EU RISK MANAGEMENT PLAN FOR VABYSMO®/FARICIMAB

RMP version to be assessed as part of this application:

RMP Version number: 8.1

Data lock point for this RMP: 19 May 2025

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Rationale for Submitting an Updated Risk Management Plan (RMP)

The EU RMP version 8.1 has been prepared to update section SVII.2 “New Safety Concerns and Reclassification with a Submission of an Updated RMP” to include a high-level summary of the comprehensive analysis that was prepared on non-ocular arterial thromboembolic events (ATE) and CNS hemorrhagic events to support the removal of ATE and CNS hemorrhagic events as an important potential risk from the EU RMP.

The EU RMP version 8.0 was prepared to support the submission of long-term safety data from the GR42691 (AVONELLE-X) study to fulfill the post-authorisation measure (PAM-MEA) commitment included in the Pharmacovigilance Plan of Vabysmo EU RMP. The EU RMP has been updated to remove the long-term extension Study GR42691 (AVONELLE-X) from the list of required additional pharmacovigilance (PV) activities. This change pertains to the missing information on long-term safety of faricimab in the neovascular age-related macular degeneration (nAMD) indication given the availability of the final Clinical Study Report (CSR). Following the completion of the extension studies RHONE-X (GR41987) and AVONELLE-X (GR42691), the safety concern of long-term safety is no longer considered missing information and has thus been removed. In addition, the important potential risk of ATE and CNS hemorrhagic events was further characterized through both extension studies and the results from both RHONE-X and AVONELLE-X in conjunction with the pivotal Phase III trials did not confirm a causal association with faricimab. As no additional PV activities are required to further characterize this risk, ATE and CNS hemorrhagic events have been removed from the E.U. RMP list of safety concerns. The clinical trial exposure and information relating to important identified risks has been updated to include AVONELLE-X study data.

Summary of Significant Changes in this EU RMP

- Part II Module SV: Post-authorisation exposure data have been updated based on Periodic Benefit-Risk Evaluation Report (PBRER) 1136491 with the data lock point of 27 January 2025.
- Part II Modules SV1.2, SIII: Clinical trial exposure data have been updated to include data from Study GR42691 (AVONELLE-X).
- Part II Modules SVII and SVIII, Part III.1 and III.2, Part V.2 and V.3, Part VI II.A and II.B: Information relating to important identified and important potential risk have been updated to include data from Study GR42691 (AVONELLE-X).
- Part II Module SVII.2 has been updated to include the justifications for the removal of long-term safety and important potential risk of ATE and CNS hemorrhagic events from the list of safety concerns. Consequently, Part II Modules SVII.3, SVIII, and Parts VI II.A and VI II.B have been updated to remove long-term safety and ATE and CNS hemorrhagic events. Additionally, Parts V.1 and V.3 have been updated to remove ATE and CNS hemorrhagic events.
- Part II Module SVII.2 has also been updated to include a summary of the Drug Safety Report (DSR) on non-ocular ATE and CNS hemorrhagic events (Version 8.1)

- Part II Module SVII.3.2, Part III.1: Based on feedback received from the European Medicines Agency (EMA), the text on the Roche standard pregnancy follow-up process included under Routine Pharmacovigilance Activities has been removed. The standard pregnancy follow-up form remains part of Roche procedures and pregnancy cases will continue to be followed up according to Roche standard procedures.
- Part III.3: Study GR42691 (AVONELLE-X) has been removed as a Category 3 study from the List of Required Additional pharmacovigilance activities upon its completion.
- Annex 2: Study GR42691 (AVONELLE-X) has been moved to completed studies.
- Annex 3: Protocol for Study GR42691 (AVONELLE-X) has been removed upon its completion.
- Annex 4: A new version of the Vabysmo Guided Questionnaire (GQ) for endophthalmitis and intraocular inflammation has been added.
- Annex 7: The ‘Exposure Tables’ and ‘CSR and Summaries Outputs’ have been updated to include Study GR42691 (AVONELLE-X) study data and remove data related to the important potential risk of ATE and CNS hemorrhagic events. References have been updated to include the Study GR42691 (AVONELLE-X) Final CSR. The cumulative marketing exposure table was updated from PBRER 1136491
- Annex 7D: List of Referenced Studies has been updated to include the citation of DSR1153704 on non-ocular ATE and CNS hemorrhagic events (Version 8.1)
- Annex 8: Updated to reflect key changes made in this RMP (Versions 8.0 and 8.1) and to include the approval date for the EU RMP v7.1.

Other RMP Versions under Evaluation

None

Details of Currently Approved RMP

RMP Version Number: 7.1

Approved with Procedure Number: EMEA/H/C/005642/II/0016
Date of approval (opinion date): 8 May 2025

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Dr. [redacted] (Deputy EU QPPV)	Date

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Dr. [redacted]	Date

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active Substance(s) (INN or common name)	Faricimab
Pharmacotherapeutic group(s) (ATC Code)	Ophthalmologicals, antineovascularisation agents (ATC Code: S01LA09)
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	Vabysmo
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Faricimab is a humanised bispecific IgG1 antibody.
	Summary of mode of action: Faricimab acts through inhibition of two distinct pathways by neutralisation of both Ang-2 and VEGF-A. Ang-2 causes vascular instability by promoting endothelial destabilisation, pericyte loss, and pathological angiogenesis, thus potentiating vascular leakage and inflammation. It also sensitizes blood vessels to the activity of VEGF-A resulting in further vascular destabilisation. Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularisation. By dual inhibition of Ang-2 and VEGF-A, faricimab reduces vascular permeability and inflammation, inhibits pathological angiogenesis and restores vascular stability.
	Important information about its composition: Faricimab is a humanised antibody produced in mammalian Chinese Hamster Ovary cell culture by recombinant DNA technology.
Hyperlink to the Product Information	Refer to the Product Information
Indication(s) in the EEA	Current: Vabysmo is indicated for the treatment of adult patients with: • nAMD • Visual impairment due to DME • Visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
	Proposed: Not applicable

Dosage in the EEA	Current: This medicinal product must be administered by a qualified physician experienced in intravitreal injections. Each pre-filled syringe or vial should only be used for the treatment of a single eye.
	nAMD The recommended dose is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks (monthly) for the first 3 doses. Thereafter, an assessment of disease activity based on anatomic and/or visual outcomes is recommended 16 and/or 20 weeks after treatment initiation so that treatment can be individualised. In patients without disease activity, administration of faricimab every 16 weeks (4 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) or 12 weeks (3 months) should be considered. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly, and interval reduction should be implemented if anatomic and/or visual outcomes deteriorate. There is limited safety data on treatment intervals of 8 weeks or less between injections. Monitoring between the dosing visits should be scheduled based on the patient's status and at the physician's discretion, but there is no requirement for monthly monitoring between injections. **RVO** The recommended dose is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks (monthly); 3 or more consecutive, monthly injections may be needed. Thereafter, treatment is individualized using a treat-and-extend approach. Based on the physician’s judgement of the patient’s anatomic and/or visual outcomes, the dosing interval may be extended, in increments of up to 4 weeks. If anatomic and/or visual outcomes change, the treatment interval should be adjusted accordingly, and interval reduction should be implemented if anatomic and/or visual outcomes deteriorate. Treatment intervals shorter than 4 weeks and longer than 4 months between injections have not been studied. Monitoring between the dosing visits should be scheduled based on the patient’s status and at the physician’s discretion but there is no requirement for monthly monitoring between injections.
	Proposed: Not applicable

Pharmaceutical form(s) and strengths	Current: Solution for injection. Clear to opalescent, colourless to brownish-yellow solution, with a pH of 5.5 and an osmolality of 270 – 370 mOsm/kg. One mL of solution contains 120 mg of faricimab. Pre-filled syringe (PFS): Each pre-filled syringe contains 21 mg faricimab in 0.175 mL solution. This provides a usable amount to deliver a single dose of 0.05 mL solution containing 6 mg of faricimab. Vial: Each vial contains 28.8 mg faricimab in 0.24 mL solution. This provides a usable amount to deliver a single dose of 0.05 mL solution containing 6 mg of faricimab.
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the European Union?	Yes

Ang-2 = angiopoietin-2; ATC = Anatomical Therapeutic Chemical; DME = diabetic macular edema; EEA = European Economic Area; GmbH = Gesellschaft mit beschränkter Haftung; IgG1 = immunoglobulin G1; INN = International non-proprietary name; nAMD = neovascular (wet) age-related macular degeneration; RMP = Risk Management Plan; RVO = retinal vein occlusion; VEGF-A = vascular endothelial growth factor A.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AMD	age-related macular degeneration
Ang-2	angiopoietin-2
APTC	Anti-Platelet Trialists' Collaboration
ATE	arterial thromboembolic events
BRVO	branch retinal vascular occlusion
C/HRVO	central/hemiretinal vein occlusion
CEC	Clinical Events Committee
C_{max}	maximum serum concentration
CRVO	central retinal vein occlusion
CSME	clinically significant macular edema
C_{trough}	mean trough concentration
CV	cardiovascular
DME	diabetic macular edema
DR	diabetic retinopathy
DSR	Drug Safety Report
EC	endothelial cells
EMA	European Medicines Agency
EPAR	European Public Assessment Report
HbA1c	hemoglobin A1c
IBD	International Birth Date
IHC	Immunohistochemistry
IOI	intraocular inflammation
IOP	intraocular pressure
IV	intravenous
logMAR	logarithm of the Minimum Angle of Resolution
LTE	Long-Term Extension
MAH	Marketing Authorization Holder
ME	macular edema
MedDRA	Medical Dictionary for Regulatory Activities
MESA	Multi-Ethnic Study of Atherosclerosis
nAMD	neovascular age-related macular degeneration
NOAEL	no observed adverse effect level

Abbreviation	Definition
PBRER	Periodic Benefit-Risk Evaluation Report
PED	pigment epithelial detachment
PFS	pre-filled syringe
PPV	pars plana vitrectomy
PRAC	Pharmacovigilance Risk Assessment Committee
PRP	panretinal laser photocoagulation
PSUR	Periodic Safety Update Report
PTI	personalized treatment interval
PV	pharmacovigilance
PY	person-years
Q4W	every 4 weeks
Q8W	every 8 weeks
RMP	Risk Management Plan
ROV	retinal occlusive vasculitis
RPE	retinal pigment epithelial
RV	retinal vasculitis
RVO	retinal vein occlusion
SmPC	Summary of Product Characteristics
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
U.S.	United States
VEGF	vascular endothelial growth factor

PART II: SAFETY SPECIFICATION

PART II: MODULE SI— EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATION(S)

SI.1 Neovascular Age-Related Macular Degeneration

Incidence

Incidence of neovascular age-related macular degeneration (nAMD) in Europe, the United States, Australia, and Asia are reported in Table 2.

In most studies, patients were older adults (aged 50 years and older). Cumulative incidence ranged from 0.4% over a mean of 6.5 years in Portugal (patients aged 55 years and older) to 9.8% over 14 years in Denmark (patients 60–80 years old) (Buch et al. 2005; Farinha et al. 2019a).

In the United States, a study with a follow-up of 10 years estimated an incidence of 2.6% (in patients with mean age 69±9 years) (Klein et al. 2013).

Table 2 Reported Incidence of nAMD Worldwide

Country, Study Period	Follow-Up Time, years	Sample Size	No. of Cases	Baseline Age; Mean, Mean ± SD, or Range, years	IC % or IR per 1000 PY	Reference
Portugal 2009–2017	6.5	1616	7	≥55	IC: 0.4	Farinha et al. 2019a
France 2006–2012	Mean: 4	2465 PY	22	≥73	Overall IR: 8.9 Male: 2.1 Female: 13.1	Saunier et al. 2018
United States 1998–2010	10	1700	NR	53–94	Overall IC: 2.6	Klein et al. 2013
Australia 1992–2010	15	1149	NR	64.5	Overall IC: 4.4 Men: 3.3 Women: 5.2	Joachim et al. 2015
South Korea 2010–2015	6	3,097,106 PY	912	≥40	Overall IR: 0.29 Male: 0.36 Female: 0.23	Rim et al. 2019
China 2001–2006	5	3251	NR	55 ± 10	Overall IC: 0.1 Men: 0.2 Women: 0	You et al. 2012
Singapore 2007–2015	6	2105	2	56.2 ± 9.1	Age-standardized IC: 0.40	Foo et al. 2018

IC = cumulative incidence; IR = incidence rate; nAMD = neovascular age-related macular degeneration; NR = not reported; PY = person-years.

Prevalence

In a systematic review of 22 studies published since 1996 in Europe, the overall pooled prevalence of nAMD was 1.4% in patients aged 60–81 years (Li et al. 2020a). The overall prevalence of nAMD in the U.S. population 40 years and older, in a pooled analysis of three studies was estimated to be 1.02% (Friedman et al. 2004). The prevalence did not differ statistically between the United States and Europe (Smith et al. 2001). The prevalence of nAMD was found to increase with age (Table 3; Rudnicka et al. 2012).

A cross-sectional meta-analysis of 22 Asian studies comprising of 97,213 individuals aged 40 years and above, reported a pooled prevalence of 0.5% for nAMD (Hyungtaek et al. 2020). A population-based cross-sectional survey in Australia on 4,836 individuals aged 40 years and above reported the prevalence of nAMD as 0.24% in 3,098 non-indigenous Australian adults, with no cases of nAMD reported in 1,738 indigenous Australian adults (Keel et al. 2017).

Additional recently published studies are summarized in Table 3.

Table 3 Reported Prevalence of nAMD Worldwide, 2011–2020

Country, Study Period	Study Type, Population Characteristics	Sample Size	Age, years	Prevalence, % nAMD	Reference
Europe and the United States (publications between 1950 and 2010)	Systematic review and meta-analysis of 25 studies	57,173	≥50	Predicted prevalence Europe: ranged 0.04 (in 50 years of age) to 10.5 (in 90 years of age) United States: ranged 0.06 (in 50–55 years of age) to 14.6 (in 90 years of age and older)	Rudnika et al. 2012
European countries (publications between 1996 and 2017)	Systematic review and meta-analysis of 22 studies	55,232	60–81	Pooled 1.4 (95% CI: 1.0-1.9) ≤64 years of age: 0.1 (95% CI: 0.1-0.3) 65–74 years of age: 0.8 (95% CI: 0.6-1.0) ≥75 years of age: 3.3 (95% CI: 2.5-4.2)	Li et al. 2020a
Germany 2007–2008	Prospective population-based study	NR	35–74	0.1 (95% CI: 0.0-0.2)	Korb et al. 2014
Republic of Ireland 2009-2011	Retrospective review study	4,751	61.6 ± 8.1	0.3 (95% CI: 0.1-0.5)	Akuffo et al. 2015

Table 3 Reported Prevalence of nAMD Worldwide, 2011–2020 (cont.)

Country, Study Period	Study Type, Population Characteristics	Sample Size	Age, years	Prevalence, % nAMD	Reference
Denmark, Norway, Sweden 2012	Scandinavian general population Age ≥65 years	NR	≥65	3.61	Lindekleiv and Erke 2013
Norway 2007–2008	Population-based, cross-sectional study	2,631	65–87	2.5 (95% CI: 1.9-3.1)	Erke et al. 2012
Iceland 2002–2006	Population-based cohort study	5,272	76±6	3.3 (95% CI: 2.8-3.8)	Jonasson et al. 2011
Slovakia March–May 2013	Cross-sectional, population-based survey	2,924	66.6±8.7	1.01 (95% CI: 0.65-1.38)	Krasnik et al. 2018
United Kingdom 2002–2006	Cross-sectional study	NR	≥65	1.8	Wilde et al. 2017
United Kingdom 2007–2009	Meta-analysis of published data	NR	≥50	≥50 years: 1.2 (95% CI: 0.9-1.7) ≥65 years: 2.5 (95% CI 1.8-3.4) ≥80 years: 6.3 (4.5-8.6)	Owen et al. 2012
United States Based on US Census 2000	Pooled data from three population-based studies from US	NR	≥40	1.02 (95% CI: 0.93-1.11)	Friedman et al. 2004
Australia 2015–2016	Cross-sectional Population-based survey non-indigenous Australian adults	3,098	40-98	0.24 (95% CI: 0.13-0.47)	Keel et al. 2017
Asian Countries	Cross-sectional meta-analyses	97,213	60.8±10.8	0.5 (95% CI: 0.39-0.64)	Hyungtaek et al. 2020
China (Publications between 1990 and 2016)	Systematic review and meta-analysis of nine published Chinese studies with high heterogeneity	NR	30–90	Pooled prevalence: 0.69 (95% CI: 0.11–0.76)	Song et al. 2017
South Korea 2010–2011	Population-based cross-sectional survey	8,714	55.2±0.2	0.5 (95% CI: 0.4-0.8)	Cho et al. 2014

nAMD = neovascular age-related macular degeneration; NR = not reported.

Demographics

Age: The prevalence and incidence of nAMD increases with age. According to a meta-analysis of 22 studies in Europe, the pooled prevalence of nAMD was 0.1% among people aged ≤64 years, 0.8% among people aged 65–74 years, and 3.3% among people aged ≥75 years (Table 3; Li et al. 2020a). This trend of increasing prevalence with age was reported in studies conducted in Australia, the United Kingdom, and Taiwan (Owen et al. 2012; Hu et al. 2017; Keel et al. 2017). A pooled analysis from three countries (United States, The Netherlands, and Australia) reported significantly higher risk in patients aged 80–86 years and 70–79 years compared to patients aged 50–69 years (Table 4; Smith et al. 2001).

Gender: The risk of nAMD in men and women was found to be contrasting. In a study from Europe, a higher incidence of nAMD was observed among females (2.3 per 1000 person-years [PY]) compared to men (1.3 per 1000 PY) (Rudnicka et al. 2015). Studies from Asia (China and South Korea) reported an increased risk of nAMD among men compared to women (Song et al. 2017; Rim et al. 2018).

In a retrospective, multicenter, non-interventional real-world evidence study in the United States that included 79,885 patients with nAMD, the mean age was 82.6±8.4 years and 63% of the nAMD population was female (Khanani et al. 2020). Based on studies from Europe and the United States, for all age groups (50 years and older), women were found to have a higher prevalence of nAMD than men (Owen et al. 2012; Rudnicka et al. 2012). An Asian population tends to demonstrate a reversed trend with a slightly greater predilection towards male gender (e.g., 59.6% males reported by Hu et al. 2017 and 56.6% reported by Rim et al. 2018).

Racial disparity: A prospective cohort study examined the 8-year overall incidence of late age-related macular degeneration (AMD) (including nAMD and geographic atrophy) in four major racial/ethnic groups (White, Black, Hispanic, and Chinese) living in six U.S. communities. The study reported that incidence of late AMD was highest in Whites (4.1%), intermediate in Chinese (2.2%), followed by Hispanics (0.8%), and lowest in Blacks (0.4%) (Fisher et al. 2016).

The Main Existing Treatment Options

Prior to anti-vascular endothelial growth factor (VEGF) agents, laser photocoagulation therapy and photodynamic therapy with verteporfin were the standard of care based on their ability to stabilize vision. Although these treatments remain a therapeutic option for selected patients, the current standard of care in nAMD is intravitreal injections of anti-VEGF agents as first-line treatment, including ranibizumab (Lucentis®, Accentrix®, Byooviz™, Cimerli™), aflibercept (Eylea®), and brolucizumab (Beovu®). Additionally, bevacizumab (Avastin®) is unlicensed for ocular use yet broadly used in clinical practice worldwide.

The benefit of anti-VEGF therapies and their ability to restore vision has been widely recognized since the first approval of ranibizumab in 2006 (AAO 2019). A key challenge with currently available anti-VEGF treatments is the requirement for frequent and long-term administration to maintain vision gains (Heier et al. 2012a; Maguire et al. 2016). Patients can be treated with anti-VEGF injections as often as monthly for nAMD control. Treatment intervals longer than the prescribed regimens are possible for some patients; however, frequent eye examinations and office visits are still required to monitor for disease control and to achieve the patient's best visual outcomes. Real-world data suggest that many patients with nAMD do not receive treatment at the optimal frequency, and this under-treatment in clinical practice is associated with lower visual acuity gains compared with those observed in controlled clinical trials (Cohen et al. 2013; Finger et al. 2013; Holz et al. 2015; Rao et al. 2018).

Risk Factors for the Disease

Refer to demographics for details on risk factors of advanced age, gender, and race. Risk factors are summarized in Table 4.

Table 4 Risk Factors for nAMD

Risk factor	Association	Additional comments
Increasing age (Smith et al. 2001; Li et al. 2020a)	Positive	Risk was found to be significantly higher in patients aged 80–86 years (OR: 20.0) and 70–79 years (OR: 5.96) compared to patients aged 50–69 years
Cigarette smoking (Rim et al. 2017; Detaram et al. 2020)	Positive	The risk of nAMD among past/ current smokers was 50% higher than that among never smokers (propensity-adjusted whole cohort analysis: HR: 1.48 (95% CI: 1.22, 1.79)
Obesity; (Lim et al. 2012 Cheung et al. 2017)	Positive	After adjusting for age and gender, higher BMI (≥30) was significantly associated with nAMD with OR of 1.06 (95% CI: 1.02, 1.09)
Low dietary intake of vitamins A, C, and E (Ng et al. 2019)	Positive	nAMD was associated with lower circulatory levels of carotenoids and omega-3 PUFAs, vitamins C and E
Low dietary intake of lutein and omega-3 fatty acids (Ng et al. 2019)	Positive	nAMD was associated with lower circulatory levels of carotenoids and omega-3 PUFAs, vitamins C and E
Vigorous physical activity (Rim et al. 2018)	Positive in patients aged 45–64 years	Vigorous physical activity was associated with a greater HR for nAMD in participants aged 45–64 years (HR, 1.30 [95% CI: 1.04, 1.63])
Hyperopic refraction (Cheung et al. 2017)	Positive	Results not shown

Table 4 Risk Factors for nAMD (cont.)

Risk factor	Association	Additional comments
CFH (chromosome [chr] 1) (Cheung et al. 2017; Matušková et al. 2020)	Positive	CC genotype of CFH gene polymorphism, showed the greatest risk for nAMD with OR equal to 8.43
ARMS2/HTRA1 (chr 10) (Cheung et al. 2017; Matušková et al. 2020)	Positive	TT genotype of ARMS2 gene polymorphism and AA genotype of HTRA1 gene polymorphism showed the greatest risk for nAMD with ORs equal to 10.07, 9.83, respectively
CFB (properdin; chr 6) (Matuskova et al. 2020)	Positive	Results not shown
CF1 (chr 4) (Lim et al. 2012)	Positive for any form of AMD	Results not shown
ACAD10 locus [OMIM 611181] (Hallak et al. 2019)	Positive	Genetic variant (ACAD10 locus) was associated with conversion to nAMD.
Family history (Lim et al. 2012)	Positive	Results not shown
Sleep deprivation (<6 hours) (Pérez-Canales et al. 2016)	Positive	A significant association between short sleep duration and nAMD was observed (for <6 hours, OR, 3.29 [95% CI: 1.32, 8.27] compared with the reference category of 7–8 hours).

AMD = age-related macular degeneration; ARMS2 = age-related maculopathy susceptibility 2; BMI = body mass index; CF1 = complement factor 1; CFB = complement factor B; CFH = complement factor H; chr = chromosome; HR = hazard ratio; HTRA1 = HtrA serine peptidase 1; nAMD = neovascular age-related macular degeneration; OR = odds ratio; PUFA = polyunsaturated fatty acids.

Natural history of the indicated condition in the (untreated) population:

Some patients develop both advanced stages of AMD: nAMD and geographic atrophy. Untreated nAMD eventually leads to irreversible vision loss and blindness, and it is the most debilitating form of AMD (Ghoshal et al. 2018).

A systematic review of the literature and meta-analysis of publications from 1980 to 2005 identified 4362 untreated nAMD patients. The proportion of patients who developed severe vision loss (>6 lines) from baseline increased from 21.3% at 6 months to 41.9% by 3 years. The proportion of patients with visual acuity worse than logarithm of the Minimum Angle of Resolution (logMAR) 1.0 (20/200 Snellen) increased from 19.7% at baseline to 75.7% by 3 years. nAMD developed in the fellow eye in 12.2% of patients by 12 months and in 26.8% by 4 years (Wong et al. 2008).

A major subtype of nAMD in the Asian population is polypoidal choroidal vasculopathy, which affects up to 50% of Asians with nAMD and tends to present in younger patients

sometimes acutely with massive subretinal hemorrhage and severe vision loss (Fenwick et al. 2017).

The development of nAMD typically manifests in one eye. The presence of nAMD in one eye is a major risk factor for the development of nAMD in the fellow eye (Wong et al. 2020). The symptoms of nAMD are metamorphopsia, scotoma, and blurriness in the central vision, which negatively affect patient mobility, face recognition, reading, driving, and other daily activities, including self-care (Mitchell et al. 2018). An observational study using National Health Insurance Research Database from Taiwan showed a significantly higher risk of stroke in patients with prior nAMD history than for patients without any type of AMD. Prior nAMD history was also related to a higher incidence of hemorrhagic stroke but not ischemic stroke (Lee et al. 2017).

A meta-analysis of nine studies estimated that late AMD was associated with a 20% increased risk of all-cause mortality compared to the patients without AMD. There was evidence of a 46% increased risk of cardiovascular (CV) mortality for those with late AMD compared to those without AMD (McGuinness et al. 2017). Decreased visual acuity is associated with increased five-year mortality and even relatively mild visual impairment increases the risk of death more than two-fold (McCarty et al. 2001).

Findings from long-term follow-up studies regarding a possible association of nAMD with increased mortality risk have been inconsistent. Results from some studies have observed no association between nAMD and mortality (Borger et al. 2003; Pedula et al. 2015); however, nAMD was reported as a significant risk factor for all-cause mortality in women in a population-based 14-year cohort study in people aged 60–80 years in Denmark (Buch et al. 2005) and in men in a 15-year cohort study in Australia (Gopinath et al. 2016). In a cohort study in Iceland, nAMD was associated with all-cause mortality only in the subgroup aged 83 years or older (Fisher et al. 2015), while in the Blue Mountains Eye Study, nAMD was significantly associated with all-cause mortality only among persons younger than 75 years (Cugati et al. 2007). Age-Related Eye Disease Study 2, a randomized, double-masked, controlled trial, reported that participants with nAMD in one eye at baseline had a statistically significant increased risk for mortality compared with participants with no or few drusen. Visual impairment could be associated with depression, which has been linked with poor quality of life and decreased life span (Papudesu et al. 2018).

Given that the prevalence and incidence of nAMD increases with age, and the disease is most prevalent in patients >65 years of age (Table 3; Li et al. 2020a), there is a low likelihood that female patients on treatment for nAMD will be of child-bearing age.

Important Co-morbidities

The key comorbidities in the nAMD population are listed in Table 5.

