatment groups at week 12.[45]
<u>Attrition Bias</u>: Low. ITT analysis used for primary and secondary endpoints. PP analysis was consistent with ITT analysis. Missing data were imputed using MMRM analysis assuming a missing at random mechanism. At least one missing outcome assessment from 36-48 weeks in 22% of aflibercept and 17% of faricimab patients. Clinical rationale and justification provided for non-inferiority margin of 4 letters. No adjustment for multiplicity of secondary outcomes.
<u>Reporting Bias</u>: Low. Outcomes reported as pre-specified.
<u>Other Bias:</u> Unclear. F Hoffmann-La Roche participated in the study design, data collection, analysis and interpretation, and report writing.

Applicability:
<u>Patient</u>: Most applicable to patients who are treatment-naïve with mild vision loss and a recent diagnosis. Majority of people identified as white; other races were under-represented. People with comorbid ocular conditions or recent major illness were excluded.
<u>Intervention</u>: Study visits every 4 weeks. Lack of randomization for faricimab dosing intervals prevents evaluations on comparative efficacy of each regimen (e.g., injections given every 8, 12 or 16 weeks).[45]
<u>Comparator</u>: Aflibercept administered at FDA-approved dose and intervals. Treat-and-</td>
</tr>
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<table>
<tr>
<td></td>
<td></td>
<td>- Cataract surgery within prior 3 months
- History of uveitis
- Other eye conditions related to CNV or macular pathology including myopia with refractory error >8 diopters, central serous chorioretinopathy, retinal pigment epithelial tear involving the macula, subretinal hemorrhage or fibrosis/atrophy > 50% of total lesion size, vitreous hemorrhage
- Cancer within prior 12 months
- Major illness, infection, surgery in prior 1 month</td>
<td></td>
<td>1. −136.8 µm (95% CI −142.6 to −131.0)
2. −129.4 µm (95% CI −135.2 to −123.5)
MD −7.4 µm (95% CI −15.7 to 0.8)</td>
<td></td>
<td></td>
<td></td>
<td>extend dosing regimens which are common in clinical practice were not evaluated for aflibercept.
Outcomes: Long-term outcomes are unknown, and up to 2-3 years of data may be needed to assess durability.
Setting: 149 sites in 15 countries. Enrollment in US and Canada: 54-55%.</td>
</tr>
<tr>
<td>4. Heier, et al. 2022.[49]

LUCERNE
NCT03823300</td>
<td>1. faricimab 6.0 mg every 4 weeks (4 injections) then every 8, 12, or 16 weeks based on disease activity at 20 or 24 weeks

2. Aflibercept 2.0 mg every 4 weeks for 3 injection then every 8 weeks

See TENAYA</td>
<td>Demographics:
- Age: 75-76 years
- Female: 57-61%
- White: 83-84%
- Asian: 10-11%
- Hispanic: 11-14%
- BCVA 59 letters
- CST: 353-359 µm
- IOP: 15 mmHg
- Time since diagnosis ≤ 1 month: 64-67%
- Phakic: 57%
- Intraretinal fluid: 43-47%
- Subretinal fluid: 67-68%
- CNV location
Subfoveal 58-63%
Juxtafoveal: 22-26%
Extrafoveal: 13%
- CNV lesion type
Occult 43-52%
Classic 30-33%

Key Inclusion Criteria:
See TENAYA

Key Exclusion Criteria:
See TENAYA</td>
<td>ITT:
1. 331
2. 327

PP (at least one non-missing BVCA at 40-48 weeks)
1. 302
2. 291

Attrition:
1. 18 (5%)
2. 22 (7%)</td>
<td>Primary Endpoint:
Change in BCVA at 40-48 weeks (NI margin of 4 letters)
1. 6.6 letters (95% CI 5.3 to 7.8)
2. 6.6 letters (95% CI 5.3 to 7.8)
MD 0.0 letters (95% CI –1.7 to 1.8)

Secondary Endpoints:
Dosing interval
Every 8 weeks: 70 (22%)
Every 12 weeks: 104 (33%)
Every 16 weeks: 142 (45%)

BCVA - gain in ETDRS letters (PP analysis)
<table><tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td><td>≥0</td></tr><tr><td>1</td><td>20.2</td><td>39.2</td><td>60.5</td><td>82.2</td></tr><tr><td>2</td><td>22.2</td><td>35.8</td><td>59.4</td><td>79.1</td></tr></table>MD ≥15 letters: −2.0 (95% CI −8.3 to 4.3)
MD ≥10 letters: 3.4 (95% CI −3.9 to 10.7)
MD ≥5 letters: 1.0 (95% CI −6.6 to 8.6)
MD ≥0 letters: 3.1 (95% CI −3.1 to 9.3)

