Efficacy, Safety and Durability of Faricimab in Diabetic Macular Oedema: 1-Year Phase 3 YOSEMITE and RHINE Trials

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Key Clinical Question

What is the efficacy, safety and durability 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

- Upregulation of both Ang-2 and VEGF-A are key drivers of vascular destabilisation in DMO and other retinal vascular diseases[1-3]
- Dual inhibition of Ang-2 and VEGF-A with faricimab, the first bispecific antibody designed for intraocular use, may promote vascular stability and improve outcomes beyond anti-VEGF monotherapy for DMO[4,5]
- YOSEMITE (NCT03622580) and RHINE (NCT03622593) are randomised, double-masked, active comparator–controlled, phase 3 trials of faricimab in patients with DMO

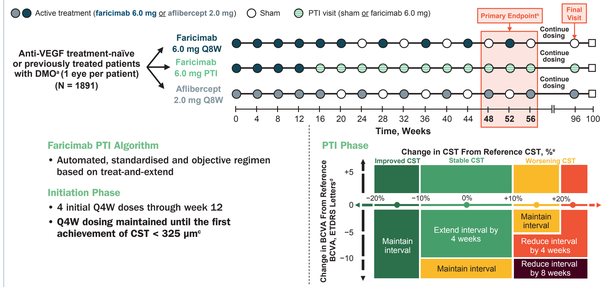
Methods

- YOSEMITE and RHINE enrolled 1891 patients across 353 study sites worldwide, including 19 UK sites
- 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 (≈20/320–20/40 Snellen equivalent) were eligible to participate
- Patients were randomised 1:1:1 to faricimab every 8 weeks (Q8W), faricimab per personalised treatment interval (PTI) or aflibercept Q8W
- From week 12, dosing intervals in the faricimab PTI arm were adjusted (from every 4 weeks [Q4W] up to every 16 weeks [Q16W]) based on CST and BCVA change at active dosing visits
- The primary endpoint was mean change in BCVA 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 Q8W or per PTI offered non-inferior vision gains versus aflibercept Q8W, while demonstrating improvements in anatomic outcomes and the potential for extended (up to Q16W) dosing at 1 year
- Data from the faricimab PTI arms showed the value of the PTI algorithm, a protocol-driven regimen based on treat-and-extend, to reduce treatment burden while optimising patient outcomes
- Faricimab was well tolerated: intraocular inflammation event rates for faricimab were low and no cases of vasculitis or occlusive retinitis were reported
- Year 2 data from YOSEMITE and RHINE will inform the long-term efficacy, safety and durability of faricimab in patients with DMO

1. YOSEMITE/RHINE Study Design and PTI Algorithm



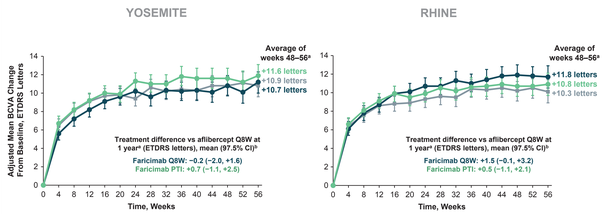
* Previously anti-VEGF–treated eyes (treated ≤ 3 months before day 1) were limited to 10–25% of the total enrolment. † Primary efficacy endpoint: BCVA change from baseline at 1 year, averaged over weeks 48, 52 and 56. ‡ CST was measured as the distance from the internal limiting membrane to Bruch's membrane. § Reference BCVA was defined as the mean of the 3 best BCVA values achieved at any prior active dosing visit. ¶ 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 were 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; DMO, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; PTI, personalised treatment interval; Q4W every 4 weeks; Q8W, every 8 weeks; VEGF, vascular endothelial growth factor.

2. Baseline Patient Characteristics Were Well Balanced Across Treatment Arms

	YOSEMITE			RHINE		
	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)	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%)
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. 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.

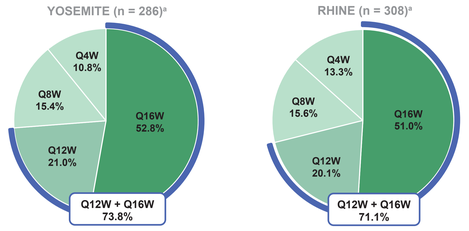
3. YOSEMITE and RHINE Met Their Primary Endpoint: 1-Year Vision Gains With Faricimab Were Non-inferior to Aflibercept



At 1 year, approximately one-third of patients across treatment arms and trials achieved a BCVA gain of ≥ 15 ETDRS letters, while ≥ 98% avoided a BCVA loss of ≥ 15 ETDRS letters

Results are based on a mixed model for repeated measures analysis; error bars show 95.04% CIs. * Primary efficacy endpoint: BCVA change from baseline at 1 year, averaged over weeks 48, 52 and 56. † 97.5% CI is a rounding of 97.52% (used to adjust for interim safety assessments conducted). BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PTI, personalised treatment interval; Q8W, every 8 weeks.

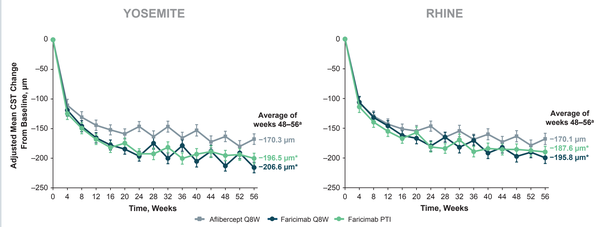
4. Strong Durability With Faricimab: > 50% of Patients in the Faricimab PTI Arm Achieved Q16W Dosing at Week 52, While > 70% Achieved ≥ Q12W Dosing



67.8% and 64.3% of the faricimab PTI arms in YOSEMITE and RHINE, respectively, achieved and maintained ≥ Q12W dosing without an interval reduction below Q12W through week 52

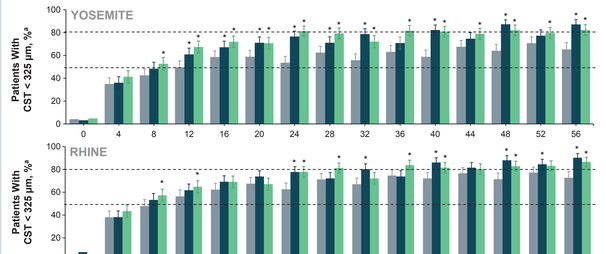
Median number of injections up to week 56 (YOSEMITE and RHINE pooled): aflibercept Q8W, 10 injections; faricimab Q8W, 10 injections; faricimab PTI, 8 injections.
* Number of patients in the faricimab PTI arm with evaluable data at week 52. Treatment interval at a given visit is defined as the treatment interval decision made at that visit. Percentages are based on the number of patients who have not discontinued the study at the week 52 visit. PTI, personalised treatment interval; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks.

5. Change in CST Over 1 Year Consistently Favoured Faricimab Over Aflibercept



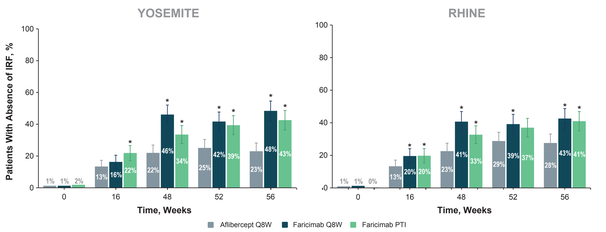
Test for superiority: * nominal $P < 0.05$ versus aflibercept Q8W for change from baseline over 1 year. Results are based on a mixed model for repeated measures analysis; error bars show 95.04% CIs. † Adjusted mean CST change from baseline at 1 year, averaged over weeks 48, 52 and 56. CST, central subfield thickness; PTI, personalised treatment interval; Q8W, every 8 weeks.

6. More Patients Treated With Faricimab Achieved Absence of DMO Compared With Aflibercept Through Week 56



CMH test for superiority: * nominal $P < 0.05$ versus aflibercept Q8W; nominal $P > 0.05$ where no star is shown. † Absence of DMO was defined as CST < 325 µm, measured as the distance from the internal limiting membrane to Bruch's membrane. 0% of patients had absence of DMO at screening, which was ≤ 28 days before day 1. Baseline values are not weighted. Proportion of patients in each treatment group from week 4 onward was estimated using the CMH method, stratified by baseline characteristics: BCVA score (< 64 letters vs ≥ 64 letters), prior intravitreal anti-VEGF therapy (yes vs no) and region (United States and Canada vs rest of the world). Weighted proportion for the aflibercept Q8W arm presented for the faricimab Q8W versus aflibercept Q8W comparison. Error bars show 95.04% CIs. 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; VEGF, vascular endothelial growth factor.