Table 5 Important Comorbidities in the nAMD Population

Comorbidity	Prevalence, %	Reference
Hyperlipidemia	58.3, 18, 4.5	Hu et al. 2017; Lee et al. 2017; Farinha et al. 2019a
Hypertension	51, 41, 19	Anastasopoulos et al. 2006; Lee et al. 2017; Rim et al. 2017
Diabetes	46, 25.1, 10, 1.6	Soubrane et al. 2007; Hu et al. 2017; Lee et al. 2017; Mao et al. 2019
Cataract	30.3, 28, 22.9, 15	Anastasopoulos et al. 2006; Cruess et al. 2007; Soubrane et al. 2007; Ruiz-Moreno et al. 2008
Depression	18.0	Ruiz-Moreno et al. 2008
Cancer	10.4, 8.2, 5.6	Cruess et al. 2007; Soubrane et al. 2007; Ruiz-Moreno et al. 2008
Renal disease	9.6	Lee et al. 2017
Liver disease	9.3, 6.1	Lee et al. 2017; Rim et al. 2017
Glaucoma	9, 8	Anastasopoulos et al. 2006; Soubrane et al. 2007
Arrhythmia	8.3	Lee et al. 2017
Coronary heart disease	4.9	Mao et al. 2019
Heart failure	4.1	Lee et al. 2017
Anxiety	3.7, 3.4, 1.5	Cruess et al. 2007; Soubrane et al. 2007; Ruiz-Moreno et al. 2008
Stroke	3.5, 2.2	Soubrane et al. 2007; Mao et al. 2019
Cerebrovascular disease	2.0	Rim et al. 2017

nAMD = neovascular age-related macular degeneration.

SI.2 Diabetic Macular Edema

Incidence

Recently published population-based studies that have provided incidence figures for diabetic macular edema (DME) and the clinically significant macular edema (CSME) form of DME are listed in Table 6. The results are grouped by diabetes subtype: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), or any diabetes (mixed population of T1DM and T2DM).

The reported cumulative incidence of DME depended mainly on the length of follow-up of the patients in the different studies and the type of diabetes (Klein et al. 2009; Jones et al. 2012; Romero-Aroca et al. 2017). The highest rates of DME among diabetics are provided by the studies in T1DM populations with very long follow-up times (e.g., 29% in a study with 25-year follow-up) (Klein et al. 2009). It is worth noting that, in the included studies, the follow-up period for T1DM is longer than T2DM because T1DM starts at a young age and the disease has more time to progress. Patients typically develop T2DM later in life; therefore, the disease has less time to progress. T2DM DME

patients often are less compliant with their glycaemia management (i.e., difficult to maintain hemoglobin A1c [HbA1c] levels) and often develop DME (Wong et al. 2006).

The global increase of DME is driven by the DME in T2DM, because there are many more patients with T2DM compared to T1DM (Table 6). When separated based on the type of diabetes, the cumulative incidence of DME ranged from 8.5% to 29% in patients with T1DM (follow-up: 9–25 years), 1.5% to 9.2% in patients with T2DM (follow-up: 5.7–10 years), and 0.8% to 5.4% in patients with any diabetes (follow-up: 4–8 years) (Table 6).

The Wisconsin Epidemiologic study on diabetic retinopathy (DR) in the United States stated that over a 25-year study period, of the 515,000 to 1.3 million Americans with T1DM, approximately 149,000 to 377,000 (approximately 29%) will develop DME and 88,000 to 221,000 (approximately 17%) will develop CSME (Klein et al. 2009).

Table 6 Incidence of DME and CSME in Diabetic Populations Worldwide

Country, Study Period	Follow-Up, years	Sample Size	No. of Cases	Baseline Mean Age ± SD or Age Range, years	IC % or IR per 1000 PY		Reference
					DME [a]	CSME [a]	
Type 1 Diabetes Mellitus							
Finland 1997–2009	30 [b]	1,354	NR	38.7 ± 11.6	—	IC: 17.8	Hietala et al. 2013
Spain 2007–2015	9	366	NR	35.58 ± 10.14	IC: 8.5	—	Romero-Aroca et al. 2017
United States 1980–2007	25	955 at baseline and 891 with at least minimum follow-up of 4 years	213 DME 128 CSME	≤ 30	IC: 29	IC: 17	Klein et al. 2009
Type 2 Diabetes Mellitus							
Spain 2007–2015	9	15,030	NR	65.84 ± 12.39	IC: 6.4	—	Romero-Aroca et al. 2017
United Kingdom, 1990–2006	10	20,686	NR	58.0–74.5	IC: 1.5	—	Jones et al. 2012
Taiwan 2002–2004	5.7	2,101	193	63.3 ± 11.9	IC: 9.2 (95% CI: 8.0, 10.5)	—	Hsieh et al. 2018

Table 6 Incidence of DME and CSME in Diabetic Populations Worldwide (cont.)

Country, Study Period	Follow-Up, years	Sample Size	No. of Cases	Baseline mean age ± SD or age range, years	Cumulative Incidence (IC) % or Incidence Rate (IR) per 1000 Person-Years		Reference
					DME [a]	CSME [a]	
Any Diabetes (mixed population of Type 1 and Type 2 Diabetes Mellitus)							
United Kingdom THIN 2000–2007	8	64,983 (T1DM: 1,757) (T2DM: 63,226)	467	T1DM 34.0; T2DM 62.8	IC: 0.8 IR: 1.8 (95% CI: 1.6, 2.0)	—	Martín-Merino et al. 2014
United States 2000–2008	4	775	NR	≥ 40	IC either eye: 5.4 1st eye 5.0 2nd eye 11.5	—	Varma et al. 2010

CI = confidence interval; CSME = clinically significant macular edema; DME = diabetic macular edema; IC = cumulative incidence; IR = incidence rate; NR = not reported; PY = person-years; SD = standard deviation; T1DM=type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; THIN = The Health Improvement Network.

[a] DME was defined as retinal thickening in the macular area. CSME was defined as the presence of retinal thickening at or within 500 µm of the center of the macula or hard exudates at or within 500 µm of the center of the macula if associated with thickening of the adjacent retina or zones of retinal thickening 1 disc area in size, at least part of which was within 1 disc diameter of the center.

[b] A regression model accounting for competing risk of death was used to estimate the cumulative incidence of CSME over 30 years of diabetes. The mean duration of diabetes of the sample was 24.6 years.

Prevalence

Several population-based studies have provided prevalence figures for DME and CSME. Selected studies are summarized in Table 7, by diabetes subtype.

A pooled analysis of 35 studies including over 20,000 diabetics from Europe, the United States, Australia, and Asia estimated a global prevalence of 6.81% for DME (Yau et al. 2012). By extrapolating prevalence to the 2010 world diabetes population, it was estimated that 20.6 million people are living with DME (Yau et al. 2012). Similar to the incidence data, the prevalence was also reported to be higher in patients with T1DM as compared to T2DM and any diabetes. Also, studies with patients having longer disease duration reported a higher prevalence of DME (Yau et al. 2012; Li et al. 2020b). The prevalence of DME (any level or definition) in studies assessing information directly from fundus photographs was estimated to range from 5.4% to 14.25% in T1DM patients, 0.18% to 5.57% in T2DM, and 2.3% to 7.05% in studies with mixed diabetes population (Table 7). The differences are attributed to different underlying populations in terms of disease etiology and duration or ethnic makeup.

A pooled analysis of 35 European studies reported an overall prevalence of 3.7% in diabetic patients aged ≥40 years (Li et al. 2020b). In Europe, the highest prevalence was reported to be in the United Kingdom, while the lowest was recorded in France. Studies from the United States estimated a DME prevalence of 2.3% to 6.0% in diabetic patients (Bressler et al. 2014; Varma et al. 2014; Bursell et al. 2018), comparatively lower than the Multi-Ethnic Study of Atherosclerosis (MESA) study from the United States in which the prevalence of DME and CSME was reported to be 9.0% and 5.6%, respectively (Wong et al. 2006). The difference may be due to the racial/ethnic composition of the participants included in the MESA study, in which non-Hispanic blacks and Hispanics comprised the majority of the study sample.

Table 7 Prevalence of DME and CSME in Diabetic Populations Worldwide

Data Source	No. of Patients	Baseline mean age ± SD or age range, years	Prevalence, % (95% CI)		Reference
			DME	CSME	
Type 1 Diabetes Mellitus					
Global, pooled analysis from studies 1980–2008	1,864	20–79	Age standardized: 14.25 (13.86, 14.64)	—	Yau et al. 2012
Poland 2012–2016	315	37.0 ± 13.55	5.4	—	Matuszewski et al. 2020
Type 2 Diabetes Mellitus					
Global, pooled analysis from studies 1980–2008	11,244	20–79	Age standardized: 5.57 (5.48, 5.66)	—	Yau et al. 2012
Poland 2012–2016	894	61.2 ± 11.13	4.81	—	Matuszewski et al. 2020
Spain 2008–2012	108,723	66.9 ± 11.0	0.18	—	Rodriguez-Poncelas et al. 2015
Germany, Austria 2000–2013	64,784	68.7	0.8	—	Hammes et al. 2015
Taiwan 2002–2004	2,135	63.3 ± 11.9	1.6	—	Hsieh et al. 2018
Any Diabetes					
Global, pooled analysis from 32 studies 2015–2018	543,448	20–80	4.6	—	Thomas et al. 2019
Global, pooled analysis from 35 studies 1980–2008	22,896	20–79	Age standardized: 6.81 (6.74, 6.89)	—	Yau et al. 2012

Table 7 Prevalence of DME and CSME in Diabetic Populations Worldwide (cont.)

Data Source	No. of Patients	Baseline mean age ± SD or age range, years	Prevalence, % (95% CI)		Reference
			DME	CSME	
Europe, pooled analysis of 35 studies until 2017	205,743	40 and older	—	Pooled: 3.7 (2.2, 6.2) Germany: 2.3 (0.6, 8.4) France: 1.3 (0.5, 2.9) UK: 5.2 (2.5, 10.7) Spain: 2.7 (1.6, 4.6)	Li et al. 2020b
United Kingdom 2007–2010	48,450	Not stated	—	13.9 Centre-involving: 7.4	Keenan et al. 2013
United Kingdom 2004–2005	27,178	Not stated	7.05 (6.75, 7.37) Bilateral: 2.33 (2.15, 2.52)	resulting in sight loss: 2.75 (2.56, 2.95)	Minassian et al 2012
Norway 2007–2008	514 (T1DM = 18)	46-87	3.9	—	Bertelsen et al. 2013
U.S. NHANES 2005–2008	1038	≥ 40	3.8 (2.7, 4.9) Black: 8.4 White: 2.6 Hispanic: 5.1	—	Varma et al. 2014
U.S. NHANES 2005–2008	798	≥ 40, mean age not stated	6.01 (4.6, 8.0)	—	Bressler et al. 2014
United States 2011–2016	46,584	52.7 ± 12.8	2.3	—	Bursell et al. 2018
Singapore Year/time period not stated	757	62.5 ± 9.42	5.7 (3.2, 9.9)	—	Wong et al. 2008

CI = confidence interval; CSME = clinically significant macular edema; DME = diabetic macular edema; NHANES = National Health and Nutrition Examination Survey; SD = standard deviation; T1DM = type 1 diabetes mellitus; U.S. = United States.

Demographics

Duration of disease: The key factor in the development of DME is diabetes duration, irrespective of disease type (Yau et al. 2012). A pooled analysis reported that the prevalence of DME was 3.1% in patients with < 10-year diabetes duration, 13.4% in 10–< 20 years diabetes duration, and 20% in patients with ≥ 20 years of diabetes duration (Yau et al. 2012). A study in the United States estimated that 70% of DME patients had a duration of diabetes of 10 years or more (Varma et al. 2014).

Age: The average age of patients depends on the diabetes type, with a mean age of T2DM patients with DME of about 60–70 years (Hietala et al. 2013; Matuszewski et al. 2020), and a mean age of T1DM patients with DME of about 37–50 years (Hsieh et al. 2018; Matuszewski et al. 2020).

Gender: The prevalence was estimated to be similar in men (7.44%) and women (7.54%) from a pooled analysis of 32 studies globally (Yau et al. 2012).

Racial disparity: Based on ethnicities, a higher prevalence was reported in African patients followed by Caucasian and Chinese and lowest in South Asian patients with diabetes (Yau et al 2012). A study from the United States reported the prevalence of 3.8% for DME and also reported the highest prevalence among African Americans (8.4%), followed by Hispanics (5.1%), and non-Hispanic Whites (2.6%) (Varma et al. 2014). A retrospective data analysis study of American Indians and Alaska Natives with diabetes reported the prevalence of 2.3% for DME (Bursell et al. 2018).

Geographical distribution: A pooled analysis of 35 European studies reported an overall prevalence of 3.7% in diabetic patients aged ≥40 years (Li et al. 2020b). The prevalence of DME and CSME in the United States in overall T1DM and T2DM patients was 4.31% and 0.23%, respectively (Thomas et al. 2019). Based on geographical distribution, the prevalence of DME (T1DM and T2DM) was estimated to be highest in African regions (21.5%). The prevalence of DME in persons with T1DM in Europe and Africa was 8.8% and 13.5%, respectively. Regarding T2DM, the prevalence of DME was much higher in Africa and Western Pacific at 41.0% and 19.1%, respectively (Thomas et al. 2019).

The Main Existing Treatment Options

Focal macular laser used to be first-line therapy in the treatment of DME, but the development of anti-VEGF biologics in the last 10 years has led to dramatic improvements in visual outcomes for patients with DME (Elman et al. 2010). Currently available approved anti-VEGF therapies for DME include ranibizumab (Lucentis®, Accentrix®, Cimerli™), aflibercept (Eylea® and Eylea HD®), and brolucizumab (Beovu®). All three therapies are approved for patients with visual impairment due to DME in the EU and the United States. Despite the significant improvements in both vision and anatomical outcomes achieved with anti-VEGF injections in DME, the current standard of care for management requires patients to undergo frequent clinical examinations and

intravitreal injections. This imposes a significant burden on patients, caregivers, treating physicians, and the healthcare system; thus, the average number of injections received and the consequent improvements in vision are lower in the real-world setting than in clinical trials (Fong et al. 2018; Hodzic-Hadzibegovic et al. 2018; Stefanickova et al. 2018; Ziemssen et al. 2018; Farinha et al. 2019b).

Other available approved options for the treatment of DME include periocular or intravitreal steroids and steroid implants. In particular, long-acting steroid implants have become popular for use in patients who are not able to come back for frequent visits and have a strong inflammatory component of the disease. In non-responders who have already been treated with anti-VEGFs (after 3–6 injections, depending on the specific response of each patient), switching to another anti-VEGF agent or, in specific cases, steroids may be recommended. However, steroids are associated with an increased and earlier risk of cataract, glaucoma, secondary infection and delay in wound healing (AAO 2013).

Risk Factors for the Disease

A study in the United Kingdom reported that DME risk increased with high alcohol use, cataracts, HbA1c ≥7%, systolic blood pressure ≥160 mm Hg, total cholesterol ≥5 mmol/L, low-density lipoprotein cholesterol ≥3 mmol/L, and microalbuminuria (Martin-Merino et al. 2017). A study in Turkey reported that duration of diabetes, use of antihypertensives, higher level of high-density lipoprotein cholesterol, alcohol consumption, nephropathy, neuropathy, previous cataract surgery, severity of DR, and insulin usage were statistically significantly associated with DME (Acan et al. 2018).

A study from the United States on 447,407 patients with diabetes reported that African-Americans and Latinos had an increased hazard of developing DME compared with Caucasians. Other risk factors identified in the study were diabetic neuropathy or diabetic nephropathy, uncomplicated hypertension, end-organ damage caused by hypertension, and increases in the baseline value of HbA1c lab tests (Talwar et al. 2013).

Natural history of the indicated condition in the (untreated) population:

DME is an advanced manifestation of DR and the major cause of central vision loss among patients with DR (Leasher et al. 2016; Yoon et al. 2019). If left untreated, DME can lead to a loss of 10 or more letters in visual acuity within 2 years in approximately 50% of patients (Ciulla et al. 2003). It can develop at any stage of the underlying disease of retinal microvasculature (Fong et al. 2004). This disease contributes to central vision loss, limiting the ability to perform tasks essential for daily life and maintaining self-sufficiency, and is associated with increased social isolation and decreased mental health in this patient population comprised primarily of working-age adults (Hariprasad et al. 2008).

A retrospective study showed that over a period of 14 months, 48 of the 153 eyes (31%) with subclinical DME progressed to CSME that, in the opinion of the treating clinicians, required treatment (Browning and Fraser 2008). In a Diabetic Retinopathy Clinical Research Network study (Protocol G), the probability of an eye developing a significantly increased central subfield thickness, or judged by clinicians to warrant treatment for DME by 1 year and by 2 years, were 27% and 38%, respectively (Bressler et al. 2012).

In one European study, 5 out of 48 eyes (10%) with baseline subclinical DME developed clinical macular edema after 12 months (Tejerina et al. 2015). Another European study reported that 6 out of 32 eyes (19%) with subclinical DME at baseline progressed to CSME over the course of 24 months, while only 20 out of 316 eyes (6%) without subclinical DME at baseline progressed to CSME, suggesting that subclinical DME is likely to progress to CSME if left untreated (Pires et al. 2013).

A meta-analysis of six studies found a linear relation between visual acuity and the risk of mortality (Zhang et al. 2016). For every 0.1 logMAR increment, the risk of mortality increased by 4%. When the analysis was restricted to the studies that were conducted in the following four continents, the risk of mortality increased by 29% in North America, 44% in Oceania, 80% in Asia, and 22% in Europe in patients with visual impairment (Zhang et al. 2016).

A study reported hazard ratios for all-cause mortality, ischemic heart disease, and stroke death for those with CSME and T1DM or T2DM (Hirai et al. 2008). Results were adjusted for age, gender, diabetes mellitus duration, body mass index, HbA1c, history of CV disease, nephropathy, hypertension, and smoking status. In the fully adjusted models when comparing to those without CSME, mortality appeared to be increased for T2DM patients with CSME, especially among those treated with insulin. In contrast, T1DM patients with CSME did not appear to be at an increased risk of death compared to T1DM without CSME (Hirai et al. 2008).

Limited information is available for prevalence of pregnancy in the DME population. Prevalence estimates for presence of DME at any time during pregnancy range from 5% to 27% in T1DM and 4% in T2DM (Morrison et al. 2016). DME may develop or worsen during pregnancy and is generally observed in pregnant patients with proteinuria or hypertension (Yenerel and Küçümen 2015). In a prospective study of 102 pregnant women with T1DM (median T1DM duration: 16 years), 10 participants with macular edema had no progression in pregnancy while 2 participants had mild-moderate progression and 4 participants had sight-threatening progression (Vestgaard et al. 2010). In a Danish study that included 121 pregnant women with T1DM for more than 1 year, DME was present in 12 participants with progression occurring in 4 of the participants (Ringholm et al. 2011). DME occurring during pregnancy is likely to resolve spontaneously in the postpartum period. Women with DME undergoing treatment with anti-VEGF medications are advised to use active contraception during treatment. Anti-VEGF medications should only be administered during pregnancy if the

potential benefit justifies the risk to the fetus and women should be appropriately informed of the risk (Morrison et al. 2016).

Important Co-morbidities

The key comorbidities in the DME population are listed in Table 8.

Table 8 Important Comorbidities in the DME Population

Comorbidity	Prevalence, %	Reference
Hypertension	66.6, 63.5, 10.6	Yau et al. 2012; Martin-Merino et al. 2017; Acan et al. 2018
Cataract	27.5, 17.1	Kiss et al. 2016; Martin-Merino et al. 2017
Hyperlipidemia	16	Acan et al. 2018
Renal disease	13.1	Kiss et al. 2016
Glaucoma	8.2, 6.2	Kiss et al. 2016; Martin-Merino et al. 2017
Congestive heart failure	5.3	Kiss et al. 2016
Cerebrovascular disease	4.5	Kiss et al. 2016
Myocardial infarction	1.9	Kiss et al. 2016
Stroke	1.4	Kiss et al. 2016

DME = diabetic macular edema.

SI.3 Retinal Vein Occlusion

Incidence

The incidence of retinal vein occlusion (RVO) in the United States, Australia, and Asia are reported in Table 9. Incidence data for RVO in the European Union are not yet available (Li et al. 2019; Song et al. 2019).

A global meta-analysis of 6 studies from the United States, Australia, Japan, and China reported the cumulative 5-year and 10-year global incidence of RVO as 0.86% and 1.63%, respectively (Song et al. 2019).

The incidence of branch RVO (BRVO) is generally higher than the incidence of central RVO (CRVO). In the United States, the 5-year incidence of BRVO was 0.6% and the incidence of CRVO was 0.2% (Klein et al. 2000); at 15 years, the incidences were 1.8% and 0.5% (Klein et al. 2008), respectively. In Australia, the incidence of BRVO (1.2%) is about three times greater than CRVO (0.4%) over 10 years (Cugati et al. 2006).

Macular edema (ME) is a major complication of RVO that results in significant visual impairment. Macular edema has been reported to develop in about 5%–15% of BRVO cases within the first year of diagnosis, while most CRVO diagnoses are accompanied by signs of ME (Laouri et al. 2011). In Australia, the frequency of ME among cases with BRVO ≥49 years of age was reported to be 18.5% in a span of 10 years (1994–2004) (Cugati et al. 2006). Klein et al. found that the frequency of ME among RVO patients was 30.4% in a span of 15 years (1990–2005). Furthermore, in Canada, the annual

incidence of visual impairment due to ME secondary to RVO among patients 40 years and older was reported to be 0.06% for BRVO and 0.02% for CRVO (Petrella et al. 2012).

Table 9 Reported Incidence of RVO Worldwide

Country, Study Period	Follow-up Time, years	Sample Size	No. of events	Baseline Mean Age ± SD or Age Range, years	IC, % (RVO)	Reference
Global, 2000–2018	10	—	—	43–89	5-year cumulative incidence 0.86 (95% CI: 0.70, 1.07) 10-year: 1.63 (95% CI: 1.38, 1.92)	Song et al. 2019
United States, 1988–1995	5	3,684	28	48–89	5-year cumulative incidence RVO: 0.80 (95% CI: 0.53, 1.1) BRVO: 0.6 (95% CI: 0.3, 0.8) CRVO: 0.2 (95% CI: 0.1, 0.3)	Klein et al. 2000
United States, 1988–2005	15	—	83	43–85	15-year cumulative incidence RVO: 2.3 BRVO: 1.8 (95% CI: 1.4, 2.2) CRVO: 0.5 (95% CI: 0.3, 0.8)	Klein et al. 2008
Australia, 1992–2004	10	2346	37	≥49	10-year cumulative incidence RVO: 1.6 (95% CI: 1.1, 2.2) BRVO: 1.2 (95% CI: 0.8, 1.7) CRVO: 0.4 (95% CI: 0.1, 1.7)	Cugati et al. 2006
China, 2001–2011	10	—	49 (51 eye)	≥40	10-year cumulative incidence RVO: 1.9 BRVO: 1.6 CRVO: 0.3	Zhou et al. 2013
South Korea, 2002–2015	12	49,705,663	240,495	—	12-year cumulative incidence RVO: 0.48 (95% CI: 0.48, 0.49)	Park et al. 2020
Japan, 1998–2007	9	1,369	41	60.0 ± 10.0	9-year cumulative incidence RVO: 3.0 (95% CI: 2.2, 4.0) BRVO: 2.7 CRVO: 0.3	Arakawa et al. 2011

BRVO = branch retinal vein occlusion; CI = confidence interval; CRVO = central retinal vein occlusion; IC = cumulative incidence; RVO = retinal vein occlusion; SD = standard deviation.

Prevalence

In Europe, a meta-analysis of four studies reported a pooled prevalence of RVO of 0.7% in the population aged 55 years and above (Li et al. 2019).

Overall, the prevalence of RVO appears to be similar across all countries; however, Japan reported a higher prevalence compared to other countries (Yasuda et al. 2010).

A pooled analysis of 17 studies reported an overall age-standardized global prevalence of RVO, BRVO, and CRVO as 0.77%, 0.64% and 0.13% respectively among individuals aged 30–89 years in 2015 (Song et al. 2019). Another pooled analysis using individual population-based data on BRVO and CRVO in the United States, Europe, Asia, and Australia estimated an age- and sex-standardized global prevalence of 0.44% for any RVO, 0.38% for BRVO, and 0.07% for CRVO in the population aged ≥30 years in 2008 (Rogers et al. 2010a). As of 2015, approximately 28.06 million adults worldwide were affected by any type RVO, of which 23.38 million are BRVO patients and 4.67 million are CRVO patients. The estimated global prevalence of RVO increased with advanced age but did not show significant differences between sexes (Song et al. 2019).

The prevalence of RVO in individual studies was reported to be 0.6% in the United States (Klein et al. 2000), 0.87% in Australia (Keel et al. 2018), 0.7% in Singapore (Lim et al. 2008), and 2.1% in Japan (Yasuda et al. 2010) in populations older than 40 years.

There are no studies specifically describing the prevalence of ME secondary to RVO. For information on the incidence of ME secondary to RVO, please refer to the incidence section above.

Table 10 represents evidence describing the prevalence of RVO.

Table 10 Reported Prevalence of RVO Worldwide

Country, Study, Period	Study Type, Population Characteristics	Sample Size	Age Range, Years	Prevalence, % (RVO)	Reference
Global	Pooled analysis of 17 studies	120,771	30–89	RVO: 0.77 (95% CI: 0.55, 1.08) BRVO: 0.64 (95% CI: 0.47, 0.87) CRVO: 0.13 (95% CI: 0.08, 0.21)	Song et al. 2019
Global	Pooled analysis of 15 population-based studies	68,751	30–101	RVO: 0.44 (95% CI: 0.40, 0.51) BRVO: 0.38 (95% CI: 0.31, 0.45) CRVO: 0.07 (95% CI: 0.05, 0.08)	Rogers et al. 2010a
Europe	Meta-analysis of 4 studies published between 1996 and 2016	25,002	55 and above	RVO: 0.7 (95% CI: 0.5, 0.9)	Li et al. 2019
United States, 1988–1995	Population-based retrospective cohort study	4,926	48–89	BRVO: 0.6 (95% CI: 0.4, 0.9) CRVO: 0.1 (95% CI: 0, 0.3)	Klein et al. 2000
Singapore, 2004	Population-based, cross-sectional study	3,280	40–80	RVO: 0.7 (95% CI: 0.4, 1.0)	Lim et al. 2008
Japan, 1998	Population-based prospective cohort study	1,775	40 years and above	RVO: 2.1 (95% CI: 1.6, 2.9) BRVO: 2.0 (95% CI: 1.4, 2.7) CRVO: 0.17 (95% CI: 0.06, 0.5)	Yasuda et al. 2010
Australia, 2015–2016	Cross-sectional, population-based study	4,692	40–98	RVO: 0.87 (95% CI: 0.64, 1.2) BRVO: 0.72 (95% CI: 0.52, 1.0) CRVO: 0.15 (95% CI: 0.07, 0.31)	Keel et al. 2018

BRVO = branch retinal vein occlusion; CI = confidence interval; CRVO = central retinal vein occlusion; RVO = retinal vein occlusion.

