Automated Segmentation of Hyperreflective Foci in DMO Shows Greater Volume Reduction With Faricimab vs Aflibercept in the Phase 3 YOSEMITE and RHINE Trials

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Purpose

- In diabetic macular oedema (DMO), hyperreflective foci (HRF) are considered to represent retinal inflammation and may be an imaging biomarker for disease progression
- We aimed to test if the anti-inflammatory properties of faricimab, a dual angiopoietin-2 (Ang-2)/vascular endothelial growth factor (VEGF)-A inhibitor, would translate into improved resolution of retinal HRF in DMO, vs aflibercept

Conclusions

HRF volumes were associated with Diabetic Retinopathy Severity Score (DRSS) and central subfield thickness (CST) at baseline, suggesting that HRF are linked to disease severity

Co-localisation of HRF and cystoid intraretinal fluid (IRF) at baseline suggests that this biomarker may have a pathogenic role in potentiating and worsening DMO

Retinal HRF volume and count reductions were observed in faricimab-treated eyes vs aflibercept-treated eyes up to week 48

These findings support the therapeutic potential of dual Ang-2/VEGF-A inhibition with faricimab for patients with DMO

Financial Disclosures
- TP: Consultant: Alimera, Apellis, Bayer, Genentech, Inc., Heidelberg, Novartis, Oxurion.
- AM, EvS, KP, ILJ, YC, CG, SF: Employee: F. Hoffmann-La Roche Ltd.
- IB: Employee: F. Hoffmann-La Roche Ltd.; Stock Options: F. Hoffmann-La Roche Ltd.
- KG: Employee: Roche Products Ltd. JW: Employee: Genentech, Inc.

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
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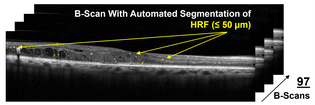
Background

- HRF are small (≤ 50 µm) highly reflective dots on spectral-domain optical coherence tomography (SD-OCT)[1] that are present throughout the retina in DMO and neovascular age-related macular degeneration[2,3]
- HRF may be an imaging biomarker of retinal disease progression and reduce with both anti-VEGF and steroid treatment[4–6]
- Presence of HRF at baseline is suggested to be predictive of poor vision outcomes in patients with DMO[4,7–9]
- There are 2 main hypotheses regarding HRF origin in DMO:
  - Activated inflammatory cells[4,10]
  - Lipid and/or protein extravasation[1,2]

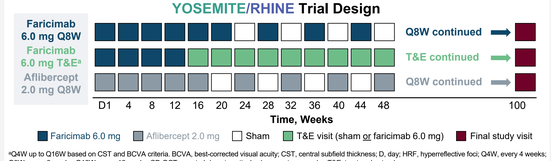
Methods

YOSEMITE/RHINE Pooled: Post Hoc Analysis

- **Data up to week 48**
- **Whole SD-OCT volumes**
- Faricimab 6.0 mg Q8W, n = 519
- Faricimab 6.0 mg T&E, n = 524
- Aflibercept 2.0 Q8W, n = 502



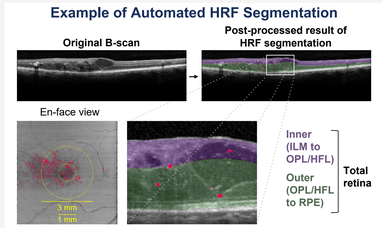
YOSEMITE/RHINE Trial Design



[a]Q4W up to Q16W based on CST and BCVA criteria. BCVA, best-corrected visual acuity; CST, central subfield thickness; D, day; HRF, hyperreflective foci; Q4W, every 4 weeks; Q8W, every 8 weeks; Q16W, every 16 weeks; SD-OCT, spectral-domain optical coherence tomography; T&E, treat-and-extend.

- To automatically segment HRF, a deep learning-based algorithm was developed with manually annotated B-scans from the phase 2 BOULEVARD trial (NCT02699450)[11]
- Using this algorithm, HRF were quantified in SD-OCT volume scans from the phase 3 YOSEMITE/RHINE trials (NCT03622580/NCT03622593)
- Study eyes were randomised to faricimab 6.0 mg every 8 weeks (Q8W; n = 512), faricimab 6.0 mg personalised treat-and-extend–based regimen (T&E; n = 519) and aflibercept 2.0 mg Q8W (n = 496)
- HRF were defined as objects ≤ 50 µm in diameter and assessed within the 1.0- and 3.0-mm diameter Early Treatment Diabetic Retinopathy Study (ETDRS) rings and by location within the inner and outer retina

Example of Automated HRF Segmentation



HFL, Henle's fibre layer; HRF, hyperreflective foci; ILM, internal limiting membrane; OPL, outer plexiform layer; RPE, retinal pigment epithelium.

