Overview of the Faricimab Safety Profile From Four Phase 3 Trials in Diabetic Macular Oedema and Neovascular Age-Related Macular Degeneration Through 2 Years

Nirodhini Narendran, MBBS, MD, FRCOphth[1]; David Kardatzke, PhD[2]; Aachal Kotecha, PhD[3]; Laura Steeples, MBChB, FRCOphth[3]; Jeffrey R. Willis, MD, PhD[2]; and Jane Ives, MSc[3]

[1]New Cross Hospital, Wolverhampton, UK; [2] Genentech, Inc., South San Francisco, CA; [3] Roche Products Ltd., Welwyn Garden City, UK

Key Clinical Question

What is the safety profile of Faricimab across the Phase 3 trials in patients with Diabetic Macular Oedema (DMO) and Neovascular Age-related Macular Degeneration (nAMD)?

Introduction

- Faricimab is the first bispecific antibody for intraocular use that independently binds and neutralizes both angiopoietin-2 and VEGF-A with high specificity and potency.
- Faricimab safety profile was extensively investigated in 4 large phase 3, global, randomized, double-masked trials involving a total of 3220 patients for up to 2 years
- YOSEMITE (NCT03622580)/RHINE (NCT03622593) and TENAYA (NCT03823287)/ LUCERNE (NCT03823300) were Phase 3 trials that evaluated the efficacy, durability and safety of faricimab compared with aflibercept in patients with DMO and nAMD with 1926 faricimab-exposed patients who received a total of 23,012 faricimab injections
- Phase 3 trial designs gave broad dosing exposure as faricimab 6.0 mg was given over a range of treatment intervals (Q4W–Q16W based on trial arm and disease assessments)

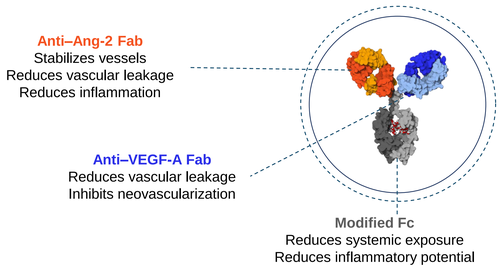
Methods

- Safety reporting in the Phase 3 YOSEMITE/RHINE and TENAYA/LUCERNE trials followed a rigorous approach
- Ocular adverse events from both the study and fellow eyes was captured
- Clear guidance was provided to investigators via the protocol
- Comprehensive study eye AE information was collected and reviewed: Clinical examination data, Severity, (mild/moderate/severe), Investigator assessment on causality (drug-relatedness), Seriousness, Management Outcome (resolution, treatment, intravitreal therapy continuation, visual acuity change)
- Reported terms were mapped to preferred terms, according to MedDRA
- APTC events were adjudicated by external independent committee

Conclusions

- Faricimab was well tolerated, with a safety profile comparable to aflibercept and no new or unexpected signals in the phase 3 DMO and nAMD faricimab patient populations (1926 patients)
- IOI rates were low across the trial program and comparable with aflibercept: DMO: 1.6% vs 1.1% (week 96); nAMD: 3.0% vs 2.3% (week 112), respectively (cut-off date of January 2023)
- DRC independently reviewed IOI cases and no safety concerns were identified
- In the post-marketing setting, no new safety concerns have been identified to date and surveillance is ongoing
- As of today, >1 million commercial faricimab vials have been distributed worldwide for the treatment of nAMD and DMO[5]

1. Faricimab Molecular Structure Was Specifically Designed to Reduce Potential for Safety Concerns



- **Faricimab** was **designed to**:
- **Abolish binding to FcγR**
  - Reduced systemic exposure
  - Decreased immune potential
- **Provide durability**
  - Reduced number of injections
- Thereby, **reducing** potential for **safety concerns**[1,2]

CrossMAb molecule representative of faricimab.
Ang-2 , angiopoietin 2; Fab, fragment antigen binding; Fc, fragment crystallizable; VEGF A, vascular endothelial growth factor A.

