# Angiopoietin-2 Signalling and Vascular Stability With Faricimab in Diabetic Macular Oedema

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## Key Clinical Question

Does dual inhibition of angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A) promote vascular stability and durable efficacy over anti-VEGF alone in diabetic macular oedema (DMO)?

## Introduction

- The Ang/Tie (tyrosine kinase with immunoglobulin-like domains) signalling pathway is a key regulator of vascular stability in the retinal vasculature
- Ang-2 and VEGF-A upregulation are key drivers of vascular destabilisation in DMO and other retinal vascular diseases[1-3]
- Dual pathway inhibition with faricimab, a novel bispecific antibody that independently binds and neutralises Ang-2 and VEGF-A, may promote vascular stability beyond current anti-VEGF therapies[4,5]
- We explored the effect of dual Ang-2/VEGF-A pathway inhibition on vascular stability in DMO using preclinical data and phase 2 and 3 trial data of faricimab

## Methods

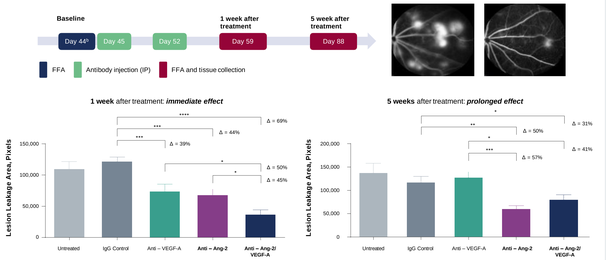
- In preclinical studies, JR5558 mice (spontaneous model of choroidal neovascularisation) were injected (intravitreal) with anti–Ang-2, anti–VEGF-A, dual anti–Ang-2/VEGF-A or none/immunoglobulin G as controls
- Vascular stability was evaluated through neovascular leakage and subretinal inflammatory cell infiltration (Iba1+, CD11b+, CD45+) at baseline and 1, 3 and 5 weeks post treatment
- In a post hoc analysis of BOULEVARD (NCT02699450), the effect of faricimab on sustained retinal stability (SRS; maintenance of central subfield thickness [CST] ≤ 325 µm to week 24) was assessed
- Vascular stability with faricimab was evaluated in the phase 3 YOSEMITE/RHINE trials (NCT03622580/NCT03622593) via anatomical endpoints measured on optical coherence tomography, and the proportion of patients in the faricimab personalised treatment interval arms receiving every-4-week (Q4W), Q8W, Q12W or Q16W dosing over 2 years

## Conclusions

- Preclinical data from JR5558 mice suggest that Ang-2 blockade may contribute to reduced inflammation and increased vascular stability
- In BOULEVARD, patients receiving faricimab achieved SRS earlier than those receiving ranibizumab
- Year 2 data from YOSEMITE/RHINE showed that faricimab demonstrated improved CST reductions,[a] absence of DMO[b] and absence of intraretinal fluid (IRF) versus aflibercept[b] and the potential for improved durability with dosing up to Q16W
- Together, these data support the involvement of Ang/Tie signalling in vascular stability in DMO and the potential for dual Ang-2/VEGF-A inhibition with faricimab to improve outcomes versus VEGF-A inhibition alone.

[a] In general, patients receiving faricimab achieved greater reductions in CST over time compared with aflibercept (not a statistically significant difference). [b] In general, a numerically greater proportion of patients receiving faricimab achieved an absence of DMO or IRF over time compared with aflibercept.

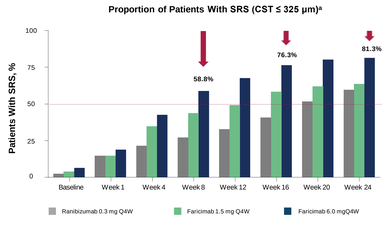
## 1. In JR5558 Mice,[a] Sustained Reduction in Lesion Leakage Area May Be Driven by Ang-2 Inhibition




[a] Model of CNV with early and persistent neovascular leakage and local para-inflammation associated with macrophage recruitment to the subretinal space. [b] Post-natal day. [c] Representative fluorescein images; adapted from Chakravarthy U et al. Presented at: ARVO Congress; May 2020; Virtual.
All appropriate controls were conducted, not shown here. n = 7–15 mice per group. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.
Adapted from: Canonica J et al. Presented at: EURETINA Congress; October 2–4, 2020; Virtual.
Ang-2, angiopoietin-2; CNV, choroidal neovascularisation; FFA, fundus fluorescein angiography; IgG, immunoglobulin G; IP, intraperitoneal; VEGF-A, vascular endothelial growth factor-A.

