EU RISK MANAGEMENT PLAN FOR VABYSMO®/FARICIMAB

RMP Version number: 1.3

Data lock point for this RMP: 31 October 2021

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Rationale for Submitting an Updated Risk Management Plan (RMP)

Not applicable

Summary of Significant Changes in this RMP

Not applicable

Other RMP Versions under Evaluation

RMP Version Number: Not applicable

Submitted on: Not applicable

Procedure Number: Not applicable

Details of Currently Approved RMP

RMP Version Number: 1.3

Approved with Procedure Number: EMEA/H/C/005642

Date of approval (opinion date): 21 July 2022

See page 1 for signature and date

Dr. Birgitt Gellert (Qualified Person responsible for Pharmacovigilance [QPPV])[1]	Date

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application

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
	Proposed: Not applicable

Dosage in the EEA	Current: The medicinal product must be administered by a qualified physician experienced in intravitreal injections. Each vial should only be used for the treatment of a single eye. **<u>nAMD</u>** The recommended dose is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks (monthly) for the first 4 doses. Thereafter, an assessment of disease activity based on anatomic and/or visual outcomes is recommended 20 and/or 24 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. 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. **<u>DME</u>** The recommended dose is 6 mg (0.05 mL solution) administered by intravitreal injection every 4 weeks (monthly) for the first 4 doses. Thereafter, treatment is individualised using a treat-and-extend approach. Based on the physician's judgement of the individual patient's anatomic and/or visual outcomes, the dosing interval may be extended up to every 16 weeks (4 months), 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 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. 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; DNA=deoxyribonucleic acid; EEA=European Economic Area; GmbH=Gesellschaft mit beschränkter Haftung; IgG1=immunoglobulin G1 nAMD=neovascular (wet) age-related macular degeneration; INN=International non-proprietary name; RMP=Risk Management Plan; 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	angiopoietin
APTC	Anti-Platelet Trialists' Collaboration
ATE	arterial thromboembolic events
CEC	Clinical Events Committee
CHMP	Committee for Medicinal Products for Human Use
CSME	clinically significant macular edema
Cmax	maximum serum concentration
CNS	central nervous system
Ctrough	mean trough concentration
CV	cardiovascular
DME	diabetic macular edema
DR	diabetic retinopathy
EC	endothelial cells
EMA	European Medicines Agency
EPAR	European Public Assessment Report
HbA1c	hemoglobin A1c
IHC	immunohistochemistry
IOI	intraocular inflammation
IOP	intraocular pressure
logMAR	logarithm of the Minimum Angle of Resolution
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MESA	Multi-Ethnic Study of Atherosclerosis
NOAEL	no observed adverse effect level
nAMD	neovascular age-related macular degeneration
PBRER	Periodic Benefit-Risk Evaluation Report
PED	pigment epithelial detachment
PopPK	population pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report

Abbreviation	Definition
PTI	personalized treatment interval
PV	Pharmacovigilance
PY	person-years
Q4W	every 4 weeks
Q8W	every 8 weeks
RMP	Risk Management Plan
RPE	retinal pigment epithelial
SmPC	Summary of Product Characteristics
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
US	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 (US), 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 US, 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 (denominator)	No. of Cases (numerator)	Baseline Mean Age ± SD or Age 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
US 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; SD=standard deviation.

- **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 US 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 US 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 US (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) US: 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
UK 2002–2006	Cross-sectional study	NR	≥65	1.8	Wilde et al. 2017
UK 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
US 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

CI=confidence interval; 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 UK, and Taiwan (Owen et al. 2012; Keel et al. 2017; Hu et al. 2017). A pooled analysis from three countries (US, 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 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 US 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 US, 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). 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®), 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. 2012; 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 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 to 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
CFH (chromosome [chr] 1) (Cheung et al. 2017; Matuskova 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; Matuskova 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.

Table 4 Risk Factors for nAMD (cont.)

Risk factor	Association	Additional comments
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; chr=chromosome; CF1= complement factor 1; CFB=complement factor B; CFH=complement factor H; CI=confidence interval; HR=hazard ratio; HTRA1=HtrA serine peptidase 1; OR=odds ratio; PUFA=polyunsaturated fatty acids; nAMD=neovascular age-related macular degeneration.

- **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 4,362 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; Lee et al. 2017; Hu 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 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; Romero-Aroca et al. 2017; Jones et al. 2012). 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 US 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 (~29%) will develop DME and 88,000 to 221,000 (~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
US 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
US 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; US=United States.

[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 US, 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 US 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 US 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
UK 2007–2010	48,450	not stated	—	13.9 Centre-involving: 7.4	Keenan et al. 2013
UK 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
US NHANES 2005–2008	1038	≥40	3.8 (2.7−4.9) Black: 8.4 White: 2.6 Hispanic: 5.1	—	Varma et al. 2014
US NHANES 2005–2008	798	≥40 y, mean age not stated	6.01 (4.6-8.0)	—	Bressler et al. 2014
US 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; SD=standard deviation; T1DM=type 1 diabetes mellitus; UK=United Kingdom; US=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 US 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 US 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 US 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®), aflibercept (Eylea®), and brolucizumab (Beovu®). All three therapies are approved for patients with visual impairment due to DME in the EU, while ranibizumab (Lucentis®) and aflibercept (Eylea®) are both approved for the treatment of patients with DME in the US. 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 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 ≥160mm Hg, total cholesterol ≥5mmol/L, low-density lipoprotein cholesterol ≥3mmol/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 US on 447,407 patients with diabetes reported that African-Americans and Latinos had an increased hazard of developing DME compared to 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 post-partum 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.

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

Key safety findings from nonclinical studies and relevance to human usage:

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 (IgG1) 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 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. Incidence of ADA induction/boosting across all Phase II studies was approximately 10%, consistent with Phase II studies, incidence of ADA induction/boosting across all Phase III studies was also approximately 10% (nAMD: 10.4% and DME: 9.6%) (Annex 7C.1, Annex 7C.2). Overall, the incidence rate of IOI was low and not more than 2% in nAMD and DME Phase III studies (Annex 7C.15 and Annex 7C.17, respectively). Based on all available data to date, no meaningful impact of ADA was observed on efficacy, pharmacodynamics, and on overall safety. Although a higher incidence of IOI was observed in ADA-positive patients (nAMD: 5/75 [6.7%], Annex 7C.3 and Annex 7C.4; DME: 15/128 [11.7%], Annex 7C.5 and Annex 7C.6) compared with ADA-negative patients (nAMD: 7/582 [1.2%], Annex 7C.7 and Annex 7C.8; DME: 5/1124 [0.4%], Annex 7C.9 and Annex 7C.10), 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.

Reproductive/developmental toxicity:

The 2- and 6-month studies in cynomolgus monkeys did not reveal any effects of faricimab on fertility, reproductive organs, or the course and outcome of pregnancy or fetal viability (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 and DME patients, respectively. 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 more than 500-fold greater than faricimab human steady-state systemic exposure estimates in nAMD and DME 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 E.U. SmPC; Avastin E.U. SmPC).

Angiopoietin (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 biotherapeutics inhibiting 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 Phase III studies (Population PK Report, Report 1105763).

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 (ICH) 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 and DME 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 RMP are derived from seven studies (Table 9).

Safety data pooling of Phase II studies (i.e., nAMD AVENUE + nAMD STAIRWAY + DME/DR BOULEVARD) and with Phase III studies (i.e., nAMD TENAYA/LUCERNE + DME/DR YOSEMITE/RHINE studies) is not appropriate because of notable differences in study design and treatment duration. Examples of notable study design differences between the Phase II and Phase III include study duration, treatment dosage, choice of active comparator and treatment frequency.

Exposure data is provided from the Phase III pivotal studies up to Week 48 for nAMD studies (i.e., the time point for primary analysis) and during the entire study (through Week 100) for DME studies. Exposure from the Phase II supportive studies is provided separately.

Table 9 Overview of Studies Contributing to the Safety Population

Protocol Name/No.	Countries	Study Design	Patient Population	Objectives	Dose, Duration	No. of Patients	Study Status
Pivotal Studies							
TENAYA (GR40306) **LUCERNE** (GR40844)	Global	Phase III, Multicenter, Randomized, Double–Masked, Active Comparator-Controlled, 112-week Study	Treatment naive patients with nAMD	Efficacy, Safety, PK and PD	• Faricimab up to Q16W: 6 mg faricimab intravitreal injections Q4W up to Week 12 followed by Q16W, Q12W or Q8W (based on disease activity assessed at Week 20 and Week 24) up to Week 60, followed by PTI to Week 108 • Aflibercept Q8W: 2 mg aflibercept intravitreal injections Q4W up to Week 8, followed by Q8W to 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	Ongoing Primary analysis at Week 40/44/48 [a] CCOD: TENAYA: 26 Oct 2020 LUCERNE: 5 Oct 2020
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 1482– treatment naive 409 – previously treated with anti-VEGF **Safety-Evaluable** YOSEMITE = 937 RHINE = 950 **Pooled** Safety-Evaluable = 1887 All faricimab: 1262/1887 Aflibercept.: 625/1887	YOSEMITE: Complete (LPLV: 3 Sep 2021) RHINE: Ongoing[c] (CCOD: 27 Aug 2021) Year 2 efficacy analysis at Week 92/96/100[e]Year 2 safety analysis at Week 100

Table 9 Overview of Studies Contributing to the Safety Population (cont.)

