Efficacy, Durability, and Safety of Faricimab in Diabetic Macular Edema (DME): 2-Year Results From YOSEMITE and RHINE

Caroline R. Baumal, MD1

John A. Wells, MD2; Carl J. Danzig, MD3; David A. Eichenbaum, MD4; Jennifer I. Lim, MD5; Patricio G. Schlottmann, MD6; Rishi P. Singh, MD, FASRS7; Hugh Lin, MD, MBA8; Shaun Mohan, MD8; David Silverman, MSc, MBChB, MRCOphth, FFPM8; Yannan Tang, PhD8; and Zdenka Haskova, MD, PhD8

On behalf of the YOSEMITE and RHINE Investigators

1 Tufts Medical Center, Boston, MA; 2 Palmetto Retina Center, Retina Consultants of America, Columbia, SC; 3 Rand Eye Institute, Deerfield Beach, FL, and Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL; 4 Retina Vitreous Associates of Florida, St Petersburg, FL and Morsani College of Medicine, University of South Florida, Tampa, FL; 5 University of Illinois at Chicago, Chicago, IL; 6 Organización Médica de Investigación, Buenos Aires, Argentina; 7 Center for Ophthalmic Bioinformatics, Cole Eye Institute, Cleveland Clinic, Stuart, FL; 8 Genentech, Inc., South San Francisco, CA; 9 Roche Products Ltd., Welwyn Garden City, UK.

Presented at the American Association of Ophthalmology Annual Meeting | Chicago, IL | Sept 30–Oct 03, 2022
Disclosures

Financial Disclosures
- CRB: Consultant: Genentech, Inc., Novartis, Ora, Regeneron, ZEISS
- JAW: Genentech, Inc.; Grant Support: Adverum, Alimera, Bayer, Clover, Genentech, Inc., Iveric Bio, Kodiak, Lowy Medical Research Institute, NIH National Eye Institute, Neurotech, Opthea, Regeneron
- CJD: Consultant: Adverum, DORC, Genentech, Inc., Iveric Bio, Novartis, Regeneron; Grant Support: Adverum, Alexion, Bayer, Genentech, Inc., Gyroscope, Iveric Bio, Kodiak, Novartis, Regeneron, REGENXBIO, Roche, UNITY; Speaker: Genentech, Inc., Novartis
- JIL: Consultant: Aura, Cognition, Eyenuk, Luxa, Opthea, Quark, Roche/Genentech, Inc., Santen, UNITY, Viridian; Grant Support: Aldeyra, Chengdu Kanghong, NGM, Regeneron, Roche/Genentech, Inc., Stealth; Recipient: Iveric Bio, Novartis
- PGS: Consultant: Roche
- RPS: Consultant: Alcon, AsclepiX, Bausch + Lomb, Genentech, Inc., Gyroscope, Novartis, Regeneron; Grant Support: NGM
- HL, SM, YT, ZH: Employee: Genentech, Inc.
- DS: Employee: Roche Products Ltd.

Study and Product Disclosures
- As of September 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 and Helen Simkins, PhD, of Envision Pharma Group
Faricimab, the First Intraocular Bispecific Antibody Inhibiting Ang-2 and VEGF-A: 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 Fc exposure
- Reduces inflammatory potential

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.

---


Ang-1, angiopoietin-1; Ang-2, angiopoietin-2; Fab, fragment antigen binding; Fc, fragment crystallizable; P, phosphorylation; Tie2, tyrosine kinase with immunoglobulin-like domains-2; VEGF-A, vascular endothelial growth factor-A; VEGFR2, vascular endothelial growth factor receptor-2.
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