- HRF distributions at baseline were analysed in a treatment-agnostic manner by best-corrected visual acuity (BCVA), CST, and IRF quartiles and DRSS groups
- Cystoid IRF was segmented in the 3.0-mm diameter ETDRS ring using a deep-learning–based algorithm developed for the quantification of IRF and subretinal fluid (SRF)[12]
- Mean values and treatment-group comparisons were estimated using a mixed model for repeated measures

References

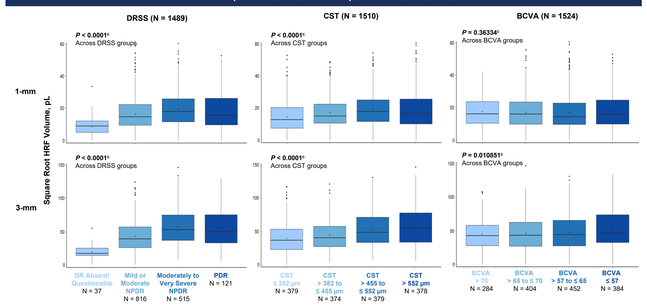
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Results

1. Baseline HRF Volumes in Total Retina[a] Were Associated With Markers of Disease Severity

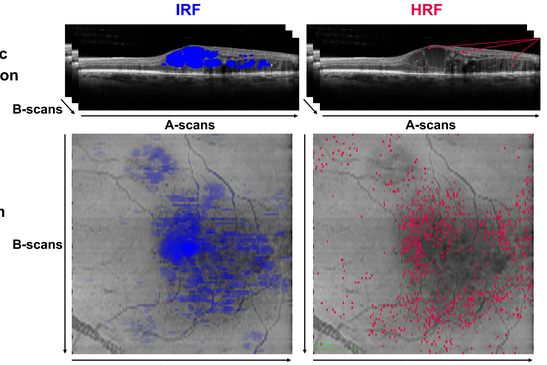
YOSEMITE/RHINE Pooled: Post Hoc Analysis

99.7% of patients had HRF present at baseline[b]



[a] ILM to RPE in the region within the 1- and 3-mm circles of the ETDRS grid. [b] Patients with HRF present (> 0) at baseline for pooled treatment groups in any one of the inner or outer, 1-mm or 3-mm rings; HRF presence is the same when calculated from volumes or counts. [c] *P* values from Kruskal-Wallis tests are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. Results are presented for the baseline HRF population, which includes all patients with an HRF measurement (≥ 0) at baseline (inner or outer, 1-mm or 3-mm rings) (n = 1527); patients were included in boxplots if they also had a non-missing DRSS, BCVA or CST measurement, respectively. Boxplots are descriptive summaries of the data. BCVA, best-corrected visual acuity; CST, central subfield thickness; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; HRF, hyperreflective foci; ILM, internal limiting membrane; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; RPE, retinal pigment epithelium.

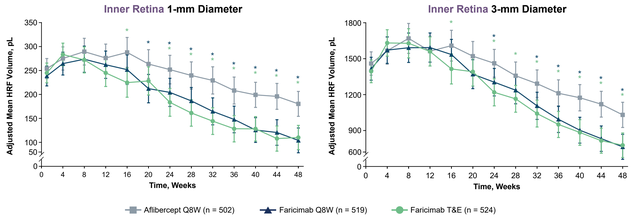
2. HRF Co-Localise to Regions of Cystoid IRF at Baseline



To ensure the presence of a significant volume of HRF, analysis was performed in the 10% of images with the greatest HRF volume (n = 159). HRF, hyperreflective foci; IRF, intraretinal fluid.