BCVA - no loss in ETDRS letters (PP analysis)
<table><tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td></tr><tr><td>1</td><td>95.8</td><td>93.8</td><td>91.2</td></tr><tr><td>2</td><td>97.3</td><td>94.6</td><td>88.5</td></tr></table>MD ≥15 letters: −1.5 (95% CI −4.4 to 1.3)
MD ≥10 letters: −0.9 (95% CI −4.5 to 2.8)</td>
<td></td>
<td>Serious non-ocular AEs
1. 38 (11%)
2. 48 (15%)

Serious Ocular AEs
1. 7 (2%)
2. 7 (2%)

Intra-ocular inflam-mation
1. 8 (2%)
2. 6 (2%)

Death, Non-fatal MI, stroke
1. 4 (1%)
2. 3 (1%)

DC due to AEs
1. 8 (2%)</td>
<td></td>
<td>Risk of Bias (low/high/unclear):
Selection Bias: Low; See TENAYA. Most baseline characteristics balanced. Imbalances in time since diagnosis and proportion of patients with occult choroidal neovascularization lesions. It’s unclear if or how these imbalances may impact results.
Performance Bias: High. See TENAYA.
Detection Bias: High See TENAYA.
Attrition Bias: Low. See TENAYA. At least one missing outcome assessment from 36-48 weeks in 16% of aflibercept and 17% of faricimab patients. Results from per protocol analysis were consistent with ITT analysis.
Reporting Bias: Low. See TENAYA.
Other Bias: Unclear. See TENAYA.

Applicability:
Patient: See TENAYA.
Intervention: See TENAYA.
Comparator: See TENAYA.
Outcomes: See TENAYA.
Setting: 122 sites in 20 countries. Enrollment in US and Canada: 40-41%</td>
</tr>
</table>

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<tr>
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<td></td>
<td>MD ≥5 letters: 2.6 (95% CI −2.1 to 7.3)

BCVA- gain of ≥ 15 ETDRS letters OR BCVA ≥84 ETDRS letters
1. 24.5 (95% CI 19.8, 29.2)
2. 26.2 (95% CI 21.2, 31.1)
MD − 1.7 (95% CI −8.5, 5.1)

BCVA Snellen equivalent ≥ 20/40
1. 55.2 (95% CI 50.1, 60.2)
2. 49.4 (95% CI 44.4, 54.4)
MD 5.7 (95% CI −1.4, 12.9)

BCVA Snellen equivalent ≤20/200
1. 7.9 (95% CI 5.0, 10.8)
2. 7.5 (95% CI 4.7, 10.3)
MD 0.4 (95% CI −3.6, 4.4)

Change in CST at 40-48 weeks
1. −137.1 µm (95% CI −143.1 to −131.2)
2. −130.8 µm (95% CI −136.8 to −124.8)
MD −6.4 µm (95% CI −14.8 to 2.1)</td>
<td></td>
<td>2. 1 (<1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Tadayoni, et al. 2024.[50]

Hattenbach, et al. 2023.[51]

BALATON NCT04740 905

MC, DB, phase 3 RCT

Duration: 72 weeks</td>
<td>1. faricimab 6 mg every 4 weeks

2. Aflibercept 2 mg every 4 weeks

After 24 weeks, all participants transitioned to faricimab with treat and extend dosing where dose interval (from 4-16 weeks) was determined based on</td>
<td><u>Demographics</u>:
- Age 64-65 years
- Female 48-53%
- White: 62%
- Asian: 33-34%
- Hispanic 17-18%
- Mean BCVA: 57 letters
- BCVA ≥55 letters: 68%
- Mean CST 558 µm
- Time since diagnosis: 1.3-1.7 months

<u>Key Inclusion Criteria</u>:
- Age ≥18 years
- Center-involved macular edema due to RVO (branched)
- BCVA 73 to 19 ETDRS letters
- CST≥325 µm

<u>Key Exclusion Criteria</u>:
- Prior treatment for macular edema (e.g., VEGF inhibitors,</td>
<td><u>ITT</u>:
1. 276
2. 277

PP:
1. 241
2. 243

<u>Attrition</u>:
1. 9 (3%)
2. 3 (1%)</td>
<td><u>Primary Endpoint</u>:
Change in BCVA at week 24 (NI margin: 4 letters)
1. 16.9 ETDRS letters (95% CI 15.7 to 18.1)
2. 17.5 ETDRS letters (95% CI 16.3 to 18.6)
MD -0.6 ETDRS (95% CI -2.2 to 1.1)

<u>Secondary Endpoints</u>:
Change in CST
1. -311.4 µm (95% CI -316.4 to -306.4)
2. -304.4 µm (95% CI -309.3 to -299.4)
Differences not reported

BCVA - gain in ETDRS letters
<table><tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td><td>≥0</td></tr><tr><td>1</td><td>56.1%</td><td>77.5%</td><td>90.9%</td><td>97.1%</td></tr><tr><td>2</td><td>60.4%</td><td>77.3%</td><td>89.6%</td><td>95.7%</td></tr></table>Differences not reported

