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+15878858911
editorial-office@sciformat.ca

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# COMPARATIVE CLINICAL OUTCOMES OF FARICIMAB VERSUS AFLIBERCEPT IN DIABETIC MACULAR EDEMA: A FOCUSED REVIEW

***Karol Kraska*** *(Corresponding Author, Email: karol.kraska04@gmail.com)*
*Medical University of Lublin, Lublin, Poland*
*ORCID ID: 0009-0003-8113-2151*

***Nadzieja Krasucka***
*Medical University of Lublin, Lublin, Poland*
*ORCID ID: 0009-0007-2777-892X*

***Aleksandra Zynkowska***
*Medical University of Lublin, Lublin, Poland*
*ORCID ID: 0009-0005-1759-5842*

***Aleksandra Magdalena Skrzyniarz***
*Medical University of Lublin, Lublin, Poland*
*ORCID ID: 0009-0003-0065-643X*

***Maria Kiełbus***
*Medical University of Lublin, Lublin, Poland*
*ORCID ID: 0009-0003-1946-3013*

***Julia Oziębło***
*Medical University of Lublin, Lublin, Poland*
*ORCID ID: 0009-0008-9794-9824*

***Magdalena Kijowska***
*Medical University of Lublin, Lublin, Poland*
*ORCID ID: 0009-0004-1086-7086*

***Karolina Klusek***
*Medical University of Lublin, Lublin, Poland*
*ORCID ID: 0009-0004-7006-0188*

***Michał Batory***
*No. 1 University Clinical Hospital in Lublin, Lublin, Poland*
*ORCID ID: 0009-0008-7018-7823*

***Jakub Jakubowski***
*Medical University of Warsaw, Warsaw, Poland*
*ORCID ID: 0009-0009-0269-1371*

**ABSTRACT**

This manuscript presents a focused narrative review with systematic literature identification of comparative evidence on faricimab versus aflibercept in adults with diabetic macular edema. The review prioritized randomized phase III evidence and selected only clinically decisive extension, post hoc, and real-world studies published from 2022 through 2025. The predefined PICO was: adults with DME; intervention faricimab; comparator aflibercept; outcomes best-corrected visual acuity, central subfield thickness, injection burden and durability, and safety. The core evidence base consisted of the YOSEMITE and RHINE randomized trials and their 2-year follow-up, supplemented by FDA regulatory documents and a small number of directly relevant post hoc and real-world studies. At year 1, faricimab achieved noninferior visual gains versus aflibercept in both trials, with numerically greater reductions in central subfield thickness. At year 2, visual acuity remained comparable, whereas anatomic outcomes and durability continued to favor faricimab, especially in the treat-and-extend arm, in which more than 60% of patients were on every-16-week dosing and approximately 80% were on every-12-week-or-longer dosing by week 96. Safety was broadly similar across randomized arms, although postmarketing retinal vasculitis warnings require continued pharmacovigilance. Direct real-world head-to-head evidence remained sparse; available switch studies suggest benefit primarily in selected aflibercept-refractory eyes. Overall, the present evidence supports faricimab as a clinically relevant alternative to aflibercept in DME when durability and anatomic control are prioritized, but not as a superior agent for letter gain alone.

**KEYWORDS**

Diabetic Macular Edema; Faricimab; Aflibercept; YOSEMITE; RHINE; Durability

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## 1. Introduction.

Diabetic macular edema is a microangiopathic retinal disorder driven by breakdown of the blood-retinal barrier, fluid accumulation within and beneath the retina, and heterogeneous angiogenic and inflammatory signaling (Das et al., 2016; Fogli et al., 2016; Miller and Fortun 2018; Ng et al., 2025). A recent international consensus review characterized DME as the most common cause of vision-threatening diabetic retinopathy and emphasized two clinical problems that frame the present review: responses to anti-VEGF therapy are heterogeneous, and standardized definitions of non-response and switching remain insufficiently resolved (Ng et al., 2025). These issues matter directly because a therapy that preserves visual outcomes while reducing injection frequency could improve adherence, clinic throughput, and real-world effectiveness (Wykoff et al., 2022; Wong et al., 2024; Peto et al., 2025).

Faricimab differs mechanistically from aflibercept in that it inhibits both vascular endothelial growth factor A (VEGF-A) and angiopoietin-2 (Ang-2), whereas aflibercept targets the VEGF pathway alone (Khan et al., 2020; Wykoff et al., 2022; Canonica et al., 2023). In the DME program, this dual-pathway strategy was tested against standard aflibercept 2 mg every 8 weeks after loading, with the explicit aim not only of preserving vision but also of improving fluid control and extending treatment intervals (Joussen et al., 2021; Wykoff et al., 2022; Wong et al., 2024). The resulting evidence must be interpreted carefully: if faricimab outperforms aflibercept, the clinically relevant question is where the advantage lies—visual acuity, retinal drying, durability, safety, or some combination of these domains (Wykoff et al., 2022; Wong et al., 2024).

The present topic also requires a scope clarification. TENAYA and LUCERNE are often discussed alongside YOSEMITE and RHINE because they share the same drug, sponsor, phase III design logic, and extended-interval treatment philosophy (Heier et al., 2022; Wykoff et al., 2022). However, TENAYA and LUCERNE enrolled treatment-naïve patients with neovascular age-related macular degeneration aged 50 years or older, not adults with DME (Heier et al., 2022; Khanani et al., 2024). They are therefore informative for

protocol context and the broader durability concept, but they are not PICO-concordant for a DME review and cannot legitimately contribute to the primary comparative efficacy synthesis in DME (Heier et al., 2022; Wykoff et al., 2022). Accordingly, this manuscript addresses a narrowly defined clinical question concerning the comparative performance of faricimab and aflibercept in adults with diabetic macular edema with respect to best-corrected visual acuity, central subfield thickness, injection burden and durability, and safety.

