Faricimab Treat-and-Extend for Diabetic Macular Edema: 2-Year Results from the Randomized Phase 3 YOSEMITE and RHINE Trials

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Abbreviations and Acronyms:
AE = adverse event; **Ang** = angiopoietin; **BCVA** = best-corrected visual acuity; **CMH** = Cochran-Mantel-Haenszel; **CI** = confidence interval; **CST** = central subfield thickness; **DME** = diabetic macular edema; **DRSS** = Diabetic Retinopathy Severity Scale; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **IRF** = intraretinal fluid; **ITT** = intention-to-treat; **MMRM** = mixed model for repeated measures; **OCT** = optical coherence tomography; **Q4W** = every 4 weeks; **Q8W** = every 8 weeks; **Q12W** = every 12 weeks; **Q16W** = every 16 weeks; **SD** = standard deviation; **VEGF** = vascular endothelial growth factor.
This article contains additional online-only material. The following should appear online-only: Figures S4, S6, S8, S10, S12, and S14 and Tables S1, S2, S3, S5, S6, S7, and S8.

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

Abstract

Purpose: To evaluate the 2-year efficacy, durability, and safety of dual angiopoietin-2/vascular endothelial growth factor (VEGF)-A pathway inhibition with intravitreal faricimab according to a personalized treat-and-extend–based regimen (T&E) with up to every-16-week (Q16W) dosing in the YOSEMITE/RHINE (NCT03622580/NCT03622593) phase 3 trials of diabetic macular edema (DME).

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

Participants: Adults with visual acuity loss due to center-involving DME.

Methods: Patients were randomized 1:1:1 to faricimab 6.0 mg Q8W, faricimab 6.0 mg T&E (previously referred to as personalized treatment interval), or aflibercept 2.0 mg Q8W. The T&E up to Q16W dosing regimen was based on central subfield thickness (CST) and best-corrected visual acuity (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/RHINE (N=940/951), noninferior year 1 visual acuity gains were maintained through year 2; mean BCVA change from baseline at 2 years (weeks 92/96/100 average) with faricimab Q8W (YOSEMITE/RHINE, +10.7/+10.9 letters) or T&E (+10.7/+10.1 letters) were comparable with aflibercept Q8W (+11.4/+9.4 letters). The median number of study drug injections was lower with faricimab T&E (YOSEMITE/RHINE, 10/11 injections) versus faricimab Q8W (15 injections) and aflibercept Q8W (14 injections) across both trials during the entire study. In the faricimab T&E arms, durability was further improved during year 2, with >60% of patients on Q16W dosing and ~80% on ≥Q12W dosing at week 96. Almost 80% of patients who achieved Q16W dosing at week 52 maintained Q16W dosing without an interval reduction through week 96. Mean CST reductions were greater, and more patients achieved absence of DME (CST <325µm) and absence of intraretinal fluid with faricimab Q8W or T&E

versus aflibercept Q8W through year 2. Overall, faricimab was well tolerated, with a safety profile comparable to aflibercept.

Conclusions: Clinically meaningful visual acuity gains from baseline, anatomic improvements, and extended durability with intravitreal faricimab up to Q16W were maintained through year 2. Faricimab given as a personalized T&E–based dosing regimen supports the role of dual angiopoietin-2/VEGF-A inhibition to promote vascular stability and provide durable efficacy for patients with DME.

Over the past decade, intravitreal anti-vascular endothelial growth factor (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 are not achieved nor maintained in real-world clinical practices.[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 pathophysiology of DME involves multiple biologic pathways [3, 11]; therefore, multi-targeted 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 (Ang)-1/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 Ang-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, Ang-2 is upregulated and acts as a competitive antagonist of Ang-1, binding to Tie2 and disrupting the vascular stabilization effects of Ang-1/Tie2 signaling, resulting in vascular permeability, instability, and remodeling.[12-15] Elevated levels of Ang-2 promotes 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, Ang-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 Ang-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) supported the hypothesis that dual Ang-2/VEGF-A pathway inhibition with faricimab may promote vascular stability, extend treatment durability (yet to be confirmed for retinal vein occlusion), and 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 (Q8W), faricimab according to a personalized treat-and-extend–based regimen (T&E) with dosing extended up to every 16 weeks (Q16W), or aflibercept 2.0 mg Q8W over 2 years.[31, 32] At 1 year, YOSEMITE and RHINE each met their primary endpoint; adjusted mean best-corrected visual acuity (BCVA) changes from baseline with faricimab Q8W and T&E up to Q16W dosing ranged between 10.8 and 11.8 Early Treatment Diabetic Retinopathy Study (ETDRS) letters and were noninferior to aflibercept Q8W.[31] Secondary endpoints at year 1 also showed greater anatomical benefits with faricimab Q8W and faricimab T&E compared with aflibercept Q8W; 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 Q16W dosing arms, clinically significant visual acuity gains and anatomic improvements were achieved with extended dosing; >70% of patients were extended to every-12-week (Q12W) or longer dosing and >50% were extended to Q16W dosing at week 52.[31] Faricimab was well tolerated through year 1 with a safety profile comparable to aflibercept, and no cases of retinal vasculitis or occlusive retinal vasculitis reported.[31]

The year 1 data from YOSEMITE and RHINE, the largest DME program ever conducted, suggest that dual Ang-2/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 (NCT03622593) were identically designed, randomized, double-masked, active comparator-controlled, phase 3 trials conducted across 353 study sites in 31 participating countries. YOSEMITE and RHINE adhered to the International Council for Harmonization E6 Guideline for Good Clinical Practice, tenets of the Declaration of Helsinki, US Food and Drug Administration regulations, European Union Clinical Trials Directive (2001/20/EC), and applicable local, state, and federal laws. Institutional Review Board (IRB)/Ethics Committee approval was obtained for study protocols as appropriate, and all patients provided written informed consent to participate.

Patients eligible for inclusion were aged ≥18 years and had center-involving DME secondary to diabetes (Type 1 or 2), defined as CST ≥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 25–73 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. Previously anti-VEGF–treated eyes (last treated ≥3 months before day 1) were eligible for inclusion but limited to 25% of total enrolment.

Patients were randomized 1:1:1 to intravitreal faricimab 6.0 mg Q8W after 6 initial every-4-week (Q4W) doses, intravitreal faricimab 6.0 mg T&E with up to Q16W dosing intervals after ≥4 initial Q4W doses, or intravitreal aflibercept Q8W after 5 initial Q4W doses. Aflibercept Q8W 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 Q4W up to Q16W) 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”, as 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 pre-specified criteria.[32] Patients randomized to the faricimab T&E arms initially received faricimab at Q4W intervals until they first reached CST <325 µm at or after week 12. Once achieved, treatment intervals were extended to an initial Q8W dosing, then could be maintained, extended by 4 weeks (up to Q16W), or reduced by 4 weeks or 8 weeks (as low as Q4W) based on prespecified CST and BCVA criteria at active dosing visits (Fig 1). To maintain masking, all patients attended Q4W study visits where they received active treatment or sham up to week 96; the final study visit was at week 100. For patients that 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 optical coherence tomography [OCT], OCT-angiography [OCT-A] where available, color fundus photography [CFP], and fundus fluorescein angiography [FFA]) that were independently assessed at central reading centers (OCT and OCT-A: Duke Reading Center, Durham, NC; Vienna Reading Center, Austria; CFP and FFA: Wisconsin Reading Center, Madison, WI).

Outcome Measures

The primary efficacy endpoint 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 endpoints 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 Q4W, Q8W, Q12W, or Q16W 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 endpoints included the proportion of patients that gained BCVA (≥15, ≥10, ≥5, or ≥0 ETDRS letters) or avoided BCVA loss (≥15, ≥10, or ≥5 ETDRS letters) at 2 years; patients that gained ≥15 ETDRS letters or achieved Snellen BCVA 20/20 or better (≥84 ETDRS letters) at 2 years; patients with Snellen BCVA 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 intent-to-treat (ITT) population, grouped by treatment arm at randomization. Adjusted means for continuous endpoints 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 endpoint. 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 implicitly imputed assuming a missing at random mechanism. For binary secondary endpoints, weighted proportions were estimated using the Cochran-Mantel-Haenszel (CMH) method stratified by baseline BCVA score (<64 letters vs. ≥64 letters), prior intravitreal anti-

VEGF therapy (yes vs. no), region (US and Canada, Asia, and the rest of the world), and study (YOSEMITE vs. RHINE; for the pooled cohort data only). For all MMRM and CMH analyses, intercurrent events related to the COVID-19 pandemic were handled using a hypothetical strategy where all values were censored after the intercurrent event, and non–COVID-19-related intercurrent events were handled using a treatment policy strategy where 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/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 ITT population of YOSEMITE included 315 patients randomized to faricimab Q8W, 313 patients randomized to faricimab T&E, and 312 patients randomized to aflibercept Q8W (Fig 2A). The ITT population of RHINE included 317 patients randomized to faricimab Q8W, 319 patients randomized to faricimab T&E, and 315 patients randomized to aflibercept Q8W (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 (60%) patients in YOSEMITE and 602 (63%) patients in RHINE (Table S1, available at www.aaojournal.org). The number, proportion of patients, and type of major protocol deviations through study end were consistent across treatment arms and trials. The majority of the major protocol deviations were procedural, such as selected missed visits (YOSEMITE: 308 [33.0%] patients; RHINE: 328 [35.0%] patients) and issues with images of the study eye (YOSEMITE: 94 [10.0%] patients; RHINE: 139 [15.0%] patients). Among patients with major protocol deviations, 191 (20%) in YOSEMITE and 279 (29%) in RHINE reported ≥1 major protocol deviation related to COVID-19, most of whom missed ≥1 study visit around the primary endpoint and/or final study visits (167 [18%] and 210 [22%] patients, respectively). Of these, only 63 (6.7%) patients in YOSEMITE and 76 (8.0%) in RHINE missed ≥1 dose of study treatment around the primary endpoint visits, and 15 (1.6%) and 48 (5.0%) patients, respectively, missed ≥1 dose of study treatment around the final study visits.