Protocol Name/No.	Countries	Study Design	Patient Population	Objectives	Dose, Duration	No. of Patients	Study Status
Supportive Studies							
STAIRWAY (CR39521)	US	Phase II, Multiple Regimen, Randomized, Active Comparator-Controlled, Subject and Assessor Masked, Three Parallel Groups, 52–week Study	Treatment naive patients with nAMD	Efficacy, Safety, PK	• Faricimab Q12W: 6 mg faricimab intravitreal injections Q4W up to Week 12, followed by Q12W up to Week 48 • Faricimab Q16W: 6 mg faricimab intravitreal injections Q4W up to Week 12, followed by Q16W up to Week 48. Patients assessed with active disease at Week 24 were switched to a Q12W regimen for the remainder of the study. • Ranibizumab Q4W: 0.5 mg ranibizumab intravitreal injections Q4W for 48 weeks	**Total** Randomized = 76 (treatment-naive) Safety-Evaluable = 71	Completed
AVENUE (BP29647)	US	Phase II, Multiple Center, Multiple Dose and Regimen, Randomized, Active Comparator-Controlled, Double-Masked, Five Parallel Groups, 36-week study	Treatment naive patients with nAMD	Safety, Tolerability, PK, Efficacy	• 1.5 mg Faricimab Q4W: 1.5 mg faricimab intravitreal injections Q4W for 32 weeks • 6 mg Faricimab Q4W: 6 mg faricimab intravitreal injections Q4W for 32 weeks • 6 mg Faricimab Q8W: 6 mg faricimab intravitreal injections Q4W up to Week 12, followed by Q8W (i.e., on Weeks 20 and 28) • 0.5 mg Ranibizumab Q4W: 0.5 mg ranibizumab intravitreal injections Q4W for 32 weeks • 0.5 mg Ranibizumab Q4W + 6 mg Faricimab Q4W: 0.5 mg ranibizumab intravitreal injections Q4W up to Week 8, followed by 6 mg faricimab intravitreal injections Q4W to Week 32	**Total** Randomized = 273 (treatment-naive) Safety-Evaluable = 262	Completed

Table 9 Overview of Studies Contributing to the Safety Population (cont.)

Protocol Name/No.	Countries	Study Design	Patient Population	Objectives	Dose, Duration	No. of Patients	Study Status
Supportive Studies							
BOULEVARD (BP30099)	US	Phase II, Multiple Center, Multiple Dose, Randomized, Active Comparator-Controlled, Double–Masked, Three Parallel Groups, 36–week Study	Patients with DME	Safety, Tolerability, PK, Efficacy	• 1.5 mg Faricimab Q4W: 1.5 mg faricimab intravitreal injections Q4W for 20 weeks • 6 mg Faricimab Q4W: 6 mg faricimab intravitreal injections Q4W for 20 weeks • 0.3 mg Ranibizumab Q4W: 0.3 mg ranibizumab intravitreal injections Q4W for 20 weeks Followed by an observational period (up to 16 weeks); if eligible, patients received one injection of 0.3 mg ranibizumab then exited the study	**Total** Randomized = 229[d] 168– treatment naive 61 – previously treated with anti-VEGF Safety-Evaluable = 224	Completed

BCVA=best corrected visual acuity; CCOD=clinical cutoff date; CST=central subfield thickness; DME=diabetic macular edema; 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; US=United States; VEGF=vascular endothelial growth factor.

[a] The primary endpoint, change from baseline in BCVA, was averaged over Weeks 40, 44, and 48 (represented by "Week 40/44/48").

[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 global enrollment phase of the study has completed; a China extension is currently ongoing.

[d] Two enrolled patients were excluded from analysis due to Good Clinical Practice non-compliance.

[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').

Duration of Exposure

The faricimab safety population provides data from 1926 patients with 2740 years person-time of exposure in the Phase III program. This population consists of 664 patients with nAMD (588 years person-time exposure) and 1262 patients with DME (2152 years person-time exposure). The majority (92.8%) of nAMD patients received treatment for 9 to 12 months consistent with the primary analysis endpoint time. The majority (87.9%) of DME patients received treatment for >1.5 years, consistent with the Week 100 time-point (Table 10).

The Phase II program provides an additional 384 patients exposed to faricimab with 194 years person-time (Annex 7A.1). All Phase II patients had a duration of exposure less than 1 year (100.0% across both indications).

Number of Study Drug Administrations in the Study Eye

Overall, in the nAMD Phase III safety population (n=664) through Week 48, the median duration of exposure was 48.1 weeks with an average of 6.4 study drug administrations (Annex 7A.2). The maximum number of study drug administrations up to study Week 48 in the nAMD faricimab Phase III safety population was eight, consistent with primary analysis endpoint time. Of the total 664 nAMD faricimab patients, 112 patients (16.9%) received the maximum eight administrations (Table 11). Most patients (89.3%, n=593) received six injections.

Overall, in the DME Phase III safety population (n=1262) during the entire study, the median duration of exposure was 96.1 weeks with an average of 12.7 study drug administrations (Annex 7A.3). Of the total 1262 DME faricimab patients, 40.2% (n=507) received 15 or more study drug administrations, with <5% receiving 18 or more injections. Twelve patients (1.0%) received the maximum 25 administrations (Table 11).

The total number of faricimab injections was 20,229 across the Phase III program: 4,239 injections in nAMD patients and 15,990 injections in DME patients (Annex 7A.4). Most patients in the Phase II program received six injections (90.6%, n=348) (Annex 7A.5). There were a total of 1,958 faricimab 6 mg injections and 696 faricimab 1.5 mg injections across both indications (Annex 7A.6).

Exposure by Age Group and Gender

In the overall faricimab safety population from the Phase III program, 1045 patients were male, and 881 patients were female (Table 12). Male patients had 1563 patient-years of exposure versus 1177 patient-years in female patients. In the pooled population, the highest proportion of males were in the <65 years age group (48.8%), and the highest proportion of females in the 65 to <75 years age group (37.9%).

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 12). 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.

The Phase II program provides exposure from 233 female and 151 male patients, with the majority in the 75 to <85 years age group (Annex 7A.7).

Exposure by Faricimab Dose

In the Phase III studies, there were a total of 664 patients with nAMD (588 years person-time exposure) and 1262 patients with DME (2152 years person-time exposure), all receiving faricimab 6 mg (Annex 7A.8).

The Phase II program provides an additional 384 patients exposed to faricimab with 194 years person-time. The Phase II program included two doses of faricimab. Most patients (73.7%, n=283) received 6 mg faricimab, and 26.3% (n=101) received 1.5 mg faricimab (Annex 7A.9).

Exposure by Race

In the overall safety population from the Phase III program, the majority (80.9%) of faricimab patients were White (1558 patients, 2199 patient-years of exposure), which was consistent across nAMD (87.3%, 580 patients, 514 patient-years of exposure) and DME (77.5%, 978 patients, 1685 patient-years of exposure) (Table 13).

Patients in the Phase II program were also mostly White (90.4%, n=347) in the pooled population (Annex 7A.10).

Exposure by Ethnicity

The ethnicity of 83.8% of the overall faricimab Phase III safety population was Not Hispanic or Latino (1614 patients, 2286 patient-years of exposure) (Table 14). This was consistent across nAMD (88.9%, 590 patients, 521 patient-years of exposure) and DME (81.1%, 1024 patients, 1765 patient-years of exposure).

The Phase II program was consistent with the Phase III population, with 90.6% (n=348) patients that were Not Hispanic or Latino (Annex 7A.11).

Table 10 Overall Extent of Exposure during Entire Study DME and through Week 48 nAMD, Safety-Evaluable Population

Overall Extent of Exposure during entire study DME and Week 48 nAMD, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	nAMD		DME		POOLED(nAMD, DME)	
	Faricimab 6 mg All (N=664)		Faricimab 6 mg All (N=1262)		Faricimab 6 mg All (N=1926)	
Duration of exposure	Patients	Person time(years)*	Patients	Person time(years)*	Patients	Person time(years)*
< 1 month	6 (0.9%)	0	8 (0.6%)	0	14 (0.7%)	0
1 to <3 months	5 (0.8%)	1	19 (1.5%)	3	24 (1.2%)	4
3 to <6 months	14 (2.1%)	5	28 (2.2%)	11	42 (2.2%)	16
6 to <9 months	23 (3.5%)	14	22 (1.7%)	14	45 (2.3%)	28
9 to <1 year	616 (92.8%)	567	25 (2.0%)	22	641 (33.3%)	589
1 to <1.5 years	0	NE	51 (4.0%)	64	51 (2.6%)	64
>1.5 years	0	NE	1109 (87.9%)	2038	1109 (57.6%)	2038
Total patients numbers/ person time	664 (100%)	588	1262 (100%)	2152	1926 (100%)	2740

* 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 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_ex_rmp.sas
Output: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/output/t_ex_rmp_SE.out
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Table 11 Number of Study Drug Administrations in the Study Eye during Entire Study DME and through Week 48 nAMD, Safety-Evaluable Population

Number of Study Drug Administrations in the Study Eye through during entire study DME and Week 48 nAMD, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	nAMD	DME	POOLED(nAMD, DME)
	Faricimab 6 mg All (N=664)	Faricimab 6 mg All (N=1262)	Faricimab 6 mg All (N=1926)
1 or more study drug administration			
n	664	1262	1926
Yes	664 (100%)	1262 (100%)	1926 (100%)
No	0	0	0
2 or more study drug administrations			
n	664	1262	1926
Yes	661 (99.5%)	1257 (99.6%)	1918 (99.6%)
No	3 (0.5%)	5 (0.4%)	8 (0.4%)
3 or more study drug administrations			
n	664	1262	1926
Yes	657 (98.9%)	1250 (99.0%)	1907 (99.0%)
No	7 (1.1%)	12 (1.0%)	19 (1.0%)
4 or more study drug administrations			
n	664	1262	1926
Yes	653 (98.3%)	1242 (98.4%)	1895 (98.4%)
No	11 (1.7%)	20 (1.6%)	31 (1.6%)
5 or more study drug administrations			
n	664	1262	1926
Yes	638 (96.1%)	1227 (97.2%)	1865 (96.8%)
No	26 (3.9%)	35 (2.8%)	61 (3.2%)

Percentages are based on the N in the column headings. For nAMD, the maximum number of injection is 8 at week 48 cut off.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_ex_rmp_admin.sas
Output: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/output/t_ex_rmp_admin_SE.out
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Table 11 Number of Study Drug Administrations in the Study Eye during Entire Study DME and through Week 48 nAMD, Safety-Evaluable Population (cont.)