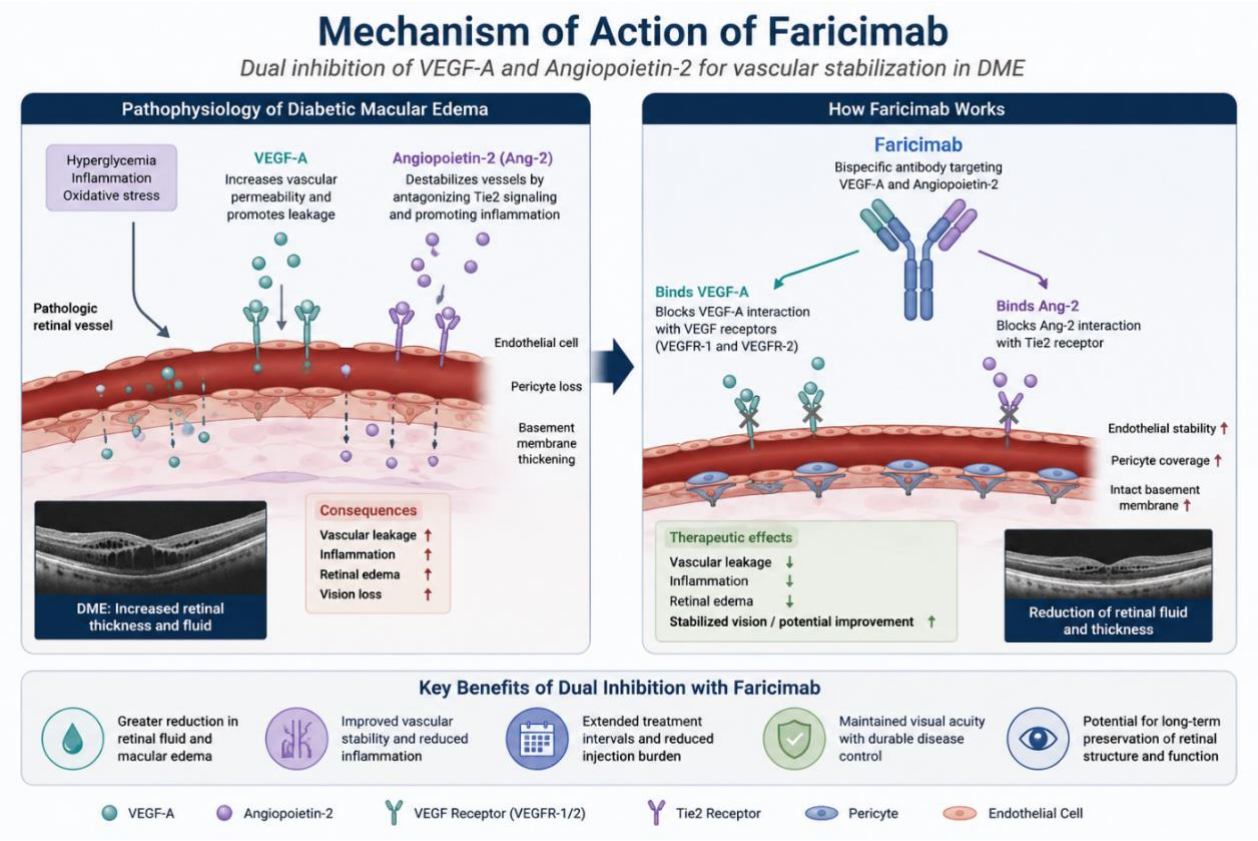


***Fig. 1.*** *Proposed mechanism of action of faricimab in diabetic macular edema.*

Faricimab simultaneously inhibits vascular endothelial growth factor A (VEGF-A) and angiopoietin-2 (Ang-2), thereby promoting vascular stabilization, reducing retinal vascular permeability and fluid accumulation, and facilitating extended treatment intervals while maintaining clinical efficacy. Illustration generated by the authors using artificial intelligence and reviewed for scientific accuracy based on data from Wykoff et al. (2022), Wong et al. (2024), and published literature regarding VEGF-A and Ang-2 signaling pathways.

## 2. Methodology.

This review was designed as a focused narrative review with systematic literature identification and predefined eligibility criteria. The objective was to prioritize the most decision-relevant comparative literature for publication-quality academic writing, while remaining transparent about omissions and scope boundaries. The prespecified PICO was: Population—adults with diabetic macular edema; Intervention—intravitreal faricimab; Comparator—intravitreal aflibercept; Outcomes—best-corrected visual acuity (BCVA), central subfield thickness (CST), injection frequency and durability, and safety. Because the review specifically prioritized phase III studies and clinically relevant follow-up data, the evidence hierarchy placed the pivotal YOSEMITE and RHINE randomized trials and subsequent long-term follow-up publications at the highest level of evidence (Wykoff et al., 2022; Wong et al., 2024), supplemented by regulatory evidence from the U.S. Food and Drug Administration (FDA, 2024). Post hoc analyses and real-world studies were considered supportive sources and were interpreted in the context of the randomized evidence base.

The literature window was restricted to 2022–2025. The focused search strategy targeted PubMed-indexed trial reports, journal full-text or abstract pages, FDA prescribing and regulatory documents, and selected real-world studies. Search terms combined “faricimab,” “aflibercept,” “diabetic macular edema,”

"YOSEMITE," "RHINE," "TENAYA," "LUCERNE," "real-world," "switch," "durability," "central subfield thickness," and "safety." Only sources that offered either primary comparative data or clinically decisive contextual data were retained, with particular emphasis placed on the pivotal YOSEMITE and RHINE phase III trials and their subsequent follow-up analyses (Wykoff et al., 2022; Wong et al., 2024), supported where appropriate by regulatory evidence (FDA, 2024) and selected real-world investigations.

