Vabysmo and Phase 3 Intraocular Inflammation Subgroup Analysis

This article responds to your request for information on Vabysmo® (faricimab) and details related to the intraocular inflammation (IOI) events reported in the Phase 3 studies through Year 2. This response was developed according to the principles of evidence-based medicine and summarizes data from the pivotal Phase 3 studies.

In brief

- The overall incidence of IOI in patients treated with faricimab was low
  - DME — 1.4% and 1.7%, in the Vabysmo Q8W and PTI arms, respectively.
  - nAMD — 3.0% in the Vabysmo up to Q16W arm.
- A subgroup analysis was performed in the patients with an IOI in the Phase 3 studies YOSEMITE/RHINE and TENAYA/LUCERNE with an IOI.
  - Across the four Phase 3 studies, the majority of IOI patients had an anterior chamber cell grade or a vitreous cell grade <2+. The majority were treated with topical steroids only.
  - In YOSEMITE/RHINE, the incidence and per-injection rate of IOI rates were low across treatment arms and considered comparable. In TENAYA/LUCERNE, the incidence of IOI rates were low across both arms, with approximately 2 more IOI events per 1000 injections in the Vabysmo arm compared with the aflibercept arm.
  - The majority of events were non-serious. There were no IOI events associated with vision loss of ≥30 letters. The majority of events were resolved or resolving.
  - The number of IVT injections prior to the first event were similar across treatment groups, and ranged from 6.5 to 7.9.

Abbreviations

DME=diabetic macular edema
FA=fluorescein angiography
FP=fundus photography
IOI=intraocular inflammation
nAMD=neovascular age-related macular degeneration
SD-OCT=spectral domain-optical coherence tomography

Incidence of IOI through Year 2

The total IOI events observed in patients treated with Vabysmo in Phase 3 clinical trials through Year 2 are presented in Table 1. The overall incidence of IOI in patients treated with faricimab was low (1.4% and 1.7%, in the Vabysmo Q8W and PTI arms, respectively in DME and 3.0% in the Vabysmo arm in nAMD).

Table 1. IOI events in DME and nAMD patients through Year 2 of YOSEMITE/RHINE[1] and TENAYA/LUCERNE[2]

AEs through study end, n (%)	Pooled YOSEMITE/RHINE			Pooled TENAYA/LUCERNE	
	Vabysmo Q8W (n=630)	Vabysmo PTI (n=632)	Aflibercept Q8W (n=625)	Vabysmo up to Q16W (n=664)	Aflibercept Q8W (n=662)
IOI events*	9 (1.4)	11 (1.7)	7 (1.1)	20 (3.0)	15 (2.3)
Uveitis	3 (0.3)	4 (0.6)	0	4 (0.6)	3 (0.5)
Iritis	1 (0.2)	4 (0.6)	2 (0.3)	8 (1.2)	3 (0.5)
Iridocyclitis	2 (0.3)	3 (0.5)	1 (0.2)	2 (0.3)	1 (0.2)
Vitritis	2 (0.3)	0	2 (0.3)	4 (0.6)	1 (0.2)
Post-procedural inflammation	1 (0.2)	1 (0.2)	2 (0.3)	0	5 (0.8)
Chorioretinitis	0	1 (0.2)	0	1 (0.2)	0
Keratic precipitates	0	1 (0.2)	0	2 (0.3)	0
Non-infectious endophthalmitis	0	0	0	0	1 (0.2)
Keratouveitis	0	1 (0.2)	0	0	0
Anterior chamber flare	0	0	0	0	1 (0.2)
Endophthalmitis events	2 (0.3)	4 (0.6)	1 (0.2)	3 (0.5)	2 (0.3)

Notes: Results are presented for the pooled 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.
*Excluding endophthalmitis.

Abbreviations: AE=adverse event; IOI=intraocular inflammation; PTI=personalized treatment interval; Q8W=every 8 weeks; Q16W=every 16 weeks.

