AMERICAN ACADEMY OF OPHTHALMOLOGY®

Faricimab Treat-and-Extend for Diabetic Macular Edema

Two-Year Results from the Randomized Phase 3 YOSEMITE and RHINE Trials

*Tien Y. Wong, MD, PhD,[1] Zdenka Haskova, MD, PhD,[2] Kemal Asik, PhD,[2] Caroline R. Baumal, MD,[3] Karl G. Csaky, MD, PhD,[4] Nicole Eter, MD, PhD,[5] Jane A. Ives, MSc,[6] Glenn J. Jaffe, MD,[7] Jean-François Korobelnik, MD,[8] Hugh Lin, MD, MBA,[2] Toshinori Murata, MD, PhD,[9] Paisan Ruamviboonsuk, MD,[10] Patricio G. Schlottmann, MD,[11] András I. Seres, MD,[12] David Silverman, MSc, MBChB,[6] Xiaodong Sun, MD, PhD,[13] Yannan Tang, PhD,[2] John A. Wells, MD,[14] Young Hee Yoon, MD, PhD,[15] Charles C. Wykoff, MD, PhD,[16] for the YOSEMITE and RHINE Investigators**

Purpose: To evaluate the 2-year efficacy, durability, and safety of dual angiopoietin-2 and vascular endothelial growth factor (VEGF) A pathway inhibition with intravitreal faricimab according to a personalized treat-and-extend (T&E)-based regimen with up to every-16-week dosing in the YOSEMITE and RHINE (ClinicalTrials.gov identifiers, NCT03622580 and NCT03622593, respectively) phase 3 trials of diabetic macular edema (DME).

Design: Randomized, double-masked, noninferiority phase 3 trials.

Participants: Adults with visual acuity loss (best-corrected visual acuity [BCVA] of 25−73 letters) due to center-involving DME.

Methods: Patients were randomized 1:1:1 to faricimab 6.0 mg every 8 weeks, faricimab 6.0 mg T&E (previously referred to as personalized treatment interval), or aflibercept 2.0 mg every 8 weeks. The T&E up to every-16-week dosing regimen was based on central subfield thickness (CST) and BCVA change.

Main Outcome Measures: Included changes from baseline in BCVA and CST, number of injections, durability, absence of fluid, and safety through week 100.

Results: In YOSEMITE and RHINE (n = 940 and 951, respectively), noninferior year 1 visual acuity gains were maintained through year 2; mean BCVA change from baseline at 2 years (weeks 92, 96, and 100 average) with faricimab every 8 weeks (YOSEMITE and RHINE, +10.7 letters and +10.9 letters, respectively) or T&E (+10.7 letters and +10.1 letters, respectively) were comparable with aflibercept every 8 weeks (+11.4 letters and +9.4 letters, respectively). The median number of study drug injections was lower with faricimab T&E (YOSEMITE and RHINE, 10 and 11 injections, respectively) versus faricimab every 8 weeks (15 injections) and aflibercept every 8 weeks (14 injections) across both trials during the entire study. In the faricimab T&E arms, durability was improved further during year 2, with > 60% of patients receiving every-16-week dosing and approximately 80% receiving every-12-week or longer dosing at week 96. Almost 80% of patients who achieved every-16-week dosing at week 52 maintained every-16-week dosing without an interval reduction through week 96. Mean CST reductions were greater (YOSEMITE/RHINE weeks 92/96/100 average: faricimab every 8 weeks −216.0/−202.6 μm, faricimab T&E −204.5/−197.1 μm, aflibercept every 8 weeks −196.3/−185.6 μm), and more patients achieved absence of DME (CST < 325 μm; YOSEMITE/RHINE weeks 92−100: faricimab every 8 weeks 87%−92%/88%−93%, faricimab T&E 78%−86%/85%−88%, aflibercept every 8 weeks 77%−81%/80%−84%) and absence of intraretinal fluid (YOSEMITE/RHINE weeks 92−100: faricimab every 8 weeks 59%−63%/56%−62%, faricimab T&E 43%−48%/45%−52%, aflibercept every 8 weeks 33%−38%/39%−45%) with faricimab every 8 weeks or T&E versus aflibercept every 8 weeks through year 2. Overall, faricimab was well tolerated, with a safety profile comparable with that of aflibercept.

Conclusions: Clinically meaningful visual acuity gains from baseline, anatomic improvements, and extended durability with intravitreal faricimab up to every 16 weeks were maintained through year 2. Faricimab given as a personalized T&E-based dosing regimen supports the role of dual angiopoietin-2 and VEGF-A inhibition to promote vascular stability and to provide durable efficacy for patients with DME.

Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology 2024;131:708-723*

Supplemental material available at www.aaojournal.org.

https://doi.org/10.1016/j.ophtha.2023.12.026
ISSN 0161-6420/24

Over the past decade, intravitreal anti-VEGF therapy has become the standard of care for patients with center-involving diabetic macular edema (DME) with visual impairment.[1–3] However, studies frequently show that the efficacy associated with anti-VEGF therapies in clinical trials is not achieved or maintained in clinical practice.[4–9] Suboptimal real-world outcomes may be attributed to undertreatment associated with the burden of frequent monitoring visits and injections and heterogeneity in anti-VEGF treatment response across patient populations.[9,10] Concurrently, it is increasingly clear that the pathophysiologic features of DME involve multiple biologic pathways[3,11]; therefore, multitargeted treatment strategies may address additional sequela that can develop in patients treated with anti-VEGF therapy and have the potential to improve durability and outcomes beyond targeting the VEGF pathway alone.

The angiopoietin-1 and Tie2 signaling pathway is a key regulator of vascular stability and controls vessel permeability, inflammation, and angiogenic responses.[12,13] Under homeostatic conditions, the agonistic ligand angiopoietin-1 binds to and activates Tie2, leading to downstream signaling that maintains vascular stability by promoting endothelial cell survival, pericyte recruitment, and improved endothelial barrier function.[12,13] In DME and other retinal vascular diseases, angiopoietin-2 is upregulated and acts as a competitive antagonist of angiopoietin-1, binding to Tie2 and disrupting the vascular stabilization effects of angiopoietin-1/Tie2 signaling, resulting in vascular permeability, instability, and remodeling.[12–15] Elevated levels of angiopoietin-2 promote retinal vessel sensitivity to proinflammatory mediators and the angiogenetic effects of VEGF[15–19] and drives inflammation by inducing expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, which leads to leukocyte adhesion and transmigration.[20] Independently of Tie2, angiopoietin-2 can have direct proangiogenic effects by signaling through integrins to promote vascular destabilization and apoptosis of pericytes and astrocytes.[21–24] Faricimab was designed as a novel bispecific antibody for intraocular use that binds and neutralizes both angiopoietin-2 and VEGF-A.[25] Data from proof-of-concept phase 2 and confirmatory phase 3 clinical trials across 3 retinal indications (DME, neovascular age-related macular degeneration, and retinal vein occlusion) support the hypothesis that dual angiopoietin-2 and VEGF-A pathway inhibition with faricimab may promote vascular stability, may extend treatment durability (yet to be confirmed for retinal vein occlusion), and may optimize outcomes for these retinal diseases.[26–31]

The phase 3 YOSEMITE and RHINE randomized active-controlled trials evaluated faricimab treatment for DME (n = 1891). Patients with DME received intravitreal faricimab every 8 weeks, faricimab according to a personalized treat-and-extend–based regimen (T&E) with dosing extended up to every 16 weeks, or aflibercept 2.0 mg every 8 weeks over 2 years.[31,32] At 1 year, YOSEMITE and RHINE each met their primary end point; adjusted mean best-corrected visual acuity (BCVA) changes from baseline with faricimab every 8 weeks and T&E up to every-16-week dosing ranged between 10.8 and 11.8 Early Treatment Diabetic Retinopathy Study (ETDRS) letters and were noninferior to aflibercept every 8 weeks.[31] Secondary end points at year 1 also showed greater anatomic benefits with faricimab every 8 weeks and faricimab T&E compared with aflibercept every 8 weeks; central subfield thickness (CST) reductions were greater with faricimab versus aflibercept at 1 year, and more faricimab-treated patients achieved absence of protocol-defined DME (CST < 325 μm) and absence of intraretinal fluid (IRF) compared with aflibercept over time.[31] Importantly, in the faricimab T&E up to every-16-week dosing arms, clinically significant visual acuity gains and anatomic improvements were achieved with extended dosing; $> 70\%$ of patients were extended to every-12-week or longer dosing, and $> 50\%$ were extended to every 16 weeks at week 52.[31] Faricimab was well tolerated through year 1 with a safety profile comparable with that of aflibercept, and no cases of retinal vasculitis or occlusive retinal vasculitis were reported.[31]

The year 1 data from YOSEMITE and RHINE suggest that dual angiopoietin-2 and VEGF-A pathway inhibition with faricimab in DME may confer anatomic and durability advantages over VEGF inhibition alone.[31] To evaluate the longer-term efficacy, durability, and safety of faricimab in patients with DME, we herein report 2-year results from the phase 3 YOSEMITE and RHINE trials.

Methods

YOSEMITE and RHINE

The study design, rationale, and primary 1-year results of YOSEMITE and RHINE are described in detail elsewhere.[31,32] In brief, YOSEMITE (ClinicalTrials.gov identifier, NCT03622580) and RHINE (ClinicalTrials.gov identifier, NCT03622593) were identically designed, randomized, double-masked, active comparator-controlled phase 3 trials conducted across 353 study sites in 31 participating countries. The YOSEMITE and RHINE studies adhered to the International Council for Harmonization E6 Guideline for Good Clinical Practice, the tenets of the Declaration of Helsinki, United States Food and Drug Administration regulations, European Union Clinical Trials Directive (2001/20/EC), and applicable local, state, and federal laws. Institutional review board or ethics committee approval was obtained for study protocols as appropriate (List of institutional review boards availaable at wwww.aaojournal.org), and all patients provided written informed consent to participate.

Patients eligible for inclusion were ≥ 18 years of age and had center-involving DME secondary to diabetes (types 1 or 2), defined as CST of ≥ 325 μm (measured as the average thickness between the internal limiting membrane and Bruch's membrane in the central 1-mm diameter of the ETDRS grid) and BCVA of 25 to 73 ETDRS letters (approximate Snellen equivalent, 20/320–20/40). Full eligibility criteria for YOSEMITE and RHINE are reported in the primary trial publication.[31] One eye per patient was designated the study eye; if both eyes were eligible, the eye with worse BCVA at screening was selected. Eyes previously treated with anti-VEGF agents (last treated ≥ 3 months before day 1) were eligible for inclusion but were limited to 25% of total enrollment.

Patients were randomized 1:1:1 to intravitreal faricimab 6.0 mg every 8 weeks after 6 initial every-4-week doses, intravitreal faricimab 6.0 mg T&E with up to every-16-week dosing intervals after ≥ 4 initial every-4-week doses, or intravitreal aflibercept 2.0 mg every 8 weeks after 5 initial every-4-week doses. Aflibercept

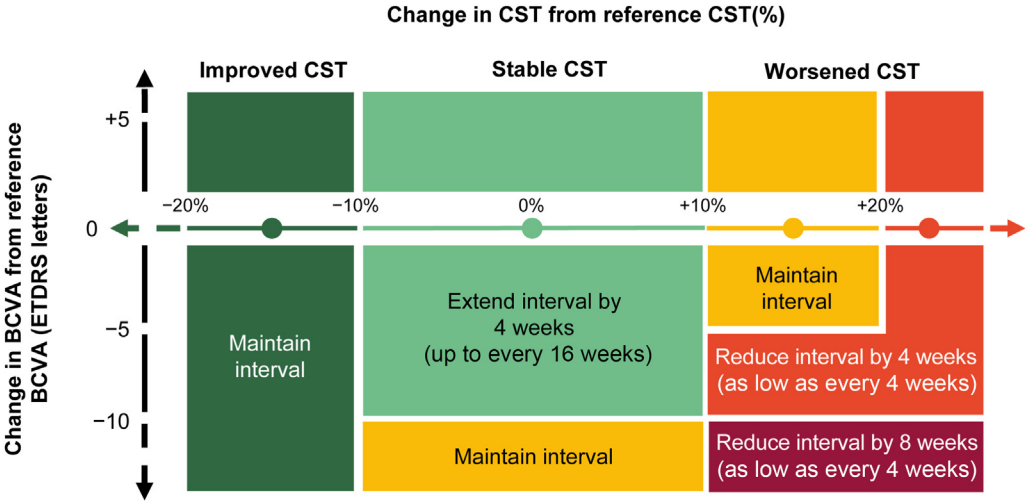


Figure 1. Faricimab treat-and-extend algorithm in the YOSEMITE and RHINE trials. Reference central subfield thickness (CST) was defined as the CST value when the initial CST threshold criteria were met (CST < 325 μm at or after the week 12 study visit). The reference CST was adjusted if CST decreased by > 10% from the previous reference CST for 2 consecutive study drug dosing visits and the values obtained were within 30 μm. The CST value obtained at the latter visit served as the new reference CST. Reference best-corrected visual acuity (BCVA) was defined as the mean of the 3 best BCVA scores obtained at any previous active dosing visit. ETDRS = Early Treatment Diabetic Retinopathy Study. (Reprinted with permission from Heier et al.[26] © 2022 Elsevier.)

