Faricimab in Diabetic Macular Edema: One-Year Results From the Phase 3 YOSEMITE and RHINE Trials

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On behalf of the YOSEMITE and RHINE Investigators

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Financial Disclosures

- XS: Consultant: Roche
- ZH: Employee: Genentech, Inc.
- DS, JI: Employee: Roche Products Ltd.
- KB: Employee: Roche Products (Ireland) Ltd.
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Study and Product Disclosures

- 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, provided by Karina D. Hamilton-Peel, PhD, CMPP, of Envision Pharma Group
- Faricimab is an investigational medicine that is being studied for the treatment of diabetic macular edema. Its efficacy and safety profile have not been established and it has not been approved by health authorities
Faricimab is the First Bispecific Antibody Designed for Intraocular Use: 1 Molecule, 2 Targets

**Anti–VEGF-A Fab**
- Reduces vascular leakage
- Inhibits neovascularization

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

**Modified Fc**
- Reduces systemic exposure
- Reduces inflammatory potential

Ang-2, angiopoietin-2; Fab, fragment antigen binding; Fc, fragment crystallizable; VEGF-A, vascular endothelial growth factor-A.
YOSEMITE and RHINE: 2 Randomized, Double-Masked, Active Comparator–Controlled, Phase 3 Trials of Faricimab in DME

Key Ocular Inclusion Criteria
Center-involving DME (CST ≥ 325 µm)\(^a\)
BCVA 25–73 ETDRS letters\(^b\)
(Snellen BCVA ~20/320–20/40)

- Anti-VEGF treatment-naïve or previously treated patients with DME\(^c\)
  (1 eye per patient)

YOSEMITE: N = 940
RHINE: N = 951

Primary Endpoint
Mean change in BCVA from baseline, averaged over weeks 48, 52, and 56

Final Visit

Time, Weeks

Faricimab 6.0 mg Q8W
Faricimab 6.0 mg PTI
Aflibercept 2.0 mg Q8W

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

\(^a\) 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 enrolment. BCVA, best-corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; PTI, personalized treatment interval; Q8W, every 8 weeks; VEGF, vascular endothelial growth factor.
PTI Algorithm: Automated, Standardized, and Objective Regimen Based on Treat-and-Extend

Initiation Phase:
- 4 initial Q4W doses through week 12
- Q4W dosing maintained until the first achievement of CST < 325 µma

Anti-VEGF treatment-naive or previously treated patients with DME (1 eye per patient)

YOSEMITE: N = 940
RHINE: N = 951

Faricimab 6.0 mg PTI

Faricimab 6.0 mg Q8W

Aflibercept 2.0 mg Q8W

**PTI Algorithm: Automated, Standardized, and Objective Regimen Based on Treat-and-Extend**

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YOSEMITE: N = 940
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Faricimab 6.0 mg PTI

Faricimab 6.0 mg Q8W

Aflibercept 2.0 mg Q8W

*CST was measured as the distance from the internal limiting membrane to Bruch's membrane. Reference BCVA was defined as the mean of the 3 best BCVA values achieved at any prior active dosing visit. Reference CST was defined as the CST value when the original reference value (CST < 325 µm) was achieved. Reference CST was adjusted if CST decreased by >10% from the previous reference CST for 2 consecutive active dosing visits and the values obtained were within 30 µm. The CST value obtained at the latter visit served as the new reference CST.
## Baseline Patient Characteristics Were Well Balanced Across Treatment Arms

<table>
<thead>
<tr>
<th></th>
<th>YOSEMITE</th>
<th>RHINE</th>
<th>RHINE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Faricimab Q8W (n = 315)</td>
<td>Faricimab PTI (n = 313)</td>
<td>Aflibercept Q8W (n = 312)</td>
</tr>
<tr>
<td>Age, years, mean (SD)a</td>
<td>61.6 (9.5)</td>
<td>62.8 (10.0)</td>
<td>62.2 (9.6)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>128 (40.6%)</td>
<td>116 (37.1%)</td>
<td>134 (42.9%)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>241 (76.5%)</td>
<td>240 (76.7%)</td>
<td>253 (81.1%)</td>
</tr>
<tr>
<td>BCVA, ETDRS letters, mean (SD)</td>
<td>62.0 (9.9)</td>
<td>61.9 (10.2)</td>
<td>62.2 (9.5)</td>
</tr>
<tr>
<td>CST, µm, mean (SD)b</td>
<td>492.3 (135.8)</td>
<td>485.8 (130.8)</td>
<td>484.5 (131.1)</td>
</tr>
<tr>
<td>Previously anti-VEGF treated, n (%)</td>
<td>77 (24.4%)</td>
<td>68 (21.7%)</td>
<td>70 (22.4%)</td>
</tr>
<tr>
<td>Baseline DR severity status, n (%):</td>
<td></td>
<td></td>
<td></td>
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<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>
<td>182 (58.3%)</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>
<td>103 (33.0%)</td>
</tr>
<tr>
<td>PDR (ETDRS-DRSS level 61, 65, 71/75)</td>
<td>22 (7.0%)</td>
<td>21 (6.7%)</td>
<td>18 (5.8%)</td>
</tr>
<tr>
<td>Cannot grade (ETDRS-DRSS level 90)</td>
<td>4 (1.3%)</td>
<td>5 (1.6%)</td>
<td>7 (2.2%)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (0.6%)</td>
<td>1 (0.3%)</td>
<td>2 (0.6%)</td>
</tr>
</tbody>
</table>

