Assessment of the Clinical Effects of Anti–Ang-2 With Faricimab Based on Key Outcomes From the YOSEMITE/RHINE Trials in Patients With DME

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Disclosures

Financial Disclosures

- JEK: Consultant, Advisory Board: Alimera, Allergan, Apellis, Astellas, Bausch + Lomb, Clearside Biomedical, Dutch Ophthalmic Research Center, Genentech, Inc./Roche, Notal Vision, Novartis, Outlook Therapeutics, Regeneron
- NM: Consultant: Genentech, Inc.; Funding: Genentech, Inc., Iveric Bio
- MA, JW, IS, FM: Employee: Genentech, Inc.
- AS: Employee: F. Hoffmann-La Roche Ltd.
- KG: Employee: Roche Products Ltd.

Study and Product Disclosures

- Faricimab is approved for the treatment of neovascular age-related macular degeneration, diabetic macular edema, and retinal vein occlusion 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
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What does Ang-2 do in pathology?[1–8]

Angiopoietin/Tie2 signalling and its role in retinal and choroidal vascular diseases: a review of preclinical data

Antonia M. Joussen, Federico Ricci, Liliana P. Paris, Claudia Korn, Carlos Quezada-Ruiz & Marco Zarbin

Eye **35**, 1305–1316 (2021) | Cite this article

Angiopoietin-2 expression in patients with an acute exacerbation of idiopathic interstitial pneumonias

Masaru Ando • Eishi Miyazaki • Tetsutaro Abe • ... Shin-ich Nureki • Toshihide Kumamoto • Junichi Kadota • Show all authors

Open Archive • Published: May 24, 2016 • DOI: https://doi.org/10.1016/j.rmed.2016.05.012 •

Increased but ineffectual angiogenic drive in nonhealing venous leg ulcers

Susan L Drinkwater, BSc • Kevin G Burnand, MS • Ren Ding, PhD • Alberto Smith, PhD

VASCULAR BIOLOGY | FEBRUARY 1, 2021

Dynamic angiopoietin-2 assessment predicts survival and chronic course in hospitalized patients with COVID-19

Clinical Trials & Observations

Erica Villa, Rosina Critelli, Simone Lasagni, Alessandra Melegari, Angela Curatolo, Ciro Celsa, Dante Romagnoli, Gabriele Melegari, Alessandra Pivetti, Lorenza Di Marco, Federico Casari, Dimitrry Arioli, Fabrizio Turrini, Valentina Zuccaro, Irene Cassanti, Mattia Riefolo, Elena de Santis, Veronica Bernabucci, Marcello Bianchini, Barbara Lei, Nicola De Maria, Lucia Carulli, Filippo Schepis, Chiara Cozzi, Silvio Malaguti, Mariagrazia Del Buono, Lucio Brugioni, Pietro Torricelli, Tiziano Tassi, Giovanni Pinelli, Elisabetta Bertolini, Nicola Bruno,

Impact of angiopoietin-1 and -2 on clinical course of idiopathic pulmonary fibrosis

Masahiro Uehara • Noriyuki Enomoto • Masashi Mikamo • ... Naoki Inui • Yutaro Nakamura • Takafumi Suda • Show all authors

Open Archive • Published: March 05, 2016 • DOI: https://doi.org/10.1016/j.rmed.2016.03.001 •

Angiopoietin-1, angiopoietin-2 and Tie-2 receptor expression in human dermal wound repair and scarring Get access

C.A. Staton, M. Valluru, L. Hoh, M.W.R. Reed, N.J. Brown

British Journal of Dermatology, Volume 163, Issue 5, 1 November 2010, Pages 920–927, https://doi.org/10.1111/j.1365-2133.2010.09940.x

Published: 01 November 2010

Angiogenic signaling pathways and anti-angiogenic therapy for cancer

Zhen-Ling Liu, Huan-Huan Chen, Li-Li Zheng, Li-Ping Sun & Lei Shi

Signal Transduction and Targeted Therapy **8**, Article number: 198 (2023) | Cite this article

Circulating angiopoietin-2 levels increase with progress of chronic kidney disease FREE

Sascha David, Philipp Kümpers, Alexander Lukasz, Danilo Fliser, Jens Martens-Lobenhoffer, Stefanie M. Bode-Böger, Volker Kliem, Hermann Haller, Jan T. Kielstein Author Notes

Nephrology Dialysis Transplantation, Volume 25, Issue 8, August 2010, Pages 2571–2579, https://doi.org/10.1093/ndt/gfq060

Ang-2 promotes vascular instability across many diseases[1–8]

The hallmark of science is reproducibility

Ang-2, angiopoietin-2; Tie2, tyrosine kinase with immunoglobulin-like domains 2.

1. Joussen AM et al. *Eye (Lond)*. 2021;35:1305-1316. 2. Drinkwater SL et al. *J Vasc Surg*. 2003;38:1106-1112. 3. Uehara M et al. *Respir Med*. 2016;114:18-26. 4. Liu ZL et al. *Signal Transduct Target Ther*. 2023;8:198.
5. Ando M et al. *Respir Med*. 2016;117:27-32. 6. Villa E et al. *Blood Adv*. 2021;5:662-673. 7. Staton CA et al. *Br J Dermatol*. 2010;163:920-927. 8. David S et al. *Nephrol Dial Transplant*. 2010;25:2571-2576.

Clinical Biomarkers for Dual Pathway Inhibition in DME

Evidence From Biology

Dual pathway inhibition with faricimab: Anti–Ang-2 + Anti–VEGF-A[1]

Elevated VEGF[2]

Elevated Ang-2[1,3,4]

Neovascularization[5,6]	Vascular leakage[7]	Inflammation[5,6,8]	Fibrosis[9–13]

Clinical Biomarkers

Neovascularization[5,6]	Vascular leakage[7]	Inflammation[5,6,8]	Fibrosis[9–13]
Greater[a] **reduction** of **fluid on OCT**[14] Greater[a] **resolution of IRF**[14]	Greater[a] **resolution** of **macular leakage**[17] Greater **reduction** of **HE**[18]	Greater[a] **reduction** of **HRF**[15]	Greater[a] **reduction** of **ERM** development[16]

Disease control with faricimab vs anti-VEGF monotherapy[14-18]

Extended durability beyond Q12W[16,19-23]

VEGF | VEGF and Ang-2 | Ang-2

[a] Based on secondary endpoints and post hoc exploratory analyses of IRF/SRF, macular leakage, HRF, and ERM in the phase 3 clinical trial program, with nominal *P* value statistical testing (not adjusted for multiple testing). No formal statistical conclusions can be drawn. Ang-2, angiopoietin-2; DME, diabetic macular edema; ERM, epiretinal membrane; HE, hard exudates; HRF, hyperreflective foci; IRF, intraretinal fluid; OCT, optical coherence tomography; Q12W, every 12 weeks; SRF, subretinal fluid; VEGF, vascular endothelial growth factor; VEGF-A, vascular endothelial growth factor-A.