every-8-week dosing was selected to align with the approved aflibercept label, in the absence of a globally accepted extended dosing regimen.[33–35] The T&E regimen is a personalized treat-and-extend–based dosing regimen that allowed adjustable dosing (from every 4 weeks up to every 16 weeks) based on protocol-prespecified CST and BCVA criteria at active dosing visits.[31,32] The personalized T&E regimen is commonly used clinically[36] but, in the registrational phase 3 trial setting, was referred to as "personalized treatment interval" because the regimen used an automated treatment algorithm driven by an interactive voice- or web-based response system to determine whether a patient's treatment interval should be reduced, maintained, or extended based on protocol-prespecified criteria.[32] Patients randomized to the faricimab T&E arms initially received faricimab at every-4-week intervals until they first reached CST of < 325 μm at or after week 12. Once achieved, treatment intervals were extended to an initial every-8-week dosing, then could be maintained, extended by 4 weeks (up to every 16 weeks), or reduced by 4 weeks or 8 weeks (as low as every 4 weeks) based on prespecified CST and BCVA criteria at active dosing visits (Fig 1). To maintain masking, all patients attended every-4-week study visits where they received active treatment or sham up to week 96; the final study visit was at week 100. For patients who received faricimab T&E, dosing interval decisions were made at active treatment visits only.

Key ocular assessments throughout the study period included BCVA, intraocular pressure, slit-lamp examination, indirect ophthalmoscopy, and retina imaging (spectral-domain OCT, OCT-angiography where available, color fundus photography, and fundus fluorescein angiography) that were assessed independently at central reading centers (OCT and OCT angiography: Duke Reading Center, Durham, NC, and Vienna Reading Center, Austria; color fundus photography and fundus fluorescein angiography: Wisconsin Reading Center, Madison, WI).

Outcome Measures

The primary efficacy end point of YOSEMITE and RHINE was change in BCVA from baseline at 1 year, averaged over weeks 48, 52, and 56.[31] Two-year trial outcomes reported herein were consistent with prespecified end points in the primary analysis[31] and included change in BCVA from baseline at 2 years (defined as the average of weeks 92, 96, and 100) and over time; the proportion of patients in the faricimab T&E dosing arms on every-4-week, every-8-week, every-12-week, or every-16-week dosing intervals at week 96 and over time; change in CST from baseline at 2 years and over time; the proportion of patients with absence of DME (CST < 325 μm based on protocol-defined DME at screening) over time; the proportion of patients with absence of IRF over time (measured in the central 1-mm ETDRS circle); and the incidence and severity of ocular and nonocular adverse events (AEs) through study end. Other 2-year efficacy end points included the proportion of patients who gained BCVA (≥ 15 ETDRS letters, ≥ 10 ETDRS letters, ≥ 5 ETDRS letters, or ≥ 0 ETDRS letters) or avoided BCVA loss (≥ 15 ETDRS letters, ≥ 10 ETDRS letters, or ≥5 ETDRS letters) at 2 years; patients who gained 15 ETDRS letters or more or achieved Snellen BCVA of 20/20 or better (≥ 84 ETDRS letters) at 2 years; patients with Snellen BCVA of 20/40 or better (≥ 69 ETDRS letters) at 2 years; and the proportion of patients with ≥ 2-step improvement on the ETDRS Diabetic Retinopathy Severity Scale (DRSS) at week 96.

Statistical Analysis

Two-year efficacy and safety analyses were performed as described in the primary 1-year trial publication.[31] Efficacy analyses were based on the intention-to-treat population, grouped by treatment arm at randomization. Adjusted means for continuous end points were assessed using a mixed model for repeated measures (MMRM), with the same analysis method and data handling rules as described previously for the primary end point. In brief, the MMRM included change from baseline as the response variable and categorical covariates of treatment group, visit, visit-by-treatment group interaction, baseline value for the response variable (continuous), study (YOSEMITE vs RHINE, for the pooled cohort data only), and randomization stratification factors as fixed effects. The model assumed an unstructured covariance structure; missing data were

imputed implicitly assuming a missing-at-random mechanism. For binary secondary end points, weighted proportions were estimated using the Cochran-Mantel-Haenszel method stratified by baseline BCVA score (< 64 letters vs ≥ 64 letters), prior intravitreal anti-VEGF therapy (yes vs no), region (United States and Canada, Asia, and the rest of the world), and study (YOSEMITE vs RHINE, for the pooled cohort data only). For all MMRM and Cochran-Mantel-Haenszel analyses, intercurrent events related to the coronavirus disease 2019 (COVID-19) pandemic were handled using a hypothetical strategy in which all values were censored after the intercurrent event, and intercurrent events not related to COVID-19 were handled using a treatment policy strategy in which all observed values were used regardless of the intercurrent event. Adjusted means and weighted proportions are reported with 95.04% confidence intervals (CIs) for the individual trial data to adjust for interim safety assessments conducted through to the completion of the primary analysis and as 95% CIs for the pooled cohort data.[31] Post hoc hypothesis tests were performed to detect differences between faricimab and aflibercept treatment arms, with *P* values presented for reference. The YOSEMITE and RHINE safety analysis population included all patients who received ≥ 1 dose of faricimab or aflibercept, grouped by actual treatment regimen received. Safety and tolerability were assessed through descriptive summaries of ocular and nonocular AEs (coded using Medical Dictionary for Regulatory Activities thesaurus terms), deaths, and ocular assessments through study end.

Results

Patient Disposition

A total of 940 and 951 patients were enrolled in YOSEMITE (September 2018 to September 2019) and RHINE (October 2018 to September 2019), respectively.[31] One eye per patient was designated as the study eye. The intention-to-treat population of YOSEMITE included 315 patients randomized to faricimab every 8 weeks, 313 patients randomized to faricimab T&E, and 312 patients randomized to aflibercept every 8 weeks (Fig 2A). The intention-to-treat population of RHINE included 317 patients randomized to faricimab every 8 weeks, 319 patients randomized to faricimab T&E, and 315 patients randomized to aflibercept every 8 weeks (Fig 2B).

Overall, 84% of patients who received ≥ 1 dose of faricimab or aflibercept in YOSEMITE and 87% of those in RHINE completed study treatment through week 100. The proportion of patients who discontinued study treatment and the reasons for discontinuation were generally balanced across treatment arms and trials (Fig 2). Major protocol deviations through study end were reported for 563 patients (60%) in YOSEMITE and 602 patients (63%) in RHINE (Table S1, available at www.aaojournal.org). The number, proportion of deviations, and type of major protocol deviations through study end were consistent across treatment arms and trials. Most of the major protocol deviations were procedural, such as selected missed visits (YOSEMITE, 308 patients [33.0%]; RHINE, 328 patients [35.0%]) and issues with images of the study eye (YOSEMITE, 94 patients [10.0%]; RHINE, 139 patients [15.0%]). Among patients with major protocol deviations, 191 patients (20%) in YOSEMITE and 279 patients (29%) in RHINE reported ≥ 1 major protocol deviations related to COVID-19, most of whom missed ≥ 1 study visits around the primary end point and/or final study visits (167 patients [18%] and 210 patients [22%], respectively). Of these, only 63 patients (6.7%) in YOSEMITE and 76 patients (8.0%) in RHINE missed ≥ 1 doses of study treatment around the primary end point visits, and 15 patients (1.6%) and 48 patients (5.0%) missed ≥ 1 doses of study treatment around the final study visits.

As reported in the primary trial publication,[31] baseline patient characteristics in YOSEMITE and RHINE generally were well balanced across treatment arms and trials.

Visual Acuity Outcomes

The YOSEMITE and RHINE trials reproducibly demonstrated visual gains with faricimab every 8 weeks and T&E that were maintained over time through year 2 and were comparable with aflibercept administered every 8 weeks, despite fewer treatment doses administered in the faricimab T&E arm (Fig 3). In YOSEMITE, adjusted mean BCVA change from baseline at 2 years (averaged over weeks 92, 96, and 100) was +10.7 ETDRS letters (95.04% CI, +9.4 to +12.1 ETDRS letters) in the faricimab every-8-week arm and +10.7 ETDRS letters (95.04% CI, +9.4 to +12.1 ETDRS letters) in the faricimab T&E arm versus +11.4 ETDRS letters (95.04% CI, +10.0 to +12.7 ETDRS letters) in the aflibercept every-8-week arm (mean difference vs aflibercept every 8 weeks, −0.7 ETDRS letters [95.04% CI, −2.6 to +1.2 ETDRS letters] and −0.7 ETDRS letters [95.04% CI, −2.5 to +1.2 ETDRS letters], respectively; nominal $P > 0.05$ for both). Corresponding 2-year BCVA gains in RHINE were +10.9 ETDRS letters (95.04% CI, +9.5 to +12.3 ETDRS letters) and +10.1 ETDRS letters (95.04% CI, +8.7 to +11.5 ETDRS letters) versus +9.4 ETDRS letters (95.04% CI, +7.9 to +10.8 ETDRS letters), respectively (mean difference vs aflibercept every 8 weeks, +1.5 ETDRS letters [95.04% CI, −0.5 to +3.6 ETDRS letters] and +0.7 ETDRS letters [95.04% CI, −1.3 to +2.7 ETDRS letters]; nominal $P > 0.05$ for both). In the pooled YOSEMITE and RHINE cohort, 2-year BCVA gains were +10.8 ETDRS letters (95% CI, +9.8 to +11.8 ETDRS letters) and +10.4 ETDRS letters (95% CI, +9.4 to +11.4 ETDRS letters) in the faricimab every-8-week and faricimab T&E arms, respectively, versus +10.3 ETDRS letters (95% CI, +9.3 to +11.3 ETDRS letters) in the aflibercept every-8-week arm (mean difference vs aflibercept every 8 weeks, +0.5 ETDRS letters [95% CI, −0.9 to +1.8 ETDRS letters] and +0.1 ETDRS letters [95% CI, −1.3 to +1.5 ETDRS letters]; nominal $P > 0.05$ for both; Fig S4, available at www.aaojournal.org). Sensitivity and supplemental analyses to test the robustness of these results were consistent across different methods for handling missing data and intercurrent events (Table S2, available at www.aaojournal.org). Additional 2-year BCVA end points were similarly consistent across treatment arms and were reproducible across trials (Table S3, available at www.aaojournal.org).