BCVA - no loss in ETDRS letters
<table><tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td></tr><tr><td>1</td><td>99.6%</td><td>99.6%</td><td>98.6%</td></tr><tr><td>2</td><td>98.6%</td><td>98.2%</td><td>97.5%</td></tr></table>Differences not reported</td>
<td>NS</td>
<td><u>Non-ocular serious AE</u>
1. 9
2. 16

<u>Serious ocular AE</u>
1. 3 (1.1%)
2. 2 (0.7%)

<u>Death, stroke, or MI</u>
1. 3 (1.1%)
2. 4 (1.5%)

<u>DC due to ocular AE</u>
None

<u>Intraocular Inflam-mation</u></td>
<td>NA</td>
<td>Risk of Bias (low/high/unclear):
<u>Selection Bias</u>: Low. Adequate randomization and allocation concealment with use of IVRS. Stratified by baseline BCVA and geographic region. Baseline characteristics were generally balanced between groups.
<u>Performance Bias</u>: Unclear. Patients and providers were masked to treatment (method not described).
<u>Detection Bias</u>: Unclear. BCVA examiners were masked to treatment and study eye. Imaging technicians and central reading center graders were masked to study treatment. Method of blinding not described.
<u>Attrition Bias</u>: Low. Low rate of patients who discontinued treatment. Primary outcome was assessed using a mixed model for repeated measures analysis with missing data imputed assuming a missing at random mechanism. Protocol deviations occurred in 26.8% of visits (missed visits accounted for 15.7%); 6% were related to COVID-19. Sensitivity analyses performed with similar results in the PP population and using various</td>
</tr>
</table>

	changes in CST and BCVA	steroids, macular laser, or panretinal coagulation) - Diagnosis > 4 months before screening - Uncontrolled blood pressure - History of other systemic or ocular disease - Macular neovascularization - Vitreomacular-interface abnormalities				None		imputation methods including imputation based on non-random data with worse outcomes. Reporting Bias: Unclear. Most outcomes reported as pre-specified. Statistical differences between groups were not reported for secondary endpoints. The National Eye Institute Visual Function Questionnaire 25 score was pre-specified as a patient-reported secondary endpoint but results were not described. Other Bias: Unclear. Funded by the manufacturer of faricimab who was involved in study design, data collection, analysis, interpretation and writing of the report. **Applicability**: Patient: Data is most applicable to people newly diagnosed with macular edema due to RVO who are treatment naïve. Most study participants identified as White (62%), Asian (33%), or Hispanic (18%). Other races were under-represented. Intervention: Monthly dosing interval is consistent with FDA-label. No comparative data available on durability of response with extended dosing intervals. Comparator: Aflibercept administered every 4 weeks is consistent with FDA-labeled dosing, but may be more frequent than dosing in clinical practice. Outcomes: Short treatment duration (~6 months) makes it difficult to assess long-term comparative durability. Setting: 22 countries; 149 sites from March 2021 to February 2022. ~22-23% of patients were in the United States or Canada.

<table>
<tr>
<td>6. Tadayoni, et al. 2024.[50]

Hattenbach, et al. 2023.[51]

COMINO NCT04740931

MC, DB, phase 3 RCT

Duration: 72 weeks</td>
<td>1. faricimab 6 mg every 4 weeks

2. Aflibercept 2 mg every 4 weeks

After 24 weeks, all participants transitioned to faricimab with treat and extend dosing where dose interval (from 4-16 weeks) was determined based on changes in CST and BCVA</td>
<td><u>Demographics</u>:
- Mean age: 65 years
- Female 45-47%
- White: 66-69%
- Asian: 24%
- Hispanic: 18-20%
- Mean BCVA: 50-51 letters
- BCVA ≥ 55 letters: 49%
- Mean CST 702-721 µm
- Time since diagnosis 1.1-1.6 months

<u>Key Inclusion Criteria</u>:
- See BALATON
- Center-involved macular edema due to RVO (central or hemiretinal)

<u>Key Exclusion Criteria</u>:
- See BALATON</td>
<td><u>ITT</u>:
1. 366
2. 363

PP:
1. 328
2. 311

<u>Attrition</u>:
1. 11 (3%)
2. 15 (4%)</td>
<td><u>Primary Endpoint</u>:
Change in BCVA at week 24 (NI margin: 4 letters)
1. 16.9 ETDRS letters (95% CI 15.4 to 18.3)
2. 17.3 ETDRS letters (95% CI 15.9 to 18.8)
MD -0.4 ETDRS letters (95% CI -2.5 to 1.6)

<u>Secondary Endpoints</u>:
Change in CST
1. -461.6 µm (95% CI -471.4 to -451.9)
2. -448.8 µm (95% CI -458.6 to -439.0)
Difference not reported

BCVA - gain in ETDRS letters
<table>
<tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td><td>≥0</td></tr>
<tr><td>1</td><td>56.6%</td><td>72.2%</td><td>85.3%</td><td>91.6%</td></tr>
<tr><td>2</td><td>58.1%</td><td>73.3%</td><td>84.6%</td><td>89.8%</td></tr>
</table>
Differences not reported