### Notes
- Results are presented for the intent-to-treat population. *Age at randomization. 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.
YOSEMITE and RHINE Met Their Primary Endpoint: 1-Year BCVA Gains With Faricimab Were Noninferior to Aflibercept

**YOSEMITE**

- **Adjusted Mean BCVA Change From Baseline, ETDRS Letters**
- **Time, Weeks**
- **Average of weeks 48–56**
  - Aflibercept Q8W (n = 312)
  - Faricimab Q8W (n = 315)
  - Faricimab PTI (n = 313)

**Treatment difference versus aflibercept Q8W at 1 year (ETDRS letters), mean (97.5% CI)**

- Faricimab Q8W: +11.6 letters
- Faricimab PTI: +10.7 letters

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**RHINE**

- **Adjusted Mean BCVA Change From Baseline, ETDRS Letters**
- **Time, Weeks**
- **Average of weeks 48–56**
  - Aflibercept Q8W (n = 315)
  - Faricimab Q8W (n = 317)
  - Faricimab PTI (n = 319)

**Treatment difference versus aflibercept Q8W at 1 year (ETDRS letters), mean (97.5% CI)**

- Faricimab Q8W: +11.8 letters
- Faricimab PTI: +10.8 letters

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**Results**

- Results are based on a mixed model for repeated measures analysis; 95.04% CI error bars are shown.
- **Primary efficacy endpoint:** BCVA change from baseline at 1 year, averaged over weeks 48, 52, and 56. **97.5% CI is a rounding of 97.52% (used to adjust for interim safety assessments conducted).**
- BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PTI, personalized treatment interval; Q8W, every 8 weeks.
Strong Durability With Faricimab: > 70% of Patients Achieved ≥ Q12W PTI Dosing at Week 52

YOSEMITE (n = 286)a

- Q4W: 10.8%
- Q8W: 15.4%
- Q12W: 21.0%
- Q16W: 52.8%
- Q12W + Q16W: 73.8%

RHINE (n = 308)a

- Q4W: 13.3%
- Q8W: 15.6%
- Q12W: 20.1%
- Q16W: 51.0%
- Q12W + Q16W: 71.1%

YOSEMITE 67.8%

RHINE 64.3%

Achieved and maintained Q12W or Q16W dosing without an interval reduction below Q12W through week 52
Greater Reductions in CST and More Patients Achieved Absence of IRF With Faricimab Versus Aflibercept Through Week 56

Test for superiority: * nominal $P < 0.05$ versus aflibercept Q8W; nominal $P > 0.05$ where no star is shown. $^a$Adjusted mean CST change from baseline at 1 year, averaged over weeks 48, 52, and 56. Adjusted mean CST change from baseline was estimated using a mixed model for repeated measures analysis. Proportion of patients with absence of IRF from week 4 onwards was estimated using the CMH method, stratified by baseline BCVA (< 64 letters 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; CST, central subfield thickness; IRF, intraretinal fluid; PTI, personalised treatment interval; Q8W, every 8 weeks; VEGF, vascular endothelial growth factor.
More Patients Treated With Faricimab Achieved Absence of DME Compared With Aflibercept Through Week 56

- **YOSEMITE**
  - Proportion at weeks 48–56
    - Aflibercept Q8W: 64.1–70.8%
    - Faricimab Q8W: 77.3–87.3%
    - Faricimab PTI: 79.8–82.3%

