Efficacy and Safety of Faricimab in ALTIMETER: A Trial Exploring Biomarkers of Ang-2 Inhibition in Patients With DMO

Deepali Varma, MBBS, MD, FRCOphth[1]; Florie Mar, PhD[2]; Manuel Amador, MD[2]; Carl Glittenberg, MD[3]; Kara Gibson, PhD[4]; Alex Kotak, MBChB[4]; and Audrey Souverain, PharmD, MSc[3]

[1] South Tyneside and Sunderland NHS Foundation Trust, Sunderland, UK; [2] Genentech, Inc., South San Francisco, CA, USA; [3] F. Hoffmann-La Roche Ltd., Basel, Switzerland; [4] Roche Products Ltd., Welwyn Garden City, UK

Key Clinical Question

What are the key clinical outcomes, imaging assessments and aqueous humour (AH) biomarker patterns in patients with diabetic macular oedema (DMO) treated with faricimab in the ALTIMETER study?

Conclusions

In ALTIMETER, faricimab led to meaningful improvements in vision and anatomy, consistent with the YOSEMITE/RHINE trials in patients with DMO

High macular leakage was associated with angiopoietin-2 (Ang-2), Ang-2–related proteins and immune regulators at baseline, which were reduced following treatment with faricimab

Safety was consistent with the known safety profile of faricimab

Additional exploratory analyses are planned to further understand the associations between imaging and AH biomarkers of vascular stability achieved with dual Ang-2/vascular endothelial growth factor (VEGF)-A inhibition

Financial Disclosures

- DV: Speaker Fees: AbbVie, Bayer, Novartis, Roche; Educational Grants: Alimera, Bayer, Novartis, Roche; Advisory Boards: Bayer, Novartis, Roche, Teva; Principal Investigator in Clinical Trials Sponsored by: Bayer, Novartis, Roche
- FM, MA: Employee: Genentech, Inc.
- CG, AS: Employee: F. Hoffmann-La Roche Ltd.
- KG, AK: Employee: Roche Products Ltd.

Study and Product Disclosures

- In the UK, faricimab is approved for the treatment of neovascular age-related macular degeneration and diabetic macular oedema. Faricimab is not currently approved for use outside these indications in the UK
- 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 Ellen M. Ross, PhD, CMPP, of Envision Pharma Group
- Roche conducted a factual accuracy check on the final article but any decision to incorporate comments was made solely at the discretion of the authors

Presented at the Royal College of Ophthalmologists Annual Congress Belfast, UK | 20–23 May 2024

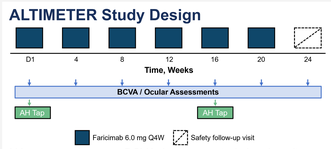
Introduction

- Faricimab is the first bispecific antibody for intraocular use that independently binds and neutralises both Ang-2 and VEGF-A[1]
- Dual pathway inhibition with faricimab in the phase 3 YOSEMITE/RHINE trials (NCT03622580/NCT03622593) has demonstrated improved vascular stability characterised by greater improvements in clinical biomarkers, ie, retinal fluid, macular leakage, hyperreflective foci (HRF) and extracellular matrix (ERM) formation vs aflibercept. In these studies, faricimab reduced macular leakage area by 53% more vs aflibercept[2]
- ALTIMETER (NCT04597918) was designed to explore associations between clinical endpoints, multimodal imaging assessments and AH biomarker patterns in patients with DMO treated with faricimab. Here, we focus on the effect of faricimab on anatomic outcomes including how macular leakage affects AH biomarkers

Methods

- In the 6-month, open-label, single-arm phase 2b exploratory ALTIMETER study, treatment-naïve patients with DMO received 6 doses of faricimab 6 mg every 4 weeks with a final visit at week 24.
- Key inclusion criteria are as follows: Age ≥ 18 years, intravitreal treatment-naïve DMO, best-corrected visual acuity (BCVA) 75–20 letters (measured using the Early Treatment Diabetic Retinopathy Study [ETDRS] chart at a starting distance of 4 m) and central subfield thickness (CST) ≥ 325 µm (measured using Spectralis spectral-domain optical coherence tomography [SD-OCT] at screening)
- Prospectively designed exploratory endpoints included change from baseline over time in BCVA, CST, intraretinal fluid (IRF), macular leakage on fluorescein angiography (FA), multimodal imaging and AH biomarker patterns
- Safety monitoring and assessments were performed as outlined below
- Ocular assessments included Ultra-WideField (UWF) colour fundus photography (CFP), CFP (7-modified field fundus imaging), SD-OCT and (if capable) source-swept optical coherence tomography (SS-OCT), SD-OCT-A or SS-OCT-A and UWF fundus fluorescein angiography (UWF-FFA)

ALTIMETER Study Design



AH, aqueous humour; BCVA, best-corrected visual acuity; Q4W, every 4 weeks.