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

Visual Acuity Outcomes

YOSEMITE and RHINE reproducibly demonstrated visual gains with faricimab Q8W and T&E that were maintained over time through year 2 and were comparable with aflibercept Q8W, 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) in the faricimab Q8W arm and +10.7 ETDRS letters (+9.4 to +12.1) in the faricimab T&E arm versus +11.4 ETDRS letters (+10.0 to

+12.7) in the aflibercept Q8W arm (mean difference vs. aflibercept Q8W, −0.7 ETDRS letters [−2.6 to +1.2] and −0.7 ETDRS letters [−2.5 to +1.2], respectively; nominal $P > 0.05$ for both). Corresponding 2-year BCVA gains in RHINE were +10.9 ETDRS letters (+9.5 to +12.3) and +10.1 ETDRS letters (+8.7 to +11.5) versus +9.4 ETDRS letters (+7.9 to +10.8), respectively (mean difference vs. aflibercept Q8W, +1.5 ETDRS letters [−0.5 to +3.6] and +0.7 ETDRS letters [−1.3 to +2.7]; nominal $P > 0.05$ for both). In the pooled YOSEMITE/RHINE cohort, 2-year BCVA gains were +10.8 ETDRS letters (+9.8 to +11.8) and +10.4 ETDRS letters (+9.4 to +11.4) in the faricimab Q8W and faricimab PTI arms, respectively, versus +10.3 ETDRS letters (+9.3 to +11.3) in the aflibercept Q8W arm (mean difference vs. aflibercept Q8W, +0.5 ETDRS letters [−0.9 to +1.8] and +0.1 ETDRS letters [−1.3 to +1.5]; 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 endpoints were similarly consistent across treatment arms and reproducible across trials (Table S3, available at www.aaojournal.org).

In the safety analysis population, the median (mean [standard deviation (SD)]) number of study drug injections in each of the YOSEMITE and RHINE faricimab T&E arms was 8 injections (YOSEMITE 8.4 [2.45], RHINE 8.7 [2.50]) in year 1 (baseline to week 56), compared with 10 injections in each of the faricimab Q8W (YOSEMITE 9.5 [1.41], RHINE 9.3 [1.52]) and aflibercept Q8W (YOSEMITE 9.2 [1.47], RHINE 9.3 [1.36]) arms. During year 2 (week 60 to week 96), the faricimab T&E arms received a median (mean [SD]) of 3 study drug injections (YOSEMITE 3.5 [1.76], RHINE 3.6 [1.98]), versus 5 injections in each of the faricimab Q8W (YOSEMITE 4.7 [0.74], RHINE 4.7 [0.82]) and aflibercept Q8W (YOSEMITE 4.5 [0.92], RHINE 4.5 [0.99]) arms. From baseline during the entire study, the median (mean [SD]) number of study drug injections in the T&E arms was 10 (11.5 [3.98]) in YOSEMITE and 11 (12.1 [4.12]) in

RHINE, compared with 15 (YOSEMITE 13.6 [2.87], RHINE 13.5 [2.87]) in the faricimab Q8W arms and 14 (YOSEMITE 13.3 [2.75], RHINE 13.4 [2.66]) in the aflibercept Q8W 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 arm extending their dosing while maintaining comparable visual acuity gains and greater anatomical benefits versus aflibercept (Fig 5). At week 96, 211 (78%) patients in the faricimab T&E arm of YOSEMITE and 224 (78%) patients in RHINE achieved ≥Q12W dosing intervals (557 patients [78%] in the pooled YOSEMITE/RHINE cohort), which included 162 (60%) and 185 (64%) patients, respectively, who achieved Q16W dosing (Fig 5A; pooled YOSEMITE/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 Q16W through week 96 is shown in the dosing interval schematic, which shows that in most patients who achieved Q12W or Q16W dosing at 1 year, it was possible to maintain and/or extend their dosing interval through year 2 (Fig 5B; Fig S6B for the pooled YOSEMITE/RHINE cohort, available at www.aaojournal.org). Approximately 79% of patients who achieved ≥Q12W dosing at week 52 maintained ≥Q12W dosing without an interval reduction below Q12W through week 96 (YOSEMITE, 150 [75%] patients; RHINE, 172 [83%] patients). Similarly, 76% of patients that achieved Q16W dosing at week 52 maintained Q16W dosing without an interval reduction through week 96 (YOSEMITE, 100 [70%] patients; RHINE, 121 [82%] patients). Approximately 18% of patients rapidly achieved Q16W dosing at week 32 (i.e., the earliest time point that Q16W dosing was possible due to the study design) and subsequently maintained Q16W dosing through week 96 (YOSEMITE, 44 [16%] patients; RHINE, 58 [20%] patients). Conversely, <5% of patients extended to Q8W dosing at or after week 12, and then remained on Q8W or Q4W dosing through week 96 (YOSEMITE, 10 [4%] patients; RHINE, 16 [6%] patients). In approximately 4%

of patients it was not possible to extend the dosing interval beyond Q4W from baseline through week 96 (YOSEMITE, 7 [3%] patients; RHINE, 15 [5%] patients).

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) in the faricimab Q8W arm, which was greater than that in the aflibercept Q8W arm (−196.3 µm [−204.3 to −188.2]; nominal *P* = 0.0007) (Fig 7). In RHINE, mean 2-year CST reductions were also greater with faricimab Q8W versus aflibercept Q8W (−202.6 µm [−211.1 to −194.2] vs. −185.6 µm [−194.1 to −177.1]; nominal *P* = 0.0052) (Fig 7). In the faricimab T&E arms, adjusted mean CST change at 2 years was comparable with aflibercept Q8W in YOSEMITE (−204.5 µm [−212.4 to −196.5]; nominal *P* > 0.05) and RHINE (−197.1 µm [−205.3 to −188.9]; nominal *P* > 0.05), but was achieved with most patients on Q16W dosing (Fig 7). In the pooled YOSEMITE/RHINE cohort, mean 2-year CST reductions were greater in both the faricimab Q8W arm (−209.4 µm [−215.2 to −203.6]) and the faricimab T&E arm (−201.0 µm [−206.7 to −195.3]) compared with the aflibercept Q8W arm (−190.9 µm [−196.7 to −185.0]; nominal *P* < 0.0001 and *P* = 0.0150 vs aflibercept Q8W, respectively [Fig S8]).

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 Q8W arm and 78%–86% in the faricimab T&E arm, compared with 77%–81% in the aflibercept Q8W arm. Corresponding proportions in RHINE were 88%–93% and 85%–88% versus 80%–84%, respectively (Fig 9). In the pooled YOSEMITE/RHINE cohort, the proportion of patients who achieved absence of DME at weeks

92–100 was 88%–92% in the faricimab Q8W arm, 81%–86% in the faricimab T&E arm, and 79%–83% in the aflibercept Q8W arm (Fig S10, available at www.aaojournal.org).

Absence of IRF was also achieved by more patients treated with faricimab when compared to 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 Q8W arm and 43%–48% in the faricimab T&E arm, compared with 33%–38% in the aflibercept Q8W arm. Proportions were similar in RHINE (56%–62% and 45%–52% vs. 39%–45%, respectively). Corresponding proportions for the pooled YOSEMITE/RHINE cohort were 57%–63% and 44%–48% in the faricimab Q8W and faricimab T&E arms, respectively, vs. 36%–41% in the aflibercept Q8W arm (Fig S12, available at www.aaojournal.org).

The proportion of patients that had ≥2-step ETDRS-DRSS improvement from baseline at week 96 was similar across treatment arms and trials (Fig 13). In YOSEMITE, 51.4% (95.04% CI, 44.8–57.9) of patients in the faricimab Q8W arm had ≥2-step ETDRS-DRSS improvement at week 96 compared with 42.2% (35.9–48.5) in the aflibercept Q8W arm (nominal $P > 0.05$). In RHINE, the corresponding estimate was 53.5% (46.9–60.1) in the faricimab Q8W dosing arm, which was greater than that in the aflibercept Q8W arm (43.8% [37.2–50.4]; nominal $P = 0.0475$). In the faricimab T&E arms, the proportion of patients that had ≥2-step ETDRS-DRSS improvement at week 96 was comparable with aflibercept Q8W in YOSEMITE (42.8% [36.6–49.0]; nominal $P > 0.05$) and RHINE (44.3% [37.9–50.7]; nominal $P > 0.05$) (Fig 13). Corresponding proportions in the YOSEMITE/RHINE pooled cohort were 52.4% (47.8–57.0) in the faricimab Q8W arm and 43.5% (39.1–48.0) in the faricimab T&E arms versus 43.0% (38.4–47.5) in the aflibercept Q8W arm (nominal $P = 0.0058$ and $P > 0.05$ vs. aflibercept Q8W, 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 Q8W and aflibercept Q8W arms (5 injections) in year 2.