- **RHINE**
  - Proportion at weeks 48–56
    - Aflibercept Q8W: 71.4–77.2%
    - Faricimab Q8W: 84.5–90.2%
    - Faricimab PTI: 82.8–86.6%

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CMH test for superiority: * nominal P < 0.05 versus aflibercept Q8W; nominal P > 0.05 where no star is shown. Absence of DME was defined as CST < 325 μm, measured as the distance from the internal limiting membrane to Bruch's membrane. Proportion of patients with absence of DME from week 4 onwards was estimated using the CMH method, stratified by baseline BCVA (< 64 letters vs ≥ 64 letters), prior intravitreal anti-VEGF therapy (yes vs no), and region (United States and Canada vs the 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 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; CST, central subfield thickness; DME, diabetic macular edema; PTI, personalized treatment interval; Q8W, every 8 weeks; SD-OCT, spectral-domain optical coherence tomography; VEGF, vascular endothelial growth factor.
Faricimab Was Well Tolerated: Rates of Ocular and Nonocular AEs Through Week 56 Were Low

<table>
<thead>
<tr>
<th>Selected AEs Through Week 56</th>
<th>YOSEMITE</th>
<th>RHINE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Faricimab Q8W (n = 313)</td>
<td>Faricimab PTI (n = 313)</td>
</tr>
<tr>
<td>Total number of AEs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1062</td>
<td>1016</td>
</tr>
<tr>
<td>Total number of serious AEs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>171</td>
<td>114</td>
</tr>
<tr>
<td>Patients with any ocular AE, n (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>98 (31.3%)</td>
<td>106 (33.9%)</td>
</tr>
<tr>
<td>Patients with any ocular serious AE, n (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 (1.9%)</td>
<td>9 (2.9%)</td>
</tr>
<tr>
<td>Patients with any ocular AE of special interest, n (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6 (1.9%)</td>
<td>8 (2.6%)</td>
</tr>
<tr>
<td>Patients with any IOI event, n (%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>5 (1.6%)</td>
<td>7 (2.2%)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>2 (0.6%)</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Vitritis</td>
<td>2 (0.6%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Iritis</td>
<td>0</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Iridocyclitis</td>
<td>2 (0.6%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Anterior chamber inflammation</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Chorioretinitis</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Keratic precipitates</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Keratouveitis</td>
<td>0</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Patients with any endophthalmitis event, n (%)</td>
<td>0</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>Patients with any retinal vasculitis event, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients with any retinal occlusive event, n (%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Patients with any APTC event, n (%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>9 (2.9%)</td>
<td>10 (3.2%)</td>
</tr>
</tbody>
</table>

Results are presented for the safety-evaluable population. <sup>a</sup>Total number of AEs and SAEs includes nonocular events and ocular events in the study or fellow eye. <sup>b</sup>Ocular AEs and SAEs in the study eye only are presented in all safety outputs. <sup>c</sup>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 that cause a visual acuity loss of ≥ 30 letters for > 1 hour. <sup>d</sup>Excluding endophthalmitis. <sup>e</sup>APTC events were adjudicated by an external independent committee; all other events were investigator reported. Percentages are based on n values in the column headings. Multiple occurrences of the same AE in an individual are counted only once, except for the "Total number of AEs" and "Total number of SAEs" rows, in which multiple occurrences of the same AE are counted separately. Includes AEs with onset up to day 405 (last day of week 56 analysis visit window). AE, adverse event; APTC, Anti-Platelet Trialists' Collaboration; IOI, intraocular inflammation; PTI, personalised treatment interval; Q8W, every 8 weeks; SAE, serious adverse event.
At 1 Year, Faricimab Demonstrated Noninferior Vision Gains, Improved Anatomic Outcomes, and Potential for Extended Dosing

**YOSEMITE and RHINE** met primary endpoint

- **BCVA gains at 1 year** with faricimab Q8W or PTI up to Q16W were **noninferior to aflibercept Q8W** in patients with DME

**DME disease control with faricimab**

- **Improved anatomic outcomes** with faricimab versus aflibercept:
  - Change in CST favored faricimab
  - More patients achieved **absence of DME**
  - More patients achieved **absence of IRF**

- **Durability with up to Q16W dosing** in the faricimab PTI arm

**Safety outcomes**

- Faricimab was well tolerated. **No cases of vasculitis or occlusive retinitis** were reported

**Long-term outcomes**

- YOSEMITE and RHINE are 2-year studies. The RHONE-X long-term extension study will generate 4-year data

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

BCVA, best-corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; IRF, intraretinal fluid; PTI, personalized treatment interval; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks.