Faricimab Reduces Macular Leakage vs Aflibercept in Patients With DMO

Ben Burton, MBBS, MRCP, FRCOphth[1]; Kara Gibson, PhD[2]; Florie Mar, PhD[3]; Tracey Wang, MSc[4]; and Jeffrey Willis, MD, PhD[3]

On behalf of the YOSEMITE and RHINE Investigators

[1] James Paget University Hospitals NHS Foundation Trust; [2] Roche Products Ltd., Welwyn Garden City, UK; [3] Genentech, Inc., South San Francisco, CA, USA; [4] F. Hoffmann-La Roche Ltd., Mississauga, ON, Canada

Purpose

To determine if dual angiopoietin-2 (Ang-2)/vascular endothelial growth factor-A (VEGF-A) inhibition with faricimab improves macular leakage, a biomarker of vascular stability, vs VEGF inhibition with aflibercept in patients with diabetic macular oedema (DMO)

Conclusions

In patients with DMO, dual inhibition of Ang-2 and VEGF-A with faricimab in the head-to-head dosing phase of YOSEMITE/RHINE resulted in:

- Larger reduction in macular leakage area vs aflibercept
- Resolution of macular leakage in more patients than with aflibercept

Faricimab as a first-line treatment to stabilise vessels may improve outcomes beyond anti-VEGF treatment alone

References

1. Sarici K et al. *Ophthalmol Retina*. 2023;7(6):543-552.
2. Goldberg RA et al. Presented at: Retina Society Annual Meeting; September 29-October 2, 2021; Chicago, IL.
3. Brown DM et al. Presented at: Retina Society Annual Meeting; November 2-5, 2022; Pasadena, CA.
4. Benest AV et al. *PLoS One*. 2013;8(8):e70459.

Financial Disclosures

- BB: Advisor: Bayer, Roche; Research: Bayer, Roche
- KG: Employee: Roche
- FM, JW: Employee: Genentech, Inc.
- TW: F. Hoffmann-La Roche Ltd., Mississauga, ON, Canada

Study and Product Disclosures

- In the UK, Faricimab is approved for the treatment of neovascular age-related macular degeneration and diabetic macular oedema. Faricimab is not currently approved for use outside these indications in the UK. 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 Gary Vang, PharmD of Envision Pharma Group
- Roche conducted a factual accuracy check on the final article but any decision to incorporate comments was made solely at the discretion of the authors

Presented at the Royal College of Ophthalmologists Annual Congress Belfast, UK | 20–23 May 2024

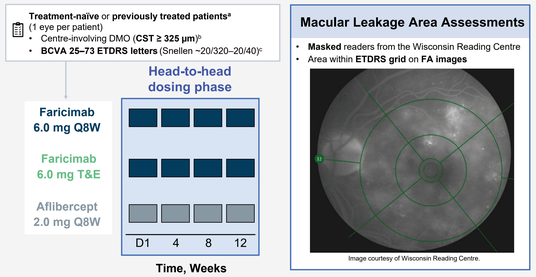
Background

- Increased vascular permeability is a hallmark feature of DMO, and change in macular leakage area correlates with functional and vision outcomes[1,2]
  - In the RUBY study[1]:
    - Reduction in macular leakage correlated with improved anatomical outcomes
    - Reduction in macular leakage area correlated with vision improvements (0.7-letter increase for every 1 mm^2 decrease in macular leakage area)
  - In the PANORAMA study, increased macular leakage area was associated with increased risk of developing centre-involving DMO[2]
- Increasing the dosage of anti-VEGF (aflibercept) up to 4 × in the PHOTON study did not further decrease macular leakage area[3]
- However, dual Ang-2/VEGF-A inhibition in mouse models was associated with larger vascular leakage reductions vs Ang-2 or VEGF-A inhibition alone, suggesting Ang-2/VEGF-A synergism on vascular instability[4]

Methods

- In this post hoc analysis of the identical phase 3 YOSEMITE/RHINE trials of faricimab, macular leakage data were collected from the head-to-head dosing phase, when all patients received the assigned study drug every 4 weeks
- As all faricimab-treated patients received the same dosing regimen during this period, data from the faricimab every 8 weeks and treat-and-extend arms were pooled
- Macular leakage area within the Early Treatment Diabetic Retinopathy Study grid was assessed in a masked manner based on fluorescein angiography images obtained at baseline and during follow-up by the Wisconsin Reading Centre

Macular Leakage Was Evaluated During the Matched Head-to-Head Dosing Phase of YOSEMITE/RHINE

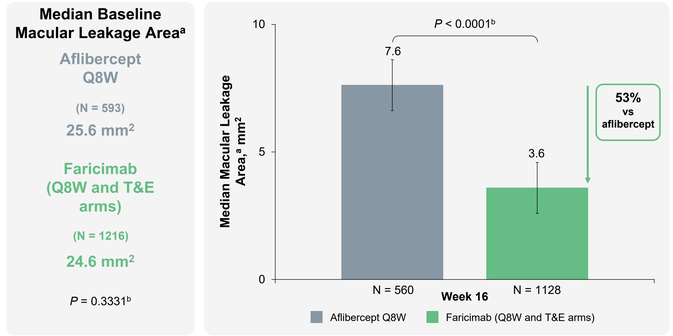


YOSEMITE (NCT03622580); RHINE (NCT03622593). [a] Previously anti-VEGF–treated eyes (treated ≥ 3 months before day 1) were limited to 25% of the total enrolment. [b] CST was measured as the distance from the ILM to Bruch's membrane. [c] BCVA was measured using the ETDRS VA chart at a starting distance of 4 m. 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; DMO, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fluorescein angiography; ILM, internal limiting membrane; Q8W, every 8 weeks; T&E, treat-and-extend; VA, visual acuity; VEGF, vascular endothelial growth factor.

Results

Larger Reduction in Macular Leakage Area, a Biomarker of Vascular Stability, With Faricimab vs Aflibercept in the Head-to-Head Dosing Phase

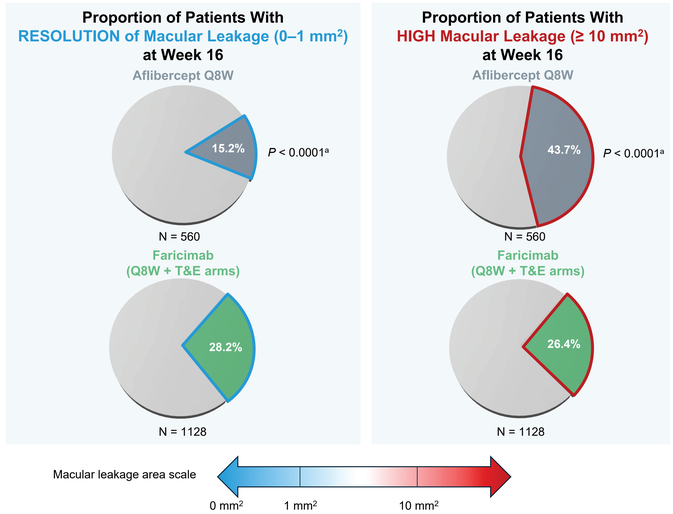
YOSEMITE/RHINE Pooled: Post Hoc Analysis



Population: patients with available macular leakage data at baseline or week 16 according to the timepoint of the analysis. [a] Macular leakage area determined by FA. [b] The *P* value from Wilcoxon 2-sample rank test is nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. 95% CIs are shown. CI, confidence interval; FA, fluorescein angiography; Q8W, every 8 weeks; T&E, treat-and-extend.

More Patients Treated With Faricimab vs Aflibercept Achieved Resolution of Macular Leakage After Head-to-Head Dosing Phase

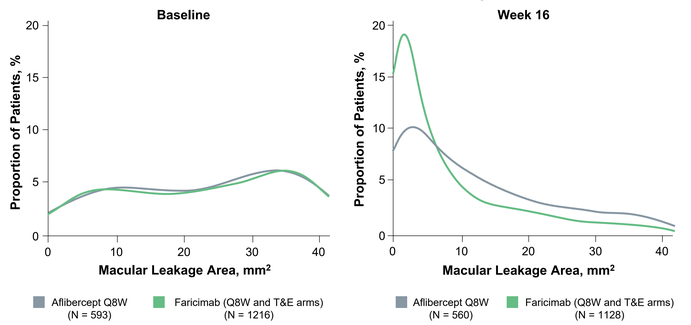
YOSEMITE/RHINE Pooled: Post Hoc Analysis



Population: patients with available macular leakage data at week 16. Proportion of patients with macular leakage 0–1 mm^2 at baseline: aflibercept Q8W: 0.5%; faricimab Q8W and T&E arms: 1.2%. Proportion of patients with macular leakage ≥ 10 mm^2 at baseline: aflibercept Q8W: 80.4%; faricimab Q8W and T&E arms: 78.3%. The proportion estimates were weighted using CMH method stratified by baseline BCVA score (< 64 letters vs ≥ 64 letters), prior intravitreal anti-VEGF therapy (yes vs no), region (US and Canada vs the rest of the world) and study (GR40349 vs GR40398). [a] The *P* value (< 0.0001) from CMH test is nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. N values: faricimab N = 1216 at day 1, N = 1128 at week 16; aflibercept N = 593 at day 1, N = 560 at week 16. BCVA, best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel; Q8W, every 8 weeks; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

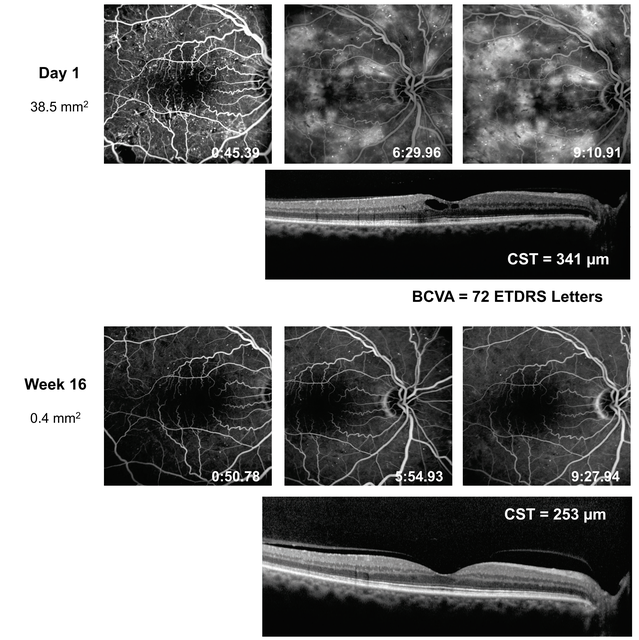
Distribution of Macular Leakage Area at Baseline and Week 16

YOSEMITE/RHINE Pooled: Post Hoc Analysis



Population: patients with available macular leakage data at baseline and week 16. Curves represent kernel density estimation of macular leakage area (mm^2) determined by FA. FA, fluorescein angiography; Q8W, every 8 weeks; T&E, treat-and-extend.

Case: Fundus FA Leakage Images From a Faricimab Patient Achieving Resolution of Macular Leakage



No serious ocular adverse drug reactions were observed/reported in the treated eye. BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fluorescein angiography.