COMPARATIVE CLINICAL EFFICACY OF NEXT-GENERATION ANTI-VEGF AGENTS IN DIABETIC MACULAR EDEMA: FARICIMAB AND HIGH-DOSE AFLIBERCEPT

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ABSTRACT

Background: Diabetic macular edema (DME) is a major cause of visual impairment in people with diabetes. Standard intravitreal anti–vascular endothelial growth factor (anti-VEGF) therapy improves vision but often requires repeated visits and injections. Objective: To compare published evidence for the efficacy, durability and safety of emerging anti-VEGF strategies—dual Ang-2/VEGF-A inhibition with faricimab and higher-dose aflibercept (8 mg)—against established aflibercept 2 mg therapy. Methods: A focused narrative synthesis of randomized clinical trials, 2-year follow-up reports and evidence-based guidance, prioritizing YOSEMITE/RHINE and PHOTON. Results: In YOSEMITE/RHINE, 2-year mean visual-acuity gains with faricimab were comparable to aflibercept 2 mg, while many eyes on personalized faricimab treatment achieved 12–16-week intervals. In PHOTON, aflibercept 8 mg at 12- or 16-week intervals preserved visual improvement through week 96 with fewer injections than aflibercept 2 mg every 8 weeks. Conclusions: Both strategies offer evidence-supported durability while maintaining visual outcomes, but they have not been directly compared in the same randomized DME trial. Treatment selection should integrate baseline vision, optical coherence tomography findings, follow-up reliability, safety and affordability. No new patient data are presented.

Keywords: diabetic macular edema; faricimab; aflibercept 8 mg; anti-VEGF; angiopoietin-2; intravitreal injection; visual acuity; optical coherence tomography; treat-and-extend.

INTRODUCTION

Diabetic macular edema is a vision-threatening manifestation of diabetic retinal microvascular disease. Chronic hyperglycemia, inflammation and disruption of the inner blood–retinal barrier promote leakage from retinal vessels, leading to intraretinal fluid accumulation and visual dysfunction. Center-involving DME with reduced visual acuity is commonly treated with intravitreal agents targeting vascular endothelial growth factor A (VEGF-A), supported by repeated assessment of visual function and optical coherence tomography (OCT) [7, 10].

A major challenge is the frequency of injections and monitoring visits. Although many eyes gain vision during the first months of anti-VEGF therapy, durable disease control may require long-term treatment. Transport costs, appointment fatigue and limited access to retinal services can create gaps in follow-up. New agents are therefore evaluated not only for maximal mean visual improvement but also for their capacity to maintain anatomical control with longer intervals between treatments [1–4].

Faricimab is a bispecific antibody designed to inhibit both VEGF-A and angiopoietin-2 (Ang-2); the latter pathway contributes to vascular instability. High-dose aflibercept (8 mg) preserves the target profile of aflibercept while increasing the intravitreal dose. These approaches represent distinct mechanisms for extending treatment durability and should not be assumed equivalent on the basis of dosing interval alone [1–4].

AIM OF THE ARTICLE

To critically compare clinical efficacy, OCT-based anatomical response, treatment durability and safety of faricimab and aflibercept 8 mg for center-involving DME, emphasizing the interpretation of randomized trial evidence and implications for individualized ophthalmic practice.

MATERIALS AND METHODS

This article is a targeted narrative literature review, not a prospective clinical experiment or a formal systematic review. Evidence was drawn from peer-reviewed, randomized clinical studies and follow-up analyses published up to November 2026, together with the NICE guideline NG242. Priority was given to the phase 3 YOSEMITE/RHINE trials of faricimab, the phase 2/3 PHOTON trial of aflibercept 8 mg, and comparative-effectiveness evidence for established anti-VEGF agents [1–7].

The synthesis used four prespecified domains: (1) change in best-corrected visual acuity (BCVA), expressed in ETDRS letters; (2) retinal thickness and fluid on OCT; (3) injection burden and attained dosing intervals; and (4) treatment-emergent safety outcomes. Because the trials differ in enrollment criteria, baseline characteristics, loading doses, extension rules and outcome timings, cross-trial numerical contrasts are descriptive and cannot establish superiority of one emerging agent over the other.

RESULTS AND DISCUSSION

1. Evidence from the YOSEMITE and RHINE trials: dual Ang-2/VEGF-A inhibition

YOSEMITE (n = 940) and RHINE (n = 951) were multicenter, randomized, double-masked phase 3 trials comparing faricimab 6 mg every 8 weeks or a personalized treat-and-extend regimen with aflibercept 2 mg every 8 weeks. The key year-1 visual-acuity noninferiority findings were sustained through the second year, supporting clinically meaningful visual recovery with both treatments [1, 2].

At approximately 2 years (average of weeks 92, 96 and 100), mean BCVA changes in YOSEMITE were +10.7 letters for faricimab every 8 weeks, +10.7 for faricimab treat-and-extend and +11.4 for aflibercept 2 mg; corresponding results in RHINE were +10.9, +10.1 and +9.4 letters [1]. These numbers support comparable mean functional outcomes under the studied regimens; they do not prove that faricimab is universally superior or that every individual eye can safely tolerate longer intervals.

Personalized intervals in the faricimab arm were adjusted based on both BCVA change and central subfield thickness. In the pooled treat-and-extend populations, approximately 78% of patients remaining on study treatment achieved an interval of at least 12 weeks by week 96, including about 62% on 16-week dosing [1]. This suggests a possibility of reducing visit burden for suitable patients while continuing OCT-guided surveillance.

2. Evidence from PHOTON: 8-mg aflibercept with extended intervals

The PHOTON trial assigned patients with center-involving DME to aflibercept 8 mg every 12 weeks (8q12), aflibercept 8 mg every 16 weeks (8q16), or aflibercept 2 mg every 8 weeks (2q8), following regimen-specific initial monthly injections. In the 48-week primary analysis, both 8-mg regimens met predefined noninferiority criteria for BCVA versus 2q8 [3, 4].

At week 96, among 658 treated participants, mean BCVA changes were +8.8 letters (8q12), +7.5 letters (8q16) and +8.4 letters (2q8). Mean central retinal thickness changes were −185.3, −155.0 and −187.0 μm, respectively [3]. Average numbers of active injections through week 96 were 9.5, 7.8 and 13.8. Thus, in the studied population, extended dosing reduced the number of injections while maintaining overall visual gains. The effect should not be interpreted as permission to extend every patient automatically: dose intervals were adjusted when prespecified evidence of disease activity emerged.

Among participants who completed week 96, 88% assigned to 8q12 maintained dosing of at least every 12 weeks and 83% assigned to 8q16 maintained at least every 16 weeks. Some participants qualified for longer intervals, but eligibility for interval extension was conditional on trial monitoring [3].

3. Comparison of pivotal evidence and interpretation of noninferiority

Table 1 summarizes the most directly relevant randomized-trial comparisons. Importantly, each study used its own comparator and distinct retreatment criteria. Faricimab and aflibercept 8 mg were not randomized against one another in these trials, so ranking them on the basis of raw BCVA gains or percentages reaching a 16-week interval would be methodologically unsound.

Table 1. Selected pivotal clinical evidence in diabetic macular edema

Study / follow-up	Intervention vs comparator	BCVA change (ETDRS letters)	Clinical interpretation
YOSEMITE / RHINE, 2 years [1]	Faricimab 6 mg Q8W or T&E vs aflibercept 2 mg Q8W	YOSEMITE: +10.7 / +10.7 vs +11.4; RHINE: +10.9 / +10.1 vs +9.4	Comparable functional gains; personalized faricimab intervals reached up to 16 weeks
PHOTON, week 96 [3]	Aflibercept 8 mg Q12W / Q16W vs aflibercept 2 mg Q8W	+8.8 / +7.5 vs +8.4	Visual gains maintained with fewer injections in 8-mg groups
Protocol T, 2 years [5]	Aflibercept 2 mg vs bevacizumab vs ranibizumab	+12.8 vs +10.0 vs +12.3	Baseline visual acuity modifies comparative benefit

Q8W/Q12W/Q16W: every 8/12/16 weeks; T&E: treat-and-extend; ETDRS: Early Treatment Diabetic Retinopathy Study. Findings belong to separate trial populations and are not a direct cross-drug comparison.

