Faricimab in Diabetic Macular Oedema: 2-Year Results From the Phase 3 YOSEMITE and RHINE Trials

Faruque Ghanchi, MBBS, FRCOphth[1]; Zdenka Haskova, MD, PhD[2]; Shaun Mohan, MD[2]; David Silverman, MSc, MBChB, MRCOphth, FFPM[3]; Yannan Tang, PhD[2]; and Hugh Lin, MD, MBA[2]

[1] Bradford Teaching Hospitals, Bradford, UK; [2] Genentech, Inc., South San Francisco, CA, USA; [3] Roche Products Ltd., Welwyn Garden City, UK

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 are key drivers of, vascular destabilisation in DMO[1]
- Year 1 data from YOSEMITE and RHINE suggest that dual Ang-2/VEGF-A inhibition with faricimab may promote vascular stability and durable efficacy beyond current anti-VEGF therapies for DMO[2]
- 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

Methods

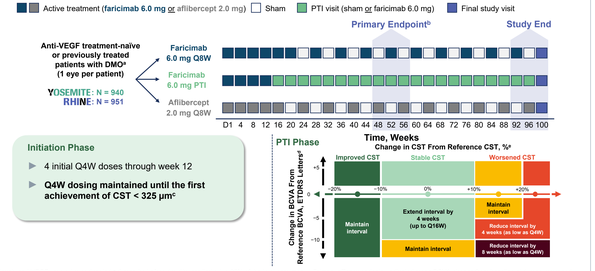
- YOSEMITE and RHINE enrolled adults with centre-involving DMO (central subfield thickness [CST] ≥ 325 µm) and best-corrected visual acuity (BCVA) 25–73 Early Treatment Diabetic Retinopathy Study letters (Snellen equivalent ~20/320–20/40)
- Patients were randomised 1:1:1 to faricimab every 8 weeks (Q8W),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

Conclusions

- Faricimab targets 2 distinct disease pathways to promote vascular stability, which may lead to a more durable therapy while maintaining long-term vision gains
- Comparable 1-year BCVA gains with faricimab up to Q16W versus aflibercept Q8W were maintained through year 2
- Nearly 80% of patients who achieved Q16W dosing at week 52 maintained Q16W dosing without an interval reduction through week 96
- Improved anatomic outcomes with faricimab up to Q16W versus aflibercept Q8W were maintained over 2 years:
  - Change in CST favoured faricimab[a]
  - More patients achieved absence of DMO[b]
  - More patients achieved absence of intraretinal fluid (IRF)[b]
- Faricimab was well tolerated, and no cases of retinal vasculitis or occlusive retinal vasculitis were reported
- The ongoing RHONE-X long-term extension study will generate 4-year data

[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. YOSEMITE/RHINE Study Design and PTI Regimen



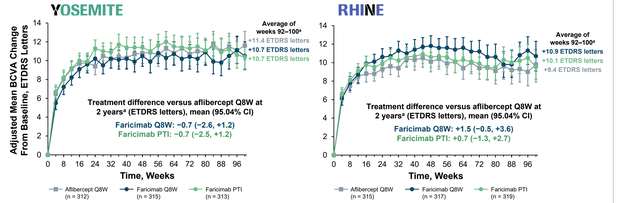
[a] Previously anti-VEGF–treated eyes (treated ≥ 3 months before day 1) were limited to 25% of the total enrolment. [b] Primary efficacy endpoint: adjusted mean BCVA change from baseline at 1 year, averaged over weeks 48, 52 and 56. [c] CST was measured as the distance from the internal limiting membrane to Bruch's membrane. [d] Reference BCVA was defined as the mean of the 3 best BCVA values achieved at any prior active dosing visit. [e] Reference CST was defined as the CST value when the original reference value (CST < 325 µm) was achieved. Reference CST was adjusted if CST decreased by > 10% from the previous reference CST for 2 consecutive active dosing visits and the values obtained later within 30 µm. The CST value obtained at the latter visit served as the new reference CST.
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; Q4W, every 4 weeks; Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF, vascular endothelial growth factor.