458

459 **Safety Outcomes**

460 Consistent with the 1-year primary analysis,[31] faricimab was well tolerated with a safety profile
461 that remained comparable to aflibercept through study end (Table 4 and Tables S5–S8
462 [available at www.aaojournal.org]). The incidence of ocular AEs in the study eye through study
463 end was similar between the faricimab Q8W (YOSEMITE, 147 [47%] patients; RHINE, 166
464 [52%] patients), faricimab T&E (146 [47%] patients; 165 [52%] patients), and aflibercept Q8W
465 arms (144 [46%] patients; 140 [45%] patients). Most ocular AEs were mild or moderate in
466 severity, and common ocular AEs reported were generally balanced across faricimab and
467 aflibercept treatment arms. The incidence of serious ocular AEs through study end was low and
468 comparable between patients receiving faricimab Q8W (YOSEMITE, 12 [4%] patients; RHINE,
469 14 [4%] patients), faricimab T&E (14 [4%] patients; 20 [6%] patients), and aflibercept Q8W (7
470 [2%] patients; 13 [4%] patients). Nonocular AEs and Anti-Platelet Trialists' Collaboration events
471 were also similar across treatment arms and trials. The incidence of intraocular inflammation
472 (IOI) events through study end was low and similar among patients receiving faricimab Q8W
473 (YOSEMITE, 6 [2%] patients; RHINE, 3 [1%] patients), faricimab T&E (7 [2%] patients; 4 [1%]
474 patients), and aflibercept Q8W (5 [2%] patients; 2 [1%] patients). All IOI events were considered
475 by the investigator to be mild or moderate in severity with the exception of 4 events in
476 YOSEMITE. There was 1 case of severe vitritis reported in the faricimab Q8W arm, which led to
477 treatment withdrawal; this event was treated and not associated with BCVA loss and had
478 recovered/resolved by end of study. Three cases of severe uveitis were reported in the
479 faricimab T&E arm and led to treatment withdrawal: 1 patient with moderate chorioretinitis and
480 severe uveitis associated with BCVA loss of 11 ETDRS letters (treated with topical steroids), 1
481 patient with severe uveitis associated with BCVA loss of 31 ETDRS letters (treated with topical
482 steroids), and one patient with mild keratic precipitates and severe uveitis associated with BCVA
483 loss of 37 ETDRS letters (treated with topical antibiotics and non-steroidal anti-inflammatory

484 drugs). There were no severe IOI events in the aflibercept Q8W arms of YOSEMITE or RHINE.
485 All IOI events except 1 in YOSEMITE (mild iritis in the faricimab up to Q16W dosing arm) had
486 recovered/resolved or were recovering/resolving by end of study. No IOI events were
487 associated with retinal occlusive events, and there were no cases of retinal vasculitis or
488 occlusive retinal vasculitis reported through study end.
489

490 ## Discussion

491 Building on the year 1 primary outcome analysis,[31] we report the 2-year data from the phase 3
492 YOSEMITE and RHINE trials. We demonstrated consistency of results across 2 years;
493 comparable clinically meaningful BCVA gains and greater anatomic improvements with
494 faricimab versus aflibercept were maintained through study end at year 2. In the faricimab T&E
495 arms, the year 1 durability findings were further improved and extended in year 2. These
496 findings further support the role of Ang/Tie signalling in vascular stability and the potential for
497 dual Ang-2/VEGF-A inhibition to promote vascular stability and extend treatment durability
498 beyond targeting VEGF inhibition alone for DME.
499 The current standard of care for DME using available anti-VEGF agents is limited by the
500 considerable burden of frequent visits, which can lead to undertreatment and, as a result, real-
501 world clinical practice outcomes often appear to not match those achieved in trial participants.[4-9]
502 In YOSEMITE and RHINE, patients randomized to faricimab T&E received fewer injections per
503 year (a median of 8 and 3 injections during year 1 and 2, respectively) compared with patients in
504 the faricimab Q8W arm (a median of 10 and 5 injections, respectively). Furthermore, the median
505 number of faricimab T&E injections received during the 2-year YOSEMITE and RHINE trials
506 was less than those reported in previous clinical trials of anti-VEGF treatments administered
507 using as-needed (pro re nata) dosing regimens. In the Diabetic Retinopathy Clinical Research
508 Network (DRCR.Net) 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 9–10 anti-VEGF injections were given across treatment arms in year 1, and 5–6 injections during year 2.[37, 38] As patients in the active comparator arms of YOSEMITE and RHINE received aflibercept Q8W, it was not possible to assess whether the median number of aflibercept injections received during the 2-year trials differed to that reported in the DRCR.Net 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 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 Q8W and faricimab T&E were maintained through year 2 and remained comparable with aflibercept Q8W. In the year 1 primary analysis, faricimab Q8W and faricimab T&E demonstrated greater anatomic improvements over aflibercept Q8W 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 Q8W and faricimab T&E dosing versus aflibercept Q8W, and greater proportions of patients achieved absence of DME and absence of IRF with faricimab Q8W and faricimab T&E versus aflibercept Q8W at most time points across both trials. Together, these data suggest that dual Ang-2/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 to guide treatment decisions; however, the clinical implications of the observed difference remain to be determined as visual acuity was similar between the faricimab and aflibercept arms through the trial. Guidance from future studies is needed to definitively answer remaining questions about whether there are differences in BCVA efficacy between these treatments over the course of more long-term follow up. Similar to the anatomical findings of YOSEMITE/RHINE, the phase 2 RUBY (NCT02712008) study of

nesvacumab (anti–Ang-2 antibody) and aflibercept combination treatment for DME showed greater anatomical 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 anatomical outcomes when both Ang-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 on Q16W dosing increased from 52% to 62% between week 52 and week 96, and the proportion of patients on Q12W dosing or longer increased from 72% to 78% over the same period. Furthermore, for the majority of patients on Q12W or Q16W 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 Q4W dosing throughout the entire period of both studies, and these patients never qualified for interval extension because the CST did not drop below 325 µm. These results demonstrate the potential for faricimab to extend treatment durability for patients with DME when given in a real-world 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 the registrational clinical trials, we used the term “personalized treatment interval” as patients were required to undergo monthly visits to maintain masking and to 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

561 extensions were based on standard routine criteria in clinical practice. In YOSEMITE and
562 RHINE, the faricimab T&E arms were designed with treatment intervals that could be extended
563 by 4-week increments following the 4 initial monthly loading doses (and when CST of <325 µm
564 was met). Although physicians across global real-world clinical practices may follow variable
565 patterns, including T&E extensions and reductions of ~2-week increments (dependent on the
566 individual patient's situation and scheduling availability),[36] the objective in a clinical trial setting
567 is to ensure a feasible schedule with minimal variability to minimize potential bias. Our results of
568 visual acuity stability and anatomical improvements achieved over 2 years with faricimab dosed
569 up to Q16W support extension of faricimab dosing intervals by up to 4-week increments in the
570 real world, and the potential to decrease both the number of injections and frequency of clinic
571 visits for patients with DME.

572 Consistent with the year 1 primary analysis,[31] faricimab remained well tolerated through
573 study end and no new safety signals were identified. Ocular AEs in the study eye were mostly
574 mild or moderate in severity, and the incidence of these events was similar across faricimab and
575 aflibercept treatment arms. The incidence of IOI events through study end was low (1.6% and
576 1.1% for faricimab- and aflibercept-treated patients, respectively); most IOI events were mild or
577 moderate in severity, and none were associated with retinal vasculitis or retinal occlusive
578 events.

579 Our study has some limitations that warrant discussion. First, the fixed dosing faricimab
580 Q8W arms of YOSEMITE and RHINE were designed to evaluate the maximal efficacy of
581 faricimab, whereas the faricimab T&E arms were designed to test optimal durability. However,
582 following the 5 initial Q4W does, the active comparator arms received aflibercept Q8W per the
583 globally aligned aflibercept label,[35] which precluded a head-to-head comparison of durability
584 between faricimab and aflibercept. The number of injections across treatment arms was not
585 compared statistically as only patients in the faricimab T&E arms could receive a variable
586 number of injections. The globally aligned and accepted aflibercept posology was selected due

587 to the registrational nature of the YOSEMITE and RHINE trials, and because no extended
588 dosing regimen exists for aflibercept that is globally approved or uniformly practiced.[33-35]
589 Second, the YOSEMITE and RHINE trials were conducted throughout the COVID-19 pandemic,
590 which affected patient participation at some sites and had an impact on the rate of major
591 protocol deviations; however, sensitivity and supplemental analyses showed that the pandemic
592 had limited impact on data integrity and study outcomes. Third, and as discussed in more detail
593 above, although the faricimab T&E arms were designed with treatment intervals that could be
594 extended by 4-week increments and may differ from variable patterns followed by physicians in
595 real-world clinical practice,[32, 36] we believe the criteria used in our T&E regimen for treatment
596 interval extension, maintenance, or reduction can be readily applied in clinical settings.
597 The substantial potential of dual Ang-2/VEGF-A inhibition for DME should be confirmed with
598 further studies. The YOSEMITE and RHINE trials enrolled a large cohort of 1891 patients
599 across 353 study sites worldwide, which to our knowledge, is the largest study in patients with
600 DME. Patients who completed YOSEMITE and RHINE were eligible to enter the RHONE-X
601 long-term extension study (NCT04432831), which will continue to provide data on the safety
602 and tolerability of faricimab, administered open label and T&E, for a further 2 years, and will
603 provide data on the effects of switching from bimonthly aflibercept to faricimab T&E. The
604 majority of patients in YOSEMITE and RHINE were of white race or ethnicity; the treatment
605 response to faricimab in underrepresented patients with DME will be evaluated in the phase 4
606 ELEVATUM trial (NCT05224102). Additionally, VOYAGER (NCT05476926), an observational,
607 prospective, multinational, multicenter study, will offer real-world insights for both faricimab and
608 the Port Delivery System with ranibizumab among patients with DME and neovascular age-
609 related macular degeneration in routine clinical practice globally. Furthermore, the phase 2b
610 ALTIMETER (NCT04597918) biomarker hypothesis-generating study will explore the
611 associations between clinical endpoints, multimodal imaging assessments, and aqueous humor
612 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 endpoints will evaluate changes from baseline over time in multimodal imaging, including CST and absence of IRF and subretinal fluid, and aqueous humor protein/metabolite composition to identify potential biomarkers of the Ang-2 effect of faricimab.

In conclusion, the 2-year results from the phase 3 YOSEMITE and RHINE trials demonstrate and confirm the durability, efficacy, and safety of faricimab in patients with DME. Clinically significant 1-year visual acuity gains with faricimab Q8W and T&E were maintained through year 2 and remained comparable to aflibercept Q8W, while anatomic improvements remained greater with faricimab over aflibercept Q8W. The impact of the anatomical improvements with faricimab on long-term visual acuity outcomes will be further evaluated in the RHONE-X extension study. The durability of faricimab was further extended in year 2, with more patients in the faricimab T&E arms achieving and maintaining dosing intervals of up to Q16W. During year 2, the median number of faricimab T&E injections was 3 (vs. 5–6 for the DRCR.Net Protocol T study)[38], which may translate into fewer clinic visits and might reduce treatment burden with real-world faricimab use. These data reinforce the potential of dual inhibition of Ang-2 and VEGF-A with faricimab as a novel, multitargeted strategy that may extend DME treatment durability and improve outcomes beyond VEGF inhibition alone.

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Roche Data Sharing Statement

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 here (https://go.roche.com/data_sharing). Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification

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):143-55.

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):1179-87.

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):216-21.

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):577-86.

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):1209-15.

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):3489-98.

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;14:4173-85.

673 10. Ashraf M, Souka A, Adelman R. Predicting outcomes to anti-vascular endothelial growth
674 factor (VEGF) therapy in diabetic macular oedema: a review of the literature. Br J Ophthalmol
675 2016;100(12):1596-604.
676 11. Daruich A, Matet A, Moulin A, et al. Mechanisms of macular edema: beyond the surface.
677 Prog Retin Eye Res 2018;63:20-68.
678 12. Heier JS, Singh RP, Wykoff CC, et al. The angiopoietin/Tie pathway in retinal vascular
679 diseases: a review. Retina 2021;41(1):1-19.
680 13. Joussen AM, Ricci F, Paris LP, et al. Angiopoietin/Tie2 signalling and its role in retinal
681 and choroidal vascular diseases: a review of preclinical data. Eye (Lond) 2021;35(5):1305-16.
682 14. Saharinen P, Eklund L, Alitalo K. Therapeutic targeting of the angiopoietin-TIE pathway.
683 Nat Rev Drug Discov 2017;16(9):635-61.
684 15. Yancopoulos GD, Davis S, Gale NW, et al. Vascular-specific growth factors and blood
685 vessel formation. Nature 2000;407(6801):242-8.
686 16. Benest AV, Kruse K, Savant S, et al. Angiopoietin-2 is critical for cytokine-induced
687 vascular leakage. PLoS One 2013;8(8):e70459.
688 17. Murata T, Ishibashi T, Khalil A, et al. Vascular endothelial growth factor plays a role in
689 hyperpermeability of diabetic retinal vessels. Ophthalmic Res 1995;27(1):48-52.
690 18. Murata T, Nakagawa K, Khalil A, et al. The relation between expression of vascular
691 endothelial growth factor and breakdown of the blood-retinal barrier in diabetic rat retinas. Lab
692 Invest 1996;74(4):819-25.
693 19. Oshima Y, Deering T, Oshima S, et al. Angiopoietin-2 enhances retinal vessel sensitivity
694 to vascular endothelial growth factor. J Cell Physiol 2004;199(3):412-7.
695 20. Fiedler U, Reiss Y, Scharpfenecker M, et al. Angiopoietin-2 sensitizes endothelial cells
696 to TNF-alpha and has a crucial role in the induction of inflammation. Nat Med 2006;12(2):235-9.
697 21. Felcht M, Luck R, Schering A, et al. Angiopoietin-2 differentially regulates angiogenesis
698 through TIE2 and integrin signaling. J Clin Invest 2012;122(6):1991-2005.

699 22. Hakanpaa L, Sipila T, Leppanen VM, et al. Endothelial destabilization by angiopoietin-2
700 via integrin β1 activation. Nat Commun 2015;6:5962.
701 23. Park SW, Yun JH, Kim JH, et al. Angiopoietin 2 induces pericyte apoptosis via α3β1
702 integrin signaling in diabetic retinopathy. Diabetes 2014;63(9):3057-68.
703 24. Yun JH, Park SW, Kim JH, et al. Angiopoietin 2 induces astrocyte apoptosis via αvβ5-
704 integrin signaling in diabetic retinopathy. Cell Death Dis 2016;7(2):e2101.
705 25. Regula JT, Lundh von Leithner P, Foxton R, et al. Targeting key angiogenic pathways
706 with a bispecific CrossMAb optimized for neovascular eye diseases. EMBO Mol Med
707 2016;8(11):1265-88.
708 26. Heier JS, Khanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of
709 intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration
710 (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials.
711 Lancet 2022;399(10326):729-40.
712 27. Khanani AM, Patel SS, Ferrone PJ, et al. Efficacy of every four monthly and quarterly
713 dosing of faricimab vs ranibizumab in neovascular age-related macular degeneration: the
714 STAIRWAY phase 2 randomized clinical trial. JAMA Ophthalmol 2020;138(9):964-72.
715 28. Sahni J, Dugel PU, Patel SS, et al. Safety and efficacy of different doses and regimens
716 of faricimab vs ranibizumab in neovascular age-related macular degeneration: the AVENUE
717 phase 2 randomized clinical trial. JAMA Ophthalmol 2020;138(9):955-63.
718 29. Sahni J, Patel SS, Dugel PU, et al. Simultaneous inhibition of angiopoietin-2 and
719 vascular endothelial growth factor-A with faricimab in diabetic macular edema: BOULEVARD
720 phase 2 randomized trial. Ophthalmology 2019;126(8):1155-70.
721 30. Tadayoni R, Paris LP, Abreu F, et al. Faricimab in RVO: results from the BALATON and
722 COMINO phase 3 studies. Angiogenesis, Exudation, and Degeneration Virtual Congress.
723 February 11, 2023.

724 31. Wykoff CC, Abreu F, Adamis AP, et al. Efficacy, durability, and safety of intravitreal
725 faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema
726 (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. Lancet
727 2022;399(10326):741-55.
728 32. Eter N, Singh RP, Abreu F, et al. YOSEMITE and RHINE: phase 3 randomized clinical
729 trials of faricimab for diabetic macular edema: study design and rationale. Ophthalmol Sci
730 2021;2(1):100111.
731 33. Medicines.org.uk. 2012. Eylea 40mg/ml solution for injection in a vial. Summary of
732 product characteristics. Avavilable at: medicines.org.uk/emc/product/2879/smpc#.
733 34. Eylea [package insert]. Osaka, Japan: Bayer Yakuhin, 2015.
734 35. Eylea [package insert]. Tarrytown, NY,: Regeneron Pharmaceuticals, Inc., 2021.
735 36. Rezaei KA, Stone TW. 2015 Global Trends in Retina Survey. Chicago, IL: American
736 Society of Retina Specialists, 2015.
737 37. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for
738 diabetic macular edema. N Engl J Med 2015;372(13):1193-203.
739 38. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for
740 diabetic macular edema: two-year results from a comparative effectiveness randomized clinical
741 trial. Ophthalmology 2016;123(6):1351-9.
742 39. Brown DM, Boyer DS, Csaky K, et al. Intravitreal nesvacumab (antiangiopoietin 2) plus
743 aflibercept in diabetic macular edema: phase 2 RUBY randomized trial. Retina 2022;42(6):1111-
744 20.
745 40. Hui VWK, Szeto SKH, Tang F, et al. Optical coherence tomography classification
746 systems for diabetic macular edema and their associations with visual outcome and treatment
747 responses - an updated review. Asia Pac J Ophthalmol (Phila) 2022;11(3):247-57.