Eligibility criteria were intentionally narrow. Included sources had to be one of the following: pivotal randomized DME trials; official regulatory documents for the same trials; extension or 2-year trial publications; DME-specific post hoc analyses with direct faricimab–aflibercept comparisons and numeric outcomes; or real-world studies with immediate clinical relevance, especially where prior aflibercept exposure made the comparison clinically interpretable. Excluded were narrative reviews, broad indirect comparisons, non-DME populations, aflibercept 8 mg–only comparative programs, and meeting abstracts that did not add uniquely decisive numeric evidence. Under these criteria, the YOSEMITE and RHINE phase III trials and their long-term follow-up publications constituted the core evidence base (Wykoff et al., 2022; Wong et al., 2024). TENAYA and LUCERNE were screened but excluded from the primary DME synthesis because they enrolled patients with neovascular age-related macular degeneration rather than diabetic macular edema (Heier et al., 2022).

Outcome extraction was predefined. For each eligible study, the review extracted numerical BCVA change in ETDRS letters, CST change in micrometers, number of injections, frequency of every-12-week and every-16-week dosing, and adverse-event patterns including ocular inflammation and arterial thromboembolic events where reported. These outcomes were selected because they represent the principal efficacy, durability, and safety endpoints reported in the pivotal YOSEMITE and RHINE phase III trials and their long-term follow-up analyses (Wykoff et al., 2022; Wong et al., 2024). Synthesis was narrative, with structured numeric reporting, because the final evidence set combined randomized trials, regulatory analyses, post hoc biomarker studies, and observational cohorts whose designs and endpoints were too heterogeneous to support a methodologically robust pooled meta-analysis (Wykoff et al., 2022; Wong et al., 2024; FDA, 2024).

Risk of bias was assessed using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2) and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) framework for observational cohorts (Sterne et al., 2019; Sterne et al., 2016). The pivotal YOSEMITE and RHINE trials were judged primarily on randomization, masking, endpoint measurement, completeness of follow-up, and appropriateness of analysis for the primary BCVA outcome (Wykoff et al., 2022; Wong et al., 2024). Observational real-world studies were judged mainly on confounding by indication, selection bias, absence of concurrent controls, and differential prior treatment exposure. The focused PRISMA-style selection pathway is summarized in Figure 2. The counts refer to the curated screening set used for manuscript synthesis rather than to all raw search-engine hits.

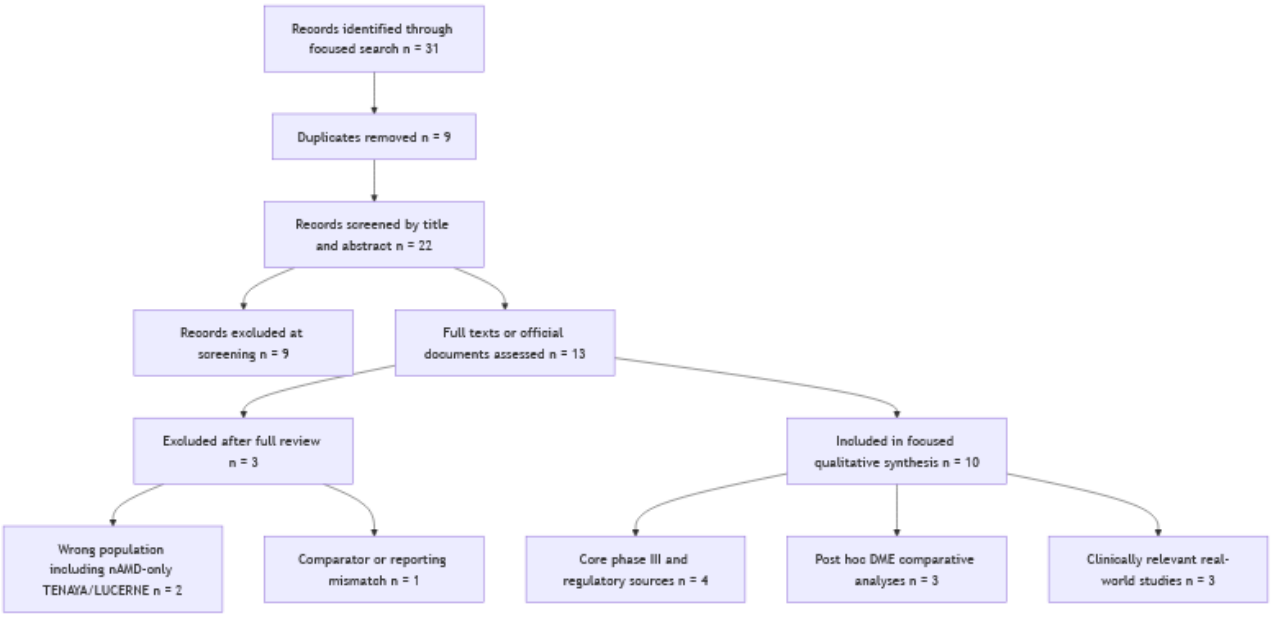


***Fig. 2.*** *Study selection process for the focused literature review conducted between 2022 and 2025.*

## 3. Results.

The final synthesis was dominated by the YOSEMITE/RHINE evidence platform. The randomized phase III program enrolled 1,891 adults across the two DME trials, with 940 patients in YOSEMITE and 951 in RHINE; the overall population had a mean age of 62.2 years, and 78% were anti-VEGF naïve while 22% had prior VEGF inhibitor exposure. Patients were randomized 1:1:1 to faricimab every 8 weeks, faricimab personalized treatment interval (PTI) dosing, or aflibercept every 8 weeks after protocol-defined loading. Adults had center-involving diabetic macular edema with baseline BCVA between 25 and 73 ETDRS letters (Wykoff et al., 2022; Wong et al., 2024; Lim et al., 2025).

