**7/31/2023 12:00 am**

**Diabetic Retinopathy Symposium 3**

**Four-Year Visual Outcomes in the Protocol W Randomized Trial of Intravitreous Aflibercept for Prevention of Vision-Threatening Complications of Diabetic Retinopathy**


- Hani Salehi-Had, MD

**Objective:** To compare 4-year visual acuity and rates of vision-threatening complications of diabetes in eyes with moderate to severe non-proliferative diabetic retinopathy (NPDR) that were treated with intravitreal aflibercept versus sham injections.
**Purpose:** To determine if there are long-term anatomical and visual acuity benefits of early treatment with aflibercept in eyes with NPDR, good vision, and no center-involved diabetic macular edema (CI-DME) compared with treatment only if disease worsens.

**Methods:** Eyes with moderate to severe NPDR and no CI-DME were randomized to receive aflibercept (2.0-mg) or sham injections at baseline, 1, 2, and 4 months and every 4 months through 4 years, with injections in the second 2 years allowed to be deferred if the eye had no worse than mild NPDR on clinical exam. Both groups initiated an aflibercept treatment regimen if high-risk proliferative diabetic retinopathy (PDR) or CI-DME with vision loss developed. The primary outcomes were time to the development of PDR or CI-DME with vision loss (whichever came first) and visual acuity change from baseline to 4 years.

**Results:** There were 399 eyes from 328 participants (mean age 56 years; 42.4% female) across 64 sites in the US and Canada randomized to aflibercept (n = 200) or sham (n = 199). The 4-year cumulative probability of developing PDR or CI-DME with vision loss was 33.9% with aflibercept vs. 56.9% with sham [adjusted hazard ratio = 0.40 (97.5% CI: 0.28, 0.57; P<0.001)]. The mean (standard deviation) change in visual acuity from baseline to 4 years was -2.7 (6.5) letters with aflibercept and -2.4 (5.8) letters with sham [adjusted mean difference= -0.5 letters (97.5% CI: -2.3 to 1.3, P=0.52)].

**Conclusion:** Aflibercept treatment for NPDR, compared with aflibercept treatment only after disease worsened, resulted in statistically significant anatomic improvement but no improvement in visual acuity through at least 4 years. Early aflibercept treatment as a preventive strategy, as used in this trial, may not be generally warranted for patients with NPDR without CI-DME.

**IRB APPROVAL** Yes

**7/31/2023 12:00 am**

**Diabetic Retinopathy Symposium 3**

**Baseline Characteristics of Patients Who Did or Did Not Maintain 12-Week and 16-Week Aflibercept 8 mg Dosing Intervals in the Phase 2/3 PHOTON Trial**

Eric Schneider, MD

**Objective:** To evaluate baseline demographic and clinical characteristics of patients with diabetic macular edema (DME) who received intravitreal aflibercept 8 mg and maintained their randomized dosing intervals versus those whose intervals were shortened after meeting prespecified criteria through Week 48. **Purpose:** To identify any differences in baseline demographic or clinical characteristics between aflibercept 8 mg-treated patients who maintained their randomized dosing intervals and those whose dosing intervals were shortened in the PHOTON trial.
**Methods:** PHOTON is an ongoing, double-masked, 96-week, non-inferiority trial that randomized patients with DME to receive aflibercept 8 mg every 12 or 16 weeks after 3 monthly doses (8q12 [n=328] or 8q16 [n=163]) or aflibercept 2 mg every 8 weeks after 5 monthly doses (2q8 [n=167]). Beginning at Week 16, dosing intervals were shortened to a minimum of 8 weeks if aflibercept 8 mg-treated patients met prespecified dose regimen modification (DRM) criteria denoting disease activity.