1. Regula JT et al. *EMBO Mol Med*. 2016;8:1265-1288. 2. Aiello LP et al. *N Engl J Med*. 1994;331:1480-1487. 3. Tsai T et al. *PLoS One*. 2023;18:e0280488. 4. Ng D et al. *Sci Rep*. 2017;7:45081. 5. Kim S-Y et al. *Ann Eye Sci*. 2021;6:24. 6. Collazos-Aleman JD et al. *Diabetes Ther*. 2022;13:1811. 7. Rangasamy S et al. *Invest Ophth Vis Sci*. 2011;52-59. 8. Hirasawa M et al. *J Biol Chem*. 2016;291:7373-7385. 9. Larsen OH et al. *Ophth Ther*. 2023;12:2253-2264. 10. Canonica J et al. *Front Cell Neurosci*. 2023;17:1192464. 11. Klaassen I et al. *PLoS One*. 2017;12:e0187304. 12. Takagi H et al. *Invest Ophth Vis Sci*. 2003;44:393-402. 13. Umeda N et al. *Ophth Res*. 2003;35:217-223. 14. Pollreiz A et al. *Invest Ophthalmol Vis Sci*. 2023;64:2817. 15. Maunz A, et al. *Invest Ophthalmol Vis Sci*. 2023;64:PB0039. 16. Jaffe G et al. Presented at ASRS 2023, presentation available at medically.roche.com. 17. Goldberg RA et al. *Invest Ophthalmol Vis Sci*. 2023;64:2816. 18. Goldberg RA et al. Presented at ARVO 2024. 19. Chaudhary V et al. *Invest Ophthalmol Vis Sci*. 2023;64:5056. 20. Lim JI et al. *Invest Ophthalmol Vis Sci*. 2023;64:2185. 21. Freund KB et al. *Retina*. 2015;35:1489-1506. 22. Flaxel CJ et al. *Ophthalmology*. 2020;127:146-181. 23. Kertes PJ et al. *JAMA Ophthal*. 2020;138:244-250.

YOSEMITE and RHINE Trial Design

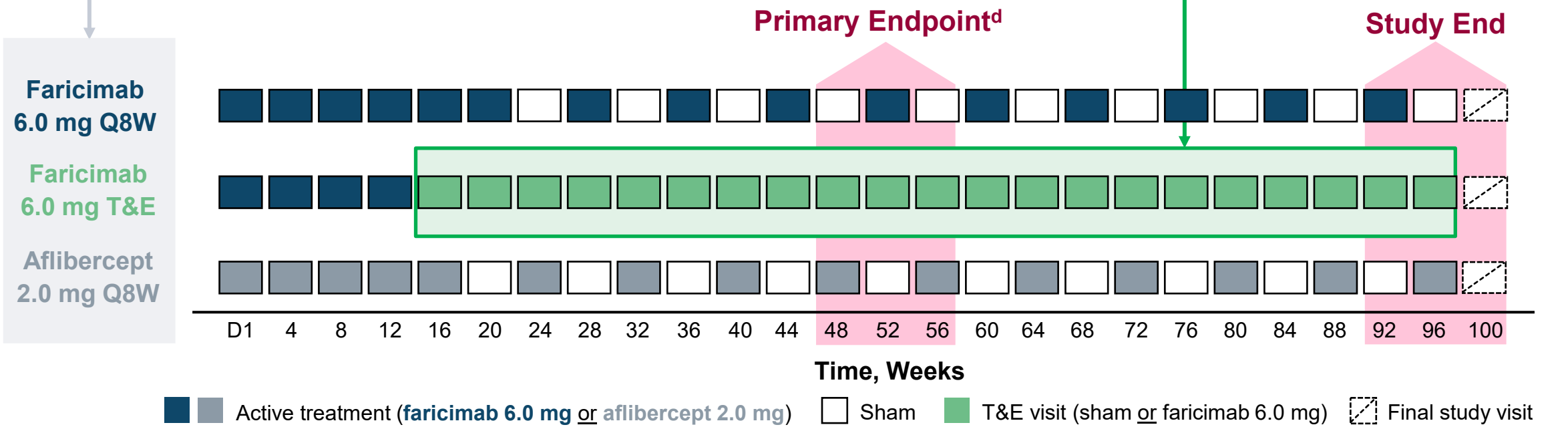
Faricimab DME Trials Use Disease Criteria Reflective of Clinical Practice

Phase 3, randomized, double-masked, active comparator–controlled trials

- **Treatment-naïve** or **previously treated patients**[a] (1 eye per patient)
- Center-involving DME (**CST ≥ 325 µm**)[b]
- **BCVA 25–73 ETDRS letters** (Snellen ~20/320–20/40)[c]

Personalized T&E–Based Dosing Regimen

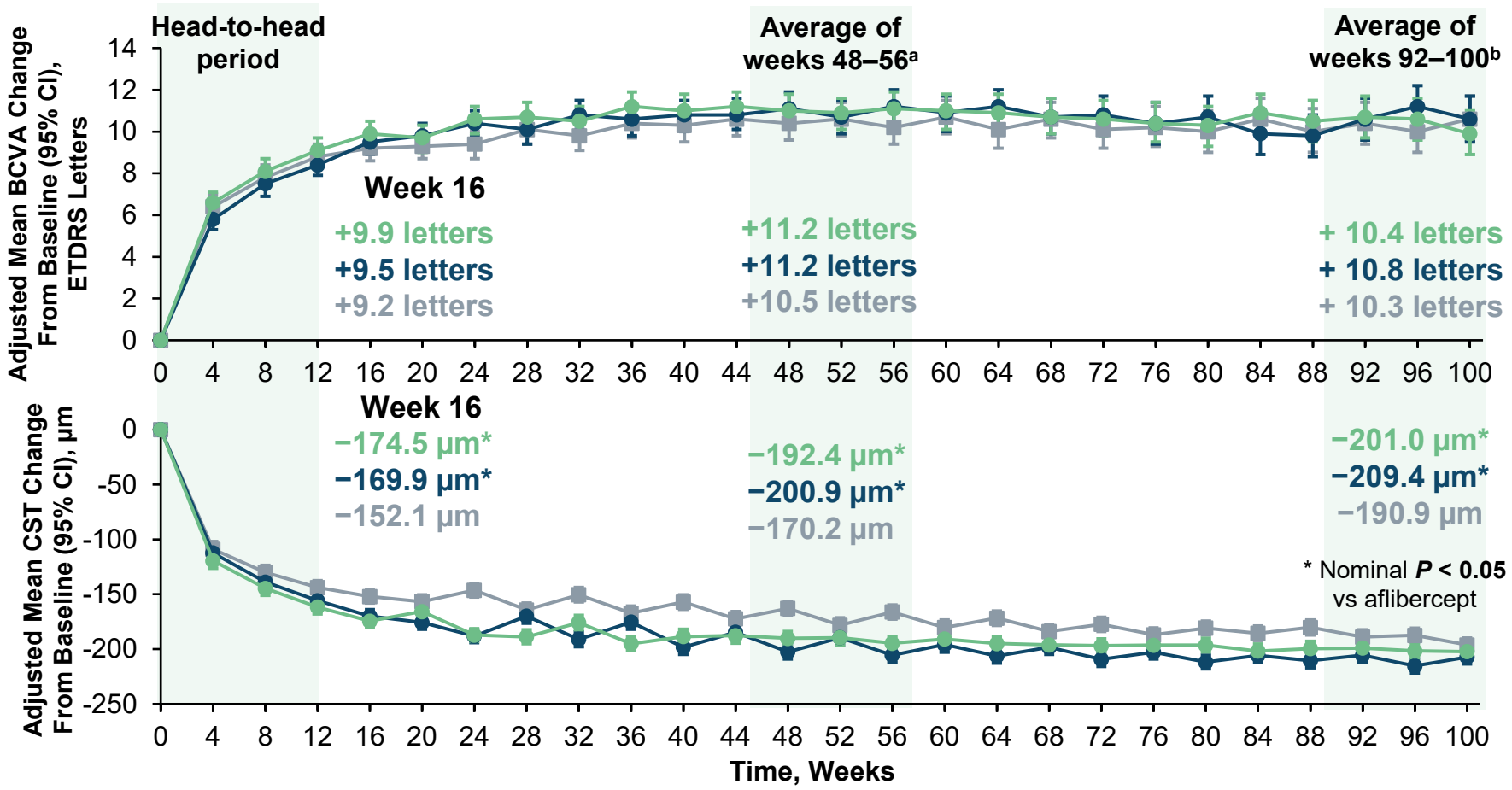
- **Stable CST + BCVA**: Dosing **extended** (by 4 weeks, max Q16W)
- **Worsening CST ± BCVA:** Dosing **reduced** (by 4 or 8 weeks, min Q4W)
- **Extension or reduction criteria not met:** Dosing **maintained**



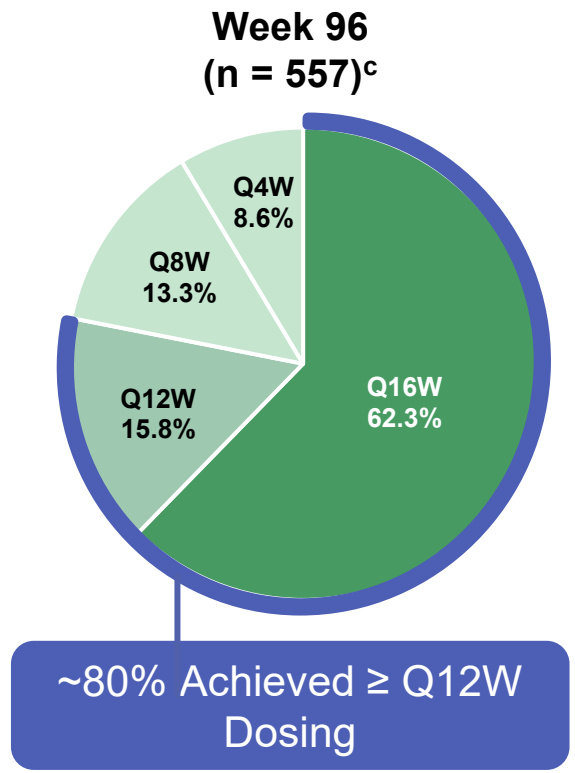
YOSEMITE (NCT03622580); RHINE (NCT03622593). [a] Previously anti-VEGF–treated eyes (treated ≥ 3 months before day 1) were limited to 25% of the total enrollment. [b] CST was measured as the distance from the ILM to Bruch's membrane. [c] BCVA was measured using the ETDRS VA chart at a starting distance 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; DME, diabetic macular edema; 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. Finn A. Presented at: 56th Retina Society Annual Scientific Meeting; October 11-14, 2023, New York, NY.

Robust Vision Gains and Greater CST Reductions With Faricimab at Year 1 and Maintained Through Year 2 With ≥ 60% of Faricimab T&E Arms on Q16W Dosing