Number of Study Drug Administrations in the Study Eye through during entire study DME and Week 48 nAMD, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	nAMD	DME	POOLED(nAMD, DME)
	Faricimab 6 mg All (N=664)	Faricimab 6 mg All (N=1262)	Faricimab 6 mg All (N=1926)
6 or more study drug administrations			
n	664	1262	1926
Yes	593 (89.3%)	1213 (96.1%)	1806 (93.8%)
No	71 (10.7%)	49 (3.9%)	120 (6.2%)
7 or more study drug administrations			
n	664	1262	1926
Yes	261 (39.3%)	1196 (94.8%)	1457 (75.6%)
No	403 (60.7%)	66 (5.2%)	469 (24.4%)
8 or more study drug administrations			
n	664	1262	1926
Yes	112 (16.9%)	1175 (93.1%)	1287 (66.8%)
No	552 (83.1%)	87 (6.9%)	639 (33.2%)
9 or more study drug administrations			
n	664	1262	1926
Yes	0	1145 (90.7%)	1145 (59.4%)
No	664 (100%)	117 (9.3%)	781 (40.6%)

Percentages are based on the N in the column headings. For nAMD, the maximum number of injection is 8 at week 48 cut off.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_ex_rmp_admin.sas
Output: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/output/t_ex_rmp_admin_SE.out
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Table 11 Number of Study Drug Administrations in the Study Eye during Entire Study DME and through Week 48 nAMD, Safety-Evaluable Population (cont.)

Number of Study Drug Administrations in the Study Eye through during entire study DME and Week 48 nAMD, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	nAMD	DME	POOLED(nAMD, DME)
	Faricimab 6 mg All (N=664)	Faricimab 6 mg All (N=1262)	Faricimab 6 mg All (N=1926)
10 or more study drug administrations			
n	664	1262	1926
Yes	0	1073 (85.0%)	1073 (55.7%)
No	664 (100%)	189 (15.0%)	853 (44.3%)
11 or more study drug administrations			
n	664	1262	1926
Yes	0	874 (69.3%)	874 (45.4%)
No	664 (100%)	388 (30.7%)	1052 (54.6%)
12 or more study drug administration			
n	664	1262	1926
Yes	0	788 (62.4%)	788 (40.9%)
No	664 (100%)	474 (37.6%)	1138 (59.1%)
13 or more study drug administration			
n	664	1262	1926
Yes	0	726 (57.5%)	726 (37.7%)
No	664 (100%)	536 (42.5%)	1200 (62.3%)
14 or more study drug administration			
n	664	1262	1926
Yes	0	641 (50.8%)	641 (33.3%)
No	664 (100%)	621 (49.2%)	1285 (66.7%)

Percentages are based on the N in the column headings. For nAMD, the maximum number of injection is 8 at week 48 cut off.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_ex_rmp_admin.sas
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Table 11 Number of Study Drug Administrations in the Study Eye during Entire Study DME and through Week 48 nAMD, Safety-Evaluable Population (cont.)

Number of Study Drug Administrations in the Study Eye through during entire study DME and Week 48 nAMD, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	nAMD	DME	POOLED(nAMD, DME)
	Faricimab 6 mg All (N=664)	Faricimab 6 mg All (N=1262)	Faricimab 6 mg All (N=1926)
15 or more study drug administrations			
n	664	1262	1926
Yes	0	507 (40.2%)	507 (26.3%)
No	664 (100%)	755 (59.8%)	1419 (73.7%)
16 or more study drug administrations			
n	664	1262	1926
Yes	0	99 (7.8%)	99 (5.1%)
No	664 (100%)	1163 (92.2%)	1827 (94.9%)
17 or more study drug administrations			
n	664	1262	1926
Yes	0	74 (5.9%)	74 (3.8%)
No	664 (100%)	1188 (94.1%)	1852 (96.2%)
18 or more study drug administrations			
n	664	1262	1926
Yes	0	57 (4.5%)	57 (3.0%)
No	664 (100%)	1205 (95.5%)	1869 (97.0%)

Percentages are based on the N in the column headings. For nAMD, the maximum number of injection is 8 at week 48 cut off.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_ex_rmp_admin.sas
Output: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/output/t_ex_rmp_admin_SE.out
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Table 11 Number of Study Drug Administrations in the Study Eye during Entire Study DME and through Week 48 nAMD, Safety-Evaluable Population (cont.)

Number of Study Drug Administrations in the Study Eye through during entire study DME and Week 48 nAMD, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	nAMD	DME	POOLED(nAMD, DME)
	Faricimab 6 mg All (N=664)	Faricimab 6 mg All (N=1262)	Faricimab 6 mg All (N=1926)
19 or more study drug administrations			
n	664	1262	1926
Yes	0	46 (3.6%)	46 (2.4%)
No	664 (100%)	1216 (96.4%)	1880 (97.6%)
20 or more study drug administrations			
n	664	1262	1926
Yes	0	40 (3.2%)	40 (2.1%)
No	664 (100%)	1222 (96.8%)	1886 (97.9%)
21 or more study drug administrations			
n	664	1262	1926
Yes	0	28 (2.2%)	28 (1.5%)
No	664 (100%)	1234 (97.8%)	1898 (98.5%)
22 or more study drug administrations			
n	664	1262	1926
Yes	0	23 (1.8%)	23 (1.2%)
No	664 (100%)	1239 (98.2%)	1903 (98.8%)
23 or more study drug administrations			
n	664	1262	1926
Yes	0	19 (1.5%)	19 (1.0%)
No	664 (100%)	1243 (98.5%)	1907 (99.0%)

Percentages are based on the N in the column headings. For nAMD, the maximum number of injection is 8 at week 48 cut off.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_ex_rmp_admin.sas
Output: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/output/t_ex_rmp_admin_SE.out
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Table 11 Number of Study Drug Administrations in the Study Eye during Entire Study DME and through Week 48 nAMD, Safety-Evaluable Population (cont.)

Number of Study Drug Administrations in the Study Eye through during entire study DME and Week 48 nAMD, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	nAMD	DME	POOLED(nAMD, DME)
	Faricimab 6 mg All (N=664)	Faricimab 6 mg All (N=1262)	Faricimab 6 mg All (N=1926)
24 or more study drug administrations			
n	664	1262	1926
Yes	0	16 (1.3%)	16 (0.8%)
No	664 (100%)	1246 (98.7%)	1910 (99.2%)
25 or more study drug administrations			
n	664	1262	1926
Yes	0	12 (1.0%)	12 (0.6%)
No	664 (100%)	1250 (99.0%)	1914 (99.4%)

Percentages are based on the N in the column headings. For nAMD, the maximum number of injection is 8 at week 48 cut off.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_ex_rmp_admin.sas
Output: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/output/t_ex_rmp_admin_SE.out
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Table 12 Overall Extent of Exposure during Entire Study DME and through Week 48 nAMD by Age Group and Gender, Safety-Evaluable Population

Overall Extent of Exposure during entire study DME and through Week 48 nAMD by Age Group and Gender, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	nAMD					
	Faricimab 6 mg All (N=664)					
	Male		Female		Total	
Age Group (years)	Patients	Person time(years)*	Patients	Person time(years)*	Patients	Person time(years)*
<65	33 (12.2%)	30	31 (7.9%)	28	64 (9.6%)	58
65 to <75	86 (31.9%)	76	136 (34.5%)	122	222 (33.4%)	199
75 to <85	118 (43.7%)	104	170 (43.1%)	150	288 (43.4%)	255
>=85	33 (12.2%)	29	57 (14.5%)	48	90 (13.6%)	76
Total patients numbers/person time	270 (100%)	240	394 (100%)	348	664 (100%)	588

* 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 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_ex_rmp_age.sas
Output: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/output/t_ex_rmp_age_SE.out
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Table 12 Overall Extent of Exposure during Entire Study DME and through Week 48 nAMD by Age Group and Gender, Safety-Evaluable Population (cont.)