Demographics

Age: Across the age spectrum from the early 30s to late 80s, the prevalence of any RVO increased steadily with increasing age. Based on a meta-analysis of 17 prevalence studies, the prevalence of BRVO ranges between 0.23% in people aged 30–39 years to 2.64% in those aged 80–89 years, and that of CRVO from 0.03% (30–39 year age group) to 0.75% (80–89 year age group). For any RVO, the prevalence increased from 0.26% in individuals aged 30–39 years to 3.39% in those aged 80–89 years (Song et al. 2019).

Gender: A systematic review described that the prevalence of RVO was similar between men and women in all studies that reported the prevalence by gender (Laouri et al. 2011). A similar finding was observed by another systematic review and meta-analysis with overall prevalence of any RVO (aged 30–89 years) was 0.74% in men and 0.81% in women. In subtype analysis, the overall prevalence in men versus women was also similar for BRVO (0.64% vs 0.65%) and CRVO (0.13% vs 0.13%) (Song et al. 2019).

Racial disparity: Limited studies compared the prevalence of RVO by race, as most of the studies enrolled subjects belonging to a single ethnic group. Prevalence varied by race/ethnicity and increased with age, but did not differ by gender. In the pooled analysis, the age- and sex-standardized prevalence of any RVO was 0.37% (95% CI: 0.28, 0.46) in Whites (5 studies), 0.39% (95% CI: 0.18, 0.60%) in Blacks (1 study), 0.57% (95% CI: 0.45, 0.68%) in Asians (6 studies), and 0.69% (95% CI: 0.57, 0.83%) in Hispanics (3 studies). The prevalence for CRVO was lower than BRVO in all ethnic populations. The prevalence for any RVO was highest in Asians and Hispanics and lowest in Whites (Rogers et al. 2010a).

The Main Existing Treatment Options

Based on clinical practice guidelines in Europe (Schmidt-Erfurth et al. 2019), United States (Flaxel et al. 2020), and the United Kingdom (The Royal College of Ophthalmologists 2022), anti-VEGF agents are recommended as the first-line treatment of ME secondary to RVO, based on the fact that VEGF-A is a key cytokine that mediates vascular leakage which causes ME in RVO. Currently, two anti-VEGF drugs are used to treat RVO, ranibizumab and aflibercept, which are both EMA and U.S. FDA approved. Additionally, bevacizumab (Avastin®), which is unlicensed for ocular use, is broadly used to treat RVO in clinical practice worldwide.

Intravitreal corticosteroids are also used to treat RVO patients, but largely as a second-line treatment, due to the risk of complications such as steroid-induced cataract and glaucoma (Ip et al. 2009). However, corticosteroids may be considered as a first-line therapy for patients who have had a recent history of a major cardiovascular event and who are therefore contraindicated for anti-VEGF treatment. Corticosteroids may also be considered as first-line therapy in patients who are non-compliant with monthly injections (and/or monitoring) in the first six months of therapy. Triamcinolone was the first steroid used intravitreally as an off-label treatment for ME (Schmidt-Erfurth et al. 2019). The

EMA (in 2010) and U.S. FDA (in 2009) approved a sustained-release intravitreal 0.7 mg dexamethasone (Ozurdex®) delivery system for the treatment of ME secondary to RVO. The drug is also licensed in the United Kingdom for the treatment of adult patients with ME following CRVO.

Panretinal laser photocoagulation (PRP) is the standard of care for the treatment of neovascular complications associated with RVO. These include retinal and disc neovascularization secondary to BRVO or CRVO, as well as iris neovascularization. Laser treatment can be withheld in patients with extensive retinal ischemia who require close follow-up until neovascularization is detected. Otherwise, prophylactic laser photocoagulation should be considered. Laser treatment for ME secondary to BRVO has been shown to be effective for visual improvement but in view of the availability of anti-VEGF therapy, focal laser photocoagulation should be considered only as a second-line treatment (Schmidt-Erfurth et al. 2019; Flaxel et al. 2020;The Royal College of Ophthalmologists 2022).

Risk Factors for the Disease

The most recognized risk factors for RVO are age and systemic vascular disorders. In over half of the cases, the age of onset is over 65 years. Systemic diseases such as hypertension, hyperlipidemia, and diabetes mellitus are very strongly associated with the development of RVO (Kolar 2014). The most common ocular risk factor associated with RVO is glaucoma. Some known risk factors are summarized in Table 11.

Table 11 Risk Factors for RVO

Systemic risk factors	Ocular risk factors
Hypertension	Glaucoma
Diabetes mellitus	Decreased ocular perfusion pressure
Hyperlipidemia	External retrobulbar compression-orbital neoplasma and endocrine orbitopathy
Atherosclerotic associated diseases: ischemic heart disease, obesity (high body mass index), and cigarette smoking	Retinal arteriolar signs-focal arteriolar narrowing and arteriovenous nicking
Systemic vasculitis: systemic lupus erythematosus, sarcoidosis, and syphilis	
Hematologic neoplasia: polycythemia vera, multiple myeloma, and leukemia	
Hypercoagulation diseases: antiphospholipid syndrome, and protein S deficiency	
Drug therapy: oral contraceptives, diuretics, and hypotensive drugs	

RVO = retinal vein occlusion.
Source: Kolar 2014.

Natural history of the indicated condition in the (untreated) population: Disease Progression and Outcome:

A systematic review of the natural history of BRVO patients found that the overall visual acuity in untreated symptomatic BRVO cases is poor at baseline, ranging from 20/40 to less than 20/200 (Rogers et al. 2010b). Over time, visual acuity generally improves, with between one-third and three-quarters of eyes with BRVO showing at least a 2-line improvement in visual acuity, and mean visual acuity improving by 1 letter at 3 months to 15 letters over 18 months. However, clinically significant improvement beyond 20/40 is uncommon. The review suggested that over a 1-year period, 5% to 15% of eyes with BRVO develop ME, although for those with ME at baseline, 18% to 41% resolve. BRVO is categorized as mild, moderate, or marked, based on the level of capillary nonperfusion seen angiographically.

Eyes with BRVO and significant capillary nonperfusion can develop retinal neovascularization and vitreous hemorrhage, but they are much less likely to develop neovascular glaucoma than eyes with CRVO or hemi-CRVO (Flaxel et al. 2020). Early clinical findings include vascular tortuosity, venous dilation of the affected veins, retinal edema, intraretinal hemorrhages, cotton wool spots, and occasionally hard exudates or even retinal detachment in the affected region. Over time, the acute process resolves, and the hemorrhages may clear, along with the cotton wool spots. In general, the ME persists and is a common cause of visual dysfunction unless appropriately treated. Collaterals may also develop between the superior and inferior retinal veins in a BRVO (Flaxel et al. 2020).

Typically, patients present with acute visual symptoms in one eye due to ME. At the time patients were recruited to the studies from the systematic review, bilateral BRVO was present in 4.5% to 6.5% of BRVO cases. Nine percent of patients with BRVO had RVO in the fellow eye, but it is unclear whether this was at baseline or developed over time (Rogers et al. 2010b). Over an unknown length of time, 10% of BRVO cases developed a BRVO in the second eye (Rogers et al. 2010b).

A systematic review of the natural history of untreated CRVO patients found that in all CRVO cases, including nonischemic CRVO, baseline visual acuity was generally poor ($<$20/40) and most studies reported a mean decrease in visual acuity over time. Ischemic CRVO cases had poorer vision (i.e., baseline visual acuity of 9 letters; approximate Snellen equivalent 20/640) at presentation and follow-up. Up to 34% of nonischemic CRVO eyes converted to ischemic CRVO over a 3-year period (McIntosh et al. 2010).

Patients with CRVO were likely to develop ME (Laouri et al. 2011). Additionally, approximately 25% of patients with CRVO will develop iris neovascularization, and some patients may go on to develop retinal neovascularization (Hayreh and Zimmerman 2012; Flaxel et al. 2020). In patients with nonischemic CRVO, ME resolved in approximately 30% over time and development of neovascular glaucoma was rare. In ischemic CRVO

cases, neovascular glaucoma developed in at least 23% within 15 months (McIntosh et al. 2010). At the time of presentation, bilateral CRVO was present in 0.4% to 43% of CRVO cases (note that the latter proportion is based on a case series of 7 patients). Over the various follow-up periods, 1.4% of CRVO cases developed a CRVO in the second eye over a 3-year period, 5% developed a BRVO in the second eye over a 30-month period, and 5% of CRVO cases developed any RVO over a 1-year period (McIntosh et al. 2010).

Mortality and Morbidity: Patients with a CRVO have a higher mortality rate than controls in an age-adjusted general population. A register-based cohort study in Denmark reported that mortality was higher in patients with CRVO (adjusted HR 1.45; 95% CI: 1.19, 1.76) compared to the control cohort (adjusted for age, gender, and time of diagnosis). However, the risk association became less pronounced and statistically insignificant between the two groups (HR: 1.19; 95% CI: 0.96, 1.46) when adjusting for overall occurrence of cardiovascular disease and diabetes (Bertelsen et al. 2014). Another study in Denmark found that RVO was associated with incident cardiovascular disorders (adjusted HR 1.13; 95% CI: 1.09, 1.17) but not mortality (adjusted HR 1.01; 95% CI: 0.98, 1.03). Almost similar risks of CVD were found for patients with BRVO and CRVO (adjusted HR 1.14; 95% CI: 1.03, 1.25, and adjusted HR 1.12; 95% CI: 1.00, 1.25, respectively), but only patients with CRVO exhibited increased mortality (adjusted HR 1.18; 95% CI: 1.11, 1.26) (Frederiksen et al. 2022).

Important Co-morbidities

The key comorbidities in the RVO population in patients aged 40 years and above are listed in Table 12.

Table 12 Important Comorbidities in the RVO Population

Comorbidity	Prevalence, %	Reference
Cardiovascular disease*	79	Bertelsen et al, 2012
Hypertension	83.6; 72	Bertelsen et al, 2012; Chen et al. 2020
Hyperlipidemia	29.8	Chen et al. 2020
Diabetes	19.8; 13	Bertelsen et al, 2012; Chen et al. 2020
Glaucoma	12.4	Chen et al. 2020
Obesity	11.1	Chen et al. 2020
Ischemic heart disease	11	Bertelsen et al. 2012
Cerebrovascular disease	6.6	Bertelsen et al. 2012
Peripheral artery disease	4.4	Bertelsen et al, 2012
Myocardial Infarction	3.8	Bertelsen et al. 2012
Heart failure	2.2	Bertelsen et al. 2012
Renal disease	1.4	Bertelsen et al. 2012
Liver disease	0.6	Bertelsen et al. 2012

Note: *Cardiovascular disease includes hypertension, cerebrovascular disease, ischemic heart disease, congestive heart failure, peripheral vascular disease, and use of cardiovascular drugs.

PART II: MODULE SII — NONCLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from nonclinical studies and relevance to human usage are presented below.

Repeat-dose Toxicity:

In the 2-month and 6-month Good Laboratory Practice studies in cynomolgus monkeys (Report 1053361; Report 1057630), dose-dependent ocular inflammatory cell infiltration and clinical signs of ocular inflammation occurred in faricimab-treated eyes following intravitreal injection every 4 weeks (Q4W), starting from the mid doses of 3- or 1.5-mg/eye/dose up to the high doses of 6- and 3-mg/eye/dose, respectively. Ocular findings in the 2- and 6-month studies generally correlated with the systemic presence of anti-drug antibodies (ADAs) and exposure loss in the serum of all animals with ocular inflammation until the end of the treatment period. Subsequent immunohistochemistry (IHC) evaluations confirmed these findings to be consistent with an immune-mediated response (and subsequent complement activation) to a humanized antibody such as faricimab in non-human primates, as previously shown in rabbits (Meyer 1987).

No clinical ocular findings were observed in recovery animals after a 4- or 13-week treatment-free recovery period in the 2- and 6-month studies, respectively. Histopathological ocular findings of inflammatory cell infiltration seen in recovery animals were considered to represent partial reversal of the inflammatory cell infiltration seen at the terminal sacrifice in other animals. There were no relevant findings in the untreated eyes receiving vehicle injections Q4W up to 6 months of treatment.

At the end of the 4-week recovery period in the 2-month study, faricimab-related minimal mixed cell inflammation was present in the aortic root in one male from each of the 6 mg/eye/dose intravitreal injection and 5 mg/kg intravenous (IV) dose groups. IHC evaluations also confirmed these findings to be consistent with an immune-mediated response (and subsequent complement activation) in monkeys. No extra-ocular findings were observed in the 6-month study in monkeys (Report 1057630).

Relevance to Human Use:

The observed inflammatory response in the eye and at the aortic root is attributed to an immune-mediated response against the humanized full-length immunoglobulin G1 antibody faricimab in cynomolgus monkeys. Therefore, limited clinical relevance is attributed to these findings in terms of predicting the potential immunogenicity/ADA formation against faricimab in humans. This assessment is further supported by the development experience with the anti-VEGF antibody fragment ranibizumab. Although the repeat-dose intravitreal injection ocular toxicity studies in monkeys with ranibizumab resulted in ADA-related intraocular inflammation (IOI), the clinical safety and ADA data from the Phase I, II, and III studies across multiple disease indications showed no clear correlation between serum antibodies and ocular inflammation or decrease in visual

acuity (Lucentis Summary of Product Characteristics [SmPC]). These findings further support that immunogenicity in nonclinical species is caused by xenoantigens (i.e., immune reactions not occurring in the autologous species) and is of limited value as a predictor of immunogenicity in humans (van Meer et al. 2013).

As with all therapeutic proteins, there is a potential for immunogenicity with faricimab. ADAs are indicators of an immune response to the administered therapeutic protein, which for intravitreal injection drugs could potentially result in IOI. The incidence of ADA induction/boosting across all pivotal Phase III studies was approximately 10% (nAMD: 13.8%; DME: 9.6%, RVO: 8.0%) (Annex 7C.1; Annex 7C.2; Annex 7C.3). Overall, the incidence rate of IOI was low in nAMD (3.0%), DME (1.6%), and RVO (1.4%) pivotal Phase III studies (Annex 7C.10; Annex 7C.12; Annex 7C.14). Based on all available data to date, no meaningful impact of ADA was observed on efficacy, pharmacodynamics, and overall safety. A higher incidence of IOI was observed in ADA-positive patients (nAMD: 12/98 [12.2%], Annex 7C.4; DME: 15/128 [11.7%], Annex 7C.5; RVO: 1/54 [1.9%], Annex 7C.6) compared with ADA-negative patients (nAMD: 8/562 [1.4%], Annex 7C.7; DME: 5/1124 [0.4%], Annex 7C.8; RVO: 8/543 [1.5%], Annex 7C.9), however the clinical impact of this observation is currently unknown. Based on the small number of ADA-positive patients compared to ADA-negative patients, and the low incidence of IOI for which the majority of the events were of mild-to-moderate severity and had a reversible character, patients receiving faricimab in ongoing Phase III clinical trials will continue to be monitored for signs and symptoms that might be suggestive of immunogenicity.

Reproductive/Developmental Toxicity:
The 2- and 6-month studies in cynomolgus monkeys did not reveal any effects of faricimab on fertility or reproductive organs (Report 1053361; Report 1057630). In the 6-month monkey toxicology study, systemic exposures at the highest dose were 8–10-fold greater than faricimab human steady-state systemic exposure estimates in nAMD, DME, and RVO patients. In an embryofetal development study in pregnant cynomolgus monkeys there were no effects of faricimab on the course and outcome of pregnancy or fetal viability following 5 weekly IV injections at up to 3 mg/kg (Report 1093222). Serum exposure (maximum serum concentration [C_{max}]) at the no-observed-adverse-effect-level (NOAEL) dose of 3 mg/kg was approximately 500-fold greater than faricimab human steady-state systemic exposure estimates in nAMD, DME, and RVO patients.

Relevance to Human Use:
VEGF is a major angiogenic factor involved in the formation of new blood vessels during embryonic and fetal development and placentation. VEGF inhibition has been shown to affect follicular development, corpus luteum function, and fertility. The pharmacological inhibition of angiogenesis by faricimab is generally expected to have adverse consequences on the female reproductive cycle, since angiogenesis plays a critical role in ovarian and endometrial function (Klauber et al. 1997). In general, all anti-angiogenic

agents are expected to be teratogenic or otherwise harmful for the fetus and are thus not recommended for use during pregnancy (Lambertini et al. 2015; Lucentis EU SmPC; Avastin EU SmPC).

Angiopoietin-2 (Ang-2) is expressed at sites of vascular remodeling in the embryo and placenta (Seval et al. 2008). Knockout mice deficient in Ang-2 die at birth due to vessel defects as Ang-2 is required for postnatal angiogenesis and lymphatic patterning, and only the latter role is rescued by Ang-1 (Gale et al. 2002). As with VEGF, inhibition of Ang-2 is expected to cause impairment in embryofetal development, if systemic exposure and transplacental uptake is sufficient. In the eye, Ang-2 depletion caused pericyte dropout in the normal retina (Hammes et al. 2004). There are currently no marketed drugs that solely inhibit Ang-2.

In patients, the systemic exposure to faricimab following unilateral intravitreal administrations of 6 mg faricimab is low, with a mean C_{max} of 0.2 μg/mL appearing approximately 2 days post-dose and mean trough concentration (C_{trough}) of 0.003 μg/mL, for every 8 weeks (Q8W) dosing without accumulation after multiple administrations. In line with the low systemic exposure, no suppression from baseline in VEGF-A or Ang-2 was observed in plasma of patients dosed with faricimab in the pivotal Phase III studies (TENAYA, LUCERNE, YOSEMITE, RHINE, BALATON, COMINO).

Furthermore, in pregnant cynomolgus monkeys, faricimab at serum exposure (C_{max}) more than 500-times greater than the faricimab human steady-state systemic exposure estimates there were no developmental toxicity, teratogenicity, or effect on weight or structure of the placenta observed. However, because of the anti-angiogenic mechanism of action, faricimab should be regarded as potentially teratogenic and embryo-/fetotoxic, and as a precautionary measure it is preferable to avoid use during pregnancy unless the potential benefit outweighs the potential risk to the fetus.

General Safety Pharmacology:

In compliance with International Council for Harmonisation S6 (R1) guidance, safety pharmacological endpoints were integrated in the 2- and 6-month cynomolgus monkey studies (Report 1053361; Report 1057630). Faricimab did not induce any neurological findings up to 6 months of treatment. Heart rate and electrocardiogram endpoints, including QT and QTc, were comparable between control and faricimab-dosed groups. In addition, no notable findings were recorded for respiratory rate or body temperature measurements.

Relevance to Human Use:

In patients, the systemic exposure to faricimab via intravitreal injections is low. No adverse effects on general safety pharmacology endpoints were observed in the nonclinical program up to the highest doses, achieving C_{max} of about 10- up to more than 700-fold greater than faricimab human steady-state systemic exposure estimates in nAMD, DME, and RVO patients (based on human exposures from population

pharmacokinetics [popPK] model following 6 mg Q8W dosing). Consistent with the absence of nonclinical effects on safety pharmacology endpoints, the incidence of non-ocular adverse events (AEs) in the faricimab arms was comparable to the ranibizumab and aflibercept arms across the clinical development program. Faricimab was generally well tolerated by patients, with no systemic toxicities observed for any system organ class.

Other Toxicity-related Information or Data:
No unspecific tissue binding of faricimab was observed in cross reactivity studies of normal human tissues (Report 1055832; Report 1056445). The results from *in vitro* whole blood assays suggest that there is no substantial risk of cytokine release syndrome, direct complement activation, or peripheral immune-cell depletion with administration of faricimab (Report 1055400; Report 1059118).

Relevance to Human Use:
In line with nonclinical data, there was no evidence for cytokine release syndrome in the clinical development program.

PART II: MODULE SIII — CLINICAL TRIAL EXPOSURE

The exposure and safety data included in this Risk Management Plan (RMP) are derived from eight studies (Table 13).

Exposure data during the entire global enrollment phase from Phase III pivotal studies (excluding regional extensions) are included for the nAMD studies (TENAYA and LUCERNE), and DME studies (YOSEMITE and RHINE). Exposure data to the day before the Week 24 visit (hereafter referred to as “before the Week 24 visit”; i.e., the time point for primary analysis) from the global enrollment phase of Phase III pivotal studies are included for RVO studies (BALATON and COMINO).

In addition, 1464 patients who had previously completed either YOSEMITE or RHINE and 1025 patients who had previously completed either TENAYA (including Japan extension) or LUCERNE were enrolled and received faricimab in GR41987 (RHONE-X) or GR42691 (AVONELLE-X), respectively. Both RHONE-X and AVONELLE-X studies were designed to evaluate the long-term safety and tolerability of faricimab 6 mg administered in patients with DME or nAMD, respectively, by intravitreal injection at personalized treatment intervals. Exposure data for these patients during the entire RHONE-X and AVONELLE-X studies are also included.

In YOSEMITE and RHINE, 1262 patients were initially exposed to faricimab. In RHONE–X, 473 patients who had received aflibercept in YOSEMITE/RHINE were also switched to and received faricimab. Five patients were not included in the analysis due

to a GCP breach at a U.S. site[1]. In total, 1731 patients were exposed to faricimab in Phase III DME studies (YOSEMITE/RHINE/RHONE-X) and are included in the exposure output. Exposure of a patient is counted from the first exposure to faricimab throughout YOSEMITE/RHINE/RHONE-X.

In TENAYA and LUCERNE, 664 patients were initially exposed to faricimab. An additional 40 patients were initially exposed to faricimab in the TENAYA Japan extension. In AVONELLE–X, 505 patients who had received aflibercept in TENAYA[2]/LUCERNE were also switched to and received faricimab. Seven patients were not included in the analysis due to a GCP breach at a U.S. site[1]. In total, 1207 patients were exposed to faricimab in Phase III nAMD studies (TENAYA/LUCERNE/AVONELLE–X) and are included in the exposure output. Exposure of a patient is counted from the first exposure to faricimab throughout the studies TENAYA/LUCERNE/AVONELLE–X.

The pivotal Phase III studies (i.e., DME YOSEMITE/RHINE, nAMD TENAYA/LUCERNE, and RVO BALATON/COMINO studies) along with the Phase III long-term extension (LTE) studies (DME RHONE-X and nAMD AVONELLE–X) were pooled to derive exposure data; therefore, the reference to Phase III studies in the RMP includes the pivotal Phase III studies, RHONE-X, and AVONELLE–X[2].

[1] A critical audit finding was identified during a Sponsor-conducted audit of studies GR40550, GR41675, GR40549, and GR44277 at a U.S. Site investigating another product. As an outcome of the GCP non-compliance with a different investigational product, the Sponsor decided as a precautionary measure to not include the data from the 5 RHONE-X and 7 AVONELLE-X patients enrolled at the above-mentioned site, even though there was no direct evidence suggesting a risk to RHONE-X or AVONELLE-X data integrity.

[2] The AVONELLE-X study population included all eligible patients enrolled to AVONELLE-X from the pivotal Phase III studies TENAYA/LUCERNE or Japan extension neovascular age-related macular degeneration (nAMD) studies.

Table 13 Overview of Studies Contributing to the Safety Population

Protocol Name/No.	Countries	Study Design	Patient Population	Objectives	Dose, Duration	No. of Patients	Study Status
Phase III Pivotal Studies							
BALATON (GR41984) **COMINO** (GR41986)	Global	Phase III, Two-Part, Multicenter, Randomized, Double-Masked, Active Comparator controlled[a], Parallel-Group Study	Patients with RVO: BRVO (BALATON) or CRVO/ HRVO (COMINO)	Efficacy, Safety, PK and PD	• Part 1 (Q4W dosing): • Arm A: 6 mg faricimab IVT injections Q4W from Day 1 through Week 20 (6 injections) • Arm B: 2 mg aflibercept IVT injections Q4W from Day 1 through Week 20 (6 injections) • Part 2 (PTI regimen [b]): Patients in both Arms A and B received 6 mg faricimab IVT injections according to a PTI dosing regimen from Week 24 through Week 68	**Total** Randomized = 1282 **Safety-Evaluable** BALATON = 550 COMINO = 726 **Pooled** Safety-Evaluable = 1276 All faricimab: 641/1276 All aflibercept: 635/1276	BALATON: Completed (LPLV 12 June 2023) COMINO: Completed (LPLV 9 August 2022) Primary analysis through Week 24

Table 13 Overview of Studies Contributing to the Safety Population

Protocol Name/No.	Countries	Study Design	Patient Population	Objectives	Dose, Duration	No. of Patients	Study Status
TENAYA (GR40306) **LUCERNE** (GR40844)	Global	Phase III, Multicenter, Randomized, Double–Masked, Active Comparator-Controlled, 112-week Study	Treatment naive patients with nAMD	Efficacy, Safety, Durability, PK and PD	• Faricimab up to Q16W: 6 mg faricimab intravitreal injections Q4W up to Week 12 followed by fixed Q16W, Q12W or Q8W (based on disease activity assessed at Week 20 and Week 24) up to Week 60, followed by PTI through Week 108 • Aflibercept Q8W: 2 mg aflibercept intravitreal injections Q4W up to Week 8, followed by Q8W through Week 108 • Patients will return for a final visit at Week 112	**Total** Randomized = 1329 (treatment-naive) **Safety-Evaluable** TENAYA = 669 LUCERNE = 657 **Pooled** Safety-Evaluable = 1326 All faricimab: 664/1326 Aflibercept: 662/1326	TENAYA: Completed (LPLV 13 July 2022) LUCERNE: Completed (LPLV 7 January 2022) Efficacy analysis at Week 104/108 /112 [c] Safety analysis through Week 112

Table 13 Overview of Studies Contributing to the Safety Population

Protocol Name/No.	Countries	Study Design	Patient Population	Objectives	Dose, Duration	No. of Patients	Study Status
YOSEMITE (GR40349) **RHINE** (GR40398)	Global	Phase III, Randomized, Double–Masked, Active Comparator-Controlled, Three Parallel Groups, 100–week Study	Patients with DME	Efficacy, Safety, PK and PD	• Faricimab Q8W: 6 mg faricimab intravitreal injections Q4W to Week 20 followed by Q8W to Week 96 • Faricimab PTI [b]: 6 mg faricimab intravitreal injections Q4W to at least Week 12, followed by PTI to Week 96 • Aflibercept Q8W: 2 mg aflibercept intravitreal injections Q4W to Week 16 followed by Q8W to Week 96	**Total** Randomized = 1891 1481– treatment naive 410 – previously treated with anti-VEGF **Safety-Evaluable** YOSEMITE = 937 RHINE = 950 **Pooled** Safety-Evaluable = 1887 All faricimab: 1262/1887 Aflibercept: 625/1887	YOSEMITE: Completed (LPLV 3 September 2021) RHINE: Completed (LPLV 27 August 2021)[d] Efficacy analysis at Week 92/96/100[e] Safety analysis through Week 100

Table 13 Overview of Studies Contributing to the Safety Population

Protocol Name/No.	Countries	Study Design	Patient Population	Objectives	Dose, Duration	No. of Patients	Study Status
Phase III Long-term Extension Studies							
RHONE-X (GR41987)	Global	Phase III, Multicenter, Open-Label Extension Study	Patients with DME, rolled over from YOSEMITE/RHINE	Long-term safety and tolerability, PK, immunogenicity, and efficacy	• Faricimab PTI [b]: 6 mg faricimab IVT injections according to a PTI dosing regimen	**Total** Rolled over = 1474[f] Safety-Evaluable = 1464	Completed (LPLV: 11 October 2023)
AVONELLE-X [g] (GR42691)	Global	Phase III, Multicenter, Open-Label Extension Study	Patients with nAMD rolled over from TENAYA[g]/LUCERNE	Long-term safety and tolerability, PK, immunogenicity, and efficacy	• Faricimab PTI[b] 6 mg faricimab IVT injections according to a PTI dosing regimen	**Total** Rolled over = 1029[f] Safety-Evaluable = 1025	Completed (LPLV: 29 July 2024)

BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; CST = central subfield thickness; DME = diabetic macular edema; HRVO = hemiretinal vein occlusion; IVT = intravitreal; LPLV = Last Patient Last Visit; nAMD = neovascular age-related macular degeneration; PD = pharmacodynamics; PK = pharmacokinetics; PTI = personalized treatment interval; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; Q16W = every 16 weeks; RVO = retinal vein occlusion; VEGF = vascular endothelial growth factor.