YOSEMITE/RHINE Pooled



Faricimab T&E

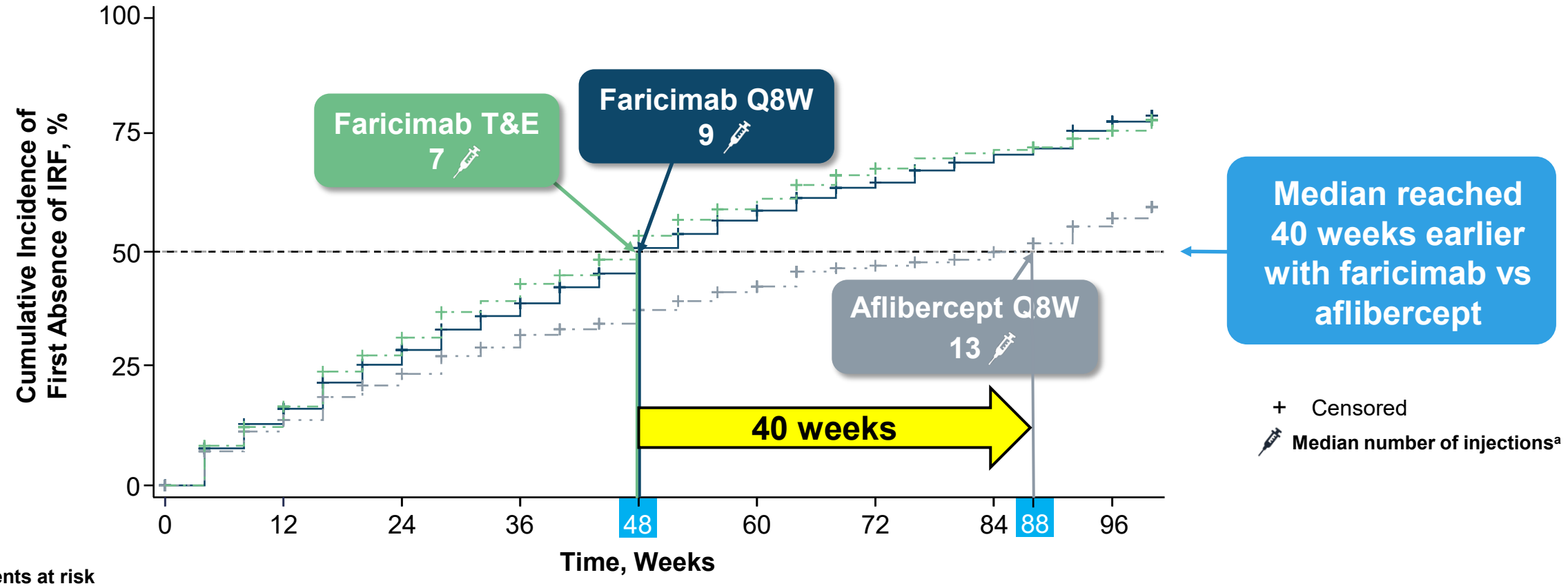


* *P* values are nominal and not adjusted for multiplicity (nominal *P* value < 0.05 vs aflibercept 2 mg Q8W); no formal statistical conclusion should be made based on the *P* values. [a] Adjusted mean change from baseline at year 1, averaged over weeks 48, 52, and 56. [b] Adjusted mean change from baseline at year 2, averaged over weeks 92, 96, and 100. Results are based on an MMRM analysis, adjusted for treatment group, visit, visit-by-treatment group interaction, baseline BCVA (continuous) or baseline CST (continuous) as applicable, baseline BCVA (< 64 vs ≥ 64 ETDRS letters), prior intravitreal anti-VEGF therapy (yes vs no), region (United States and Canada, Asia, and the rest of the world), and study (YOSEMITE vs RHINE). 95% CI error bars are shown. [c] 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. BCVA, best-corrected visual acuity; CI, confidence interval; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; MMRM, mixed model for repeated measures; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

Median Time to First Absence of IRF: Achieved With Faricimab More Than 9 Months Faster and With Fewer Injections vs Aflibercept

Patients with IRF at baseline

YOSEMITE/RHINE Pooled: Post Hoc Analysis



Patients at risk

Aflibercept Q8W	611	534	470	411	375	331	291	277	227
Faricimab Q8W	621	532	445	373	310	241	196	163	122
Faricimab T&E	618	533	431	357	300	233	187	160	136

HR (95% CI)[b]: 1.62 (1.40, 1.88), *P* < 0.0001

HR (95% CI)[b]: 1.65 (1.42, 1.91), *P* < 0.0001

Summaries of time to first absence of IRF are Kaplan–Meier estimates. Patients with absence of IRF at baseline and patients with no data at baseline were excluded from the analysis. *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 (United States and Canada, Asia, and the rest of the world) and study (YOSEMITE vs RHINE). [a] The number of injections includes any active drug administered (faricimab or aflibercept), including medication errors.
[b] Results from stratified analyses are presented for HR and log-rank test vs aflibercept. An HR > 1 favors faricimab over aflibercept. BCVA, best-corrected visual acuity; CI, confidence interval; HR, hazard ratio; IRF, intraretinal fluid; Q8W, every 8 weeks; T&E, treat-and-extend; VEGF, vascular endothelial growth factor. Finn A. Presented at: 56th Retina Society Annual Scientific Meeting; October 11-14, 2023, New York, NY.

Reduced Macular Leakage Area With Faricimab vs Aflibercept in the Head-to-Head Dosing Phase

YOSEMITE/RHINE Pooled: Post Hoc Analysis

Macular Leakage Area Assessments in YOSEMITE/RHINE

- **Masked** readers from the Wisconsin Reading Center
- Area within **ETDRS grid** on **FA images**