Overall Extent of Exposure during entire study DME and through Week 48 nAMD by Age Group and Gender, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	DME					
	Faricimab 6 mg All (N=1262)					
	Male		Female		Total	
Age Group (years)	Patients	Person time(years)*	Patients	Person time(years)*	Patients	Person time(years)*
<65	477 (61.5%)	821	238 (48.9%)	404	715 (56.7%)	1225
65 to <75	242 (31.2%)	413	198 (40.7%)	336	440 (34.9%)	749
75 to <85	52 (6.7%)	84	51 (10.5%)	89	103 (8.2%)	172
>=85	4 (0.5%)	6	0	NE	4 (0.3%)	6
Total patients numbers/person time	775 (100%)	1323	487 (100%)	828	1262 (100%)	2152

* 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 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_ex_rmp_age.sas
Output: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/output/t_ex_rmp_age_SE.out
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Table 12 Overall Extent of Exposure during Entire Study DME and through Week 48 nAMD by Age Group and Gender, Safety-Evaluable Population (cont.)

Overall Extent of Exposure during entire study DME and through Week 48 nAMD by Age Group and Gender, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	POOLED(nAMD, DME) Faricimab 6 mg All (N=1926)					
	Male		Female		Total	
Age Group (years)	Patients	Person time(years)*	Patients	Person time(years)*	Patients	Person time(years)*
<65	510 (48.8%)	851	269 (30.5%)	432	779 (40.4%)	1283
65 to <75	328 (31.4%)	489	334 (37.9%)	458	662 (34.4%)	947
75 to <85	170 (16.3%)	188	221 (25.1%)	239	391 (20.3%)	427
>=85	37 (3.5%)	35	57 (6.5%)	48	94 (4.9%)	82
Total patients numbers/person time	1045 (100%)	1563	881 (100%)	1177	1926 (100%)	2740

* 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 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_ex_rmp_age.sas
Output: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/output/t_ex_rmp_age_SE.out
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Table 13 Overall Extent of Exposure during Entire Study DME and through Week 48 nAMD by Race, Safety-Evaluable Population

Overall Extent of Exposure during entire study DME and through Week 48 nAMD by Race, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	nAMD		DME		POOLED(nAMD, DME)	
	Faricimab 6 mg All (N=664)		Faricimab 6 mg All (N=1262)		Faricimab 6 mg All (N=1926)	
Race	Patients	Person time(years)*	Patients	Person time(years)*	Patients	Person time(years)*
American Indian or Alaska Native	2 (0.3%)	2	11 (0.9%)	18	13 (0.7%)	20
Asian	64 (9.6%)	56	127 (10.1%)	223	191 (9.9%)	279
Black or African American	2 (0.3%)	2	88 (7.0%)	145	90 (4.7%)	147
Native Hawaiian or other Pacific Islander	0	NE	4 (0.3%)	6	4 (0.2%)	6
White	580 (87.3%)	514	978 (77.5%)	1685	1558 (80.9%)	2199
Multiple	1 (0.2%)	1	4 (0.3%)	4	5 (0.3%)	4
Unknown	15 (2.3%)	13	50 (4.0%)	71	65 (3.4%)	85
Total patients numbers/person time	664 (100%)	588	1262 (100%)	2152	1926 (100%)	2740

* 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 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_ex_rmp_race.sas
Output: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/output/t_ex_rmp_race_SE.out
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Table 14 Overall Extent of Exposure during Entire Study DME and through Week 48 nAMD by Ethnicity, Safety-Evaluable Population

Overall Extent of Exposure during entire study DME and through Week 48 nAMD by Ethnicity, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	nAMD		DME		POOLED(nAMD, DME)	
	Faricimab 6 mg All (N=664)		Faricimab 6 mg All (N=1262)		Faricimab 6 mg All (N=1926)	
Ethnicity	Patients	Person time(years)*	Patients	Person time(years)*	Patients	Person time(years)*
Hispanic or Latino	61 (9.2%)	55	211 (16.7%)	345	272 (14.1%)	399
Not Hispanic or Latino	590 (88.9%)	521	1024 (81.1%)	1765	1614 (83.8%)	2286
Not Stated	6 (0.9%)	6	16 (1.3%)	26	22 (1.1%)	32
Unknown	7 (1.1%)	6	11 (0.9%)	17	18 (0.9%)	23
Total patients numbers/person time	664 (100%)	588	1262 (100%)	2152	1926 (100%)	2740

* 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 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_ex_rmp_ethn.sas
Output: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/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 15.

Table 15 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	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.
	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.

Table 15 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	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.
	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.

Table 15 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.)				
DME	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.
Systemic				
All indications	Systemic treatment for suspected or active systemic infection	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)	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.

Table 15 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.)				
All indications (cont.)	Stroke (cerebral vascular 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.
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; 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
- 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 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 16 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. Three pregnancy cases were reported during the conduct of the Phase III studies (Annex 7A.12), of which one patient was treated with faricimab: GR40349 – 1 pregnancy case (outcome: live birth without congenital anomaly)
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, 65% of faricimab treated patients with available serum creatinine measurements had renal impairment (mild 38%, moderate 24%, and severe 2%) (popPK Report, Report 1105763).
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 13. Clinical trial exposure data by ethnicity are provided in Table 14.
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

This section is not applicable because faricimab has not yet been approved in any country.

SV.1.2 Exposure

This section is not applicable because faricimab has not yet been approved in any country.

PART II: MODULE SVI— ADDITIONAL E.U. 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

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 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 (Annex 7C.11). In the 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 (Annex 7C.12). 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 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 (Annex 7C.11). 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 Phase III studies (i.e., up to Week 48 for nAMD studies [TENEYA 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 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 (Annex 7C.11, Annex 7C.12).

  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 ADAs 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 Phase III studies of approximately 10% (nAMD: 10.4%, Annex 7C.1 and DME: 9.6%, Annex 7C.2). Incidence rate of IOI was low and not more than 2% in the nAMD and DME Phase III studies (Annex 7C.15 and Annex 7C.17, respectively). Although a higher incidence of IOI was observed in ADA-positive patients (nAMD: 5/75 [6.7%], Annex 7C.3 and Annex 7C.4; DME: 15/128 [11.7%], Annex 7C.5 and Annex 7C.6) compared with ADA-negative patients (nAMD: 7/582 [1.2%], Annex 7C.7 and Annex 7C.8; DME: 5/1124 [0.4%], Annex 7C.9 and Annex 7C.10), 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 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 Phase III studies (GR40306 TENAYA, GR40844 LUCERNE, GR40349 YOSEMITE, and GR40398 RHINE) was 6 events (0.3%) (Table 19). 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 (Annex 7B.1). The event rate per-1000 injections in the Phase III studies was 0.3 (Annex 7A.4). 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 (Table 21). 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 (Annex 7B.2). All except for one event were mild in severity in the Phase II studies. In the 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 (CNS) 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 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 17 . ATE and CNS hemorrhagic events (adjudicated) were reported in 3.7% (n=71) of patients treated with faricimab in the Phase III studies (Table 23). 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 17 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.

Source: Annex 7C.13; Annex 7C.14.

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 (Annex 7B.3).

Overall, the majority of faricimab-treated patients experienced severe ATE and CNS hemorrhagic events in the Phase III and Phase II trials (refer to Table 23 and Annex 7B.3, respectively). 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 ongoing long-term extension 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 (see Part II: Module SIII). Although limited long-term safety data are available, faricimab is intended for long-term use. Thus, long-term safety data is being collected and monitored from the ongoing long-term extension clinical studies, AVONELLE-X (nAMD) and RHONE-X (DME). Refer to Part III.2, 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

Not applicable.

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

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 Phase III studies (GR40306 TENAYA, GR40844 LUCERNE, GR40349 YOSEMITE, and GR40398 RHINE) and the Phase II studies (BP29647 AVENUE, CR39521 STAIRWAY, and BP30099 BOULEVARD).

The frequency of endophthalmitis reported with approved intravitreal anti-VEGF monotherapies is presented in Table 18.

Table 18 Frequency of Occurrence of Endophthalmitis in other Observational Studies and Clinical Trials

	nAMD Population (incidence proportion)		DME Population (incidence proportion)	
Event type	**Observational Studies**	**Clinical Trials**	**Observational Studies**	**Clinical Trials**
All events	NR	0.45%–0.93%	NR	0.61%
Source	—	Meredith et al. 2015; Berg et al. 2016	—	Bhavsar et al. 2009
Serious events	0.14%	0.13%–0.85%	0.08%	0.51%–2.0%
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

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

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:

In the Phase III studies with nAMD (i.e., TENAYA and LUCERNE), there were no events of infectious endophthalmitis in the study eye reported in the faricimab arms (n=664) (Table 19).

Of the 1262 faricimab-treated patients from the 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 19). 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 during the entire study (through Week 100).

There was a per-1000 injection rate of 0.3 events of infectious endophthalmitis (Annex 7A.4) in the overall Phase III population, pooled across both indications.