**Table 1.** Summary of Included Studies and Risk-of-Bias Assessment.

| Study/source | Design and setting | Population | Comparator structure | Follow-up | Key outcomes extracted | Bias appraisal |
|---|---|---|---|---|---|---|
| YOSEMITE/RHINE phase III | Randomized, double-masked, active-comparator noninferiority trials | Adults with center-involving DME | Faricimab Q8W; faricimab variable/PTI vs aflibercept Q8W | Year 1 | BCVA, CST, interval distribution, safety | Low risk for primary efficacy |
| YOSEMITE/RHINE 2-year follow-up | Randomized year-two continuation of phase III trials | Same cohorts | Same arms | 100 weeks | BCVA, CST, injection totals, durability, safety | Low risk for core efficacy, some concern for durability interpretation |
| FDA statistical review | Independent regulatory reanalysis | YOSEMITE/RHINE ITT and safety populations | Same | Week 56 primary-year analyses | BCVA, CST, interval distribution, safety tables | Low risk as regulatory secondary source |
| FDA U.S. prescribing information | Official label synthesis | Pooled program populations | Faricimab vs aflibercept | Baseline to week 100 for selected DME outcomes | Efficacy table, common adverse reactions, ATEs, warnings | Official regulatory source |
| Anatomic Control 2025 | Post hoc pooled OCT biomarker analysis | YOSEMITE/RHINE pooled eyes | Faricimab Q8W/T&E vs aflibercept Q8W | 100 weeks | IRF absence, CST <280 µm, time-to-drying | Some concerns, exploratory |
| Angiographic Leakage 2025 | Post hoc angiographic leakage analysis | YOSEMITE/RHINE | Same | Week 16 to week 52 linkage | Leakage resolution and relation to Q16W durability | Some concerns, exploratory |
| Hyperreflective Foci 2025 | Post hoc imaging biomarker analysis | YOSEMITE/RHINE | Same | 48 weeks | HRF reduction | Some concerns, exploratory |
| Pichi 2024 | Retrospective single-center switch study | 100 aflibercept-treated DME eyes | Pre-switch aflibercept, post-switch faricimab | 6 months | BCVA, CST | Serious risk due confounding and no concurrent control |
| Huber 2024 | Real-world retrospective switch abstract | Aflibercept-responsive and nonresponsive DME eyes | Pre-switch aflibercept, post-switch faricimab | 12 weeks | CST response, treatment interval | Serious risk due confounding and short follow-up |
| FARWIDE-DMO 2025 | Multicenter UK real-world EMR cohort | 2,147 DME eyes with 12-month follow-up | Single-arm faricimab cohort, many previously on aflibercept | 12 months | Visual outcomes, injection burden, safety | Serious risk for comparative inference |

Table 1 summarizes the core trial publications, official FDA documents, selected DME-specific post hoc analyses, and the most clinically relevant real-world studies retained after focused screening.

The pivotal year-1 efficacy message was consistent across YOSEMITE and RHINE: faricimab produced noninferior, rather than superior, visual gains compared with aflibercept. In YOSEMITE, mean BCVA change at the year-1 endpoint (average of weeks 48, 52, and 56) was +10.7 letters with faricimab Q8W, +11.6 letters with faricimab personalized treatment interval (PTI) dosing, and +10.9 letters with aflibercept Q8W. In RHINE, the corresponding gains were +11.8, +10.8, and +10.3 letters, respectively (Wykoff et al., 2022). The FDA

statistical review explicitly concluded that superiority of faricimab over aflibercept for the primary BCVA endpoint was not established, although the predefined noninferiority criterion was successfully met (FDA, 2024). These findings remained consistent with the longer-term follow-up analyses reported subsequently (Wong et al., 2024).

Anatomic outcomes favored faricimab more clearly than visual acuity outcomes. At the composite year-1 CST endpoint (average of weeks 48, 52, and 56), YOSEMITE showed mean CST reductions of −204.4 µm with faricimab Q8W, −195.9 µm with faricimab personalized treatment interval (PTI) dosing, and −168.9 µm with aflibercept; RHINE showed reductions of −195.0 µm, −186.1 µm, and −169.3 µm, respectively (Wykoff et al., 2022). These findings demonstrate a consistent pattern across both trials: faricimab maintained visual gains comparable to aflibercept while producing numerically greater reductions in retinal thickness, suggesting superior anatomical control of disease activity (Wykoff et al., 2022; Wong et al., 2024).

Durability was the most clinically distinctive feature of faricimab. At week 52, among eyes remaining evaluable in the personalized treatment interval (PTI) arm, 52.8% of patients in YOSEMITE and 51.0% of patients in RHINE achieved every-16-week dosing, while 73.8% and 71.1%, respectively, achieved dosing intervals of every 12 weeks or longer (Wykoff et al., 2022). In pooled week-56 exposure analyses, the median number of study-drug injections was 10 for faricimab Q8W, 8 for faricimab PTI, and 10 for aflibercept, indicating that the durability signal was already clinically meaningful during the first year of treatment (Wykoff et al., 2022). Subsequent long-term follow-up analyses further supported the sustainability of these extended treatment intervals without compromising visual outcomes (Wong et al., 2024; Peto et al., 2025).

Year-two results demonstrated that the fundamental trade-off of faricimab—comparable visual outcomes with reduced treatment burden—was maintained. At 100 weeks, mean BCVA change was +10.7 letters with faricimab Q8W, +10.7 letters with faricimab treat-and-extend (T&E), and +11.4 letters with aflibercept in YOSEMITE; in RHINE, the corresponding values were +10.9, +10.1, and +9.4 letters, respectively (Wong et al., 2024). Over the full study period, median study-drug injections were 15 for faricimab Q8W, 10 in YOSEMITE and 11 in RHINE for faricimab T&E, and 14 for aflibercept in both trials (Wong et al., 2024). In the faricimab T&E arms, more than 60% of patients were receiving every-16-week dosing and approximately 80% were receiving every-12-week or longer dosing by week 96; moreover, nearly 80% of patients who had achieved every-16-week dosing at week 52 maintained that interval through week 96 without interval reduction (Wong et al., 2024). These findings reinforce durability as the principal differentiating characteristic of faricimab relative to aflibercept in diabetic macular edema.