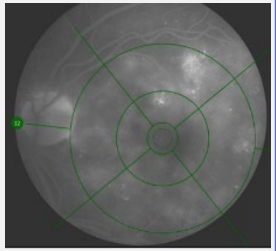
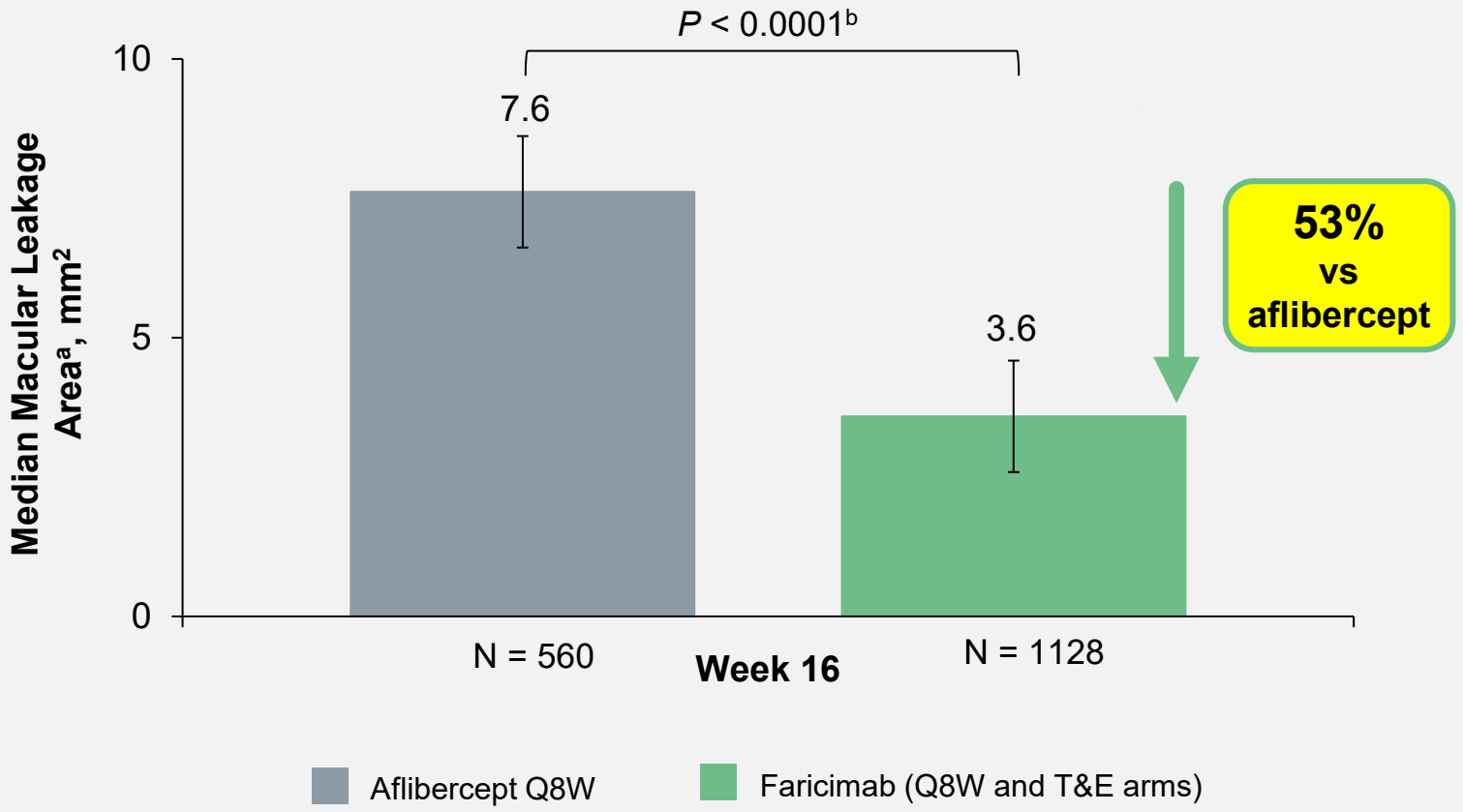


Image courtesy of Wisconsin Reading Center

Median Baseline Macular Leakage Area[a]

Aflibercept Q8W	Faricimab (Q8W and T&E arms)
(n = 593)	(n = 1216)
25.6 mm^2	24.6 mm^2

$P = 0.3331$[b]



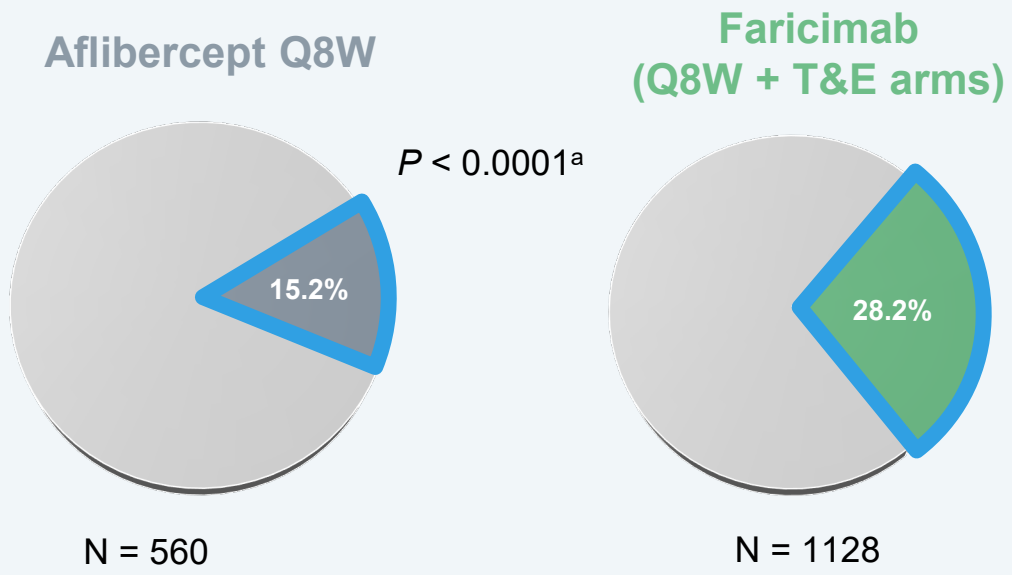
Population: patients with available macular leakage data at baseline or week 16 according to the time point of the analysis. [a] Macular leakage area determined by fluorescein angiography.
[b] The *P* value from the median 2-sample test is nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. 95% CIs are shown.
CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; Q8W, every 8 weeks; T&E, treat-and-extend.

More Patients Treated With Faricimab vs Aflibercept Achieved Resolution of Macular Leakage After Head-to-Head Dosing Phase