Table 19 Important Identified Endophthalmitis Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI during Entire Study DME and through Week 48 nAMD in the Study Eye, Safety-Evaluable Population

Important Identified Endophthalmitis Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI during entire study DME and through Week 48 nAMD in the Study Eye, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	nAMD (N=1326)		DME (N=1887)		POOLED (nAMD, DME) (N=3213)	
	Faricimab (N=664)	Aflibercept (N=662)	Faricimab (N=1262)	Aflibercept (N=625)	Faricimab (N=1926)	Aflibercept (N=1287)
Number (%) of patients with at least one AE	0	1 (0.2%)	6 (0.5%)	1 (0.2%)	6 (0.3%)	2 (0.2%)
95% CI for % of patients with at least one AE	(0.00%, 0.58%)	(0.03%, 0.85%)	(0.22%, 1.03%)	(0.03%, 0.90%)	(0.14%, 0.68%)	(0.04%, 0.56%)
Difference in % of patients with at least one AE	-0.2%		0.3%		0.2%	
95% CI for difference	(-0.85%, 0.44%)		(-0.47%, 0.89%)		(-0.29%, 0.54%)	
Total number of AEs	0	1	6	1	6	2
Number (%) of patients with at least one AE by severity						
Mild	0	0	0	0	0	0
Moderate	0	1 (0.2%)	3 (0.2%)	0	3 (0.2%)	1 (<0.1%)
Severe	0	0	3 (0.2%)	1 (0.2%)	3 (0.2%)	1 (<0.1%)
Number (%) of patients with at least one serious AE	0	1 (0.2%)	6 (0.5%)	1 (0.2%)	6 (0.3%)	2 (0.2%)
Number (%) of patients with at least one AE by outcome						
Fatal	0	0	0	0	0	0
Not recovered/Resolved	0	0	1 (16.7%)	0	1 (16.7%)	0
Recovering/Resolving	0	0	1 (16.7%)	0	1 (16.7%)	0
Recovered/Resolved	0	1 (100%)	4 (66.7%)	0	4 (66.7%)	1 (50.0%)
Resolved with sequelae	0	0	0	1 (100%)	0	1 (50.0%)
Unknown outcome	0	0	0	0	0	0

Investigator text for AEs encoded using MedDRA version 23.1 for nAMD and MedDRA version 24.0 for DME. 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 Q8W and personalized treatment interval.
Aflibercept dosing is Aflibercept 2 mg Q8W.
Endophthalmitis terms = Endophthalmitis, Candida endophthalmitis, Mycotic endophthalmitis, Pseudoendophthalmitis.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.
Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_saf_rmp.sas
Output: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/output/t_saf_rmp_ENDO_SE.out
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In the Phase II studies in nAMD, one patient (2.2%) receiving 1.5 mg faricimab experienced infectious endophthalmitis in the study eye (Annex 7B.1). The reported event was a serious AE and evaluated as severe. The event was considered resolved by the end of study.

In the Phase II study in DME (BP30099 BOULEVARD), no faricimab patients (n=135) experienced endophthalmitis in the study eye.

There was a per-1000 injection rate of 1.44 events of endophthalmitis in the pooled faricimab Phase II patients (Annex 7A.6).

Based on data available to date for the clinical development program, the risk of infectious endophthalmitis has been sufficiently characterized and the frequency of occurrence is shown to be consistent with 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 pars plana vitrectomy. 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 ≥1/1,000 to <1/100 events.

Intraocular Inflammation

Potential mechanisms:

Several potential mechanisms could explain 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 develop because of a specific immunogenic response to the administered protein agent (ADAs) (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 Phase III studies (GR40306 TENAYA, GR40844 LUCERNE, GR40349 YOSEMITE, and GR40398 RHINE) and the Phase II studies (BP29647 AVENUE, CR39521 STAIRWAY, and BP30099 BOULEVARD).

The frequency of IOI reported with approved intravitreal anti-VEGF monotherapies is presented in Table 20.

Table 20 Frequency of Occurrence of Intraocular Inflammation in Clinical Trials with Intravitreal Anti-VEGF Monotherapies

Event	nAMD Population (incidence proportion)		DME Population (incidence proportion)	
	Clinical Trials (All Events)	Clinical Trials (Serious Events)	Clinical Trials (All Events)	Clinical Trials (Serious Events)
Intraocular Inflammation (defined per respective study)	0.6%–17.1%	NR	1%–8%	NR
Source	Brown et al. 2009; Dugel et al. 2021	—	Wells et al. 2015; Sivaprasad et al. 2017	—
Iridocyclitis	0.6%–2.2% (25, 26)	0.09%	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%
Source	Busbee et al. 2013; Dugel et al. 2021	—	Wells et al. 2015	Brown et al. 2013
Uveitis	0.13%–1.5%	0.33%–0.71%	NR	NR
Source	Dugel et al. 2021, Rosenfeld et al. 2006	Brown et al. 2009; Chakravarthy et al. 2012; Dugel et al. 2021	—	—
Vitritis	NR	0.10%	NR	NR
Source	—	Dugel et al. 2021	—	—

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

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 Phase III faricimab safety population with nAMD (i.e., TENAYA and LUCERNE), 2.0% of patients (n=13) experienced at least one event of IOI in the study eye (Table 21). Five events (0.8%) were considered serious. By severity, a mild event was experienced by 0.9% (n=6) of patients, moderate in 0.6% (n=4) of patients and severe in

0.5% (n=3) of patients. Of the patients with events, one (7.7%) patient had at least one event that was considered not recovered/resolved and two (15.4%) patients had at least one event recovering/resolving by Week 48.

By Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term, 0.5% of patients (n=3) experienced iridocyclitis, 0.5% of patients (n=3) experienced iritis, 0.3% of patients (n=2) experienced uveitis, and 0.5% of patients (n=3) experienced vitritis in the Phase III nAMD population (Annex 7C.15). The per-1000 injection rate by Preferred Term was 1.18 for iridocyclitis and 0.71 for iritis, uveitis, and vitritis (Annex 7C.16).

In the faricimab arms from the 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 21). Four patients (0.3%) experienced at least one serious event. By severity, the most severe event was mild in 0.6% (n=7) of patients, moderate in 0.7% (n=9), and severe in 0.3% (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 Phase III DME population (Annex 7C.17). The per-1000 injection rate by Preferred Term was 0.56 for uveitis, 0.31 for both iritis and iridocyclitis, and 0.13 for both post procedural inflammation and vitritis (Annex 7C.18).

In the overall Phase III population pooled across both indications, the per-1000 injection rate of IOI events was 2.08 (Annex 7A.4).

Table 21 Important Identified Intraocular Inflammation Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI during Entire Study DME and through Week 48 nAMD in the Study Eye, Safety-Evaluable Population

Important Identified Intraocular Inflammation (IOI) Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI during entire study DME and through Week 48 nAMD in the Study Eye, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	nAMD (N=1326)		DME (N=1887)		POOLED(nAMD, DME) (N=3213)	
	Faricimab (N=664)	Aflibercept (N=662)	Faricimab (N=1262)	Aflibercept (N=625)	Faricimab (N=1926)	Aflibercept (N=1287)
Number (%) of patients with at least one AE	13 (2.0%)	8 (1.2%)	20 (1.6%)	7 (1.1%)	33 (1.7%)	15 (1.2%)
95% CI for % of patients with at least one AE	(1.15%, 3.32%)	(0.61%, 2.37%)	(1.03%, 2.44%)	(0.54%, 2.29%)	(1.22%, 2.40%)	(0.71%, 1.91%)
Difference in % of patients with at least one AE	0.7%		0.5%		0.5%	
95% CI for difference	(-0.66%, 2.24%)		(-0.83%, 1.49%)		(-0.35%, 1.37%)	
Total number of AEs	16	9	26	10	42	19
Number (%) of patients with at least one AE by severity						
Mild	6 (0.9%)	4 (0.6%)	7 (0.6%)	5 (0.8%)	13 (0.7%)	9 (0.7%)
Moderate	4 (0.6%)	3 (0.5%)	9 (0.7%)	2 (0.3%)	13 (0.7%)	5 (0.4%)
Severe	3 (0.5%)	1 (0.2%)	4 (0.3%)	0	7 (0.4%)	1 (<0.1%)
Number (%) of patients with at least one serious AE	5 (0.8%)	1 (0.2%)	4 (0.3%)	1 (0.2%)	9 (0.5%)	2 (0.2%)
Number (%) of patients with at least one AE by outcome						
Fatal	0	0	0	0	0	0
Not recovered/Resolved	1 (7.7%)	1 (12.5%)	1 (5.0%)	0	2 (6.1%)	1 (6.7%)
Recovering/Resolving	2 (15.4%)	0	6 (30.0%)	0	8 (24.2%)	0
Recovered/Resolved	11 (84.6%)	7 (87.5%)	14 (70.0%)	7 (100%)	25 (75.8%)	14 (93.3%)
Resolved with sequelae	0	0	2 (10.0%)	0	2 (6.1%)	0
Unknown outcome	0	0	0	0	0	0

Investigator text for AEs encoded using MedDRA version 23.1 for nAMD and MedDRA version 24.0 for DME. 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 Q8W and personalized treatment interval.
Aflibercept dosing is Aflibercept 2 mg Q8W.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_saf_rmp.sas
Output: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/output/t_saf_rmp_IOI_SE.out
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In the Phase II studies in nAMD, 6.5% of patients (n=3) receiving 1.5 mg faricimab and 2.0% of patients (n=4) receiving 6 mg faricimab experienced IOI in the study eye (Annex 7B.2). One event in the 1.5 mg arm was serious. All events were mild except for one reported as severe. The majority of events resolved by end of study.

In the Phase II study in DME (BP30099 BOULEVARD), no faricimab patients (n=135) experienced IOI events in the study eye.

There was a per-1000 injection rate of 4.31 and 2.04 events of IOI in the 1.5 mg and 6 mg pooled faricimab Phase II patients, respectively (Annex 7A.6).

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

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 ADAs).

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; Witkin 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
Arterial Thromboembolic Events (ATE) and Central Nervous System (CNS) hemorrhagic events

Potential mechanisms:

Interaction of VEGF with VEGF-receptor on endothelial cells (ECs) induces production of nitric oxide and prostaglandin I2, both of which are important for EC survival, proliferation and migration, vasodilatation, as well as maintenance of the integrity and antithrombotic/antiadherent state of the EC lining. Inhibition of the VEGF pathway may therefore impair angiogenesis, disrupt vascular integrity, and disturb the normal EC interaction with platelets. This may compromise the integrity of the EC lining and promote platelet aggregation, thereby increasing the risk of ATE events (Chen and Cleck 2009).