References

1. Regula JT et al. *EMBO Mol Med*. 2016;8(11):1265-1288, with erratum in Regula JT et al. *EMBO Mol Med*. 2019;11(5):e10666.
2. Ferrone PJ et al. Presented at: 11th FLORetina - ICOOR Meeting November 30–3 December 2023; Rome, Italy.

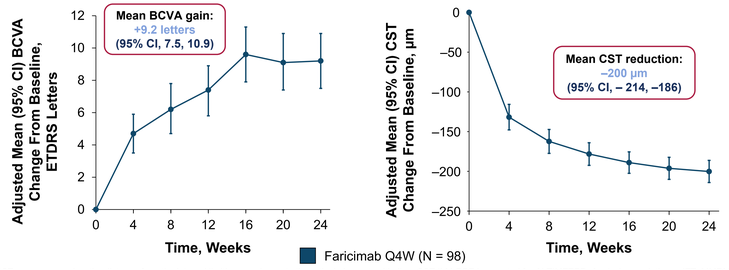
Results

Demographics and Baseline Patient Characteristics

	Faricimab 6 mg Q4W N = 99
Age, years, mean (SD)[a]	59.5 (9.8)
Male, n (%)	61 (61.6)
White, n (%)	86 (86.9)
BCVA, ETDRS letters, mean (SD)	62.5 (11.8)
CST, µm, mean (SD)[b]	464.0 (149.5)
Global DR status, n (%)[c]	
Mild-to-severe NPDR[d]	79 (79.8)
Mild to high-risk PDR[e]	11 (11.1)
Questionable, microaneurysms only or cannot grade[f]	9 (9.1)

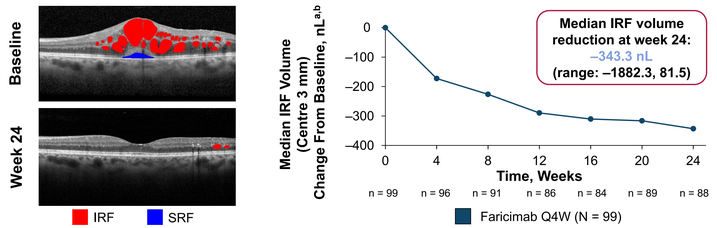
Results are presented for the mITT population, defined as all patients enrolled in ALTIMETER who received any amount of study treatment.
[a] Age at enrolment. [b] CST was measured as the distance from the internal limiting membrane to the retinal pigment epithelium. [c] UWF-CFP. [d] ETDRS-DRSS levels 61A–B, 65A–C, 71A–D. [e] ETDRS-DRSS levels 35A–F, 43A–B, 47A–D, 53A–E. [f] ETDRS-DRSS levels 14A–C, 14Z, 15, 20, 90. BCVA, best-corrected visual acuity; CFP, colour fundus photography; CST, central subfield thickness; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; mITT, modified intent to treat; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; Q4W, every 4 weeks; SD, standard deviation; UWF, Ultra-WideField.

Robust Vision Gains and CST Reductions With Faricimab



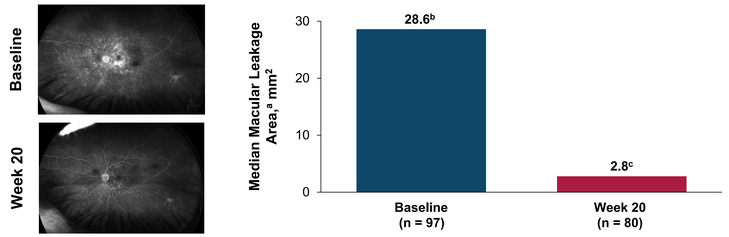
CST was measured as the distance from the internal limiting membrane to the retinal pigment epithelium CST ILM-RPE is reported for ALTIMETER. Analysis population: mITT. MMRM models: ALTIMETER, adjusted for visit, age (continuous), baseline BCVA/CST value (continuous) and region (United States and Canada, Asia and the rest of the world). BCVA, best-corrected visual acuity; CI, confidence interval; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; ILM, internal limiting membrane; mITT, modified intent to treat; MMRM, mixed-effect model with repeated measures; Q4W, every 4 weeks; RPE, retinal pigment epithelium.