2. Baseline Patient Characteristics Were Well Balanced Across Treatment Arms and Trials

	YOSEMITE			RHINE		
Characteristic	Faricimab Q8W (n = 315)	Faricimab PTI (n = 313)	Aflibercept Q8W (n = 312)	Faricimab Q8W (n = 317)	Faricimab PTI (n = 319)	Aflibercept Q8W (n = 315)
Age, years, mean (SD)[a]	61.6 (9.5)	62.8 (10.0)	62.2 (9.6)	62.5 (10.1)	61.6 (10.1)	62.3 (10.1)
Female, n (%)	128 (40.6%)	116 (37.1%)	134 (42.9%)	123 (38.8%)	120 (37.6%)	129 (41.0%)
White, n (%)	241 (76.5%)	240 (76.7%)	253 (81.1%)	250 (78.9%)	249 (78.1%)	253 (80.3%)
BCVA, ETDRS letters, mean (SD)	62.0 (9.9)	61.9 (10.2)	62.2 (9.5)	61.9 (10.1)	62.5 (9.3)	62.1 (9.4)
CST, µm, mean (SD)[b]	492.3 (135.8)	485.8 (130.8)	484.5 (131.1)	466.2 (119.4)	471.3 (127.0)	477.3 (129.4)
Previously anti-VEGF treated, n (%)	77 (24.4%)	68 (21.7%)	70 (22.4%)	63 (19.9%)	64 (20.1%)	67 (21.3%)
Baseline DR severity status, n (%):						
DR questionable, mild to moderate NPDR (ETDRS-DRSS level 10/12, 14/20, 35, 43)	174 (55.2%)	187 (59.7%)	182 (58.3%)	183 (57.7%)	178 (55.8%)	180 (57.1%)
Moderately severe and severe NPDR (ETDRS-DRSS level 47, 53)	113 (35.9%)	99 (31.6%)	103 (33.0%)	109 (34.4%)	99 (31.0%)	105 (33.3%)
PDR (ETDRS-DRSS level 61, 65, 71/75)	22 (7.0%)	21 (6.7%)	18 (5.8%)	20 (6.3%)	37 (11.6%)	20 (6.3%)
Cannot grade (ETDRS-DRSS level 90)	4 (1.3%)	5 (1.6%)	7 (2.2%)	2 (0.6%)	5 (1.6%)	5 (1.6%)
Missing	2 (0.6%)	1 (0.3%)	2 (0.6%)	3 (0.9%)	0	5 (1.6%)

Results are presented for the intent-to-treat population.
[a] Age at randomisation. [b] CST was measured as the distance from the internal limiting membrane to Bruch's membrane.
BCVA, best-corrected visual acuity; CST, central subfield thickness; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PTI, personalised treatment interval; Q8W, every 8 weeks; VEGF, vascular endothelial growth factor.

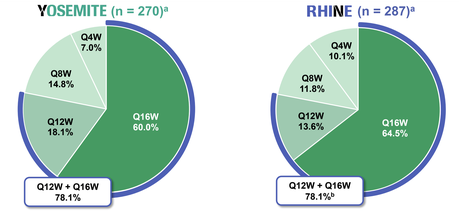
3. Vision Gains With Faricimab Q8W and PTI Up to Q16W Were Non-inferior to Aflibercept Q8W at 1 Year and Maintained Through Year 2



Comparable proportions of patients gained (~one-third) and avoided loss (≥ 97%) of ≥ 15 ETDRS letters with faricimab Q8W and PTI up to Q16W vs aflibercept Q8W at 2 years

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.
[a] Adjusted mean BCVA change from baseline at 2 years, averaged over weeks 92, 96 and 100.
BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PTI, personalised treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks.