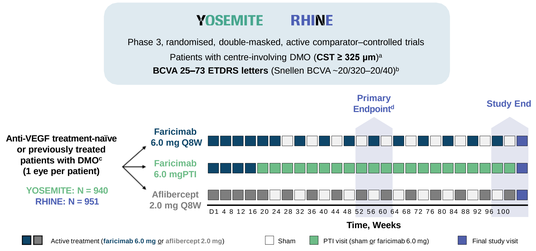
## 2. In BOULEVARD, More Faricimab-Treated Patients Achieved SRS Earlier Than Ranibizumab-Treated Patients

**SRS** was defined as:
- Achieving CST ≤ 325 µm AND
- Maintaining CST ≤ 325 µm until the primary endpoint visit (week 24)



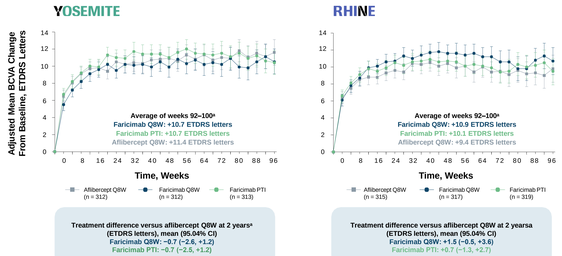

BOULEVARD: NCT02699450. The phase 2 BOULEVARD trial assessed the efficacy and safety of faricimab 1.5 mg and 6.0 mg Q4W versus ranibizumab 0.3 mg Q4W up to week 24 in treatment-naive patients with DMO.[3]
[a] Intent-to-treat population.
CST, central subfield thickness; DMO, diabetic macular oedema; Q4W, every 4 weeks; SRS, sustained retinal stability.

## 3. YOSEMITE and RHINE Investigated Faricimab Q8W or Treat-and-Extend–Based PTI Dosing With Up to Q16W Intervals



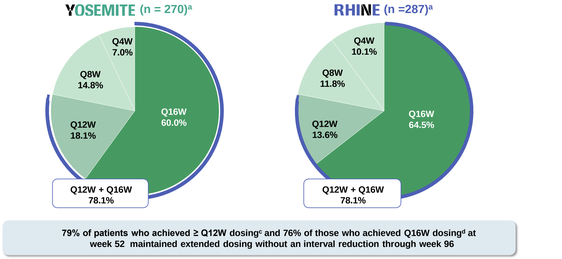

YOSEMITE: NCT03622580; RHINE: NCT03622593. [a] CST was measured as the distance from the internal limiting membrane to Bruch's membrane. [b] BCVA was measured using the ETDRS visual acuity chart at a starting distance of 4 m. [c] Previously anti-VEGF–treated eyes (treated ≥ 3 months before day 1) were limited to 25% of the total enrolment. [d] 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; PTI, personalised treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF, vascular endothelial growth factor.

## 4. Vision Gains With Faricimab Q8W and PTI Up to Q16W Were Non-inferior to Aflibercept Q8W at 1 Year and Maintained Through Year 2




[a] Adjusted mean BCVA 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 (continuous), baseline BCVA (< 64 vs ≥ 64 ETDRS letters), prior intravitreal anti-VEGF therapy (yes vs no) and region (United States and Canada, Asia and rest of the world). 95.04% CI error bars are shown. BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PTI, personalised treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF, vascular endothelial growth factor.

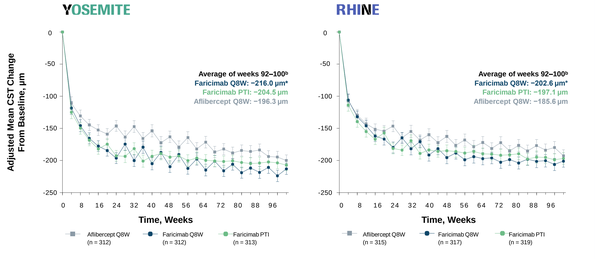
## 5. More than 60% of Patients in the Faricimab PTI Arms Achieved Q16W Dosing at Week 96




**79% of patients who achieved ≥ Q12W dosing[c] and 76% of those who achieved Q16W dosing[d] at week 52 maintained extended dosing without an interval reduction through week 96**