748 41. Szeto SK, Hui VWK, Tang FY, et al. OCT-based biomarkers for predicting treatment
749 response in eyes with centre-involved diabetic macular oedema treated with anti-VEGF
750 injections: a real-life retina clinic-based study. Br J Ophthalmol 2023;107(4):525-33.

Figure Legends

Figure 1. Faricimab T&E algorithm in YOSEMITE/RHINE. Reference 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 two 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 BCVA was defined as the mean of the three best BCVA scores obtained at any previous active dosing visit. BCVA = best-corrected visual acuity; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; Q4W = every 4 weeks; Q16W = every 16 weeks; T&E = treat-and-extend. Reprinted from The Lancet, Vol. 399, Wykoff CC 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, Pages 741–755, Copyright (2022), with permission from Elsevier.

Figure 2. CONSORT flow diagram for YOSEMITE (**A**) and RHINE (**B**). Q8W = every 8 weeks; T&E = treat-and-extend.

Figure 3. Adjusted mean change in BCVA from baseline through week 100. [a]Adjusted mean BCVA change from baseline at 2 years, averaged over weeks 92, 96, and 100. Results are based on a MMRM analysis of the intention-to-treat population. Treatment policy strategy and hypothetical strategy were applied to non–COVID-19-related and COVID-19-related intercurrent events, respectively. Missing data were implicitly imputed by the MMRM. Error bars represent 95.04% CI. BCVA = best-corrected visual acuity; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; MMRM = mixed model for repeated measures; Q8W = every 8 weeks; T&E = treat-and-extend.

778 **Figure 5.** Proportion of patients in the faricimab T&E arms who achieved Q4W, Q8W,
779 Q12W, or Q16W dosing at week 96 (**A**), and dosing intervals in the faricimab T&E arms
780 through week 96 (**B**). Analyses included patients in the faricimab T&E arms who had not
781 discontinued the study at the week 96 visit (YOSEMITE, n = 270; RHINE, n = 287).
782 Treatment interval at week 96 was defined as the treatment interval decision made at that
783 visit in (**A**), and treatment interval at a given visit is shown as the interval at the start of the
784 visit in (**B**). The week 96 decision (calculated/recorded at week 96) is shown in the last
785 column. Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; Q16W =
786 every 16 weeks; T&E = treat-and-extend.
787
788 **Figure 7.** Adjusted mean change in CST from baseline through week 100. *Nominal *P* <
789 0.05 vs. aflibercept Q8W for adjusted mean CST change from baseline at 2 years, averaged
790 over weeks 92, 96, and 100. Results are based on a MMRM analysis of the intention-to-treat
791 population. Treatment policy strategy and hypothetical strategy were applied to non–COVID-
792 19-related and COVID-19-related intercurrent events, respectively. Missing data were
793 implicitly imputed by the MMRM. Error bars represent 95.04% CI. CST was defined as the
794 average thickness between the internal limiting membrane and Bruch's membrane in the
795 central 1-mm diameter of the Early Treatment Diabetic Retinopathy Study grid. CI =
796 confidence interval; CST = central subfield thickness; MMRM = mixed model for repeated
797 measures; Q8W = every 8 weeks; T&E = treat-and-extend.
798
799 **Figure 9.** Proportion of patients with absence of DME through week 100. *Nominal *P* < 0.05
800 vs. aflibercept Q8W; nominal *P*>0.05 where no asterisk is shown. Weighted proportions
801 were estimated for the intention-to-treat population using the CMH method; weighted
802 proportions for the aflibercept Q8W arms are presented for the faricimab Q8W vs. aflibercept
803 Q8W comparison. Baseline values (defined as the last available measurement obtained on
804 or before randomization) are based on observed data. Treatment policy strategy and
805 hypothetical strategy were applied to non–COVID-19-related and COVID-19-related

intercurrent events, respectively. Missing data were not imputed. Error bars represent 95.04% CI; CI estimates <0% and >100% were imputed as 0% and 100%, respectively. [a]Absence of DME was defined as CST <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. CMH = Cochran-Mantel-Haenszel; CI = confidence interval; CST = central subfield thickness; DME = diabetic macular edema; Q8W = every 8 weeks; T&E = treat-and-extend.

Figure 11. Proportion of patients with absence of IRF through week 100. *Nominal $P < 0.05$ vs. aflibercept Q8W; nominal $P > 0.05$ where no asterisk is shown. Weighted proportions were estimated for the intention-to-treat population using the CMH method; weighted proportions for the aflibercept Q8W arms are presented for the faricimab Q8W vs. aflibercept Q8W 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 non–COVID-19-related and COVID-19-related intercurrent events, respectively. Missing data were not imputed. Error bars represent 95.04% CI; CI estimates <0% and >100% were imputed as 0% and 100%, respectively. [a]IRF was measured in the central 1-mm diameter of the Early Treatment Diabetic Retinopathy Study grid. CI = confidence interval; CMH = Cochran-Mantel-Haenszel; IRF = intraretinal fluid; Q8W = every 8 weeks; T&E = treat-and-extend.

Figure 13. Proportion of patients with ≥2-step ETDRS-DRSS improvement from baseline at week 96. *Nominal $P < 0.05$ vs. aflibercept Q8W; 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 CMH method; weighted proportions for the aflibercept Q8W arms are presented for the faricimab Q8W vs. aflibercept Q8W comparison. Treatment policy strategy and hypothetical strategy were applied to non–COVID-19-related and COVID-19-related intercurrent events,

respectively. Missing data were not imputed. Error bars represent 95.04% CI; CI estimates <0% and >100% were imputed as 0% and 100%, respectively. CI = confidence interval; CMH = Cochran-Mantel-Haenszel; DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; Q8W = every 8 weeks; T&E = treat-and-extend.

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

	YOSEMITE (N = 937)			RHINE (N = 950)		
	Faricimab Q8W (n = 313)	**Faricimab T&E (n = 313)**	**Aflibercept Q8W (n = 311)**	**Faricimab Q8W (n = 317)**	**Faricimab T&E (n = 319)**	**Aflibercept Q8W (n = 314)**
Summary of AEs, n (%)						
Total number of AEs*	1621	1632	1476	1658	1420	1386
Total number 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, n (%)†,§						
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)
Vitritis	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, n (%)†,¶						
Endophthalmitis	0	3 (1.0)	0	2 (0.6)	1 (0.3)	1 (0.3)
Intraocular pressure increased	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, n (%)†						
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, n (%)‖						
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)

*Total number of AEs and SAEs includes nonocular events and ocular events in the study or fellow eye.

†Ocular AEs in the study eye only are presented.

‡Ocular AEs of special interest were defined as events associated with severe IOI, events requiring surgical or medical intervention to prevent permanent loss of sight, or events associated with BCVA loss of ≥30 ETDRS letters for >1 hour. A full list of ocular AEs of special interest is provided in Table S6 (available at www.aaojournal.org).

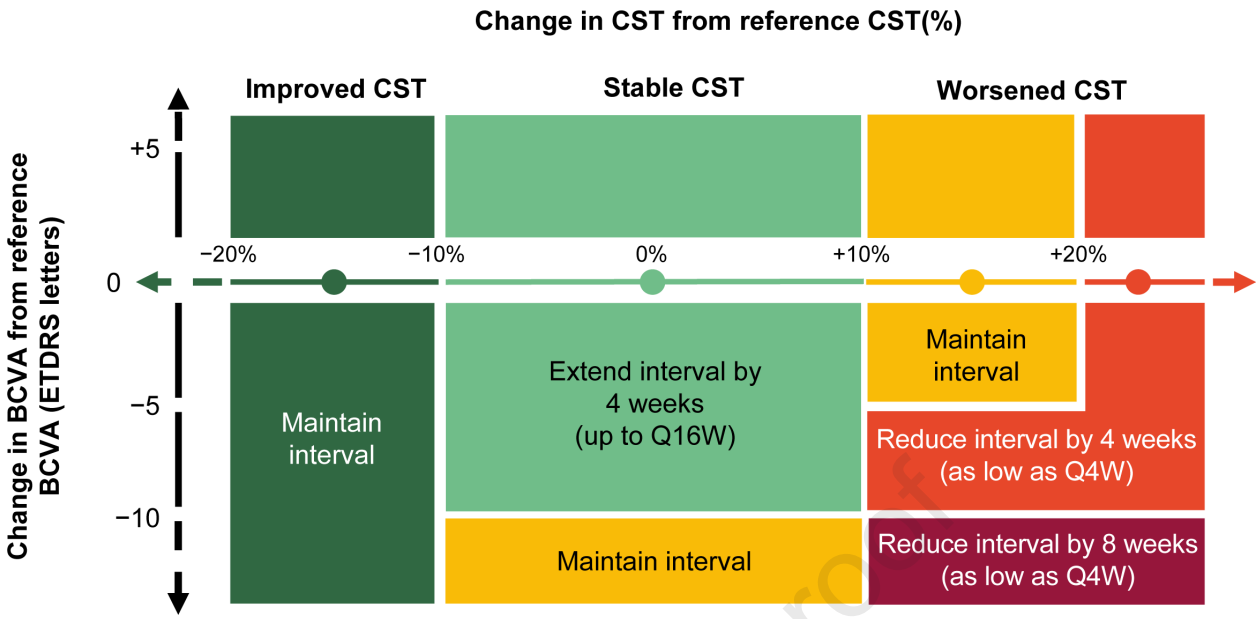
§Includes serious and nonserious IOI events; excludes endophthalmitis events.

¶A full list of ocular SAEs is provided in Table S5 (available at www.aaojournal.org).

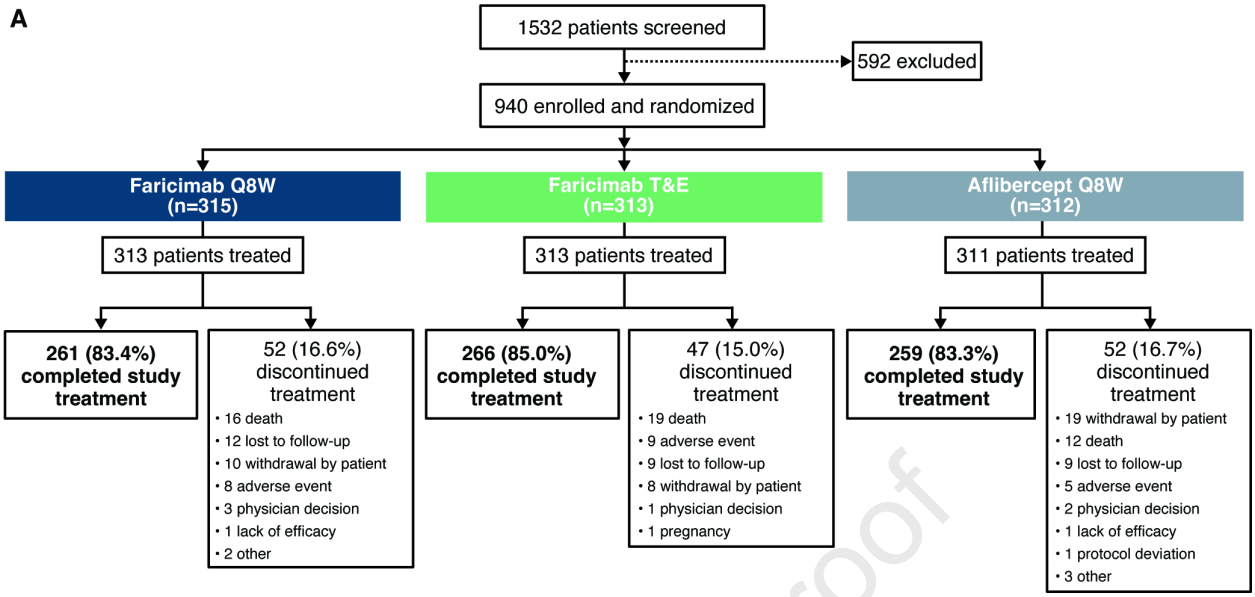
||APTC events were externally adjudicated; all other events were investigator reported.

Includes AEs with onset from the first dose of study drug through study end; percentages are based on n values in the column headings. Multiple occurrences of the same AE in 1 individual are counted only once, except for the “Total number of events” rows, in which multiple occurrences of the same AE are counted separately.

AE = adverse event; APTC = Anti-Platelet Trialists’ Collaboration; BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; IOI = intraocular inflammation; Q8W = every 8 weeks; SAE = serious adverse event; T&E = treat-and-extend; VEGF = vascular endothelial growth factor



A



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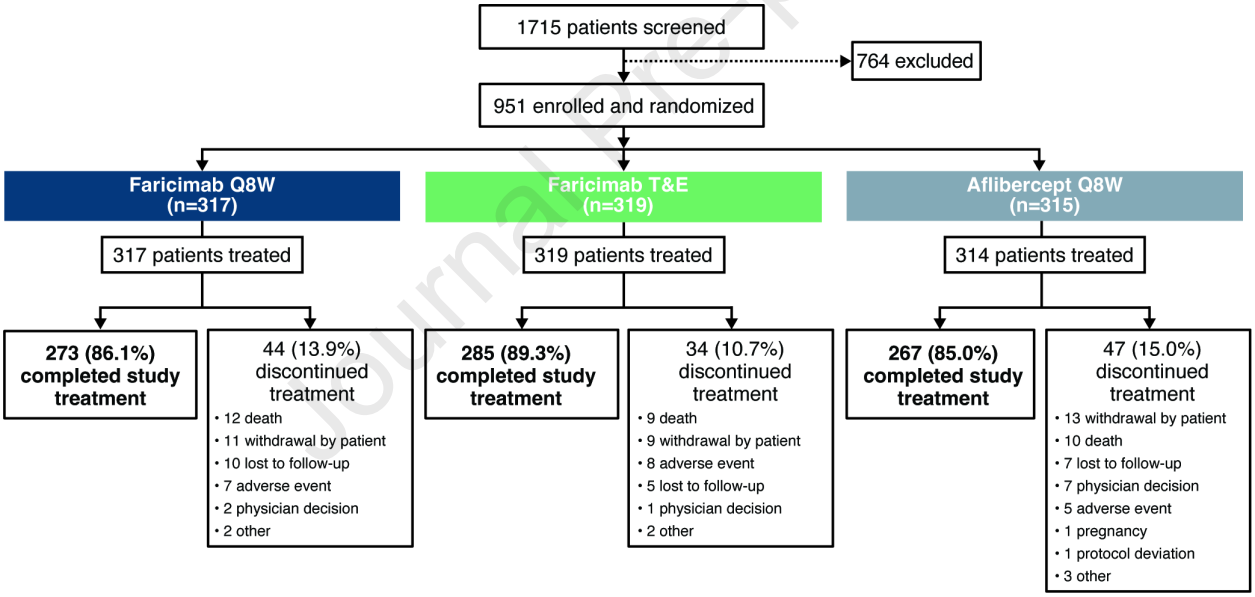
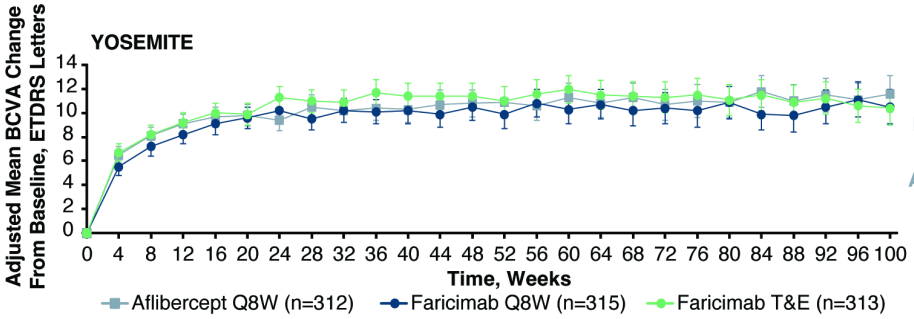
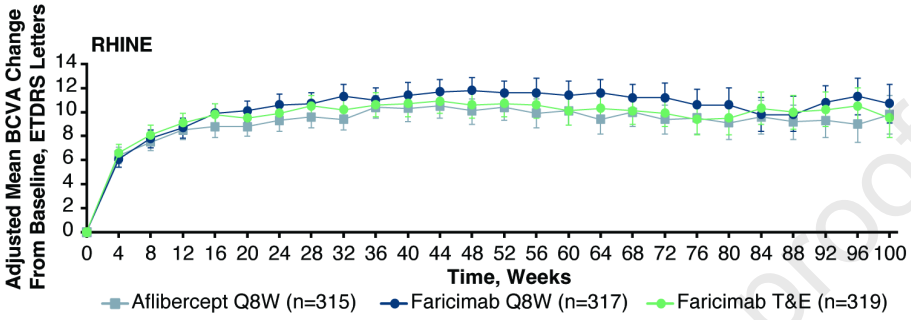
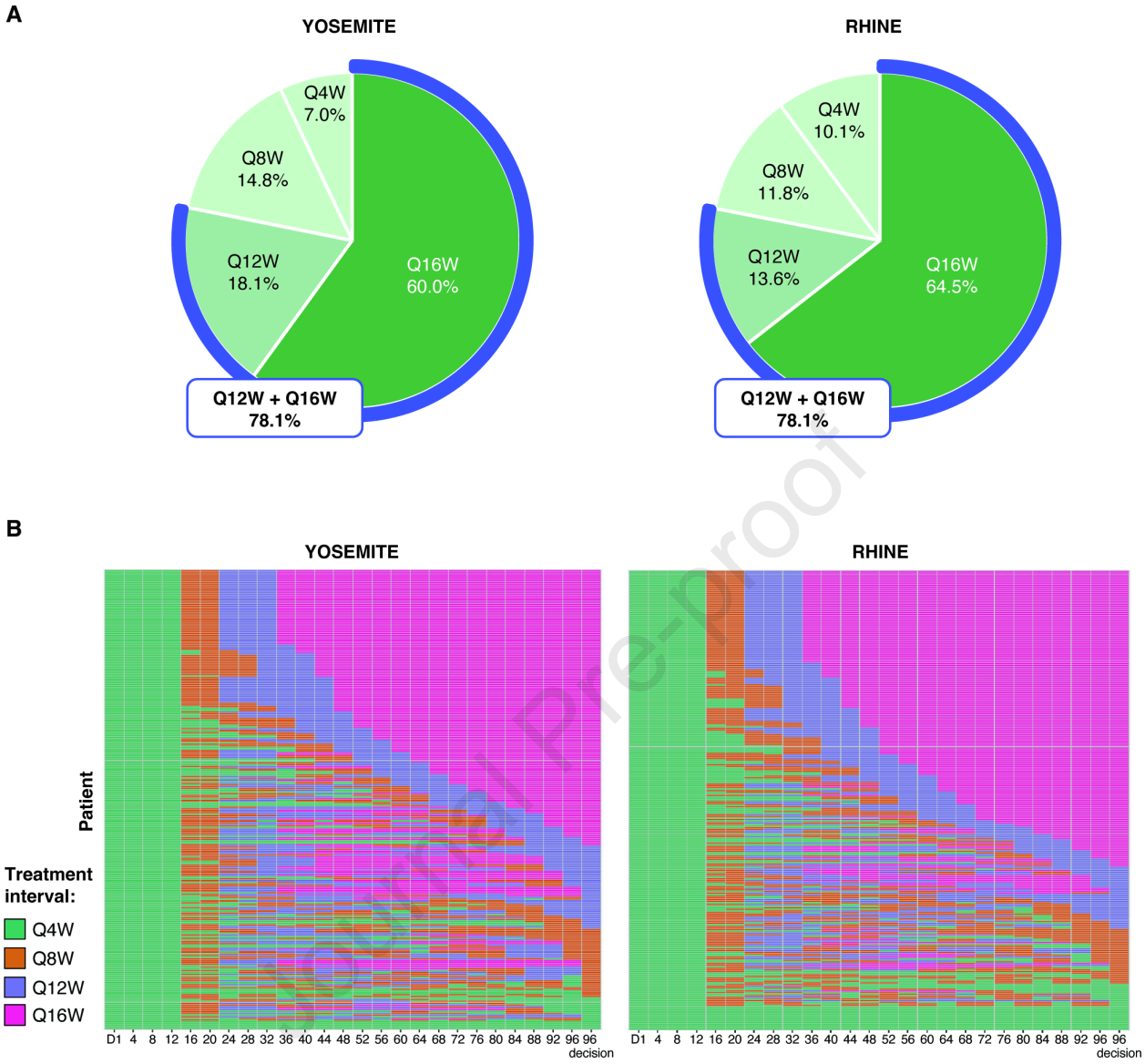