In the safety analysis population, the median (mean ± standard deviation) number of study drug injections in each of the YOSEMITE and RHINE faricimab T&E arms was 8 injections (YOSEMITE, 8.4 ± 2.45 injections; RHINE, 8.7 ± 2.50 injections) in year 1 (baseline−week 56), compared with 10 injections in each of the faricimab every-8-week arms (YOSEMITE, 9.5 ± 1.41 injections; RHINE, 9.3 ± 1.52 injections) and aflibercept every-8-week arms (YOSEMITE, 9.2 ± 1.47 injections; RHINE, 9.3 ± 1.36 injections). During year 2 (week 60−week 96), the faricimab T&E arms received a median (mean ± standard deviation) of 3 study drug injections (YOSEMITE, 3.5 ± 1.76 injections; RHINE, 3.6 ± 1.98 injections) versus 5 injections in each of the faricimab every-8-week arms (YOSEMITE, 4.7 ± 0.74 injections; RHINE, 4.7 ± 0.82 injections) and aflibercept every-8-week arms (YOSEMITE, 4.5 ± 0.92 injections; RHINE, 4.5 ± 0.99 injections). From baseline during the entire study, the median (mean ± standard deviation) number of study drug injections in the T&E arms was 10 injections (11.5 ± 3.98 injections) in YOSEMITE and 11 injections (12.1 ± 4.12 injections) in RHINE, compared with 15 injections (YOSEMITE, 13.6 ± 2.87 injections; RHINE, 13.5 ± 2.87 injections) in the faricimab every-8-week arms and 14 injections

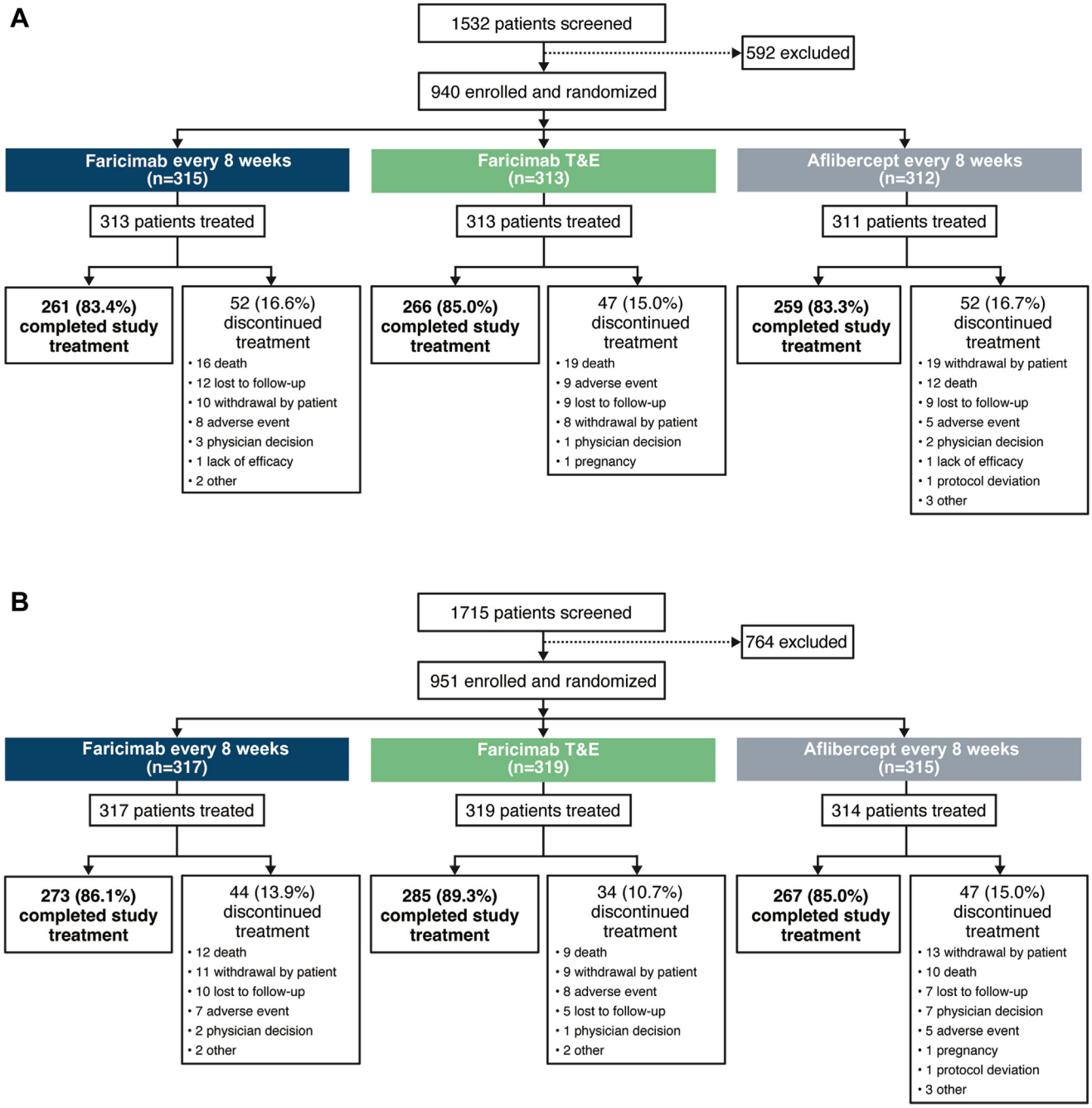


Figure 2. A, B, Consolidated Standards of Reporting Trials flow diagram for (**A**) YOSEMITE and (**B**) RHINE. T&E = treat-and-extend.

(YOSEMITE, 13.3 ± 2.75 injections; RHINE, 13.4 ± 2.66 injections) in the aflibercept every-8-week arms.

Durability Outcomes

The durability of faricimab reported in the 1-year primary analysis[31] was further improved during year 2 of YOSEMITE and RHINE, with greater proportions of patients in the T&E arms extending their dosing while maintaining comparable visual acuity gains and greater anatomic benefits versus aflibercept (Fig 5). At week 96, 211 patients (78%) in the faricimab T&E arm of YOSEMITE and 224 patients (78%) in RHINE achieved every-12-week dosing intervals or longer (557 patients [78%] in the pooled YOSEMITE and RHINE cohort), which included 162 patients (60%) and 185 patients (64%), respectively, who achieved every-16-week dosing (Fig 5A; pooled YOSEMITE and RHINE cohort, 347 patients [62%]; Fig S6A, available at www.aaojournal.org). Patient ability to achieve and/or maintain extended faricimab dosing intervals up to every 16 weeks through week 96 is shown in the dosing-interval schematic, which shows that in most patients who achieved every-12-week or every-16-week dosing at 1 year, it was possible to maintain and/or extend their dosing interval through year 2 (Fig 5B; Fig S6B, available at www.aaojournal.org, for the pooled YOSEMITE and RHINE cohort). Approximately 79% of patients who achieved every-12-week dosing or longer at week 52 maintained every-12-

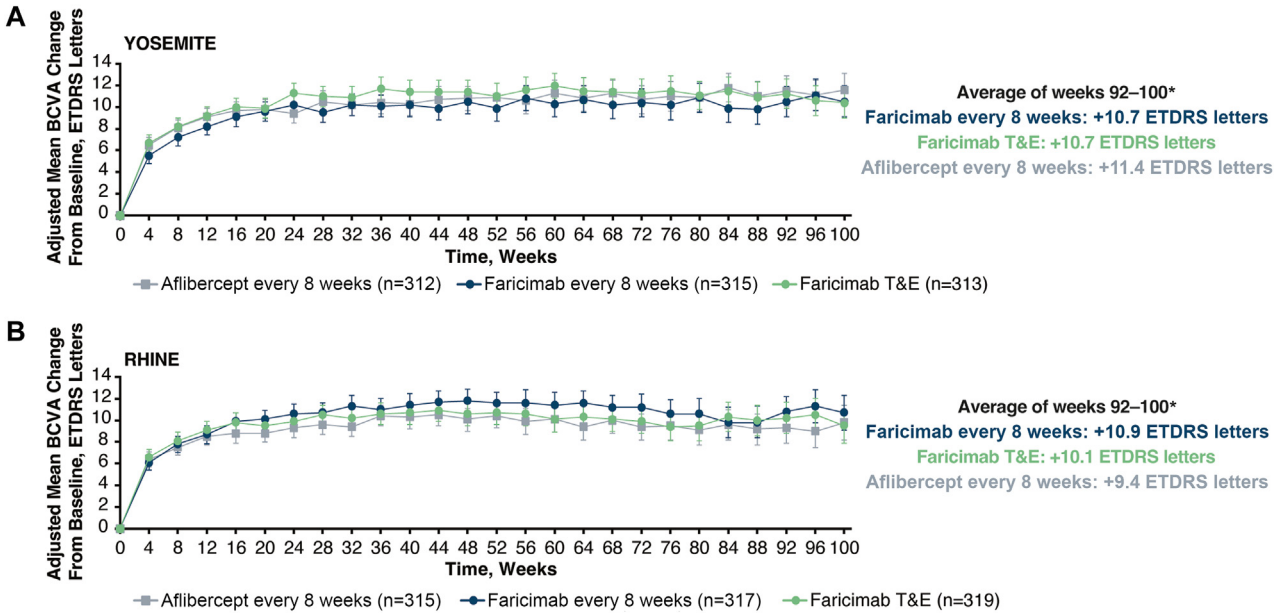


Figure 3. **A**, **B**, Line graphs showing adjusted mean change in best-corrected visual acuity (BCVA) from baseline through week 100 in (**A**) YOSEMITE and (**B**) RHINE. *Adjusted mean BCVA change from baseline at 2 years, averaged over weeks 92, 96, and 100. Results are based on a mixed model for repeated measures (MMRM) analysis of the intention-to-treat population. Treatment policy strategy and hypothetical strategy were applied to intercurrent events not related to and related to the coronavirus disease 2019 pandemic, respectively. Missing data were imputed implicitly by the MMRM. Error bars represent 95.04% confidence intervals (CIs). ETDRS = Early Treatment Diabetic Retinopathy Study; T&E = treat-and-extend.

week dosing or longer without an interval reduction below every 12 weeks through week 96 (YOSEMITE, 150 patients [75%]; RHINE, 172 patients [83%]). Similarly, 76% of patients who achieved every-16-week dosing at week 52 maintained every-16-week dosing without an interval reduction through week 96 (YOSEMITE, 100 patients [70%]; RHINE, 121 patients [82%]). Approximately 18% of patients rapidly achieved every-16-week dosing at week 32 (i.e., the earliest time point that every-16-week dosing was possible because of the study design) and subsequently maintained every-16-week dosing through week 96 (YOSEMITE, 44 patients [16%]; RHINE, 58 patients [20%]). Conversely, < 5% of patients extended to every-8-week dosing at or after week 12, and then remained on every-8-week or every-4-week dosing through week 96 (YOSEMITE, 10 patients [4%]; RHINE, 16 patients [6%]). In approximately 4% of patients, it was not possible to extend the dosing interval beyond every 4 weeks from baseline through week 96 (YOSEMITE, 7 patients [3%]; RHINE, 15 patients [5%]).

Anatomic Outcomes

Overall, improved anatomic outcomes achieved with faricimab versus aflibercept at 1 year[31] were maintained through year 2. In YOSEMITE, adjusted mean CST change from baseline at year 2 (averaged over weeks 92, 96, and 100) was −216.0 μm (95.04% CI, −224.0 to −208.0 μm) in the faricimab every-8-week arm, which was greater than that in the aflibercept every-8-week arm (−196.3 μm [95.04% CI, −204.3 to −188.2 μm]; nominal P = 0.0007; Fig 7). In RHINE, mean 2-year CST reductions were also greater with faricimab every 8 weeks versus aflibercept every 8 weeks (−202.6 μm [95.04% CI, −211.1 to −194.2 μm] vs −185.6 μm [95.04% CI, −194.1 to −177.1 μm]; nominal P = 0.0052; Fig 7). In the faricimab T&E arms, adjusted mean CST change at 2 years was comparable with that of aflibercept every 8 weeks in YOSEMITE (−204.5 μm [95.04% CI, −212.4 to −196.5 μm]; nominal P > 0.05) and RHINE (−197.1 μm [95.04% CI, −205.3 to −188.9 μm]; nominal P > 0.05), but was achieved with most patients receiving every-16-week dosing (Fig 7). In the pooled YOSEMITE and RHINE cohort, mean 2-year CST reductions were greater in both the faricimab every-8-week arm (−209.4 μm [95% CI, −215.2 to −203.6 μm]) and the faricimab T&E arm (−201.0 μm [95% CI, −206.7 to −195.3 μm]) compared with the aflibercept every-8-week arm (−190.9 μm [95% CI, −196.7 to −185.0 μm]; nominal P < 0.0001 and P = 0.0150 vs aflibercept every 8 weeks, respectively [Fig S8, available at www.aaojournal.org]).

Consistent with the 1-year primary analysis,[31] the proportion of patients who achieved absence of protocol-defined DME was higher for faricimab compared with aflibercept through year 2 (Fig 9). The proportion of patients in YOSEMITE who achieved absence of DME at weeks 92−100 was 87%−92% in the faricimab every-8-week arm and 78%−86% in the faricimab T&E arm, compared with 77%−81% in the aflibercept every-8-week arm. Corresponding proportions in RHINE were 88%−93% and 85%−88% versus 80%−84%, respectively (Fig 9). In the pooled YOSEMITE and RHINE cohort, the proportion of patients who achieved absence of DME at weeks 92−100 was 88%−92% in the faricimab every-8-week arm, 81%−86% in the faricimab T&E arm, and 79%−83% in the aflibercept every-8-week arm (Fig S10, available at www.aaojournal.org).