IOI subgroup analysis in DME

A subgroup analysis was performed in the patients in YOSEMITE and RHINE with an IOI.

Baseline characteristics

The number of patients with intraocular inflammation was low and comparable between treatment groups (Table 2). Baseline characteristics of the patients were similar across treatment groups.[3,4]

Table 2. Baseline characteristics of subgroup with IOI in YOSEMITE/RHINE through Year 2[3,4]

	Vabysmo Q8W (n=630)	Vabysmo PTI (n=632)	Aflibercept Q8W (n=625)
Patients with ≥ 1 IOI, n	**9**	**11**	**7**
Age, mean (min-max) in years	62.3 (53-70)	65.3 (54-85)	61.1 (50-79)
Female gender, n	5	6	1
Race White, n	3	5	3
BCVA at baseline, mean (min-max) in ETDRS letters	60.1 (52-73)	63.3 (48-76)	52.4 (27-71)
Patients with prior anti-VEGF therapy, n	2	2	4
Time since last anti-VEGF treatment in previously treated patients, mean (min-max) in months	25.5 (23-28)	4.0 (3-5)	14.7 (8-35)
Notes: Results are presented for patients with ≥ 1 IOI in study eye only BCVA=best-corrected visual acuity; ETDRS=Early treatment diabetic retinopathy study; VEGF=vascular endothelial growth factor; IOI=intraocular inflammation; Q8W=every 8 weeks; PTI=personalized treatment interval.			

Clinical assessment and management of IOI events

The majority of patients had an anterior chamber cell grade or a vitreous cell grade <2+ (Table 3). The majority were treated with topical steroids only.[3,4]

Table 3. Clinical assessment and management in subgroup with IOI in YOSEMITE/RHINE through Year 2[3,4]

	Vabysmo Q8W (n=630)	Vabysmo PTI (n=632)	Aflibercept Q8W (n=625)
Patients with ≥ 1 IOI, n	**9**	**11**	**7**
Patients with AC cell grade ≥2+, n	2	3	1
Patients with vitreous cell grade ≥2+, n	3	5	1
Patients receiving ANY medication for IOI, n	9	11	5
Management with topical steroids only, n	9	10	5
Required oral steroid or local steroid injection, n	0	1	0
Notes: Results are presented for patients with ≥ 1 IOI in study eye only AC=anterior chamber; IOI=intraocular inflammation; Q8W=every 8 weeks; PTI=personalized treatment interval.			

Clinical outcomes of IOI events

The incidence and per-injection rate of intraocular inflammation rates were low across treatment arms and considered comparable. The majority of events were non-serious. The majority of events were resolved or resolving.[3,4]

Timing of IOI events

The number of IVT injections prior to the first event were similar across treatment groups, and ranged from 7.3 to 7.8.

Table 4. Event level data and clinical outcomes in subgroup with IOI in YOSEMITE/RHINE through Year 2[3,4]

	Vabysmo Q8W (n=630)	Vabysmo PTI (n=632)	Aflibercept Q8W (n=625)
Patients with ≥ 1 IOI, n	**9**	**11**	**7**
Total number of IOI* events	**10**	**16**	**10**
Number of IOI events per 1000 injections	2.15	1.17	1.20
Serious IOI events, n	0	6	1
Time from first IVT injection to first event, mean (min-max) in days	299.6 (38-562)	284.5 (120-561)	276.6 (62-542)
Time from most recent IVT injection to first event, mean (min-max) in days	30.8 (16-58)	34.8 (0-205)	16.1 (0-55)
Number of IVT injections prior to first event, mean (min-max)	7.8 (2-13)	7.7 (4-17)	7.3 (3-12)
BCVA decrease ≥15 ETDRS letters, n	0	2	0
BCVA decrease ≥30 ETDRS letters, n	0	2	0
Study treatment discontinuation, n	2	3	0
Recovered/resolved or recovering/resolving, n	10	13	10

Notes: Results are presented for patients with ≥ 1 IOI in study eye only
BCVA=best-corrected visual acuity; ETDRS=Early treatment diabetic retinopathy study; IOI=intraocular inflammation; IVT=intravitreal injection; Q8W=every 8 weeks; PTI=personalized treatment interval.