Evidence source(s) and strength of evidence:

This important potential risk is based on data from the faricimab safety population in the Phase III studies (GR40306 TENAYA, GR40844 LUCERNE, GR40349 YOSEMITE, and GR40398 RHINE) and the Phase II studies (BP29647 AVENUE, CR39521 STAIRWAY, and BP30099 BOULEVARD).

The frequency of ATE and CNS hemorrhagic events reported with approved intravitreal anti-VEGF monotherapies is presented in Table 22.

Table 22 Frequency of Occurrence of APTC Events in Clinical Trials with Intravitreal anti-VEGF Monotherapies

Event	nAMD Population (incidence proportion) Clinical Trials (All Events)	DME Population (incidence proportion) Clinical Trials (All Events)
APTC events	2.0% – 3.2%	4.1% – 6.4%
Source	Busbee et al. 2013; Schmidt-Erfurth et al. 2014; Zarbin et al. 2018	Nguyen et al. 2012; Brown et al. 2015; Zarbin et al. 2017
ATE	0.68% – 6.0%	0.4% – 5.2%
Source	Boyer et al. 2009; Chakravarthy et al. 2012; Busbee et al. 2013; Zarbin et al. 2018; Martin et al. 2011	Mitchell et al. 2011; Ishibashi et al. 2015; Zarbin et al. 2017
Vascular deaths	0.32% – 1.4%	0.7% – 2.2%
Source	Rosenfeld et al. 2006; Boyer et al. 2009; Brown et al. 2009; Chakravarthy et al. 2012; Busbee et al. 2013; Schmidt-Erfurth et al. 2014; Zarbin et al. 2018; Martin et al. 2011	Nguyen et al. 2012; Brown et al. 2015; Zarbin et al. 2017
MI	0.3% – 2.2%	0.5% – 3.2%
Source	Rosenfeld et al. 2006; Antoszyk et al. 2008; Brown et al. 2009; Chakravarthy et al. 2012; Busbee et al. 2013; Schmidt-Erfurth et al. 2014; Silva et al. 2018; Zarbin et al. 2018; Holz et al. 2020; Martin et al. 2011	Mitchell et al. 2011; Nguyen et al. 2012; Brown et al. 2015; Ishibashi et al. 2015; Wells et al. 2015; Zarbin et al. 2017; Chen et al. 2020
Stroke	0.55% – 1.9%	1.0% – 2.1%
Source	Rosenfeld et al.2006; Boyer et al. 2009; Chakravarthy et al. 2012; Busbee et al. 2013; Schmidt-Erfurth et al. 2014; Zarbin et al. 2018; Martin et al. 2011	Mitchell et al. 2011; Brown et al. 2015; Wells et al. 2015; Zarbin et al. 2017
TIA	0.32% – 0.95%	0.2 – 1.0%
Source	Antoszyk et al. 2008; Chakravarthy et al. 2012; Silva et al. 2018; Martin et al. 2011	Nguyen et al. 2012; Brown et al. 2015
CVA	0.3% – 4.7%	0.4% – 2.2%
Source	Antoszyk et al. 2008; Brown et al. 2009; Silva et al. 2013; Silva et al. 2018; Holz et al. 2020	Mitchell et al. 2011; Nguyen et al. 2012; Brown et al. 2015

APTC = Anti-Platelet Trialists' Collaboration, ATE = arterial thromboembolic events; CVA = cerebrovascular accident; DME=diabetic macular edema; MI = myocardial infarction; nAMD=neovascular age-related macular degeneration; TIA = transient ischemic attack; VEGF = vascular endothelial growth factor.

Characterization of the risk:

Of the 664 faricimab-treated with patients from the Phase III safety population with nAMD (i.e., TENAYA and LUCERNE), 1.1% of patients (n=7) experienced at least one adjudicated APTC-defined event (Table 23). All seven patients had severe events, and all were considered serious.

Of the 1262 faricimab-treated patients from the Phase III safety population with DME (i.e., YOSEMITE and RHINE), 5.1% of patients (n=64) experienced at least one adjudicated APTC-defined event (Table 23). Of these, 4.0% of patients (n=51) had severe events and 1.0% of patients (n=12) had moderate events. Most of these events were considered serious.

In the overall Phase III population pooled across both indications, the per-1000 injection rate of ATE/CNS hemorrhagic events (adjudicated) was 3.51 (Annex 7A.13).

Table 23 Important Potential Adjudicated Anti-Platelet Trialists' Collaboration (APTC)-defined Adverse Event Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI during Entire Study DME and through Week 48 nAMD, Safety-Evaluable Population

Important Potential Adjudicated APTC-Defined Adverse Events Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI during entire study DME and through Week 48 nAMD, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: TENAYA 26OCT2020, LUCERNE 05OCT2020

	nAMD (N=1326)		DME (N=1887)		POOLED(nAMD, DME) (N=3213)	
	Faricimab (N=664)	Aflibercept (N=662)	Faricimab (N=1262)	Aflibercept (N=625)	Faricimab (N=1926)	Aflibercept (N=1287)
Number (%) of patients with at least one AE	7 (1.1%)	6 (0.9%)	64 (5.1%)	32 (5.1%)	71 (3.7%)	38 (3.0%)
95% CI for % of patients with at least one AE	(0.51%, 2.16%)	(0.42%, 1.96%)	(3.99%, 6.42%)	(3.65%, 7.14%)	(2.93%, 4.62%)	(2.16%, 4.03%)
Difference in % of patients with at least one AE	0.1%		0.0%		0.7%	
95% CI for difference	(-1.04%, 1.36%)		(-2.34%, 1.95%)		(-0.58%, 1.96%)	
Total number of AEs	7	6	64	32	71	38
Number (%) of patients with at least one AE by severity						
Mild	0	0	1 (<0.1%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)
Moderate	0	1 (0.2%)	12 (1.0%)	5 (0.8%)	12 (0.6%)	6 (0.5%)
Severe	7 (1.1%)	5 (0.8%)	51 (4.0%)	25 (4.0%)	58 (3.0%)	30 (2.3%)
Number (%) of patients with at least one serious AE	7 (1.1%)	6 (0.9%)	61 (4.8%)	31 (5.0%)	68 (3.5%)	37 (2.9%)
Number (%) of patients with at least one AE by outcome						
Fatal	2 (28.6%)	3 (50.0%)	30 (46.9%)	14 (43.8%)	32 (45.1%)	17 (44.7%)
Not recovered/Resolved	1 (14.3%)	0	2 (3.1%)	2 (6.3%)	3 (4.2%)	2 (5.3%)
Recovering/Resolving	0	0	2 (3.1%)	0	2 (2.8%)	0
Recovered/Resolved	2 (28.6%)	3 (50.0%)	21 (32.8%)	15 (46.9%)	23 (32.4%)	18 (47.4%)
Resolved with sequelae	2 (28.6%)	0	9 (14.1%)	1 (3.1%)	11 (15.5%)	1 (2.6%)
Unknown outcome	0	0	0	0	0	0

Investigator text for AEs encoded using MedDRA version 23.1 for nAMD and MedDRA version 24.0 for DME. 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 Q8W and personalized treatment interval. Aflibercept dosing is Aflibercept 2 mg Q8W.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.
Program: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/program/t_saf_rmp.sas
Output: root/clinical_studies/RO6867461/share/pool_RMP_DMEY2_AMD48_PH2/prod/output/t_saf_rmp_APTC_SE.out
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In the Phase II studies in nAMD, one patient (2.2%) receiving 1.5 mg faricimab and seven patients (3.4%) receiving 6 mg faricimab experienced an ATE/CNS hemorrhagic event (unadjudicated) (Annex 7B.3). Six patients experienced events that were serious (one patient in the 1.5 mg faricimab arm, and five patients in the 6 mg faricimab arm).

In the Phase II studies in DME, one patient (1.8%) receiving 1.5 mg faricimab and three patients (3.8%) receiving 6 mg faricimab experienced an ATE/CNS hemorrhagic event (unadjudicated) (Annex 7B.3). Two patients experienced events that were serious (both reported in the 6 mg faricimab arm).

There was a per-1000 injection rate of 2.87 and 6.13 events of ATE/CNS hemorrhagic events (unadjudicated) in the 1.5 mg and 6 mg pooled faricimab Phase II patients, respectively (Annex 7A.14).

Risk factors and risk groups:

nAMD is associated with CV disease and the risk factors include moderate to severe hypertension, raised high density lipoprotein levels, and anatomic measures of atherosclerotic disease. Patients with nAMD with comorbidities such as hypertension, arrhythmias, or a previous history of myocardial infarction and cerebral vascular accidents have an increased risk of experiencing ATEs (Alexander et al. 2007). The majority of subjects in ranibizumab trials who experienced an ATE had a medical history that included ≥ 1 cardiovascular risk factors and were ≥ 75 years old (Rosenfeld et al. 2006.

DME is more common in older patients with T2DM. The risk of CV diseases in diabetic patients increases by two to threefold (hypertension increases the prevalence of DME to threefold) (Acan et al. 2018). There is also a correlation between patients with DR and CV disease, who are at an increased risk of stroke and heart failure (Bandello et al. 2020). In a retrospective cohort study (US) (2006–2015) with DME patients that had a history of cerebrovascular and CV diseases, the prevalence of myocardial infarction, CV disease, stroke, hemorrhagic stroke, and transient ischemic attack was 5.5%, 13%, 5.2%, 0.38%, and 3.3% respectively (Maloney et al. 2019).