At year 2, the anatomical advantage of faricimab persisted. Across weeks 92, 96, and 100, mean CST reductions were greater with faricimab than with aflibercept: in YOSEMITE, −216.0 µm for faricimab Q8W, −204.5 µm for faricimab treat-and-extend (T&E), and −196.3 µm for aflibercept; in RHINE, the corresponding reductions were −202.6 µm, −197.1 µm, and −185.6 µm, respectively (Wong et al., 2024). Likewise, the proportion of eyes achieving absence of DME, defined as CST <325 µm, at weeks 92–100 was 87%–92% and 78%–86% for the two faricimab arms versus 77%–81% for aflibercept in YOSEMITE, and 88%–93%, 85%–88%, and 80%–84%, respectively, in RHINE (Wong et al., 2024). The proportion of eyes with absence of intraretinal fluid at weeks 92–100 was also higher with faricimab: 59%–63% and 43%–48% versus 33%–38% in YOSEMITE, and 56%–62% and 45%–52% versus 39%–45% in RHINE (Wong et al., 2024). Collectively, these findings indicate that the durability advantage of faricimab was accompanied by sustained improvements in anatomical disease control over two years of follow-up.

**Table 2.** Comparative Clinical Outcomes of Faricimab and Aflibercept in YOSEMITE and RHINE.

| Outcome | Faricimab Q8W | Faricimab PTI/T&E | Aflibercept Q8W |
|---|---|---|---|
| **Year-1 BCVA change** | YOSEMITE +10.7; RHINE +11.8 letters | YOSEMITE +11.6; RHINE +10.8 letters | YOSEMITE +10.9; RHINE +10.3 letters |
| **Year-1 CST change** | YOSEMITE −204.4; RHINE −195.0 μm | YOSEMITE −195.9; RHINE −186.1 μm | YOSEMITE −168.9; RHINE −169.3 μm |
| **Week-52 durability** | Fixed Q8W | YOSEMITE 52.8% Q16W and 73.8% ≥Q12W; RHINE 51.0% Q16W and 71.1% ≥Q12W | Fixed Q8W |
| **Week-56 median injections** | 10 pooled | 8 pooled | 10 pooled |
| **Year-2 BCVA change** | YOSEMITE +10.7; RHINE +10.9 letters | YOSEMITE +10.7; RHINE +10.1 letters | YOSEMITE +11.4; RHINE +9.4 letters |
| **Year-2 CST change** | YOSEMITE −216.0; RHINE −202.6 μm | YOSEMITE −204.5; RHINE −197.1 μm | YOSEMITE −196.3; RHINE −185.6 μm |
| **Year-2 total median injections** | 15 in both trials | 10 in YOSEMITE; 11 in RHINE | 14 in both trials |
| **Week-96 durability** | Fixed Q8W | >60% on Q16W; ~80% on ≥Q12W; almost 80% of week-52 Q16W achievers maintained Q16W | Fixed Q8W |

The values in Table 2 are drawn from the pivotal year-1 and year-2 publications and FDA regulatory analyses. The key interpretation is that faricimab improved durability and anatomy, while visual acuity remained clinically comparable rather than superior.

Selected post hoc analyses further clarified the clinical significance of the anatomical advantage observed with faricimab. In a pooled OCT analysis of YOSEMITE and RHINE, higher proportions of eyes achieved absence of intraretinal fluid with faricimab Q8W (58%–63%) and faricimab treat-and-extend (T&E) dosing (44%–49%) than with aflibercept (36%–41%) at weeks 92–100 (Lim et al., 2025). Among eyes with intraretinal fluid at baseline, the median time to first absence of intraretinal fluid was achieved approximately 40 weeks earlier with faricimab than with aflibercept (Lim et al., 2025). Similarly, the proportion of eyes achieving CST <280 μm at weeks 92–100 was 70%–74% with faricimab Q8W, 61%–65% with faricimab T&E, and 61%–63% with aflibercept; among eyes with CST ≥280 μm at baseline, the median time to first achievement of CST <280 μm occurred approximately 16 weeks earlier with faricimab (Lim et al., 2025). These findings suggest that faricimab not only improved long-term anatomical outcomes but also accelerated the achievement of key OCT-defined treatment milestones.

Angiographic and hyperreflective-foci analyses pointed in the same direction. In the angiographic leakage study, 28% of faricimab-treated patients versus 15% of aflibercept-treated patients achieved resolution of macular leakage by week 16 (Goldberg et al., 2025). Within the faricimab treat-and-extend (T&E) arm, 63% of patients with leakage resolution at week 16 and 45% of those with high leakage at week 16 achieved every-16-week dosing at week 52, suggesting that early vascular control may predict later durability (Goldberg et al., 2025). In a subsequent hyperreflective-foci analysis, adjusted mean inner-retinal 1-mm HRF volume at week 48 was 104.1 pL with faricimab Q8W, 110.1 pL with faricimab T&E, and 180.3 pL with aflibercept, again favoring faricimab (Chakravarthy et al., 2025).

Safety in the randomized DME program was broadly comparable between therapies. In the pooled YOSEMITE/RHINE week-56 safety population, overall adverse events occurred in 81.4% of patients receiving faricimab Q8W, 76.9% receiving faricimab personalized treatment interval (PTI) dosing, and 78.1% receiving aflibercept. Ocular adverse events occurred in 37.3%, 35.6%, and 34.4% of patients, respectively; serious adverse events in 23.7%, 19.9%, and 18.2%; and adjudicated Anti-Platelet Trialists' Collaboration (APTC) thromboembolic events in 2.1%, 1.9%, and 2.2%, respectively (Wykoff et al., 2022; Lim et al., 2025). Common adverse reactions reported in the U.S. prescribing information were similarly balanced between treatment groups, including cataract (15% with faricimab versus 12% with aflibercept), conjunctival hemorrhage (8% versus 7%), vitreous detachment (5% versus 4%), increased intraocular pressure (4% versus 3%), and intraocular inflammation (1% in both groups) (FDA, 2024). The prescribing information also reports arterial thromboembolic events from baseline to week 100 in 5% of faricimab-treated patients and 5% of

aflibercept-treated patients with diabetic macular edema, further supporting the overall similarity of the safety profiles (FDA, 2024).

