Efficacy, Durability, and Safety of Faricimab in Diabetic Macular Edema: 2-Year Results From the Phase 3 YOSEMITE and RHINE Trials

David A. Eichenbaum, MD

John A. Wells, MD; Jennifer I. Lim, MD; Carl J. Danzig, MD; Kemal Asik, PhD; Zdenka Haskova, MD, PhD; Shaun Mohan, MD; David Silverman, MSc, MBChB, MRCOphth, FFPM; Yannan Tang, PhD; and Hugh Lin, MD, MBA

On behalf of the YOSEMITE and RHINE Investigators

1 Retina Vitreous Associates of Florida, St. Petersburg, FL, and Morsani College of Medicine, University of South Florida, Tampa, FL; 2 Palmetto Retina Center, Retina Consultants of America, Columbia, SC; 3 University of Illinois at Chicago, Chicago, IL; 4 Rand Eye Institute, Deerfield Beach, FL, and Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL; 5 Genentech, Inc., South San Francisco, CA; 6 Roche Products Ltd., Welwyn Garden City, UK

Presented at the American Society of Retina Specialists Annual Meeting | New York, NY | July 13–16, 2022
Disclosures

Financial Disclosures


- JAW: Consultant: Genentech, Inc.; Financial Support: Adverum, Alimera, Bayer, Clover Therapeutics, Genentech, Inc., Iveric Bio, Kodiak, Lowy Medical Research Institute, National Eye Institute, Neurotech, Opthea, Regeneron


- CJD: Consultant: Adverum, DORC, Genentech, Inc., Iveric Bio, Novartis, Regeneron; Financial Support: Adverum, Alexion, Bayer, Genentech, Inc., Gyroscope, Iveric Bio, Kodiak, Novartis, Regeneron, Roche; Nonremunerative: Novartis

- KA, ZH, SM, YT, HL: Employee: Genentech, Inc.

- DS: Employee: Roche Products Ltd.

Study and Product Disclosures

- As of July 2022, faricimab is approved for the treatment of neovascular age-related macular degeneration and diabetic macular edema in several countries in North America (including the United States), Europe, and Asia-Pacific, and is being studied for the treatment of macular edema due to retinal vein occlusion. Please note that faricimab is not currently approved for use outside these countries, or for use outside its approved indications

- This study includes research conducted on human subjects

- Institutional Review Board approval was obtained prior to study initiation

- Funding was provided by F. Hoffmann-La Roche Ltd. for the study and third-party writing assistance, which was provided by Nicole Tom, PhD, of Envision Pharma Group
Faricimab, the First Intraocular Bispecific Antibody: 1 Molecule With 2 Disease Pathway Targets for Durable Efficacy

Anti–Ang-2 Fab
Stabilizes vessels
Reduces vascular leakage
Reduces inflammation

Anti–VEGF-A Fab
Reduces vascular leakage
Inhibits neovascularization

Modified Fc
Reduces systemic exposure
Reduces inflammatory potential

Multifactorial retinal and choroidal vascular diseases may require neutralization of more than just the VEGF pathway

Dual inhibition of Ang-2 and VEGF-A with faricimab may result in stabilized vessels and reduced neovascularization, leading to durable efficacy when treating retinal diseases

CrossMAb molecule representative of faricimab.
Ang-2, angiopoietin-2; Fab, fragment antigen binding; Fc, fragment crystallizable; VEGF-A, vascular endothelial growth factor-A.
YOSEMITE and RHINE Investigated Faricimab Q8W or Treat-and-Extend–Based PTI Dosing With Up to Q16W Intervals

**YOSEMITE and RHINE**

Phase 3, randomized, double-masked, active comparator–controlled trials

Patients with center-involving DME (CST ≥ 325 µm)a

BCVA 25–73 ETDRS letters (Snellen BCVA ~20/320–20/40)b

---

**Personalized Treatment Interval (PTI)**

Treat-and-extend–based dosing regimen

Intervals adjusted (from Q4W up to Q16W) based on CST and BCVA change at active dosing visits