Preventability:

Patients with CV comorbidities or a previous history of myocardial infarction and cerebral vascular accidents are at an increased risk of ATE events. Due to the lack of early warning signs of onset of most ATEs, patients with known risk factors should be informed of this risk and monitored following faricimab intravitreal injection.

Impact on the benefit-risk balance of the product:

A few ATE/CNS hemorrhagic events are associated with serious and life-threatening consequences, particularly in high-risk patients and in certain clinical settings. However, the incidence rate of ATE/CNS hemorrhagic events has been low in the overall faricimab

clinical development program and most of the events were assessed as unrelated to the study treatment by the investigators, or the events were confounded by the patient's concurrent medical history.

Also, considering no suppression from baseline in VEGF-A or ANG-2 was observed in plasma of patients dosed with faricimab in the Phase III studies (popPK Report, Report 1105763) and that the incidence of ATE/CNS hemorrhagic events in the faricimab arm was consistent with what have been observed with approved intravitreal anti-VEGF monotherapies, the risk of ATE events associated with faricimab remains theoretical like other intravitreal treatments. Therefore, the impact of ATE/CNS hemorrhagic events on the benefit-risk balance of faricimab is considered low.

Public health impact:

While the risk of ATE/CNS hemorrhagic events remains theoretical with faricimab treatment, the incidence of ATE/CNS hemorrhagic events is expected to be common (frequency of ≥1/100 to <1/10 events) in nAMD and DME patients with underlying risk factors.

SVII.3.2 Presentation of the Missing Information

Information on Missing Information

Long-term Safety

Evidence source:

Patients are expected to receive faricimab over a long treatment duration. The faricimab safety population provides data from 1926 patients with 2740 years person-time of exposure in the Phase III program (see Part II: Module SIII). The duration of exposure achieved during the clinical development program of faricimab is not yet sufficient to determine any difference in the safety profile in patients with long-term exposure.

Anticipated risk/consequence of the missing information:

The safety profile of faricimab has been well characterized in the clinical trial setting and continues to be analyzed. The safety profile in long-term use is not expected to be significantly different to the current knowledge of the safety profile.

Long-term safety data will be collected and monitored from the ongoing long-term extension studies: AVONELLE-X (nAMD) and RHONE-X (DME). Refer to Part III, III.2 for further details.

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).

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, and RHINE), 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 three pregnancies (YOSEMITE [n=1] and RHINE [n=2]) have been reported during the conduct of the Phase III studies (all in DME treated patients); one in the faricimab personalized treatment interval (PTI) arm and two in the aflibercept Q8W arm (Annex 7A.12). 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 had a normal delivery with an APGAR score within the expected range (CSR YOSEMITE narratives, Report 1102956, p. 1655).

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, recognizing that pregnancy is possible in the DME patient population, the use of faricimab in pregnant patients will be closely monitored, following Roche's standard pregnancy follow-up process (refer to Part III.1 for further details). In addition, pregnancy cases will be summarized in Periodic Safety Update Reports (PSURs)/ Periodic Benefit-Risk Evaluation Report (PBRERs).

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 24 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Infectious endophthalmitis Intraocular inflammation
Important potential risks	Arterial thromboembolic events and Central Nervous System hemorrhagic events
Missing information	Long-term safety 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.

The Roche standard pregnancy follow-up process has also been implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life. Cumulative data will be presented in PSURs/ PBRERs.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Two long-term extension studies (AVONELLE-X and RHONE-X) are currently ongoing to evaluate the long-term safety and tolerability of intravitreal faricimab, which will address the missing information of long-term safety of faricimab and will provide a cumulative 4 years of exposure data (Table 25 and Table 26). In addition, data from these two long-term extension studies will also further characterize the important potential risk of ATE/CNS hemorrhagic events.

Table 25 Study GR42691 (AVONELLE-X)

Study/activity short name and title: Study GR42691 (AVONELLE-X): A multicenter, open-label extension study to evaluate the long-term safety and tolerability of faricimab in patients with nAMD.
Rationale and study objectives: The objective of this study is to evaluate the long-term safety and tolerability of the intravitreal faricimab in patients with nAMD, who have completed either of the Phase III (GR40306 or GR40844) studies. The primary objective is to monitor patients who have received at least one injection of faricimab during the LTE, regardless of adherence to treatment or to the protocol, on the basis of the following endpoints: • Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events.
Study design: This is a global, multicenter, open-label, study designed to evaluate the long-term safety and tolerability of faricimab 6 mg administered by intravitreal injection at a PTI to patients who enrolled in and completed one of the Phase III studies (GR40306 or GR40844), also referred to as the parent studies.
Study populations: Patients with nAMD will be enrolled upon completion of the end-of-study visit in the parent study (i.e., Week 112 visit in studies GR40306 and GR40844). All assessments from the parent study end-of-study visit must be completed prior to the LTE study enrollment visit assessments. Approximately 1280 patients are expected to participate in this LTE study after completion of the parent studies.
Milestones: FPFV: 19 April 2021 Database lock planned April 2024. Final Clinical Study Report planned Q1 2025.

FPFV=first patient first visit; GR40306=TENAYA; GR40844=LUCERNE; LPLV=last patient last visit; LTE=long-term extension; nAMD=neovascular age-related macular degeneration; PTI=personalized treatment interval.

Table 26 Study GR41987 (RHONE-X)

Study/activity short name and title: Study GR41987 (RHONE-X): A multicenter, open-label extension study to evaluate the long-term safety and tolerability of faricimab in patients with DME.
Rationale and study objectives: The objective of this study is to evaluate the long-term safety, tolerability and efficacy of intravitreal faricimab in patients with diabetic macular edema who have completed either of the Phase III (GR40349 or GR40398) studies. The primary objective is to monitor patients who have received at least one injection of faricimab during the LTE, regardless of adherence to treatment or to the protocol, on the basis of the following endpoints: • Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events.
Study design: This is a global, multicenter, open-label, study designed to evaluate the long-term safety and tolerability of faricimab 6 mg administered by intravitreal injection at a PTI to patients who enrolled in and completed one of the Phase III studies (GR40349 or GR40398), also referred to as the parent studies.
Study populations: Patients with DME will be enrolled upon completion of the end-of-study visit in the parent study (i.e., Week 100 visit in studies (GR40349 or GR40398). All assessments from the parent study end-of-study visit must be completed prior to the LTE study enrollment visit assessments. A total of 1479 patients were enrolled in this extension study after completion of the parent studies. Last patient in occurred on 15 September 2021.
Milestones: FPFV: 5 August 2020 Database lock planned December 2023. Final Clinical Study Report planned Q4 2024.

DME=diabetic macular edema; FPFV=first patient first visit; GR40349=YOSEMITE; GR40398=RHINE; LPLV=last patient last visit; LTE=long-term extension; PTI=personalized treatment interval.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

See Table 27.

Table 27 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 GR42691 (AVONELLE-X): A multicenter, open-label extension study to evaluate the long-term safety and tolerability of faricimab in patients with nAMD.	The objective of this study is to evaluate the long-term safety and tolerability of the intravitreal faricimab in patients with nAMD, who have completed either of the Phase III (GR40306 or GR40844) studies. The primary objective is to monitor patients who have received at least one injection of faricimab during the LTE, regardless of adherence to treatment or to the protocol, on the basis of the following endpoints: • Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events	Long-term safety ATE and CNS hemorrhagic events	FPFV	19 April 2021
			Database Lock	Planned April 2024
			Final Clinical Study Report	Planned Q1 2025

Table 27 Ongoing and Planned Additional Pharmacovigilance Activities (cont.)

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 3 (cont.)				
Study GR41987 (RHONE-X): A multicenter, open-label extension study to evaluate the long-term safety and tolerability of faricimab in patients with DME.	The objective of this study is to evaluate the long-term safety, tolerability and efficacy of intravitreal faricimab in patients with DME who have completed either of the Phase III (GR40349 or GR40398) studies. The primary objective is to monitor patients who have received at least one injection of faricimab during the LTE, regardless of adherence to treatment or to the protocol, on the basis of the following endpoints: • Incidence and severity of ocular adverse events • Incidence and severity of non-ocular adverse events.	Long-term safety ATE and CNS hemorrhagic events	FPFV	5 August 2020
			Database Lock	Planned December 2023
			Final Clinical Study Report	Planned Q4 2024

ATE=arterial thromboembolic events; CHMP=Committee for Medicinal Products for Human Use; CNS=central nervous system; DME=diabetic macular edema; FPFV=first patient first visit; HCP=health care provider; GR40306=TENAYA; GR40349=YOSEMITE; GR40398=RHINE; GR40844=LUCERNE; LTE=long-term extension; nAMD=neovascular age-related macular degeneration; NCA=National Competent Authority; PRAC=Pharmacovigilance Risk Assessment Committee; PTI=personalized treatment interval; TBD=to be determined.

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 28 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.
Arterial thromboembolic events and Central Nervous System hemorrhagic events	**Routine risk communication:** • SmPC Section 4.4 • PIL Section 2 **Routine risk-minimization activities recommending specific clinical measures to address the risk:**

Table 28 Description of Routine Risk-Minimization Measures by Safety Concern

Safety Concern	Routine Risk-Minimization Activities
	None **Other risk minimization measures beyond the Product Information:** None **Medicine's Legal Status:** Vabysmo is a prescription only medicine.
Long-term safety	**Routine risk minimization measures:** None **Other risk minimization measures beyond the Product Information:** None
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 29 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 and DME, and 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.