Absence of IRF was also achieved by more patients treated with faricimab when compared with those treated with aflibercept through year 2 (Fig 11). At weeks 92−100 of YOSEMITE, the proportion of patients who achieved absence of IRF was 59%−63% in the faricimab every-8-week arm and 43%−48% in the faricimab T&E arm, compared with 33%−38% in the aflibercept every-8-week arm. Proportions were similar in RHINE (56%−62% and 45%−52% vs 39%−45%, respectively). Corresponding

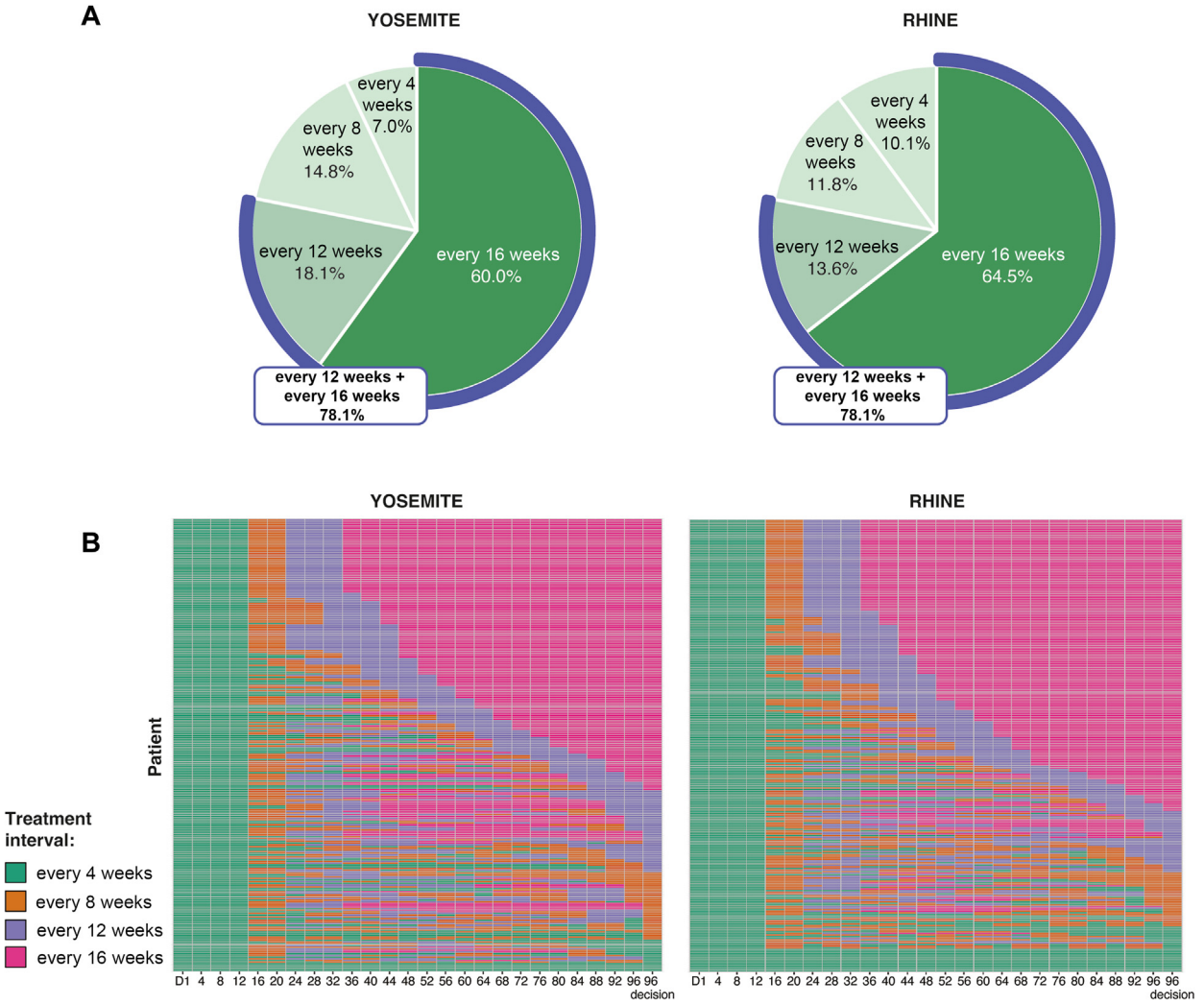


Figure 5. **A**, **B**, Proportion of patients in the faricimab treat-and-extend (T&E) arms who achieved every-4-week, every-8-week, every-12-week, or every-16-week dosing at week 96 (**A**) and dosing intervals in the faricimab T&E arms through week 96 (**B**). Analyses included patients in the faricimab T&E arms who had not discontinued the study at the week 96 visit (YOSEMITE, n = 270; RHINE, n = 287). Treatment interval at week 96 was defined as the treatment interval decision made at that visit in (**A**), and treatment interval at a given visit is shown as the interval at the start of the visit in (**B**). The week 96 decision (calculated or recorded at week 96) is shown in the last column. D = day.

proportions for the pooled YOSEMITE and RHINE cohort were 57%–63% and 44%–48% in the faricimab every-8-week and faricimab T&E arms, respectively, versus 36%–41% in the aflibercept every-8-week arm (Fig S12, available at www.aaojournal.org).

The proportion of patients who had at least 2-step ETDRS DRSS improvement from baseline at week 96 was similar across treatment arms and trials (Fig 13). In YOSEMITE, 51.4% of patients (95.04% CI, 44.8%–57.9%) in the faricimab every-8-week arm had at least 2-step ETDRS DRSS improvement at week 96, compared with 42.2% (95.04% CI, 35.9%–48.5%) in the aflibercept every-8-week arm (nominal $P > 0.05$). In RHINE, the corresponding estimate was 53.5% (95.04% CI, 46.9%–60.1%) in the faricimab every-8-week dosing arm, which was greater than that in the aflibercept every-8-week arm (43.8% [95.04% CI, 37.2%–50.4%]; nominal $P = 0.0475$). In the faricimab T&E arms, the proportion of patients who achieved at least 2-step ETDRS DRSS improvement at week 96 was comparable with aflibercept every 8 weeks in YOSEMITE (42.8% [95.04% CI, 36.6%–49.0%]; nominal $P > 0.05$) and RHINE (44.3% [95.04% CI, 37.9%–50.7%]; nominal $P > 0.05$; Fig 13). Corresponding proportions in the YOSEMITE and RHINE pooled cohort were 52.4% (95% CI, 47.8%–57.0%) in the faricimab every-8-week arm and 43.5% (95% CI, 39.1%–48.0%) in the faricimab T&E arms versus 43.0% (95% CI, 38.4%–47.5%) in the aflibercept every-8-week arm (nominal $P = 0.0058$ and $P > 0.05$ vs aflibercept every 8 weeks, respectively; Fig S14, available at www.aaojournal.org). These findings were achieved in the T&E arms with 60% (3 injections) of the median number of injections received in the faricimab every-8-week and aflibercept every-8-week arms (5 injections) in year 2.

Safety Outcomes

Consistent with the 1-year primary analysis,[31] faricimab was well tolerated with a safety profile that remained comparable with that

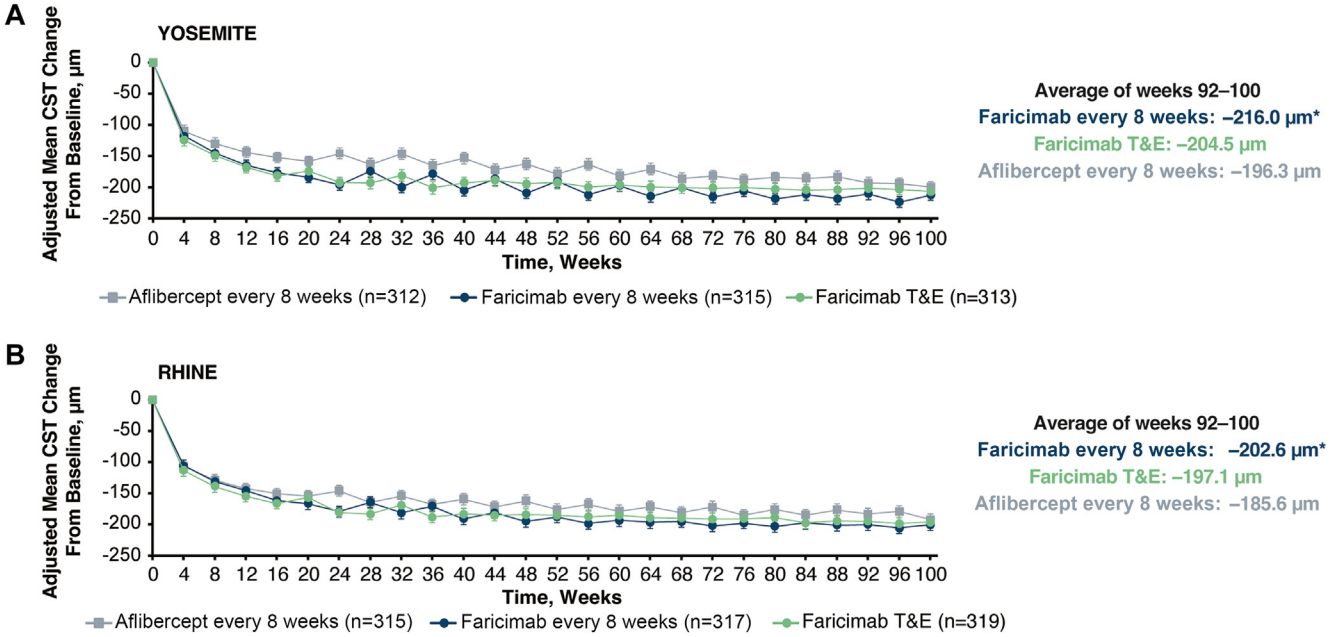


Figure 7. A, B, Line graphs showing adjusted mean change in central subfield thickness (CST) from baseline through week 100 in (**A**) YOSEMITE and (**B**) RHINE. *Nominal $P < 0.05$ versus aflibercept every 8 weeks for adjusted mean CST change from baseline at 2 years, averaged over weeks 92, 96, and 100. Results are based on a mixed model for repeated measures (MMRM) analysis of the intention-to-treat population. Treatment policy strategy and hypothetical strategy were applied to intercurrent events not related to and related to the coronavirus disease 2019 pandemic, respectively. Missing data were imputed implicitly by the MMRM. Error bars represent 95.04% confidence intervals (CIs). CST was defined as the average thickness between the internal limiting membrane and Bruch's membrane in the central 1-mm diameter of the Early Treatment Diabetic Retinopathy Study grid. T&E = treat-and-extend.

of aflibercept through study end (Table 4; Tables S5–S8, available at www.aaojournal.org). The incidence of ocular AEs in the study eye through study end was similar between the faricimab every-8-week arms (YOSEMITE, 147 patients [47%]; RHINE, 166 patients [52%]), faricimab T&E arms (146 patients [47%]; 165 patients [52%]), and aflibercept every-8-week arms (144 patients [46%]; 140 patients [45%]). Most ocular AEs were mild or moderate in severity, and common ocular AEs reported were generally balanced across faricimab and aflibercept treatment arms. The incidence of serious ocular AEs through study end was low and comparable between patients receiving faricimab every 8 weeks (YOSEMITE, 12 patients [4%]; RHINE, 14 patients [4%]), faricimab T&E (14 patients [4%]; 20 patients [6%]) and aflibercept every 8 weeks (7 patients [2%]; 13 patients [4%]). Nonocular AEs and Anti-Platelet Trialists' Collaboration events also were similar across treatment arms and trials. The incidence of intraocular inflammation (IOI) events through study end was low and similar among patients receiving faricimab every 8 weeks (YOSEMITE, 6 patients [2%]; RHINE, 3 patients [1%]), faricimab T&E (7 patients [2%]; 4 patients [1%]), and aflibercept every 8 weeks (5 patients [2%]; 2 patients [1%]). All IOI events were considered by the investigator to be mild or moderate in severity with the exception of 4 events in YOSEMITE. One case of severe vitreitis was reported in the faricimab every-8-week arm, which led to treatment withdrawal; this event was treated and not associated with BCVA loss and had recovered or resolved by the end of the study. Three cases of severe uveitis were reported in the faricimab T&E arm and led to treatment withdrawal: 1 patient with moderate chorioretinitis and severe uveitis associated with BCVA loss of 11 ETDRS letters (treated with topical steroids), 1 patient with severe uveitis associated with BCVA loss of 31 ETDRS letters (treated with topical steroids), and 1 patient with mild keratic precipitates and severe uveitis associated with BCVA loss of 37 ETDRS letters (treated with topical antibiotics and nonsteroidal anti-inflammatory drugs). No severe IOI events occurred in the aflibercept every-8-week arms of YOSEMITE or RHINE. All IOI events except 1 in YOSEMITE (mild iritis in the faricimab up to every-16-week dosing arm) had recovered or resolved or were recovering or resolving by the end of the study. No IOI events were associated with retinal occlusive events, and no cases of retinal vasculitis or occlusive retinal vasculitis were reported through study end.