BCVA - no loss in ETDRS letters
<table>
<tr><td></td><td>≥15</td><td>≥10</td><td>≥5</td></tr>
<tr><td>1</td><td>96.2%</td><td>95.1%</td><td>94.0%</td></tr>
<tr><td>2</td><td>96.7%</td><td>95.9%</td><td>93.7%</td></tr>
</table>
Differences not reported</td>
<td>NS</td>
<td><u>Non-ocular serious AE</u>
1. 22
2. 23

<u>Serious ocular AEs</u>
1. 9 (2.5%)
2. 12 (3.3%)

<u>Death, stroke, or MI</u>
1. 4 (1.1%)
2. 5 (1.4%)

<u>DC due to ocular AE</u>
1. 3
2. 2

<u>Intraocular inflam-mation</u>
1. 8 (2.2%)
2. 4 (1.1%)</td>
<td>NA</td>
<td>Risk of Bias (low/high/unclear):
<u>Selection Bias</u>: Low. See BALATON. Slight differences in CST between groups but the clinical significance of these differences is unclear.
<u>Performance Bias</u>: Unclear. See BALATON
<u>Detection Bias</u>: Unclear. See BALATON
<u>Attrition Bias</u>: Low. See BALATON. Protocol deviations occurred in 29.8% of visits (missed visits accounted for 17.1%); 7% were related to COVID-19.
<u>Reporting Bias</u>: Unclear. See BALATON
<u>Other Bias:</u> Unclear. See BALATON

Applicability:
<u>Patient</u>: See BALATON
<u>Intervention</u>: See BALATON
<u>Comparator</u>: See BALATON
<u>Outcomes</u>: See BALATON
<u>Setting</u>: 22 countries; 149 sites from March 2021 to February 2022. ~25-26% of patients were in the United States or Canada.</td>
</tr>
<tr>
<td colspan="8"><u>Abbreviations</u> [alphabetical order]: AC = active comparison; ARR = absolute risk reduction; BCVA = best corrected visual acuity; BMI = body mass index; CI = confidence interval; CNV = choroidal neovascularization; CST = central subfield thickness; DB = double blind; DC = discontinuation; DME = diabetic macular edema; DR = diabetic retinopathy; DRSS = diabetic retinopathy severity scale; ETDRS=early treatment diabetic retinopathy study; HbA1c = glycated hemoglobin IOP = intraocular pressure; ITT = intention to treat; MC = multicenter; MD = mean difference; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; nAMD = neovascular age-related macular degeneration; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol; PRP = panretinal photocoagulation; RCT = randomized clinical trial; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; VEGF = vascular endothelial growth factor
*Ocular AEs of interest were defined as events associated with severe intraocular inflammation, events requiring surgical or medical intervention to prevent permanent loss of sight, or events associated with BCVA loss of 30 ETDRS letters or more for more than 1 hour.</td>
</tr>
</table>

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
bevacizumab	AVASTIN	VIAL	INTRAVEN	Y
aflibercept	EYLEA	SYRINGE	INTRAOCULR	N
aflibercept	EYLEA	VIAL	INTRAOCULR	N
brolucizumab-dbll	BEOVU	SYRINGE	INTRAOCULR	N
brolucizumab-dbll	BEOVU	VIAL	INTRAOCULR	N
faricimab-svoa	VABYSMO	VIAL	INTRAOCULR	N
ranibizumab	LUCENTIS	SYRINGE	INTRAOCULR	N
ranibizumab	LUCENTIS	VIAL	INTRAOCULR	N
ranibizumab	SUSVIMO	VIAL	IMPLANT	N
ranibizumab/init fill needle	SUSVIMO	VIAL	IMPLANT	N
ranibizumab-nuna	BYOOVIZ	VIAL	INTRAOCULR	N

Appendix 2: Abstracts of Comparative Clinical Trials

Jhaveri CD, Glassman AR, Ferris FL, 3rd, et al. Aflibercept Monotherapy or Bevacizumab First for Diabetic Macular Edema. *The New England journal of medicine.* 2022;387(8):692-703.