**Results:** At baseline, best-corrected visual acuity (BCVA), central retinal thickness (CRT), and Diabetic Retinopathy Severity Scale (DRSS) scores were generally balanced across all 3 treatment groups. Of patients completing the Week 48 visit, 273/300 (91.0%) in the 8q12 group and 139/156 (89.1%) in the 8q16 group maintained their randomized dosing intervals. In the 8q12 and 8q16 groups, 27/300 (9.0%) and 17/156 (10.9%) patients, respectively, met DRM criteria and had their dosing intervals shortened. Mean (SD) baseline BCVA in eyes with maintained vs shortened dosing intervals was 63.9 (10.1) vs 59.4 (10.0) letters in the 8q12 group and 62.7 (11.2) vs 53.7 (12.8) letters in the 8q16 group. Mean (SD) central retinal thickness (CRT) at baseline (maintained vs shortened dosing intervals) was 444.9 (129.8) vs 511.4 (117.5) μm in the 8q12 group and 447.1 (112.5) vs 534.8 (134.3) μm in the 8q16 group. Baseline DRSS score (maintained vs shortened dosing intervals) was 47 or worse in 33.7% vs 40.7% of patients in the 8q12 group and 26.6% vs 41.2% of patients in the 8q16 group. No clinically meaningful differences were observed based on age, BMI, or HbA1c at baseline.

**Conclusion:** The vast majority of patients with DME who received aflibercept 8 mg maintained 12- or 16-week dosing. Patients who did not maintain their randomized dosing intervals appeared to have more severe disease at baseline than patients who maintained their randomized dosing intervals, and this trend was more pronounced in the 8q16 group.

**IRB APPROVAL** Yes

**7/31/2023 12:00 am**

**Diabetic Retinopathy Symposium 3**

**Six Monthly Intravitreal Aflibercept to Improve Macular Perfusion in Diabetic Retinopathy Without Macular Edema**


- Yoon Jeon Kim, MD
- Yu Jeong Park
- Young Hee Yoon, MD, PhD



**Objective:** Six monthly repeated aflibercept injections resulted in improvement of mean fractal dimension and vessel density in retinal deep capillary plexus (DCP) at 6 months, notably in a patient with advanced stage of diabetic retinopathy or lower vessel density at baseline.

**Purpose:** To evaluate the effect of monthly aflibercept injections on macular perfusion in eyes with diabetic retinopathy (DR), using optical coherence tomography angiography (OCTA).

**Methods:** Twenty-one eyes from 21 patients with DR without macular edema (ME) were treated with 6 monthly aflibercept. Untreated 23 eyes (age-sex matched control) were served as control. OCTA (AngioVue, 3x3mm) was acquired at baseline (BL), 6 and 12M. We measured fractal dimensions (FD) and vascular density (VD) from superficial and deep capillary plexus (SCP and DCP).

**Results:** When compared with baseline, VD and FD in DCP increased at 6M following six consecutive aflibercept treatments ($P$=0.039 and $P$=0.079, respectively), but the increase was not significant at 12M ($P$=0.187 and $P$=0.149, respectively). VD or FD in SCP did not improve. Control eyes showed no interval change in VD/FD. Eyes with more severe DR or lower DCP VD at BL showed prominent improvement in DCP VD at 6M.

**Conclusion:** When compared with baseline, VD and FD in DCP increased at 6M following six consecutive aflibercept treatments ($P$=0.039 and $P$=0.079, respectively), but the increase was not significant at 12M ($P$=0.187 and $P$=0.149, respectively). VD or FD in SCP did not improve. Control eyes showed no interval change in VD/FD. Eyes with more severe DR or lower DCP VD at BL showed prominent improvement in DCP VD at 6M.


**IRB APPROVAL** Yes

**7/31/2023 12:00 am**

**Diabetic Retinopathy Symposium 3**

**Comparison of Snellen Visual Acuity Measurements in Retinal Clinical Practice With Electronic ETDRS Protocol Visual Acuity Assessment**