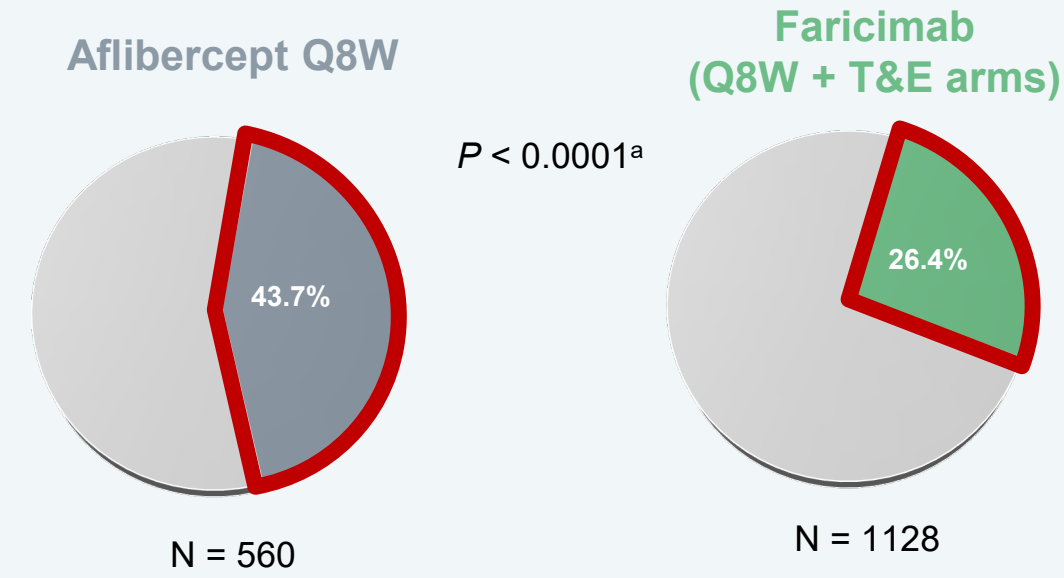
ITT population

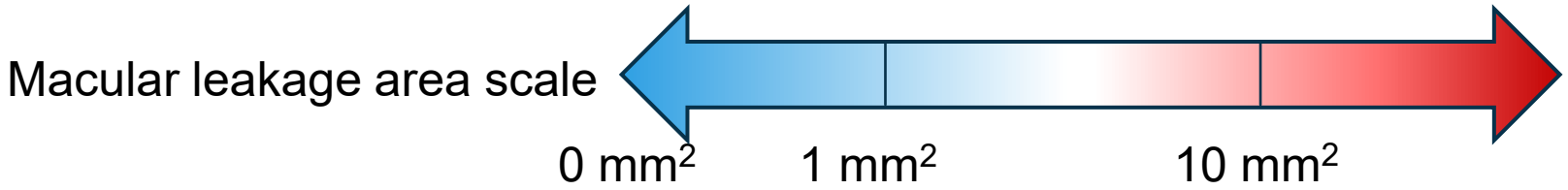
YOSEMITE/RHINE Pooled: Post Hoc Analysis

Proportion of Patients With RESOLUTION of Macular Leakage at Week 16



Proportion of Patients With HIGH Macular Leakage at Week 16





Proportion of patients with macular leakage 0–1 mm^2 at baseline: aflibercept Q8W, 0.5%; faricimab Q8W and T&E arms, 1.2%. Proportion of patients with macular leakage ≥ 10 mm^2 at baseline: aflibercept Q8W, 80.4%; faricimab Q8W and T&E arms, 78.3%. The proportion estimates were weighted using CMH method stratified by baseline BCVA score (< 64 vs ≥ 64 letters), prior intravitreal anti-VEGF therapy (yes vs no), region (US and Canada vs the rest of the world), and study (GR40349 vs GR40398).

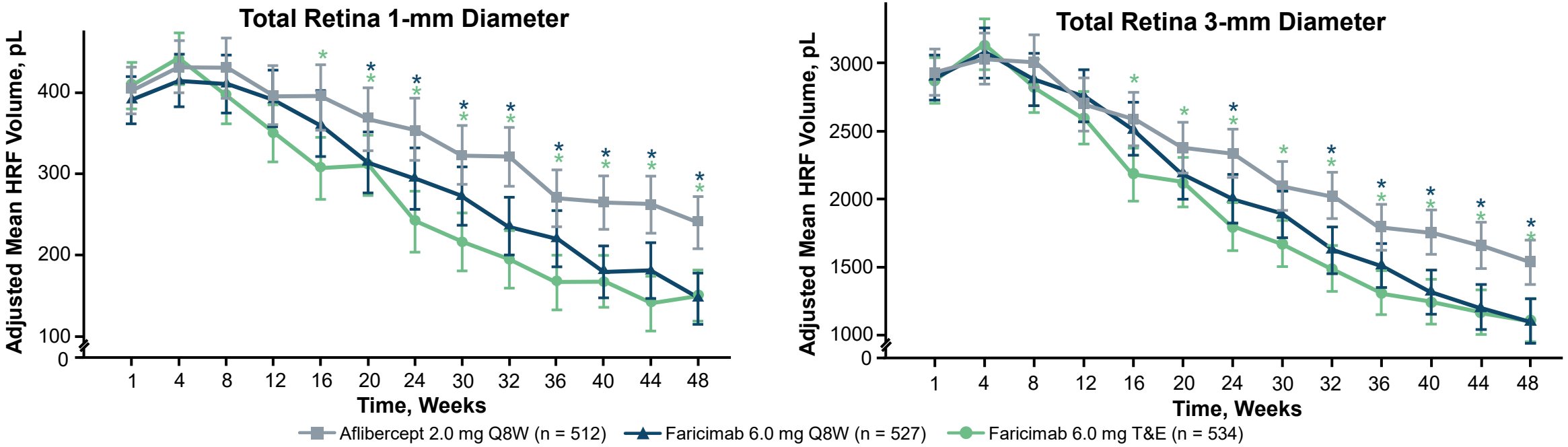
[a] The *P* value (< 0.0001) from CMH test is nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. N values: faricimab, N = 1216 at day 1, N = 1128 at week 16; aflibercept, N = 593 at day 1, N = 560 at week 16. BCVA, best-corrected visual acuity; CMH, Cochran-Mantel-Haenszel; ITT, intent-to-treat; Q8W, every 8 weeks; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

Greater Reductions in HRF Volumes in the Total Retina[a] With Faricimab vs Aflibercept

Volumetric Analysis of HRF in YOSEMITE/RHINE

- Objects ≤ 50 µm in diameter automatically segmented on SD-OCT
- HRF assessed within the 1- and 3-mm–diameter ETDRS rings

YOSEMITE/RHINE Pooled: Post Hoc Analysis



* *P* values are nominal and not adjusted for multiplicity (nominal *P* value < 0.05 vs aflibercept 2 mg Q8W); no formal statistical conclusion should be made based on the *P* values. [a] ILM to RPE. 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 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; ETDRS, Early Treatment Diabetic Retinopathy Study; HRF, hyperreflective foci; ILM, internal limiting membrane; MMRM, mixed model for repeated measures; Q8W, every 8 weeks; RPE, retinal pigment epithelium;SD-OCT, spectral-domain optical coherence tomography; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