---

Anti-VEGF treatment-naïve or previously treated patients with DMEc

(1 eye per patient)

**YOSEMITE:** N = 940

**RHINE:** N = 951

---

Faricimab 6.0 mg Q8W

Faricimab 6.0 mg PTI

Aflibercept 2.0 mg Q8W

---

D1 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96 100

**Primary Endpointd**

Study End

---

Time, Weeks

Active treatment (faricimab 6.0 mg or aflibercept 2.0 mg)  
Sham  
PTI visit (sham or faricimab 6.0 mg)  
Final study visit

---

**YOSEMITE:** NCT03622580; **RHINE:** NCT03622593. a CST was measured as the distance from the internal limiting membrane to Bruch’s membrane. b BCVA was measured using the ETDRS visual acuity chart at a starting distance of 4 m. c Previously anti-VEGF–treated eyes (treated ≥ 3 months before day 1) were limited to 25% of the total enrollment. d Primary efficacy endpoint: adjusted mean BCVA change from baseline at 1 year, averaged over weeks 48, 52, and 56. BCVA, best-corrected visual acuity; CST, central subfield thickness; D, day; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; PTI, personalized treatment interval; Q4W, every 4 weeks; Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF, vascular endothelial growth factor.
Baseline Patient Characteristics Were Well Balanced Across Treatment Arms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>YOSEMITE</th>
<th>RHINE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Faricimab Q8W (n = 315)</td>
<td>Faricimab PTI (n = 313)</td>
</tr>
<tr>
<td>Age, years, mean (SD)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>61.6 (9.5)</td>
<td>62.8 (10.0)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>128 (40.6%)</td>
<td>116 (37.1%)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>241 (76.5%)</td>
<td>240 (76.7%)</td>
</tr>
<tr>
<td>BCVA, ETDRS letters, mean (SD)</td>
<td>62.0 (9.9)</td>
<td>61.9 (10.2)</td>
</tr>
<tr>
<td>CST, µm, mean (SD)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>492.3 (135.8)</td>
<td>485.8 (130.8)</td>
</tr>
<tr>
<td>Previously anti-VEGF treated, n (%)</td>
<td>77 (24.4%)</td>
<td>68 (21.7%)</td>
</tr>
<tr>
<td>Baseline DR severity status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DR questionable, mild to moderate NPDR (ETDRS-DRSS level 10/12, 14/20, 35, 43)</td>
<td>174 (55.2%)</td>
<td>187 (59.7%)</td>
</tr>
<tr>
<td>Moderately severe and severe NPDR (ETDRS-DRSS level 47, 53)</td>
<td>113 (35.9%)</td>
<td>99 (31.6%)</td>
</tr>
<tr>
<td>PDR (ETDRS-DRSS level 61, 65, 71/75)</td>
<td>22 (7.0%)</td>
<td>21 (6.7%)</td>
</tr>
<tr>
<td>Cannot grade (ETDRS-DRSS level 90)</td>
<td>4 (1.3%)</td>
<td>5 (1.6%)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (0.6%)</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>

Results are presented for the intent-to-treat population. <sup>a</sup> Age at randomization. <sup>b</sup> CST was measured as the distance from the internal limiting membrane to Bruch’s membrane. BCVA, best-corrected visual acuity; CST, central subfield thickness; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PTI, personalized treatment interval; Q8W, every 8 weeks; VEGF, vascular endothelial growth factor.
Vision Gains With Faricimab Q8W and PTI Up to Q16W Were Noninferior to Aflibercept Q8W at 1 Year

**YOSEMITE**

Average of weeks 48–56a
- Faricimab Q8W: +10.7 ETDRS letters
- Faricimab PTI: +11.6 ETDRS letters
- Aflibercept Q8W: +10.9 ETDRS letters

**RHINE**

Average of weeks 48–56a
- Faricimab Q8W: +11.8 ETDRS letters
- Faricimab PTI: +10.8 ETDRS letters
- Aflibercept Q8W: +10.3 ETDRS letters

Results are based on a mixed model for repeated measures analysis, adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (< 64 vs ≥ 64 ETDRS letters), prior intravitreal anti-VEGF therapy (yes vs no), and region (United States and Canada, Asia, and rest of the world). 95.04% CI error bars are shown.

a Primary efficacy endpoint: adjusted mean BCVA change from baseline at 1 year, averaged over weeks 48, 52, and 56.