- Carl Baker, MD, FASRS



**Objective:** What is the discrepancy between clinical trial VA measurements and routine clinical practice measurements.
**Purpose:** To better understand the differences between VA measurements in clinical trials that inform treatment recommendations and VA measurements routinely made in clinical practices.
**Methods:** A retrospective chart review compared baseline protocol eETRDS VA of study and fellow eyes of participants enrolled in DRCR Retina Network Protocols AC and AE (diabetic macular edema), and W (non-proliferative diabetic retinopathy) with clinical Snellen VA recorded within 3 months before the protocol visit. Linear mixed models analyzed the differences in letter scores (protocol eETRRS – clinical Snellen fraction converted to eETDRS) and their association with patient and ocular factors in univariable and multivariable models, with random effects for correlations within sites and participants. This study evaluated data from 1016 eyes (511 participants) across 74 sites.
**Results:** The mean visual acuity was 68.6 letters (Snellen equivalent 20/50) at the clinical visit and 76.3 letters (Snellen equivalent 20/32) at the protocol visit, and the mean (standard deviation, SD) time between visits was 26 (21) days. Protocol VA was better than clinical VA by a mean (SD) of 7.6 (9.6) letters overall, 10.7 (12.6) letters in eyes with clinical VA ≤20/50 (n = 376), and 5.8 (6.6) letters in eyes with clinical VA ≥20/40 (n = 640). On average, for every 1-line (5 letters) increase in clinical VA, the difference with protocol VA was 1.3 letters smaller ($p < 0.001$). Mean (SD) differences by clinical correction of refractive error were 3.9 (9.0) letters with refraction, 6.9 (9.2) letters with glasses/contact lenses, 7.9 (11.5) letters with pinhole, and 9.8 (9.3) letters without correction ($p=0.06$).
**Conclusion:** On average, clinical Snellen VA is likely 1-2 lines worse than eETDRS protocol refraction and VA testing, which may partly explain why results from clinical trials are not always replicated in clinical practice. The magnitude of the differences tended to be larger among eyes with lower clinical measurements and those tested without clinical refraction. Considering the potential discrepancies between clinical and protocol VA measurements, refracting eyes in the clinic may benefit patients when determining treatment plans and study referrals based on vision.


**IRB APPROVAL** Yes

**7/31/2023 12:00 am**

**Diabetic Retinopathy Symposium 3**

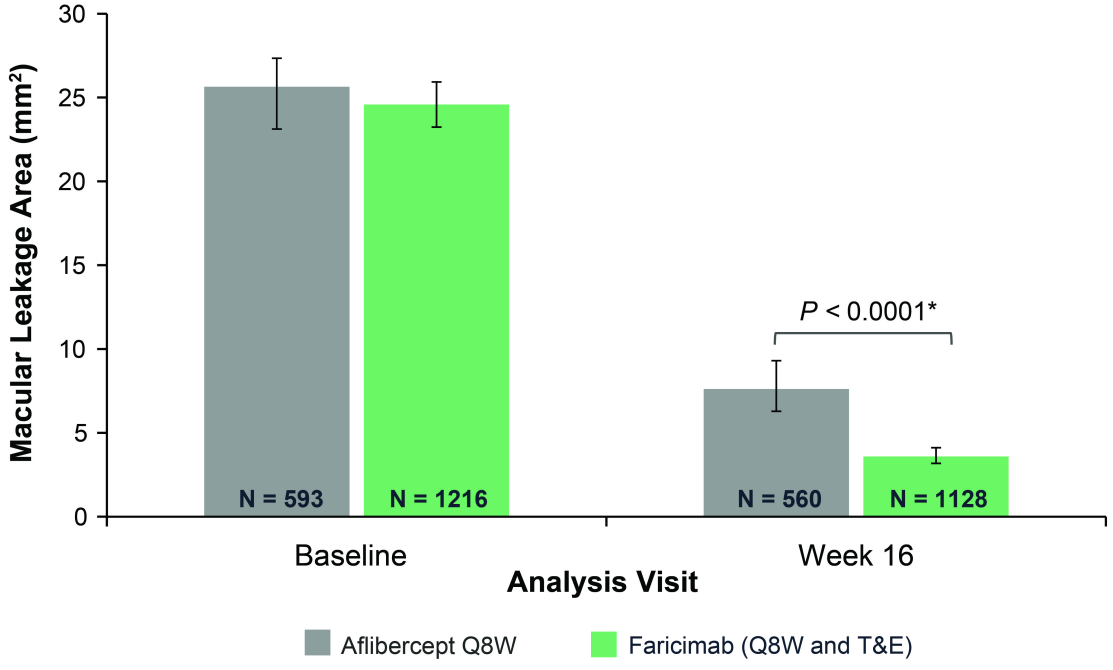
**Faricimab Reduces Macular Leakage vs Aflibercept in Patients With DME**