At the same time, safety interpretation cannot stop at the registration trials. The U.S. prescribing information for faricimab explicitly includes a postmarketing warning regarding retinal vasculitis with or without retinal vascular occlusion (FDA, 2024). Thus, while comparative phase III safety outcomes appear reassuring and broadly comparable between faricimab and aflibercept (Wykoff et al., 2022; Wong et al., 2024), continued long-term pharmacovigilance remains essential when applying faricimab widely in routine clinical practice (FDA, 2024).

Real-world evidence was considerably less mature than the randomized evidence base and, importantly, was rarely truly head-to-head. No robust routine-practice cohort published between 2022 and 2025 directly comparing faricimab and aflibercept 2 mg under matched contemporary conditions was identified in this focused review. Instead, the most clinically relevant real-world studies primarily evaluated switching from aflibercept to faricimab or reported outcomes in mixed prior-treatment populations (Pichi et al., 2024; Rush et al., 2023). Consequently, real-world evidence provides useful insights into treatment effectiveness in routine practice but remains methodologically weaker than the randomized phase III evidence generated by YOSEMITE and RHINE (Wykoff et al., 2022; Wong et al., 2024).

Among the most informative switch studies, Pichi and colleagues analyzed 100 eyes switched to faricimab after a mean of 6.8 ± 3.3 prior aflibercept injections (Pichi et al., 2024). At 6 months, eyes classified as poor visual responders to previous therapy (n = 62) gained approximately +5 ETDRS letters and demonstrated a mean CST reduction of −67.9 μm following the switch; eyes with poor prior anatomical response achieved a mean visual gain of +4.5 letters and a CST reduction of −95.1 μm (Pichi et al., 2024). The study further suggested that eyes already responding satisfactorily to aflibercept derived limited additional benefit from conversion to faricimab, an observation with important implications for individualized treatment decision-making in routine clinical practice (Pichi et al., 2024).

A second switch analysis by Huber and colleagues found that after 12 weeks of faricimab treatment, 54% of eyes previously responding to aflibercept and 25% of previously nonresponding eyes achieved either a >20% reduction in central subfield thickness (CST) or a CST ≤250 μm (Huber et al., 2024). An additional 46% and 50% of eyes, respectively, demonstrated CST stabilization within ±20%, while 73% of previously responding eyes and 47% of previously nonresponding eyes achieved an extended treatment interval of at least 8 weeks (Huber et al., 2024). Although these findings originate from a relatively short observational study, they support the clinical impression that faricimab may be particularly useful when the therapeutic objective is interval extension or enhanced anatomical control in selected aflibercept-experienced patients (Huber et al., 2024).

The largest clinically relevant 12-month real-world cohort identified in the present review was FARWIDE-DMO, which included 2,147 eyes with 12-month follow-up after faricimab initiation, comprising 690 treatment-naïve eyes and 1,457 previously treated eyes (Peto et al., 2025). In treatment-naïve eyes, mean visual acuity increased from 63.9 to 68.4 ETDRS letters, corresponding to a gain of approximately +4.7 letters, whereas visual acuity remained broadly stable in previously treated eyes (Peto et al., 2025). Mean injection counts over 12 months were 6.4 in treatment-naïve eyes and 6.9 in previously treated eyes, with treatment burden notably lower during months 7–12 than during months 1–6 (Peto et al., 2025). Among previously treated eyes, 84.6% had received aflibercept 2 mg immediately before switching to faricimab (Peto et al., 2025). The investigators reported rates of intraocular inflammation (IOI) and potentially infectious endophthalmitis that were broadly consistent with those observed in the phase III clinical program (Peto et al., 2025).

## 4. Discussion.

The present evidence supports a clear but nuanced conclusion. If the benchmark outcome is letter gain alone, faricimab should not be described as superior to aflibercept in diabetic macular edema. The randomized evidence consistently demonstrates noninferiority, rather than superiority, with respect to BCVA outcomes across the YOSEMITE and RHINE clinical trials (Wykoff et al., 2022; Wong et al., 2024). Furthermore, the FDA statistical review explicitly concluded that superiority of faricimab over aflibercept for the primary efficacy endpoint was not established, despite successful achievement of the predefined noninferiority criterion (FDA, 2024). This distinction is important both scientifically and clinically. Overstating the visual efficacy advantage of faricimab would not be supported by the available evidence.

If, however, the clinical benchmark is broadened to include anatomical control and treatment durability, the balance shifts meaningfully in favor of faricimab. Across both year-1 and year-2 analyses, faricimab produced consistently greater reductions in central subfield thickness and higher proportions of fluid-free or

near-dry retinas while enabling a substantial proportion of patients in the personalized treatment interval (PTI) or treat-and-extend (T&E) arms to achieve dosing intervals of every 12 or 16 weeks (Wykoff et al., 2022; Wong et al., 2024). Over two years, the faricimab T&E strategy maintained visual outcomes comparable to aflibercept while requiring approximately three to four fewer injections, a difference likely to be clinically meaningful for patients, caregivers, and healthcare systems (Wong et al., 2024). This interpretation is not speculative; rather, it follows directly from the combination of preserved BCVA outcomes and reduced cumulative treatment burden observed throughout the YOSEMITE and RHINE programs (Wykoff et al., 2022; Wong et al., 2024).

A second important interpretive point is that faricimab's durability advantage should not be interpreted as a direct comparison against an equally flexible aflibercept regimen. The FDA review documentation explicitly notes that the clinical utility of the disease-activity criteria used to guide personalized treatment interval (PTI) dosing has not been fully established, that the proportions of patients achieving extended treatment intervals may not be generalizable to broader diabetic macular edema populations, and that no similarly flexible aflibercept arm was included for a direct interval-for-interval durability comparison (FDA, 2024). Consequently, although the extended-interval outcomes observed with faricimab are clinically compelling, they remain partly dependent on the trial protocol and should not be interpreted as definitive evidence that aflibercept would be unable to achieve different durability outcomes under a matched treat-and-extend design (FDA, 2024; Wykoff et al., 2022).