IOI subgroup analysis in nAMD

A subgroup analysis was performed in the patients in TENAYA and LUCERNE with an IOI.

Baseline characteristics

The number of patients with IOI was low and comparable between treatment groups (Table 5). Baseline characteristics of the patients were similar across treatment groups.[5,6]

Table 5. Baseline characteristics of subgroup with IOI in TENAYA/LUCERNE through Year 2[5,6]

	Vabysmo up to Q16W (n=664)	Aflibercept Q8W (n=662)
Patients with ≥ 1 IOI, n	20	15
Age, mean (min-max) in years	72.1 (50-92)	78.1 (61-91)
Female gender, n	15	11
Race White, n	18	15
BCVA at baseline, mean (min-max) in ETDRS letters	60.4 (29-78)	60.5 (31-78)
Patients with prior anti-VEGF therapy, n	0†	0†

Notes: Results are presented for patients with ≥ 1 IOI in study eye only
† Not allowed per exclusion criteria.
BCVA=best-corrected visual acuity; ETDRS=Early treatment diabetic retinopathy study; VEGF=vascular endothelial growth factor; IOI=intraocular inflammation; Q8W=every 8 weeks; Q16W=every 16 weeks.

Clinical assessment and management of IOI events

The majority of patients had an anterior chamber cell grade or a vitreous cell grade <2+ (Table 6). The majority were treated with topical steroids only.[5,6]

Table 6. Clinical assessment and management in subgroup with IOI in TENAYA/LUCERNE through Year 2[5,6]

	Vabysmo up to Q16W (n=664)	Aflibercept Q8W (n=662)
Patients with ≥ 1 IOI, n	**20**	**15**
Patients with AC cell grade ≥2+, n	5	6
Patients with vitreous cell grade ≥2+, n	7	5

Patients receiving ANY medication for IOI, n	16	13
Management with topical steroids only, n	12	10
Required oral steroid or local steroid injection, n	4	1
Notes: Results are presented for patients with ≥ 1 IOI in study eye only AC=anterior chamber; IOI=intraocular inflammation; Q8W=every 8 weeks; Q16W=every 16 weeks.		

Clinical outcomes of IOI events

The incidence of IOI rates were low across both arms, with approximately 2 more IOI events per 1000 injections in the Vabysmo arm compared with the aflibercept arm (Table 7). The majority of events were non-serious. There were no IOI events associated with vision loss of ≥30 letters. The majority of events were resolved or resolving.[5,6]

Timing of IOI events

The number of IVT injections prior to the first event were similar across treatment groups, and ranged from 6.5 to 7.9.

Table 7. Event level data and clinical outcomes in subgroup with IOI in TENAYA/LUCERNE through Year 2[5,6]

	Vabysmo up to Q16W (n=664)	Aflibercept Q8W (n=662)
Patients with ≥ 1 IOI, n	20	15
Total number of IOI* events	26	16
Number of IOI events per 1000 injections	3.70	1.78
Serious IOI events, n	5	3
Time from first IVT injection to first event, mean (min-max) in days	307.1 (8-638)	358.3 (88-655)
Time from most recent IVT injection to first event, mean (min-max) in days	25.2 (0-70)	22.1 (0-77)
Number of IVT injections prior to first event, mean (min-max)	6.5 (1-12)	7.9 (3-13)
BCVA decrease ≥15 ETDRS letters, n	1	0
BCVA decrease ≥30 ETDRS letters, n	0	0
Study treatment discontinuation, n	6	2

Recovered/resolved or recovering/resolving, n	19	13
Notes: Results are presented for patients with ≥ 1 IOI in study eye only BCVA=best-corrected visual acuity; ETDRS=Early treatment diabetic retinopathy study; IOI=intraocular inflammation; IVT=intravitreal injection; Q8W=every 8 weeks; Q16W=every 16 weeks.		

