Efficacy, Durability and Safety of Faricimab in Diabetic Macular Oedema: 2-Year Results From the Phase 3 YOSEMITE and RHINE Trials

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Key Clinical Question

What is the longer-term efficacy, durability and safety of faricimab, a dual angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A) inhibitor, in patients with diabetic macular oedema (DMO)?

Introduction

- Ang-2 and VEGF-A are upregulated in, and key drivers of, vascular destabilisation in DMO[1]
- YOSEMITE (NCT03622580; N = 940) and RHINE (NCT03622593; N = 951) are identical, randomised, double-masked, active comparator-controlled trials of faricimab in treatment-naïve and previously anti-VEGF–treated patients with DMO[2]
- Year 1 data from the YOSEMITE and RHINE trials suggest that dual Ang-2/VEGF-A inhibition with faricimab may promote vascular stability and durable efficacy in patients with DMO beyond current anti-VEGF therapies for DMO[2]
- Year 2 of YOSEMITE and RHINE aimed to evaluate the longer-term efficacy, durability and safety of faricimab in DMO

Methods

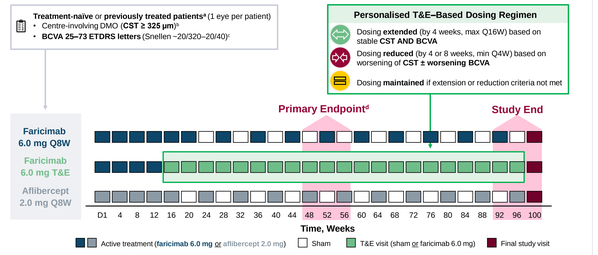
- YOSEMITE and RHINE enroled adults with centre-involving DMO (central subfield thickness [CST] ≥ 325 µm) and best-corrected visual acuity (BCVA) 25–73 Early Treatment Diabetic Retinopathy Study letters (Snellen equivalent ~20/320–20/40)
- Patients were randomised 1:1:1 to faricimab 6.0 mg every 8 weeks (Q8W), faricimab 6.0 mg per a personalised treat-and-extend-based (T&E) regimen or aflibercept 2.0 mg Q8W (YOSEMITE/RHINE, N = 940/951)
- Patients in the faricimab T&E arm followed a regimen with dosing intervals extended, maintained or reduced from Q4W up to Q16W dosing based on CST and BCVA change at active dosing visits from week 12
- The primary endpoint was mean change in BCVA from baseline at 1 year, averaged over weeks 48, 52 and 56
- Other efficacy and safety measures were assessed through week 100

Conclusions

- Over 2 years, faricimab demonstrated durable efficacy through greater disease control with up to Q16W dosing:
  - Robust vision gains and greater CST reductions with faricimab at year 1 were maintained through year 2
  - Faricimab-treated patients experienced faster fluid resolution with fewer injections vs aflibercept
  - Durable vision gains and anatomic outcomes with faricimab were achieved in ~80% of patients with ≥ Q12W dosing
- Asian country subgroup results were consistent with the overall results
- Faricimab was well tolerated, with an acceptable safety profile
- The ongoing RHONE-X long-term extension study will generate 4-year data. Patients in the ongoing RHONE-X extension trial for DMO will be administered faricimab according to the T&E-based PTI dosing regimen.

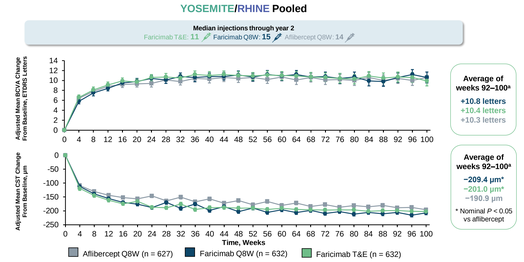
1. YOSEMITE and RHINE Trial Design

Faricimab DMO Trials Use Disease Criteria Reflective of Clinical Practice



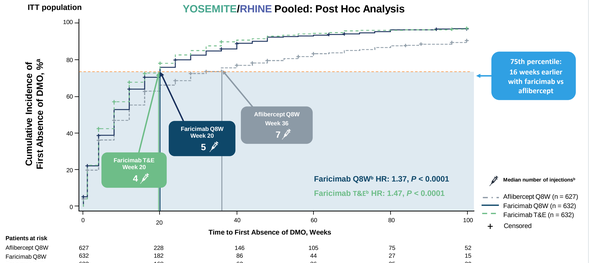
YOSEMITE (NCT03622580); RHINE (NCT03622593). [a] Previously anti-VEGF–treated eyes (treated ≥ 3 months before day 1) were limited to 25% of the total enrolment. [b] CST was measured as the distance from the ILM to Bruch's membrane. [c] BCVA was measured using the ETDRS VA chart at a starting distance of 4 m. [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; ILM, internal limiting membrane; max, maximum; min, minimum; Q4W, every 4 weeks; Q8W, every 8 weeks; Q16W, every 16 weeks; T&E, treat-and-extend; VA, visual acuity; VEGF, vascular endothelial growth factor.