Removal of Additional Risk-Minimization Activities

Not applicable.

V.3 Summary of Risk Minimization Measures

Table 30 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

Table 28 Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern (cont.)

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:** None
Arterial thromboembolic events and Central Nervous System hemorrhagic events	**Routine risk minimization measures:** • SmPC Section 4.4 • PIL Section 2 • Vabysmo is a prescription only medicine. **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:** Ongoing long-term extension studies: AVONELLE-X (GR42691) RHONE-X (GR41987)

Table 28 Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern (cont.)

Long-term safety	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Ongoing long-term extension studies: AVONELLE-X (GR42691) RHONE-X (GR41987)
Use in pregnancy	**Routine risk minimization measures:** • SmPC Section 4.6 • PIL Section 2 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Roche standard pregnancy follow-up 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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List of Referenced Studies

Final Clinical Study Report – GR40349 (YOSEMITE): A Phase III, Multicenter, Randomized, Double-Masked, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of Faricimab (RO6867461) in Patients with Diabetic Macular Edema. Report No. 1111791. January 2022.

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

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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) and visual impairment due to diabetic macular oedema (DME) (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.

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., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Infectious endophthalmitis Intraocular inflammation
Important potential risks	Arterial thromboembolic events and Central Nervous System hemorrhagic events
Missing information	Long-term safety 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 Phase III studies (GR40306 TENAYA, GR40844 LUCERNE, GR40349 YOSEMITE, and GR40398 RHINE) and the Phase II studies (BP29647 AVENUE, CR39521 STAIRWAY, and BP30099 BOULEVARD).
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 Phase III studies (GR40306 TENAYA, GR40844 LUCERNE, GR40349 YOSEMITE, and GR40398 RHINE) and the Phase II studies (BP29647 AVENUE, CR39521 STAIRWAY, and BP30099 BOULEVARD).
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:** None

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

Important Potential Risk: ATE and CNS hemorrhagic events	
Evidence for linking the risk to the medicine	This important potential risk is based on data from the faricimab safety population from the Phase III studies (GR40306 TENAYA, GR40844 LUCERNE, GR40349 YOSEMITE, and GR40398 RHINE) and the Phase II studies (BP29647 AVENUE, CR39521 STAIRWAY, and BP30099 BOULEVARD).
Risk factors and risk groups	Patients with hypertension, hyperlipidemia, arrhythmias, and those with a previous history of myocardial infarction and cerebral vascular accidents are at an increased risk of ATE events. Older age and underlying diabetes mellitus are also risk factors.
Risk-minimization measures	**Routine risk minimization measures:** Routine risk communication is described in: • SmPC Section 4.4 • PIL Section 2 **Routine risk-minimization activities recommending specific clinical measures to address the risk:** None **Medicine's Legal Status** Vabysmo is a prescription only medicine. **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:** Ongoing long-term extension studies: GR42691 (AVONELLE-X) GR41987 (RHONE-X)

ATE=Arterial thromboembolic events; CNS=Central Nervous System; PBRER=Periodic Benefit-Risk Evaluation Report; PIL=Patient Information Leaflet; PSUR=Periodic Safety Update Report; SmPC=Summary of Product Characteristics.

Missing Information: Long-term Safety	
Risk-minimization measures	**Routine risk minimization measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Ongoing long-term extension studies: GR42691 (AVONELLE-X) GR41987 (RHONE-X)

Missing Information: Use in Pregnancy	
Risk-minimization measures	**Routine risk minimization measures:** Routine risk communication is described in: • SmPC Section 4.6 • PIL Section 2 **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Roche standard pregnancy follow-up 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 are two studies in the post-authorization development plan for Vabysmo:

1. Study short name: Study GR42691 (AVONELLE-X)

Purpose of the study: To evaluate the long-term safety and tolerability of the intravitreal Vabysmo (6 mg) in patients with nAMD.

2. Study short name: Study GR41987 (RHONE-X):

   Purpose of the study: To evaluate the long-term safety and tolerability of the intravitreal Vabysmo (6 mg) in patients with DME.

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:	
Site No:	
Patient ID/Initials:	
Patient Gender:	❑ M ❑ F

Local Case ID:	
Patient Date of Birth (dd-MMM-yyyy):	

Intraocular inflammation and/or Endophthalmitis have been observed in some patients treated with Vabysmo (faricimab).

By filling in this questionnaire, you will help us to understand more fully the risk factors for this condition.

Patient Details:				
Country of Incidence	Age at time of the event	Height (cm)	Weight (kg)	Ethnic Origin or Race

Drug therapy details – Vabysmo	
Product:	**Vabysmo**
Indication:	
In which eye was treatment administered?	☐ Right eye ☐ Left eye ☐ Both eyes
Date(s) started (dd-MMM-yyyy):	
Date(s) stopped (dd-MMM-yyyy) / ongoing:	
Treatment regimen/frequency:	
Batch/Lot No. of last dose before AE onset	
Drug therapy details - Fellow Eye Treatment	
Product:	
Date(s) started (dd-MMM-yyyy):	
Date(s) stopped (dd-MMM-yyyy) / ongoing:	
AE suspected to be caused by Fellow Eye treatment?	☐ Yes ☐ No ☐ N/A

Drug therapy details -- Any other suspect drug associated with adverse event						
Drug	**Indication**	**Date(s) started (dd-MMM-yyyy)**	**Date(s) stopped/ongoing (dd-MMM-yyyy):**	**Route of administration**	**If Ocular, specify which eye**	**Dose/regimen**

Description of the event:

Onset date of event (dd/MMM/yyyy): ____/_____/_____
Date of Recovery (dd/MMM/yyyy): ____/_____/_____ (If, final outcome resolved)
Date of last Vabysmo injection (dd/MMM/yyyy): ____/_____/_____
Total number of Vabysmo injections received prior to event: _____

Please check adverse event that applies and provide the relevant information:
(Please provide appropriate assessment details in the Assessment and clinical examination Section)

☐ **Endophthalmitis** Event occurred in: ☐ Right eye ☐ Left eye ☐ Both eyes

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?) ☐ No ☐ Unknown :
_____

Is patient immunocompromised? ☐ Yes (If yes, when? 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

Was there any intervention required? If so, please specify:_____

Please provide a description of the event including clinical findings, management and outcome:
_____
_____
Other relevant information:
_____
_____

☐ **Intraocular inflammation** Event occurred in: ☐ Right eye ☐ Left eye ☐ Both eyes

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

Iritis	Iridocyclitis	Anterior uveitis	Vitritis	Intermediate Uveitis	Retinitis	Chorioretinitis	Posterior Uveitis	Panuveitis	Retinal 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)

_____

Systemic condition(s) known to be associated with uveitis? (e.g. infections, autoimmune diseases, HLAB27 or other known genetic predisposition)?

☐ Yes (If yes, when? 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

Was there any intervention required? If so, please specify:_____

_____

Please provide a description of the event including clinical findings, management and outcome:

_____

_____

Other relevant information:

_____

_____

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	

***If treatment was required for event, please specify:**

Treatment	**Select (if Given)**	**Route**	**Drug name**
Steroid	☐	☐ IVT, ☐ Topical, ☐ Oral	
Antibiotic	☐	☐ IVT, ☐ Topical, ☐ Oral	
Other therapy	☐	☐ IVT, ☐ Topical, ☐ Oral	
Other therapy	☐	☐ IVT, ☐ Topical, ☐ Oral	
Surgical vitrectomy	☐		

Do any of the following criteria apply as a consequence of the event?		**What is the final outcome?**
☐ **Life-threatening at the time the event(s) occurred** (Any adverse event where the patient was at immediate risk of death at the time the adverse event occurred)	☐ **Resulted in Death** Cause of Death: _____ Date of death:____/_____/_____ (dd/MMM/yyyy)	☐ Complete recovery ☐ Recovered with sequelae ☐ Condition improving ☐ Condition unchanged
Persistence of significant disability or incapacity (A substantial disruption of a person's	☐ **Involved or prolonged inpatient hospitalization**	

ability to conduct normal life functions, resulting in significant, persistent or permanent change, impairment, damage or disruptions in the patient's body function, physical activities and/or quality of life)	Date of admission:____/_____/_____ (dd/MMM/yyyy) Date of discharge: ____/_____/_____ (dd/MMM/yyyy)	☐ Condition deteriorating ☐ Fatal ☐ Outcome unknown
☐ **Congenital anomaly or birth defect** Provide details:	☐ **Medically significant** (An adverse event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other serious outcomes)	
☐ **None of the above**		

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			☐
Ophthalmic examination: Slit lamp, Indirect ophthalmoscope			☐
IOP measurement			☐
OCT			☐
Fluorescein angiography			☐
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: (e.g PCR test, Syphilis test, HLA-B27, X-ray/CT findings)			

Concurrent/previous medication to the adverse event:

Drug name	**Indication for use**	**Date(s) started (dd-MMM-yyyy)**	**Date(s) stopped/ongoing (dd-MMM-yyyy):**	**Route of administration**	**If Ocular, specify which eye**	**Dose/regimen**

Completed by:

Name: ..... Position: .....

Signature: ..... Date: .....

E-mail: .....

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES

Draft Key Messages of the Additional Risk-Minimization Measures

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) and diabetic macular edema (DME)
- 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.