Primary Endpointd
Study End

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

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

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>Faricimab Q8W n = 632</th>
<th>Faricimab PTI n = 632</th>
<th>Aflibercept Q8W n = 627</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>62.1 (9.8)</td>
<td>62.2 (10.1)</td>
<td>62.3 (9.8)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>251 (39.7%)</td>
<td>236 (37.3%)</td>
<td>263 (41.9%)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>491 (77.7%)</td>
<td>489 (77.4%)</td>
<td>506 (80.7%)</td>
</tr>
<tr>
<td>BCVA, ETDRS letters, mean (SD)</td>
<td>61.9 (10.0)</td>
<td>62.2 (9.8)</td>
<td>62.1 (9.5)</td>
</tr>
<tr>
<td>CST, µm, mean (SD)</td>
<td>479.2 (128.4)</td>
<td>478.5 (129.0)</td>
<td>480.9 (130.2)</td>
</tr>
<tr>
<td>Previously anti-VEGF treated, n (%)</td>
<td>140 (22.2%)</td>
<td>132 (20.9%)</td>
<td>137 (21.9%)</td>
</tr>
<tr>
<td>Baseline DR severity status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DR questionable, mild to moderate NPDR</td>
<td>357 (56.5%)</td>
<td>365 (57.8%)</td>
<td>362 (57.7%)</td>
</tr>
<tr>
<td>Moderately severe and severe NPDR</td>
<td>222 (35.1%)</td>
<td>198 (31.3%)</td>
<td>208 (33.2%)</td>
</tr>
<tr>
<td>PDR (ETDRS-DRSS level 61, 65, 71/75)</td>
<td>42 (6.6%)</td>
<td>58 (9.2%)</td>
<td>38 (6.1%)</td>
</tr>
<tr>
<td>Cannot grade (ETDRS-DRSS level 90)</td>
<td>6 (0.9%)</td>
<td>10 (1.6%)</td>
<td>12 (1.9%)</td>
</tr>
<tr>
<td>Missing</td>
<td>5 (0.8%)</td>
<td>1 (0.2%)</td>
<td>7 (1.1%)</td>
</tr>
</tbody>
</table>

Results are presented for the intent-to-treat population. * Age at randomisation. † 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, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PTI, personalised treatment interval; Q8W, every 8 weeks; VEGF, vascular endothelial growth factor.
Robust Vision Gains and CST Reductions With Faricimab Q8W and PTI Up to Q16W Were Maintained 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. a Adjusted mean 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 BCVA or CST (continuous) as applicable, baseline BCVA (< 64 vs ≥ 64 ETDRS letters), prior intravitreal anti-VEGF therapy (yes vs no), region (United States and Canada, Asia and rest of the world) and study (YOSEMITE vs RHINE). 95% CI error bars are shown.

BCVA, best-corrected visual acuity; CST, central subfield thickness; 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/RHINE Pooled (n = 557a)

- Q12W 15.8%
- Q16W 62.3%
- Q4W 8.6%
- Q8W 13.3%

79% of patients who achieved Q12W or Q16W dosing at week 52 maintained ≥ Q12W dosing without an interval reduction below Q12W through week 96c

76% of patients who achieved Q16W dosing at week 52 maintained Q16W dosing without an interval reduction through week 96d

Median number of injections in year 2 (weeks 60–96)b
- Faricimab PTI: 3 injections
- Faricimab Q8W: 5 injections
- Aflibercept Q8W: 5 injections

---

a Proportion of patients in the pooled faricimab PTI arms on Q4W, Q8W, Q12W, or Q16W dosing at week 96, among those who had not discontinued the study at the week 96 visit. b Results are presented for the pooled YOSEMITE/RHINE safety evaluable population (faricimab Q8W, n = 630; faricimab PTI, n = 632; aflibercept Q8W, n = 625). c 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). d 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.
Stable Q16W Durability With Faricimab Through 2 Years

Analyses included patients in the faricimab PTI arms who had not discontinued the study at the week 96 visit (YOSEMITE, n = 270; RHINE, n = 287).

Treatment interval at a given visit is shown as the interval at the start of the visit. The week 96 decision (recorded/calculated at week 96) is shown in the last column.

D, day; PTI, personalized treatment interval; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks.
More Patients Achieved Absence of DME and Absence of IRF With Faricimab Q8W and Up to Q16W vs Aflibercept Q8W Through Year 2

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 or absence of IRF over time compared with aflibercept. *Absence of DME was defined as CST $< 325 \mu m$, measured as the distance from the internal limiting membrane to Bruch’s membrane. *IRF was measured in the central 1-mm diameter of the ETDRS grid. 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), region (United States and Canada vs rest of the world) and study (YOSEMITE vs RHINE). 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% CI error bars are shown. BCVA, best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel; CST, central subfield thickness; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; IRF, intraretinal fluid; PTI, personalized treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF, vascular endothelial growth factor.
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 Treated With Faricimab Q8W and Up to Q16W Achieved Absence of DME Earlier and With Fewer Injections Than Aflibercept (Post Hoc)