[a] Studies BALATON (GR41984) and COMINO (GR41986) are only active comparator-controlled during Part 1.

[b] Study drug dosing for patients on the PTI is extended, reduced or maintained at study drug dosing visits using 4-week increments to a maximum of Q16W or a minimum of Q4W based on the relative change of the CST and BCVA compared with the patient's reference CST and reference BCVA.

[c] The Week 112 efficacy analysis, change from baseline in BCVA, was averaged over Weeks 104, 108, and 112 (represented by 'Week 104/108/112').

Table 13 Overview of Studies Contributing to the Safety Population (cont.)

[d] The global enrollment phase of RHINE was completed with the LPLV on 27 August 2021.

[e] The Year 2 efficacy analysis, change from baseline in BCVA, was averaged over Weeks 92, 96, and 100 (represented by 'Week 92/96/100').

[f] A critical audit finding was identified during a Sponsor-conducted audit of studies GR40550, GR41675, GR40549, and GR44277 at a U.S. Site investigating another product. As an outcome of the GCP non-compliance with a different investigational product, the Sponsor decided as a precautionary measure to not include the data from the 5 RHONE-X and 7 AVONELLE-X patients enrolled at the above-mentioned site, even though there was no direct evidence suggesting a risk to RHONE-X or AVONELLE-X data integrity.

[g] The AVONELLE-X study population included all eligible patients enrolled to AVONELLE-X, from the pivotal Phase III studies TENAYA/LUCERNE or Japan extension nAMD studies.

Duration of Exposure

The faricimab safety population provides data from 3579 patients with 8177 years person-time of exposure in the Phase III program. This population consists of 1207 patients with nAMD (3167 years person-time exposure), 1731 patients with DME (4767 years person-time exposure), 276 patients with BRVO (104 years person-time exposure), and 365 patients with central/hemiretinal RVO (C/HRVO) (139 years person-time exposure). In nAMD studies, 52.0% of patients completed ≥2 years of treatment. In DME studies, 58.5% of patients completed ≥2 years of treatment. The majority of BRVO patients (97.1%) and C/HRVO patients (98.1%) received treatment for 3 to <6 months as of the primary endpoint (Week 24) (Table 14).

Number of Study Drug Administrations in the Study Eye

Of the total 1207 nAMD faricimab patients, 30.5% (n=368) patients received 17 or more faricimab administrations, with <5% receiving 28 or more injections. One patient (<0.1%%) received the maximum number of 37 injections (Table 15).

Of the total 1731 DME faricimab patients, 33.9% (n=586) received 22 or more faricimab administrations, with <5% receiving 32 or more injections. Two patients (0.1%) received the maximum number of 50 administrations (Table 15).

Of the total 276 BRVO patients, 85.9% (n=237) received the maximum number of 6 administrations (Table 15). Of the total 365 C/HRVO patients, 83.0% (n=303) received the maximum number of 6 administrations (Table 15).

The total number of faricimab injections was 48,887 across the Phase III program: 15,914 injections in nAMD patients, 29,284 injections in DME patients,1591 injections in BRVO, and 2098 injections in C/HRVO patients (Annex 7A.1).

Exposure by Age Group and Gender

In the overall faricimab safety population from the Phase III program, 1889 patients were male and 1690 patients were female (Table 16). Male patients had 4387 patient-years of exposure versus 3791 patient-years in female patients. In the pooled population, the highest proportion of males were in the <65 years age group (47.8%), and the highest proportion of females in the 65 to <75 years age group (36.4%).

The majority of faricimab patients with nAMD were female, and the highest proportion of patients of each gender were in the 75 to <85 years age group (Table 16). In the faricimab DME group, the majority of patients were male, and the majority of patients of both genders were in the <65 years age group (Table 16).

In the BRVO group, there was a comparable number of male and female patients, with the highest proportion of male patients in the <65 years age group and the highest proportion of female patients in the 65 to <75 years age group. In the C/HRVO group,

there was a comparable number of male and female patients, and the highest proportion of patients of each gender were in the <65 years age group (Table 16).

Exposure by Faricimab Dose

In the Phase III studies, there were a total of 1207 patients with nAMD (3167 years person-time exposure), 1731 patients with DME (4767 years person-time exposure), 276 patients with BRVO (104 years person-time exposure), and 365 patients with CRVO (139 years person-time exposure), all receiving faricimab 6 mg (Table 17).

Exposure by Race

In the overall safety population from the Phase III program, the majority of faricimab patients were White (77%, 2756 patients, 6528 patient-years of exposure): nAMD (81.2%, 980 patients, 2579 patient-years of exposure), DME (78.7%, 1362 patients, 3791 patient-years of exposure), BRVO (62.3%, 172 patients, 65 patient-years of exposure), and C/HRVO (66.3%, 242 patients, 92 patient-years of exposure) (Table 18).

Exposure by Ethnicity

The ethnicity of 83.5% of the overall faricimab Phase III safety population was Not Hispanic or Latino (2988 patients, 6911 patient-years of exposure) (Table 19). This was consistent across nAMD (89.1%, 1075 patients, 2807 patient-years of exposure), DME (81.1%, 1404 patients, 3910 patient-years of exposure), BRVO (81.2%, 224 patients, 84 patient-years of exposure), and C/HRVO (78.1%, 285 patients, 109 patient-years of exposure) (Table 19).

Table 14 Overall Extent of Exposure during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO), Safety-Evaluable Population

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

	nAMD* (N=1207)		DME/DR* (N=1731)		BRVO (N=276)		C/HRVO (N=365)	
	Faricimab (N=1207)		Faricimab (N=1731)		Faricimab (N=276)		Faricimab (N=365)	
Duration of exposure	Patients	Person time (years)**	Patients	Person time (years)**	Patients	Person time (years)**	Patients	Person time (years)**
< 1 month	11 (0.9%)	1	15 (0.9%)	0	4 (1.4%)	0	1 (0.3%)	0
1 to <3 months	15 (1.2%)	3	25 (1.4%)	4	4 (1.4%)	1	6 (1.6%)	1
3 to <6 months	21 (1.7%)	8	35 (2.0%)	14	268 (97.1%)	103	358 (98.1%)	138
6 to <9 months	26 (2.2%)	16	34 (2.0%)	21	0	NE	0	NE
9 to <1 year	35 (2.9%)	30	39 (2.3%)	34	0	NE	0	NE
1 to <1.5 years	55 (4.6%)	68	70 (4.0%)	88	0	NE	0	NE
1.5 to <2 years	417 (34.5%)	772	500 (28.9%)	914	0	NE	0	NE
2 to <2.5 years	119 (9.9%)	248	72 (4.2%)	156	0	NE	0	NE
2.5 to <3 years	18 (1.5%)	51	38 (2.2%)	105	0	NE	0	NE
3 to <3.5 years	13 (1.1%)	41	24 (1.4%)	79	0	NE	0	NE
3.5 to <4 years	173 (14.3%)	678	876 (50.6%)	3340	0	NE	0	NE
>= 4 years	304 (25.2%)	1252	3 (0.2%)	12	0	NE	0	NE
Total patients numbers/person time	1207 (100%)	3167	1731 (100%)	4767	276 (100%)	104	365 (100%)	139

*Includes prior Aflibercept patients in Phase III who crossed over to Faricimab in LTE (Year 2-4), and all patients in faricimab arm in Phase III studies (Year 0-4).
**Person time is the sum of exposure across all patients in unit: years (days/365.25).
Duration of treatment is defined as the time from first study treatment to treatment end date (as defined in the individual study).
NE = Not Evaluable.
nAMD pools GR40306, GR40844 and GR42691; DME pools GR40349, GR40398 and GR41987; BRVO GR41984; C/HRVO GR41986; POOLED(nAMD, DME, BRVO, C/HRVO) pools all eight studies.

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Table 14 Overall Extent of Exposure during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO), Safety-Evaluable Population (cont.)

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

	Combined Indications (N=3579)	
	Faricimab (N=3579)	
Duration of exposure	Patients	Person time (years)**
< 1 month	31 (0.9%)	1
1 to <3 months	50 (1.4%)	9
3 to <6 months	682 (19.1%)	263
6 to <9 months	60 (1.7%)	36
9 to <1 year	74 (2.1%)	64
1 to <1.5 years	125 (3.5%)	155
1.5 to <2 years	917 (25.6%)	1686
2 to <2.5 years	191 (5.3%)	404
2.5 to <3 years	56 (1.6%)	156
3 to <3.5 years	37 (1.0%)	121
3.5 to <4 years	1049 (29.3%)	4018
>= 4 years	307 (8.6%)	1264
Total patients numbers/person time	3579 (100%)	8177

*Includes prior Aflibercept patients in Phase III who crossed over to Faricimab in LTE (Year 2-4), and all patients in faricimab arm in Phase III studies (Year 0-4).
**Person time is the sum of exposure across all patients in unit: years (days/365.25).
Duration of treatment is defined as the time from first study treatment to treatment end date (as defined in the individual study).
NE = Not Evaluable.
nAMD pools GR40306, GR40844 and GR42691; DME pools GR40349, GR40398 and GR41987; BRVO GR41984; C/HRVO GR41986; POOLED(nAMD, DME, BRVO, C/HRVO) pools all eight studies.

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Table 15 Number of Study Drug Administrations in the Study Eye during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO), Safety-Evaluable Population

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

Number of Study Drug Administrations (at least)	nAMD* (N=1207)	DME/DR* (N=1731)	BRVO (N=276)	C/HRVO (N=365)	Combined Indications (N=3579)
1 or more study drug administration					
n	1207	1731	276	365	3579
Y	1207 (100%)	1731 (100%)	276 (100%)	365 (100%)	3579 (100%)
N	0	0	0	0	0
2 or more study drug administration					
n	1207	1731	276	365	3579
Y	1198 (99.3%)	1717 (99.2%)	274 (99.3%)	363 (99.5%)	3552 (99.2%)
N	9 (0.7%)	14 (0.8%)	2 (0.7%)	2 (0.5%)	27 (0.8%)
3 or more study drug administration					
n	1207	1731	276	365	3579
Y	1181 (97.8%)	1707 (98.6%)	272 (98.6%)	362 (99.2%)	3522 (98.4%)
N	26 (2.2%)	24 (1.4%)	4 (1.4%)	3 (0.8%)	57 (1.6%)
4 or more study drug administration					
n	1207	1731	276	365	3579
Y	1166 (96.6%)	1689 (97.6%)	270 (97.8%)	358 (98.1%)	3483 (97.3%)
N	41 (3.4%)	42 (2.4%)	6 (2.2%)	7 (1.9%)	96 (2.7%)
5 or more study drug administration					
n	1207	1731	276	365	3579
Y	1139 (94.4%)	1663 (96.1%)	262 (94.9%)	347 (95.1%)	3411 (95.3%)
N	68 (5.6%)	68 (3.9%)	14 (5.1%)	18 (4.9%)	168 (4.7%)
6 or more study drug administration					
n	1207	1731	276	365	3579
Y	1111 (92.0%)	1638 (94.6%)	237 (85.9%)	303 (83.0%)	3289 (91.9%)
N	96 (8.0%)	93 (5.4%)	39 (14.1%)	62 (17.0%)	290 (8.1%)
7 or more study drug administration					
n	1207	1731	276	365	3579
Y	1070 (88.6%)	1602 (92.5%)	0	0	2672 (74.7%)
N	137 (11.4%)	129 (7.5%)	276 (100%)	365 (100%)	907 (25.3%)
8 or more study drug administration					
n	1207	1731	276	365	3579
Y	844 (69.9%)	1439 (83.1%)	0	0	2283 (63.8%)
N	363 (30.1%)	292 (16.9%)	276 (100%)	365 (100%)	1296 (36.2%)

Table 15 Number of Study Drug Administrations in the Study Eye during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO), Safety-Evaluable Population (cont.)

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

Number of Study Drug Administrations (at least)	nAMD* (N=1207)	DME/DR* (N=1731)	BRVO (N=276)	C/HRVO (N=365)	Combined Indications (N=3579)
9 or more study drug administration					
n	1207	1731	276	365	3579
Y	765 (63.4%)	1351 (78.0%)	0	0	2116 (59.1%)
N	442 (36.6%)	380 (22.0%)	276 (100%)	365 (100%)	1463 (40.9%)
10 or more study drug administration					
n	1207	1731	276	365	3579
Y	709 (58.7%)	1288 (74.4%)	0	0	1997 (55.8%)
N	498 (41.3%)	443 (25.6%)	276 (100%)	365 (100%)	1582 (44.2%)
11 or more study drug administration					
n	1207	1731	276	365	3579
Y	653 (54.1%)	1239 (71.6%)	0	0	1892 (52.9%)
N	554 (45.9%)	492 (28.4%)	276 (100%)	365 (100%)	1687 (47.1%)
12 or more study drug administration					
n	1207	1731	276	365	3579
Y	618 (51.2%)	1185 (68.5%)	0	0	1803 (50.4%)
N	589 (48.8%)	546 (31.5%)	276 (100%)	365 (100%)	1776 (49.6%)
13 or more study drug administration					
n	1207	1731	276	365	3579
Y	590 (48.9%)	1145 (66.1%)	0	0	1735 (48.5%)
N	617 (51.1%)	586 (33.9%)	276 (100%)	365 (100%)	1844 (51.5%)
14 or more study drug administration					
n	1207	1731	276	365	3579
Y	560 (46.4%)	1105 (63.8%)	0	0	1665 (46.5%)
N	647 (53.6%)	626 (36.2%)	276 (100%)	365 (100%)	1914 (53.5%)
15 or more study drug administration					
n	1207	1731	276	365	3579
Y	533 (44.2%)	1059 (61.2%)	0	0	1592 (44.5%)
N	674 (55.8%)	672 (38.8%)	276 (100%)	365 (100%)	1987 (55.5%)
16 or more study drug administration					
n	1207	1731	276	365	3579
Y	506 (41.9%)	1006 (58.1%)	0	0	1512 (42.2%)
N	701 (58.1%)	725 (41.9%)	276 (100%)	365 (100%)	2067 (57.8%)

Table 15 Number of Study Drug Administrations in the Study Eye during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO), Safety-Evaluable Population (cont.)

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

Number of Study Drug Administrations (at least)	nAMD* (N=1207)	DME/DR* (N=1731)	BRVO (N=276)	C/HRVO (N=365)	Combined Indications (N=3579)
17 or more study drug administration					
n	1207	1731	276	365	3579
Y	368 (30.5%)	890 (51.4%)	0	0	1258 (35.1%)
N	839 (69.5%)	841 (48.6%)	276 (100%)	365 (100%)	2321 (64.9%)
18 or more study drug administration					
n	1207	1731	276	365	3579
Y	305 (25.3%)	805 (46.5%)	0	0	1110 (31.0%)
N	902 (74.7%)	926 (53.5%)	276 (100%)	365 (100%)	2469 (69.0%)
19 or more study drug administration					
n	1207	1731	276	365	3579
Y	259 (21.5%)	749 (43.3%)	0	0	1008 (28.2%)
N	948 (78.5%)	982 (56.7%)	276 (100%)	365 (100%)	2571 (71.8%)
20 or more study drug administration					
n	1207	1731	276	365	3579
Y	212 (17.6%)	697 (40.3%)	0	0	909 (25.4%)
N	995 (82.4%)	1034 (59.7%)	276 (100%)	365 (100%)	2670 (74.6%)
21 or more study drug administration					
n	1207	1731	276	365	3579
Y	172 (14.3%)	653 (37.7%)	0	0	825 (23.1%)
N	1035 (85.7%)	1078 (62.3%)	276 (100%)	365 (100%)	2754 (76.9%)
22 or more study drug administration					
n	1207	1731	276	365	3579
Y	146 (12.1%)	586 (33.9%)	0	0	732 (20.5%)
N	1061 (87.9%)	1145 (66.1%)	276 (100%)	365 (100%)	2847 (79.5%)
23 or more study drug administration					
n	1207	1731	276	365	3579
Y	119 (9.9%)	427 (24.7%)	0	0	546 (15.3%)
N	1088 (90.1%)	1304 (75.3%)	276 (100%)	365 (100%)	3033 (84.7%)
24 or more study drug administration					
n	1207	1731	276	365	3579
Y	101 (8.4%)	327 (18.9%)	0	0	428 (12.0%)
N	1106 (91.6%)	1404 (81.1%)	276 (100%)	365 (100%)	3151 (88.0%)

Table 15 Number of Study Drug Administrations in the Study Eye during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO), Safety-Evaluable Population (cont.)

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

Number of Study Drug Administrations (at least)	nAMD* (N=1207)	DME/DR* (N=1731)	BRVO (N=276)	C/HRVO (N=365)	Combined Indications (N=3579)
25 or more study drug administration					
n	1207	1731	276	365	3579
Y	82 (6.8%)	267 (15.4%)	0	0	349 (9.8%)
N	1125 (93.2%)	1464 (84.6%)	276 (100%)	365 (100%)	3230 (90.2%)
26 or more study drug administration					
n	1207	1731	276	365	3579
Y	72 (6.0%)	214 (12.4%)	0	0	286 (8.0%)
N	1135 (94.0%)	1517 (87.6%)	276 (100%)	365 (100%)	3293 (92.0%)
27 or more study drug administration					
n	1207	1731	276	365	3579
Y	61 (5.1%)	185 (10.7%)	0	0	246 (6.9%)
N	1146 (94.9%)	1546 (89.3%)	276 (100%)	365 (100%)	3333 (93.1%)
28 or more study drug administration					
n	1207	1731	276	365	3579
Y	43 (3.6%)	156 (9.0%)	0	0	199 (5.6%)
N	1164 (96.4%)	1575 (91.0%)	276 (100%)	365 (100%)	3380 (94.4%)
29 or more study drug administration					
n	1207	1731	276	365	3579
Y	35 (2.9%)	135 (7.8%)	0	0	170 (4.7%)
N	1172 (97.1%)	1596 (92.2%)	276 (100%)	365 (100%)	3409 (95.3%)
30 or more study drug administration					
n	1207	1731	276	365	3579
Y	27 (2.2%)	107 (6.2%)	0	0	134 (3.7%)
N	1180 (97.8%)	1624 (93.8%)	276 (100%)	365 (100%)	3445 (96.3%)
31 or more study drug administration					
n	1207	1731	276	365	3579
Y	22 (1.8%)	90 (5.2%)	0	0	112 (3.1%)
N	1185 (98.2%)	1641 (94.8%)	276 (100%)	365 (100%)	3467 (96.9%)
32 or more study drug administration					
n	1207	1731	276	365	3579
Y	18 (1.5%)	76 (4.4%)	0	0	94 (2.6%)
N	1189 (98.5%)	1655 (95.6%)	276 (100%)	365 (100%)	3485 (97.4%)

Table 15 Number of Study Drug Administrations in the Study Eye during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO), Safety-Evaluable Population (cont.)

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

Number of Study Drug Administrations (at least)	nAMD* (N=1207)	DME/DR* (N=1731)	BRVO (N=276)	C/HRVO (N=365)	Combined Indications (N=3579)
33 or more study drug administration					
n	1207	1731	276	365	3579
Y	12 (1.0%)	64 (3.7%)	0	0	76 (2.1%)
N	1195 (99.0%)	1667 (96.3%)	276 (100%)	365 (100%)	3503 (97.9%)
34 or more study drug administration					
n	1207	1731	276	365	3579
Y	6 (0.5%)	52 (3.0%)	0	0	58 (1.6%)
N	1201 (99.5%)	1679 (97.0%)	276 (100%)	365 (100%)	3521 (98.4%)
35 or more study drug administration					
n	1207	1731	276	365	3579
Y	2 (0.2%)	44 (2.5%)	0	0	46 (1.3%)
N	1205 (99.8%)	1687 (97.5%)	276 (100%)	365 (100%)	3533 (98.7%)
36 or more study drug administration					
n	1207	1731	276	365	3579
Y	1 (<0.1%)	38 (2.2%)	0	0	39 (1.1%)
N	1206 (>99.9%)	1693 (97.8%)	276 (100%)	365 (100%)	3540 (98.9%)
37 or more study drug administration					
n	1207	1731	276	365	3579
Y	1 (<0.1%)	29 (1.7%)	0	0	30 (0.8%)
N	1206 (>99.9%)	1702 (98.3%)	276 (100%)	365 (100%)	3549 (99.2%)
38 or more study drug administration					
n	1207	1731	276	365	3579
Y	0	24 (1.4%)	0	0	24 (0.7%)
N	1207 (100%)	1707 (98.6%)	276 (100%)	365 (100%)	3555 (99.3%)
39 or more study drug administration					
n	1207	1731	276	365	3579
Y	0	22 (1.3%)	0	0	22 (0.6%)
N	1207 (100%)	1709 (98.7%)	276 (100%)	365 (100%)	3557 (99.4%)
40 or more study drug administration					
n	1207	1731	276	365	3579
Y	0	16 (0.9%)	0	0	16 (0.4%)
N	1207 (100%)	1715 (99.1%)	276 (100%)	365 (100%)	3563 (99.6%)
41 or more study drug administration					
n	1207	1731	276	365	3579
Y	0	13 (0.8%)	0	0	13 (0.4%)
N	1207 (100%)	1718 (99.2%)	276 (100%)	365 (100%)	3566 (99.6%)

Table 15 Number of Study Drug Administrations in the Study Eye during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO), Safety-Evaluable Population (cont.)

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

Number of Study Drug Administrations (at least)	nAMD* (N=1207)	DME/DR* (N=1731)	BRVO (N=276)	C/HRVO (N=365)	Combined Indications (N=3579)
42 or more study drug administration					
n	1207	1731	276	365	3579
Y	0	12 (0.7%)	0	0	12 (0.3%)
N	1207 (100%)	1719 (99.3%)	276 (100%)	365 (100%)	3567 (99.7%)
43 or more study drug administration					
n	1207	1731	276	365	3579
Y	0	8 (0.5%)	0	0	8 (0.2%)
N	1207 (100%)	1723 (99.5%)	276 (100%)	365 (100%)	3571 (99.8%)
44 or more study drug administration					
n	1207	1731	276	365	3579
Y	0	7 (0.4%)	0	0	7 (0.2%)
N	1207 (100%)	1724 (99.6%)	276 (100%)	365 (100%)	3572 (99.8%)
45 or more study drug administration					
n	1207	1731	276	365	3579
Y	0	6 (0.3%)	0	0	6 (0.2%)
N	1207 (100%)	1725 (99.7%)	276 (100%)	365 (100%)	3573 (99.8%)
46 or more study drug administration					
n	1207	1731	276	365	3579
Y	0	6 (0.3%)	0	0	6 (0.2%)
N	1207 (100%)	1725 (99.7%)	276 (100%)	365 (100%)	3573 (99.8%)
47 or more study drug administration					
n	1207	1731	276	365	3579
Y	0	5 (0.3%)	0	0	5 (0.1%)
N	1207 (100%)	1726 (99.7%)	276 (100%)	365 (100%)	3574 (99.9%)
48 or more study drug administration					
n	1207	1731	276	365	3579
Y	0	4 (0.2%)	0	0	4 (0.1%)
N	1207 (100%)	1727 (99.8%)	276 (100%)	365 (100%)	3575 (99.9%)
49 or more study drug administration					
n	1207	1731	276	365	3579
Y	0	4 (0.2%)	0	0	4 (0.1%)
N	1207 (100%)	1727 (99.8%)	276 (100%)	365 (100%)	3575 (99.9%)

Table 15 Number of Study Drug Administrations in the Study Eye during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO), Safety-Evaluable Population (cont.)

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

Number of Study Drug Administrations (at least)	nAMD* (N=1207)	DME/DR* (N=1731)	BRVO (N=276)	C/HRVO (N=365)	Combined Indications (N=3579)
50 or more study drug administration					
n	1207	1731	276	365	3579
Y	0	2 (0.1%)	0	0	2 (<0.1%)
N	1207 (100%)	1729 (99.9%)	276 (100%)	365 (100%)	3577 (>99.9%)

*Includes prior Aflibercept patients in Phase III who crossed over to Faricimab in LTE (Year 2-4), and all patients in faricimab arm in Phase III studies (Year 0-4).
Percentages are based on the N in the column headings. For BRVO and C/HRVO, the maximum number of injection is 6 at week 24 cut off.
nAMD pools GR40306, GR40844 and GR42691; DME pools GR40349, GR40398 and GR41987; BRVO GR41984; C/HRVO GR41986; POOLED(nAMD, DME, BRVO, C/HRVO) pools all eight studies.

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Table 16 Overall Extent of Exposure during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO) by Age Group and Gender, Safety-Evaluable Population

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

	nAMD* (N=1207)					
	Faricimab (N=1207)					
	Male		Female		Total	
Age Group (years)	Patients	Person time (years)**	Patients	Person time (years)**	Patients	Person time (years)**
<65	66 (12.8%)	187	59 (8.5%)	156	125 (10.4%)	343
65 to <75	183 (35.6%)	495	217 (31.3%)	633	400 (33.1%)	1128
75 to <85	206 (40.1%)	528	305 (44.0%)	802	511 (42.3%)	1330
>=85	59 (11.5%)	130	112 (16.2%)	235	171 (14.2%)	365
TOTAL	514 (100%)	1340	693 (100%)	1827	1207 (100%)	3167

	DME/DR* (N=1731)					
	Faricimab (N=1731)					
	Male		Female		Total	
Age Group (years)	Patients	Person time (years)**	Patients	Person time (years)**	Patients	Person time (years)**
<65	661 (63.6%)	1871	343 (49.6%)	938	1004 (58.0%)	2809
65 to <75	308 (29.6%)	866	285 (41.2%)	734	593 (34.3%)	1600
75 to <85	67 (6.4%)	176	62 (9.0%)	173	129 (7.5%)	349
>=85	4 (0.4%)	8	1 (0.1%)	2	5 (0.3%)	10
TOTAL	1040 (100%)	2920	691 (100%)	1847	1731 (100%)	4767

Table 16 Overall Extent of Exposure during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO) by Age Group and Gender, Safety-Evaluable Population (cont.)

