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# Anatomic Control with Faricimab versus Aflibercept in the YOSEMITE/RHINE Trials in Diabetic Macular Edema

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***Purpose:*** To compare anatomic biomarkers on spectral-domain OCT between faricimab, a dual angiopoietin-2 (Ang-2)/VEGF-A inhibitor, and aflibercept in a pooled analysis of results from the YOSEMITE/RHINE trials in diabetic macular edema (DME).

***Design:*** YOSEMITE/RHINE (NCT03622580/NCT03622593) were identical, randomized, double-masked, active comparator-controlled, 100-week phase III noninferiority trials.

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

***Methods:*** Patients were randomized 1:1:1 to faricimab 6.0 mg every 8 weeks (Q8W), faricimab 6.0 mg treat-and-extend (T&E), or aflibercept 2.0 mg Q8W for 100 weeks. The T&E up to every 16 weeks dosing regimen was based on central subfield thickness (CST) and best-corrected visual acuity changes.

***Main Outcome Measures:*** Post hoc analyses comparing faricimab with aflibercept on CST change; the proportion of eyes with an absence of intraretinal fluid (IRF), subretinal fluid, or both IRF and subretinal fluid or achieving a CST <280 μm at key timepoints during the trials; time to first absence of IRF; and time to first achieving CST <280 μm.

***Results:*** In total, 1891 patients were enrolled across YOSEMITE/RHINE (n = 632 faricimab Q8W; n = 632 faricimab T&E; n = 627 aflibercept). There were greater CST reductions from baseline with both faricimab dosing regimens compared with aflibercept over the 100 weeks (adjusted means and area-under-the-curve analysis). Higher proportions of eyes achieved an absence of IRF with faricimab Q8W (58%–63%) and faricimab T&E (44%–49%) versus aflibercept (36%–41%) at weeks 92 to 100. In eyes with IRF at baseline, the median time to first absence of IRF was achieved 40 weeks earlier with faricimab versus aflibercept. The proportion of eyes achieving a CST <280 μm at weeks 92 to 100 was 70% to 74% with faricimab Q8W, 61% to 65% with faricimab T&E, and 61% to 63% with aflibercept. In eyes with CST ≥280 μm at baseline, the median time to first instance of CST <280 μm was achieved 16 weeks earlier with faricimab versus aflibercept.

***Conclusions:*** Dual Ang-2/VEGF-A inhibition with faricimab resulted in greater and faster improvements in anatomic outcomes compared with aflibercept at key timepoints over the pooled YOSEMITE/RHINE trials.

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Diabetic macular edema (DME) continues to be a leading cause of vision loss worldwide in working-age and older adults.[1,2] The condition is characterized by inflammation and increased vascular permeability, leading to thickening of the retina.[3,4] From a pathophysiological perspective, it is known that diabetes-associated increase of retinal inflammatory mediators contributes to retinopathy by enhancing vascular permeability[5] and that VEGF signaling is a major player in DME pathogenesis.[3,6]

This is supported by a wealth of trial data demonstrating the clinical effectiveness of inhibiting VEGF with anti-VEGF therapies for patients with DME.[1] However, despite the efficacy of anti-VEGF therapy in reducing vision loss, suboptimal outcomes in patients with DME have been observed in clinical practice and clinical trials.[7,8] Data suggest that in a clinical setting, patients are underdosed relative to clinical trials for a variety of reasons, potentially explaining the suboptimal outcomes.[8,9] Further, although



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the role of VEGF in DME pathogenesis is well established, the pathophysiology of DME is complex, involving multiple different signaling molecules and biological pathways, and VEGF inhibitors do not address the multifactorial nature of this disease.[3,10] As such, there remains an unmet need for treatments that use new mechanisms of action to treat additional non-VEGF factors of DME pathogenesis and to offer an extended duration of action.

Angiopoietin-2 (Ang-2) is an inflammatory mediator that is upregulated in retinal vascular diseases and is involved in several pathogenetic pathways of DME in addition to VEGF.[6] Under homeostatic conditions, angiopoietin-1 binds to the tyrosine kinase with immunoglobulin-like and endothelial growth factor−like domains 2 receptor promoting vascular stability, whereas under pathologic conditions, Ang-2 is upregulated and competitively binds to the tyrosine kinase with immunoglobulin-like and endothelial growth factor−like domains 2 receptor, thereby inactivating the angiopoietin-1/tyrosine kinase with immunoglobulin-like and endothelial growth factor−like domains 2 pathway and promoting vascular instability, characterized by vascular leakage, neovascularization, and inflammation.[6] Angiopoietin-2 also has direct proangiogenic effects via integrin signaling to promote vascular destabilization and glial cell apoptosis[11−14] and proinflammatory effects via induced expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1.[15] In addition, Ang-2 sensitizes retinal vessels to the effects of VEGF, further promoting vascular permeability, angiogenesis, and inflammation.[16−19] These data collectively support Ang-2 as a potential target for pharmacotherapeutic intervention in the treatment of DME.

Faricimab is a humanized, bispecific, immunoglobulin G monoclonal antibody that independently targets and inhibits both Ang-2 and VEGF-A.[6] In the phase III YOSEMITE and RHINE trials, intravitreal faricimab every 8 weeks (Q8W) or according to a treat-and-extend (T&E) personalized treatment interval of up to every 16 weeks (Q16W) was noninferior to aflibercept 2.0 mg Q8W in terms of best-corrected visual acuity (BCVA) change from baseline to year 1 (weeks 48−56).[20−22] Both faricimab arms demonstrated greater reductions in central subfield thickness (CST) and retinal fluid compared with aflibercept over the same 1-year period. Moreover, in the T&E arm, almost three-quarters (72.4%) of patients achieved extended dosing of every 12 weeks or more, with more than half (51.9%) on Q16W dosing at week 52. The gains in visual acuity and anatomic improvements were maintained by patients randomized to faricimab through year 2 (weeks 92−100), with even more patients in the T&E regimens achieving extended dosing intervals up to Q16W (62.3%). Faricimab was well tolerated with a safety profile comparable to aflibercept across both 1- and 2-year timepoints.[21,22]

The available data generally support that treatment decisions about anti-VEGF dosing and treatment intervals for retinal vascular diseases, including DME, should be driven by disease activity assessments centered around visual acuity or anatomic outcomes or both (e.g., presence of retinal fluid).[23,24] The importance of anatomic outcomes in guiding DME treatment decisions with anti-VEGFs is reflected in their inclusion in the DME management guidelines from professional organizations, such as the American Academy of Ophthalmology,[1] the International Council of Ophthalmology,[25] the American Society of Retina Specialists,[26] the European Society of Retina Specialists,[27] and the UK National Institute for Health and Care Excellence.[28−30] As such, anatomic outcomes may represent objective measurements that can be accurately and reproducibly assessed to evaluate treatment effectiveness, including disease control and treatment durability. Moreover, understanding the importance of anatomic treatment responses in relation to long-term outcomes in patients with DME may help to inform clinicians on future treatment decisions and personalized treatment.

The objective of this analysis was to evaluate whether dual Ang-2/VEGF-A inhibition with faricimab demonstrated anatomic improvements on OCT over aflibercept in DME. For this analysis, outcomes were assessed at 16, 56, and 100 weeks using pooled data from the YOSEMITE/RHINE trials. Week 16 was selected as a key timepoint, because it corresponds to 4 weeks after the 12-week head-to-head dosing period, when all patients received an assigned study drug, faricimab or aflibercept, every 4 weeks (Q4W).

## Methods

### Study Design

The rationale and study design for the identical, multicenter, global, randomized, double-masked, active comparator-controlled, phase III YOSEMITE (NCT03622580) and RHINE (NCT03622593) noninferiority trials have previously been described.[20,22] To summarize, these trials investigated the efficacy, safety, and durability of intravitreal faricimab 6.0 mg Q8W, faricimab 6.0 mg T&E, and aflibercept 2.0 mg Q8W in patients with DME over 100 weeks. Patients with DME could be treatment naïve or previously treated (if the last treatment was ≥3 months before the day 1 study visit).[20,22] Both trials were conducted in accordance with the International Council for Harmonization E6 Guideline for Good Clinical Practice, tenets of the Declaration of Helsinki, US Food and Drug Administration regulations, and the European Union Clinical Trials Directive (2001/20/EC) as appropriate and all applicable local, state, and federal laws. Study protocols were approved by applicable institutional review boards and ethics committees before trial commencement. All patients provided written informed consent to participate.

### Participants

The inclusion and exclusion criteria for YOSEMITE/RHINE have been previously described.[20,22] Briefly, participants were ≥18 years of age with center-involving macular edema secondary to diabetes (type 1 or 2) and CST ≥325 μm. One eye per patient was designated as the study eye, based on which eye had the worst BCVA at screening. Study eyes were either treatment naïve for anti-VEGF or had received previous anti-VEGF treatment provided that the last treatment was ≥3 months before study day 1. The enrollment of previously treated eyes was capped at 25% of the total patient enrollment for each study.

## Randomization and Masking

Participants were randomized 1:1:1 to receive intravitreal faricimab 6.0 mg Q8W, faricimab 6.0 mg T&E with up to Q16W dosing intervals, or aflibercept 2.0 mg Q8W. To preserve the masked design of this study, all participants were required to attend study visits once Q4W, and sham injections were administered at non-dosing visits. Further details have previously been described.[20,22]

## Procedures

Dosing procedures have been described elsewhere.[20,22] All patients received initial doses administered Q4W. The patients in the faricimab Q8W arm received 6 initial faricimab Q4W doses up to week 20; those in the faricimab T&E received 4 initial Q4W doses up to week 12; and those in the aflibercept Q8W arm received 5 aflibercept Q4W doses up to week 16. Hence, between baseline (day 1) and week 12, all patients received 4 active treatment injections, irrespective of their assigned arm. This corresponds to the head-to-head dosing period, when patients in the 3 treatment arms received the same number of injections administered at the same dosing interval.

At or after week 12, eyes in the faricimab T&E arm that achieved a CST <325 μm were initially extended to Q8W, then followed a personalized dosing schedule with up to Q16W intervals through week 96. Personalized treatment intervals could be extended by 4 weeks (up to Q16W), maintained, or reduced by 4 or 8 weeks (as low as Q4W), based on protocol prespecified visual (BCVA) and anatomic criteria (CST).[20,22] After the initial 6 injections, eyes in the faricimab Q8W arm were maintained on a fixed Q8W interval through week 96. Eyes in the aflibercept arm received aflibercept Q8W after the initial 5 injections.

## Ocular and Anatomic Assessments

Spectral-domain OCT scans were performed at prespecified timepoints, and images were independently assessed by masked evaluators at central reading centers (Duke Reading Center or Vienna Reading Center). For additional details, see original manuscripts.[20,22]

## Outcomes

Methods and outcomes for the primary efficacy end point of mean change in BCVA from baseline to year 1 (averaged over weeks 48, 52, and 56) have already been published for the individual YOSEMITE and RHINE trials.[20,22] Central subfield thickness was defined as the distance between the internal limiting membrane and Bruch's membrane, as assessed by central reading centers. Intraretinal fluid (IRF) and subretinal fluid (SRF) were measured in the central subfield (central 1-mm diameter of the ETDRS grid). The absence of DME was prospectively defined as CST <325 μm in the protocol, but a stricter, additional exploratory end point of CST <280 μm is also explored in this analysis. This CST target of <280 μm was selected because this is considered a "typical" retina in those with diabetes without DME.[31] These outcomes will be referred to as CST < 325 μm and CST <280 μm hereafter.

This exploratory analysis of the pooled YOSEMITE and RHINE study population focused on anatomic biomarkers assessed by spectral-domain OCT at key timepoints. These outcomes include change from baseline in CST over time and through week 100, an area-under-the-curve (AUC) analysis of CST change from baseline, the proportion of eyes with the absence of IRF, SRF, and IRF and SRF, and eyes with a CST of <280 and <325 μm at baseline, week 16 (4 weeks after the head-to-head dosing period), end of year 1 (weeks 48, 52, 56), and end of year 2 (weeks 92, 96, 100). The time-to-event analyses were also performed, including time to first absence of IRF and the absence of both IRF and SRF, over 100 weeks in eyes with only IRF, and with both IRF and SRF, respectively, at baseline, and time to first instance of CST <280 and <325 μm, over 100 weeks, in eyes with CST ≥280 and ≥325 μm, at baseline, respectively.

An analysis of anatomic biomarkers assessed by spectral-domain OCT at key timepoints was also performed for pooled YOSEMITE and RHINE patients who had previously been treated with anti-VEGF therapy. Outcomes included change from baseline in CST over time and through week 100; the proportion of eyes with the absence of IRF at baseline, week 16 (4 weeks after the head-to-head dosing period), end of year 1 (weeks 48, 52, 56), and end of year 2 (weeks 92, 96, 100), respectively; and time to first absence of IRF over 100 weeks in eyes with IRF at baseline.

## Statistical Analysis

As used for the primary efficacy end point analyses, a mixed model for repeated measures was used for statistical analysis of CST measured on a continuous scale over time, with adjustment of treatment group, visit, visit-by-treatment-group interaction, baseline CST (continuous), baseline BCVA score (<64 letters vs. ≥64 letters), prior intravitreal anti-VEGF therapy (yes vs. no), region (USA and Canada, Asia, and the rest of the world), and study (YOSEMITE vs. RHINE). An unstructured covariance structure was used, and any missing data were imputed implicitly using this model.[20,22]

For the AUC analysis of the CST over time graphs, an analysis of covariance of standardized AUC was conducted. The absolute values of change in CST from baseline were used in calculation of the AUC; hence, the greater positive values of AUC reflected a greater reduction in CST. This calculation was based on observed data without imputation. The standardized AUC was then computed by dividing the AUC by the length of follow-up time for individual patients. The analysis of covariance model was adjusted for the treatment group, baseline CST (continuous), baseline BCVA (<64 letters vs. ≥64 letters), prior intravitreal anti-VEGF therapy (yes vs. no), region (USA and Canada, Asia, and the rest of the world), and study (YOSEMITE vs. RHINE).

For binary outcomes over time, stratified estimation for binomial proportions was used. The proportion of eyes in each treatment group and the overall difference in proportions between treatment groups were estimated using the Cochran–Mantel–Haenszel weighted averages[32,33] over strata defined by study (YOSEMITE vs. RHINE) and randomization factors as described previously.[20,22] The normal approximation to the weighted proportions was used to calculate the 95% confidence intervals (CIs).

Kaplan–Meier estimates were generated for time to first instance/absence end points. Hazard ratios (HRs) were estimated by Cox regression with strata defined by randomization factors (detailed previously).[20,22,34]

All randomized eyes were used as the analysis set for baseline demographics. The analysis sets for the anatomic changes from baseline analyses were all randomized eyes or randomized eyes that had been previously treated with anti-VEGF therapy. The time-to-event analyses were based on eyes that had data for the outcome in question at baseline but had not already achieved the target outcome (e.g., absence of IRF). All *P* values are nominal and unadjusted for multiplicity, and, as such, no formal statistical conclusion should be made based on the *P* values.

## Results

### Baseline Demographics and Characteristics

Between September 5, 2018, and September 19, 2019, for YOSEMITE and between October 9, 2018, and September 20, 2019, for RHINE, 3247 patients with DME were screened for eligibility (n = 1532, YOSEMITE; n = 1715, RHINE).[22] In total, 1891 eyes were enrolled across both trials and randomized to receive faricimab Q8W (n = 632) or T&E (n = 632) or aflibercept (n = 627). Of these, 410 (22%) were previously treated with anti-VEGF therapy (faricimab Q8W n = 140, faricimab T&E n = 133, aflibercept, n = 137). The mean (standard deviation) time since the last anti-VEGF treatment in previously anti-VEGF–treated patients was 20.6 (20.5) months for faricimab Q8W, 16.5 (18.1) months for faricimab T&E, and 18.3 (15.3) months for aflibercept Q8W.

Baseline demographics were generally well-balanced across treatment arms (Table 1).[22,35] The mean CST at baseline was comparable between treatment groups (~480 μm for each arm), as were the proportions of eyes with retinal fluid (IRF, SRF, both IRF and SRF, CST <280 μm, CST <325 μm). At baseline, IRF was present in 98.7% to 99.0% of eyes, whereas SRF was

Table 1. Baseline Demographics and Ocular Characteristics (Intention-to-Treat Population)

| Characteristic | Pooled YOSEMITE and RHINE (N = 1891) | | |
|---|---|---|---|
| | *Faricimab Q8W (n = 632)* | *Faricimab T&E (n = 632)* | *Aflibercept Q8W (n = 627)* |
| Age, yrs [SD] | 62.1 [9.8] | 62.2 [10.1] | 62.3 [9.8] |
| Sex | | | |
| Female | 251 (39.7) | 236 (37.3) | 263 (41.9) |
| Ethnicity or race,* no. (%) | | | |
| Hispanic or Latino | 93 (14.7) | 118 (18.7) | 104 (16.6) |
| White | 491 (77.7) | 489 (77.4) | 506 (80.7) |
| Asian | 65 (10.3) | 62 (9.8) | 59 (9.4) |
| American Indian or Alaska Native | 6 (0.9) | 5 (0.8) | 8 (1.3) |
| Black | 40 (6.3) | 48 (7.6) | 36 (5.7) |
| Region, no. (%) | | | |
| Rest of the world† | 305 (48.3) | 305 (48.3) | 304 (48.5) |
| USA and Canada | 277 (43.8) | 279 (44.1) | 277 (44.2) |
| Asia‡ | 50 (7.9) | 48 (7.6) | 46 (7.3) |
| BMI, kg/m$^2$ [SD] | 30.7 [6.5] | 30.4 [6.3] | 30.6 [6.4] |
| Systolic blood pressure, mmHg [SD] | 137.0 [15.7] | 137.9 [15.8] | 136.9 [16.1] |
| Type 2 diabetes, no. (%) | 588 [93.0] | 599 [94.8] | 597 [95.2] |
| $HbA_{1c}$, % [SD] | 7.6 [1.1] | 7.7 [1.2] | 7.6 [1.2] |
| BCVA, ETDRS letters [SD] | 61.9 [10.0] | 62.2 [9.8] | 62.1 [9.5] |
| ETDRS-DRSS status, no. (%) | | | |
| DR absent/questionable; mild to moderate NPDR (ETDRS-DRSS level 10 of 12, 14 of 20, 35, 43) | 357 (56.5) | 365 (57.8) | 362 (57.7) |
| Moderately severe to severe NPDR (ETDRS-DRSS level 47, 53) | 222 (35.1) | 198 (31.3) | 208 (33.2) |
| PDR (ETDRS-DRSS level 61, 65, 71 of 75) | 42 (6.6) | 58 (9.2) | 38 (6.1) |
| Cannot grade (ETDRS-DRSS level 90) | 6 (0.9) | 10 (1.6) | 12 (1.9) |
| Missing | 5 (0.8) | 1 (0.2) | 7 (1.1) |
| CST,§ μm [SD] | 479.2 [128.4] | 478.5 [129.0] | 480.9 [130.2] |
| Macular ischemic nonperfusion, no. (%) | 253 (40.0) | 255 (40.3) | 254 (40.5) |
| Macular leakage, no. (%) | 605 (95.7) | 610 (96.5) | 592 (94.4) |
| Previously anti-VEGF treated, no. (%) | 140 (22.2) | 133 (21.0) | 137 (21.9) |
| Time since last anti-VEGF treatment, months [SD] | 20.6 [20.5] | 16.5 [18.1] | 18.3 [15.3] |
| Intraocular pressure, mmHg [SD] | 15.3 [3.1] | 15.2 [3.0] | 15.1 [3.1] |
| Time since DME diagnosis, months [SD] | 16.3 [27.4] | 19.1 [34.7] | 18.9 [32.5] |
| Phakic, no. (%) | 476 (75.3) | 474 (75.0) | 468 (74.6) |
| Presence of IRF, no. (%) | 621 (98.7) | 618 (98.9) | 611 (99.0) |
| Presence of SRF, no. (%) | 214 (34.0) | 235 (37.7) | 232 (37.7) |
| Presence of IRF and SRF, no. (%) | 623 (99.0) | 621 (99.4) | 613 (99.4) |
| Presence of CST ≥280 μm, no. (%) | 625 (99.8) | 627 (99.8) | 617 (99.5) |
| Presence of CST ≥325 μm, no. (%) | 592 (94.6) | 600 (95.5) | 593 (95.6) |

Data are presented as mean ± SD or no. (%). Some of the data were published in Shimura et al.[35]
BCVA = best-corrected visual acuity; BMI = body mass index; CST = central subfield thickness; DME = diabetic macula edema; DR = diabetic retinopathy; DRSS = diabetic retinopathy severity scale; IRF = intraretinal fluid; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; Q8W = every 8 weeks; SD = standard deviation; SRF = subretinal fluid; T&E = treat-and-extend.
*Not all categories are listed; therefore, the sums of proportions shown do not equal 100%.
†Rest of the world includes Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Mexico, the Netherlands, New Zealand, Peru, Poland, Portugal, Russia, Slovakia, South Africa, Spain, Switzerland, Turkey, Ukraine, and the United Kingdom.
‡Asia includes China, Hong Kong, Japan, Singapore, South Korea, Taiwan, and Thailand.
§CST was measured as the distance between the internal limiting membrane and Bruch's membrane.

present in 34.0% to 37.7% of eyes. The proportions of eyes with IRF and SRF were similar to the proportions of eyes with IRF alone (99.0%–99.4%) (Figs 1A, B, and S2A, available at www.ophthalmologyretina.org). Only a handful of eyes had a CST <280 μm, with 99.5% to 99.8% and 94.6% to 95.6% of eyes having a CST ≥280 and CST ≥325 μm, respectively (Figs 1C, S2B).

## Anatomic Changes from Baseline

Faricimab Q8W and T&E demonstrated greater benefits in anatomic changes from baseline compared with aflibercept across a range of biomarkers in this post hoc analysis. Improved mean CST changes from baseline for faricimab versus aflibercept were observed as early as week 4 (1 dose) for faricimab T&E and week 12 (3 doses) for both faricimab arms (Fig 3) (nominal $P < 0.05$).

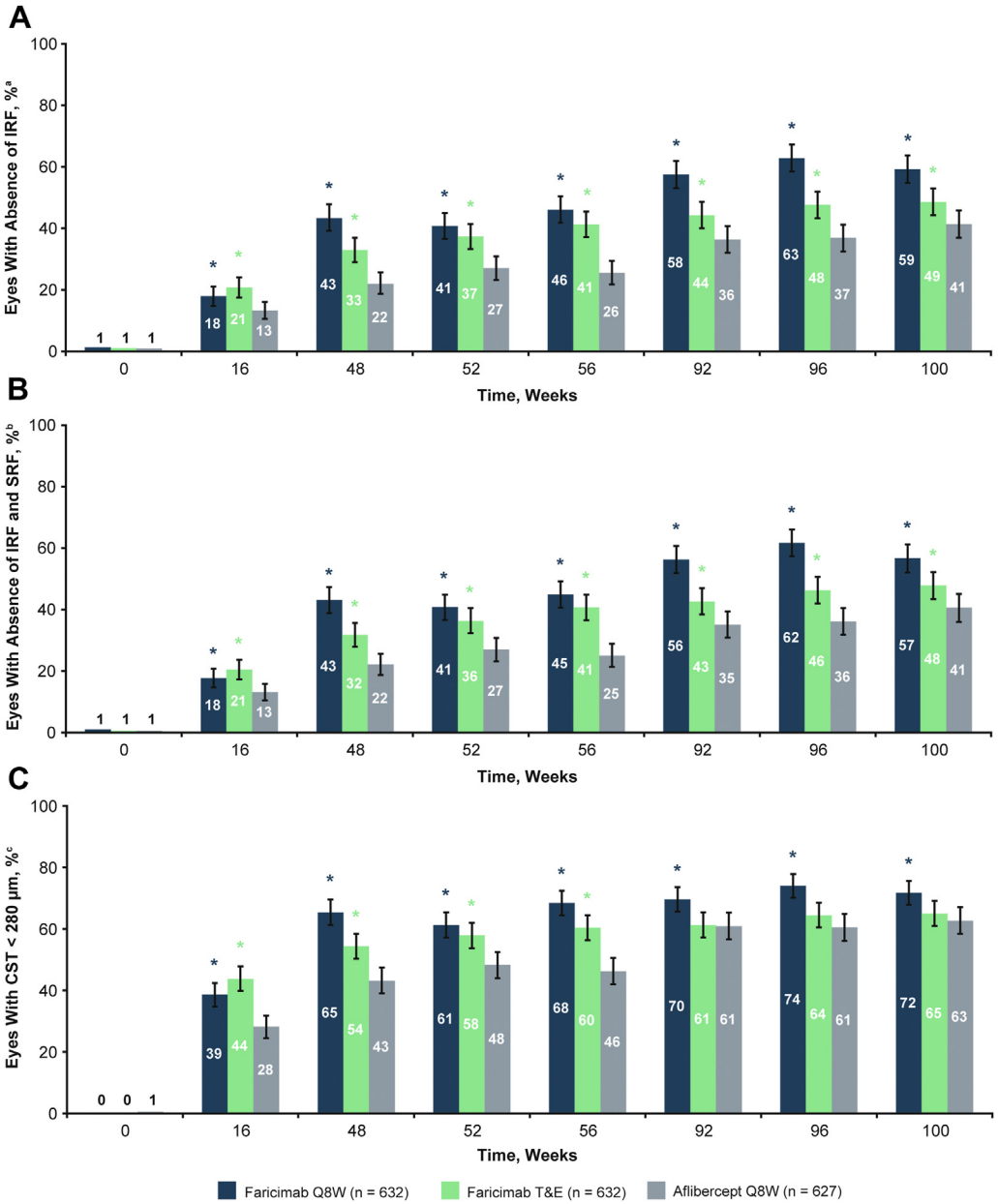


**Figure 1.** Eyes with (**A**) absence of IRF, (**B**) absence of IRF and SRF, and (**C**) presence of CST <280 μm at key timepoints during trial.. Cochran–Mantel–Haenszel test for superiority: * Nominal $P < 0.05$ versus aflibercept Q8W; nominal $P > 0.05$ where no asterisk is shown. *P* values are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. The 95% CI error bars are shown. [a]IRF and [b]SRF were measured in the central subfield (central 1-mm diameter of the ETDRS grid). [c]CST was measured as the distance between the internal limiting membrane and Bruch's membrane. CI = confidence interval; CST = central subfield thickness; IRF = intraretinal fluid; Q8W = every 8 weeks; SRF = subretinal fluid; T&E = treat-and-extend.

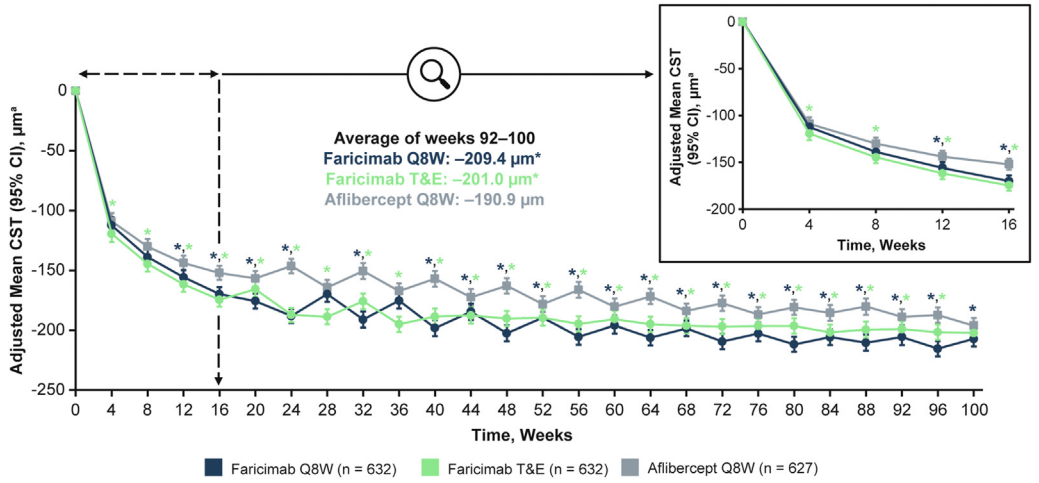


**Figure 3.** Adjusted mean change in CST over weeks 0 to 100. *Test for superiority: *Nominal $P < 0.05$ versus aflibercept Q8W. *P* values are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. The 95% CI error bars are shown. Adapted from Ophthalmology, 2023, S0161-6420(23)00933-8. Wong TY et al., Faricimab treat-and-extend for diabetic macular edema: 2-year results from the randomized phase III YOSEMITE and RHINE trials. Copyright 2023 Elsevier, with permission from Elsevier. [a]CST was measured as the distance between the internal limiting membrane and Bruch membrane. CI = confidence interval; CST = central subfield thickness; Q8W = every 8 weeks; T&E = treat-and-extend.

At 4 weeks after the end of the 12-week head-to-head dosing period (week 16), the CST reductions were greater for faricimab Q8W and T&E over aflibercept (−169.9 [95% CI, −175.7 to −164.0] and −174.5 [95% CI, −180.3 to −168.7] vs. −152.1 µm [95% CI, −158.0 to −146.2], respectively; nominal $P < 0.05$ for both) (Fig 3). The CST improvements observed with faricimab Q8W and T&E versus aflibercept were maintained over the course of the 100-week treatment period. At year 2 (averaged over weeks 92, 96, and 100), the CST reductions were greater with faricimab Q8W (−209.4 µm [95% CI, −215.2 to −203.6]) and T&E (−201.0 µm [95% CI, −206.7 to −195.3]) versus aflibercept Q8W (−190.9 µm [95% CI, −196.7 to −185.0]; nominal $P < 0.0001$ and $P < 0.05$, respectively). A comparative standardized AUC analysis of the CST over time data demonstrated that over 56 weeks of treatment, faricimab Q8W (18.7 µm; 95% CI, 11.5−25.8; nominal $P < 0.0001$) and T&E (20.4 µm; 95% CI, 13.3−27.6; nominal $P < 0.0001$) performed better than aflibercept. Over 100 weeks, these comparative standardized AUC differences were 21.1 µm (95% CI, 14.2−28.0; nominal $P < 0.0001$) and 19.4 µm (95% CI, 12.5−26.4; nominal $P < 0.0001$), respectively.

The CST benefits observed with faricimab Q8W and T&E over aflibercept were also observed in post hoc analyses of the proportion of eyes that achieved categorical CST and retinal fluid targets. A higher proportion of eyes achieved the absence of IRF for both faricimab arms compared with aflibercept (Fig 1A). This greater IRF resolution was observed as early as week 16 for faricimab Q8W and T&E (nominal $P < 0.05$ for both) and was still observed at the end points at weeks 56 and 100. At the 1-year (weeks 48−56) and 2-year timepoints (weeks 92−100), more eyes on faricimab Q8W (weighted proportions: 41%−46% and 58%−63%, respectively) and T&E (33%−41% and 44%−49%, respectively) achieved the absence of IRF than those in the aflibercept arm (22%−27% and 36%−41%, respectively; all nominal $P < 0.05$ for all in favor of faricimab).

Fewer eyes had SRF at baseline compared with IRF across all 3 treatment arms, and SRF resolved quickly after treatment with either faricimab or aflibercept and was maintained through 100 weeks (Fig S2A). Because almost all eyes (96%−97%) had achieved the absence of SRF by week 16, when evaluating the combination end point of absence of IRF and SRF, after 16 weeks, IRF was the only parameter left to resolve in the majority of eyes. Thus, similar to the effect seen for those achieving the absence of IRF, faricimab was associated with greater proportions of eyes achieving an absence of both IRF and SRF (Fig 1B).

Similar analyses of the proportion of eyes achieving a CST <280 µm for faricimab Q8W and T&E, and aflibercept, pooled from both trials, also showed more eyes achieved CST <280 µm on both faricimab dosing regimens when compared with aflibercept at weeks 16 and 56, and at week 100 for faricimab Q8W (Fig 1C). By 1 year (weeks 48−56), more eyes on faricimab Q8W (61%−68%) and T&E (54%−60%) achieved a CST <280 µm than those assigned to aflibercept treatment (43%−48%; all $P < 0.005$ for all in favor of faricimab). At the 2-year timepoint (weeks 92−100), numerically more eyes on faricimab Q8W had achieved this target (70%−74%) than eyes receiving faricimab T&E (61%−65%) or aflibercept (61%−63%; all $P < 0.05$ for all in favor of faricimab Q8W). A greater proportion of eyes from the faricimab arms was also able to achieve CST <325 µm criteria (Fig S2B).

## Time to Absence of Retinal Fluid

To assess the speed of the resolution of IRF with faricimab versus aflibercept, we performed a post hoc analysis of eyes with the presence of IRF at baseline. The median time to achieving the first absence of IRF occurred 40 weeks earlier with faricimab, for both Q8W and T&E arms than for aflibercept Q8W (48 vs. 88 weeks,

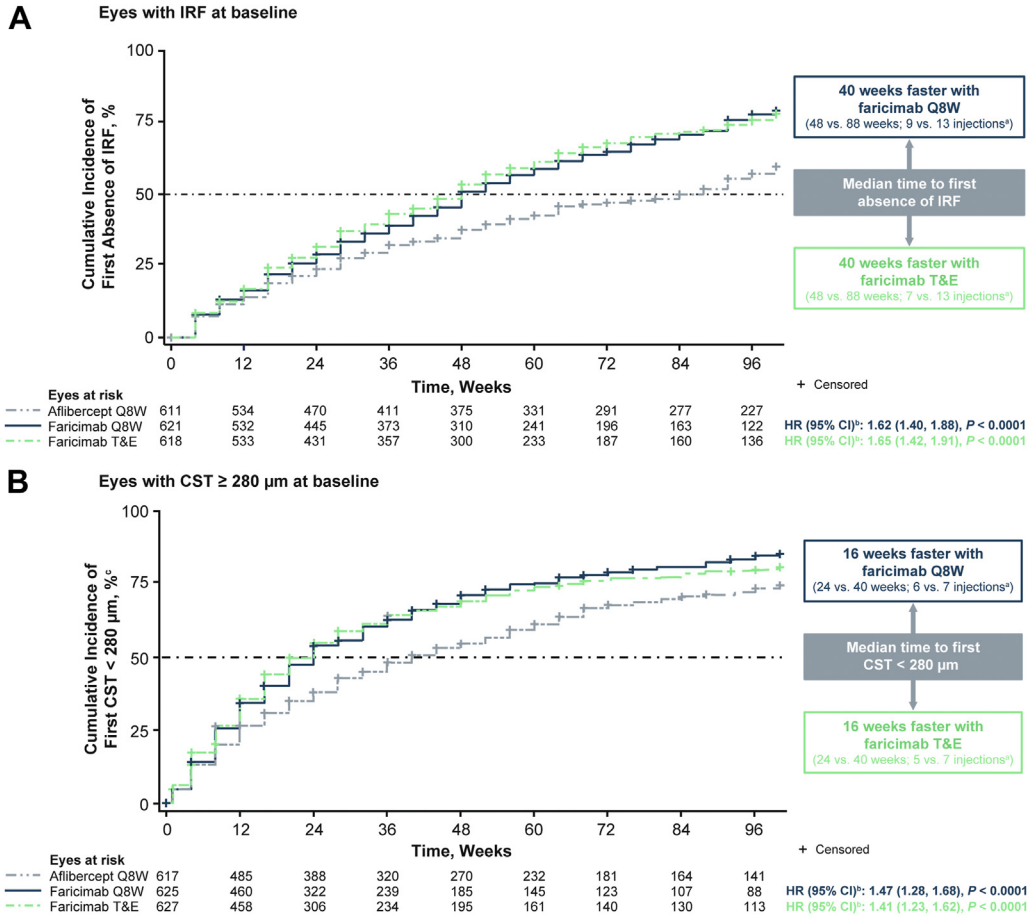


**Figure 4.** Cumulative incidence of (**A**) first absence of IRF and (**B**) first presence of CST <280 µm over 100 weeks. Summaries of time to first absence of diabetic macular edema are Kaplan–Meier estimates, with the time variable defined as the target visit week. *P* values are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. Statistics for pairwise comparisons were calculated using a separate model for each comparison. HRs were estimated by Cox regression. [a]The number of injections includes any active drug administered (faricimab or aflibercept), including medication errors. [b]Results from stratified analyses are presented for HR and log-rank test versus aflibercept. An HR >1 favors faricimab over aflibercept. [c]CST was measured as the distance between the internal limiting membrane and Bruch membrane. CI = confidence interval; CST = central subfield thickness; HR = hazard ratio; IRF = intraretinal fluid; Q8W = every 8 weeks; SRF = subretinal fluid; T&E = treat-and-extend.

for both; Fig 4A), and this was achieved with fewer faricimab injections than aflibercept (median: 9, 7, vs. 13, respectively). This corresponded to HRs for the first absence of IRF of 1.62 (95% CI, 1.40–1.88; nominal $P < 0.0001$) and 1.65 (95% CI, 1.42–1.91; nominal $P < 0.0001$) favoring faricimab Q8W and T&E over aflibercept. The 75th percentile of the time to first absence of IRF was achieved at weeks 92 and 96 for faricimab Q8W and T&E but was never reached for eyes randomized to aflibercept through 100 weeks.

A similar analysis showed that eyes randomized to faricimab achieved a median time to first absence of IRF and SRF 40 weeks earlier than eyes randomized to aflibercept, among those with either IRF, SRF, or both at baseline (48 vs. 88 weeks, for both; Fig S5A, available at www.ophthalmologyretina.org). Hazard ratios also confirmed an increased chance of the first absence of IRF and SRF compared with aflibercept over 100 weeks for both faricimab Q8W (HR, 1.67 [95% CI, 1.44–1.93]; nominal $P < 0.0001$) and faricimab T&E (HR, 1.69 [95% CI, 1.46–1.95]; nominal $P < 0.0001$). As almost all eyes (95.7%–97.1%) had achieved the absence of SRF by week 16, a time to first absence analysis of SRF was not performed.

A post hoc analysis of eyes that had CST ≥280 µm at baseline showed a 16-week faster median time to first instance of CST <280 µm with faricimab, for both Q8W and T&E, compared with aflibercept Q8W (24 vs. 40 weeks, for both) (Fig 4B), and this was achieved with fewer injections than aflibercept (median: 6, 5 vs. 7, respectively). This corresponded to HRs for the first instance of a CST <280 µm of 1.47 (95% CI, 1.28–1.68; nominal $P < 0.0001$) and 1.41 (95% CI, 1.23–1.62; nominal $P < 0.0001$) favoring faricimab Q8W and T&E over aflibercept. The 75th percentile of the time to first CST <280 µm was achieved at weeks 60 and 68 for faricimab Q8W and T&E but not achieved for aflibercept through 100 weeks. A similar analysis was conducted on time to first instance of CST <325 µm in eyes with CST ≥325 µm at baseline. Eyes in the faricimab T&E and Q8W arms reached the 75th percentile for time to first CST <325 µm 16 and 20 weeks faster, respectively, than eyes in the aflibercept arm (Fig S5B). Moreover, compared with faricimab

Q8W and T&E, this was achieved with a median of 1 or 3 fewer injections, respectively, than for eyes assigned to aflibercept.

### Anatomic Changes in Eyes Previously Treated with Anti-VEGF Therapy

In post hoc analyses of eyes that were previously treated with anti-VEGF therapy, anatomic benefits observed with faricimab Q8W and T&E versus aflibercept were similar to those in the overall YOSEMITE/RHINE population. At 4 weeks after the end of the 12-week head-to-head dosing period (week 16), the mean CST reductions from baseline were greater for faricimab Q8W and T&E compared with aflibercept in the previously anti-VEGF−treated eyes (−173.9 [95% CI, −188.5 to −159.4] and −172.6 [−187.5 to −157.7] vs. −137.6 μm [−152.4 to −122.7], respectively; nominal $P < 0.005$ for both; Fig S6, available at www.ophthalmologyretina.org). At year 2 (averaged over weeks 92, 96, and 100), the mean CST reductions were greater for faricimab Q8W (−214.0 μm [95% CI, −226.8 to −201.2]) than for aflibercept (−184.8 μm [95% CI, −198.0 to −171.5]; nominal $P < 0.01$). In the faricimab T&E arm, corresponding CST reductions were −201.4 μm (95% CI, −214.5 to −188.2) at year 2 (nominal $P > 0.05$ vs. aflibercept).

In addition, a numerically higher proportion of eyes achieved the absence of IRF with faricimab compared with aflibercept in the previously anti-VEGF−treated patients. At the 2-year timepoints (weeks 92−100), more eyes on faricimab Q8W (weighted proportions: 54%−62%) achieved the absence of IRF than those receiving aflibercept (27%−33%; nominal $P < 0.001$ at all 3 visits; Fig S7, available at www.ophthalmologyretina.org). Corresponding proportions for faricimab T&E were 32% to 45% (nominal $P < 0.05$ vs. aflibercept at week 96).

Furthermore, an analysis of the previously anti-VEGF−treated eyes with the presence of IRF at baseline showed that the median time to first absence of IRF was achieved 36 and 52 weeks earlier with faricimab Q8W and T&E compared with aflibercept (64 and 48 weeks vs. 100 weeks, respectively); this was achieved with fewer faricimab injections than aflibercept (median: 11, 8, vs. 15, respectively; Fig S8, available at www.ophthalmologyretina.org). Corresponding HRs for time to first absence of IRF were 1.88 (95% CI, 1.35−2.61; nominal $P = 0.0001$) and 1.94 (95% CI, 1.40−2.69; nominal $P < 0.0001$), favoring faricimab Q8W and T&E over aflibercept.

## Discussion

Faricimab Q8W and T&E resulted in a greater and a faster improvement in anatomic biomarkers than aflibercept Q8W in this post hoc analysis of pooled data from the phase III YOSEMITE and RHINE trials. The CST reductions observed with faricimab were rapidly achieved and stably maintained over the 100 weeks of treatment (Fig 3) demonstrating faricimab's early and sustained improvement on disease control. Similar anatomic results were observed with faricimab compared with aflibercept in patients who had previously received anti-VEGF therapy.

More eyes achieved an absence of IRF at weeks 16, 48 to 56, and 92 to 100 for both faricimab arms compared with aflibercept. Similar results were observed for proportions of eyes that achieved the absence of both IRF and SRF. In the present analysis, the median time to first absence of IRF was achieved 40 weeks earlier in eyes randomized to faricimab versus aflibercept. Among patients who had previously received anti-VEGF therapy, the median time to first absence of IRF was achieved 36 to 52 weeks earlier for eyes in the faricimab arms compared with the aflibercept arm. Similarly, 4 weeks after the end of the head-to-head dosing period (week 16), more eyes in the faricimab arms had achieved a CST <280 and <325 μm. This effect was maintained for both CST targets at weeks 48 to 56 for both faricimab dosing regimens and at weeks 92 to 100 for faricimab Q8W. The median time to achieve CST targets was 16 to 20 weeks earlier for eyes in the faricimab arm compared with the aflibercept arm. Crucially, the greater anatomic control with faricimab over aflibercept was observed regardless of whether patients received faricimab treatments Q8W or up to Q16W, suggesting that the benefits of faricimab over aflibercept are not dose-dependent.

Data from the phase III YOSEMITE and RHINE trials previously demonstrated that faricimab Q8W or T&E was associated with rapid improvements in anatomic control through year 1 and that these effects were maintained from year 1 to year 2.[21,22] The current analysis demonstrated that the median time for eyes randomized to faricimab to achieve the first absence of IRF was >9 months earlier than eyes randomized to aflibercept and that they achieved the first CST <280 μm 4 months earlier. This is important as IRF is a commonly used biomarker in clinical practice and a decision-making factor for treatment of pro re nata−treated patients and interval modification for T&E-treated patients. Moreover, the beneficial effects of faricimab on IRF are clinically notable because IRF is a key driver of DME pathogenesis and has been shown to be negatively associated with visual outcomes in DME.[36,37] Similarly, edema in the first year of treatment has also shown to be a negative prognostic factor for visual outcomes,[38] and chronic or persistent fluid in DME is associated with poor long-term outcomes.[39,40] Moreover, the anatomic benefits for faricimab Q8W or T&E versus aflibercept were observed with treatment up to Q16W.

Taken together, these data suggest that dual pathway inhibition of VEGF-A and Ang-2 with faricimab leads to greater disease control versus aflibercept while also reducing the treatment burden in a DME population that already carries significant medical burden because of comorbidities associated with systemic diabetes-related complications.[41,42] These benefits are likely driven by the addition of Ang-2 inhibition. Indeed, other studies in DME have shown that increasing the dose of anti-VEGF treatment fourfold, for instance with 2 mg ranibizumab versus 0.5 mg ranibizumab in the READ3 trial[43] or 8 mg aflibercept versus 2 mg aflibercept at 12 weeks (4 weeks after the head-to-head dosing period) in the PHOTON trial,[44] did not lead to further improvement in mean

retinal thickness. Conversely, combining an anti−Ang-2 agent with a VEGF inhibitor resulted in better disease control in DME in the phase II RUBY trial. In RUBY, targeting Ang-2 with a combination treatment of nesvacumab (antiAng-2 antibody) and aflibercept resulted in a greater reduction in the mean CST compared with aflibercept alone over the first 12 weeks of the study.[45] This finding is similar to those observed with dual Ang-2/VEGF-A inhibition with faricimab versus aflibercept in the current analysis and is further supported by preclinical data of the added beneficial effects of Ang-2 inhibition on vascular stability above and beyond that observed with VEGF inhibition alone.[20,46,47] Although caution should be applied when comparing across trials with different designs, interventions, patient populations, and methodologies, these data collectively suggest that the anatomic benefits of faricimab over aflibercept are likely because of its inhibition of Ang-2 and the synergistic effects of the dual Ang-2/VEGF-A inhibition promoting vascular stability.[6,48,49]

In the clinical setting, dosing decisions and treatment intervals are based on visual acuity and OCT anatomic biomarkers, as well as other indicators of disease activity. The current guidelines recommend that anatomic responses to treatment, including changes in IRF, SRF, and CST, are clinically useful biomarkers.[1,25,26,28−30] In particular, anatomic biomarkers are the key biomarkers of response to therapy[50] and drivers of retreatment decisions for T&E and pro re nata regimens, allowing clinicians to target durable disease control with the minimum number of injections. The rapid effects on CST and retinal fluid in the first 16 weeks of treatment of the current analysis suggest that faricimab had an early impact on DME disease activity. The sustained reductions in CST and IRF from baseline over a 56- and 100-week study period demonstrate that these greater anatomic benefits with faricimab versus aflibercept can be maintained over the long term.

Moreover, the rapid and sustained disease control seen with the T&E regimen provides a robust signal of faricimab's durability, with extended dosing intervals being achieved in the majority of eyes (>60% for Q16W dosing and approximately 80% for every 12 weeks dosing or more at week 96).[21] Notably, faricimab T&E and Q8W displayed similar anatomic benefits over aflibercept, despite the T&E regimen receiving a median of 4 to 5 fewer faricimab injections (YOSEMITE, 11; RHINE, 10) over 100 weeks than the faricimab Q8W arm (YOSEMITE/RHINE, 15).[21] The phase III RHONE-X extension study (NCT04432831) is ongoing and will provide 4-year data on the use of faricimab for the treatment of DME, furthering our understanding of the long-term effects of faricimab on disease control and treatment durability.

A limitation of this analysis is that because the analyses were not prespecified with multiplicity controls, and were therefore exploratory, the results should be interpreted with caution. A strength of the study is the robust nature of the image assessment, which was performed independently and in a prespecified manner by masked evaluators at reading centers; IRF volume quantification was not included in these assessments and may be explored in future analyses. The lack of long-term follow-up did not allow an assessment of the longitudinal effects of quicker time to fluid resolution on vision. Visual acuity gains were similar between faricimab and aflibercept through 2 years of the YOSEMITE/RHINE trials[21]; therefore, the full clinical implications of improved retinal drying with faricimab remain to be determined. The resolution of anatomy and fluid is a key therapeutic goal in DME. In addition, anatomic changes are an objective measure of treatment response and are important for evaluating and guiding treatment decisions in clinical practice. Nevertheless, the nature of the relationship between OCT markers of retinal fluid and vision outcomes in DME is still being explored[39]; future analyses will help to understand the relationship between anatomic outcomes with faricimab and vision.

In summary, faricimab demonstrated greater disease control through the improvement of key fluid biomarkers of DME activity compared with aflibercept. Central subfield thickness rapidly improved during the initial head-to-head dosing period and was maintained over the 100-week trial duration. Greater CST reductions with faricimab over aflibercept were observed as early as 8 weeks and were maintained over the length of the trial. The median time to first absence of IRF in eyes randomized to faricimab was achieved 40 weeks (or >9 months) earlier than in eyes randomized to aflibercept. Therefore, greater levels of disease control were reached with faricimab over aflibercept. This improved disease control was achieved earlier, was maintained over 100 weeks, and required fewer injections with faricimab T&E compared with aflibercept, suggestive of the therapeutic potential of combined Ang-2 and VEGF-A inhibition over anti-VEGF treatment alone.

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Availability of Data and Materials:

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 >1 data source external to Roche cannot, and should not, be linked due to a potential increase in the risk of patient reidentification. Requests for the data underlying this publication require a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and company subject matter experts. Direct such requests to Roche for consideration.

HUMAN SUBJECTS: Human subjects were included in this study. Both trials were conducted in accordance with the International Council for Harmonization E6 Guideline for Good Clinical Practice, tenets of the Declaration of Helsinki, United States Food and Drug Administration regulations, and the European Union Clinical Trials Directive (2001/20/EC) as appropriate, and all applicable local, state, and federal laws. Study protocols were approved by applicable institutional review boards and ethics committees before trial commencement. All patients provided written informed consent to participate.

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**Ang-2** = angiopoietin-2; **AUC** = area-under-the-curve; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **CST** = central subfield thickness; **DME** = diabetic macular edema; **HR** = hazard ratio; **IRF** = intraretinal fluid; **Q8W** = every 8 weeks; **Q4W** = every 4 weeks; **Q16W** = every 16 weeks; **SRF** = subretinal fluid; **T&E** = treat-and-extend.

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