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PTI, personalized treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF, vascular endothelial growth factor.
Vision Gains With Faricimab Q8W and PTI Up to Q16W Were Noninferior to Aflibercept Q8W at 1 Year and Maintained Through Year 2

Adjusted Mean BCVA Change From Baseline, ETDRS Letters

Time, Weeks

Average of weeks 92–100a
Faricimab Q8W: +10.7 ETDRS letters
Faricimab PTI: +10.7 ETDRS letters
Aflibercept Q8W: +11.4 ETDRS letters

Treatment difference versus aflibercept Q8W at 2 yearsa (ETDRS letters), mean (95.04% CI)
Faricimab Q8W: −0.7 (−2.6, +1.2)
Faricimab PTI: −0.7 (−2.5, +1.2)

Aflibercept Q8W (n = 312)  
Faricimab Q8W (n = 315)  
Faricimab PTI (n = 313)

Time, Weeks

Average of weeks 92–100a
Faricimab Q8W: +10.9 ETDRS letters
Faricimab PTI: +10.1 ETDRS letters
Aflibercept Q8W: +9.4 ETDRS letters

Treatment difference versus aflibercept Q8W at 2 yearsa (ETDRS letters), mean (95.04% CI)
Faricimab Q8W: +1.5 (−0.5, +3.6)
Faricimab PTI: +0.7 (−1.3, +2.7)

Aflibercept Q8W (n = 315)  
Faricimab Q8W (n = 317)  
Faricimab PTI (n = 319)

Results are based on a mixed model for repeated measures analysis, adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous), baseline BCVA (< 64 vs ≥ 64 ETDRS letters), prior intravitreal anti-VEGF therapy (yes vs no), and region (United States and Canada, Asia, and rest of the world). 95.04% CI error bars are shown.

a Adjusted mean BCVA change from baseline at 2 years, averaged over weeks 92, 96, and 100.

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PTI, personalized treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF, vascular endothelial growth factor.
Durable Vision Gains With Faricimab Were Achieved With Q16W Dosing in ≥ 60% of the PTI Arms at Week 96

YOSEMITE (n = 270)\(^a\)

- Q4W 7.0%
- Q8W 14.8%
- Q12W 18.1%
- Q16W 60.0%
- Q12W + Q16W 78.1%

RHINE (n = 287)\(^a\)

- Q4W 10.1%
- Q8W 11.8%
- Q12W 13.6%
- Q16W 64.5%
- Q12W + Q16W 78.1%\(^b\)

*Analyses included patients in the faricimab PTI arms who had not discontinued the study at the week 96 visit. Treatment interval at week 96 was defined as the treatment interval decision made at that visit. \(^a\) Sum of Q12W and Q16W percentages shown; calculated proportion of patients who achieved Q12W or Q16W dosing at week 96 is 78.049%. \(^b\) Results are presented for the pooled YOSEMITE/RHINE safety-evaluable population (faricimab Q8W, n = 630; faricimab PTI, n = 632; aflibercept Q8W, n = 625).

- Percentage is based on the pooled number of patients in the faricimab PTI arms who achieved Q12W or Q16W dosing at week 52 and had not discontinued the study at the week 96 visit (n = 406).

- Percentage is based on the pooled number of patients in the faricimab PTI arms who achieved Q16W dosing at week 52 and had not discontinued the study at the week 96 visit (n = 291).