BACKGROUND: In eyes with diabetic macular edema, the relative efficacy of administering aflibercept monotherapy as compared with bevacizumab first with a switch to aflibercept if the eye condition does not improve sufficiently (a form of step therapy) is unclear., METHODS: At 54 clinical sites, we randomly assigned eyes in adults who had diabetic macular edema involving the macular center and a visual-acuity letter score of 24 to 69 (on a scale from 0 to 100, with higher scores indicating better visual acuity; Snellen equivalent, 20/320 to 20/50) to receive either 2.0 mg of intravitreous aflibercept or 1.25 mg of intravitreous bevacizumab. The drug was administered at randomization and thereafter according to the prespecified retreatment protocol. Beginning at 12 weeks, eyes in the bevacizumab-first group were switched to aflibercept therapy if protocol-specified criteria were met. The primary outcome was the mean change in visual acuity over the 2-year trial period. Retinal central subfield thickness and visual acuity at 2 years and safety were also assessed., RESULTS: A total of 312 eyes (in 270 adults) underwent randomization; 158 eyes were assigned to receive aflibercept monotherapy and 154 to receive bevacizumab first. Over the 2-year period, 70% of the eyes in the bevacizumab-first group were switched to aflibercept therapy. The mean improvement in visual acuity was 15.0 letters in the aflibercept-monotherapy group and 14.0 letters in the bevacizumab-first group (adjusted difference, 0.8 letters; 95% confidence interval, -0.9 to 2.5; P = 0.37). At 2 years, the mean changes in visual acuity and retinal central subfield thickness were similar in the two groups. Serious adverse events (in 52% of the patients in the aflibercept-monotherapy group and in 36% of those in the bevacizumab-first group) and hospitalizations for adverse events (in 48% and 32%, respectively) were more common in the aflibercept-monotherapy group., CONCLUSIONS: In this trial of treatment of moderate vision loss due to diabetic macular edema involving the center of the macula, we found no evidence of a significant difference in visual outcomes over a 2-year period between aflibercept monotherapy and treatment with bevacizumab first with a switch to aflibercept in the case of suboptimal response. (Funded by the National Institutes of Health; Protocol AC ClinicalTrials.gov number, NCT03321513.).

Khanani AM, Brown DM, Jaffe GJ, et al. MERLIN: Phase 3a, Multicenter, Randomized, Double-Masked Trial of Brolucizumab in Participants with Neovascular Age-Related Macular Degeneration and Persistent Retinal Fluid. *Ophthalmology.* 2022;129(9):974-985.

PURPOSE: To assess the 52-week efficacy and safety of brolucizumab 6 mg administered every 4 weeks compared with aflibercept 2 mg dosed every 4 weeks in eyes with neovascular age-related macular degeneration (nAMD) and persistent retinal fluid. DESIGN: Multicenter, randomized, double-masked phase 3a study. PARTICIPANTS: Participants with recalcitrant nAMD (persistent residual retinal fluid despite previous frequent anti-vascular endothelial growth factor treatment). METHODS: Eyes were randomized (2:1) to intravitreal brolucizumab 6 mg or aflibercept 2 mg every 4 weeks up to and including week 100. MAIN OUTCOME MEASURES: The primary end point was analysis of noninferiority in mean best-corrected visual acuity (BCVA) change from baseline to week 52 (margin, 4 letters). Other key end points included change in central subfield thickness (CST) from baseline to week 52, fluid-free status (no intraretinal fluid and no subretinal fluid), and safety. RESULTS: At week 52, brolucizumab was noninferior to aflibercept in BCVA change from baseline (least squares mean difference, -0.6 Early Treatment Diabetic Retinopathy Study letters; 95% confidence interval [CI], -2.1 to 0.9; P < 0.001). A total of 4.8% and 1.7% of participants reported a 15-letter or more BCVA loss from baseline at week 52 in the brolucizumab and aflibercept groups, respectively. In eyes treated with brolucizumab compared with those treated with aflibercept, the CST was reduced significantly (P < 0.001), and a significantly greater proportion of eyes were fluid free at week 52 (40.4% brolucizumab vs. 19.0% aflibercept; 95% CI, 13.9-29.0; P < 0.001). Incidence of intraocular inflammation (IOI), including retinal vasculitis and retinal vascular occlusion, were 9.3% (0.8% and 2.0%) for brolucizumab versus 4.5% (0% and 0%) for aflibercept, respectively. CONCLUSIONS: Visual acuity outcomes in previously treated participants with nAMD and persistent retinal fluid receiving brolucizumab 6 mg dosed every 4 weeks were noninferior to aflibercept 2 mg dosed every 4 weeks, with superior anatomic outcomes. However, incidences of IOI, including retinal vasculitis and retinal vascular occlusion, also were higher, leading to study termination.

Regillo C, Berger B, Brooks L, et al. Archway Phase 3 Trial of the Port Delivery System with Ranibizumab for Neovascular Age-Related Macular Degeneration 2-Year Results. *Ophthalmology.* 2023;130(7):735-747.

PURPOSE: To report 2-year results from the Archway clinical trial of the Port Delivery System with ranibizumab (PDS) for treatment of neovascular age-related macular degeneration (nAMD)., DESIGN: Phase 3, randomized, multicenter, open-label, active-comparator-controlled trial., PARTICIPANTS: Patients with previously treated nAMD diagnosed within 9 months of screening and responsive to anti-vascular endothelial growth factor therapy., METHODS: Patients were randomized 3:2 to PDS with ranibizumab 100 mg/ml with fixed refill-exchanges every 24 weeks (PDS Q24W) or intravitreal ranibizumab 0.5 mg injections every 4 weeks (monthly ranibizumab).