2. Faricimab Was Well Tolerated Through Study End in YOSEMITE and RHINE Phase 3 DMO Trials[3]

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%)

MedDRA - Medical Dictionary for Regulatory Activities (version 24.0)
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] 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.

3. Faricimab Was Well Tolerated Through Study End in TENAYA and LUCERNE Phase 3 nAMD Trials[4]

AEs Through Study End, Patients With ≥ 1 AE, n (%)[a]	TENAYA/LUCERNE Pooled	
	Faricimab Up to Q16W n = 664	Aflibercept Q8W n = 662
Ocular AEs[b]	358 (53.9%)	345 (52.1%)
Serious ocular AEs[b]	29 (4.4%)	29 (4.4%)
Ocular AEs of special interest[c]	25 (3.8%)	27 (4.1%)
Intraocular inflammation events[d]	20 (3.0%)	15 (2.3%)
Uveitis	4 (0.6%)	3 (0.5%)
Iritis	8 (1.2%)	3 (0.5%)
Iridocyclitis	2 (0.3%)	1 (0.2%)
Vitritis	4 (0.6%)	1 (0.2%)
Post-procedural inflammation	0	5 (0.8%)
Chorioretinitis	1 (0.2%)	0
Keratic precipitates	2 (0.3%)	0
Non-infectious endophthalmitis	0	1 (0.2%)
Anterior chamber flare	0	1 (0.2%)
Endophthalmitis events	3 (0.5%)	2 (0.3%)
Retinal vasculitis events	0	0
Retinal occlusive events		
Retinal vein occlusion	0	0
Retinal artery occlusion	0	0
Retinal artery embolism	1 (0.2%)[e]	0
Serious non-ocular AEs	138 (20.8%)	162 (24.5%)
APTC events[f]	22 (3.3%)	20 (3.0%)

MedDRA - Medical Dictionary for Regulatory Activities (version 24.1)
[a] Results are presented for the pooled TENAYA/LUCERNE safety-evaluable populations. 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] Hollenhorst plaque that was reported at the end of year 1 and was not treatment related as per the investigator. [f] APTC events were adjudicated by an external independent committee; all other events were investigator reported.
AE, adverse event; APTC, Antiplatelet Trialists' Collaboration; BCVA, best-corrected visual acuity; Q8W, every 8 weeks; Q16W, every 16 weeks.

4. Duke Reading Centre (DRC) Reviewed Investigator-Reported IOI Cases

RATIONALE
DRC performed masked, independent case reviews to provide further confidence about drug safety and data robustness

INCLUSION CRITERIA
Events of interest
- IOI, infectious endophthalmitis, retinal vascular events (RVO, RAO) of all severity were included
- Controls included

APPROACH
Masked multi-modal imaging review
DRC pre-specified IOI grading variables
- SD-OCT
- Fluorescein angiography (FA)
- Fundus Photography (FP)

REVIEW CONCLUSION
There were no adverse events of retinal occlusive vasculitis reported in the DMO/nAMD trials, and the DRC review confirmed no evidence of stereotypical patterns suggestive of these events through 2 years.

DRC; Duke Reading Centre, IOI; intraocular inflammation, RVO; retinal vein occlusion, RAO; retinal artery occlusion, SD-OCT; spectral-domain optical coherence tomography, DMO; diabetic macular oedema, nAMD; neovascular age-related macular degeneration

Presented at the Royal College of Ophthalmologists Annual Congress
Birmingham, UK I 22-25 May 2023

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. Wang X et al. Protein Cell. 2018;9(1):63-73
3. Wykoff CC et al; YOSEMITE and RHINE Investigators. Lancet. 2022;399(10326):741 755.
4. Heier JS et al; TENAYA and LUCERNE Investigators. Lancet 2022;399(10326): 729 740
5. Eandi C. et al. Presented at SFO 2023, Paris, France, 6-8 May 2023

Financial Disclosures

- NN: Consultant: Novartis, Bayer, Roche/Genentech, Inc. (Honoraria)
- DK, JRW: Employee: Genentech, Inc.
- AK, LS, 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