Through Week 100 Faricimab Q8W Led to a 52% Reduction in the Risk of ERM Formation vs Aflibercept Q8W

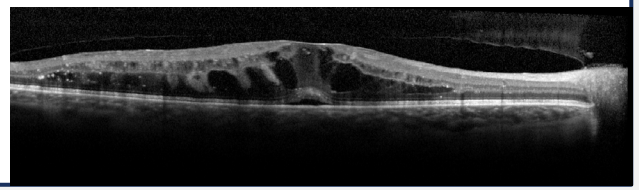
YOSEMITE/RHINE Pooled:
Post hoc analysis

Analysis of ERM Formation in YOSEMITE/RHINE

- ERM defined as presence of a membrane on the ILM, causing significant distortion of macular architecture in the central 1-mm subfield

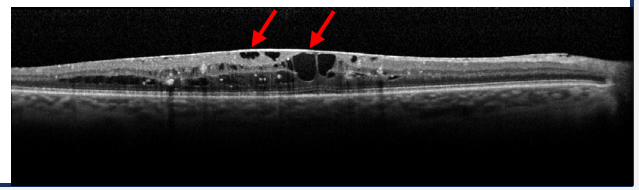
OCT at baseline with no ERM (central 1 mm)

Week 0

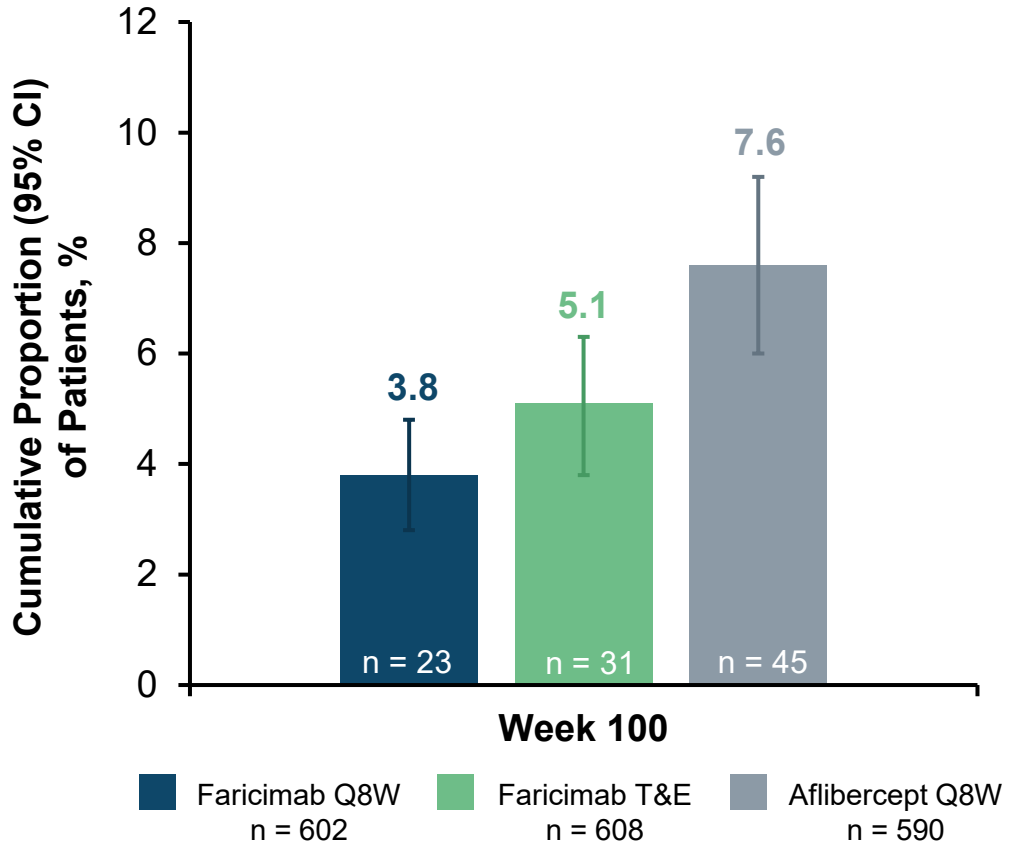


OCT with presence of ERM (central 1 mm)

Week 48



Proportion of Patients Developing ERM During the Study



At Week 100
Faricimab T&E
vs Aflibercept Q8W

Odds ratio[a]: **0.65**
95% CI: **0.41, 1.05**
P value: **0.0783**

At Week 100
Faricimab Q8W
vs Aflibercept Q8W

Odds ratio[a]: **0.48**
95% CI: **0.29, 0.81**
P value: **0.0055**

Patients with no ERM at baseline. Missing data were not imputed, and patients with no postbaseline ERM results were excluded from the analysis. ERMs defined as presence of significant distortion of macular architecture in the central subfield. [a] The adjusted odds ratio and 95% CI were produced using a multivariate logistic regression models including treatment group, baseline BCVA score (< 64 vs ≥ 64 letters), prior IVT anti-VEGF therapy (yes vs no), region (US and Canada and the rest of the world), and study (YOSEMITE vs RHINE) as covariates using cumulative data through week 100. Risk refers to the odds from logistic regression. The *P* values are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. BCVA, best-corrected visual acuity; CI, confidence interval; ERM, epiretinal membrane; ILM, internal limiting membrane; ITT, intent-to-treat; IVT, intravitreal; OCT, optical coherence tomography; Q8W, every 8 weeks; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

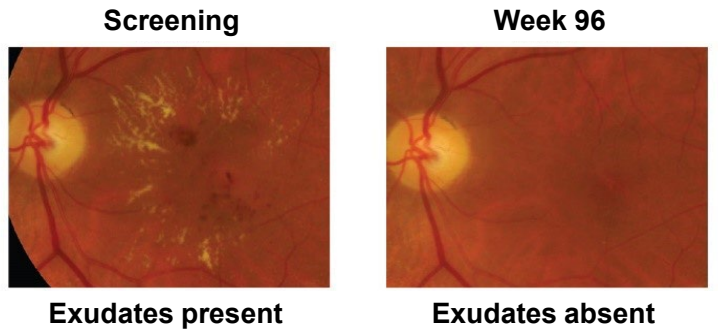
Greater Reduction in Patients With Hard Exudates for Faricimab vs Aflibercept at Week 52 and 96