Patients were followed through 4 complete refill-exchange intervals (~2 years)., MAIN OUTCOME MEASURES: Change in best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score from baseline averaged over weeks 44 and 48, weeks 60 and 64, and weeks 88 and 92 (noninferiority margin, -3.9 ETDRS letters)., RESULTS: The PDS Q24W was noninferior to monthly ranibizumab, with differences in adjusted mean change in BCVA score from baseline averaged over weeks 44/48, 60/64 and 88/92 of -0.2 (95% confidence interval [CI], -1.8 to +1.3), +0.4 (95% CI, -1.4 to +2.1) and -0.6 ETDRS letters (95% CI, -2.5 to +1.3), respectively. Anatomic outcomes were generally comparable between arms through week 96. Through each of 4 PDS refill-exchange intervals, 98.4%, 94.6%, 94.8%, and 94.7% of PDS Q24W patients assessed did not receive supplemental ranibizumab treatment. The PDS ocular safety profile was generally unchanged from primary analysis. Prespecified ocular adverse events of special interest (AESI) were reported in 59 (23.8%) PDS and 17 (10.2%) monthly ranibizumab patients. The most common AESI reported in both arms was cataract (PDS Q24W, 22 [8.9%]; monthly ranibizumab, 10 [6.0%]). Events in the PDS Q24W arm included (patient incidence) 10 (4.0%) conjunctival erosions, 6 (2.4%) conjunctival retractions, 4 (1.6%) endophthalmitis cases, and 4 (1.6%) implant dislocations. Serum ranibizumab sampling showed that the PDS continuously released ranibizumab over the 24-week refill-exchange interval and ranibizumab serum concentrations were within the range experienced with monthly ranibizumab., CONCLUSIONS: The PDS Q24W showed noninferior efficacy to monthly ranibizumab through approximately 2 years, with approximately 95% of PDS Q24W patients not receiving supplemental ranibizumab treatment in each refill-exchange interval. The AESIs were generally manageable, with learnings continually implemented to minimize PDS-related AEs., FINANCIAL DISCLOSURE(S): Proprietary or commercial disclosure may be found after the references.

Singh RP, Barakat MR, Ip MS, et al. Efficacy and Safety of Brolucizumab for Diabetic Macular Edema: The KINGFISHER Randomized Clinical Trial. *JAMA ophthalmology.* 2023;141(12):1152-1160.

Importance: Despite the effectiveness of existing anti-vascular endothelial growth factor (VEGF) therapies, a need remains for further treatment options to improve response rates and/or reduce injection or monitoring frequency in patients with diabetic macular edema (DME)., Objective: To evaluate the efficacy and safety of brolucizumab vs aflibercept dosed every 4 weeks in participants with DME., Design, Participants, and Setting: This 52-week, double-masked, phase 3 randomized clinical trial included treatment-naive adults and adults who had previously received anti-VEGF therapy. Data were collected from September 2019 to March 2020, and data were analyzed from April 2020 to February 2021., Intervention: Brolucizumab, 6 mg, intravitreal injection every 4 weeks or aflibercept, 2 mg, intravitreal injection every 4 weeks., Main Outcomes and Measures: Participants were randomized 2:1 to brolucizumab, 6 mg, or aflibercept, 2 mg. The primary end point was change from baseline in best-corrected visual acuity at week 52. Secondary end points were the proportion of participants with a 2-step improvement or greater from baseline in Diabetic Retinopathy Severity Scale score, the proportion of eyes with absence of both subretinal fluid and intraretinal fluid, change from baseline in central subfield thickness, and safety at week 52., Results: A total of 517 participants were randomized to brolucizumab (n = 346) or aflibercept (n = 171); 299 (57.8%) were male, and the mean (SD) age was 60.7 (10.2) years. Brolucizumab was noninferior to aflibercept in best-corrected visual acuity (Early Treatment Diabetic Retinopathy Study letter score) change from baseline at week 52 (brolucizumab, 12.2-letter improvement; aflibercept, 11.0-letter improvement; difference, 1.1; 95% CI, -0.6 to 2.9; noninferiority margin, 4; P < .001). Brolucizumab was superior to aflibercept for the proportion of eyes without subretinal and intraretinal fluid (brolucizumab, 144 of 346 [41.6%]; aflibercept, 38 of 171 [22.2%]; difference, 20.0%; 95% CI, 12.5to 28.6; P < .001) and mean central subfield thickness change from baseline at week 52 (brolucizumab, -237.8 mum; aflibercept, -196.5 mum; difference, -41.4; 95% CI, -58.9 to -23.8; P < .001). Incidence of intraocular inflammation was 4.0% (14 of 346) in the brolucizumab arm and 2.9% (5 of 171) in the aflibercept arm, incidence of retinal vasculitis was 0.9% (3 of 346) and 0.6% (1 of 171), respectively, and incidence of retinal vascular occlusion was 0.3% (1 of 346) and 0.6% (1 of 171). One participant in the brolucizumab arm had retinal artery occlusion., Conclusions and Relevance: In these study participants with DME, no clinically meaningful differences in visual outcomes were noted between the brolucizumab and aflibercept arms; some superior anatomic improvements were noted in the brolucizumab arm. No new safety concerns were identified., Trial Registration: ClinicalTrials.gov Identifier: NCT03917472.