Robust Reductions in IRF Volume With Faricimab



Images from a patient at baseline and at week 24 in ALTIMETER. Analysis population: mITT, defined as all patients enrolled in ALTIMETER who received any amount of study treatment. [a] Measured in ETDRS ring of 3-mm diameter. [b] Ranges: week 4: –1879.7, 336.5; week 8: –1881.9, 203.5; week 12: –1882.1, 46.0; week 16: –1882.3, 30.7; week 20: –1881.5, 121.5; week 24: –1882.3, 81.5. ETDRS, Early Treatment Diabetic Retinopathy Study; IRF, intraretinal fluid; mITT, modified intent to treat; Q4W, every 4 weeks; SRF, subretinal fluid.

Macular Leakage Area Reduced With Faricimab



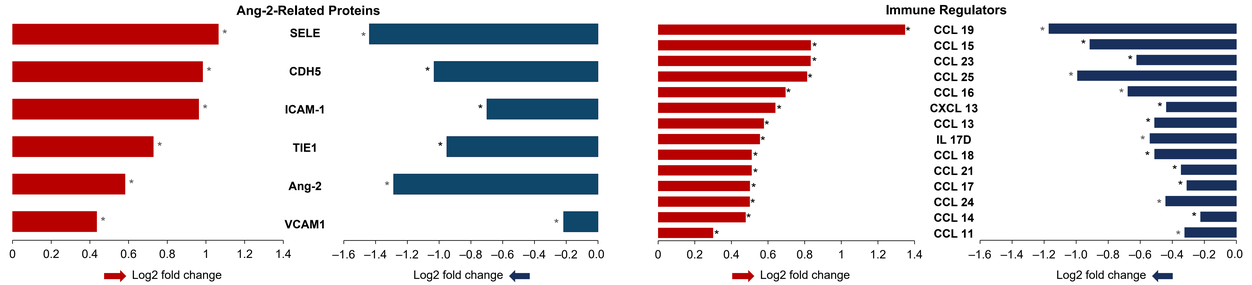
Images from a patient at baseline and at week 20 in ALTIMETER. [a] Macular leakage area within the ETDRS grid, measured using UWF-FA. [b] Range: 1.7–40.4. [c] Range: 0–38.6. ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fluorescein angiography; UWF, Ultra-WideField.

Ang-2-Related Proteins and Immune Regulators[a] Elevated at Baseline in Patients With High Macular Leakage[b] Were Reduced With Faricimab

Figure legend

Increased expression at baseline **(in high vs low macular leakage groups* at baseline)**

Reduced expression at week 16 with **faricimab** treatment **(in high macular leakage group at baseline)**



Biomarker-evaluable population in ALTIMETER (n = 94). Protein levels in AH were measured by Olink® Target 96 technology. [a] Immune regulator proteins that were significantly affected by treatment with faricimab in patients with high macular leakage at baseline were selected for inclusion. [b] Relative to patients with low macular leakage. *(Left) Significantly increased in patients with high vs low macular leakage at baseline (FDR-adjusted $P < 0.05$); (right) significantly reduced vs baseline in patients with high macular leakage at baseline treated with faricimab (FDR-adjusted $P < 0.05$). AH, aqueous; humour Ang-2, angiopoietin-2; CXCL, chemokine (C–C motif) ligand; CDH5, cadherin 5; FDR, false discovery rate; ICAM-1, intracellular adhesion molecule-1; SELE, selectin; TIE1, tyrosine kinase with immunoglobulin-like and EGF-like domains 1; VCAM-1, vascular cell adhesion molecule 1. Vujosevic S et al. Presented at: APVRS; Hong Kong; 8–10 December 2023.

***Patients with high or low macular leakage at baseline were defined as those with macular leakage above or below the median value at baseline, respectively**

Safety

- Faricimab was generally well tolerated. There were no reports of intraocular inflammation, retinal vascular occlusive disease, infectious endophthalmitis, rhegmatogenous retinal detachment or retinal tear