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

	BRVO (N=276)					
	Faricimab (N=276)					
	Male		Female		Total	
Age Group (years)	Patients	Person time (years)**	Patients	Person time (years)**	Patients	Person time (years)**
<65	80 (55.9%)	30	53 (39.8%)	20	133 (48.2%)	50
65 to <75	42 (29.4%)	16	58 (43.6%)	22	100 (36.2%)	38
75 to <85	16 (11.2%)	6	17 (12.8%)	7	33 (12.0%)	13
>=85	5 (3.5%)	2	5 (3.8%)	2	10 (3.6%)	4
TOTAL	143 (100%)	54	133 (100%)	50	276 (100%)	104

	C/HRVO (N=365)					
	Faricimab (N=365)					
	Male		Female		Total	
Age Group (years)	Patients	Person time (years)**	Patients	Person time (years)**	Patients	Person time (years)**
<65	95 (49.5%)	36	66 (38.2%)	25	161 (44.1%)	61
65 to <75	58 (30.2%)	22	55 (31.8%)	21	113 (31.0%)	44
75 to <85	30 (15.6%)	12	41 (23.7%)	15	71 (19.5%)	27
>=85	9 (4.7%)	4	11 (6.4%)	4	20 (5.5%)	8
TOTAL	192 (100%)	73	173 (100%)	66	365 (100%)	139

Table 16 Overall Extent of Exposure during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO) by Age Group and Gender, Safety-Evaluable Population (cont.)

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

	Combined Indications (N=3579)					
	Faricimab (N=3579)					
	Male		Female		Total	
Age Group (years)	Patients	Person time (years)**	Patients	Person time (years)**	Patients	Person time (years)**
<65	902 (47.8%)	2123	521 (30.8%)	1140	1423 (39.8%)	3263
65 to <75	591 (31.3%)	1399	615 (36.4%)	1411	1206 (33.7%)	2809
75 to <85	319 (16.9%)	722	425 (25.1%)	996	744 (20.8%)	1718
>=85	77 (4.1%)	143	129 (7.6%)	243	206 (5.8%)	387
TOTAL	1889 (100%)	4387	1690 (100%)	3791	3579 (100%)	8177

*Includes prior Aflibercept patients in Phase III who crossed over to Faricimab in LTE (Year 2-4), and all patients in faricimab arm in Phase III studies (Year 0-4).
** Person time is the sum of exposure across all patients in unit: years (days/365.25).
Duration of treatment is defined as the time from first study treatment to treatment end date (as defined in the individual study).
nAMD pools GR40306, GR40844 and GR42691; DME pools GR40349, GR40398 and GR41987; BRVO GR41984; C/HRVO GR41986; POOLED(nAMD, DME, BRVO, C/HRVO) pools all
eight studies.

Program: /builds/studies/clinicalreporting/P_Mol_RO6867461_OtherRegRMP_D4_A4_R24_7092036/programs/tlg/t_ex_rmp_age.sas
Output: /ocean/harbour/projects/P_Mol_RO6867461/OtherRegRMP_D4_A4_R24/prod_rmp_jun2025_v1/output/t_ex_rmp_age_SE.out
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Table 17 Overall Extent of Exposure during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO) by Dose, Safety-Evaluable Population

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

	nAMD* (N=1207)		DME/DR* (N=1731)		BRVO (N=276)	
Dose of exposure	Patients	Person time (years)**	Patients	Person time (years)**	Patients	Person time (years)**
6-mg All	1207 (100%)	3167	1731 (100%)	4767	276 (100%)	104
TOTAL	1207 (100%)	3167	1731 (100%)	4767	276 (100%)	104

	C/HRVO (N=365)		Combined Indications (N=3579)	
Dose of exposure	Patients	Person time (years)**	Patients	Person time (years)**
6-mg All	365 (100%)	139	3579 (100%)	8177
TOTAL	365 (100%)	139	3579 (100%)	8177

*Includes prior Aflibercept patients in Phase III who crossed over to Faricimab in LTE (Year 2-4), and all patients in faricimab arm in Phase III studies (Year 0-4).
** Person time is the sum of exposure across all patients in unit: years (days/365.25).
Duration of treatment is defined as the time from first study treatment to treatment end date (as defined in the individual study).
nAMD pools GR40306, GR40844 and GR42691; DME pools GR40349, GR40398 and GR41987; BRVO GR41984; C/HRVO GR41986; POOLED(nAMD, DME, BRVO, C/HRVO) pools all eight studies.

Program: /builds/studies/clinicalreporting/P_Mol_RO6867461_OtherRegRMP_D4_A4_R24_7092036/programs/tlg/t_ex_rmp_dose.sas
Output: /ocean/harbour/projects/P_Mol_RO6867461/OtherRegRMP_D4_A4_R24/prod_rmp_jun2025_v1/output/t_ex_rmp_dose_SE.out
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Table 18 Overall Extent of Exposure during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO) by Race, Safety-Evaluable Population

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

	nAMD* (N=1207)		DME/DR* (N=1731)		BRVO (N=276)		C/HRVO (N=365)	
	Faricimab (N=1207)		Faricimab (N=1731)		Faricimab (N=276)		Faricimab (N=365)	
Race	Patients	Person time (years)**	Patients	Person time (years)**	Patients	Person time (years)**	Patients	Person time (years)**
American Indian or Alaska Native	4 (0.3%)	9	15 (0.9%)	40	3 (1.1%)	1	2 (0.5%)	1
Asian	187 (15.5%)	487	171 (9.9%)	496	90 (32.6%)	34	89 (24.4%)	34
Black or African American	7 (0.6%)	15	113 (6.5%)	291	6 (2.2%)	2	10 (2.7%)	4
Native Hawaiian or other Pacific Islander	0	NE	5 (0.3%)	10	1 (0.4%)	0	0	NE
White	980 (81.2%)	2579	1362 (78.7%)	3791	172 (62.3%)	65	242 (66.3%)	92
Multiple	2 (0.2%)	3	4 (0.2%)	6	0	NE	1 (0.3%)	0
Unknown	27 (2.2%)	74	61 (3.5%)	133	4 (1.4%)	2	21 (5.8%)	8
TOTAL	1207 (100%)	3167	1731 (100%)	4767	276 (100%)	104	365 (100%)	139

Table 18 Overall Extent of Exposure during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO) by Race, Safety-Evaluable Population (cont.)

	Combined Indications (N=3579)	
	Faricimab (N=3579)	
Race	Patients	Person time (years)**
American Indian or Alaska Native	24 (0.7%)	51
Asian	537 (15.0%)	1052
Black or African American	136 (3.8%)	312
Native Hawaiian or other Pacific Islander	6 (0.2%)	10
White	2756 (77.0%)	6528
Multiple	7 (0.2%)	9
Unknown	113 (3.2%)	216
TOTAL	3579 (100%)	8177

_ *Includes prior Aflibercept patients in Phase III who crossed over to Faricimab in LTE (Year 2-4), and all patients in faricimab arm in Phase III studies (Year 0-4)
** Person time is the sum of exposure across all patients in unit: years (days/365.25).
Duration of treatment is defined as the time from first study treatment to treatment end date (as defined in the individual study).
nAMD pools GR40306, GR40844 and GR42691; DME pools GR40349, GR40398 and GR41987; BRVO GR41984; C/HRVO GR41986; POOLED(nAMD, DME, BRVO, C/HRVO) pools all
eight studies.

Program: /builds/studies/clinicalreporting/P_Mol_RO6867461_OtherRegRMP_D4_A4_R24_7092036/programs/tlg/t_ex_rmp_race.sas
Output: /ocean/harbour/projects/P_Mol_RO6867461/OtherRegRMP_D4_A4_R24/prod_rmp_jun2025_v1/output/t_ex_rmp_race_SE.out
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Table 19 Overall Extent of Exposure during Entire Study (Week 112 nAMD, Week 100 DME, Year 2-4 nAMD, and Year 2-4 DME) and through Primary Endpoint Time (Week 24 RVO) by Ethnicity, Safety-Evaluable Population

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986, GR41987, GR42691

	nAMD* (N=1207)		DME/DR* (N=1731)		BRVO (N=276)		C/HRVO (N=365)	
	Faricimab (N=1207)		Faricimab (N=1731)		Faricimab (N=276)		Faricimab (N=365)	
Ethnicity	Patients	Person time (years)**	Patients	Person time (years)**	Patients	Person time (years)**	Patients	Person time (years)**
Hispanic or Latino	112 (9.3%)	301	290 (16.8%)	761	47 (17.0%)	18	66 (18.1%)	25
Not Hispanic or Latino	1075 (89.1%)	2807	1404 (81.1%)	3910	224 (81.2%)	84	285 (78.1%)	109
Not Stated	8 (0.7%)	22	22 (1.3%)	59	1 (0.4%)	0	4 (1.1%)	2
Unknown	12 (1.0%)	37	15 (0.9%)	36	4 (1.4%)	2	10 (2.7%)	4
TOTAL	1207 (100%)	3167	1731 (100%)	4767	276 (100%)	104	365 (100%)	139

	Combined Indications (N=3579)	
	Faricimab (N=3579)	
Ethnicity	Patients	Person time (years)**
Hispanic or Latino	515 (14.4%)	1105
Not Hispanic or Latino	2988 (83.5%)	6911
Not Stated	35 (1.0%)	83
Unknown	41 (1.1%)	78
TOTAL	3579 (100%)	8177

*Includes prior Aflibercept patients in Phase III who crossed over to Faricimab in LTE (Year 2-4), and all patients in faricimab arm in Phase III studies (Year 0-4).
** Person time is the sum of exposure across all patients in unit: years (days/365.25).
Duration of treatment is defined as the time from first study treatment to treatment end date (as defined in the individual study).
nAMD pools GR40306, GR40844 and GR42691; DME pools GR40349, GR40398 and GR41987; BRVO GR41984; C/HRVO GR41986; POOLED(nAMD, DME, BRVO, C/HRVO) pools all eight studies.

Program: /builds/studies/clinicalreporting/P_Mol_RO6867461_OtherRegRMP_D4_A4_R24_7092036/programs/tlg/t_ex_rmp_ethn.sas
Output: /ocean/harbour/projects/P_Mol_RO6867461/OtherRegRMP_D4_A4_R24/prod_rmp_jun2025_v1/output/t_ex_rmp_ethn_SE.out
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PART II: MODULE SIV — POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Key exclusion criteria in pivotal clinical studies within the development program are presented in Table 20.

Table 20 Important Exclusion Criteria in Pivotal Studies in the Development Program

	Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale (if not included as missing information)
Ocular				
All indications	Active ocular inflammation or suspected or active ocular or periocular infection in either eye on Day 1	Active inflammation or infection can predispose and/or result in serious intraocular complications resulting in vision loss after an intravitreal injection. Reason for exclusion was to minimize the possibility of infectious or inflammatory complications; inability to administer study treatment for a prolonged period; impacting possibility to interpret study results in an unbiased way.	No	A contraindication in patients with active intraocular inflammation is included in the SmPC. A contraindication in patients with active or suspected ocular or periocular infection is included in the SmPC.
nAMD	CNV due to causes other than AMD, such as ocular histoplasmosis, trauma, pathological myopia, angioid streaks, choroidal rupture, or uveitis	The current studies aim to characterize the safety and efficacy profile of faricimab in patients with nAMD, not in patients with retinal and/or CNV due to other causes for which the efficacy may differ.	No	Faricimab is indicated for the treatment of adult patients with nAMD, and thus should not be administered in patients with CNV due to other causes.
	RPE tear involving the macula on Day 1	RPE tears are a complication that patients with nAMD may develop and may limit visual potential for improvement. Patients with RPE tear were not included as it may confound the efficacy and safety profile of faricimab.	No	The exclusion criterion was selected in order to avoid any potential efficacy or safety confounders. No change in the safety profile of faricimab is foreseen in this patient population. A caution regarding the initiation of faricimab treatment in patients with factors associated with higher risk of RPE tear is included in the SmPC under special Warnings and Precautions for use.

Table 20 Important Exclusion Criteria in Pivotal Studies in the Development Program (cont.)

	Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale (if not included as missing information)
Ocular (cont.)				
nAMD (cont.)	Spherical equivalent of refractive error demonstrating more than 8 diopters of myopia	To exclude patients whose CNV may be due to pathologic myopia in order to allow a clear assessment of the efficacy and safety of faricimab in patients with nAMD.	No	Patients with high myopia have a thin sclera and retina and are susceptible for retinal detachments and tears in addition to developing a CNV secondary to pathologic myopia and therefore potentially confounding the safety and efficacy profile for faricimab.
DME and nAMD	Uncontrolled glaucoma	To allow unbiased study data interpretation. Uncontrolled glaucoma could lead to serious complications, loss of vision, and need for intervention.	No	A warning to use with caution in patients with poorly controlled glaucoma and to not inject faricimab if the intraocular pressure is ≥+30mmHg is included in the SmPC.
DME and RVO	History of retinal detachment or macular hole (Stage 3 or 4)	To allow unbiased study data interpretation. These conditions could seriously and irreversible impact vision and confound proper evaluation of the safety and efficacy profile of a new pharmacological intervention.	No	Retinal detachment is an identified risk for faricimab intravitreal injections (under Section 4.8 of the SmPC), and patients with a history of retinal detachment or macular hole are at high risk of vision loss and or visual improvement limitations. This risk will be monitored through routine pharmacovigilance activities. A warning to withhold treatment in patients with rhegmatogenous retinal detachment or Stage 3 or 4 macular hole until adequately repaired is included in the SmPC under special warnings and precautions for use.

Table 20 Important Exclusion Criteria in Pivotal Studies in the Development Program (cont.)

	Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale (if not included as missing information)
Systemic				
All indications	Systemic treatment for suspected or active systemic infection on Day 1	To reduce the possibility of serious complications or death caused by active systemic infection or interference and side effects potentially caused by anti-infective treatment.	No	Precaution in clinical trial setting. It is at the prescriber's discretion to evaluate patients' eligibility for treatment, based on individual case-by-case benefit-risk evaluation.
	Uncontrolled blood pressure (defined as systolic >180 mmHg and/or diastolic >100 mmHg while a patient is at rest) on Day 1	Uncontrolled blood pressure is associated with other events (e.g., stroke, among others). Excluding patients with uncontrolled blood pressure may allow a better characterization of the safety and efficacy profile of faricimab and potentially lead to less dropouts/missed visits that could impact study interpretation.	No	Precaution in clinical trial setting. It is at the prescriber's discretion to evaluate patients' eligibility for treatment, based on individual case-by-case benefit-risk evaluation.
	Stroke (cerebrovascular accident) or MI within 6 months prior to Day 1	To allow for a cleaner assessment of the safety and efficacy profile of faricimab. A previous stroke puts a patient at higher risk of having an additional one. Included to reduce the possibility of serious complications or death caused by stroke, impacting patients' ability to continue in study, thus negatively impacting the possibility of study interpretation.	No	ATE have been reported following intravitreal injection of VEGF inhibitors and are a known class effect related to systemic VEGF inhibition. A warning regarding the potential risk of ATE related to VEGF inhibition is included in the SmPC.
	Known hypersensitivity to faricimab or any component of the faricimab injection	To eliminate the possibility of potentially lethal allergic reactions to any product that may be administered to patients during the study.	No	A contraindication in patients with hypersensitivity to faricimab or any component of the excipients listed in prescribing information is included in the SmPC.

Table 20 Important Exclusion Criteria in Pivotal Studies in the Development Program (cont.)

	Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale (if not included as missing information)
Systemic (cont.)				
DME	Administration of systemic pro-angiogenic treatments, such as VEGF-based therapies for the peripheral or coronary ischemia (e.g., limb ischemia or MI) within 3 months or 5 half-lives prior to Day 1	To reduce the possibility of interference with study treatment limiting the possibility to interpret the study results and clearly characterizing safety profile.	No	The exclusion criterion was imposed in order to avoid any potential efficacy or safety confounders and does not justify the restriction of treatment recommendation in this population. It is at the prescriber's discretion to evaluate patients' eligibility for treatment, based on individual case-by-case benefit-risk evaluation.

AMD = age-related macular degeneration; ATE = arterial thromboembolic events; CNV = choroidal neovascularization; DME = diabetic macular edema; MI = myocardial infarction; nAMD = neovascular age-related macular degeneration; RPE = retinal pigment epithelium; RVO = retinal vein occlusion; SmPC = Summary of Product Characteristics; VEGF = vascular endothelial growth factor.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

The clinical trial development program for faricimab was unable to detect adverse drug reactions that are:

- Rare adverse reactions
- Caused by prolonged exposure – Safety data collected from RHONE-X and AVONELLE-X in patients with DME and nAMD, respectively, included patients who were exposed to faricimab for 4 years. These longer duration studies did not identify any new adverse drug reactions.
- Caused by cumulative exposure
- Have a long latency

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Use in Pregnancy and Lactation

No developmental toxicity, teratogenicity, or effect on weight or structure of the placenta were observed in nonclinical studies in pregnant cynomolgus monkeys treated with faricimab (Report 1053361; Report 1057630; Report 1093222).

Pregnant women were not eligible for inclusion in the clinical development program of faricimab. Faricimab has an anti-angiogenic mechanism of action and is regarded as potentially teratogenic and embryo-/fetotoxic. As a precautionary measure, there is guidance in the Summary of Product Characteristics (SmPC) to warn against the use of faricimab during pregnancy unless the potential benefit outweighs the potential risk to the fetus. Together with the label warning and recognizing that in the DME patient population pregnancy is possible, “Use in pregnancy” is considered Missing Information for faricimab and will be further characterized as data becomes available (see Part II: SVII.3.2 for further information).

Table 21 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program. Four pregnancy cases were reported during the conduct of the Phase III studies (Annex 7A.4), of which two patients were treated with faricimab, both had the outcome "live birth without congenital anomaly" and one was from GR40349 (YOSEMITE) and the other was from GR41987 (RHONE-X).
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	
Patients with hepatic impairment	Not included in the clinical development program
Patients with renal impairment	In the overall faricimab clinical development program, 63% of faricimab-treated patients with available serum creatinine measurements had renal impairment (mild 38%, moderate 23%, and severe 2%) (Report 1120410).
Patients with cardiovascular impairment	Not included in the clinical development program
Immunocompromised patients	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Clinical trial exposure data by racial origin are provided in Table 18. Clinical trial exposure data by ethnicity are provided in Table 19.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	Not applicable

PART II: MODULE SV — POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method Used to Calculate Exposure

Faricimab estimates of exposure are based on manufacturing and sales data, the cornerstone information is the quantity sold worldwide per month.

The cumulative patient exposure from marketing experience refers to the total number of patients who have ever been exposed to faricimab up to a specific point of time (IBD – 27 January 2025; see Annex 7E).

The indication, age and gender splits are derived from the data shared by the Genentech team where the “Other” category contains all the indications except nAMD,

DME, and RVO. These proportions are calculated using data from the secondary data source.

Methodology for Patient Exposure in the European Economic Area (EEA) and Rest of World (RoW)

The estimated number of patients exposed to faricimab was based on the volume of vials sold and an estimate of the total amount administered per patient. The volume sold by Roche is sourced from Roche supply chain and financial systems (Controlling Profitability Analysis [COPA]). The sales data are provided on a monthly basis, therefore the exposure is available from the international birth date (IBD) to the nearest end of month to the point of the data lock point. Due to the limited launch of Vabysmo Pre-filled Syringe (PFS) in the European Economic Area (EEA) or Rest of World (RoW) so far, PFS data from these regions is not yet available.

Methodology for Patient Exposure in the United States

The estimated number of patients is derived using the inventory management program OUTs (total doses out of the inventory) data informed by Verana's detail on NBRx (New Prescriptions). This method considers both vial and PFS usage, either of which are considered a dose.

The monthly ratio of New vs. Continued is obtained from Verana (secondary data source) applied onto the OUTs to get the estimate. Excluding AMD, DME, and RVO indications, all remaining indications are classified under the "others" bucket.

Methodology for Patient Exposure in Japan

The estimated number of patients exposed to faricimab was calculated based on the volume of vials sold (as PFS had not launched in Japan at the time of data lock). The continuation rate and dosing frequency in nAMD, DME and RVO were calculated based on receipt data of faricimab by calculating the proportion of new/continuing patients based on the proportion of patients with new, switching in, continuing, switching out, and those who discontinued treatment. The number of newly acquired patients per month was calculated by multiplying the dosing frequency to the number of the vials supplied per month.

SV.1.2 Exposure

Since the IBD until 27 January 2025, an estimated cumulative total of 804,564 patients have received faricimab from marketing experience; see Annex 7E for further details.

PART II: MODULE SVI — ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Drugs that have a potential for misuse for illegal purposes are expected to share general characteristics such as psychoactive, stimulant, or sedative effects, or less commonly, anabolic effects or enhancement of hemoglobin levels. It is unlikely that faricimab will be misused for illegal purposes.

PART II: MODULE SVII — IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The information presented in Modules SVII.1.1 and SVII.1.2 is only applicable at the time of the initial marketing authorization application with data during the entire study period of Phase II DME and nAMD studies (i.e., BOULEVARD, AVENUE, STAIRWAY) and pivotal Phase III DME studies (i.e., YOSEMITE, RHINE), as well as data through Week 48 of pivotal Phase III nAMD studies (i.e., TENAYA, LUCERNE).

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for NOT including an identified or potential risk in the list of safety concerns in the RMP:

Known risks that required no further characterization and are followed up via routine pharmacovigilance and for which the risk-minimization messages in the Product Information are adhered to by prescribers:

- Rhegmatogenous retinal detachment/ retinal tear

  Intravitreal injection through the retina instead of the pars plana creates the risk of causing an iatrogenic retinal hole, which is the cause of most retinal tears/detachments associated with intravitreal injections. A rhegmatogenous retinal detachment occurs when a break (tear or hole) in the retina leads to fluid passage and accumulation and separation of the neurosensory retina from the underlying retinal pigment epithelium. Vitreoretinal traction is responsible for most of the rhegmatogenous retinal detachments (Sultan et al. 2020). In some eyes, strong vitreoretinal adhesions are present, and the occurrence of a posterior vitreous detachment can lead to the formation of a retinal tear. The liquefied vitreous can then seep through the tear and under the retina, leading to a retinal detachment.

  In the pivotal Phase III studies with nAMD (i.e., TENAYA and LUCERNE) through Week 48, there were no events of retinal detachment / retinal tear reported in the faricimab–treated patients. In the pivotal Phase III DME studies (i.e., YOSEMITE and RHINE) during the entire study, 0.3% of faricimab-treated patients (n=4) experienced at least one event of rhegmatogenous retinal detachment / retinal tear. Two events of retinal tear were reported as mild, one as moderate and one event of rhegmatogenous retinal detachment as severe in intensity. All four events were

considered serious and were resolved with treatment. Rhegmatogenous retinal detachment was treated with pars plana vitrectomy, and three retinal tears were treated with laser.

Overall, low incidence of rhegmatogenous retinal detachment and retinal tear was observed in faricimab clinical trials and was manageable with standard treatment. Risk of rhegmatogenous retinal detachment and retinal tear is a known risk associated with approved intravitreal anti-VEGF monotherapies. Based on data available to date from the faricimab clinical development program, the risk of rhegmatogenous retinal detachment and retinal tear is shown to be consistent with approved intravitreal anti-VEGF monotherapies and considered sufficiently characterized. This risk is considered to be adequately addressed within the Warnings and Precautions of the product labelling and will be monitored via routine pharmacovigilance (PV) activities.

- Retinal Pigment Epithelial Tear (nAMD only)

  Retinal pigment epithelial (RPE) tear can be part of the natural course of nAMD or can occur as a complication following anti-VEGF intravitreal injections. RPE tears most commonly occur in nAMD eyes with a pigment epithelial detachment (PED), but the exact mechanism of RPE tear formation is unknown. Various hypotheses have been proposed for tear formation following PEDs that include an increase in hydrostatic pressure of serous fluid that collects under the retinal pigment epithelium (i.e., within the PED) that ultimately results in a tear to the retinal pigment epithelium (Gass 1984). Important risk factors for RPE tear are the type of PED (vascularized PED), increased PED height (reports suggest that the larger the PED, the greater the risk of RPE tear development), increased surface area, and large basal diameter of PED and choroidal neovascularization lesion type (Chan et al. 2010; Doguizi and Ozdek 2014; Sarraf et al. 2014).

  In the Phase III faricimab safety population with nAMD (i.e., TENAYA and LUCERNE) through Week 48, 2.9% of patients (n = 19) experienced at least one event of RPE tear. Most events were non-serious and not severe. Non-serious AEs had minimal impact on long-term visual outcomes, with patients in general maintaining visual acuity levels similar to those prior to the AE in the majority of cases. Four patients (0.6%) experienced serious events, of which one patient sustained vision loss of ≥ 30 letters and two patients sustained vision loss of ≥ 15 letters up to Week 48 (primary analysis endpoint time).

  RPE tear most commonly occurs in nAMD eyes with a PED (i.e., confounded by an underlying condition). Monitoring of risk factors and predictors defined by retinal imaging in high-risk patients can contribute to the prevention of RPE tears. The risk factors are adequately described within the Warnings and Precautions of the product labelling. There are no additional risk minimization measures proposed for this risk. Risk of RPE tear is a known risk associated with approved intravitreal anti-VEGF monotherapies. Based on the data available to date from the faricimab clinical development program, the risk is shown to be consistent with approved intravitreal anti-VEGF monotherapies and considered sufficiently characterized and will be monitored via routine PV activities.

Risks with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Traumatic cataract

  Intravitreal injections have been associated with traumatic cataract. The potential risk of traumatic cataract with faricimab treatment is based on the observed association of traumatic cataract with the intravitreal injection administration of anti-VEGF monotherapy agents. During the intravitreal injection, any direct trauma to the lens by the needle touching the lens could result in traumatic cataract. However, no case of traumatic cataract in the study eye was reported in the faricimab treatment arms of the completed Phase II studies and pivotal Phase III studies (i.e., up to Week 48 for nAMD studies [TENAYA and LUCERNE] and during the entire study for DME studies [YOSEMITE and RHINE]). Therefore, traumatic cataract will remain as a potential risk not important for inclusion in the RMP and will be monitored via routine PV activities.

Known risks that do not impact the risk-benefit profile:

- Transient post intravitreal injection-related intraocular pressure (IOP) increases

  Transient IOP increase is attributed to an increase in vitreous volume after faricimab injection. Increases in IOP have been observed while being treated with repeated intravitreal injections of anti-VEGF monotherapy agents.

  In the pivotal Phase III studies of faricimab in nAMD and DME, transient increases in IOP have been observed within 30±15 minutes of injection. IOP-increased AEs in the study eye were observed in 17 patients (2.6%) in the faricimab arms of the nAMD Phase III studies through Week 48 and in 53 patients (4.2%) in the faricimab arms of the DME Phase III studies during the entire study.