Vader MJC, Schauwvlieghe A-SME, Verbraak FD, et al. Comparing the Efficacy of Bevacizumab and Ranibizumab in Patients with Retinal Vein Occlusion: The Bevacizumab to Ranibizumab in Retinal Vein Occlusions (BRVO) study, a Randomized Trial. *Ophthalmology Retina.* 2020;4(6):576-587.

PURPOSE: Comparing the efficacy of intravitreal injections of bevacizumab to ranibizumab in the treatment of macular edema (ME) resulting from retinal vein occlusion (RVO)., DESIGN: Comparative, randomized, double-masked, multicenter, noninferiority clinical trial. The noninferiority margin was 4 letters., PARTICIPANTS: Patients with vision loss resulting from ME secondary to a branch or (hemi) central RVO who might benefit from anti-vascular endothelial growth factor treatment were eligible for participation., METHODS: From June 2012 through February 2018, 277 participants were randomized to receive injections of 1.25 mg bevacizumab (n = 139) or 0.5

mg ranibizumab (n = 138). The follow-up was 6 months with a monthly dosing interval., MAIN OUTCOME MEASURES: The primary outcome was a change in visual acuity from baseline at 6 months. Changes in the central area thickness and safety were studied as secondary outcomes., RESULTS: The mean visual acuity (+/-standard deviation) improved, with 15.3+/-13.0 letters for bevacizumab and 15.5+/-13.3 letters for ranibizumab after 6 months of monthly treatment. The lower limit of the 2-sided 90% confidence interval was -1.724 letters, which is within the noninferiority margin of 4 letters. Even in the branch and (hemi-)central RVO subgroups, minimal differences were found in visual acuity outcomes between treatment arms. Changes in central area thickness on OCT at 6 months did not differ significantly between treatment groups, with a decrease of 287.0+/-231.3 mum in the bevacizumab group and 300.8+/-224.8 mum in the ranibizumab group. Severe adverse events (SAEs) were also distributed equally over both treatment groups: 10 participants (7.1%) in the bevacizumab group and 13 participants (9.2%) in the ranibizumab group experienced SAEs., CONCLUSIONS: This study showed, based on the change in visual acuity, that bevacizumab is noninferior to ranibizumab for patients with ME resulting from RVO of either subtype when receiving monthly injections for a period of 6 months. In addition, anatomic and safety outcomes did not differ between treatment groups. Based on our findings, bevacizumab may be an effective alternative to ranibizumab.

Vader MJC, Schauwvlieghe A-SME, Verbraak FD, et al. Comparing the Efficacy of Bevacizumab and Ranibizumab in Patients with Diabetic Macular Edema (BRDME): The BRDME Study, a Randomized Trial. *Ophthalmology Retina.* 2020;4(8):777-788.

PURPOSE: To generate conclusive evidence regarding the noninferiority of intravitreal bevacizumab compared with ranibizumab in patients with diabetic macular edema (DME)., DESIGN: Comparative, randomized, double-masked, multicenter, noninferiority clinical trial., PARTICIPANTS: Eligible patients were older than 18 years, diagnosed with type 1 or type 2 diabetes mellitus, with glycosylated hemoglobin of less than 12%, central area thickness of more than 325 mum, and visual impairment from DME with a best-corrected visual acuity (BCVA) between 24 letters and 78 letters., METHODS: From June 2012 through February 2018, a total of 170 participants were randomized to receive 6 monthly injections of either 1.25 mg bevacizumab (n = 86) or 0.5 mg ranibizumab (n = 84)., MAIN OUTCOME MEASURES: Primary outcome was change in BCVA from baseline to month 6 compared between the 2 treatment arms. The noninferiority margin was 3.5 letters., RESULTS: The difference in mean BCVA between treatment arms was 1.8 letters in favor of ranibizumab after 6 months of follow-up; BCVA improved by 4.9+/-6.7 letters in the bevacizumab group and 6.7+/-8.7 letters in the ranibizumab group. The lower bound of the 2-sided 90% confidence interval (CI) was -3.626 letters, exceeding the noninferiority margin of 3.5 letters. Central area thickness decreased more with ranibizumab (138.2+/-114.3 mum) compared with bevacizumab (64.2+/-104.2 mum). In a post hoc subgroup analysis, participants with a worse BCVA at baseline (<=69 letters) improved by 6.7+/-7.0 letters with bevacizumab and 10.4+/-10.0 letters with ranibizumab, and central area thickness decreased significantly more in the ranibizumab arm of this subgroup compared with the bevacizumab arm. Participants with an initially better BCVA at baseline (>=70 letters) did not demonstrate differences in BCVA or OCT outcomes between treatment arms., CONCLUSIONS: Based on change in BCVA from baseline to month 6, the noninferiority of 1.25 mg bevacizumab to 0.5 mg ranibizumab was not confirmed. Only the subgroup of patients with a lower BCVA at baseline showed better visual acuity and anatomic outcomes with ranibizumab. Our study confirmed the potential differential efficacy of anti-vascular endothelial growth factor agents in the treatment of DME as well as the difference in response between patient groups with different baseline visual acuities.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to February 01, 2024