2. Robust Vision Gains and Greater CST Reductions With Faricimab at Year 1 Were Maintained Through Year 2



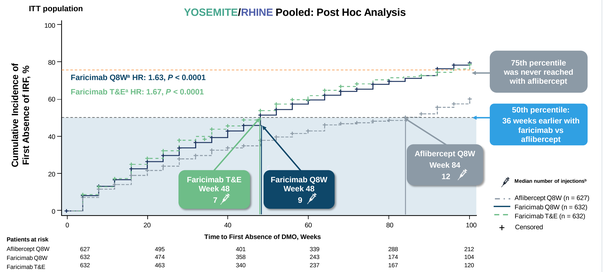
* *P* values are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. Clinical significance has not been established and conclusions regarding treatment effect cannot be drawn.
[a] Adjusted mean change from baseline at 2 years, averaged over 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) as applicable, baseline BCVA (< 64 vs ≥ 64 ETDRS letters), prior intravitreal anti-VEGF therapy (yes vs no), region (US and Canada, Asia and the rest of the world) and study (YOSEMITE vs RHINE). 95% CI error bars are shown. BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Q8W, every 8 weeks; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

3. Faricimab Patients Achieved First Absence of DMO Faster and With Fewer Injections vs Aflibercept



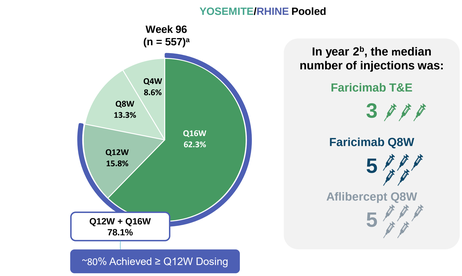
Summaries of time to first absence of IRF are Kaplan–Meier estimates. *P* values are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. Statistics for pairwise comparisons were calculated using a separate model for each comparison. HRs were estimated by Cox regression. Statistical analyses were stratified by baseline BCVA (< 64 vs ≥ 64 letters), prior intravitreal anti-VEGF therapy (yes vs no), region (US and Canada, Asia and the rest of the world) and study (YOSEMITE vs RHINE). [a] Results from stratified analyses are presented for HR and log-rank test vs aflibercept. [b] The number of injections includes any active drug administered (faricimab or aflibercept), including medication errors. BCVA, best-corrected visual acuity; HR, hazard ratio; IRF, intraretinal fluid; ITT, intent-to-treat; Q8W, every 8 weeks; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

4. Median Time to First Absence of IRF Is More Than 8 Months Earlier in Faricimab Patients and With Fewer Injections vs Aflibercept



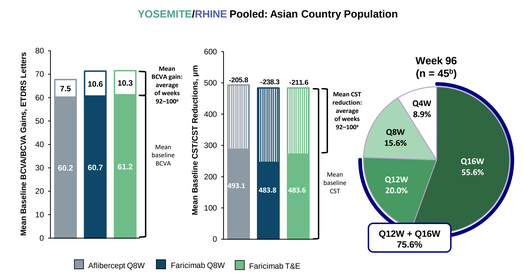
Summaries of time to first absence of IRF are Kaplan–Meier estimates. *P* values are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. Statistics for pairwise comparisons were calculated using a separate model for each comparison. HRs were estimated by Cox regression. Statistical analyses were stratified by baseline BCVA (< 64 vs ≥ 64 letters), prior intravitreal anti-VEGF therapy (yes vs no), region (US and Canada, Asia and the rest of the world) and study (YOSEMITE vs RHINE). [a] Results from stratified analyses are presented for HR and log-rank test vs aflibercept. faricimab Q8W HR (95% CI): 1.63 (1.41, 1.88). *P* < 0.0001; faricimab T&E HR (95% CI): 1.67 (1.45, 1.93). *P* < 0.0001. An HR > 1 favours faricimab over aflibercept. [b] The number of injections includes any active drug administered (faricimab or aflibercept), including medication errors. BCVA, best-corrected visual acuity; HR, hazard ratio; IRF, intraretinal fluid; ITT, intent-to-treat; Q8W, every 8 weeks; T&E, treat-and-extend.