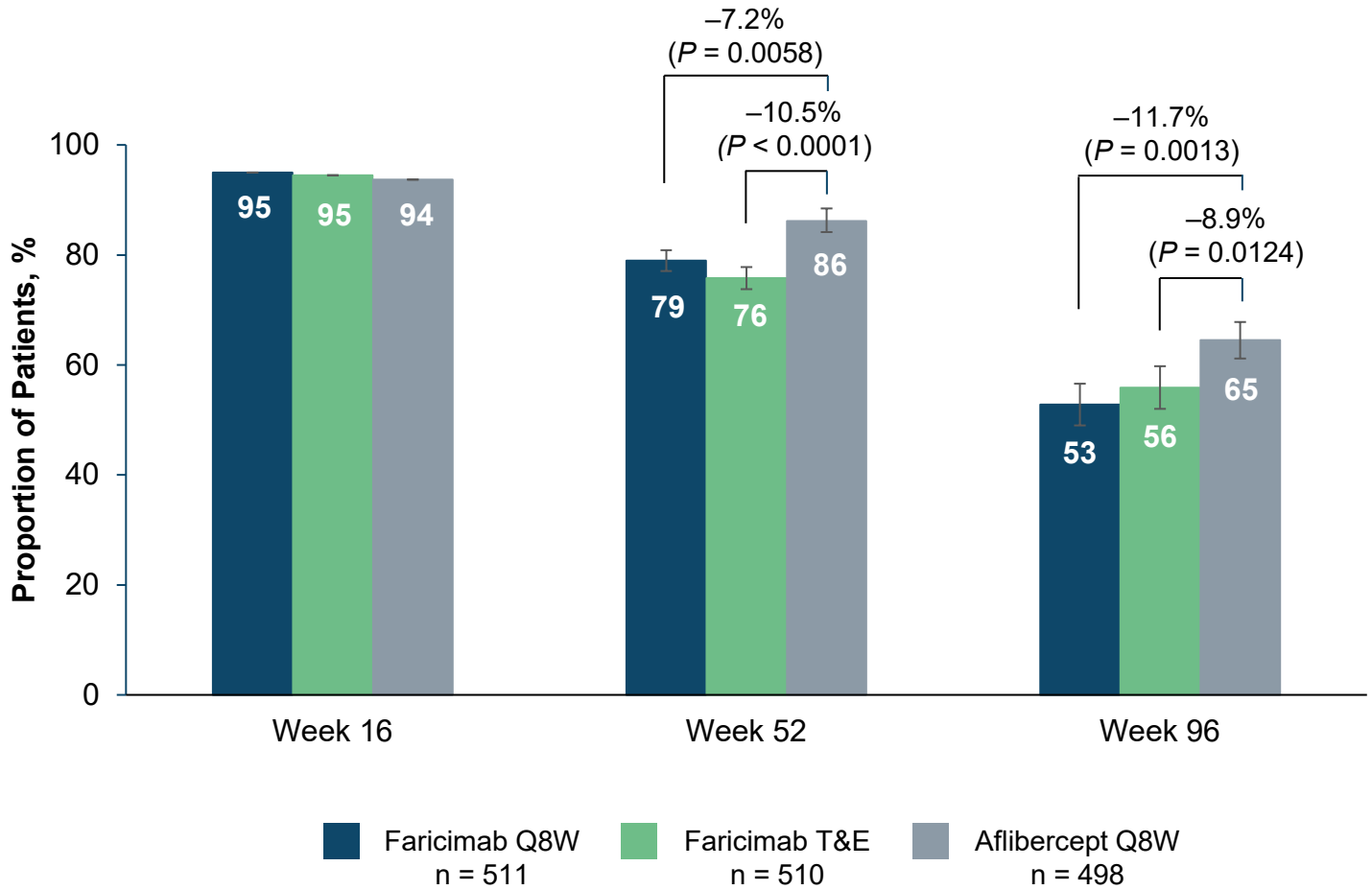
Patients with HE at baseline

YOSEMITE/RHINE Pooled: Post Hoc Analysis

Hard Exudate Assessment in YOSEMITE/RHINE

- Masked readers from the Wisconsin Reading Center
- Area within the **ETDRS grid** on **CFP images**





Analysis based on patients with HE at baseline. HE was evaluated at a central reading center using CFP. The weighted estimate is based on CMH test stratified by baseline BCVA score (< 64 vs ≥ 64 letters), prior IVT anti-VEGF therapy (yes vs no), region (US and Canada vs the rest of the world), and study (YOSEMITE vs RHINE). Missing data were not imputed. 95% CIs are reported. Estimates below 0% or above 100% are imputed as 0% or 100%, respectively. Baseline is defined as the last available measurement obtained on or before randomization. Presence of HEs is defined as HEs within the ETDRS grid equal to definite or questionable. Absence of HEs is defined as HEs within the ETDRS Grid equal to absent. The *P* values are nominal and not adjusted for multiplicity; no formal statistical conclusion should be made based on the *P* values. BCVA, best-corrected visual acuity; CFP, color fundus photography; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ETDRS, Early Treatment Diabetic Retinopathy study; HE, hard exudates; IVT, intravitreal; Q8W, every 8 weeks; T&E, treat-and-extend; VEGF, vascular endothelial growth factor.

Faricimab Demonstrated Greater Improvement in Clinical Biomarkers in DME Compared With Aflibercept 2 mg

Vascular Leakage

- **Greater** and **faster drying**
- **Greater reduction of macular leakage area**
- **Greater reduction in eyes with hard exudates**

Inflammation & Fibrosis

- **Greater reduction in retinal HRF volume**
- **Faricimab** Q8W **reduced risk of ERM** formation vs aflibercept

Early treatment with dual Ang-2/VEGF-A inhibition with faricimab may improve outcomes beyond anti-VEGF treatment alone

Ang-2, angiopoietin-2; DME, diabetic macular edema; ERM, epiretinal membrane; HRF, hyperreflective foci; Q8W, every 8 weeks; VEGF, vascular endothelial growth factor; VEGF-A, vascular endothelial growth factor-A.