- Eric Nudleman, MD, PhD
- Roger Goldberg, MD, MBA
- Karl Csaky, MD, PhD
- Anton Kolomeyer, MD, PhD
- Kara Gibson, PhD
- Florie Mar, PhD
- Tracey Wang, MSc
- Jeffrey Willis, MD/PhD



**Objective:** To evaluate if dual angiopoietin-2/vascular endothelial growth factor A (VEGF-A) inhibition with faricimab improves macular leakage over VEGF-A inhibition alone with aflibercept in patients with diabetic macular edema from the phase 3 YOSEMITE/RHINE trials.
**Purpose:** Increased vascular permeability is a hallmark feature of diabetic macular edema (DME). In preclinical mouse models, dual angiopoietin-2 (Ang-2)/vascular endothelial growth factor A (VEGF-A) inhibition was associated with greater vascular leakage reductions versus Ang-2 or VEGF-A inhibition alone, suggesting synergistic actions of Ang-2 and VEGF-A. This analysis evaluated if dual Ang-2/VEGF-A inhibition with faricimab improves macular leakage over VEGF-A inhibition alone with aflibercept in patients with DME.
**Methods:** YOSEMITE (NCT03622580) and RHINE (NCT03622593) were identical trials evaluating the efficacy and safety of 6.0-mg faricimab versus 2.0-mg aflibercept in patients with center-involving DME. Patients were randomized 1:1:1 to faricimab every 8 weeks (Q8W), faricimab according to a personalized treat-and-extend–based regimen (T&E), or aflibercept Q8W. This analysis included data from the first 16 weeks of the trials (matched dosing phase) in which all patients received assigned study drug Q4W. The faricimab Q8W and T&E arms were pooled as they received the same dosing regimen during this period. Outcomes included macular leakage area and the proportion of patients with minimal to no macular leakage (0–1 $mm^2$).
**Results:** Data from the pooled YOSEMITE/RHINE trials included 1216 patients in the pooled faricimab arms and 593 patients in the aflibercept arms. Median baseline macular leakage area was similar in the faricimab (24.58 $mm^2$) and aflibercept arms (25.64 $mm^2$). At week 16, median macular leakage area was significantly lower in the faricimab versus aflibercept arm (3.59 vs 7.62 $mm^2$, respectively; $P < 0.0001$) (Fig 1). A significantly greater proportion of patients receiving faricimab (28.4%) demonstrated minimal to no leakage at week 16 compared with those receiving aflibercept (15.2%; $P < 0.0001$).
**Conclusion:** In patients with DME, dual Ang-2/VEGF-A inhibition with faricimab resulted in a greater reduction in macular leakage and a larger proportion of patients achieving minimal to no leakage versus aflibercept. These findings suggest that dual Ang-2/VEGF inhibition provides greater vascular stability, which may contribute to the faster fluid resolution and extended durability observed with faricimab versus aflibercept in YOSEMITE/RHINE.


**IRB APPROVAL** Yes




* Determined by Cochran-Mantel-Haenszel test; 95% CI error bars are shown.
Q8W, every 8 weeks; T&E, treat-and-extend.

Fig 1. Median macular leakage area at baseline and week 16

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**Diabetic Retinopathy Symposium 3**

**Faricimab Causes Rapid and Sustained Intraocular Suppression of Ang-2 and VEGF-A for Up to 16 Weeks in nAMD and DME**


- Rajeev Muni, MD, MSC, FRCS(C), FASRS
- Katrijn Bogman
- Ivaylo Stoilov, MD
- Cheikh Diack