5. In Year 2, Faricimab Up to Q16W Achieved Durable Vision Gains With Fewer Injections vs Aflibercept in Patients With DMO



[a] Proportion of patients in the pooled faricimab T&E arms on Q4W, Q8W, Q12W or Q16W dosing at week 96, among those who had not discontinued the study at the week 96 visit; results are presented for the pooled YOSEMITE/RHINE safety-evaluable population (faricimab Q8W, n = 630; faricimab T&E, n = 632; aflibercept Q8W, n = 625). [b] Weeks 60–96. DMO, diabetic macular oedema; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

6. Asian Country Population: Faricimab Demonstrated Vision Gains and Reductions in CST Comparable to Aflibercept With > 75% of Patients on ≥ Q12W at Year 2 When Administered Based on a T&E Regimen



Asian Country Population includes all subjects from China, Taiwan, Hong Kong, Japan, South Korea, Singapore and Thailand. [a] Results are based on a mixed model for repeated measures analysis, adjusted for study, treatment group, visit, visit-by-treatment group interaction, baseline CST (continuous), baseline BCVA score (< 64 letters vs. >= 64 letters), prior intravitreal anti-VEGF therapy (yes vs. no). Adjusted mean change from baseline at 2 years, averaged over weeks 92, 96 and 100. [b] Proportion of Asian country patients in the pooled faricimab T&E arms on Q4W, Q8W, Q12W or Q16W dosing at week 96, among those who had not discontinued the study at the week 96 visit. BCVA, best-corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

7. Faricimab Was Well Tolerated Through Study End

AEs Through Study End, Patients With ≥ 1 AE, n (%)[a]	YOSEMITE/RHINE Pooled		
	Faricimab Q8W n = 630	Faricimab T&E n = 632	Aflibercept Q8W n = 625
Ocular AEs[b]	313 (49.7%)	311 (49.2%)	284 (45.4%)
Serious ocular AEs[b]	26 (4.1%)	34 (5.4%)	20 (3.2%)
Ocular AEs of special interest[c]	25 (4.0%)	33 (5.2%)	20 (3.2%)
Intraocular inflammation events[d]	9 (1.4%)	11 (1.7%)	7 (1.1%)
Uveitis	3 (0.5%)	4 (0.6%)	0
Iritis	1 (0.2%)	4 (0.6%)	2 (0.3%)
Iridocyclitis	2 (0.3%)	3 (0.5%)	1 (0.2%)
Vitritis	2 (0.3%)	0	2 (0.3%)
Post-procedural inflammation	1 (0.2%)	1 (0.2%)	2 (0.3%)
Chorioretinitis	0	1 (0.2%)	0
Keratic precipitates	0	1 (0.2%)	0
Keratouveitis	0	1 (0.2%)	0
Endophthalmitis events	2 (0.3%)	4 (0.6%)	1 (0.2%)
Retinal vasculitis events	0	0	0
Retinal occlusive events			
Retinal vein occlusion	1 (0.2%)	4 (0.6%)	0
Retinal artery occlusion	1 (0.2%)	2 (0.3%)	2 (0.3%)
Retinal artery embolism	0	0	1 (0.2%)
Arterial occlusive disease	0	0	1 (0.2%)
Serious non-ocular AEs	175 (27.8%)	161 (25.5%)	173 (27.7%)
APTC events[e]	34 (5.4%)	30 (4.7%)	32 (5.1%)

Results are presented for the pooled YOSEMITE/RHINE safety-evaluable population. [a] Percentages are based on n values in the column headings; multiple occurrences of the same AE in an individual are counted only once. [b] Ocular AEs in the study eye only are presented. [c] 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 associated with BCVA loss of ≥ 30 letters for > 1 hour. [d] Excluding endophthalmitis. [e] APTC events were adjudicated by an external independent committee; all other events were investigator reported. Includes AEs with onset from the first dose of study drug through study end. AE, adverse event; APTC, Antiplatelet Trialists' Collaboration; BCVA, best-corrected visual acuity; Q8W, every 8 weeks; T&E, treat-and-extend.

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References

1. Joussen AM et al. Eye (Lond). 2021;35(5):1305-1316.
2. Wykoff CC et al; YOSEMITE and RHINE Investigators. Lancet. 2022;399(10326):741-755.

Financial Disclosures

- TP: Consultant: Alimera, Apellis, Bayer, Genentech, Inc., Heidelberg, Novartis, Oxurion
- ZH, YT, HL: Employee: Genentech, Inc.
- JI: Employee: Roche Products Ltd.

Study and Product Disclosures

- Faricimab is approved for the treatment of neovascular age-related macular degeneration and diabetic macular oedema in multiple countries worldwide and is not currently approved for use outside these indications
- 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 writing assistance, which was provided by Saima Khokhar, Medical Affairs Partner of Roche Products Ltd, UK