7. More Patients Treated With Faricimab Achieved Absence of IRF Compared With Aflibercept Through Week 56



Rates of absence of SRF over 1 year were high (≥ 96% at week 56) and comparable between faricimab and aflibercept treatment arms

CMH test for superiority: * nominal $P < 0.05$ versus aflibercept Q8W; nominal $P > 0.05$ where no star is shown. Baseline values are not weighted. Proportion of patients in each treatment group from week 4 onwards was estimated using the CMH method, stratified by baseline characteristics: BCVA score (< 64 letters vs ≥ 64 letters), prior intravitreal anti-VEGF therapy (yes vs no) and region (United States and Canada vs rest of the world). Weighted proportion for the aflibercept Q8W arm presented for the faricimab Q8W versus aflibercept Q8W comparison. Error bars show 95.04% CIs. BCVA, best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel; IRF, intraretinal fluid; PTI, personalised treatment interval; Q8W, every 8 weeks; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

8. Rates of Reported Ocular and Non-ocular AEs Through Week 56 Were Low

	YOSEMITE			RHINE		
Selected AEs Through Week 56	Faricimab Q8W (n = 313)	Faricimab PTI (n = 313)	Aflibercept Q8W (n = 311)	Faricimab Q8W (n = 317)	Faricimab PTI (n = 319)	Aflibercept Q8W (n = 314)
Total number of AEs[a]	1062	1016	938	1107	875	914
Total number of SAEs[a]	171	114	96	101	79	95
Total number of deaths, n (%)	8 (2.6%)	9 (2.9%)	4 (1.3%)	5 (1.6%)	0	5 (1.6%)
Patients with any ocular AE, n (%)[b]	98 (31.3%)	106 (33.9%)	102 (32.8%)	137 (43.2%)	119 (37.3%)	113 (36.0%)
Patients with any ocular SAE, n (%)[b]	6 (1.9%)	9 (2.9%)	2 (0.6%)	9 (2.8%)	10 (3.1%)	6 (1.9%)
Patients with any treatment-related ocular AE, n (%)[b]	11 (3.5%)	8 (2.6%)	5 (1.6%)	8 (2.5%)	8 (2.5%)	14 (4.5%)
Patients with any treatment-related ocular SAE, n (%)[b]	0	4 (1.3%)	0	0	1 (0.3%)	0
Patients with any AE of special interest, n (%)[c]	12 (3.8%)	15 (4.8%)	6 (1.9%)	15 (4.7%)	11 (3.4%)	7 (2.2%)
Patients with any IOI event, n (%)[d]	5 (1.6%)	7 (2.2%)	3 (1.0%)	3 (1.0%)	2 (0.6%)	1 (0.3%)
Uveitis	2 (0.6%)	3 (1.0%)	0	0	1 (0.3%)	0
Vitritis	2 (0.6%)	1 (0.3%)	2 (0.6%)	1 (0.3%)	0	0
Iritis	0	3 (1.0%)	1 (0.3%)	2 (0.6%)	0	1 (0.3%)
Iridocyclitis	2 (0.6%)	1 (0.3%)	0	0	1 (0.3%)	0
Anterior chamber inflammation	0	1 (0.3%)	0	0	0	0
Chorioretinitis	0	1 (0.3%)	0	0	0	0
Keratic precipitates	0	1 (0.3%)	0	0	0	0
Keratouveitis	0	1 (0.3%)	0	0	0	0
Patients with any endophthalmitis event, n (%)	0	2 (0.6%)	0	2 (0.6%)	0	1 (0.3%)
Patients with any APTC event, n (%)[e]	9 (2.9%)	10 (3.2%)	9 (2.9%)	4 (1.3%)	2 (0.6%)	5 (1.6%)

Results are presented for the safety-evaluable population. [a] Total number of AEs and SAEs include events in the study or fellow eye. [b] Ocular AEs and SAEs in the study eye only are presented in all safety outputs. [c] AEs of special interest are events associated with severe intraocular inflammation, events requiring surgical or medical intervention to prevent permanent loss of sight, or events that cause a visual acuity loss of ≥ 30 letters for > 1 hour. [d] Excluding endophthalmitis. [e] APTC events were adjudicated by an external independent committee; all other events are investigator reported. Percentages are based on n values in the column headings. Multiple occurrences of the same AE in an individual are counted only once, except for the "Total number of AEs" and "Total number of SAEs" rows, in which multiple occurrences of the same AE are counted separately. Includes AEs with onset up to day 405 (last day of week 56 analysis visit window). AE, adverse event; APTC, Anti-Platelet Trialists' Collaboration; IOI, intraocular inflammation; PTI, personalised treatment interval; Q8W, every 8 weeks; SAE, serious adverse event.

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- FG: Consultant: Novartis, Roche; Recipient: Alimera, Allergan
- JRW, ZH, HL: Employee: Genentech, Inc.
- DS, JI: Employee: Roche Products Ltd.
- KB: Employee: Roche Products (Ireland) Ltd.

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