Discussion

Building on the year 1 primary outcome analysis,[31] we report the 2-year data from the phase 3 YOSEMITE and RHINE trials. We demonstrated consistency of results across 2 years; comparable clinically meaningful BCVA gains and greater anatomic improvements with faricimab versus aflibercept were maintained through study end at year 2. In the faricimab T&E arms, the year 1 durability findings were improved further and were extended in year 2. These findings further support the role of angiopoietin and Tie signaling in vascular stability and the potential for dual angiopoietin-2 and VEGF-A inhibition to promote vascular stability and extend treatment durability beyond targeting VEGF inhibition alone for DME.

The current standard of care for DME using available anti-VEGF agents is limited by the considerable burden of frequent visits, which can lead to undertreatment, and, as a result, clinical practice outcomes often seem to not match those achieved in trial participants.[4–9] In YOSEMITE and RHINE, patients randomized to faricimab T&E received

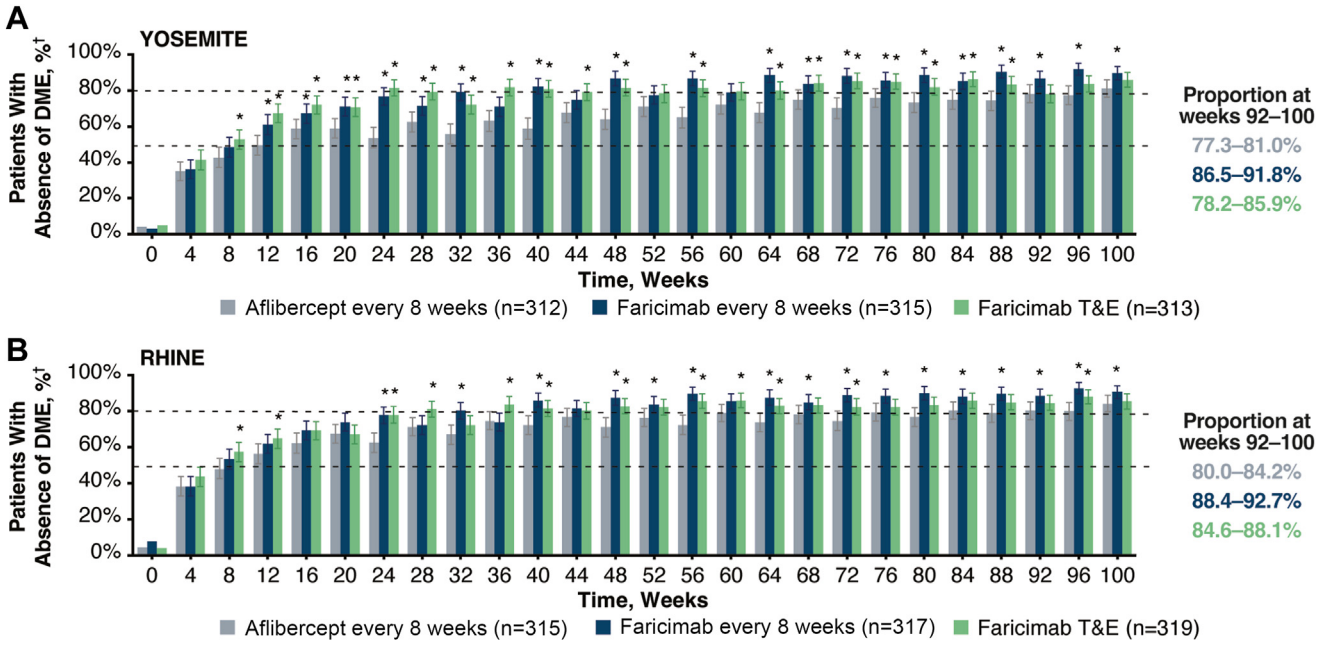


Figure 9. **A**, **B**, Bar graphs showing the proportion of patients with absence of diabetic macular edema (DME) through week 100 in (**A**) YOSEMITE and (**B**) RHINE. *Nominal $P < 0.05$ versus aflibercept every 8 weeks; nominal $P > 0.05$ where no asterisk is shown. Weighted proportions were estimated for the intention-to-treat population using the Cochran-Mantel-Haenszel method; weighted proportions for the aflibercept every-8-week arms are presented for the faricimab every-8-week versus aflibercept every-8-week comparison. Baseline values (defined as the last available measurement obtained on or before randomization) are based on observed data. Treatment policy strategy and hypothetical strategy were applied to intercurrent events not related to and related to the coronavirus disease 2019 pandemic, respectively. Missing data were not imputed. Error bars represent 95.04% confidence intervals (CIs); CI estimates < 0% and > 100% were imputed as 0% and 100%, respectively. †Absence of DME was defined as central subfield thickness of < 325 μm, measured as the average thickness between the internal limiting membrane and Bruch's membrane in the central 1-mm diameter of the Early Treatment Diabetic Retinopathy Study grid. T&E = treat-and-extend.

fewer injections per year (a median of 8 and 3 injections during years 1 and 2, respectively) compared with patients in the faricimab every-8-week arm (a median of 10 and 5 injections, respectively). Furthermore, the median number of faricimab T&E injections received during the 2-year YOSEMITE and RHINE trials was less than those reported in previous clinical trials of anti-VEGF treatments administered using as-needed (pro re nata) dosing regimens. In the Diabetic Retinopathy Clinical Research Network protocol T study, where patients with DME received intravitreal aflibercept 2.0 mg, bevacizumab 1.25 mg, or ranibizumab 0.3 mg as needed based on protocol-specified BCVA and CST retreatment criteria, a median of 9 to 10 anti-VEGF injections were given across treatment arms in year 1 and 5 to 6 injections during year 2.[37,38] Because patients in the active comparator arms of YOSEMITE and RHINE received aflibercept every 8 weeks, it was not possible to assess whether the median number of aflibercept injections received during the 2-year trials differed from that reported in the Diabetic Retinopathy Clinical Research Network protocol T study, where as-needed dosing regimens were used. Overall, these findings highlight the potential for T&E dosing with faricimab to extend treatment durability and to reduce the burden of frequent visits and injections for patients with DME over 2 years.

Year 2 data from YOSEMITE and RHINE showed that initial 1-year visual acuity gains achieved with faricimab every 8 weeks and faricimab T&E were maintained through year 2 and remained comparable with aflibercept every 8 weeks. In the year 1 primary analysis, faricimab every 8 weeks and faricimab T&E demonstrated greater anatomic improvements over aflibercept every 8 weeks through year 1[31]; this faricimab-associated benefit was maintained through year 2. The adjusted mean CST change from baseline at 2 years was greater with faricimab every 8 weeks and faricimab T&E dosing versus aflibercept every 8 weeks, and greater proportions of patients achieved absence of DME and absence of IRF with faricimab every 8 weeks and faricimab T&E versus aflibercept every 8 weeks at most time points across both trials. Together, these data suggest that dual angiopoietin-2 and VEGF-A inhibition with faricimab may improve resolution of retinal fluid compared with VEGF inhibition alone and that fewer faricimab injections may be needed to reach this outcome. In clinical practice, retinal drying is important to assess treatment effectiveness and guide treatment decisions; however, the clinical implications of the observed difference remain to be determined because visual acuity was similar between the faricimab and aflibercept arms through the trial. Guidance from future studies is needed to answer remaining questions definitively about

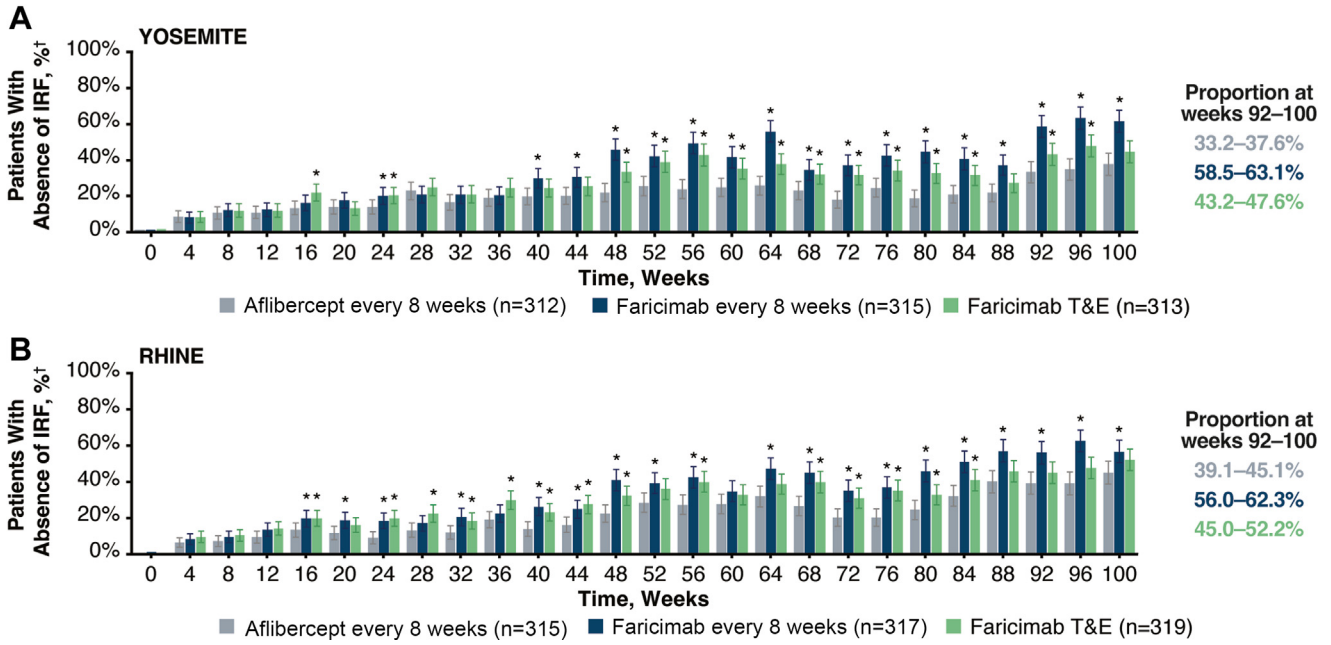


Figure 11. A, **B**, Bar graphs showing the proportion of patients with absence of intraretinal fluid (IRF) through week 100 in (**A**) YOSEMITE and (**B**) RHINE. *Nominal $P < 0.05$ versus aflibercept every 8 weeks; nominal $P > 0.05$ in which no asterisk is shown. Weighted proportions were estimated for the intention-to-treat population using the Cochran-Mantel-Haenszel method; weighted proportions for the aflibercept every-8-week arms are presented for the faricimab every-8-week versus aflibercept every-8-week comparison. Baseline values (defined as the last available measurement obtained on or before randomization) are based on observed data. Treatment policy strategy and hypothetical strategy were applied to intercurrent events not related to and related to the coronavirus disease 2019 pandemic, respectively. Missing data were not imputed. Error bars represent 95.04% confidence intervals (CIs); CI estimates < 0% and > 100% were imputed as 0% and 100%, respectively. †IRF was measured in the central 1-mm diameter of the Early Treatment Diabetic Retinopathy Study grid. T&E = treat-and-extend.

whether differences in BCVA efficacy exist between these treatments over the course of more long-term follow-up. Similar to the anatomic findings of YOSEMITE and RHINE, the Phase 2 Anti-vasculaR Endothelial Growth Factor plUs Anti-angiopoietin 2 in Fixed comBination therapY: Evaluation for the Treatment of Diabetic Macular Edema (RUBY)

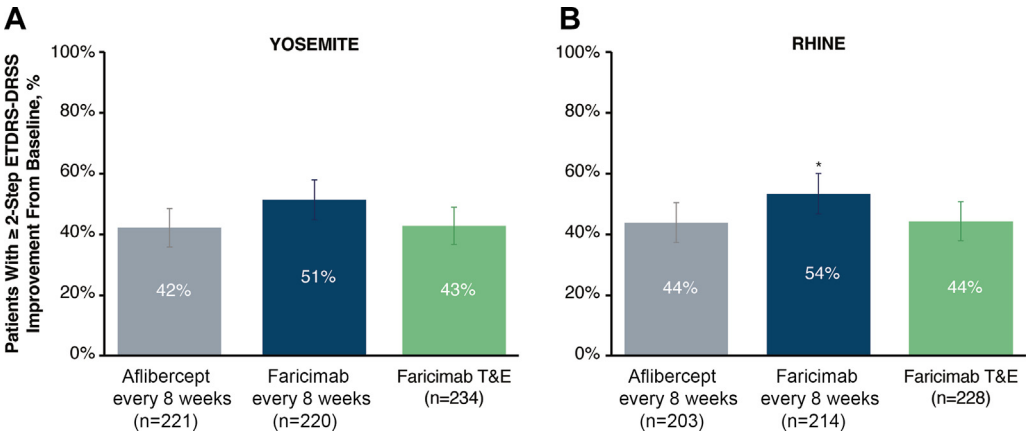


Figure 13. A, **B**, Bar graphs showing proportion of patients with 2-step or more Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS) improvement from baseline at week 96 in (**A**) YOSEMITE and (**B**) RHINE. *Nominal $P < 0.05$ versus aflibercept every 8 weeks; nominal $P > 0.05$ where no asterisk is shown. Analyses included patients with evaluable color fundus photographs at baseline and week 96. Weighted proportions were estimated for the intention-to-treat population using the Cochran-Mantel-Haenszel method; weighted proportions for the aflibercept every-8-week arms are presented for the faricimab every-8-week versus aflibercept every-8-week comparison. Treatment policy strategy and hypothetical strategy were applied to intercurrent events not related to and related to the coronavirus disease 2019 pandemic, respectively. Missing data were not imputed. Error bars represent 95.04% confidence intervals (CIs); CI estimates < 0% and > 100% were imputed as 0% and 100%, respectively. T&E = treat-and-extend.

Table 4. Summary of Key Adverse Events through Study End (Safety Analysis Population)

Variable	YOSEMITE (n = 937)			RHINE (n = 950)		
	Faricimab		Aflibercept	Faricimab		Aflibercept
	Every 8 Weeks (n = 313)	T&E (n = 313)	Every 8 Weeks (n = 311)	Every 8 Weeks (n = 317)	T&E (n = 319)	Every 8 Weeks (n = 314)
Summary of AEs						
Total no. of AEs*	1621	1632	1476	1658	1420	1386
Total no. of SAEs*	234	201	174	173	152	189
Patients with ≥ 1 ocular AE†	147 (47.0)	146 (46.6)	144 (46.3)	166 (52.4)	165 (51.7)	140 (44.6)
Patients with ≥ 1 ocular SAE†	12 (3.8)	14 (4.5)	7 (2.3)	14 (4.4)	20 (6.3)	13 (4.1)
Patients with ≥ 1 nonocular AE	240 (76.7)	251 (80.2)	242 (77.8)	220 (69.4)	218 (68.3)	231 (73.6)
Patients with ≥ 1 nonocular SAE	99 (31.6)	97 (31.0)	84 (27.0)	76 (24.0)	64 (20.1)	89 (28.3)
Patients with ≥ 1 treatment-related ocular AE†	10 (3.2)	7 (2.2)	6 (1.9)	10 (3.2)	14 (4.4)	15 (4.8)
Patients with ≥ 1 treatment-related ocular SAE†	0	4 (1.3)	0	0	3 (0.9)	0
Patients with ≥ 1 ocular AE of special interest†,‡	11 (3.5)	13 (4.2)	8 (2.6)	14 (4.4)	20 (6.3)	12 (3.8)
IOI events†,§						
Patients with ≥ 1 IOI event	6 (1.9)	7 (2.2)	5 (1.6)	3 (0.9)	4 (1.3)	2 (0.6)
Uveitis	3 (1.0)	3 (1.0)	0	0	1 (0.3)	0
Iritis	1 (0.3)	2 (0.6)	1 (0.3)	0	2 (0.6)	1 (0.3)
Iridocyclitis	1 (0.3)	1 (0.3)	0	1 (0.3)	2 (0.6)	1 (0.3)
Vitreitis	1 (0.3)	0	2 (0.6)	1 (0.3)	0	0
Postprocedural inflammation	0	1 (0.3)	2 (0.6)	1 (0.3)	0	0
Chorioretinitis	0	1 (0.3)	0	0	0	0
Keratic precipitates	0	1 (0.3)	0	0	0	0
Keratouveitis	0	1 (0.3)	0	0	0	0
Ocular SAEs associated with intravitreal anti-VEGF therapy†,‖						
Endophthalmitis	0	3 (1.0)	0	2 (0.6)	1 (0.3)	1 (0.3)
Intraocular pressure increase	0	0	0	1 (0.3)	0	0
Retinal tear	0	1 (0.3)	0	0	2 (0.6)	0
Rhegmatogenous retinal detachment	1 (0.3)	0	0	0	0	0
Traumatic cataract	0	0	0	0	0	0
Retinal vasculitis and noninflammatory occlusive events†						
Retinal vasculitis	0	0	0	0	0	0
Retinal artery occlusion	0	0	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)
Retinal vein occlusion	1 (0.3)	2 (0.6)	0	0	2 (0.6)	0
Arterial occlusive disease	0	0	0	0	0	1 (0.3)
Retinal artery embolism	0	0	0	0	0	1 (0.3)
APTC events¶						
Patients with ≥ 1 APTC event	23 (7.3)	22 (7.0)	18 (5.8)	11 (3.5)	8 (2.5)	14 (4.5)
Nonfatal myocardial infarction	4 (1.3)	4 (1.3)	4 (1.3)	3 (0.9)	1 (0.3)	3 (1.0)
Nonfatal stroke	8 (2.6)	6 (1.9)	7 (2.3)	3 (0.9)	4 (1.3)	4 (1.3)
Death	11 (3.5)	12 (3.8)	7 (2.3)	5 (1.6)	3 (0.9)	7 (2.2)

AE = adverse event; APTC = Anti-Platelet Trialists' Collaboration; IOI = intraocular inflammation; SAE = serious adverse event; T&E = treat-and-extend; VEGF = vascular endothelial growth factor.

Data are presented as no. (%). Includes AEs with onset from the first dose of study drug through study end; percentages are based on number values in the column headings. Multiple occurrences of the same AE in 1 individual are counted only once, except for the rows showing total number of events, in which multiple occurrences of the same AE are counted separately.

*Includes nonocular events and ocular events in the study or fellow eye.

†Only in the study eye.

‡Defined as events associated with severe IOI, events requiring surgical or medical intervention to prevent permanent loss of sight, or events associated with best-corrected visual acuity loss of ≥ 30 Early Treatment Diabetic Retinopathy Study letters for > 1 hour. A full list of ocular AEs of special interest is provided in Table S6.

§Includes serious and nonserious IOI events; excludes endophthalmitis events.

‖A full list provided in Table S5.

¶Adjudicated externally; all other events were investigator reported.

study (ClincalTrials.gov identifier, NCT02712008) of nesvacumab (an anti–angiopoietin-2 antibody) and aflibercept combination treatment for DME showed greater anatomic improvements with aflibercept plus high-dose nesvacumab compared with aflibercept alone at week 12 of the trial, including greater CST changes from baseline and increased proportions of eyes with complete resolution of fluid at the foveal center and normalization of macular thickness.[39]

Although direct comparisons are limited by differences between the trials, including different treatment regimens and patient populations, overall, the results of RUBY further support the potential for improved anatomic outcomes when both angiopoietin-2 and VEGF are inhibited in patients with DME.

In the faricimab T&E arms, it was possible to extend the dosing intervals by the end of year 2 compared with the end of year 1[31] while maintaining durable visual acuity gains and anatomic improvements through year 2. Overall, the proportion of patients receiving every-16-week dosing increased from 52% to 62% between week 52 and week 96, and the proportion of patients receiving every-12-week dosing or longer increased from 72% to 78% over the same period. Furthermore, for most patients receiving every-12-week or every-16-week dosing at 1 year, it was possible to maintain the extended dosing regimen without an interval reduction through year 2. Only approximately 4% of patients required continued every-4-week dosing throughout the entire period of both studies, and these patients never qualified for interval extension because the CST did not decrease < 325 μm. These results demonstrate the potential for faricimab to extend treatment durability for patients with DME when given in a clinical practice treatment scenario.

The T&E regimen in YOSEMITE and RHINE was designed specifically to test the durability of faricimab using a T&E-based regimen commonly used in clinical practice to reduce the burden of frequent clinic visits.[32] In the setting of registered clinical trials, we used the term "personalized treatment interval" because patients were required to undergo monthly visits to maintain masking and enable collection of monthly efficacy and safety data. Of note, dosing-interval decisions in the T&E arms were dependent on BCVA and CST values from active dosing visits only, and, as such, the criteria for treatment-interval reductions, maintenance, or extensions were based on standard routine criteria in clinical practice. In YOSEMITE and RHINE, the faricimab T&E arms were designed with treatment intervals that could be extended by 4-week increments after the 4 initial monthly loading doses (and when CST of < 325 μm was met). Although physicians across global clinical practices may follow variable patterns, including T&E extensions and reductions of approximately 2-week increments (dependent on the individual patient's situation and scheduling availability),[36] the objective in a clinical trial setting is to ensure a feasible schedule with minimal variability to minimize potential bias. Our results of visual acuity stability and anatomic improvements achieved over 2 years with faricimab dosed up to every 16 weeks support extension of faricimab dosing intervals by up to 4-week increments in clinical practice and the potential to decrease both the number of injections and frequency of clinic visits for patients with DME.

Consistent with the year 1 primary analysis,[31] faricimab remained well tolerated through study end and no new safety signals were identified. Ocular AEs in the study eye mostly were mild or moderate in severity, and the incidence of these events was similar across faricimab and aflibercept treatment arms. The incidence of IOI events through study end was low (1.6% and 1.1% for faricimab-treated and aflibercept-treated patients, respectively); most IOI events were mild or moderate in severity, and none were associated with retinal vasculitis or retinal occlusive events.

Our study has some limitations that warrant discussion. First, the fixed-dosing faricimab every-8-week arms of YOSEMITE and RHINE were designed to evaluate the maximum efficacy of faricimab, whereas the faricimab T&E arms were designed to test optimal durability. However, after the 5 initial every-4-week doses, the active comparator arms received aflibercept every 8 weeks per the globally aligned aflibercept label,[35] which precluded a head-to-head comparison of durability between faricimab and aflibercept. The number of injections across treatment arms was not compared statistically because only patients in the faricimab T&E arms could receive a variable number of injections. The globally aligned and accepted aflibercept posology was selected because of the registrational nature of the YOSEMITE and RHINE trials and because no extended dosing regimen exists for aflibercept that is approved globally or practiced uniformly.[33–35] Second, the YOSEMITE and RHINE trials were conducted throughout the COVID-19 pandemic, which affected patient participation at some sites and had an impact on the rate of major protocol deviations; however, sensitivity and supplemental analyses showed that the pandemic had limited impact on data integrity and study outcomes. Third, as discussed in more detail above, although the faricimab T&E arms were designed with treatment intervals that could be extended by 4-week increments and may differ from variable patterns followed by physicians in clinical practice,[32,36] we believe the criteria used in our T&E regimen for treatment interval extension, maintenance, or reduction can be applied readily in clinical settings.

The substantial potential of dual angiopoietin-2 and VEGF-A inhibition for DME should be confirmed with further studies. The YOSEMITE and RHINE trials enrolled a large cohort of 1891 patients across 353 study sites worldwide, which to our knowledge is the largest study of patients with DME. Patients who completed YOSEMITE and RHINE were eligible to enter the RHONE-X long-term extension study (ClincalTrials.gov identifier, NCT04432831), which will continue to provide data on the safety and tolerability of faricimab, administered on an open-label and T&E bases, for a further 2 years and will provide data on the effects of switching from bimonthly aflibercept to faricimab T&E. Most patients in YOSEMITE and RHINE were White; the treatment response to faricimab in underrepresented patients with DME will be evaluated in the phase 4 ELEVATUM trial (ClincalTrials.gov identifier, NCT05224102). Additionally, VOYAGER (ClincalTrials.gov identifier, NCT05476926), an observational, prospective, multinational, multicenter study, will offer real-world insights for both faricimab and the Port Delivery System with ranibizumab among patients with DME and neovascular age-related macular degeneration in routine clinical practice globally. Furthermore, the phase 2b ALTIMETER (ClincalTrials.gov identifier, NCT04597918) biomarker hypothesis-generating study will explore the associations between clinical end points, multimodal imaging assessments, and aqueous humor

biomarker patterns in patients with DME treated with faricimab. Previous studies have explored associations between specific characteristics on OCT with outcomes of patients with DME in an effort to identify OCT imaging biomarkers predictive of treatment response to anti-VEGF therapy.[40,41] In ALTIMETER, exploratory end points will evaluate changes from baseline over time in multimodal imaging, including CST and absence of IRF and subretinal fluid, and aqueous humor protein and metabolite composition to identify potential biomarkers of the angiopoietin-2 effect of faricimab.

In conclusion, the 2-year results from the phase 3 YOSEMITE and RHINE trials demonstrated and confirmed the durability, efficacy, and safety of faricimab in patients with DME. Clinically significant 1-year visual acuity gains with faricimab every 8 weeks and T&E were maintained through year 2 and remained comparable with those of aflibercept every 8 weeks, whereas anatomic improvements remained greater with faricimab versus aflibercept every 8 weeks. The impact of the anatomic improvements with faricimab on long-term visual acuity outcomes will be evaluated further in the RHONE-X extension study. The durability of faricimab was extended further in year 2, with more patients in the faricimab T&E arms achieving and maintaining dosing intervals of up to every 16 weeks. During year 2, the median number of faricimab T&E injections was 3 (vs 5−6 for the Diabetic Retinopathy Clinical Research Network protocol T study),[38] which may translate into fewer clinic visits and might reduce treatment burden with use of faricimab in clinical practice. These data reinforce the potential of dual inhibition of angiopoietin-2 and VEGF-A with faricimab as a novel, multitargeted strategy that may extend DME treatment durability and may improve outcomes beyond VEGF inhibition alone.

Acknowledgments

The authors thank Christopher Brittain, Aachal Kotecha, and Jeffrey R. Willis for their contributions to the faricimab phase 3 trial program.

Footnotes and Disclosures

Originally received: August 9, 2023.
Final revision: December 15, 2023.
Accepted: December 18, 2023.
Available online: December 28, 2023.Manuscript no. OPHTHA-D-23-01470.

[1] Tsinghua Medicine, Tsinghua University, Beijing, China, and Singapore National Eye Centre, Singapore, Republic of Singapore.

[2] Genentech, Inc., South San Francisco, California.

[3] New England Eye Center, Tufts Medical Center, Boston, Massachusetts.

[4] Retina Foundation of the Southwest, Dallas, Texas.

[5] Department of Ophthalmology, University of Münster, Münster, Germany.

[6] Roche Products Ltd., Welwyn Garden City, United Kingdom.

[7] Department of Ophthalmology, Duke University, Durham, North Carolina.

[8] Centre Hospitalier Universitaire (CHU) de Bordeaux, Service d'Ophtalmologie, Université de Bordeaux, INSERM, BPH, UMR1219, Bordeaux, France.

[9] Department of Ophthalmology, Shinshu University, Nagano, Japan.

[10] Department of Ophthalmology, College of Medicine, Rangsit University, Rajavithi Hospital, Bangkok, Thailand.

[11] Organización Médica de Investigación, Buenos Aires, Argentina.

[12] Budapest Retina Associates, Budapest, Hungary.

[13] Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

[14] Palmetto Retina Center, Retina Consultants of America, Columbia, South Carolina.

[15] Department of Ophthalmology, Asan Medical Center, University of Ulsan, College of Medicine, Seoul, South Korea.

[16] Retina Consultants of Texas, Retina Consultants of America, Blanton Eye Institute, Houston Methodist Hospital, Houston, Texas.

*A list of members of the YOSEMITE and RHINE Investigators appears online (at www.aaojournal.org).

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s):

T.Y.W.: Consultant − Bayer, Boehringer Ingelheim, Genentech, Inc., Iveric Bio, Novartis, Roche, Sanofi, Shanghai Henlius, Zhaoke; Financial support − Bayer, Genentech, Inc., Novartis, Roche; Cofounder − EyRiS, VISRE

Z.H.: Employee − Genentech, Inc.

K.A.: Employee − Genentech, Inc.

C.R.B.: Employee − Apellis; Consultant − Eyepoint, Genentech, Inc., Ocuphire, Opthea, Ora

K.G.C.: Consultant − AbbVie, Adverum, Annexon, Cognition Therapeutics, Endogena, EyeBio, Genentech, Inc./Roche, Gyroscope, Heidelberg Engineering, Johnson & Johnson, Merck, NGM Bio, Novartis Pharma AG, Ocular Therapeutix, ReNeuron, Retrotope, Ribomic; Lecturer − Genentech, Inc.; Financial support − Alexion, Annexon, Boehringer Ingelheim, Genentech, Inc., Gyroscope, Iveric Bio, NGM Bio

N.E.: Financial support − Bayer, Novartis; Lecturer − Allergan, Apellis, Bayer, Novartis, Roche

J.A.I.: Employee − Roche Products, Ltd.

G.J.J.: Consultant − 4D Molecular Therapeutics, Adverum, Annexon, Editas, EyePoint Pharmaceuticals, Neurotech, Novartis, Regeneron, Roche/Genentech, Inc.

J.-F.K.: Consultant − AbbVie, Apellis, Bayer, Carl Zeiss Meditec, Janssen, NanoRetina, Roche, Thea; Data safety monitoring board − Alexion, Novo Nordisk, Oxular

H.L.: Employee − Genentech, Inc.

T.M.: Lecturer − Bayer, Novartis, Santen, Zeiss

P.R.: Consultant − Bayer, Novartis, Roche

P.G.S.: Consultant − Roche

A.I.S.: Advisory board − Roche; Consultant − Novartis, Roche, Syneos Health

D.S.: Employee − Roche Products, Ltd.

X.S.: Consultant − Alcon, Allergan, Bayer HealthCare, Carl Zeiss Meditec, Inc., Innovent Biologics, Inc., Kanghong Biotech, Inc., Novartis, Roche

Y.T.: Employee − Genentech, Inc.

J.A.W.: Consultant − Genentech, Inc.; Financial support − Adverum, Alimera, Bayer, Clover Therapeutics, Genentech, Inc., Iveric Bio, Kodiak, Lowy Medical Research Institute, Neurotech, National Institutes of Health National Eye Institute, Opthea, Regeneron

Y.H.Y.: Financial support − Allergan, Amgen, Bayer, Novartis, Roche, Samsung Bioepis; Consultant − Alcon, Allergan, Bayer, Roche, Samsung Bioepis; Honoraria or Travel Reimbursement − Allergan, Bayer, Roche.

C.C.W.: Consultant − 4DMT, AbbVie, Adverum, Aerie, AGTC, Alcon, Alimera, Allergan, Allgenesis, Alnylam, Annexon, Apellis, Arrowhead, Ascidian, Aviceda, Bausch + Lomb, Bayer, Bionic Vision Technologies, Boehringer Ingelheim, Cholgene, Clearside, Curacle, Eyebiotech, EyePoint, Foresite, Frontera, Genentech, Inc., Gyroscope, IACTA, InGel, Iveric Bio, Janssen, Kato, Kiora, Kodiak, Kriya, Merck, Nanoscope, Neurotech, NGM, Notal Vision, Novartis, OccuRx, Ocular Therapeutix, Ocuphire, Ocuterra, OliX, ONL, Opthea, Oxular, Palatin, PerceiveBio, Perfuse, PolyPhotonix, Ray, RecensMedical, Regeneron, RegenxBio, Resonance, Roche, Sandoz, Sanofi, SciNeuro, Stealth, Surrozen, Suzhou Raymon, Takeda, THEA, Therini, TissueGen, Valo, Verana, Visgenx; Financial support − 4DMT, Adverum, AffaMed, Aldeyra, Alexion, Alimera, Alkahest, Allergan, Allgenesis, Amgen, Annexin, Annexon, Apellis, Asclepix, Bayer, Boehringer Ingelheim, Chengdu Kanghong, Clearside, Curacle, Eyebiotech, EyePoint, Gemini, Genentech, Inc., GlaxoSmithKline, Graybug, Gyroscope, IONIS, iRENIX, Iveric Bio, Janssen, Kodiak, LMRI, McMaster University, Nanoscope, Neurotech, NGM, Novartis, Ocular Therapeutix, Ocuphire, OcuTerra, OliX, Ophthotech, Opthea, Oxular, Oxurion, Oyster Point, PerceiveBio, RecensMedical, Regeneron, RegenxBio, Rezolute, Roche, SamChunDang Pharm, Sandoz, Senju, Shanghai Henlius, Taiwan Liposome Co., UNITY, Verily, Xbrane; Data safety monitoring board − Aerie, Kato; Board member − ASRS, Vit-Buckle Society; Equity owner − InGel, ONL, PolyPhotonix, RecensMedical, TissueGen, Visgenx, Vitranu

Supported by F. Hoffmann-La Roche Ltd., Basel, Switzerland, including third-party writing assistance, which was provided by Ellen M. Ross, PhD, and Karina D. Hamilton-Peel, PhD, CMPP, of Envision Pharma Group. The sponsor participated in the design of the study; collection, management, analysis, and interpretation of data; and preparation, review, and approval of manuscript.

For eligible studies, qualified researchers may request access to individual patient-level clinical data through a data request platform. At the time of writing, this request platform is Vivli (https://vivli.org/ourmember/roche/). For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://go.roche.com/data_sharing. Anonymized records for individual patients across more than 1 data source external to Roche cannot, and should not, be linked because of the potential increase in risk of patient re-identification.

Presented in part at: Angiogenesis, Exudation, and Degeneration 2022 Virtual Congress, February 2022; Fuji Retina 2022 Annual Meeting, April 2022, Tokyo, Japan; Advanced Technologies & Treatments for Diabetes, April 2022, Barcelona, Spain, and virtual; Retina World Congress, May 2022, Fort Lauderdale, Florida; Association for Research in Vision and Ophthalmology Annual Meeting, May 2022, Denver, Colorado; Royal College of Ophthalmologists Annual Congress, May 2022, Glasgow, United Kingdom and Virtual; American Diabetes Association 82nd Scientific Sessions, June 2022, New Orleans, Louisiana, Los Angeles, California, and virtual; Macula Society 45th Annual Meeting, June 2022, Berlin, Germany; 34th International Congress of German Ophthalmic Surgery (DOC), June 2022, Nuremberg, Germany; Oxford Ophthalmological Congress, July 2022, Oxford, United Kingdom; American Society of Retina Specialists Annual Meeting, July 2022, New York, New York; Congress of the Swiss Society of Ophthalmology, August 2022, Basel, Switzerland; World Ophthalmology Virtual Congress, September 2022; 22nd EURETINA Congress, September 2022, Hamburg, Germany; Kongress der DOG, Deutsche Ophthalmologische Gesellschaft, September−October 2022, Berlin, Germany; American Academy of Ophthalmology Annual Meeting, September−October 2022, Chicago, Illinois; 55th Annual Scientific Meeting of the Retina, November 2022, Pasadena, California; 15th Congress of the Asia-Pacific Vitreo-retina Society, November 2022, Taipei, Chinese Taipei; 53 Congrés de la Societat Catalana d'Oftalmologia, November 2022, Barcelona, Spain; 61st Annual Meeting of Japanese Retina and Vitreous Society, December 2022, Osaka, Japan; Congreso de la Sociedad Oftalmológica de Madrid, Reunión Anual 2022, December 2022, Madrid, Spain; 2023 RANZCO NSW Branch ASM, March 2023, Sydney, Australia; 10th EURETINA Winter Meeting, March 2023, Vilnius, Lithuania; 14th Annual Congress on Controversies in Ophthalmology, March 2023, Lisbon, Portugal; XIII Congreso Sociedad Oftalmológica de Castilla la Mancha, April 2023, Alcázar de San Juan, Spain; and Royal College of Ophthalmologists Annual Congress, May 2023, Birmingham, United Kingdom.

HUMAN SUBJECTS: Human subjects were included in this study. The institutional review boards at each institution approved the study (list of institutional review boards available online at www.aaojournal.org). All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Haskova, Asik, Ives, Lin, Silverman, Tang

Analysis and interpretation: Wong, Haskova, Asik, Baumal, Csaky, Eter, Ives, Jaffe, Korobelnik, Lin, Murata, Ruamviboonsuk, Schlottmann, Seres, Silverman, Sun, Tang, Wells, Yoon, Wykoff

Data collection: Wong, Haskova, Asik, Baumal, Csaky, Eter, Ives, Jaffe, Korobelnik, Lin, Murata, Ruamviboonsuk, Schlottmann, Seres, Silverman, Sun, Tang, Wells, Yoon, Wykoff

Obtained funding: N/A

Overall responsibility: Wong, Haskova, Asik, Baumal, Csaky, Eter, Ives, Jaffe, Korobelnik, Lin, Murata, Ruamviboonsuk, Schlottmann, Seres, Silverman, Sun, Tang, Wells, Yoon, Wykoff

Abbreviations and Acronyms:
AE = adverse event; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **COVID-19** = coronavirus disease 2019; **CST** = central subfield thickness; **DME** = diabetic macular edema; **DRSS** = Diabetic Retinopathy Severity Scale; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **IOI** = intraocular inflammation; **IRF** = intraretinal fluid; **MMRM** = mixed model for repeated measures; **SD** = standard deviation; **T&E** = treat-and-extend; **VEGF** = vascular endothelial growth factor.