Reporting of IOI in Phase 3 clinical trials

The safety and efficacy of Vabysmo in 3,220 patients with nAMD or DME were assessed in four Phase 3 clinical studies: 2 studies were conducted in nAMD (TENAYA/LUCERNE)[5,6] and 2 studies were conducted in DME (YOSEMITE/RHINE).[3,4]

IOI terms were reported based on investigators' assessments and events were coded according to MedDRA using investigator-reported verbatim terms which mapped to specific Preferred Terms presented in the results. Instructors used the SUN criteria to grade the severity of an adverse event using.

Intraocular inflammation was defined by the following Preferred Terms[3-6]

- anterior chamber flare
- anterior chamber inflammation
- chorioretinitis
- cyclitis
- eye inflammation
- iridocyclitis
- iritis
- keratic precipitates
- keratouveitis
- non-infective chorioretinitis
- non-infectious endophthalmitis
- ocular vasculitis
- post-procedural inflammation
- retinal vasculitis
- uveitis, and
- vitritis.

Sites were queried to ensure appropriate mapping of verbatim terms to Preferred Terms.

The list of terms includes terms beyond the recognised SUN criteria for IOI to ensure a conservative approach was taken to identify any possible types of inflammation as well as rare events.

Independent review of all IOI cases

The Duke Reading Center (DRC) performed masked, independent reviews of all investigator-reported IOI cases in nAMD (TENAYA/LUCERNE) and DME (YOSEMITE/RHINE) Phase 3 studies to provide further confidence about drug safety and data robustness. Intraocular inflammation, retinal vascular changes and IOI terms reflective of clinical reporting were evaluated.[7]

The inclusion criteria comprised events of interest, including[7]

- IOI
- infectious endophthalmitis
- retinal vein occlusion and retinal artery occlusion of all severity, and
- controls.

Reviews were conducted with masked multi-modal imaging review and DRC pre-specified IOI grading variables using SD-OCT, FA, and FP.[7]

The Duke Reading Center found no stereotypical patterns or trends suggestive of IOI-associated occlusive retinal vasculitis in either the DME or nAMD trials through 2 years.[7]

References

1. Baumal C, Wells J, Danzig C, et al. Efficacy, Durability, and Safety of Faricimab in Diabetic Macular Edema (DME): 2-Year Results From YOSEMITE and RHINE. Presented at the American Association of Ophthalmology Annual Meeting in Chicago, IL, USA; September 30 - October 3, 2022. AAO Oral presentation.

2. Singh R, Khanani A, Demetriades A, et al. Faricimab in Neovascular Age-Related Macular Degeneration: Year 2 Results From the Phase 3 TENAYA and LUCERNE Trials. Presented at the American Association of Ophthalmology Annual Meeting in Chicago, IL, USA; September 30 - October 3, 2022. AAO Oral presentation.

3. Roche Internal Clinical Study Report (YOSEMITE)(Accessed on 1 August 2023).

4. Roche Internal Clinical Study Report (RHINE)(Accessed on 1 August 2023).

5. Roche Internal Clinical Study Report (TENAYA)(Accessed on 1 August 2023).

6. Roche Internal Clinical Study Report (LUCERNE)(Accessed on 1 August 2023).

7. Jaffe G, Kardatzke D, Kotecha A, et al. Overview of the Faricimab Safety Profile From Four Phase 3 Trials in Diabetic Macular Edema and Neovascular Age-Related Macular Degeneration Through 2 Years. Presented at the Retina Society in Pasadena, CA, USA; November 2-5, 2022. Retina Society Oral presentation.