- PTI, personalized treatment interval; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks.
Greater Reductions in CST With Faricimab Q8W and PTI Up to Q16W vs Aflibercept Q8W Through Year 2

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. Clinical significance has not been established and conclusions regarding treatment effect cannot be drawn. * In general, patients receiving faricimab achieved greater reductions in CST over time compared with aflibercept (not a statistically significant difference). b Adjusted mean CST change from baseline at 2 years, averaged over weeks 92, 96, and 100. Results are based on a mixed model for repeated measures analysis, adjusted for treatment group, visit, visit-by-treatment group interaction, baseline CST (continuous), baseline BCVA (< 64 vs ≥ 64 letters), prior intravitreal anti-VEGF therapy (yes vs no), and region (United States and Canada, Asia, and rest of the world). 95.04% CI error bars are shown.

BCVA, best-corrected visual acuity; CST, central subfield thickness; PTI, personalized treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF, vascular endothelial growth factor.
More Patients Achieved Absence of DME With Faricimab Q8W and PTI Up to Q16W vs Aflibercept Q8W Through Year 2

Aflibercept Q8W

Faricimab Q8W

Faricimab PTI

Patients With Absence of DME, %

Time, Weeks

Proportion at weeks 92–100
77.3–81.0%
86.5–91.8%
78.2–85.9%

Proportion at weeks 92–100
80.0–84.2%
88.4–92.7%
84.6–88.1%

CMH 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. Clinical significance has not been established and conclusions regarding treatment effect cannot be drawn. * In general, a numerically greater proportion of patients receiving faricimab achieved absence of DME over time compared with aflibercept. * Absence of DME was defined as CST < 325 μm, measured as the distance from the internal limiting membrane to Bruch’s membrane. Weighted proportions were estimated using the CMH method, stratified by baseline BCVA (< 64 vs ≥ 64 letters), prior intravitreal anti-VEGF therapy (yes vs no), and region (United States and Canada vs rest of the world). Baseline values are not weighted; 0% of patients had absence of DME at screening, which was up to 28 days ahead of baseline. Weighted proportions for the aflibercept Q8W arm presented for the faricimab Q8W versus aflibercept Q8W comparison. 95.04% CI error bars are shown.

BCVA, best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel; CST, central subfield thickness; DME, diabetic macular edema; PTI, personalized treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF, vascular endothelial growth factor.
Patients Treated With Faricimab Q8W and PTI Up to Q16W First Achieved Absence of DME Earlier Than Afiblercept Q8W (Post Hoc)

Summaries of time to first absence of DME are Kaplan-Meier estimates, with the time variable defined as the target visit week.

Absence of DME was defined as CST < 325 μm, measured as the distance from the internal limiting membrane to Bruch's membrane.

CST, central subfield thickness; DME, diabetic macular edema; PTI, personalized treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks.
More Patients Achieved Absence of IRF With Faricimab Q8W and PTI Up to Q16W vs Aflibercept Q8W Through Year 2a

CMH 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.

Clinical significance has not been established and conclusions regarding treatment effect cannot be drawn. * In general, a numerically greater proportion of patients receiving faricimab achieved absence of IRF over time compared with aflibercept.

Weighted proportions were estimated using the CMH method, stratified by baseline BCVA (< 64 vs ≥ 64 letters), prior intravitreal anti-VEGF therapy (yes vs no), and region (United States and Canada vs rest of the world); baseline values are not weighted.

Weighted proportion for the aflibercept Q8W arm presented for the faricimab Q8W versus aflibercept Q8W comparison. 95.04% CI error bars are shown.

BCVA, best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel; IRF, intraretinal fluid; PTI, personalized treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF, vascular endothelial growth factor.

Aflibercept Q8W
Faricimab Q8W
Faricimab PTI

Patients With Absence of IRF,%

Time, Weeks

Proportion at weeks 92–100
33.2–37.6%
58.5–63.1%
43.2–47.6%

Proportion at weeks 92–100
39.1–45.1%
56.0–62.3%
45.0–52.2%
Proportion of Patients With ≥ 2-Step DRSS Improvement Was Consistent Across Studies and Treatment Arms