1	exp bevacizumab/ or exp ranibizumab/	16610
2	aflibercept.mp.	3072
3	brolucizumab.mp.	220
4	pegaptanib.mp.	665
5	exp vascular endothelial growth factors/	62006
6	faricimab.mp.	48
7	exp Retinal Degeneration/	49090
8	exp Retinal Diseases/	147642
9	1 or 2 or 3 or 4 or 5 or 6	73918
10	7 or 8	147642
11	9 and 10	10607
12	limit 11 to yr="2020 -Current"	2090
13	limit 12 to (english language and humans)	1897
14	limit 13 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or "systematic review")	427

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VABYSMO safely and effectively. See full prescribing information for VABYSMO.

VABYSMO® (faricimab-svoa) injection, for intravitreal use
Initial U.S. Approval: 2022

RECENT MAJOR CHANGES

Indications and Usage, Macular Edema Following Retinal Vein Occlusion (RVO) (1.3)	10/2023
Dosage and Administration, Diabetic Macular Edema (2.3)	1/2023
Dosage and Administration, Macular Edema Following Retinal Vein Occlusion (2.4)	10/2023
Warnings and Precautions, Retinal Vasculitis and/or Retinal Vascular Occlusion (5.4)	10/2023

INDICATIONS AND USAGE

VABYSMO is a vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (nAMD) (1.1)
- Diabetic Macular Edema (DME) (1.2)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.3)

DOSAGE AND ADMINISTRATION

For intravitreal injection. (2.1)

- Neovascular (Wet) Age-Related Macular Degeneration (nAMD)
  - The recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days, monthly) for the first 4 doses, followed by optical coherence tomography and visual acuity evaluations 8 and 12 weeks later to inform whether to give a 6 mg dose via intravitreal injection on one of the following three regimens: 1) Weeks 28 and 44; 2) Weeks 24, 36 and 48; or 3) Weeks 20, 28, 36 and 44. Although additional efficacy was not demonstrated in most patients when VABYSMO was dosed every 4 weeks compared to every 8 weeks, some patients may need every 4 week (monthly) dosing after the first 4 doses. Patients should be assessed regularly. (2.2)

- Diabetic Macular Edema (DME)
  - VABYSMO is recommended to be dosed by following one of these two dose regimens: 1) 6 mg (0.05 mL of 120 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days ± 7 days, monthly) for at least 4 doses. If after at least 4 doses, resolution of edema based on the central subfield thickness (CST) of the macula as measured by optical coherence tomography is achieved, then the interval of dosing may be modified by extensions of up to 4 week interval increments or reductions of up to 8 week interval increments based on CST and visual acuity evaluations; or 2) 6 mg dose of VABYSMO can be administered every 4 weeks for the first 6 doses, followed by 6 mg dose via intravitreal injection at intervals of every 8 weeks (2 months). Although additional efficacy was not demonstrated in most patients when VABYSMO was dosed every 4 weeks compared to every 8 weeks, some patients may need every 4 week (monthly) dosing after the first 4 doses. Patients should be assessed regularly. (2.3)

- Macular Edema Following Retinal Vein Occlusion (RVO)
  - The recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL) administered by intravitreal injection every 4 weeks (approximately every 28 ± 7 days, monthly) for 6 months. (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/mL solution in a single-dose vial (3)

CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events (ATEs) associated with VEGF inhibition. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥ 5%) reported in patients receiving VABYSMO were cataract (15%) and conjunctival hemorrhage (8%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2023

Appendix 5: Key Inclusion Criteria

Population	Ocular conditions associated with macular edema
Intervention	VEGF inhibitor in Appendix 1
Comparator	VEGF inhibitor in Appendix 1
Outcomes	Visual acuity, function, quality of life, thromboembolic events, serious ocular events
Setting	Outpatient treatment

Appendix 6: Prior Authorization Criteria

Ocular Vascular Endothelial Growth Factors

Goal(s):

- Promote use of preferred drugs and ensure that non-preferred drugs are used appropriately for OHP-funded conditions
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	**Yes**: Go to #3	**No**: Go to #4

Approval Criteria		
3. Will the prescriber consider a change to a preferred product? Message: Preferred products do not require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No**: Approve for 12 months, or for length of the prescription, whichever is less

4. RPh only: All other indications need to be evaluated as to whether they are funded or contribute to a funded diagnosis on the OHP prioritized list.
 	
• If funded and clinic provides supporting literature: Approve for 12 months, or for length of the prescription, whichever is less.
• If not funded:
  ○ Current age ≥ 21 years: Deny; not funded by the OHP
  ○ Current age < 21 years: If clinic provides supporting literature, and documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc) then approve for 12 months, or for length of the prescription, whichever is less.		

P&T / DUR Review: *4/24 (SS); 8/20; 3/17*
Implementation: *TBD*