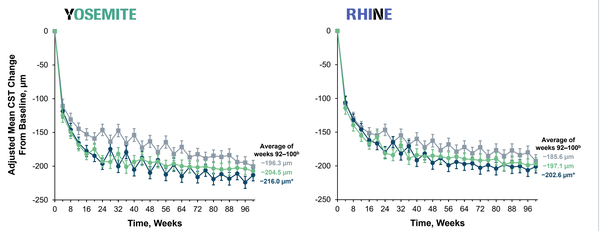
4. More Than 60% of Patients in the Faricimab PTI Arms Achieved Q16W Dosing at Week 96



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

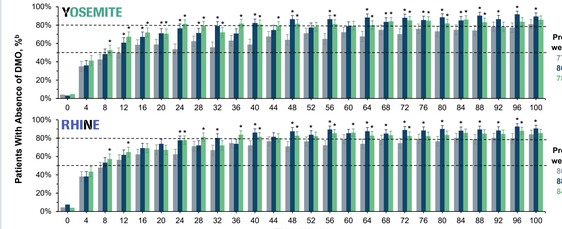
Median number of injections in year 2 (weeks 60–96; YOSEMITE and RHINE pooled): aflibercept Q8W, 5 injections; faricimab Q8W, 5 injections; faricimab PTI, 3 injections. Results are presented for the pooled YOSEMITE/RHINE safety-evaluable population (faricimab Q8W, n = 630; faricimab PTI, n = 632; aflibercept Q8W, n = 625).
[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.

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



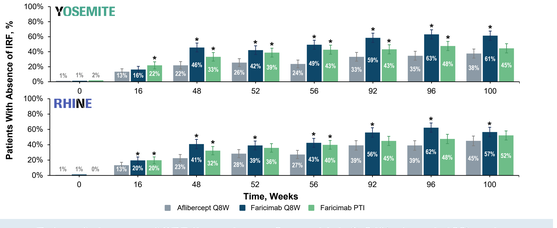
Test for superiority: [a] Nominal *P* < 0.05 versus aflibercept Q8W. *P* values are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. Clinical significance has not been established and conclusions regarding treatment effect cannot be drawn. [b] In general, patients receiving faricimab achieved greater reductions in CST over time compared with aflibercept (not a statistically significant difference). [c] 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.

6. 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: [a] 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. [b] In general, a numerically greater proportion of patients receiving faricimab achieved absence of DMO over time compared with aflibercept. [c] 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.

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



Rates of absence of SRF through year 2 were high (≥ 94% at week 100) and comparable with faricimab Q8W and PTI up to Q16W vs aflibercept Q8W

CMH test for superiority: [a] 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. [b] 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; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

8. Faricimab Was Well Tolerated Through Study End; Intraocular Inflammation and Retinal Occlusive Events Were Low and Comparable Across Treatment Arms