The post hoc studies strengthen the biological plausibility of faricimab's clinical profile. Faster reductions in intraretinal fluid, earlier attainment of lower-thickness thresholds, greater early angiographic leakage resolution, and lower hyperreflective-foci burden all point in the same direction (Lim et al., 2025; Goldberg et al., 2025; Chakravarthy et al., 2025). Collectively, these findings support the hypothesis that dual angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A) inhibition may improve vascular stability and retinal drying beyond VEGF-only blockade (Wykoff et al., 2022; Wong et al., 2024). Nevertheless, these analyses remain exploratory and should be interpreted as mechanistic reinforcement of the primary randomized evidence rather than as independent proof of clinical superiority. Their principal value lies in explaining the durability and anatomical-control signals observed in YOSEMITE and RHINE rather than replacing the primary comparative efficacy question addressed by those trials (Wykoff et al., 2022; Wong et al., 2024).

The real-world literature, by contrast, remains relatively immature. Available studies suggest that switching from aflibercept to faricimab may benefit selected eyes with persistent edema, incomplete anatomical response, or insufficient treatment-interval extension, but they do not establish whether faricimab is globally superior to well-delivered aflibercept in routine clinical practice (Pichi et al., 2024; Huber et al., 2024). Confounding by indication is an inherent limitation of switch studies, as clinicians are more likely to transition patients who are responding suboptimally, experiencing disease plateau, or facing a substantial treatment burden. Although this limitation does not invalidate the observed improvements following conversion to faricimab, it prevents strong comparative causal inferences (Pichi et al., 2024; Huber et al., 2024). The FARWIDE-DMO cohort provides valuable evidence regarding feasibility, safety, and treatment-burden reduction in routine practice, yet it remains a single-arm observational study rather than a concurrent head-to-head comparison with aflibercept (Peto et al., 2025). Consequently, randomized evidence from YOSEMITE and RHINE continues to provide the most reliable basis for comparative efficacy assessment (Wykoff et al., 2022; Wong et al., 2024).

Safety findings are reassuring but should not be interpreted complacently. Within the randomized DME program, adverse-event profiles were broadly similar between faricimab and aflibercept, and rates of arterial thromboembolic events did not differ meaningfully across treatment groups (Wykoff et al., 2022; Wong et al., 2024). Nevertheless, the current U.S. prescribing information includes an explicit postmarketing warning regarding retinal vasculitis with or without retinal vascular occlusion, highlighting a safety consideration that extends beyond the registration-trial experience (FDA, 2024). Consequently, faricimab should not be discussed merely as a routine anti-VEGF substitute without acknowledging the need for continued pharmacovigilance. The most balanced interpretation of the available evidence is that clinical-trial safety was broadly comparable to aflibercept, whereas postmarketing surveillance has introduced an additional clinically relevant layer of caution (FDA, 2024; Wykoff et al., 2022; Wong et al., 2024).

This review also clarifies the role of TENAYA and LUCERNE within the broader faricimab evidence base. Because these trials enrolled patients with neovascular age-related macular degeneration rather than diabetic macular edema, they cannot contribute directly to efficacy conclusions regarding DME (Heier et al.,

2022). Their primary relevance lies in demonstrating that Roche/Genentech consistently pursued a durability-focused phase III development strategy for faricimab across multiple retinal diseases and in explaining why these studies are frequently discussed alongside YOSEMITE and RHINE (Heier et al., 2022; Wykoff et al., 2022). However, for a DME-focused review, TENAYA and LUCERNE should be regarded as contextual evidence supporting the broader durability concept rather than as studies contributing to comparative efficacy inference in diabetic macular edema (Heier et al., 2022; Wykoff et al., 2022).

Open questions and limitations. The most important limitations are structural. First, this review was intentionally designed as a focused review rather than an exhaustive systematic review with formal meta-analysis. Second, no robust real-world head-to-head cohort published between 2022 and 2025 directly comparing faricimab with aflibercept 2 mg in diabetic macular edema was identified. Third, no randomized DME extension publication beyond the 2-year (100-week) follow-up of the YOSEMITE and RHINE programs was identified within the prespecified literature window (Wong et al., 2024; Chakravarthy et al., 2025). Fourth, the imaging-based post hoc analyses should be regarded as hypothesis-generating and mechanistically informative rather than as substitutes for the prespecified functional primary endpoint of BCVA (Lim et al., 2025; Goldberg et al., 2025; Chakravarthy et al., 2025). These limitations do not invalidate the central findings of the review, which remain grounded primarily in the randomized phase III evidence base (Wykoff et al., 2022; Wong et al., 2024), but they do define the appropriate boundaries within which the conclusions should be interpreted.

## 5. Conclusions.

Faricimab is best understood not as a vision-superior therapy compared with aflibercept in diabetic macular edema, but rather as a durability-advantaged and anatomically stronger alternative that preserves comparable visual outcomes. In the YOSEMITE and RHINE trials, faricimab achieved the clinically important benchmark of noninferior BCVA improvement at year 1 and maintained comparable visual outcomes through year 2, while producing greater reductions in central subfield thickness and substantially increasing the likelihood of extended treatment intervals in the personalized treatment interval/treat-and-extend arms (Wykoff et al., 2022; Wong et al., 2024). For clinicians and healthcare systems, these characteristics make faricimab particularly attractive when treatment burden, interval extension, and long-term anatomical disease control are major therapeutic priorities (Wong et al., 2024). Accordingly, the most scientifically rigorous interpretation of the current evidence is that faricimab offers efficacy comparable to aflibercept, combined with improved durability and anatomical control, rather than categorical superiority in visual acuity gain (FDA, 2024; Wykoff et al., 2022; Wong et al., 2024).

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## REFERENCES

1. Canonica, J., Foxton, R., & Garrido, M. G. (2023). Delineating effects of angiopoietin-2 inhibition on vascular permeability and inflammation in models of retinal neovascularization and ischemia/reperfusion. *Frontiers in Cellular Neuroscience, 17*, Article 1192464. https://doi.org/10.3389/fncel.2023.1192464
2. Chakravarthy, U., Chaudhary, V., Sadda, S. R., Tan, C. S., Vujosevic, S., Fauser, S., et al. (2025). Effect of faricimab versus aflibercept on hyperreflective foci in patients with diabetic macular edema from the YOSEMITE/RHINE trials. *Ophthalmology Science, 5*(5), Article 100798. https://doi.org/10.1016/j.xops.2025.100798
3. Cheema, A. A., & Cheema, H. R. (2024). Diabetic macular edema management: A review of anti-vascular endothelial growth factor (VEGF) therapies. *Cureus*. https://doi.org/10.7759/cureus.52676
4. Das, A., McGuire, P. G., & Rangasamy, S. (2015). Diabetic macular edema: Pathophysiology and novel therapeutic targets. *Ophthalmology, 122*, 1375–1394. https://doi.org/10.1016/j.ophtha.2015.03.024
5. Fogli, S., Mogavero, S., Egan, C. G., Del Re, M., & Danesi, R. (2016). Pathophysiology and pharmacological targets of VEGF in diabetic macular edema. *Pharmacological Research, 103*, 149–157. https://doi.org/10.1016/j.phrs.2015.11.003
6. Food and Drug Administration. (2022). *BLA 761235: Statistical review and evaluation*. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761235Orig1s000StatR.pdf

7. Food and Drug Administration. (2024). *Vabysmo (faricimab-svoa) injection, for intravitreal use: U.S. prescribing information*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761235s005lbl.pdf
8. Goldberg, R. A., Mar, F. A., Csaky, K., Amador, M., et al. (2025). Resolution of angiographic macular leakage with faricimab versus aflibercept in patients with diabetic macular edema in YOSEMITE/RHINE. *Ophthalmology Retina, 9*(6), 515–526. https://doi.org/10.1016/j.oret.2024.11.015
9. Huber, K. L., Stino, H., Steiner, I., et al. (2024). Real-world outcomes after switch from aflibercept to faricimab in eyes with diabetic macular edema. *Investigative Ophthalmology & Visual Science, 65*(14), Article 46. https://doi.org/10.1167/iovs.65.14.46
10. Joussen, A. M., Ricci, F., Paris, L. P., Korn, C., Quezada-Ruiz, C., & Zarbin, M. (2021). Angiopoietin/Tie2 signalling and its role in retinal and choroidal vascular diseases: A review of preclinical data. *Eye, 35*, 1305–1316. https://doi.org/10.1038/s41433-020-01377-x
11. Khan, M., Aziz, A. A., Shafi, N. A., et al. (2020). Targeting angiopoietin in retinal vascular diseases: A literature review and summary of clinical trials involving faricimab. *Cells, 9*(8), Article 1869. https://doi.org/10.3390/cells9081869
12. Khanani, A. M., Kotecha, A., Chang, A., et al. (2024). TENAYA and LUCERNE: Two-year results from the phase 3 neovascular age-related macular degeneration trials of faricimab with treat-and-extend dosing in year 2. *Ophthalmology, 131*(8), 914–926. https://doi.org/10.1016/j.ophtha.2024.02.014
13. Lim, J. I., Amador, M. J., Dhoot, D. S., et al. (2025). Anatomic control with faricimab versus aflibercept in the YOSEMITE/RHINE trials in diabetic macular edema. *Ophthalmology Retina, 9*(7), 655–666. https://doi.org/10.1016/j.oret.2025.01.017
14. Miller, K., & Fortun, J. A. (2018). Diabetic macular edema: Current understanding, pharmacologic treatment options, and developing therapies. *Asia-Pacific Journal of Ophthalmology, 7*, 28–35. https://doi.org/10.22608/APO.2017529
15. Ng, D. S. C., Yu, S. Y., He, N., et al. (2025). International consensuses and controversies on causes, diagnosis and management of diabetic macular edema. *Progress in Retinal and Eye Research, 109*, Article 101406. https://doi.org/10.1016/j.preteyeres.2025.101406
16. Peto, T., Pearce, I., Talks, J., de Salvo, G., Patel, P. J., et al. (2025). Real-world treatment patterns and visual outcomes of faricimab in patients with diabetic macular oedema in the UK at 12 months: The FARWIDE-DMO study. *Eye*. Advance online publication. https://doi.org/10.1038/s41433-025-04059-8
17. Pichi, F., Abdi, A., Aljneibi, S., El Ghrably, I., Agarwal, A., & Ghazi, N. G. (2024). Switch to faricimab after initial treatment with aflibercept in eyes with diabetic macular edema. *International Ophthalmology, 44*, Article 275. https://doi.org/10.1007/s10792-024-03226-2
18. TENAYA and LUCERNE Investigators. (2022). Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): Two randomised, double-masked, phase 3, non-inferiority trials. *The Lancet, 399*(10326), 729–740. https://doi.org/10.1016/S0140-6736(22)00010-1
19. Wong, T. Y., Haskova, Z., Asik, K., Baumal, C. R., Csaky, K. G., Eter, N., et al. (2024). Faricimab treat-and-extend for diabetic macular edema: Two-year results from the randomized phase 3 YOSEMITE and RHINE trials. *Ophthalmology, 131*(6), 708–723. https://doi.org/10.1016/j.ophtha.2023.12.026
20. Wykoff, C. C., Abreu, F., Adamis, A. P., Basu, K., Eichenbaum, D. A., Haskova, Z., et al. (2022). Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): Two randomised, double-masked, phase 3 trials. *The Lancet, 399*(10326), 741–755. https://doi.org/10.1016/S0140-6736(22)00018-6
21. Rush, R. B. (2023). One-year results of faricimab for aflibercept-resistant diabetic macular edema. *Clinical Ophthalmology, 17*, 2397–2403. https://doi.org/10.2147/OPTH.S424314
22. Sterne, J. A. C., et al. (2016). ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ, 355*, Article i4919. https://doi.org/10.1136/bmj.i4919
23. Sterne, J. A. C., et al. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ, 366*, Article l4898. https://doi.org/10.1136/bmj.l4898