  These AEs of IOP increase were mostly non-serious and self-limiting or managed with standard of care. There were two serious events of IOP increased reported (one each in the nAMD and DME studies); one was reported as secondary to herpetic uveitis and second was considered related to procedure. Both events resolved with treatment.

  In addition, there were no clinically meaningful differences in the mean change from pre-dose to post-dose IOP across the treatment arms, and there was no observable increase in pre-dose IOP from baseline over time.

  Based on available data, transient post intravitreal injection-related IOP increases are not expected to impact the benefit-risk profile of faricimab; the risk is not considered important for inclusion in the RMP, and it will be addressed within the Warnings and Precautions of the product labelling. In addition, risk of transient IOP increase is considered sufficiently characterized and monitored via routine PV activities.

- Immunogenicity

  Potential risk factors which may contribute to an induction of a humoral immune response (ADA response) to the administered drug in patients include patient- and disease-specific factors (e.g., disease state, age, concomitant medications), trial design specific factors (e.g., dose level and frequency, duration and route of administration), and drug product specific factors (e.g., protein sequence and structure, formulation, aggregation and protein modifications, contaminants and impurities). Consequences for ADA may be, but are not limited to, immune-mediated AEs or AEs related to immune complex formation, decrease of efficacy, and alteration of pharmacokinetics. These risk factors were taken into consideration in assessing the likelihood of an immune response to faricimab. This information, in addition to the potential clinical consequences of an immune response, including how severe the consequences of an immune response might be, were considered in assessing the immunogenicity risk of faricimab in the nAMD and DME patient populations.

  The risk of immunogenicity from faricimab was low, with an incidence of ADA induction/boosting across all pivotal Phase III studies of approximately 10% (nAMD: 10.4%; DME: 9.6%). Incidence rate of IOI was low and not more than 2% in the pivotal nAMD and DME Phase III studies. Although a higher incidence of IOI was observed in ADA-positive patients (nAMD: 5/75 [6.7%]; DME: 15/128 [11.7%]) compared with ADA-negative patients (nAMD: 7/582 [1.2%]; DME: 5/1124 [0.4%]), this observation is not currently considered to be clinically relevant. Based on the low incidence of immunogenicity, the low incidence of IOI for which the majority of the events were of mild to moderate severity and had a reversible character. Patients receiving faricimab in clinical trials will continue to be monitored for signs and symptoms that might be suggestive of immunogenicity.

  IOI events are included in this RMP as important identified risks. In addition, a patient/carer education guide will be provided to facilitate awareness regarding the presenting signs and symptoms of these adverse reactions so that they can promptly inform the treating physician to ensure appropriate intervention and treatment as needed. The impact of ADA on safety, especially the incidence and severity of IOI events, will continue to be monitored via routine PV in all ongoing pivotal Phase III faricimab studies.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk of Infectious Endophthalmitis

Risk-benefit impact:

In total, seven infectious endophthalmitis events have been reported in faricimab-treated patients in the clinical development program. The frequency of infectious endophthalmitis in the pivotal Phase III studies (GR40306 TENAYA, GR40844

LUCERNE, GR40349 YOSEMITE, and GR40398 RHINE) was 6 events (0.3%). In the Phase II studies, no events were reported in the faricimab 6 mg arms, and the frequency of events was 1.0% (1 event) in the pooled (nAMD and DME) faricimab 1.5 mg arm. The event rate per-1000 injections in the pivotal Phase III studies was 0.3. Four events were reported as severe and three as moderate in intensity, and all events were considered serious. All but two events were resolved, one event was resolving, and the remaining event had not resolved. All except one patient in general achieved visual acuity levels similar to those prior to the AE; the remaining patient had early termination following event onset, visual acuity was improving at the time of last visit.

Infectious endophthalmitis usually presents with sudden onset of decreased vision and severe eye pain. It can result in variable degree of visual loss, including some cases reporting total loss of vision and no light perception. It requires prompt intervention to reduce risk of vision loss and maximize recovery potential. Considering the severity and seriousness of these events, it represents an important risk for faricimab. Although the observed events in faricimab-treated patients were serious, they were generally manageable with antibiotic and steroid treatment with or without vitrectomy, and the overall frequency of infectious endophthalmitis events reported in the faricimab clinical development program was low. Therefore, the impact of infectious endophthalmitis on the benefit-risk balance of faricimab is considered low. Appropriate labelling and patient/carer educational materials as a risk minimization activity increases the likelihood of an early diagnosis followed by appropriate treatment, further reducing the impact of infectious endophthalmitis on the benefit-risk balance of the product.

Important Identified Risk of Intraocular Inflammation

Risk-benefit impact:

IOI, including the wide selection of preferred terms of anterior chamber inflammation, chorioretinitis, iridocyclitis, iritis, keratic precipitates, keratouveitis, uveitis, and vitritis, were reported in 1.7% (n=33) of patients treated with faricimab in the Phase III studies. The frequency of IOI in the Phase II studies was 3.0% (n=3) in the faricimab 1.5 mg arms and 1.4% (n=4) in the faricimab 6 mg arms . All except for one event were mild in severity in the Phase II studies. In the pivotal Phase III studies, the majority of faricimab-treated patients experienced events that were mild (0.7%, n=13) or moderate (0.7%, n=13) in severity. Mild or moderate IOI events had no long-term impact on patients' visual outcomes. Seven (0.4%) patients experienced severe events, of which five patients had a visual acuity reduction of ≥15 letters (2 patients) and ≥30 letters (3 patients). These severe events were managed with treatment for the AE and study drug interruption (2 patients) or discontinuation (5 patients).

IOI can range from a mild inflammation of the eye that may resolve without vision loss to severe with sequelae leading to vision loss. Permanent visual acuity loss of two or more lines has been associated with rapid presentation, severely diminished visual acuity at presentation, the presence of fibrin, and older patient age. Considering the low incidence of severe events, and that the majority of intraocular events observed in

faricimab-treated patients were manageable with standard treatment and that most events resolved, the impact on the benefit-risk balance of faricimab is considered low. Appropriate labelling and the patient/carer educational materials as a risk minimization activity increases the likelihood of an early diagnosis followed by appropriate treatment, further reducing the impact of IOI on the benefit-risk balance of the product.

Important Potential Risk of Arterial Thromboembolic Events (ATE) and Central Nervous System Hemorrhagic Events

To account for variations in how thrombotic and hemorrhagic events may be reported, CNS hemorrhagic events (hemorrhagic CNS vascular conditions and cerebrovascular accidents) are included with ATE (as a safety concern for faricimab), in line with the Anti-Platelet Trialists' Collaboration (APTC) defined events which include both thrombotic and hemorrhagic events.

In pivotal Phase III studies in nAMD (GR40306 TENAYA and GR40844 LUCERNE) and in DME/DR (GR40349 YOSEMITE and GR40398 RHINE), potential APTC events reported during the study were adjudicated (according to APTC definition) by an independent Clinical Events Committee (CEC) at Cleveland Clinic. The role of the CEC was to adjudicate potential APTC events in a blinded, consistent, and unbiased manner. Events based on external adjudication are presented in Table 22. ATE and CNS hemorrhagic events (adjudicated) were reported in 3.7% (n = 71) of patients treated with faricimab in the Phase III studies. Overall, incidence of APTC events in the faricimab arm was low across all four Phase III studies, and consistent with what has been observed with approved intravitreal anti-VEGF monotherapies (Rosenfeld et al. 2006; Brown et al. 2009; Schmidt-Erfurth et al. 2014; Heier et al. 2016; Zarbin et al. 2017; Zarbin et al. 2018).

Table 22 Adjudicated APTC-Defined Adverse Events

APTC Event	nAMD TENAYA and LUCERNE (through Week 48) Faricimab (N = 664)	DME YOSEMITE and RHINE (during the Entire Study) Faricimab (N = 1262)
Vascular or cardiac death or death of unknown cause	2 (0.3%)	31 (2.5%)
Non-fatal myocardial infarction	3 (0.5%)	12 (1.0%)
Non-fatal stroke	2 (0.3%)	21 (1.7%)
Combined APTC events	7 (1.1%)	64 (5.1%)

APTC = Anti-Platelet Trialists' Collaboration; DME = diabetic macular edema; nAMD = neovascular age-related macular degeneration.

The frequency of ATE and CNS hemorrhagic events (unadjudicated) in the Phase II studies was 2.0% (n = 2) in the faricimab 1.5 mg arms and 3.5% (n = 10) in the faricimab 6 mg arms.

Overall, the majority of ATE and CNS hemorrhagic events experienced by faricimab-treated patients in the Phase III and Phase II trials were severe. While these events have been observed in the faricimab clinical development program, most of the events were assessed as unrelated to the study treatment by the investigators in all treatment arms, or the events were confounded by the patient's concurrent medical history.

It is well known that there is an increased risk of thromboembolic events and non-ocular hemorrhage associated with IV administration of high doses of VEGF-inhibitors used in the treatment of cancer. Cancer itself is also a risk factor for these types of events. (Navi et al. 2019). Yet, there is currently no clear evidence of this class effect leading to an increased incidence of systemic thromboembolic events and non-ocular hemorrhage when much lower intravitreal doses of VEGF-inhibitors are administered in patients with nAMD and DME (Thulliez et al. 2014; Zarbin et al. 2017; Zarbin et al. 2018).

The systemic exposure to faricimab, following unilateral intravitreal administrations of 6 mg faricimab is low (refer to Part II: Module SII for further details) therefore, systemic PD effects including the development of ATEs and non-ocular hemorrhagic events are unlikely, and the risk remains potential.

The safety concern of ATE and CNS hemorrhagic events will be further characterized for long-term use by two long-term extension (LTE) studies (AVONELLE-X and RHONE-X). No additional risk minimization is proposed for this risk as healthcare professionals are well aware of the class effect related to systemic VEGF inhibition and guidance is also provided in the faricimab EU SmPC to sufficiently mitigate this risk.

Missing Information of Long-term Safety

Benefit-risk impact:

The current overall extent of exposure to faricimab accounts for a limited number of patients followed up for a restricted amount of time (beyond 1 year). Currently, there is data available from the Phase III pivotal studies up to Week 48 for nAMD studies (i.e., the time point for primary analysis) and the entire study (through Week 100) for DME studies. Although limited long-term safety data are available, faricimab is intended for long-term use. Thus, long-term safety data are being collected and monitored from the LTE clinical studies, AVONELLE-X (nAMD) and RHONE-X (DME). Refer to Part III.2 and Part III.3 for further details.

Missing Information of Use in Pregnancy

Benefit-risk impact:

No developmental toxicity, teratogenicity, or effect on weight or structure of the placenta were observed in nonclinical studies in pregnant cynomolgus monkeys treated with faricimab (Report 1053361; Report 1057630; Report 1093222).

Pregnant women were not eligible for inclusion in the clinical development program of faricimab. Faricimab has an anti-angiogenic mechanism of action and is regarded as

potentially teratogenic and embryo-/fetotoxic. As a precautionary measure, there is guidance in the SmPC to warn against the use of faricimab during pregnancy unless the potential benefit outweighs the potential risk to the fetus. Together with the label warning and recognizing that in the DME patient population pregnancy is possible, “Use in pregnancy” is considered Missing Information for faricimab and will be further characterized as data becomes available (see PART II, SVII.3.2 for further information).

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Long term safety (missing information) and ATE and CNS hemorrhagic events (important potential risk)

Long-term safety, previously classified as missing information, has been removed from the list of safety concerns. Additionally, the important potential risk of ATE and CNS hemorrhagic events has been removed from the list of safety concerns. The available data regarding long-term safety in patients with DME or nAMD following completion of the LTE clinical studies RHONE-X and AVONELLE-X (in DME and nAMD, respectively) have been incorporated into this EU RMP.

The reasons for changes to the list of safety concerns are based on the following:

The LTE studies in DME and nAMD included patients who had completed the pivotal Phase III studies for DME (YOSEMITE and RHINE) or nAMD (TENAYA and LUCERNE). Patients consented to participate and were subsequently enrolled into RHONE-X (n = 1474 patients) and AVONELLE-X (n = 1029 patients), respectively.

Following the completion of studies RHONE-X and AVONELLE-X, evaluation of the safety data obtained has demonstrated that faricimab remains well tolerated with an acceptable safety profile consistent with that of the pivotal Phase III studies in patients treated for DME and nAMD, respectively. Evaluation of the cumulative 4-year safety data for faricimab from RHONE-X and AVONELLE-X also demonstrated that the safety profile remains unchanged. The reported events were either consistent with the known safety profile of faricimab, or as anticipated by the disease/population under study. For the important identified risks of intraocular inflammation and endophthalmitis, the incidence remained low in the cumulative 4-year group.

Overall, the evaluation of the cumulative 4-year safety data for faricimab in both RHONE-X and AVONELLE-X was consistent with the known safety profile of faricimab observed from the respective pivotal Phase III studies for both DME and nAMD , and this information has been included in the EU SmPC accordingly (SmPC Section 5.1). No new adverse drug reactions or safety signals have been associated with long-term use of faricimab.

With regards to the important potential risk of ATE and CNS hemorrhagic events, this risk was further characterized through RHONE-X and AVONELLE-X and the data from the extension studies in conjunction with the pivotal Phase III trials did not confirm a causal association with faricimab. This is further supported by a comprehensive analysis of clinical trial, post-marketing, literature and epidemiology data which concluded that there is insufficient evidence to establish a causal association between these events and faricimab administration. Additionally, systemic exposure following intravitreal administration is very low with plasma concentrations approximately 6,000-fold lower than in the vitreous. Furthermore, no suppression of systemic free VEGF-A or Ang-2 was observed in patients receiving faricimab (DSR, report no. 1153704 [Annex 7D]). Consequently, no additional risk minimization measures nor additional PV activities are required to further characterize this risk and it has been removed from the EU RMP list of safety concerns.

The Marketing Authorization Holder (MAH) will continue to perform routine pharmacovigilance activities (ongoing signal detection) to closely monitor the safety profile of faricimab and will continue to present the safety data in relation to the risk of ATE and CNS hemorrhagic events in the upcoming PSURs/PBRERs.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

Safety data presented in this module are derived from faricimab safety population in the pivotal Phase III studies (GR40306 [TENAYA], GR40844 [LUCERNE], GR40349 [YOSEMITE], GR40398 [RHINE], GR41984 [BALATON] and GR41986 [COMINO]) and the Phase III LTE studies (GR41987 [RHONE-X] and GR42691 [AVONELLE-X]).

For the purpose of presenting the safety data for each important identified or important potential risk, data from pivotal Phase III studies are pooled across indications. Pooling is considered meaningful based on similar study designs, same comparator, and an overall similar safety profile of nAMD, DME and RVO. In total, 664 patients exposed to faricimab in the TENAYA and LUCERNE studies, and 641 patients exposed in the BALATON and COMINO studies, are included (Table 13). Additionally, 1262 patients initially exposed to faricimab in YOSEMITE and RHINE are also included.

Safety data for each important identified or potential risk for the long-term-extension studies RHONE- X and AVONELLE-X are presented separately and not pooled with pivotal Phase III studies, as there is no comparator arm, and they do not share the same study design as the pivotal studies. Five patients in RHONE-X and seven patients in AVONELLE-X were not included in the safety analysis due to a critical audit finding identified in February 2024 (Table 13), however they were included in the pivotal Phase III DME and nAMD studies respectively, as the timing of the issues identified did not overlap with the pivotal studies. In total, 1464 patients and 1025 patients were included in RHONE-X and AVONELLE-X, respectively.

Of the 1464 patients in RHONE-X[2,3], 991 had previously received faricimab (prior faricimab), and 473 had previously received aflibercept (prior aflibercept) in the pivotal Phase III studies (YOSEMITE and RHINE).

Of the 1025 patients in AVONELLE-X, 520 had previously received faricimab (prior faricimab) and 505 had previously received aflibercept (prior aflibercept) in the pivotal Phase III studies (TENAYA and LUCERNE).

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1 Information on Important Identified Risks

Infectious Endophthalmitis

Potential mechanisms:

Improper sterile technique during the administration of the intravitreal injections procedure may lead to intraocular contamination with microorganisms, eventually leading to infectious endophthalmitis (Avery et al. 2014; Storey et al. 2020).

Evidence source(s) and strength of evidence:

This important identified risk is based on data from the faricimab safety population in the pivotal Phase III studies (GR40306 TENAYA, GR40844 LUCERNE, GR40349 YOSEMITE, GR40398 RHINE, GR41984 BALATON, and GR41986 COMINO) and the Phase III LTE studies, (GR41987 RHONE-X and GR42691 AVONELLE-X).

The frequency of endophthalmitis reported with approved intravitreal anti-VEGF monotherapies is presented in Table 23.

[2] The AVONELLE-X study population included eligible patients enrolled to AVONELLE-X from the pivotal Phase III studies TENAYA/LUCERNE or Japan extension of neovascular age-related macular degeneration (nAMD) studies.

[3] Note that for the purpose of the RMP outputs, a total of 1464 patients and 1025 patients enrolled in RHONE-X and AVONELLE-X treatment groups, respectively, are referred to as “Combined LTE”

Table 23 Frequency of Occurrence of Endophthalmitis in other Observational Studies and Clinical Trials

Event type	nAMD Population (incidence proportion)		DME Population (incidence proportion)		RVO Population (incidence proportion)	
	Observational Studies	Clinical Trials	Observational Studies	Clinical Trials	Observational Studies	Clinical Trials
All events	NR	0.45%–0.93%	NR	0.61%		0.6%
Source	—	Meredith et al. 2015; Berg et al. 2016	—	Bhavsar et al. 2009	—	Scott et al. 2017
Serious events	0.14%	0.13%–0.85%	0.08%	0.51%–2.0%	—	0.4%–0.9%
Source	Holz et al. 2020	Busbee et al. 2013; Silva et al. 2013; Schmidt-Erfurth et al. 2014; Silva et al. 2018; Dugel et al. 2021	Ziemssen et al. 2018	Massin et al. 2010; Brown et al. 2013; Heier et al. 2016	—	Brown et al. 2011; Boyer et al. 2012; Heier et al. 2012b

DME = diabetic macular edema; nAMD = neovascular age-related macular degeneration; NR = not reported; RVO = retinal vein occlusion.

In an observational study that reported per injection rate of endophthalmitis with other anti-VEGF treatments, the rate of endophthalmitis following aflibercept, bevacizumab, and ranibizumab intravitreal injections was 0.100% (136/135,973), 0.056% (268/481,572), and 0.047% (94/201,013), respectively (Kiss et al. 2018).

Characterization of the risk:

Of the 664 faricimab-treated patients from the pivotal Phase III studies with nAMD (i.e., TENAYA and LUCERNE), 0.5% of patients (n=3) experienced at least one event of infectious endophthalmitis in the study eye (Table 24). All three events were considered serious and reported as severe and were also considered resolved by the end of the study.

Of the 1025 patients receiving faricimab in AVONELLE-X, 0.5% of patients (n=5) experienced at least one event of infectious endophthalmitis in the study eye (Table 25). All five events were reported as severe and were either resolved (n=4) or resolved with sequelae (n=1) by the end of the study.

Of the 1262 faricimab-treated patients from the pivotal Phase III population with DME (i.e., YOSEMITE and RHINE), 0.5% of patients (n=6) experienced at least one event of infectious endophthalmitis in the study eye (Table 24). These events were considered serious. Three events were reported as severe and three were reported as moderate in severity. Of the patients with events (n=6), four patients had events that were considered resolved, one patient had an event that was resolving, and one patient had an event that had not resolved by study completion (through Week 100).

Of the 1464 patients receiving faricimab in RHONE-X, 0.2% of patients (n=3) experienced at least one event of infectious endophthalmitis in the study eye (Table 25). Two events were reported as severe, and one was reported as moderate in severity; all three events were resolved by the end of the study.

No faricimab-treated patients from the pivotal Phase III population with BRVO (i.e., BALATON) and C/HRVO (i.e., COMINO) experienced any infectious endophthalmitis event in the study eye through Week 24 (Table 24).

The per 1000 injection rate of infectious endophthalmitis events was 0.34 (Annex 7A.2) in the faricimab pivotal Phase III population, pooled across all indications.

The per 1000 injection rate of infectious endophthalmitis events was 0.37 (Annex 7A.3) in the pooled LTE (RHONE-X and AVONELLE-X) study population.

Table 24 Important Identified Endophthalmitis Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI during Entire Study (Week 112 nAMD and Week 100 DME) and through Primary Endpoint Time (Week 24 RVO) in the Study Eye, Safety-Evaluable Population

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986
Clinical Cutoff Date: BALATON 06JUL2022, COMINO 09AUG2022

	nAMD (N=1326)		DME (N=1887)	
	Faricimab (N=664)	Aflibercept (N=662)	Faricimab (N=1262)	Aflibercept (N=625)
Number (%) of patients with at least one AE	3 (0.5%)	2 (0.3%)	6 (0.5%)	1 (0.2%)
95% CI for % of patients with at least one AE	(0.15%, 1.32%)	(0.08%, 1.09%)	(0.22%, 1.03%)	(0.03%, 0.90%)
Difference in % of patients with at least one AE	0.1%		0.3%	
95% CI for difference	(-0.70%, 1.04%)		(-0.47%, 0.89%)	
Total number of AEs	3	2	6	1
Number (%) of patients with at least one AE by severity				
Mild	0	0	0	0
Moderate	0	1 (0.2%)	3 (0.2%)	0
Severe	3 (0.5%)	1 (0.2%)	3 (0.2%)	1 (0.2%)
Number (%) of patients with at least one serious AE	3 (0.5%)	2 (0.3%)	6 (0.5%)	1 (0.2%)
Number (%) of patients with at least one AE by outcome				
Fatal	0	0	0	0
Not recovered/Resolved	0	1 (50.0%)	1 (16.7%)	0
Recovering/Resolving	0	0	1 (16.7%)	0
Recovered/Resolved	3 (100%)	1 (50.0%)	4 (66.7%)	0
Resolved with sequelae	0	0	0	1 (100%)
Unknown outcome	0	0	0	

Table 24 Important Identified Endophthalmitis Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI during Entire Study (Week 112 nAMD and Week 100 DME) in the Study Eye and through Primary Endpoint Time (Week 24 RVO), Safety-Evaluable Population (cont.)

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986
Clinical Cutoff Date: BALATON 06JUL2022, COMINO 09AUG2022

	BRVO (N=550)		C/HRVO (N=726)	
	Faricimab (N=276)	Aflibercept (N=274)	Faricimab (N=365)	Aflibercept (N=361)
Number (%) of patients with at least one AE	0	0	0	1 (0.3%)
95% CI for % of patients with at least one AE	(0.00%, 1.37%)	(0.00%, 1.38%)	(0.00%, 1.04%)	(0.05%, 1.55%)
Difference in % of patients with at least one AE	NE		-0.3%	
95% CI for difference	NE		(-1.55%, 0.79%)	
Total number of AEs	0	0	0	1
Number (%) of patients with at least one AE by severity				
Mild	0	0	0	0
Moderate	0	0	0	0
Severe	0	0	0	1 (0.3%)
Number (%) of patients with at least one serious AE	0	0	0	1 (0.3%)
Number (%) of patients with at least one AE by outcome				
Fatal	0	0	0	0
Not recovered/Resolved	0	0	0	0
Recovering/Resolving	0	0	0	0
Recovered/Resolved	0	0	0	0
Resolved with sequelae	0	0	0	1 (100%)
Unknown outcome	0	0	0	0

Table 24 Important Identified Endophthalmitis Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI during Entire Study (Week 112 nAMD and Week 100 DME) in the Study Eye and through Primary Endpoint Time (Week 24 RVO), Safety-Evaluable Population (cont.)

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986
Clinical Cutoff Date: BALATON 06JUL2022, COMINO 09AUG2022

	Combined Indications (N=4489)	
	Faricimab (N=2567)	Aflibercept (N=1922)
Number (%) of patients with at least one AE	9 (0.4%)	4 (0.2%)
95% CI for % of patients with at least one AE	(0.18%, 0.67%)	(0.08%, 0.53%)
Difference in % of patients with at least one AE	0.1%	
95% CI for difference	(-0.22%, 0.48%)	
Total number of AEs	9	4
Number (%) of patients with at least one AE by severity		
Mild	0	0
Moderate	3 (0.1%)	1 (<0.1%)
Severe	6 (0.2%)	3 (0.2%)
Number (%) of patients with at least one serious AE	9 (0.4%)	4 (0.2%)
Number (%) of patients with at least one AE by outcome		
Fatal	0	0
Not recovered/Resolved	1 (11.1%)	1 (25.0%)
Recovering/Resolving	1 (11.1%)	0
Recovered/Resolved	7 (77.8%)	1 (25.0%)
Resolved with sequelae	0	2 (50.0%)
Unknown outcome	0	0

Investigator text for AEs encoded using MedDRA version 24.1 for nAMD, MedDRA version 24.0 for DME and MedDRA version 25.0 for RVO (BRVO and C/HRVO).
Percentages for "Number of patients with at least one AE", "Number of patients with at least one serious AE", and "Number of patients with at least one AE by severity" are based on the N in the column headings.
Percentages for "Number of patients with at least one AE by outcome" are based on the N in "Number of patients with at least one AE".
Table summary includes adverse events that started or worsened (for existing condition) on or after the date of the first injection of active study drug.
AE=adverse event; CI=Confidence Interval; 95% CI were computed using the Wilson method. Difference in frequency rates is relative to AFLIBERCEPT and 95% CI of the difference were computed using Newcombe Risk difference. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst severity.
Faricimab dosing is Faricimab 6MG intravitreal Q4W, Q8W and personalized treatment interval.
Aflibercept dosing is Aflibercept 2 mg Q4W and Q8W.
Endophthalmitis terms = Endophthalmitis, Candida endophthalmitis, Mycotic endophthalmitis, Pseudoendophthalmitis.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; BRVO GR41984; C/HRVO GR41986; POOLED(nAMD, DME, BRVO, C/HRVO) pools all six studies.
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Table 25 Important Identified Endophthalmitis Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI for Safety-Evaluable Population through RHONE-X (Year 2-4 DME) and AVONELLE-X (Year 2-4 nAMD), Safety-Evaluable Population

Protocol: GR41987, GR42691

	nAMD (N=1025)		DME (N=1464)		Combined (N=2489)
	Prior Faricimab (n=520)	Prior Aflibercept (n=505)	Prior Faricimab (n=991)	Prior Aflibercept (n=473)	
Number (%) of patients with at least one AE	2 (0.4%)	3 (0.6%)	2 (0.2%)	1 (0.2%)	8 (0.3%)
95% CI for % of patients with at least one AE	(0.11%, 1.39%)	(0.20%, 1.73%)	(0.06%, 0.73%)	(0.04%, 1.19%)	(0.16%, 0.63%)
Total number of AEs	2	3	2	1	8
Number (%) of patients with at least one AE by severity					
Mild	0	0	0	0	0
Moderate	0	0	1 (0.1%)	0	1 (<0.1%)
Severe	2 (0.4%)	3 (0.6%)	1 (0.1%)	1 (0.2%)	7 (0.3%)
Number (%) of patients with at least one serious AE	2 (0.4%)	3 (0.6%)	2 (0.2%)	1 (0.2%)	8 (0.3%)
Number (%) of patients with at least one AE by outcome					
Fatal	0	0	0	0	0
Not recovered/Resolved	0	0	0	0	0
Recovering/Resolving	0	0	0	0	0
Recovered/Resolved	2 (100%)	2 (66.7%)	2 (100%)	1 (100%)	7 (87.5%)
Resolved with sequelae	0	1 (33.3%)	0	0	1 (12.5%)
Unknown outcome	0	0	0	0	0

Percentages for "Number of patients with at least one AE", "Number of patients with at least one serious AE", and "Number of patients with at least one AE by severity" are based on the N in the column headings.
Percentages for "Number of patients with at least one AE by outcome" are based on the N in "Number of patients with at least one AE".
Table summary includes adverse events that started or worsened (for existing condition) on or after the date of the first injection of active study drug.
AE=adverse event; CI=Confidence Interval; 95% CI were computed using the Wilson method. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst severity.
Endophthalmitis terms = Endophthalmitis, Candida endophthalmitis, Mycotic endophthalmitis, Pseudoendophthalmitis.

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Based on data available to date from the clinical development program, the risk of infectious endophthalmitis has been sufficiently characterized and the frequency of occurrence is shown to be consistent with other approved intravitreal anti-VEGF monotherapies.

Risk factors and risk groups:

Patients with ocular or periocular infections or patients with active IOI are at increased risk of endophthalmitis. There is an increased risk of endophthalmitis if the intravitreal injection procedure is not performed under aseptic conditions.

Preventability:

Use of proper aseptic injection technique when administering faricimab is required to minimize the risk of endophthalmitis (Avery et al. 2014; Storey et al. 2020). Patients with ocular or periocular infection should not receive faricimab. Patients should be monitored following the injection and instructed to promptly report symptoms that may be associated with endophthalmitis. These measures would permit early diagnosis and treatment, should an infection occur, limiting the possibility of long-term sequelae.

Impact on the benefit-risk balance of the product:

Endophthalmitis presents with sudden onset of decreased vision and severe eye pain that leads to urgent visit to an ophthalmologist. Cases may develop with variable degree of visual loss, including some cases reporting total loss of vision and no light perception, which, in time, would lead to phthisis. An aqueous/vitreous sample tap should be performed, and patients treated with standard of care, including intravitreal antibiotic injections (e.g., vancomycin and ceftazidime) with or without ophthalmic or intravitreal steroids. An additional component of treatment which may be performed in some situations is PPV. Full recovery is expected for most cases; however, loss of vision and loss of the eye itself has also been reported with cases of endophthalmitis (Kresloff et al. 1998; Verma and Chakravarti 2017). Based on the data available to date from the faricimab clinical development program, the reporting rate of infectious endophthalmitis following an intravitreal injection of faricimab is low and reported events were generally manageable with treatment. The impact of infectious endophthalmitis on the benefit-risk balance of faricimab is considered low.

Public health impact:

Infectious endophthalmitis is expected to be uncommon, with a frequency of $\geq$1/1,000 to $<$1/100 events.

Intraocular Inflammation

Potential mechanisms:

Several potential mechanisms could explain the development of IOI after the intravitreal injection administration of anti-VEGF agents. Mechanical injury during the invasive

injection procedure could elicit a mild intraocular inflammatory response associated with the trauma, which may manifest with anterior chamber cells and flare.

IOI could also develop because of a specific immunogenic response to the administered protein agent (Baumal et al. 2020) or due to an innate inflammatory reaction caused by the active substance or its excipients (Cox et al. 2021). There is no current evidence from the published literature or from the post-marketing data to support the occurrence of these events due to immunogenic response in patients treated with the currently approved anti-VEGF agents ranibizumab and aflibercept.

Other causes unrelated to intravitreal injection include autoimmune or other immune-mediated and inflammatory disorders, infections (e.g., herpes zoster), and eye injury or surgery.

Evidence sources and strength of evidence:

This important identified risk is based on data from the faricimab safety population from the pivotal Phase III studies (GR40306 TENAYA, GR40844 LUCERNE, GR40349 YOSEMITE, GR40398 RHINE, GR41984 BALATON, and GR41986 COMINO) and the Phase III LTE studies (GR41987 RHONE-X and GR42691 AVONELLE-X).

The frequency of IOI reported with approved intravitreal anti-VEGF monotherapies is presented in Table 26.

Table 26 Frequency of Occurrence of Intraocular Inflammation in Clinical Trials with Intravitreal Anti-VEGF Monotherapies

Event	nAMD Population (incidence proportion) Clinical Trials (All Events)	nAMD Population (incidence proportion) Clinical Trials (Serious Events)	DME Population (incidence proportion) Clinical Trials (All Events)	DME Population (incidence proportion) Clinical Trials (Serious Events)	RVO Population (incidence proportion) Clinical Trials (All Events)	RVO Population (incidence proportion) Clinical Trials (Serious Events)
Intraocular Inflammation (defined per respective study)	0.6%–17.1%	NR	1%–8%	NR	1.0%-1.9%	NR
Source	Brown et al. 2009; Dugel et al. 2021	—	Wells et al. 2015; Sivaprasad et al. 2017	—	Brown et al. 2010; Brown et al. 2011; Holz et al. 2013	—
Iridocyclitis	0.6%–2.2% (25, 26)	0.09%	NR	NR	NR	NR
Source	Dugel et al. 2017; Khurana et al. 2020	Busbee et al. 2013	—	—	—	—
Iritis	0.27%–1.1%	NR	0.46%–2.0%	0.2%	1.5%	NR
Source	Busbee et al. 2013; Dugel et al. 2021	—	Wells et al. 2015	Brown et al. 2013	Brown et al. 2010	—
Uveitis	0.13%–1.5%	0.33%–0.71%	NR	NR	1%	NR
Source	Rosenfeld et al. 2006; Dugel et al. 2021	Brown et al. 2009; Chakravarthy et al. 2012; Dugel et al. 2021	—	—	Holz et al. 2013	—
Vitritis	NR	0.10%	NR	NR	0.8%	NR
Source	—	Dugel et al. 2021	—	—	Brown et al. 2010	—

DME = diabetic macular edema; nAMD = neovascular age-related macular degeneration; NR = not reported; VEGF = vascular endothelial growth factor; RVO = retinal vein occlusion.

Characterization of the risk:

For the purposes of reporting of IOI, iritis, iridocyclitis, and vitritis are types of uveitis reported based on the anatomical location of inflammation (Jabs et al. 2005).

In the pivotal Phase III faricimab safety population with nAMD (i.e., TENAYA and LUCERNE), 3.0% of patients (n=20) experienced at least one event of IOI in the study eye (Table 27). Five events (0.8%) were considered serious. By severity, a mild event was experienced by 1.7% (n=11) of patients, moderate in 0.9% (n=6) of patients, and severe in 0.5% (n=3) of patients. Of the patients with IOI events, two (10.0%) patients had at least one event that was considered not recovered/resolved, one (5.0%) patient had at least one event recovering/resolving, and one (5.0%) patient had at least one event resolved with sequelae.

By Medical Dictionary for Regulatory Activities (MedDRA) preferred term, 1.2% of patients (n=8) experienced iritis, 0.6% of patients (n=4) experienced uveitis, 0.6% of patients (n=4) experienced vitritis, and 0.3% of patients (n=2) experienced iridocyclitis in the pivotal Phase III nAMD population (Annex 7C.10). The per-1000 injection rate by preferred term was 1.28 for iritis, 0.71 for both uveitis and vitritis, and 0.57 for iridocyclitis (Annex 7C.11).

Of the 1025 patients receiving faricimab in AVONELLE-X, 2.1% of patients experienced at least one event of IOI in the study eye (22 patients experienced 24 events; Table 28). Five patients (0.5%) experienced at least one serious IOI event. By severity, mild events were experienced by 1.2% of patients (n=12), moderate by 0.9% of patients (n=9) and severe by 0.1% of patients (n=1). For the majority of patients experiencing at least one IOI event (n=20), the event was reported as resolved; in 4 patients at least one IOI event was not recovered/resolved.

By MedDRA preferred term, 0.8% of patients (n=8) experienced iridocyclitis, 0.5% of patients (n=5) experienced iritis, 0.3% of patients (n=3) experienced post procedural inflammation, 0.2% of patients (n=2) experienced uveitis, 0.2% of patients (n=2) experienced vitritis, and <0.1% of patients (n=1) experienced keratic precipitates and non-infectious endophthalmitis (Annex 7C.12). The per-1000 injection rate by preferred term was 0.94 for iridocyclitis, 0.59 for iritis, 0.35 for post procedural inflammation, 0.24 for both uveitis and vitritis, and 0.12 for both non-infectious endophthalmitis and keratic precipitates (Annex 7C.13).

In the faricimab arms from the pivotal Phase III safety population with DME (i.e., YOSEMITE and RHINE), 1.6% of patients (n=20) experienced at least one event of IOI in the study eye (Table 27). Four patients (0.3%) experienced at least one serious event. By severity, the mild events were experienced by 0.6% of patients (n=7), moderate by 0.7% of patients (n=9), and severe by 0.3% of patients (n=4). Of the patients with events, one (5.0%) patient had at least one event that was considered not

recovered/resolved, two (10.0%) patients had at least one event resolved with sequelae, and six (30.0%) patients had at least one event recovering/resolving.

By MedDRA preferred term, 0.6% of patients (n=7) experienced uveitis, 0.4% of patients (n=5) experienced iritis, 0.4% of patients (n=5) experienced iridocyclitis, 0.2% of patients (n=2) experienced post procedural inflammation, and 0.2% of patients (n=2) experienced vitritis in the pivotal Phase III DME population (Annex 7C.14). The per-1000 injection rate by preferred term in the pivotal Phase III DME population was 0.56 for uveitis, 0.31 for both iritis and iridocyclitis, and 0.13 for both post procedural inflammation and vitritis (Annex 7C.15).

Of the 1464 patients receiving faricimab in RHONE-X, 1.2% of patients (n=18) experienced at least one event of IOI in the study eye (Table 28). Three patients (0.2%) experienced at least one serious event. By severity, mild events were experienced by 0.5% of patients (n= 8), moderate by 0.6% of patients (n=9) and severe by <0.1% of patients (n=1). For the majority (n=16; 88.9%) of patients experiencing at least one IOI event, the event was reported as resolved; in two patients (11.1%) the event was considered recovering/resolving and one (5.6%) patient had at least one event not resolved/resolved by the end of the study.

By MedDRA preferred term, 0.5% of patients (n=7) experienced iritis, 0.3% (n=5) experienced iridocyclitis, 0.3% experienced uveitis and vitritis each (n=4 each), and <0.1% of patients (n=1) experienced post procedural inflammation in RHONE-X (Annex 7C.16). The per-1000 injection rate by preferred term in RHONE-X was 0.60 for iritis, 0.37 for both vitritis and iridocyclitis, 0.30 for uveitis, and 0.07 for post procedural inflammation and vitritis (Annex 7C.17).

In the pivotal Phase III faricimab safety population with BRVO (i.e., BALATON), there were no IOI events occurring in the study eye (1 patient in the faricimab arm had 1 event of vitreal cells [by MedDRA preferred term] reported but the verbatim term was “non-inflammatory vitreous cells”) (Table 27; Annex 7C.18). In the Phase III faricimab safety population with C/HRVO (i.e., COMINO), 2.2% of patients (n=8) experienced at least one event of IOI in the study eye (Table 27). Two patients (0.5%) experienced at least one serious event. By severity, a mild event was experienced by 1.6% (n=6) patients and moderate in 0.5% (n=2) of patients. Of the patients with IOI events, only one patient had at least one event recovering/resolving, while all seven other patients had at least one recovered/resolved event.

By MedDRA preferred term, 3 patients (0.8%) experienced vitritis, 2 patients (0.5%) experienced iritis, 2 patients (0.5%) experienced uveitis, and 1 patient (0.3%) experienced iridocyclitis in the Phase III C/HRVO population (Annex 7C.18). The per-1000 injection rate by preferred term was 0.81 for vitritis, 0.54 for both iritis and uveitis, and 0.27 for iridocyclitis (Annex 7C.19).

In the pivotal Phase III population pooled across all indications, the rate of IOI events per 1000 injections was 2.28 (Annex 7A.2).

In the pooled LTE (RHONE-X and AVONELLE-X) study population, the rate of IOI events per 1000 injections was 2.11 (Annex 7A.3).

Table 27 Important Identified Intraocular Inflammation Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI during Entire Study (Week 112 nAMD and Week 100 DME) and through Primary Endpoint Time (Week 24 RVO), in the Study Eye, Safety-Evaluable Population

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986
Clinical Cutoff Date: BALATON 06JUL2022, COMINO 09AUG2022_

	nAMD (N=1326)		DME (N=1887)	
	Faricimab (N=664)	Aflibercept (N=662)	Faricimab (N=1262)	Aflibercept (N=625)
Number (%) of patients with at least one AE	20 (3.0%)	15 (2.3%)	20 (1.6%)	7 (1.1%)
95% CI for % of patients with at least one AE	(1.96%, 4.61%)	(1.38%, 3.70%)	(1.03%, 2.44%)	(0.54%, 2.29%)
Difference in % of patients with at least one AE	0.7%		0.5%	
95% CI for difference	(-1.04%, 2.57%)		(-0.83%, 1.49%)	
Total number of AEs	26	16	26	10
Number (%) of patients with at least one AE by severity				
Mild	11 (1.7%)	8 (1.2%)	7 (0.6%)	5 (0.8%)
Moderate	6 (0.9%)	5 (0.8%)	9 (0.7%)	2 (0.3%)
Severe	3 (0.5%)	2 (0.3%)	4 (0.3%)	0
Number (%) of patients with at least one serious AE	5 (0.8%)	3 (0.5%)	4 (0.3%)	1 (0.2%)
Number (%) of patients with at least one AE by outcome				
Fatal	0	0	0	0
Not recovered/Resolved	2 (10.0%)	2 (13.3%)	1 (5.0%)	0
Recovering/Resolving	1 (5.0%)	0	6 (30.0%)	0
Recovered/Resolved	17 (85.0%)	13 (86.7%)	14 (70.0%)	7 (100%)
Resolved with sequelae	1 (5.0%)	0	2 (10.0%)	0
Unknown outcome	0	0	0	0

Table 27 Important Identified Intraocular Inflammation Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI during Entire Study (Week 112 nAMD and Week 100 DME) and through Primary Endpoint Time (Week 24 RVO), in the Study Eye, Safety-Evaluable Population (cont)

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986
Clinical Cutoff Date: BALATON 06JUL2022, COMINO 09AUG2022

	BRVO (N=550)		C/HRVO (N=726)	
	Faricimab (N=276)	Aflibercept (N=274)	Faricimab (N=365)	Aflibercept (N=361)
Number (%) of patients with at least one AE	1 (0.4%)	0	8 (2.2%)	4 (1.1%)
95% CI for % of patients with at least one AE	(0.06%, 2.02%)	(0.00%, 1.38%)	(1.11%, 4.26%)	(0.43%, 2.81%)
Difference in % of patients with at least one AE	0.4%		1.1%	
95% CI for difference	(-1.05%, 2.02%)		(-0.93%, 3.26%)	
Total number of AEs	1	0	8	4
Number (%) of patients with at least one AE by severity				
Mild	1 (0.4%)	0	6 (1.6%)	3 (0.8%)
Moderate	0	0	2 (0.5%)	1 (0.3%)
Severe	0	0	0	0
Number (%) of patients with at least one serious AE	0	0	2 (0.5%)	1 (0.3%)
Number (%) of patients with at least one AE by outcome				
Fatal	0	0	0	0
Not recovered/Resolved	0	0	0	0
Recovering/Resolving	0	0	1 (12.5%)	0
Recovered/Resolved	1 (100%)	0	7 (87.5%)	4 (100%)
Resolved with sequelae	0	0	0	0
Unknown outcome	0	0	0	0

Table 27 Important Identified Intraocular Inflammation Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI during Entire Study (Week 112 nAMD and Week 100 DME) and through Primary Endpoint Time (Week 24 RVO) in the Study Eye, Safety-Evaluable Population (cont)

Protocol: GR40349, GR40398, GR40306, GR40844, GR41984, GR41986
Clinical Cutoff Date: BALATON 06JUL2022, COMINO 09AUG2022

	Combined Indications (N=4489)	
	Faricimab (N=2567)	Aflibercept (N=1922)
Number (%) of patients with at least one AE	49 (1.9%)	26 (1.4%)
95% CI for % of patients with at least one AE	(1.45%, 2.51%)	(0.92%, 1.97%)
Difference in % of patients with at least one AE	0.6%	
95% CI for difference	(-0.22%, 1.30%)	
Total number of AEs	61	30
Number (%) of patients with at least one AE by severity		
Mild	25 (1.0%)	16 (0.8%)
Moderate	17 (0.7%)	8 (0.4%)
Severe	7 (0.3%)	2 (0.1%)
Number (%) of patients with at least one serious AE	11 (0.4%)	5 (0.3%)
Number (%) of patients with at least one AE by outcome		
Fatal	0	0
Not recovered/Resolved	3 (6.1%)	2 (7.7%)
Recovering/Resolving	8 (16.3%)	0
Recovered/Resolved	39 (79.6%)	24 (92.3%)
Resolved with sequelae	3 (6.1%)	0
Unknown outcome	0	0

Investigator text for AEs encoded using MedDRA version 24.1 for nAMD, MedDRA version 24.0 for DME and MedDRA version 25.0 for RVO (BRVO and C/HRVO).
Percentages for "Number of patients with at least one AE", "Number of patients with at least one serious AE", and "Number of patients with at least one AE by severity" are based on the N in the column headings. Percentages for "Number of patients with at least one AE by outcome" are based on the N in "Number of patients with at least one AE". Table summary includes adverse events that started or worsened (for existing condition) on or after the date of the first injection of active study drug. AE=adverse event; CI=Confidence Interval; 95% CI were computed using the Wilson method. Difference in frequency rates is relative to AFLIBERCEPT and 95% CI of the difference were computed using Newcombe Risk difference. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst severity.
Faricimab dosing is Faricimab 6MG intravitreal Q4W, Q8W and personalized treatment interval. Aflibercept dosing is Aflibercept 2 mg Q4W and Q8W.
Intraocular inflammation (IOI) terms = Anterior chamber cell, Anterior chamber flare, Anterior chamber inflammation, Chorioretinitis, Choroiditis, Cyclitis, Eye inflammation, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Noninfective chorioretinitis, Non-infectious Endophthalmitis, Ocular vasculitis, Post procedural inflammation, Retinal occlusive vasculitis, Retinal vasculitis, Haemorrhagic occlusive retinal vasculitis, Uveitis, Vitritis, and Vitreal cells.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; BRVO GR41984; C/HRVO GR41986; POOLED(nAMD, DME, BRVO, C/HRVO) pools all six studies.
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Table 28 Important Identified Intraocular Inflammation Risks: Risks Seriousness, Outcomes, Severity, Frequency with 95% CI for Safety-evaluable population through RHONE-X (Year 2-4 DME) and AVONELLE-X (Year 2-4 nAMD) , Safety-Evaluable Population

Protocol: GR41987, GR42691

	nAMD (N=1025)		DME (N=1464)		Combined (N=2489)
	Prior Faricimab (n=520)	Prior Aflibercept (n=505)	Prior Faricimab (n=991)	Prior Aflibercept (n=473)	
Number (%) of patients with at least one AE	10 (1.9%)	12 (2.4%)	13 (1.3%)	5 (1.1%)	40 (1.6%)
95% CI for % of patients with at least one AE	(1.05%, 3.50%)	(1.36%, 4.11%)	(0.77%, 2.23%)	(0.45%, 2.45%)	(1.18%, 2.18%)
Total number of AEs	12	12	14	8	46
Number (%) of patients with at least one AE by severity					
Mild	7 (1.3%)	5 (1.0%)	6 (0.6%)	2 (0.4%)	20 (0.8%)
Moderate	2 (0.4%)	7 (1.4%)	6 (0.6%)	3 (0.6%)	18 (0.7%)
Severe	1 (0.2%)	0	1 (0.1%)	0	2 (<0.1%)
Number (%) of patients with at least one serious AE	2 (0.4%)	3 (0.6%)	2 (0.2%)	1 (0.2%)	8 (0.3%)
Number (%) of patients with at least one AE by outcome					
Fatal	0	0	0	0	0
Not recovered/Resolved	2 (20.0%)	2 (16.7%)	1 (7.7%)	0	5 (12.5%)
Recovering/Resolving	0	0	1 (7.7%)	1 (20.0%)	2 (5.0%)
Recovered/Resolved	10 (100%)	10 (83.3%)	11 (84.6%)	5 (100%)	36 (90.0%)
Resolved with sequelae	0	0	0	0	0
Unknown outcome	0	0	0	0	0

Percentages for "Number of patients with at least one AE", "Number of patients with at least one serious AE", and "Number of patients with at least one AE by severity" are based on the N in the column headings.
Percentages for "Number of patients with at least one AE by outcome" are based on the N in "Number of patients with at least one AE".
Table summary includes adverse events that started or worsened (for existing condition) on or after the date of the first injection of active study drug.
AE=adverse event; CI=Confidence Interval; 95% CI were computed using the Wilson method. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst severity.
Intraocular Inflammation events include Anterior chamber cell, Anterior chamber flare, Anterior chamber inflammation, Chorioretinitis, Choroiditis, Cyclitis, Eye inflammation, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Noninfective chorioretinitis, Non-infectious Endophthalmitis, Ocular vasculitis, Post procedural inflammation, Retinal occlusive vasculitis, Retinal vasculitis, Haemorrhagic occlusive retinal vasculitis, Uveitis, Vitritis, and Vitreal cells.

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Based on data available to date from the clinical development program, the risk of IOI has been sufficiently characterized and the frequency of occurrence is shown to be consistent with other approved intravitreal anti-VEGF monotherapies.

Post-Marketing Information:

Intraocular inflammation can occur in any part of the eye and is generally categorized per the predominant site of the inflammation using the Standard Uveitis Nomenclature criteria. In very rare cases, IOI presents with concurrent RV or can progress to include RV, which is an inflammation of the blood vessels in the retina involving a cascade of inflammatory processes.

In the clinical trials data described above, there were no observed AEs of RV or ROV. In the post-marketing setting, from the IBD through 29 August 2023, there were 26 spontaneously reported AEs of RV (17 cases) and ROV (9 cases). The majority (23/26) of cases were reported as serious. The impact on patient's vision was not reported in 7/26 cases. In the remaining 19 cases, the impact on vision varied from mild to severe. In 9/19 cases, reporting vision loss, 7 patients reported a vision loss of $\geq$30 letters; in one patient, the vision loss was $\geq$15 letters, and in one patient, visual acuity was not provided before the event but patient had light perception only.

By the end of August 2023, the cumulative post-marketing exposure of faricimab vials dosed was 1,513,099 vials, with an estimated cumulative patient exposure of 270,936 patients. Based on cumulative post-marketing exposure for faricimab and the number of post-marketing cases for RV or ROV (n=26) identified from the Company's safety database (data cutoff date: 29 August 2023), an estimated reporting rate for combined RV and ROV events is 0.01 per 100 patients and 0.017 per 1000 faricimab intravitreal injections. Separately, the estimated reporting rate for RV is 0.006 per 100 patients and 0.011 per 1000 faricimab intravitreal injections; for ROV is 0.003 per 100 patients and 0.006 per 1000 faricimab intravitreal injections (DSR 1126314).

Risk factors and risk groups:

Patients with ocular or periocular infections or patients with known hypersensitivity to faricimab or any of the excipients are at increased risk of IOI. IOI could develop because of a specific immunogenic response to the administered protein agent (positive ADA).

Preventability:

Proper aseptic injection techniques must always be used when administering faricimab. In the post-marketing setting, patients should be instructed to report any signs or symptoms of IOI such as pain, photophobia, or worsening redness, which might be a clinical sign attributable to hypersensitivity. These measures would permit early diagnosis and treatment, should an inflammation occur, limiting the possibility of long-term sequelae.

Impact on the benefit-risk balance of the product:

IOI can range from a mild inflammation of the eye to severe with sequelae leading to vision loss. Symptoms can consist of blurred vision, floaters, pain, and photophobia. Pain is significantly associated with severe vitreous or anterior chamber inflammation. IOI associated with intravitreal administration of VEGF inhibitors may resolve without vision loss. Treatment is typically non-invasive, consisting of observation alone or topical corticosteroids. This can be supplemented with topical antibiotics, cycloplegics, or systemic corticosteroids. More invasive interventions have also been employed, including in-office vitreous tap, intravitreal antibiotics, and PPV (Agrawal et al. 2013; Cox et al. 2021). Severe vision loss has been reported in some cases of posterior uveitis such as retinal vasculitis and/or retinal vascular occlusion, typically occurring in the presence of IOI (Novartis 2020; Whitkin et al. 2020).

Based on the data available to date from the faricimab clinical development program, the frequency of occurrence and the severity of these events is outweighed by the overall benefit of faricimab.

Public health impact:

IOI is expected to be common, with a frequency of ≥1/100 to < 1/10 events.

SVII.3.1.2 Information on Important Potential Risks

There are no important potential risks for faricimab.

SVII.3.2. Presentation of the Missing Information

Information on Missing Information

Use in Pregnancy

Evidence source:

Given that the prevalence and incidence of nAMD increases with age, and the disease is most prevalent in patients > 65 years of age (Li et al. 2020a), there is a low likelihood that female patients on treatment for nAMD will be of childbearing potential.

The data on the prevalence of pregnancy in the DME population are limited. Prevalence estimates for presence of DME at any time during pregnancy ranged from 5% to 27% in T1DM and 4% in T2DM (Morrison et al. 2016).

RVO is an extremely rare event in the young population and even rarer among pregnant women. The diagnosis is always associated with active systemic diseases in young adults and needs thrombophilia workup. Therefore, any suspected RVO event in the pregnancy population should raise suspicion for underlying diseases such as hypertension, diabetes, autoimmune diseases, migraine, pre-eclampsia syndrome, and thrombophilia (Bahar et al. 2022).

Although pregnancy in this patient population is possible, the likelihood is low, and there is low systemic exposure to faricimab after ocular administration; the rapid plasma clearance of faricimab resulted in systemic plasma exposure approximately 6000-fold lower than in the vitreous. In plasma, mean C_{max} of 0.2 μg/mL was reached after approximately 2 days post-dose. No apparent suppression of free VEGF-A and free Ang-2 was observed in plasma of patients receiving faricimab in the Phase III studies (TENAYA, LUCERNE, YOSEMITE, RHINE, BALATON, COMINO), consistent with the low faricimab plasma levels.