3. Reductions in HRF Volumes in the Inner Retina[a] With Faricimab vs Aflibercept Over Time

YOSEMITE/RHINE Pooled: Post Hoc Analysis

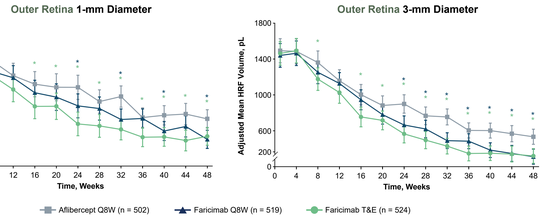


Similar results were seen for HRF counts

* *P* value < 0.05 vs aflibercept 2.0 mg Q8W. *P* values are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. [a] ILM to OPL-HFL. Results are based on an MMRM adjusted for baseline HRF result, treatment arm, visit, visit-by-treatment arm interaction, baseline BCVA, baseline BCVA category (< 64 letters vs ≥ 64 letters), region (US and Canada, Asia and the rest of the world) and prior intravitreal anti-VEGF therapy (yes vs no). An unstructured covariance structure was used. 95% CI error bars are shown. MMRM analyses performed on original units (µm[3]) but axis values converted to pL for mean plots. BCVA, best-corrected visual acuity; CI, confidence interval; HFL, Henle's fibre layer; HRF, hyperreflective foci; ILM, internal limiting membrane; MMRM, mixed model for repeated measures; OPL, outer plexiform layer; Q8W, every 8 weeks; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

4. Reductions in HRF Volumes in the Outer Retina[a] With Faricimab vs Aflibercept Over Time

YOSEMITE/RHINE Pooled: Post Hoc Analysis

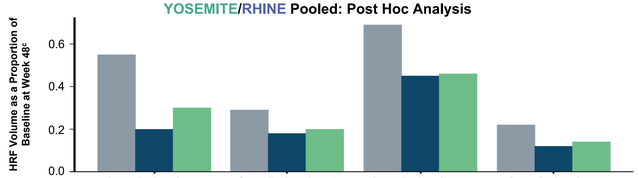


Similar results were seen for HRF counts

* *P* value < 0.05 vs aflibercept 2.0 mg Q8W. *P* values are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. [a] OPL-HFL to RPE. Results are based on a mixed model for repeated measures adjusted for baseline HRF result, treatment arm, visit, visit-by-treatment arm interaction, baseline BCVA, baseline BCVA category (< 64 letters vs ≥ 64 letters), region (US and Canada, Asia and the rest of the world) and prior intravitreal anti-VEGF therapy (yes vs no). An unstructured covariance structure was used. 95% CI error bars are shown. MMRM analyses performed on original units (µm[3]) but axis values converted to pL for mean plots. BCVA, best-corrected visual acuity; CI, confidence interval; HFL, Henle's fibre layer; HRF, hyperreflective foci; MMRM, mixed model for repeated measures; OPL, outer plexiform layer; Q8W, every 8 weeks; RPE, retinal pigment epithelium; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

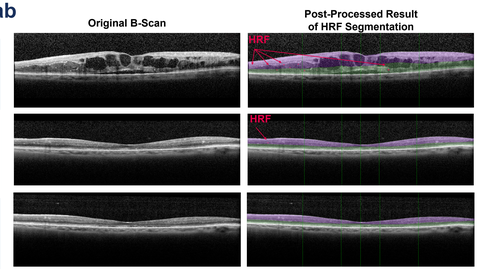
5. Faricimab Reduced HRF Volumes in the Inner[a] and Outer[b] Retina, Whereas Aflibercept's Effects Were Localised to the Outer Retina

YOSEMITE/RHINE Pooled: Post Hoc Analysis



[a] ILM to OPL-HFL. [b] OPL-HFL to RPE. [c] Based on the median (1st Q3 if median zero) at week 48 relative to baseline. [d] The upper quartile is presented for this parameter as the median values are zero in the faricimab arms. Each bar represents the ratio of the median (or Q3) HRF volume at week 48 to baseline for the relevant treatment group and location. HFL, Henle's fiber layer; HRF, hyperreflective foci; ILM, internal limiting membrane; OPL, outer plexiform layer; Q3, quartile 3; Q8W, every 8 weeks; RPE, retinal pigment epithelium; T&E, treat-and-extend.

6. Case: Reduction of HRF From Baseline to Week 48 With Faricimab



[a] HRF count is in the total retina 3-mm diameter. Case images are from a 77-year-old female who received faricimab T&E. No serious ocular adverse drug reactions were observed/reported in the treated eye. BCVA, best-corrected visual acuity; CST, central subfield thickness; HRF, hyperreflective foci; T&E, treat-and-extend.