Keywords:
Angiopoietin-2, Diabetic macular edema, Faricimab, Vascular endothelial growth factor A, Vascular stability.

Correspondence:
Tien Y. Wong, MD, PhD, Tsinghua Medicine Office, Medical Sciences Building, Beijing 100084, China. E-mail: wongtienyin@tsinghua.edu.cn.

References

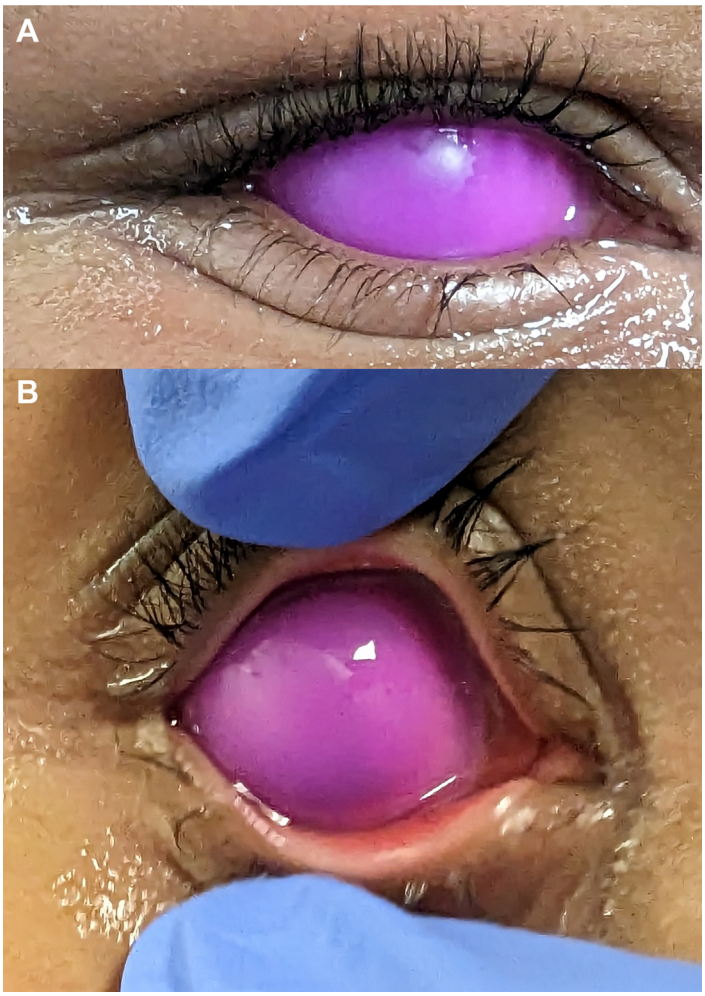
1. Flaxel CJ, Adelman RA, Bailey ST, et al. Diabetic retinopathy Preferred Practice Pattern®. *Ophthalmology*. 2020;127(1): P66−P145.

2. Tan GS, Cheung N, Simo R, et al. Diabetic macular oedema. *Lancet Diabetes Endocrinol*. 2017;5(2):143−155.

3. Wong TY, Cheung CM, Larsen M, et al. Diabetic retinopathy. *Nat Rev Dis Primers*. 2016;2:16012.
4. Ciulla TA, Bracha P, Pollack J, Williams DF. Real-world outcomes of anti-vascular endothelial growth factor therapy in diabetic macular edema in the United States. *Ophthalmol Retina*. 2018;2(12):1179–1187.
5. Ciulla TA, Pollack JS, Williams DF. Visual acuity outcomes and anti-VEGF therapy intensity in diabetic macular oedema: a real-world analysis of 28 658 patient eyes. *Br J Ophthalmol*. 2021;105(2):216–221.
6. Massin P, Creuzot-Garcher C, Kodjikian L, et al. Real-world outcomes after 36-month treatment with ranibizumab 0.5 mg in patients with visual impairment due to diabetic macular edema (BOREAL-DME). *Ophthalmic Res*. 2021;64(4):577–586.
7. Shimura M, Kitano S, Muramatsu D, et al. Real-world management of treatment-naive diabetic macular oedema in Japan: two-year visual outcomes with and without anti-VEGF therapy in the STREAT-DME study. *Br J Ophthalmol*. 2020;104(9):1209–1215.
8. Sugimoto M, Handa C, Hirano K, et al. Intravitreal aflibercept for diabetic macular edema in real-world clinical practice in Japan: 24-month outcomes. *Graefes Arch Clin Exp Ophthalmol*. 2022;260(11):3489–3498.
9. Van Aken E, Favreau M, Ramboer E, et al. Real-world outcomes in patients with diabetic macular edema treated long term with ranibizumab (VISION study). *Clin Ophthalmol*. 2020;14:4173–4185.
10. Ashraf M, Souka A, Adelman R. Predicting outcomes to anti-vascular endothelial growth factor (VEGF) therapy in diabetic macular oedema: a review of the literature. *Br J Ophthalmol*. 2016;100(12):1596–1604.
11. Daruich A, Matet A, Moulin A, et al. Mechanisms of macular edema: beyond the surface. *Prog Retin Eye Res*. 2018;63:20–68.
12. Heier JS, Singh RP, Wykoff CC, et al. The angiopoietin/Tie pathway in retinal vascular diseases: a review. *Retina*. 2021;41(1):1–19.
13. Joussen AM, Ricci F, Paris LP, et al. Angiopoietin/Tie2 signalling and its role in retinal and choroidal vascular diseases: a review of preclinical data. *Eye (Lond)*. 2021;35(5):1305–1316.
14. Saharinen P, Eklund L, Alitalo K. Therapeutic targeting of the angiopoietin-TIE pathway. *Nat Rev Drug Discov*. 2017;16(9):635–661.
15. Yancopoulos GD, Davis S, Gale NW, et al. Vascular-specific growth factors and blood vessel formation. *Nature*. 2000;407(6801):242–248.
16. Benest AV, Kruse K, Savant S, et al. Angiopoietin-2 is critical for cytokine-induced vascular leakage. *PLoS One*. 2013;8(8):e70459.
17. Murata T, Ishibashi T, Khalil A, et al. Vascular endothelial growth factor plays a role in hyperpermeability of diabetic retinal vessels. *Ophthalmic Res*. 1995;27(1):48–52.
18. Murata T, Nakagawa K, Khalil A, et al. The relation between expression of vascular endothelial growth factor and breakdown of the blood-retinal barrier in diabetic rat retinas. *Lab Invest*. 1996;74(4):819–825.
19. Oshima Y, Deering T, Oshima S, et al. Angiopoietin-2 enhances retinal vessel sensitivity to vascular endothelial growth factor. *J Cell Physiol*. 2004;199(3):412–417.
20. Fiedler U, Reiss Y, Scharpfenecker M, et al. Angiopoietin-2 sensitizes endothelial cells to TNF-alpha and has a crucial role in the induction of inflammation. *Nat Med*. 2006;12(2):235–239.
21. Felcht M, Luck R, Schering A, et al. Angiopoietin-2 differentially regulates angiogenesis through TIE2 and integrin signaling. *J Clin Invest*. 2012;122(6):1991–2005.
22. Hakanpaa L, Sipila T, Leppanen VM, et al. Endothelial destabilization by angiopoietin-2 via integrin β1 activation. *Nat Commun*. 2015;6:5962.
23. Park SW, Yun JH, Kim JH, et al. Angiopoietin 2 induces pericyte apoptosis via α3β1 integrin signaling in diabetic retinopathy. *Diabetes*. 2014;63(9):3057–3068.
24. Yun JH, Park SW, Kim JH, et al. Angiopoietin 2 induces astrocyte apoptosis via αvβ5-integrin signaling in diabetic retinopathy. *Cell Death Dis*. 2016;7(2):e2101.
25. Regula JT, Lundh von Leithner P, Foxton R, et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases. *EMBO Mol Med*. 2016;8(11):1265–1288.
26. Heier JS, Khanani AM, Quezada Ruiz C, et al. 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. *Lancet*. 2022;399(10326):729–740.
27. Khanani AM, Patel SS, Ferrone PJ, et al. Efficacy of every four monthly and quarterly dosing of faricimab vs ranibizumab in neovascular age-related macular degeneration: the STAIRWAY phase 2 randomized clinical trial. *JAMA Ophthalmol*. 2020;138(9):964–972.
28. Sahni J, Dugel PU, Patel SS, et al. Safety and efficacy of different doses and regimens of faricimab vs ranibizumab in neovascular age-related macular degeneration: the AVENUE phase 2 randomized clinical trial. *JAMA Ophthalmol*. 2020;138(9):955–963.
29. Sahni J, Patel SS, Dugel PU, et al. Simultaneous inhibition of angiopoietin-2 and vascular endothelial growth factor-A with faricimab in diabetic macular edema: BOULEVARD phase 2 randomized trial. *Ophthalmology*. 2019;126(8):1155–1170.
30. Tadayoni R, Paris LP, Danzig CJ, et al; for the BALATON and COMINO Investigators. Efficacy and safety of Faricimab for macular edema due to retinal vein occlusion: 24-week results from the BALATON and COMINO trials. *Ophthalmology*; 2024 Jan 25. S0161-6420(24)00090-3 http://doi.org/10.1016/j.ophtha.2024.01.029. Online ahead of print.
31. Wykoff CC, Abreu F, Adamis AP, et al. 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. *Lancet*. 2022;399(10326):741–755.
32. Eter N, Singh RP, Abreu F, et al. YOSEMITE and RHINE: phase 3 randomized clinical trials of faricimab for diabetic macular edema: study design and rationale. *Ophthalmol Sci*. 2021;2(1):100111.
33. Medicines.org.uk. Eylea 40mg/ml solution for injection in a vial. Summary of product characteristics. Available at: medicines.org.uk/emc/product/2879/smpc#; 2012. Accessed January 24, 2024.
34. Yakuhin Bayer. *Eylea [package insert]*. Osaka, Japan: Bayer Yakuhin; 2015.
35. Regeneron Pharmaceuticals. *Inc. Eylea [package insert]*. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2021.
36. Rezaei KA, Stone TW. *2015 Global Trends in Retina Survey*. Chicago, IL: American Society of Retina Specialists; 2015.
37. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372(13):1193–1203.
38. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology*. 2016;123(6):1351–1359.

39. Brown DM, Boyer DS, Csaky K, et al. Intravitreal nesvacumab (antiangiopoietin 2) plus aflibercept in diabetic macular edema: phase 2 RUBY randomized trial. *Retina*. 2022;42(6):1111–1120.
40. Hui VWK, Szeto SKH, Tang F, et al. Optical coherence tomography classification systems for diabetic macular edema and their associations with visual outcome and treatment responses—an updated review. *Asia Pac J Ophthalmol (Phila)*. 2022;11(3):247–257.
41. Szeto SK, Hui VWK, Tang FY, et al. OCT-based biomarkers for predicting treatment response in eyes with centre-involved diabetic macular oedema treated with anti-VEGF injections: a real-life retina clinic-based study. *Br J Ophthalmol*. 2023;107(4):525–533.

Pictures & Perspectives



The Influence of Social Media: Fidget Toy Placed in Eye

A 9-year-old girl presented with a circular popping fidget toy in her right eye. She reported getting the idea from social media. The fidget toy was removed using jeweler's forceps, with a second examiner holding her head still. Following the removal, fluorescein staining revealed moderate diffuse punctate epithelial erosions, but no corneal abrasion. The patient's family planned to communicate with the patient's teacher to ensure no other students attempted a similar act; (**A**) shows the toy in her eye; (**B**) depicts an examiner opening the eye, illustrating the relative sizes of the toy and the eye (Magnified version of Figure **A**-**B** is available online at www.aaojournal.org).

Alexander B. Crane, MD, MS
Aditya Uppuluri, MD
Mohammad H. Dastjerdi, MD

Institute of Ophthalmology and Visual Sciences, New Jersey Medical School, Rutgers Biomedical Health Sciences, Newark, New Jersey