Furthermore, in pregnant cynomolgus monkeys, the faricimab serum exposure (C_{max} at the NOAEL dose of 3 mg/kg) was more than 500-times greater than the faricimab human steady-state systemic exposure estimates, and did not reveal any developmental toxicity, teratogenicity, or effect on weight or structure of the placenta (Report 1053361; Report 1057630; Report 1093222).

While pregnant women were not eligible for inclusion in the clinical development program of faricimab, a total of four pregnancies (YOSEMITE [n=1], RHINE [n=2] and RHONE-X [n=1]) have been reported during the conduct of the Phase III studies (all cases in DME studies, none in nAMD and RVO studies).

Of the patients enrolled in YOSEMITE and RHINE; one pregnancy occurred in the faricimab personalized treatment interval (PTI) arm and two in the aflibercept Q8W arm. The patient in the faricimab PTI arm received a total of 4 injections of study treatment prior to the confirmation of pregnancy and underwent permanent discontinuation of study treatment due to pregnancy. The patient delivered a baby at a gestation age of 36 weeks and 6 days; the Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score at 10 minutes was normal with a score of 8/9 (Clinical Study Report YOSEMITE narratives, Report 1102956, p. 1655).

Of the patients enrolled in RHONE-X; one pregnancy occurred in the faricimab PTI group. The patient received 6 doses of faricimab; the last dose being administered on Study Day 561. On Study Day 666 the patient was discontinued from the study due to her pregnancy. On Study Day 834, 32nd gestation week, she delivered a healthy infant (RHONE-X Final CSR narratives, Report 1129577, p. 1393).

Anticipated risk/consequence of the missing information:

Faricimab has an anti-angiogenic mechanism of action and is regarded as potentially teratogenic and embryo-/fetotoxic, and for this reason there is precautionary guidance in the SmPC to warn against the use of faricimab during pregnancy unless the potential benefit outweighs the potential risk to the fetus. In addition, pregnancy cases will be summarized in Periodic Safety Update Reports (PSURs)/ Periodic Benefit-Risk Evaluation Reports (PBRERs).

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 29 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Infectious endophthalmitis Intraocular inflammation
Important potential risks	None
Missing information	Use in pregnancy

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The following routine pharmacovigilance activities have been implemented beyond adverse reaction reporting and signal detection for faricimab:

Specific guided questionnaire for the following important identified risks:

- Infectious endophthalmitis
- Intraocular inflammation

The purpose of the guided questionnaire is to ensure the adequate follow-up of post-marketing case reports and the robust collection of all of the appropriate information deemed necessary to further characterize the important identified risks associated with faricimab. The guided questionnaire is provided in Annex 4 of the RMP.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

A secondary data use, retrospective observational study (CR45271) is being conducted to further characterize the incidence of RV and ROV (categorized under the important identified risk of IOI) with faricimab compared to other intravitreal therapies (Table 30).

Table 30 Study CR45271 (Real-World Data Study)

Study/activity short name and title: Study CR45271 (real-world data study): A secondary data use, retrospective observational study to evaluate the incidence of RV and ROV.
Rationale and Study Objectives: The primary objective of this study is to assess and compare the incidence of RV, RV with RO, and IOI (including RV) with RO events across eyes treated with different approved IVT anti-VEGF agents after diagnosis of nAMD or DME, as recorded in an EHR database.
Study design: This is a secondary data use, retrospective observational cohort study. The study will analyze anonymized EHR data from private retina specialists in the United States to assess the incidence of RV, RV with RO, and IOI (including RV) with RO among eyes with nAMD or DME. Incidence will be assessed among eyes treated with IVT anti-VEGF agents approved in nAMD or DME.
Study populations: Patient eyes with nAMD or DME seen at private retina specialist clinics in the routine clinical care setting in the United States.
Milestones: Last Data Extraction: 30 September 2026 Final Clinical Study Report planned: 30 September 2027

DME = diabetic macular edema; EHR = electronic health records; IOI = intraocular inflammation; IVT = intravitreal; nAMD = neovascular age-related macular degeneration; RO = retinal vascular occlusion; ROV = retinal occlusive vasculitis; RV = retinal vasculitis; VEGF = vascular endothelial growth factor.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

See Table 31.

Table 31 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 1—Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorization				
Not applicable				
Category 2—Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk minimization activities				
Study CR45271 (real-world data study): A secondary data use, retrospective observational study to evaluate the incidence of RV and ROV	The primary objective of this study is to assess and compare the incidence of RV, RV with RO, and IOI (including RV) with RO events across eyes treated with different approved IVT anti-VEGF agents after diagnosis of nAMD or DME, as recorded in an EHR database.	IOI	Last data extraction	Planned 30 September 2026
			Final Clinical Study Report	Planned 30 September 2027

CHMP = Committee for Medicinal Products for Human Use; DME = diabetic macular edema; EHR = electronic health records; IOI = intraocular inflammation; IVT = intravitreal; nAMD = neovascular age-related macular degeneration; NCA = National Competent Authority; PRAC = Pharmacovigilance Risk Assessment Committee; RO = retinal vascular occlusion; RV = retinal vasculitis; VEGF = vascular endothelial growth factor.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no agreed post-authorization efficacy studies with faricimab.

PART V: RISK-MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK-MINIMIZATION ACTIVITIES)

RISK-MINIMIZATION PLAN

V.1 Routine Risk-Minimization Measures

Table 32 Description of Routine Risk-Minimization Measures by Safety Concern

Safety Concern	Routine Risk-Minimization Activities
Infectious endophthalmitis	**Routine risk communication:** • SmPC Sections 4.2, 4.3, 4.4 and 4.8. • PIL Sections 2 and 4 **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • Recommendation that proper aseptic injection techniques always be used when administering Vabysmo. **Other risk minimization measures beyond the Product Information:** None **Medicine's Legal Status:** • Vabysmo is a prescription only medicine.
Intraocular inflammation	**Routine risk communication:** • SmPC Sections 4.3, 4.4 and 4.8 • PIL Sections 2 and 4 **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • Recommendation that proper aseptic injection techniques always be used when administering Vabysmo. **Other risk minimization measures beyond the Product Information:** None **Medicine's Legal Status:** Vabysmo is a prescription only medicine.
Use in pregnancy	**Routine risk minimization measures:** • SmPC Section 4.6 • PIL Section 2 **Other risk minimization measures beyond the Product Information:** None

PIL = Patient Information Leaflet; SmPC = Summary of Product Characteristics.

V.2. Additional Risk-Minimization Measures

Table 33 Additional Risk-Minimization Measures

Additional risk-minimization measure	Patient/Carer Guide
Objective(s)	Patient/carer guide will promote awareness of the information contained within the Vabysmo Package Leaflet. It aims to inform patients/carers adequately on the risks, the key signs and symptoms of those risks, and when to seek urgent attention from their physician with the objective to minimize the important identified risks of infectious endophthalmitis and intraocular inflammation; and to promote communication between the patient and their physician.
Rationale for the additional risk-minimization activity	To provide instructions to patients for early recognition of key signs and symptoms of potential adverse reactions, and timely reporting to their physicians, encouraging prompt intervention to reduce the risk of vision loss and to maximize recovery potential.
Target audience and planned distribution path	The guide is targeted to use in adult patients with nAMD, DME, and RVO it is provided to the physician for distribution to the patient after faricimab is prescribed to them, but prior to their first administration.
Plans for evaluating the effectiveness of the interventions and criteria for success	How effectiveness will be measured: • Distribution metrics of patient educational materials • Monitoring of reporting rate and severity of infectious endophthalmitis and intraocular inflammation, through routine pharmacovigilance (i.e., observed vs expected analysis) Milestones for reporting: • Periodically in PSURs/PBRERs

DME = diabetic macular edema; nAMD = neovascular age-related macular degeneration; PBRER = Periodic Benefit-Risk Evaluation Report; PSUR = Periodic Safety Update Report, RVO = retinal vein occlusion.

Removal of Additional Risk-Minimization Activities

Not applicable.

V.3 Summary of Risk Minimization Measures

Table 34 Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infectious endophthalmitis	**Routine risk minimization measures:** • SmPC Section 4.2 Posology and Method of Administration • SmPC Section 4.3 Contraindications • SmPC Section 4.4 Special Warnings and Precautions for Use • SmPC Section 4.8 Undesirable Effects • PIL Section 2 What you need to know before you use Vabysmo • PIL Section 4 Possible side effects Recommendation that proper aseptic injection techniques always be used when administering Vabysmo. Vabysmo is a prescription only medicine. **Additional risk minimization measures:** Patient/carer guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire Assess as part of routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** None
Intraocular inflammation	**Routine risk minimization measures:** • SmPC Section 4.3 Contraindications • SmPC Section 4.4 Special Warnings and Precautions for Use • SmPC Section 4.8 Undesirable effects • PIL Section 2 What you need to know before you use Vabysmo • PIL Section 4 Possible side effects • Recommendation that proper aseptic injection techniques always be used when administering Vabysmo Vabysmo is a prescription only medicine. **Additional risk minimization measures:** Patient/carer guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire Assess as part of routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** Study CR45271 **Final Study Report Due Dates:** Study CR45271: 30 September 2027

Use in pregnancy	**Routine risk minimization measures:** • SmPC Section 4.6 Fertility, pregnancy and lactation • PIL Section 2 What you need to know before you use Vabysmo **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Assess as part of routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** None

PBRER = Periodic Benefit-Risk Evaluation Report; PIL = Patient Information Leaflet; PSUR = Periodic Safety Update Report; SmPC = Summary of Product Characteristics.

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Final CSR Study GR41987 (RHONE-X): A Phase III, Multicenter, Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of Faricimab in Patients with Diabetic Macular Edema. Report No. 1129577. September 2024.

Final CSR Study GR42691 (AVONELLE-X): A Phase III, multicenter, open-label extension study to evaluate the long-term safety and tolerability of faricimab in patients with neovascular age-related macular degeneration. Report No. 1136215. May 2025.

Periodic Benefit-Risk Evaluation Report. Roche report No. 1136491.

Roche Report 1057630. 26-Week partial ascending dose toxicity and toxicokinetic study following once monthly intravitreous injections in cynomolgus monkeys with a 13-week recovery. July 2015.

Roche Report 1093222. RO6867461 Intravenous administration embryofetal development study in the cynomolgus monkey. December 2020.

Roche Report 1055832. A tissue cross-reactivity study of RO6867461 in a limited panel of normal human tissues. July 2013.

Roche Report 1056445. A tissue cross-reactivity study of RO6867461 in normal human tissues. July 2013.

Roche Report 1055400. Evaluation of RO6867461 for the risk of cytokine release and immune cell depletion in an in vitro 24h-format human whole blood cell assay. March 2013 (amended November 2013).

Roche Report 1059118. In vitro evaluation of RO6867461 in a Human Complement Activation Assay for the pre-clinical Risk Assessment of Anaphylatoxins and Complement split fragment generation. April 2014.

PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR VABYSMO™ (FARICIMAB)

This is a summary of the risk-management plan (RMP) for Vabysmo. The RMP details important risks of Vabysmo, how these risks can be minimized, and how more information will be obtained about Vabysmo's risks and uncertainties (missing information).

Vabysmo's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Vabysmo should be used.

This summary of the RMP for Vabysmo should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Vabysmo's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Vabysmo is indicated for the treatment of adult patients with neovascular (wet) age-related macular degeneration (nAMD), visual impairment due to diabetic macular oedema (DME), and visual impairment due to macular edema secondary to retinal vein occlusion (RVO; branch RVO or central RVO) (see SmPC for the full indication). It contains faricimab as the active substance, and it is given by intravitreal injection.

Further information about the evaluation of Vabysmo's benefits can be found in Vabysmo's EPAR, including in its plain-language summary, available on the EMA Web site, under the medicine's Web page:
https://www.ema.europa.eu/en/medicines/human/EPAR/vabysmo

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Vabysmo, together with measures to minimize such risks and the proposed studies for learning more about Vabysmo's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging

– The authorized pack size—The amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly.
– The medicine's legal status—The way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Vabysmo, these measures are supplemented with *additional risk-minimization* measures mentioned under relevant risks below:

- Patient/Carer Guide

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. Also, a guided questionnaire has been designed to ensure the adequate follow-up of adverse events and the robust collection of all of the appropriate information deemed necessary to further characterize the important identified risks associated with Vabysmo. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Vabysmo is not yet available, it is listed under "missing Information" below.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Vabysmo are risks that need special risk-management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Vabysmo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information about the safety of the medicinal product that is currently missing and needs to be collected (e.g., use of the medicine in pregnant patients).

List of Important Risks and Missing Information	
Important identified risks	Infectious endophthalmitis Intraocular inflammation
Important potential risks	None
Missing information	Use in pregnancy

II.B SUMMARY OF IMPORTANT RISKS

Important Identified Risk: Infectious Endophthalmitis	
Evidence for linking the risk to the medicine	This important identified risk is based on data from the faricimab safety population in the pivotal Phase III studies (GR40306 TENAYA, GR40844 LUCERNE, GR40349 YOSEMITE, GR40398 RHINE, GR41984 BALATON, and GR41986 COMINO) and the Phase III LTE studies(GR41987 RHONE-X and GR42691 AVONELLE-X).
Risk factors and risk groups	Patients with ocular or periocular infections or patients with active intraocular inflammation are at increased risk of endophthalmitis. There is an increased risk of endophthalmitis if the intravitreal injection procedure is not performed under aseptic conditions.
Risk-minimization measures	**Routine risk minimization measures:** Routine risk communication is described in: • SmPC Section 4.2 Posology and Method of Administration • SmPC Section 4.3 Contraindications • SmPC Section 4.4 Special Warnings and Precautions for Use • SmPC Section 4.8 Undesirable Effects • PIL Section 2 What you need to know before you use Vabysmo • PIL Section 4: Possible side effects • **Routine risk-minimization activities recommending specific clinical measures to address the risk:** Recommendation that proper aseptic injection techniques always be used when administering Vabysmo. **Medicine's Legal Status** Vabysmo is a prescription only medicine. **Additional risk minimization measures:** Patient/carer guide
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire Assess as part of routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** None

PBRER = Periodic Benefit-Risk Evaluation Report; PIL = Patient Information Leaflet; PSUR = Periodic Safety Update Report; SmPC = Summary of Product Characteristics.

Important Identified Risk: Intraocular Inflammation	
Evidence for linking the risk to the medicine	This important identified risk is based on data from the faricimab safety population from the pivotal Phase III studies (GR40306 TENAYA, GR40844 LUCERNE, GR40349 YOSEMITE, GR40398 RHINE, GR41984 BALATON, and GR41986 COMINO) and the Phase III LTE studies (GR41987 RHONE-X and GR42691 AVONELLE-X).
Risk factors and risk groups	Patients with ocular or periocular infections or patients with known hypersensitivity to faricimab or any of the excipients are at increased risk of intraocular inflammation. Intraocular inflammation could develop because of a specific immunogenic response to the administered protein agent (positive anti-drug antibodies).
Risk-minimization measures	**Routine risk minimization measures:** Routine risk communication is described in: • SmPC Section 4.3 Contraindications • SmPC Section 4.4 Special Warnings and Precautions for Use • SmPC Section 4.8 Undesirable effects • PIL Section 2 What you need to know before you use Vabysmo • PIL Section 4 Possible side effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** Recommendation that proper aseptic injection techniques always be used when administering Vabysmo. **Medicine's Legal Status** Vabysmo is a prescription only medicine. **Additional risk minimization measures:** Patient/carer guide
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire Assess as part of routine PSUR/PBRER reporting. **Additional pharmacovigilance activities:** Study CR45271

PBRER = Periodic Benefit-Risk Evaluation Report; PIL = Patient Information Leaflet; PSUR = Periodic Safety Update Report; SmPC = Summary of Product Characteristics.

Missing Information: Use in Pregnancy	
Risk-minimization measures	**Routine risk minimization measures:** Routine risk communication is described in: • SmPC Section 4.6 Fertility, pregnancy and lactation • PIL Section 2 What you need to know before you use Vabysmo **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Assess as part of routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** None

PBRER = Periodic Benefit-Risk Evaluation Report; PIL = Patient Information Leaflet; PSUR = Periodic Safety Update Report; SmPC = Summary of Product Characteristics.

II.C POST-AUTHORIZATION DEVELOPMENT PLAN

II.C.1 Studies That Are Conditions of the Marketing Authorization

There are no studies that are conditions of the marketing authorization or specific obligation of Vabysmo.

II.C.2 Other Studies in Post-Authorization Development Plan

There is one study in the post-authorization development plan for Vabysmo:

1. Study short name: Study CR45271

   Purpose of the study: To assess and compare the incidence of retinal vasculitis (RV), RV with retinal vascular occlusion (RO), and intraocular inflammation (IOI; including RV) with RO events across eyes treated with different approved intravitreal (IVT) anti-vascular endothelial growth factor (VEGF) agents after diagnosis of nAMD or DME, as recorded in an electronic health records (EHR) database.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Specific Adverse Reactions Follow-Up Forms/Questionnaires

There is a specific guided questionnaire for faricimab for the following important identified risks:

- Infectious endophthalmitis
- Intraocular inflammation

Guided Questionnaire

AER:	
Local Case ID:	

Patient ID/Initials:	
Patient Sex:	❑ M ❑ F ❑ Unknown ❑ Undifferentiated

You have received this questionnaire because you have reported Intraocular inflammation and/or endophthalmitis with Vabysmo Please provide additional information below, if available to you. By providing this information, you are actively participating in safety monitoring of Vabysmo use.

Your responses are confidential and used for pharmacovigilance purposes only. Personal identifiers will not be disclosed beyond regulatory requirements.

Drug therapy details – Vabysmo	Unilateral Vabysmo treatment	**Bilateral Vabysmo Treatment (if applicable)**
Product:	☐ Vial ☐ PFS	☐ Vial ☐ PFS
If PFS selected, date of transition from vial (dd-MMM-yyyy) (Enter "N/A" if PFS was used from the start without prior vial use)		
Indication:		
In which eye was treatment administered?	☐ Right eye ☐ Left eye	N/A
Date of last dose before AE onset		
Number of Vabysmo injections prior to event		
Treatment regimen/frequency:		
Batch/Lot No. of last dose before AE onset		
AE suspected to be caused by treatment	☐ Yes ☐ No ☐ N/A	
Type of injection needle used (PFS only)	☐ Copacked needle ☐ Other (specify): _____	☐ Copacked needle ☐ Other (specify): _____

List any prior IVT and/or Co-suspect drug associated with AE							
Drug	**Indication**	**Date(s) started (dd-MMM-yyyy)**	**Date(s) stopped/ ongoing (dd-MMM-yyyy):**	**Route of administration e.g. IVT, Topical, PO**	**If Ocular, specify which eye**	**Dose/regimen**	**Indicate whether this is the suspect drug associated with AE and/or Prior IVT therapy**
					☐ Right ☐ Left		Prior IVT ☐ Co-suspect Associated with AE ☐
					☐ Right ☐ Left		Prior IVT ☐ Co-suspect Associated with AE ☐
					☐ Right ☐ Left		Prior IVT ☐ Co-suspect Associated with AE ☐

Medical History

Relevant medical history/concurrent conditions:

☐ Cardiovascular (if selected, please specify)_____

☐ Endocrine (if selected, please specify)_____

☐ Autoimmune disease (if selected, please specify)_____

☐ Renal (if selected, please specify)_____

☐ Infections (if selected, please specify)_____

Other relevant medical history (e.g. HLAB27 or other known genetic predisposition)_____

_____

_____

Please indicate any actions taken with the suspected medication: (Check all that apply)		
☐ Drug continued	☐ Drug discontinued	☐ Drug interruption
☐ Drug treatment of event	☐ Non-drug treatment of event	☐ Other (please explain):
Did the adverse event abate after stopping the suspect drug? ☐ Yes ☐ No ☐ Unknown ☐ N/A	Did the adverse event recur after re-administration of the suspect drug? ☐ Yes ☐ No ☐ Unknown ☐ N/A	

Assessments, clinical examinations:

Please indicate if any of the following tests have been performed, and the result:

Test		**Date** (dd-MMM-yyyy)	**Result**	Not Done
Visual Acuity	Before event onset			☐
	After event			
	At last follow up			
Ophthalmic examination: Slit lamp ☐ Indirect ophthalmoscope ☐ Other ☐ : _____			AC cells ☐ Grade _____ Vitreous cells ☐ Grade _____ Hypopyon ☐ Stellate Keratic Precipitates ☐ Mutton-fat keratic precipitates ☐ Other:	☐
Intraocular pressure (IOP)	Before event onset			☐
	After event			
	At last follow up			
Optical Coherence Tomography (OCT)				☐
Fundus photos **Please provide images if available.**				☐
Fluorescein angiography (Describe features:) **Please provide images if available.**				☐
Specimen taken and results of culture and sensitivity (Specify type of sample and if it was taken prior to IVT administration or later)				☐

Other relevant findings and assessments: (Yes indicated test was performed, If yes please provide result)	PCR test: Yes ☐ No ☐ Result _____ Syphilis test: Yes ☐ No ☐ Result _____ HLA-B27: Yes ☐ No ☐ Results_____ CT findings: Yes ☐ No ☐ Results_____ X-ray: Yes ☐ No ☐ Results_____ Other, please specify: Yes ☐ No ☐ Results_____

Treatment for AE			
Treatment	**Select (if Given)**	**Route (tick all that apply)**	**Drug name** (specify route if multiple drugs of the same treatment were used)
Steroid	☐	☐ Topical ☐ Sub-conjunctival ☐ IVT ☐ Oral ☐ IV ☐ Other	
Antibiotic	☐	☐ IVT, ☐ Topical, ☐ Oral ☐ Other	
Other therapy	☐	☐ IVT, ☐ Topical, ☐ Oral ☐ Other	
Surgical vitrectomy	☐		

Please complete the relevant sections as applicable. PART A Endophthalmitis and/or PART B IOI

PART A: Endophthalmitis Event occurred in: ☐ Right eye ☐ Left eye ☐ Both eyes

Description of event:

Onset date of event (dd/MMM/yyyy): ____/_____/_____

Date of Recovery (dd/MMM/yyyy): ____/_____/_____ (If final outcome has resolved)

Was aseptic technique used when injection was administered? ☐ Yes ☐ No ☐ Unknown
(e.g. use of sterile gloves, drape, eye speculum, broad-spectrum microbicide)

Other relevant information: _____

Did the patient receive prophylactic topical antibiotics prior to injection? ☐ Yes (If yes, for how many days?)___ ☐ No ☐ Unknown

Other relevant information: _____

Did the patient receive topical antibiotics post injection? ☐ Yes (If yes, for how many days?) ____ ☐ No ☐ Unknown

Other relevant information: _____

Prior eye surgery or trauma to eye? ☐ Yes (If yes, when and what surgery/trauma?) ☐ No ☐ Unknown

_____

Is the patient immunocompromised? ☐ Yes (If yes, please describe.) ☐ No ☐ Unknown

_____

Symptoms:

Eye pain? ☐ Yes ☐ No ☐ Unknown Red eye? ☐ Yes ☐ No ☐ Unknown

Floaters? ☐ Yes ☐ No ☐ Unknown Photophobia? ☐ Yes ☐ No ☐ Unknown

Worsening of vision? ☐ Yes ☐ No ☐ Unknown

Other relevant information: e.g. other findings, management and interventions..

_____

_____

_____

Final outcome:
☐ Complete recovery ☐ Recovered with sequelae ☐ Condition improving ☐ Condition unchanged
☐ Condition deteriorating ☐ Outcome unknown

If **bilateral**, please provide further details here.

_____
_____

PART B Intraocular inflammation (IOI) Event occurred in: ☐ Right eye ☐ Left eye ☐ Both eyes

Description of event:
Onset date of event (dd/MMM/yyyy): ____/_____/_____
Date of Recovery (dd/MMM/yyyy): ____/_____/_____ (If, final outcome resolved)

Was aseptic technique used when injection was administered? ☐ Yes ☐ No ☐ Unknown
(e.g. use of sterile gloves, drape, eye speculum, broad-spectrum microbicide)
Other relevant information: _____

Description of inflammation/associated diagnosis: (tick all that apply)

	Iritis ☐	Iridocyclitis ☐	Anterior uveitis ☐	Intermediate Uveitis ☐	Vitritis ☐	Retinitis ☐
	Chorioretinitis ☐	Posterior Uveitis ☐	Panuveitis ☐	Retinal vasculitis ☐	Retinal occlusive vasculitis ☐	

If none of above, please provide description of inflammation/associated diagnosis:_____

Prior intraocular inflammation? ☐ Yes ☐ No ☐ Unknown (if yes, Event occurred in: ☐ Right eye ☐ Left eye ☐ Both eyes)
(If yes, please describe inflammation, when it occurred and treatment given)

_____

Symptoms:

Eye pain? ☐ Yes ☐ No ☐ Unknown Red eye? ☐ Yes ☐ No ☐ Unknown

Floaters? ☐ Yes ☐ No ☐ Unknown Photophobia? ☐ Yes ☐ No ☐ Unknown

Worsening of vision? ☐ Yes ☐ No ☐ Unknown

Other relevant information: e.g. other findings, management and interventions..

_____
_____

Final outcome:

☐ Complete recovery ☐ Recovered with sequelae ☐ Condition improving ☐ Condition unchanged
☐ Condition deteriorating ☐ Outcome unknown

If **bilateral**, please provide further details here.

_____
_____

Completed by:			
Name:		Position:	
Signature:		Date:	
E-mail:			

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES

Prior to the launch of Vabysmo® in each Member State, the Marketing Authorization Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at adequately informing patients/carers on the risks of Vabysmo, the key signs and symptoms of those risks, and when to seek urgent attention from their physician with the objective to minimize the risks, and any resultant complications by encouraging prompt intervention.

The MAH shall ensure that in each Member State where Vabysmo is marketed, all patients/carers who are expected to use Vabysmo have access to both written and audio versions of the educational material (i.e., the patient/carer guide).

TABLE OF CONTENTS

1. HEALTHCARE PROFESSIONALS

Not applicable.

2. PATIENTS/CARERS

The patient information pack consists of the patient information leaflet and a patient/carer guide.

2.1 PATIENT ALERT CARD

Not applicable.

2.2 PATIENT/CARER GUIDE

The key elements of the patient/carer guide provide:

- A description of neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and branch/central retinal vein occlusion (B/CRVO)
- A description of Vabysmo, how it works, and what to expect from Vabysmo treatment
- A description of the key signs and symptoms of the key risks associated with Vabysmo, i.e., infectious endophthalmitis and intraocular inflammation
- A description of when to seek urgent attention from the health care provider should signs and symptoms of these risks present themselves
- Recommendations for adequate care after the injection

2.3 PATIENT DIARY

Not applicable.

2.4 PREGNANCY PREVENTION PROGRAMS

Not applicable.

Signature Page for RIM-PVG-205229 v1.0

Approval Task	[redacted] Company Signatory 27-Apr-2026 11:05:39 GMT+0000

Approval Task	[redacted] Deputy EU QPPV 27-Apr-2026 11:30:00 GMT+0000

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