	Patients With ≥ 1 AE, n (%)[a]			Exposure-Adjusted Incidence Rate, Events Per 100 Patient-Years (95% CI)[a]		
AEs Through Study End, YOSEMITE/RHINE Pooled	Faricimab Q8W (n = 630)	Faricimab PTI (n = 632)	Aflibercept Q8W (n = 625)	Faricimab Q8W (n = 630)	Faricimab PTI (n = 632)	Aflibercept Q8W (n = 625)
Total patient-years at risk[b]	–	–	–	1138.9	1167.2	1138.2
Ocular AEs[c]	313 (49.7%)	311 (49.2%)	284 (45.4%)	58.65 (54.29, 63.27)	55.13 (50.94, 59.58)	43.58 (39.83, 47.59)
Serious ocular AEs[c]	26 (4.1%)	34 (5.4%)	20 (3.2%)	2.99 (2.07, 4.17)	3.72 (2.69, 5.01)	1.93 (1.21, 2.93)
Ocular AEs of special interest[c,d]	25 (4.0%)	33 (5.2%)	20 (3.2%)	2.81 (1.92, 3.97)	3.28 (2.32, 4.51)	1.93 (1.21, 2.93)
Non-ocular AEs	460 (73.0%)	469 (74.2%)	473 (75.7%)	180.53 (172.81, 188.50)	164.44 (157.15, 172.01)	165.70 (158.30, 173.35)
Serious non-ocular AEs	175 (27.8%)	161 (25.5%)	173 (27.7%)	30.56 (27.43, 33.94)	25.15 (22.34, 28.21)	28.38 (25.37, 31.65)
APTC events[e]	34 (5.4%)	30 (4.7%)	32 (5.1%)	2.99 (2.07, 4.17)	2.59 (1.75, 3.70)	2.81 (1.92, 3.97)
Death	16 (2.5%)	15 (2.4%)	14 (2.2%)	1.40	1.30	1.23
Non-fatal stroke	11 (1.7%)	10 (1.6%)	11 (1.8%)	0.97	0.86	0.97
Non-fatal myocardial infarction	7 (1.1%)	5 (0.8%)	7 (1.1%)	0.61	0.43	0.61
Retinal vein occlusion events	1 (0.2%)	4 (0.6%)	0	0.09	0.43	0
Retinal artery occlusion events	1 (0.2%)	2 (0.3%)	0	0.09	0.17	0.18
Retinal artery embolism events	0	0	1 (0.2%)	0	0	0.09
Intraocular inflammation events[f]	9 (1.4%)	11 (1.74%)	7 (1.12%)	0.88 (0.42, 1.61)	1.38 (0.79, 2.25)	0.88 (0.42, 1.62)
Uveitis	3 (0.5%)	4 (0.6%)	0	0.35	0.43	0
Iritis	1 (0.2%)	4 (0.6%)	2 (0.3%)	0.09	0.35	0.18
Iridocyclitis	2 (0.3%)	3 (0.5%)	1 (0.2%)	0.18	0.26	0.09
Vitritis	2 (0.3%)	0	2 (0.3%)	0.18	0	0.35
Post-procedural inflammation	1 (0.2%)	1 (0.2%)	2 (0.3%)	0.09	0.09	0.26
Chorioretinitis	0	1 (0.2%)	0	0	0.09	0
Keratic precipitates	0	1 (0.2%)	0	0	0.09	0
Keratouveitis	0	1 (0.2%)	0	0	0.09	0
Endophthalmitis events	2 (0.3%)	4 (0.6%)	1 (0.2%)	0.18	0.35	0.09
Retinal vasculitis events	0	0	0	0	0	0
Occlusive retinal vasculitis events	0	0	0	0	0	0

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] Total patient-years at risk is the sum of all time intervals (in years) for all patients, from the first dose of study treatment until the patient completes or withdraws from the study. [c] Ocular AEs in the study eye only are presented. [d] 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. [e] APTC events were adjudicated by an external independent committee; all other events were investigator reported. [f] Excluding endophthalmitis. [g] Events per 100 patient-years is calculated as the number of events/total patient-years at risk × 100; multiple occurrences of the same AE in an individual are counted as separate events. Includes AEs with onset from the first dose of study drug through study end; all events are investigator reported.
AE, adverse event; APTC, Anti-Platelet Trialists' Collaboration; BCVA, best-corrected visual acuity; PTI, personalised treatment interval; Q8W, every 8 weeks.

Presented at the Royal College of Ophthalmologists Annual Congress Glasgow, UK & Virtual I 23–26 May 2022

References

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2. Wykoff CC et al; YOSEMITE and RHINE Investigators. *Lancet*. 2022;399(10326):741-755.

Financial Disclosures

- FG: Consultant: Allergan, Apellis, Boehringer Ingelheim, Novartis, Roche; Grant Recipient: Novartis, Roche; Speaker: Allergan, Heidelberg, Novartis, Roche
- ZH, SM, YT, HL: Employee: Genentech, Inc.
- DS: Employee: Roche Products 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
- Funding was provided by F. Hoffmann-La Roche Ltd. for the study and third-party writing assistance, which was provided by Nicole Tom of Envision Pharma Group