YOSEMITE/RHINE Pooled

<table>
<thead>
<tr>
<th>Time to 75th percentile</th>
<th>Mean number of injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 20</td>
<td>4.2</td>
</tr>
<tr>
<td>Week 36</td>
<td>6.7</td>
</tr>
<tr>
<td>Week 42</td>
<td>8.2</td>
</tr>
</tbody>
</table>

Cumulative Incidence of Absence of DME, %

- Aflibercept Q8W (n = 627)
- Faricimab Q8W (n = 632)
- Faricimab PTI (n = 632)
- Censored

Time, Weeks

Cumulative Incidence of Absence of DME, %

- Aflibercept Q8W (n = 627)
- Faricimab Q8W (n = 632)
- Faricimab PTI (n = 632)
- Censored

0 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

Week 20 4.2
Week 36 6.7

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 Treated With Faricimab Q8W and Up to Q16W Achieved Absence of IRF Earlier and With Fewer Injections Than Aflibercept (Post Hoc)

Summaries of Time to first absence of intraretinal fluid are Kaplan-Meier estimates.

IRF, interetinal fluid; PTI, personalized treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks.
Faricimab Was Well Tolerated Through Study End

<table>
<thead>
<tr>
<th>AEs Through Study End, Patients With ≥ 1 AE, n (%)(^a)</th>
<th>YOSEMITE/RHINE Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Faricimab Q8W n = 630</td>
</tr>
<tr>
<td>Ocular AEs(^b)</td>
<td>313 (49.7%)</td>
</tr>
<tr>
<td>Serious ocular AEs(^b)</td>
<td>26 (4.1%)</td>
</tr>
<tr>
<td>Ocular AEs of special interest(^c)</td>
<td>25 (4.0%)</td>
</tr>
<tr>
<td>Intraocular inflammation events(^d)</td>
<td>9 (1.4%)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>Iritis</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Iridocyclitis</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Vitritis</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Postprocedural inflammation</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Chorioretinitis</td>
<td>0</td>
</tr>
<tr>
<td>Keratic precipitates</td>
<td>0</td>
</tr>
<tr>
<td>Keratouveitis</td>
<td>0</td>
</tr>
<tr>
<td>Endophthalmitis events</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Retinal vasculitis events</td>
<td>0</td>
</tr>
<tr>
<td>Retinal occlusive events</td>
<td></td>
</tr>
<tr>
<td>Retinal vein occlusion</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Retinal artery occlusion</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Retinal artery embolism</td>
<td>0</td>
</tr>
<tr>
<td>Serious nonocular AEs</td>
<td>175 (27.8%)</td>
</tr>
<tr>
<td>APTC events(^e)</td>
<td>34 (5.4%)</td>
</tr>
</tbody>
</table>

Results are presented for the pooled YOSEMITE/RHINE safety-evaluable population. \(^a\) Percentages are based on n values in the column headings; multiple occurrences of the same AE in an individual are counted only once. \(^b\) Ocular AEs in the study eye only are presented. \(^c\) Ocular AEs of special interest were defined as events associated with severe intraocular inflammation, events requiring surgical or medical intervention to prevent permanent loss of sight or events associated with BCVA loss of ≥ 30 letters for > 1 hour. \(^d\) Excluding endophthalmitis. \(^e\) APTC events were adjudicated by an external independent committee; all other events were investigator reported. Includes AEs with onset from the first dose of study drug through study end. AE, adverse event; APTC, Antiplatelet Trialists' Collaboration; BCVA, best-corrected visual acuity; PTI, personalized treatment interval; Q8W, every 8 weeks.
Over 2 Years, Faricimab Demonstrated Durable Efficacy Through Greater Disease Control With Up to Q16W Dosing

Safety outcomes

Faricimab was well tolerated. 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.

> 155,000 vials of faricimab have been distributed in the US as of September 25, 2022

* 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).

BCVA, best-corrected visual acuity; CST, central subfield thickness; PTI, personalized treatment interval; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks.