Impact of Faricimab vs Aflibercept on Epiretinal Membrane Formation Over 2 Years in Eyes With DMO in the YOSEMITE/RHINE Phase 3 Trials

Simona Degli Esposti, MD[1]; Yuichiro Ogura, MD, PhD[2]; Gábor Deák, MD, PhD[3]; Kara Gibson, PhD[4]; Ursula Schmidt-Erfurth, MD[5]; Tracey Wang, MSc[6]; Peter Westenskow, PhD[7]; and Jeffrey Willis, MD, PhD[8]

[1] Moorfields Eye Hospital NHS Foundation Trust, London, UK; [2] Department of Ophthalmology and Visual Science, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [3] Vienna Reading Centre, Medical University of Vienna, Austria; [4] Roche Products Ltd., Welwyn Garden City, UK; [5] Department of Ophthalmology, Medical University of Vienna, Austria; [6] F. Hoffmann-La Roche Ltd., Mississauga, ON, Canada; [7] F. Hoffmann-La Roche Ltd., Basel, Switzerland; [8] Genentech, Inc., South San Francisco, CA, USA

Purpose

To assess whether epiretinal membrane (ERM) development influences vision, anatomy and durability outcomes

Conclusions

Faricimab every 8 weeks (Q8W) reduced risk of ERM formation by 52% compared with aflibercept Q8W in eyes with diabetic macular oedema (DMO)

Among eyes with ERM development: lower vision, worse anatomical outcomes and less extension were observed

These are the first phase 3 trial data that suggest a potential anti-fibrotic effect for faricimab

Financial Disclosures

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- GD, US-E: None
- KG: Employee: Roche Products Ltd.
- TW, PW: Employee: F. Hoffmann-La Roche Ltd.
- JW: Employee: Genentech, Inc.

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 Trishan Gajanand, PhD, 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

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Background

- ERMs represent potentially useful markers of fibrotic proliferation in retinal disease
- ERMs are associated with DMO, and real-world data indicate that they can be found in almost 10% of eyes with DMO treated with intravitreal injections over a 2-year period[1]
- The underlying pathophysiology of ERMs is complex and multifactorial, but they are frequently associated with inflammation, elevated angiopoietin-2 (Ang-2) levels and several retinal vascular diseases[2-4]
- Faricimab is a dual Ang-2/vascular endothelial growth factor (VEGF)-A inhibitor and the first bispecific antibody designed for intraocular use
- Preclinical data suggest that Ang-2 and VEGF-A inhibition reduces inflammation and fibrosis more than inhibition of VEGF alone[5]
- There are limited phase 3 data on what drives ERM development and their impact on clinical outcomes like vision and anatomy

Methods

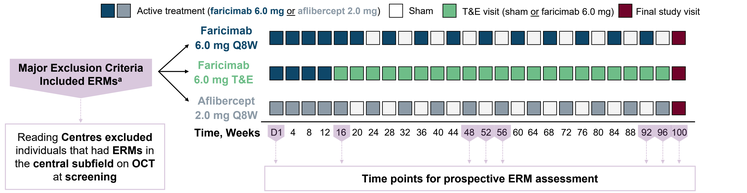
- YOSEMITE/RHINE (NCT03622580/NCT03622593) were randomised, double-masked, phase 3 trials of faricimab in patients with centre-involving DMO
- Patients (N = 1891) were randomised 1:1:1 to faricimab 6.0 mg personalised treat-and-extend or Q8W, or aflibercept 2.0 mg Q8W through week 100
- ERMs were a major exclusion criteria for the trials
- In YOSEMITE/RHINE, ERMs were measured at baseline, at the end of the head-to-head period at week 16, and over 3 time points around 1 and 2 years each

References

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2. Gilbert C et al. *Eye (Lond).* 1988;2 Suppl:S140-S156.
3. Fung AT et al. *Clin Exp Ophthalmol.* 2021;49:289-308.
4. Takagi H et al. *Invest Ophthalmol Vis Sci.* 2003;44:393-402.
5. Canonica J et al. *Front Cell Neurosci.* 2023;17:1192464.

Results

1. YOSEMITE/RHINE Trial Design: When Were ERMs Assessed?



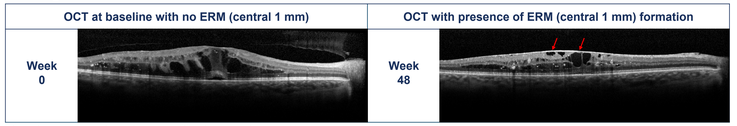
To our knowledge, this is the **first time ERMs** have been **presented** from a **phase 3 trial** setting

[a] Defined as presence of significant distortion of macular architecture in the central subfield (ie, centre 1 mm). YOSEMITE (NCT03622580); RHINE (NCT03622593).
D, day; ERM, epiretinal membrane; OCT, optical coherence tomography; Q8W, every 8 weeks; T&E, treat-and-extend.

2. Evaluation of ERMs Using OCT

Two reading centres (Duke and Vienna institutes) acted as **Central Reading Centres** and **were masked** to treatment assignments

ERMs were **defined** as "the presence of a membrane on the ILM, causing **significant distortion** of **macular architecture** in the central subfield (ie, **centre 1 mm**) **[Y/N]**"



ERM, epiretinal membrane; ILM, internal limiting membrane; OCT, optical coherence tomography; Y/N, yes/no.

3. Baseline Characteristics Were Generally Balanced Across Arms

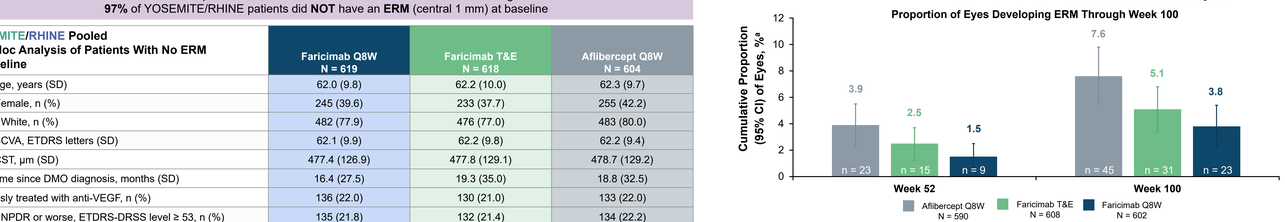
ERMs were part of exclusion criteria for YOSEMITE/RHINE at screening
97% of YOSEMITE/RHINE patients did **NOT** have an **ERM** (central 1 mm) at baseline

YOSEMITE/RHINE Pooled Post Hoc Analysis of Patients With No ERM at Baseline	Faricimab Q8W N = 619	Faricimab T&E N = 618	Aflibercept Q8W N = 604
Mean age, years (SD)	62.0 (9.8)	62.2 (10.0)	62.3 (9.7)
Sex – Female, n (%)	245 (39.6)	233 (37.7)	255 (42.2)
Race – White, n (%)	482 (77.9)	476 (77.0)	483 (80.0)
Mean BCVA, ETDRS letters (SD)	62.1 (9.9)	62.2 (9.8)	62.2 (9.4)
Mean CST, µm (SD)	477.4 (126.9)	477.8 (129.1)	478.7 (129.2)
Mean time since DMO diagnosis, months (SD)	16.4 (27.5)	19.3 (35.0)	18.8 (32.5)
Previously treated with anti-VEGF, n (%)	136 (22.0)	130 (21.0)	133 (22.0)
Severe NPDR or worse, ETDRS-DRSS level ≥ 53, n (%)	135 (21.8)	132 (21.4)	134 (22.2)
Baseline posterior vitreous detachment, n (%)	101 (16.3)	113 (18.3)	109 (18.0)

ERMs defined as presence of significant distortion of macular architecture in the central subfield. BCVA, best-corrected visual acuity; CST, central subfield thickness; DMO, diabetic macular oedema; DRSS, Diabetic Retinopathy Severity Scale; ERM, epiretinal membrane; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, non-proliferative diabetic retinopathy; Q8W, every 8 weeks; SD, standard deviation; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

4. Risk of ERM Formation With Faricimab and Aflibercept Through Week 100

YOSEMITE/RHINE Pooled: Post Hoc Analysis



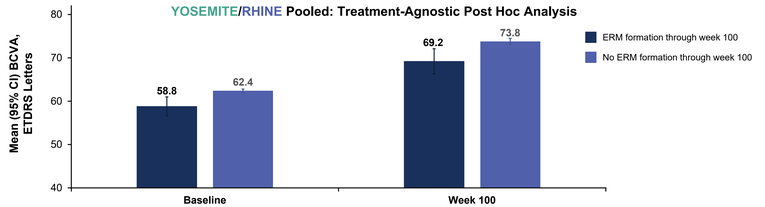
At week 100
Faricimab Q8W
vs Aflibercept Q8W
Odds ratio*: **0.48**
95% CI: **0.29, 0.81**
P value: **0.0055**

At week 100
Faricimab T&E
vs Aflibercept Q8W
Odds ratio*: **0.65**
95% CI: **0.41, 1.05**
P value: **0.0783**

Patients with no ERM at baseline. Missing data were not imputed, and patients with no post-baseline ERM results were excluded from the analysis. ERMs defined as presence of significant distortion of macular architecture in the central subfield. * The adjusted odds ratio and 95% CI were produced using a multivariate logistic regression models including treatment group, baseline BCVA score (< 64 letters vs ≥ 64 letters), prior IVT anti-VEGF therapy (yes vs no), region (U.S. and Canada, and the rest of the world) and study (YOSEMITE vs RHINE) as covariates using cumulative data through week 100. Risk refers to the odds from logistic regression. The *P* values are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. BCVA, best-corrected visual acuity; CI, confidence interval; ERM, epiretinal membrane; IVT, intravitreal; Q8W, every 8 weeks; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

5. Mean BCVA Values in the Study Eye by ERM Formation Through Week 100

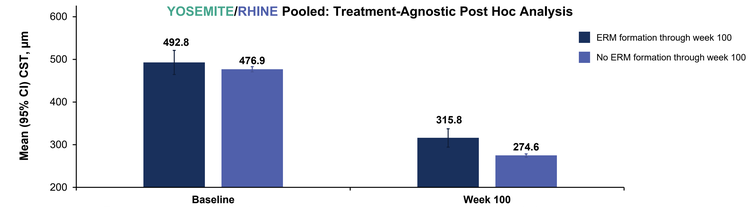
YOSEMITE/RHINE Pooled: Treatment-Agnostic Post Hoc Analysis



Patients with no ERM at baseline. Missing data were not imputed, and patients with invalid BCVA values or no post-baseline ERM results were excluded from the analysis. Data are descriptive statistics (mean 95% CI for pooled). No hypothesis testing was done thus no *P* value was derived. Due to the limitations of the post-baseline subgroup analyses, no causal relationship should be concluded based on the results. ERMs defined as presence of significant distortion of macular architecture in the central subfield. Baseline was defined as the last available measurement obtained on or before randomisation. BCVA, best-corrected visual acuity; CI, confidence interval; ERM, epiretinal membrane; ETDRS, Early Treatment Diabetic Retinopathy Study.

6. Mean CST Values in the Study Eye by ERM Formation Through Week 100

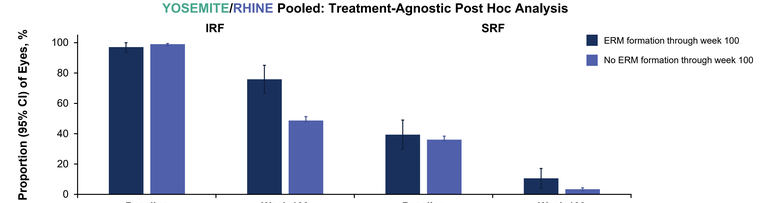
YOSEMITE/RHINE Pooled: Treatment-Agnostic Post Hoc Analysis



Patients with no ERM at baseline. Missing data were not imputed, and patients with no CST values or no post-baseline ERM results were excluded from the analysis. Data are descriptive statistics (mean 95% CI for pooled); No hypothesis testing was done thus no *P* value was derived. Due to the limitations of the post-baseline subgroup analyses, no causal relationship should be concluded based on the results. ERMs defined as presence of significant distortion of macular architecture in the central subfield. Baseline was defined as the last available measurement obtained on or before randomisation. CST is defined as the distance between internal limiting membrane and Bruch's membrane as assessed by Central Reading Centre. CI, confidence interval; CST, central subfield thickness; ERM, epiretinal membrane.

7. Proportion of Eyes With IRF or SRF by ERM Formation Through Week 100

YOSEMITE/RHINE Pooled: Treatment-Agnostic Post Hoc Analysis

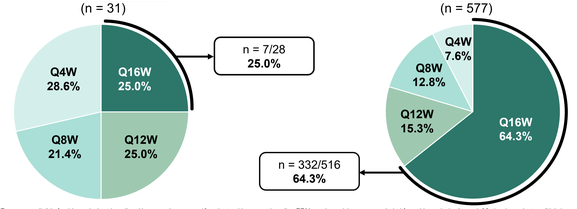


Patients with no ERM at baseline. Missing data were not imputed, and patients with no IRF/SRF or no post-baseline ERM results were excluded from the analysis. Data are descriptive statistics (proportion 95% CI for pooled), values below 0% or above 100% are imputed as 0% or 100%, respectively; No hypothesis testing was done thus no *P* value was derived. Due to the limitations of the post-baseline subgroup analyses, no causal relationship should be concluded based on the results. ERMs defined as presence of significant distortion of macular architecture in the central subfield. Baseline was defined as the last available measurement obtained on or before randomisation. CI, confidence interval; ERM, epiretinal membrane; IRF, intraretinal fluid; SRF, subretinal fluid.

8. Fewer Faricimab T&E Patients Who Developed ERMs Extended to Q16W

YOSEMITE/RHINE Pooled: Post Hoc Analysis

Proportions of Patients at Week 96



Note: 618 patients in the T&E arm were eligible for this analysis at baseline. However, there were 10 patients with no post-baseline ERM results and they were excluded from this analysis. At week 96, the denominators (Ns) dropped due to missing data from study discontinuation or missed visit. ERMs defined as presence of significant distortion of macular architecture in the central subfield (ie, centre 1 mm). ERM, epiretinal membrane; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.