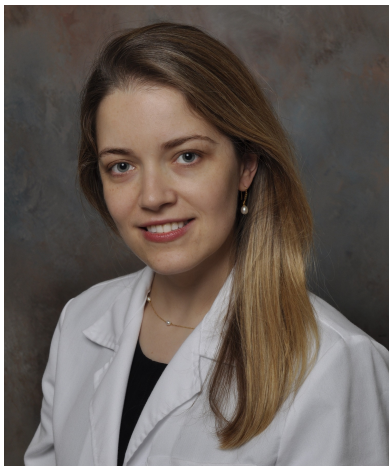
**Objective:** To characterize the extent and duration of suppression of angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A) in the aqueous humor of patients with neovascular age-related macular edema (nAMD) or diabetic macular edema (DME) treated with faricimab.
**Purpose:** Faricimab is a bispecific antibody designed to inhibit Ang-2 and VEGF-A, promote vascular stability, and improve outcomes in nAMD and DME. The purpose of this analysis was to evaluate the intraocular pharmacodynamics of faricimab.
**Methods:** Optional aqueous humor (AH) samples were collected from patients in randomized, double-masked, active comparator–controlled, phase 2/3 trials in nAMD (AVENUE [NCT02484690], STAIRWAY [NCT03038880], TENAYA [NCT03823287], LUCERNE [NCT03823300]) and DME (BOULEVARD [NCT02699450], YOSEMITE [NCT03622580], RHINE [NCT03622593]). Free Ang-2 and VEGF-A levels were measured using validated assays. A population pharmacokinetic/pharmacodynamic model (popPKPD) was developed using phase 2/3 pooled data, including AH data from ~300 patients, corresponding to 1025 free Ang-2 concentrations, 1345 free VEGF-A concentrations, and 1095 faricimab concentrations. Only patients with ³ 1 non–below the limit of quantification (BLQ) sample were included in the popPKPD analysis.
**Results:** Mean baseline VEGF-A levels were 135 and 58 pg/mL in patients with DME and nAMD, respectively. Mean baseline Ang-2 levels were 13.4 and 8.1 pg/mL in patients with DME and nAMD, respectively. Approximately 75% of post-dose Ang-2 observations were BLQ. The popPKPD model described the observed data well. The model derived Ang-2 and VEGF-A concentration-time profiles showed that following intravitreal injection of faricimab, AH concentrations of Ang-2 and VEGF-A were rapidly suppressed to nearly unquantifiable levels. At 8 weeks post dose, median Ang-2 concentrations remained suppressed by ~80%. At 16 weeks post dose, median VEGF-A concentrations returned to baseline, but median Ang-2 levels remained below baseline.
**Conclusion:** PopPKPD analyses showed that faricimab treatment leads to rapid and sustained suppression of AH Ang-2 and VEGF-A levels, with Ang-2 suppression through 16 weeks post dose, supporting the extended durability demonstrated in phase 3 trials.


**IRB APPROVAL** Yes

**7/31/2023 12:00 am**

**Diabetic Retinopathy Symposium 3**

# Time to Retinal Fluid Control With Faricimab vs Aflibercept in Patients With DME in the Phase 3 YOSEMITE/RHINE Trials




- Aleksandra Rachitskaya, MD, FASRS
- Kara Gibson, PhD
- Florie Mar, PhD
- Yannan Tang, PhD
- Jeffrey Willis, MD/PhD



**Objective:** To evaluate if angiopoietin-2/vascular endothelial growth factor A inhibition with faricimab is associated with faster time to retinal fluid control vs aflibercept in patients with DME from the phase 3 YOSEMITE/RHINE trials.

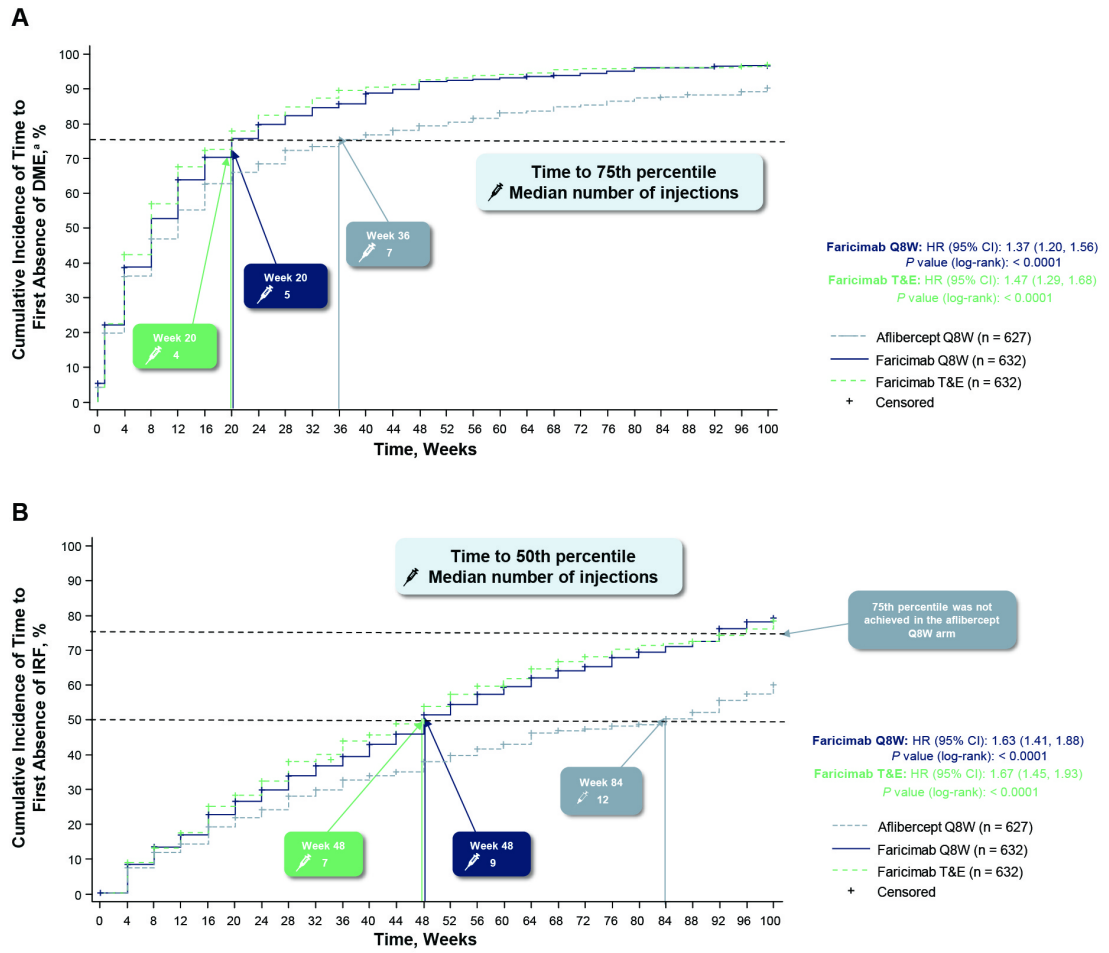
**Purpose:** Two-year data from YOSEMITE/RHINE (NCT03622580/NCT03622593) demonstrated that vision outcomes in diabetic macular edema (DME) with faricimab, a dual angiopoietin-2 (Ang-2)/vascular endothelial growth factor A (VEGF-A) inhibitor, were comparable to aflibercept and achieved with extended dosing, fewer injections, and anatomic benefits vs aflibercept. The purpose of the analysis was to assess the time to retinal fluid control in this population.

**Methods:** YOSEMITE/RHINE were double-masked, active comparator–controlled, phase 3 trials investigating the efficacy, safety, and durability of faricimab 6.0 mg vs aflibercept 2.0 mg in patients with DME. In total, 1891 patients were randomized 1:1:1 to faricimab every 8 weeks (FAR Q8W) after 6 initial Q4W doses, faricimab using a personalized treat-and-extend–based regimen (FAR T&E) after 4 initial Q4W doses, or aflibercept Q8W (AFL Q8W) after 5 initial Q4W doses through week 96. This post hoc analysis compared time to absence of DME (central subfield thickness on spectral-domain optical coherence tomography: < 325 µm [Heidelberg Spectralis] or < 315 µm [ZEISS Cirrus/Topcon]) and intraretinal fluid (IRF) between patients treated with faricimab and aflibercept.

**Results:** Noninferior vision gains achieved at 1 year were maintained through year 2 across treatment arms. Nearly 80% of FAR T&E patients who achieved Q16W dosing at week 52 remained on Q16W with no interval reduction through study end. At week 96, 62% of FAR T&E patients achieved Q16W dosing and 78% achieved ≥ Q12W dosing. Time to the 75th percentile for first absence of DME was 36 weeks for AFL Q8W after a median of 7 injections vs 20 weeks for the FAR Q8W (hazard ratio [HR] 1.37; 95% CI: 1.20, 1.56; $P < 0.0001$) and T&E (HR 1.47 [95% CI: 1.29, 1.68]; $P < 0.0001$) arms after a median of 5 and 4 injections, respectively (Fig 1A). Time to the 50th percentile for first absence of IRF was 84 weeks for AFL Q8W after a median of 12 injections vs 48 weeks for FAR Q8W (HR 1.63 [95% CI: 1.41, 1.88]; $P < 0.0001$) and T&E (HR 1.67 [95% CI: 1.45, 1.93]; $P < 0.0001$) arms after a median of 9 and 7 injections, respectively (Fig 1B).

**Conclusion:** These data demonstrate that dual Ang-2/VEGF-A inhibition with faricimab enables patients with DME to reach absence of DME/IRF faster and with fewer injections vs aflibercept.


**IRB APPROVAL** Yes




[a] CST on spectral-domain optical coherence tomography: < 325 µm for Heidelberg Spectralis or < 315 µm for ZEISS Cirrus or Topcon.
CST, central subfield thickness; DME, diabetic macular edema; HR, hazard ratio; IRF, intraretinal fluid; T&E, treat-and-extend; Q8W, every 8 weeks.

Fig 1. Time to first absence of DME (A) and IRF (B)

**7/31/2023 12:00 am**

**Diabetic Retinopathy Symposium 3**

**Early Treatment Patterns and Outcomes in Patients With Diabetic Macular Edema Treated With Faricimab: FARETINA-DME Study**


- Durga Borkar, MD
- David Tabano, PhD
- Vincent Garmo, MHS
- Theodore Leng, MD, MS, FASRS
- Jacqueline Shaia
- Blanche Kuo, BS
- Rachel Myers
- Andrew LaPrise
- Rishi Singh, MD



**Objective:** To describe real world treatment patterns and early clinical response of DME patients initiating faricimab.
**Purpose:** Anti-Vascular Endothelial Growth Factor (VEGF) intravitreal agents are the standard of care for diabetic macular edema (DME), and may require frequent injections. Faricimab (VABYSMO$^{TM}$) is the only bispecific antibody for intraocular use that independently binds and neutralizes both angiopoietin-2 and VEGF-A. While other multi-center studies are evaluating use of this new therapy, FARETINA-DME describes the largest real-world evaluation of injection frequency and clinical response of faricimab in patients with DME.
**Methods:** FARETINA-DME is a retrospective real world study using electronic health record (EHR) data from the IRIS Registry$^{TM}$. Data were analyzed February-September 2022 to identify faricimab starts among patients diagnosed with DME. Rules-based text search using regular expression keywords was used to identify faricimab use. Patients with ≥ 12 months of EHR data prior to initiation and known laterality were included. Patients with ≥6 months of EHR data following faricimab initiation (through December 2022) were included in injection intervals. Injection intervals were categorized as “extended” if any interval was >6 weeks apart.
**Results:** 3,229 eyes (2,543 patients) were treated with faricimab for DME, with a mean (SD) of 2.9 (1.7) faricimab injections over a mean (SD) of 123.9 (65.5) days of follow-up. 616 (19.1%) of eyes were anti-VEGF treatment naïve; 2,613 (80.9%) were previously treated. Most (64.3%) previously treated eyes received aflibercept. Nearly half of eyes (43.8% treatment naïve; 48.0% previously treated) had 20/40 or better BDVA at faricimab initiation.

128 (20.8%) treatment naïve and 605 (23.2%) previously treated eyes had ≥ 6 months follow-up. Mean (SD) faricimab injections were 4.2 (2.2) and 4.3 (2.2) for previously treated and treatment naïve eyes, respectively. 104 (81.3%) of treatment naïve and 503 (83.1%) of previously treated eyes “extended” after 1-3 injections; >50% “extended” after 1 injection across eyes with ≥ 6 months follow-up.
**Conclusion:** Over 2,300 eyes treated with faricimab for DME were identified the IRIS registry through August 2022. Among eyes with ≥ 6 months follow-up, a majority of eyes began extending treatment intervals in 1-3 initial doses. Early treatment extensions may indicate a positive anatomical response to faricimab in DME patients.


**IRB APPROVAL** Yes