Analyses included patients with evaluable color fundus photograph images at baseline and week 52 and/or week 96. Weighted proportions were estimated using the CMH method, stratified by baseline BCVA (< 64 vs ≥ 64 ETDRS letters), prior intravitreal anti-VEGF therapy (yes vs no), and region (United States and Canada vs rest of the world). Weighted proportions for the aflibercept Q8W arm presented for the faricimab Q8W versus aflibercept Q8W comparison. 97.52% CI error bars are shown at week 52; 95.04% CI error bars are shown at week 96. BCVA, best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; PTI, personalized treatment interval; Q8W, every 8 weeks; VEGF, vascular endothelial growth factor.
Faricimab Was Well Tolerated Through Study End

<table>
<thead>
<tr>
<th>AEs Through Study End, YOSEMITE/RHINE Pooled</th>
<th>Patients With ≥ 1 AE, n (%)a</th>
<th>Exposure-Adjusted Incidence Rate, Events Per 100 Patient-Years (95% CI)g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Faricimab Q8W n = 630</td>
<td>Faricimab PTI n = 632</td>
</tr>
<tr>
<td></td>
<td>Faricimab Q8W n = 630</td>
<td>Faricimab PTI n = 632</td>
</tr>
<tr>
<td>Total patient-years at riskb</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ocular AEsbc</td>
<td>313 (49.7%)</td>
<td>311 (49.2%)</td>
</tr>
<tr>
<td>Serious ocular AEsbc</td>
<td>26 (4.1%)</td>
<td>34 (5.4%)</td>
</tr>
<tr>
<td>Ocular AEs of special interestd</td>
<td>25 (4.0%)</td>
<td>33 (5.2%)</td>
</tr>
<tr>
<td>Intraocular inflammation eventsc</td>
<td>9 (1.4%)</td>
<td>11 (1.7%)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>3 (0.5%)</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>Iritis</td>
<td>1 (0.2%)</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>Iridocyclitis</td>
<td>2 (0.3%)</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>Vitritis</td>
<td>2 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Postprocedural inflammation</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Chorioretinitis</td>
<td>0</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Keratic precipitates</td>
<td>0</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Keratouveitis</td>
<td>0</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Endophthalmitis events</td>
<td>2 (0.3%)</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>Retinal vasculitis events</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Occlusive retinal vasculitis events</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Noninflammatory retinal occlusive events</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AE, adverse event; APTC, Anti-Platelet Trialists' Collaboration; BCVA, best-corrected visual acuity; PTI, personalized treatment interval; Q8W, every 8 weeks.
Over 2 Years, Faricimab Demonstrated Durable Efficacy Through Disease Control With Up to Q16W Dosing

Faricimab targets **2 distinct disease pathways** to promote **vascular stability**, which may lead to a **more durable therapy** while maintaining **long-term vision gains**.

**Durable vision gains**

**Comparable 1-year BCVA gains** with faricimab up to Q16W versus aflibercept Q8W were **maintained through year 2**.

**DME disease control**

**Improved anatomic outcomes** with faricimab up to Q16W versus aflibercept Q8W were **maintained over 2 years**:  
• **Change in CST** favored faricimab\(^a\)  
• More patients achieved **absence of DME**\(^{b,c}\)  
• More patients achieved **absence of IRF**\(^c\)

**Safety outcomes**

Faricimab was well tolerated through study end, and **no cases of retinal vasculitis or occlusive retinal vasculitis** were reported.

**Long-term outcomes**

The ongoing RHONE-X long-term extension study will generate 4-year data.

\(^a\) In general, patients receiving faricimab achieved greater reductions in CST over time compared with aflibercept (not a statistically significant difference).  
\(^b\) Absence of DME was defined as CST < 325 μm, measured as the distance from the internal limiting membrane to Bruch’s membrane.  
\(^c\) In general, a numerically greater proportion of patients receiving faricimab achieved absence of DME or absence of IRF over time compared with aflibercept.  
\(^d\) Proportion of patients in the pooled faricimab PTI arms who achieved ≥ Q12W or Q16W dosing at week 96, among those who had not discontinued the study at the week 96 visit (YOSEMITE, n = 270; RHINE, n = 287).

>70,000 vials of faricimab have been distributed in the US as of July 3, 2022.