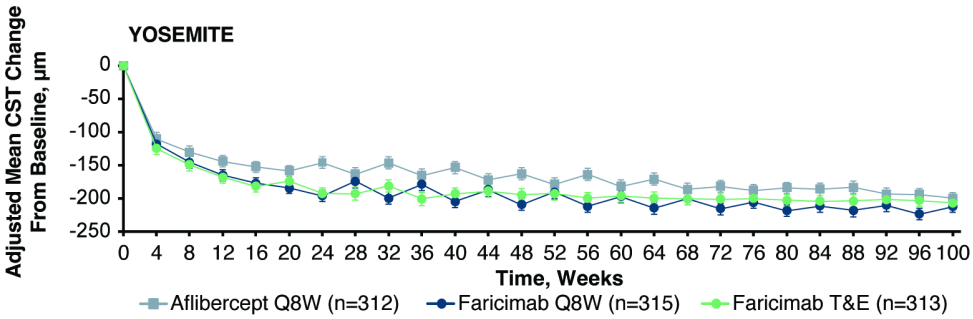


Average of weeks 92–100[a]
Faricimab Q8W: +10.7 ETDRS letters
Faricimab T&E: +10.7 ETDRS letters
Aflibercept Q8W: +11.4 ETDRS letters

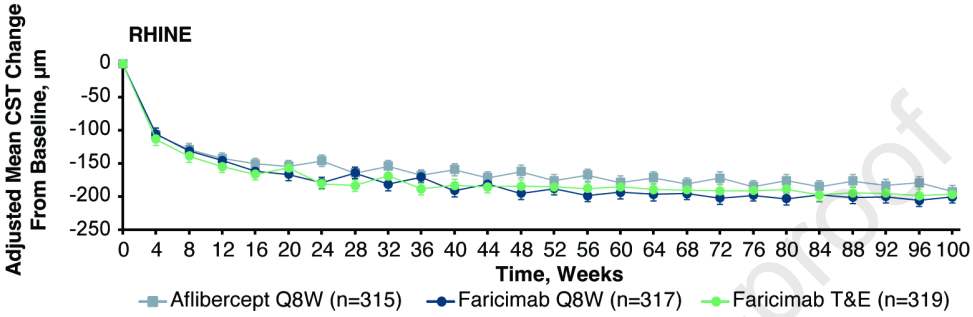


Average of weeks 92–100[a]
Faricimab Q8W: +10.9 ETDRS letters
Faricimab T&E: +10.1 ETDRS letters
Aflibercept Q8W: +9.4 ETDRS letters