4. Comparative context: established anti-VEGF strategies and cost

Earlier DRCR Retina Network data remain relevant when deciding whether a newer agent is needed. Protocol T demonstrated that mean two-year BCVA improvements occurred with aflibercept 2 mg, bevacizumab and ranibizumab, although comparative efficacy varied with presenting visual acuity [5, 10]. In eyes with poorer baseline vision,

aflibercept produced better average outcomes than bevacizumab at 2 years, whereas differences were less pronounced in eyes with better presenting vision.

The Protocol AC randomized trial compared aflibercept monotherapy with an initial bevacizumab strategy followed by aflibercept when prespecified response criteria were not met. Across 2 years, mean visual improvements were 15.0 and 14.0 letters, respectively, without a statistically significant between-group difference; 70% of eyes in the bevacizumab-first group ultimately switched to aflibercept [6]. These findings underscore that drug acquisition costs, adherence and an explicit plan for reassessment can influence the overall value of treatment, particularly where ophthalmic resources are constrained.

5. Individualized selection and follow-up strategy

Treatment should begin by classifying the type of DME, the extent of central involvement, baseline BCVA and OCT features. In patients with center-involving DME and reduced vision, anti-VEGF therapy is a major evidence-supported option; however, center-involving DME with good visual acuity may sometimes be managed with observation or laser after individualized discussion, depending on clinical circumstances and local guidance [7]. Non-center-involving disease should not simply be assigned the same injection algorithm.

A practical approach is to document BCVA, OCT central subfield thickness, intraretinal/subretinal fluid, ocular history and the patient's capacity to maintain follow-up. After an initial treatment phase, assess anatomic and functional response together. Longer dosing intervals can be considered when disease is sufficiently controlled, but should be shortened if new fluid, retinal thickening or meaningful visual decline indicates recurrent activity. Persistent macular ischemia, retinal structural damage and comorbid ocular pathology may limit visual improvement even when OCT thickness decreases.

In routine practice, a successful long-interval strategy must be judged by vision preserved, treatment persistence, visits actually completed and patient-reported burden, not by the theoretical maximum interval alone. Multidisciplinary diabetes care—including

glycemic and cardiovascular risk-factor management—remains essential because intravitreal therapy treats ocular manifestations rather than the systemic cause of diabetic retinal injury [7].

6. Safety, evidence limitations and research priorities

In the pivotal trials, faricimab and aflibercept 8 mg generally had safety profiles judged acceptable under controlled conditions. Nevertheless, all intravitreal injections carry procedural risks, including infectious endophthalmitis, increased intraocular pressure, intraocular inflammation and retinal complications. A 2025 single-center case series identified noninfectious intraocular inflammation after aflibercept 8 mg in 5 of 41 treated patients; this small, selected cohort cannot establish the population-level incidence or directly overturn randomized-trial safety findings [8]. Safety surveillance and patient counseling about pain, redness, sudden vision loss or new floaters remain essential.

Three interpretive limitations should be emphasized. First, noninferiority for mean BCVA under a specific trial design is not the same as superiority in all patient subgroups. Second, numbers of injections and achieved intervals are influenced by loading schedules, disease-activity rules and differential follow-up across trials. Third, extension results from controlled randomized settings may not translate fully to care systems with variable OCT access or appointment adherence. A future direct head-to-head randomized study of faricimab versus aflibercept 8 mg, including patient-reported burden and economic outcomes, would be more informative than indirect numerical comparisons.

CONCLUSION

Current randomized evidence indicates that both faricimab and aflibercept 8 mg can sustain meaningful visual-acuity improvements in center-involving DME with the possibility of longer dosing intervals compared with established aflibercept 2 mg protocols. YOSEMITE/RHINE supports a personalized faricimab treat-and-extend strategy; PHOTON supports extended-interval dosing with aflibercept 8 mg. Neither trial establishes clinical superiority of one emerging agent over the other. Individualized care

should integrate functional and OCT response, disease activity, ocular safety, financial accessibility and reliable follow-up. Stronger comparative effectiveness research is needed to establish the best patient-specific sequencing strategies.

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