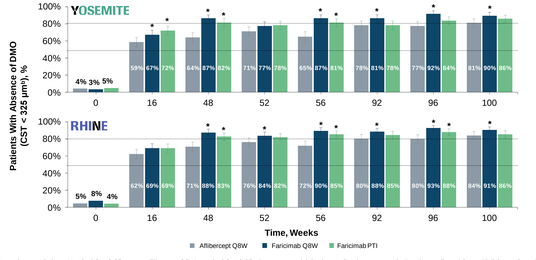
[a] Analyses included patients in the faricimab PTI arms who had not discontinued the study at the week 96 visit. Treatment interval at week 96 was defined as the treatment interval decision made at that visit. [b] Sum of Q12W and Q16W percentages shown; calculated proportion of patients who achieved Q12W or Q16W dosing at week 96 is 78.049%. [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, personalised treatment interval; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks.

## 6. Greater Reductions in CST With Faricimab Q8W and PTI Up to Q16W vs Aflibercept Q8W Through Year 2[a]



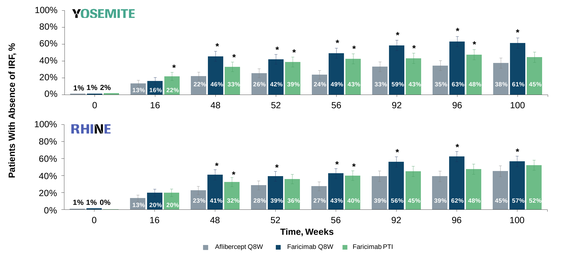

Test for superiority: * Nominal $P < 0.05$ versus aflibercept Q8W. $P$ values are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the $P$ values. Clinical significance has not been established and conclusions regarding treatment effect cannot be drawn. [a] In general, patients receiving faricimab achieved greater reductions in CST over time compared with aflibercept (not a statistically significant difference). [b] Adjusted mean CST 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 CST (continuous), baseline BCVA (< 64 vs ≥ 64 letters), prior intravitreal anti-VEGF therapy (yes vs no) and region (United States and Canada, Asia and rest of the world). 95.04% CI error bars are shown. BCVA, best-corrected visual acuity; CST, central subfield thickness; PTI, personalised treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF, vascular endothelial growth factor.

## 7. More Patients Achieved Absence of DMO With Faricimab Q8W and PTI Up to Q16W vs Aflibercept Q8W Through Year 2[a]




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. [a] In general, a numerically greater proportion of patients receiving faricimab achieved absence of DMO over time compared with aflibercept. [b] Absence of DMO was defined as CST < 325 µm, measured as the distance from the internal limiting membrane to Bruch's membrane. Weighted proportions were estimated using the CMH method, stratified by baseline BCVA (< 64 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; 0% of patients had absence of DMO 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. 95.04% CI error bars are shown.
BCVA, best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel; CST, central subfield thickness; DMO, diabetic macular oedema; PTI, personalised treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF, vascular endothelial growth factor.

## 8. More Patients Achieved Absence of IRF With Faricimab Q8W and PTI Up to Q16W vs Aflibercept Q8W Through Year 2[a]




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.
[a] In general, a numerically greater proportion of patients receiving faricimab achieved absence of IRF over time compared with aflibercept. Weighted proportions were estimated using the CMH method, stratified by baseline BCVA (< 64 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; IRF, intraretinal fluid; PTI, personalised treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF, vascular endothelial growth factor.

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## References

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## Financial Disclosures

- DV: Speaker Fees: Bayer, Novartis, Roche; Educational Grants: Alimera, Allergan, Bayer, Novartis, Roche; Advisory Boards: Allergan, Bayer, Novartis, Roche; Principal Investigator in Clinical Trials Sponsored by: Bayer, Novartis, Roche
- JRW, ZH: Employee: Genentech, Inc.
- PW: Employee: F. Hoffmann-La Roche Ltd.

## Study and Product Disclosures

- Faricimab has been approved for the treatment of neovascular age-related macular degeneration and diabetic macular oedema in the United States and Japan, and is currently being studied for the treatment of macular oedema due to retinal vein occlusion. Please note that faricimab has not been 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
- Animal experiments were approved and conducted in strict adherence to the Swiss federal ordinance on animal protection and welfare (reference BS-2734), as well as according to the rules of the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research guidelines, European Directive 86/609/EEC and the Roche Ethics Committee on Animal Welfare
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