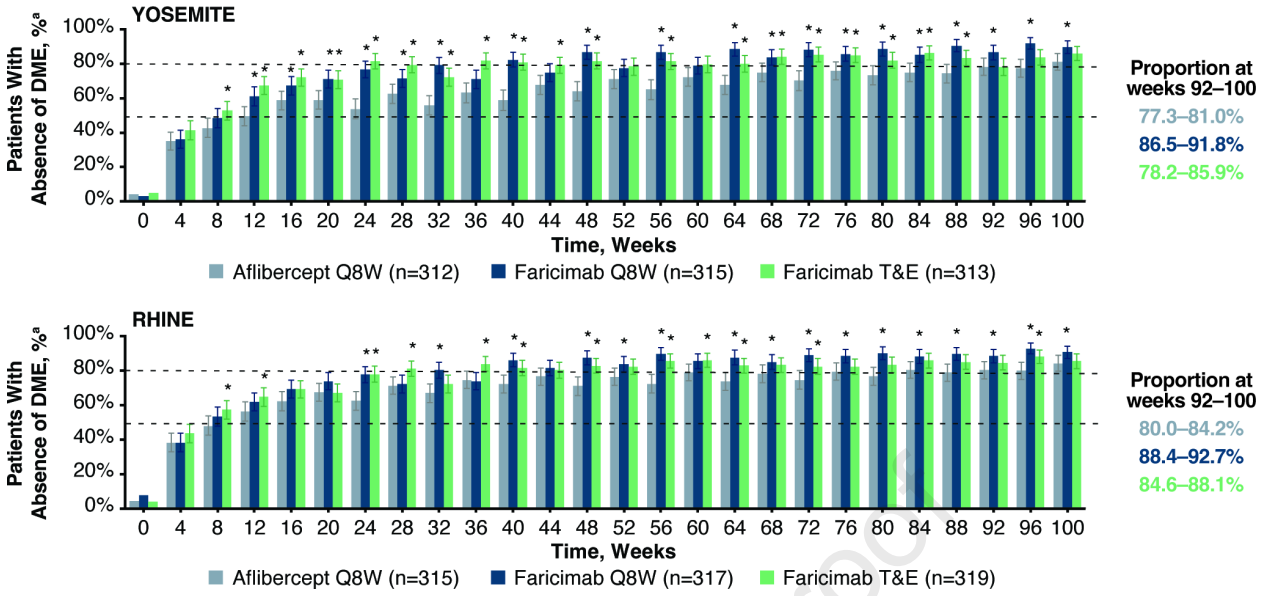


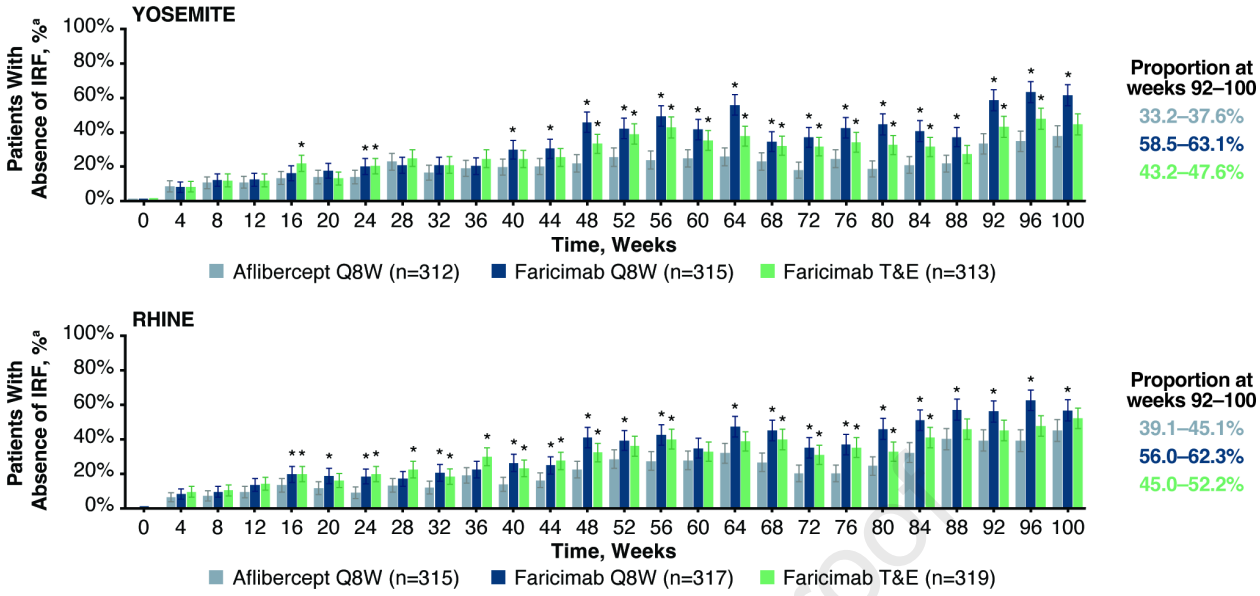


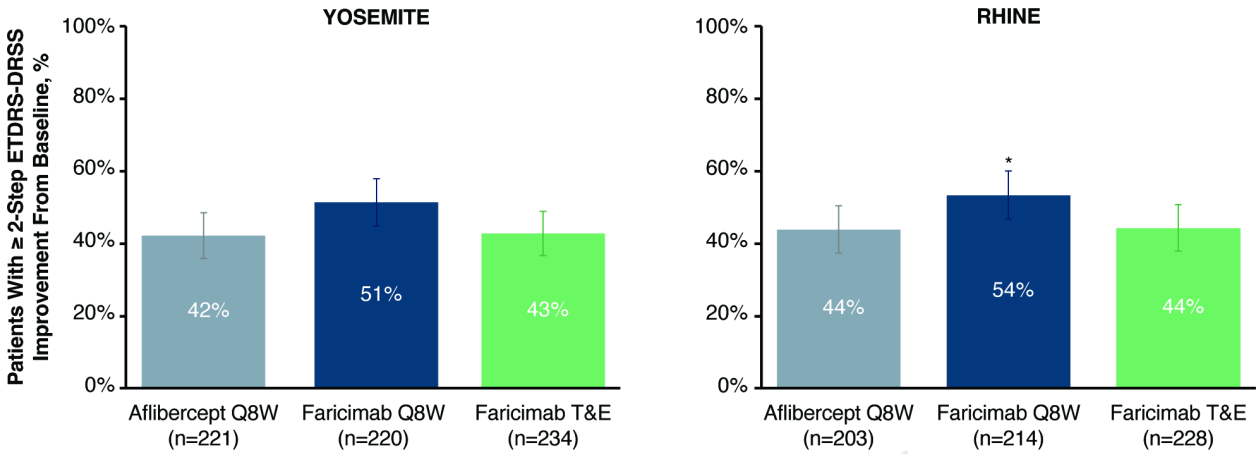
Average of weeks 92–100
Faricimab Q8W: –216.0 µm*
Faricimab T&E: –204.5 µm
Aflibercept Q8W: –196.3 µm



Average of weeks 92–100
Faricimab Q8W: –202.6 µm*
Faricimab T&E: –197.1 µm
Aflibercept Q8W: –185.6 µm







Précis

Over 2 years, faricimab offered comparable visual acuity gains and improved anatomic outcomes compared with aflibercept. In the faricimab treat-and-extend arms, durable visual acuity gains, and anatomic improvements were maintained with up to every-16-week dosing.

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Seong	Lee
Jaime	Levy
Blandina	Lipkova
Mimi	Liu
Judy	Liu
Chris P	Lohmann
Nikolas	London
Katrin	Lorenz
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David	Lozano Rechy
Silvio	Lujan
Patrick	Ma
Takatoshi	Maeno
Sajjad	Mahmood

Fuad	Makkouk
Khurram	Malik
Dennis	Marcus
Alan	Margherio
Leonardo	Mastropasqua
Raj	Maturi
Frank	McCabe
Martin	McKibbin
Hemal	Mehta
Geeta	Menon
Jale	Mentes
Katarzyna	Michalska-Malecka
Aneta	Misheva
Yoshinori	Mitamura
Paul	Mitchell
Yasha	Modi
Quresh	Mohamed
Javier	Montero
Jeffrey	Moore
Virgilio	Morales Canton
Haia	Morori-Katz
Tatiana	Morugova
Tomoaki	Murakami
Maria	Muzyka-Wozniak
Marco	Nardi
Jan	Nemcansky
Kamila	Nester-Ostrowska
Julio	Neto
Charles	Newell
Massimo	Nicolo
Jared	Nielsen
Kousuke	Noda
Akira	Obana
Nahoko	Ogata
Hideyasu	Oh
Kean	Oh
Matthew	Ohr
Piotr	Oleksy
Scott	Oliver
Sebastien	Olivier
James	Osher
Sehnaz	Ozcalışkan
Banu	Ozturk
Andras	Papp
Kyu Hyung	Park
D Wilkin	Parke
Maria Cristina	Parravano
Sugat	Patel
Sunil	Patel

Ian	Pearce
Joel	Pearlman
Fernando	Penha
Irfan	Perente
Stephen	Perkins
Grazia	Pertile
Iva	Petkova
Tunde	Peto
Dante	Pieramici
Andreas	Pollreisz
Pear	Pongsachareonnont
Nadezhda	Pozdeyeva
Siegfried	Priglinger
Jawad	Qureshi
Dorota	Raczynska
Rajesh	Rajagopalan
Juan	Ramirez Estudillo
Paul	Raskauskas
Rajiv	Rathod
Hessam	Razavi
Carl	Regillo
Federico	Ricci
Soraya	Rofagha
Dominika	Romanczak
Bożena	Romanowska-Dixon
Daniel	Rosberger
Irit	Rosenblatt
Brett	Rosenblatt
Adam	Ross
Paisan	Ruamviboonsuk
Jose Maria	Ruiz Moreno
Gustavo	Salomão
Sukhpal	Sandhu
Dirk	Sandner
Laura	Sararols
Osamu	Sawada
Ramin	Schadlu
Patricio	Schlottmann
Claudia	Schuart
Berthold	Seitz
András	Seres
Figen	Sermet
Sandeep	Shah
Ankur	Shah
Rohan	Shah
Sumit	Sharma
Thomas	Sheidow
Veeral	Sheth
Akito	Shimouchi

Masahiko	Shimura
Bartosz	Sikorski
Rufino	Silva
Michael	Singer
Lawrence	Singerman
Rishi	Singh
Eric	Souied
David J	Spinak
Georg	Spital
Nathan	Steinle
Jeffrey	Stern
Glenn	Stoller
Robert	Stoltz
Cameron	Stone
Amy	Stone
Eric	Suan
Masahiko	Sugimoto
Iichiro	Sugita
Jennifer	Sun
Xiaodong	Sun
Ivan	Suner
Lajos	Szalczer
Timea	Szecsko
Ali	Tabassian
Ramin	Tadayoni
Hitoshi	Takagi
Kei	Takayama
Alexandre	Taleb
James	Talks
Gavin	Tan
Teruyo	Tanabe
Stanford	Taylor
Allen	Thach
John	Thompson
Paul	Tlucek
Robert	Torti
Daniela	Tosheva Guneva
Edit	Toth-Molnar
Eduardo	Uchiyama
Attila	Vajas
Deepali	Varma
Balazs	Varsanyi
Petja	Vassileva
Sara	Vaz-Pereira
Miroslav	Veith
Jose Ignacio	Vela
Francesco	Viola
Gianni	Virgili
Gábor	Vogt

Henrik	Vorum
Pamela	Weber
Thoalf	Wecke
Raymond	Wee
Martin	Weger
Paul	Weishaar
John A	Wells
Sanjeewa	Wickremasinghe
Thomas Reginald	Williams
Thomas	Williams
Geoff	Williams
Armin	Wolf
Jeremy	Wolfe
James	Wong
David	Wong
Ian	Wong
Robert	Wong
Bogumil	Wowra
Charles C	Wykoff
Edward	Wylęgała
Chang-Hao	Yang
Tsutomu	Yasukawa
Paul	Yates
Gursel	Yilmaz
Glenn	Yiu
Young Hee	Yoon
Barak	Yoreh
Shigeo	Yoshida
Hyeong Gon	Yu
Seung Young	Yu
Tatiana	Yurieva
Leandro	Zacharias
Karolina	Zaczek Zakrzewska
Alberto	Zambrano
Barbara	Zatorska
Carlos	Zeolite
Jeffrey	Zheutlin