EU RISK MANAGEMENT PLAN (RMP)

Eylea®

BAY 86-5321
(Aflibercept)

No. 35.1

Date of Report:
23 APR 2024

[redacted]

EU Risk Management Plan for Eylea® (aflibercept)

RMP version to be assessed as part of this application:

RMP Version number: 35.1

Data lock point for this RMP: 23 APR 2024

Date of final sign off: 23 APR 2024

Other RMP versions under evaluation: EU RMP V34.1: EMEA/H/C/002392/II/0090 (96 week data of PULSAR/PHOTON study, 8mg Aflibercept)

Rationale for submitting an updated RMP:

EU RMP V35.1:

- The new application format Eylea 114.3 mg/mL (8mg dose) pre-filled syringe (PFS) was integrated into this EU RMP.
- Removal of the post-authorization measure (PAM) that required the submission of annual safety reports on IOP increase and the 40 mg/ml (2mg dose) Eylea PFS (deletion from Part III.1.2). The deletion was based on the PRAC assessment of the 2nd annual safety report, Procedure Number EMEA/H/C/002392/MEA/021.1. As per PRAC the PAM is completed, and no other regulatory actions are required. The commitment was requested to be removed from the EU RMP.

Updated parts:

- Part I: 8mg PFS format and content added
- Part II, SVII Identified and potential Risks: PFS format added as applicable for Eylea 114.3. mg/mL
- Part III, Pharmacovigilance Plan
    - Section III.1.1 updated
    - Section III.1.2: Other Forms of Routine Pharmacovigilance Activities for safety concerns: post-authorization measure (annual safety report for IOP increase with 2mg PFS) deleted based on PRAC recommendation
- Part V: Risk Minimisation Meausure
    - Section V.2 Additional Risk Minimisation Measures, V2.1 Educational Program: 8mg PFS format added
    - Section V.3: post-authorization measure (annual safety report for IOP increase with 2mg PFS) deleted based on PRAC recommendation
- PART VI: Summary of Activities in the Risk Management Plan by Product: 8mg PFS format added
- Annex 6 – Key Messages of Educational Material: 8mg PFS format added
- Annex 8 updated to reflect changes made to this RMP version

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EU RMP V34.1:

Week 96 data of the pivotal PULSAR (indication nAMD) and PHOTON (indication: DME) studies were integrated into this RMP version.

Summary of significant changes in this RMP were:

- Part I: Updated to present summary of significant changes compared to last approved EU RMP 33.4.
- Part II SI: Not updated.
- Part II SII: Not updated.
- Part II SIII: Not updated.
- Part II SIV: Not updated.
- Part II SV: Not updated.
- Part II SVI: Not updated.
- Part II SVII: Updated with pooled week 96 data of the PULSAR/PHOTON, and CANDELA week 44 data
- Part II SVIII: Not updated.
- Part III: Not updated.
- Part IV: Not updated.
- Part V: Not updated.
- Part VI: Not updated.
- Part VII:
    - Annex 1: Not updated.
    - Annex 2: Not updated.
    - Annex 3: Not updated.
    - Annex 4: Updated questionnaires added:
        - intraocular inflammation/endophthalmitis
        - intraocular pressure increase with PFS
    - Annex 5: Not Updated.
    - Annex 6: Not updated.
    - Annex 7: Not updated.
    - Annex 8: Updated

Details of the currently approved RMP:

Version number: 33.4

Approved with procedure: EMEA/H/C/002392/X/0084/G

Date of approval (opinion date): 09 NOV 2023

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QPPV signature:

EU QPPV name	Dr. Jutta Pospisil

Electronic QPPV signature is attached at the end of the document.

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List of abbreviations

%	Percent
<	Less than
≤	Less than or equal to
≥	Greater than or equal to
AE	Adverse Event
AMD	Age-Related Macular Degeneration
AMD-PCV	Polypoidal Choroidal Vasculopathy, subtype of AMD
anti-VEGF	anti-Vascular Endothelial Growth Factor
APTC	Anti-Platelet Trialists Collaboration
ATE	Arterial Thromboembolic Events
AUC	Area Under the Concentration Time Curve
BCVA	Best Corrected Visual Acuity
BPD	Bronchopulmonary Dysplasia
BRAO	Branch Retinal Artery Occlusion
BRVO	Branch Retinal Vein Occlusion
BW	Birth Weight
C_{max}	Maximum Plasma Concentration
CA	Competent Authority
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLD	Chronic Lung Disease
CNV	Choroidal Neovascularization
CRAO	Central Retinal Artery Occlusion
CRT	Central Retinal Thickness
CRVO	Central Retinal Vein Occlusion

CSR	Clinical Study Report
DLP	Data Lock Point
DME	Diabetic Macular Edema
DNA	Deoxyribonucleic Acid
DRSS	Diabetic Retinopathy Severity Scale
DS	Domestic Sales
ECG	Electrocardiogram
EEA	European Economic Area
EEG	Electroencephalography
EM	Educational Material
EMA	European Medicine Agency
EPAR	European Public Assessment Report
ERT	Excess Retinal Thickness
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EudraCT	European Union Drug Regulation Clinical Trials
EURETINA	European Society of Retina Specialists
EV	Expected Value
FA	Fluorescein Angiography
FDA	Food and Drug Administration
FIREFLEYE	Study 20090 - aFlIbeRcEpt For ROP - IVT injection versus Laser thErapY(E) study
GA	Gestational Age
GVP	Good Pharmacovigilance Practices
GW	Gestational Week
g	gram

HCP	Health Care Professional
HD	High Dose (8 mg Aflibercept)
HGC	Human chorionic gonadotropin
IAI	Intravitreal Aflibercept Injection
ICH	International Conference on Harmonization
ID	Identifier
incl.	Including or Inclusive
INN	International Non-proprietary Names
IOI	Intraocular inflammation
IOP	Intraocular Pressure
ISS	Investigator Sponsored Studies
IVT	Intravitreal
LOCF	Last-Observation-Carried-Forward
LLOQ	Lower Limit of Quantification
LOAEL	Lowest Observed Adverse Effect Level
LPLV	Last Patient Last Visit
MAH	Marketing Authorization Holder
mg	miligram
mL	MiliLitre
mCNV	Myopic Choroidal Neovascularization
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
nAMD	Neovascular Age-Related Macular Degeneration
NICU	Neonatal Intensive Care Unit
NIS	Non-Interventional Study
NMR	Neonatal Mortality Rate

NPDR	Non-proliferative Diabetic Retinopathy
NSAID	Non-steroidal Anti-Inflammatory Drugs
OS	Observational Studies
PAES	Post-Authorisation Efficacy Study
PASS	Post-authorization Safety Study
PCV	Polypoidal Choroidal Vasculopathy
PD	Pharmacodynamics
PDA	Patent Ductus Arteriosus
PED	Pigment Epithelium Detachment
PFS	Pre-filled Syringe
PICLEO	Brand name of paediatric dosing device
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PlGF	Placental Growth Factor
PMA	Post-Menstrual Age
PRAC	Pharmacovigilance Risk Assessment Committee
PRN	Pro Re Nata (as needed)
PT	Preferred Term
PV/PhV	Pharmacovigilance
QoL	Quality of Life
QPPV	Qualified Person for Pharmacovigilance
RM	Risk Management
RMP	Risk Management Plan
ROP	Retinopathy of Prematurity
RPE	Retinal Pigment Epithelium
RVO	Retinal Vein Occlusion

SAE	Serious Adverse Event
SAF	Safety Analysis Set
s.c.	Subcutaneous
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	Standard of Care
STD	Standard Deviation
TEAE	Treatment-Emergent Adverse Event
TESAEs	Treatment-Emergent Serious Adverse Event
TIA	Transient Ischemic Attack
TC	Traumatic Cataract
UK	United Kingdom
USA/US	United States of America/United States
VA	Visual Acuity
VEGF	Vascular endothelial growth factor

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Part I: Product(s) Overview

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Table Part I.1 – Product(s) Overview

Active substance (INN or common name):	Aflibercept
Pharmaco-therapeutic group (ATC Code):	S01LA05
Marketing Authorisation Holder:	Bayer AG
Medicinal products to which this RMP refers:	2
Invented name in the European Economic Area (EEA)	Eylea® 40 mg/mL Eylea® 114.3 mg/mL
Marketing authorisation procedure:	Centralised
Brief description of the product	Chemical class: Aflibercept is a recombinant fusion protein consisting of portions of human VEGF (Vascular Endothelial Growth Factor) receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1. Aflibercept is a specific blocker that binds and inactivates vascular endothelial growth factor (VEGF) and the related molecule, placental growth factor (PlGF). Summary of mode of action: It is designed to interfere with the increase in vascular permeability and growth of pathological new blood vessels that lead to retinal oedema, ischemia and haemorrhage in diseases accompanied by ocular neovascularization. Important information about its composition: Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.
Hyperlink to the Product Information	Eylea 40 mg/mL (0.4/2 mg doses) and Eylea 114.3 mg/mL (8 mg dose) Please refer to European Medicine Agency (EMA) website: https://www.ema.europa.eu/en/medicines/human/EPAR/eylea

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Table Part I.1 – Product(s) Overview

Indication(s) in the EEA	Current:Eylea 40 mg/mL (2 mg dose) is indicated for adults for the treatment of: • Neovascular (wet) age-related macular degeneration (AMD). • Visual impairment due to macular edema secondary to retinal vein occlusion (branch RVO or central RVO). • Visual impairment due to diabetic macular edema (DME). • Visual impairment due to myopic choroidal neovascularisation (myopic CNV). Eylea 40 mg/mL (0.4 mg dose) is indicated in preterm infants for the treatment of: • Retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease Eylea 114.3 mg/mL (8 mg dose) is indicated for adults for the treatment of: • Neovascular (wet) age-related macular degeneration (AMD). • Visual impairment due to diabetic macular edema (DME).
Dosage in the EEA	Current: adult patients – Eylea 40 mg/mL (2 mg dose): In adult patients, the injection volume of Eylea is 50 microlitres (µL) (equivalent to 2 mg aflibercept). Wet AMD The recommended dose for Eylea 40 mg/mL is 2 mg aflibercept, equivalent to 50 microlitres. Macular edema secondary to RVO The recommended dose for Eylea 40 mg/mL is 2 mg aflibercept, equivalent to 50 microlitres. Diabetic macular edema The recommended dose for Eylea 40 mg/mL is 2 mg aflibercept, equivalent to 50 microlitres. Myopic CNV The recommended dose for Eylea 40 mg/mL is 2 mg aflibercept, equivalent to 50 microlitres. Retinopathy of Prematurity: The recommended dose for Eylea 40 mg/mL is 0.4 mg aflibercept, equivalent to 10 microlitres. Current: adult patients – Eylea 114.3 mg/mL (8 mg dose): Wet AMD The recommended dose for Eylea 114.3 mg/mL is 8 mg aflibercept, equivalent to 70 microlitres. Diabetic macular edema The recommended dose for Eylea 114.3 mg/mL is 8 mg aflibercept, equivalent to 70 microlitres.

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Table Part I.1 – Product(s) Overview

Pharmaceutical form(s) and strengths	Currently approved Eylea 40 mg/mL (2 mg dose) 1) Solution for injection in a pre-filled syringe. One pre-filled syringe contains 3.6 mg aflibercept in 90 microlitres (40 mg/mL) in iso-osmotic solution. Delivers a single dose of 2 mg/0.05 mL. 2) Solution for injection in a vial. One vial contains 4 mg aflibercept in 100 microlitres (40 mg/mL) in iso-osmotic solution. Delivers a single dose of 2 mg/0.05 mL. ROP: Currently approved Eylea 40 mg/mL (0.4 mg dose) One pre-filled syringe contains an extractable volume of at least 0.09 mL, equivalent to at least 3.6 mg aflibercept. This provides a usable amount to deliver a single dose of 0.05 mL containing 2 mg aflibercept to adult patients or a single dose of 0.01 mL containing 0.4 mg aflibercept to preterm infants. For treatment of preterm infants with ROP, the paediatric dosing device PICLEO in combination with the Eylea pre-filled syringe is used for administration of a single dose of 0.4 mg aflibercept (equivalent to 0.01 mL solution for injection) Currently approved Eylea 114.3 mg/mL (8 mg dose) in adults: 1) Solution for injection in a vial. One vial contains 11.4 mg aflibercept in 100 microliters (114.3 mg/ml) in iso-osmotic solution. Delivers a single dose of 8 mg/0.07 mL. 2) Proposed: Solution for injection in a pre-filled syringe. One pre-filled syringe contains 21 mg aflibercept in 0.184 mL iso-osmotic solution (Eylea 114.3 mg/mL). Delivers a single dose of 8 mg/0.07 mL.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: Safety Specification

PART II: Module SI: Epidemiology of the Indications and Target Population(s)

SI.1 Indications

Eylea (brand name: Eylea® 40 mg/mL, 2 mg dose) is indicated for adults for the treatment of:

- Neovascular (wet) age-related macular degeneration (wet AMD),
- Visual impairment due to macular edema secondary to retinal vein occlusion (Retinal Vein Occlusion [RVO]; Branch RVO [BRVO] or Central RVO [CRVO]),
- Visual impairment due to diabetic macular edema (DME),
- Visual impairment due to myopic choroidal neovascularization (myopic Choroidal Neovascularization [CNV]).

In addition, Eylea (brand name: Eylea® 40 mg/mL, 0.4 mg dose) is indicated in preterm infants for the treatment of:

- Retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease.

Eylea (brand name: Eylea® 114.3 mg/mL, 8 mg dose) is indicated for adults for the treatment of:

- Neovascular (wet) age-related macular degeneration (wet AMD)
- Diabetic macular edema (DME)

These indications are described in this module in the following order: AMD, CRVO, BRVO, myopic CNV, DME, and ROP.

SI.2 Epidemiology of the disease

SI.2.1 Wet age-related macular degeneration (wet AMD)

Characteristics of target indication

Age-related macular degeneration (AMD) is a medical condition which usually affects older adults and results in a loss of vision in the centre of the visual field (the macula) because of damage to the retina. It is a leading cause of severe central visual loss in older people (1, 2). With increased life expectancy, the proportion of people over 65 years of age is expected to double by 2030 (1) and the prevalence and burden of AMD is, therefore, expected to increase.

The stages of AMD are categorized as early, in which visual symptoms are inconspicuous, and late, in which severe loss of vision is usual. Late AMD has "dry" and "wet" forms (3). It is the advanced stages of each of these which are responsible for severe vision loss. Dry AMD may eventually lead to a more severe form called “geographic atrophy” (GA), which is characterized by deposits known as drusen and by atrophy of the photoreceptors in the macula. The first sign of wet or neovascular (exudative) AMD (in the following referred to as wet AMD) is serous or haemorrhagic fluid that causes the neuroretina to detach from Bruch's membrane. The fluid originates from a subretinal neovascular membrane. The detachment

disturbs the fine arrangement of the photoreceptors and causes image distortion and vision loss (3, 4).

Incidence of target indication

A population-based study in Wisconsin, United States (US), the Beaver Dam Eye Study (5), reported a 15-year cumulative incidence for advanced wet AMD of 2.0%. The risk increased with age: in persons aged 43 to 54 years the 15-year cumulative incidence was 0.4% and rose to 2.9% for individuals aged 75 to 86 years.

A 5% sample of US Medicare medical claims data from the Standard Analytical File (n = 1,041,009) was used to develop a longitudinal study cohort by the Wilmer Ophthalmological Institute investigators. The 3-year (1995-1998) incidence of wet AMD ranged between 0.37% (95% confidence interval [CI], 0.35-0.38) and 1.14% (95% CI, 1.12-1.16) depending on the ascertained criteria chosen (6).

A population-based study, the Los Angeles Latino Eye Study (7), reported a 4-year incidence of early AMD of 7.5% and advanced AMD of 0.2%. The overall 4-year progression of any AMD in either eye was 9.2% (95% confidence interval [CI]: 8.3, 10.1). Increasing age was associated with higher rates of progression (test of trend, $p < 0.0001$), ranging from 6.2% in people aged 40 to 49 years at baseline to 21.7% in those over 80 years of age. Age-specific incidence and progression of AMD in Latinos were lower than in non-Hispanic whites.

In the Netherlands the estimated yearly AMD incidence was 0.1% (8).

In Germany approximately 300,000 new cases of AMD are diagnosed each year, generating a yearly incidence of 0.4% (9).

A Nigerian study to determine the incidence of age-related macular degeneration in Nigerian people 50 years of age and older showed that the incidence of AMD between 1997 and 2004 was 3.2% (256 out of 7,966 patients) (10).

Prevalence of target indication

The overall prevalence of wet AMD and/or geographic atrophy (advanced dry AMD) in the US population among people 40 years and older is estimated to be 1.47% (95% CI, 1.38% to 1.55%), with 1.75 million citizens having AMD.

In the Baltimore Eye Survey (11) among people 40 years of age and older, the prevalence of wet AMD was 0.61% in whites and 0.11% in blacks. When directly adjusting for age (minimum variance method), the rate among whites was 1.82%.

In a Medicare study (12) among people 65 years of age and older, the prevalence of wet AMD was 2.2% (2.3% in women [65% of wet AMD population] versus 1.7% in men and 2.3% in whites versus 1.2% in blacks; $p < 0.01$ for both gender and race differences).

In Europe (the EUREYE study), the prevalence of any AMD or wet AMD in either eye was reported as 3.32% and 2.29%, respectively. The corresponding percentages for AMD and wet AMD were reported in men versus women as follows: ages 65-69 years, 0.90% *vs.* 1.03%, 0.38% *vs.* 0.92%, ages 70-74 years, 1.97% *vs.* 2.36%, 1.40% *vs.* 1.42%, ages 75-79 years, 4.07% *vs.* 3.15%, 2.63% *vs.* 2.17%, ages 80 and older, 6.94% *vs.* 15.00%, 5.56% *vs.* 10.50%, and in ages 65 and older, 2.49% *vs.* 4.00%, 1.69% *vs.* 2.78% (13).

In Germany, about 1 to 4.5 million people are affected by AMD in a population of about 80 million people (1.25%-5.6%) (9).

The prevalence of AMD increases dramatically with age, with more than 15% of the white women older than 80 years having wet AMD and/or geographic atrophy. More than 7 million individuals have drusen measuring 125 µm or larger and are, therefore, at substantial risk of developing AMD. Owing to the rapidly aging population, the number of persons having AMD is likely to increase by 50% to 2.95 million in 2020.

Age-related macular degeneration (AMD) is more prevalent among white than among black persons (14). A systematic review and meta-analysis by Kawasaki *et al.* showed that among Asians 40 to 79 years of age, the age-specific prevalence of late AMD was comparable with that reported from white populations, but early AMD signs were less common among Asians (15).

Mortality in target indication

A 2005 report from the Age-Related Eye Disease Study (AREDS) (16) showed that during a median follow-up of 6.5 years, 534 of 4,753 participants (11%) died. Participants with advanced AMD had increased mortality compared to participants with few, if any, drusen (relative risk [RR] 1.41; 95% CI 1.08 to 1.86). Advanced AMD was significantly associated with cardiovascular deaths (RR 1.92; 95% CI 1.18 to 3.12).

Potential health risk

The neovascular form of AMD is responsible for severe vision loss associated with the disease in 90% of the cases (4, 17, 18). As demonstrated in several studies (19, 20) this condition has serious implications on quality of life and is associated with increased risk of falls and depression. Wet AMD patients also reported that the need for assistance with daily activities was more than 10 times greater compared to controls (26.5% *vs.* 2.2%; $p < 0.0001$) and the prevalence of falls was 3 times that of the control group (13.3% *vs.*4.3%; $p = 0.031$). Similar results were reported in Canada (20), and in a multicentre European study (18). In a 12-month prospective study in Vancouver (21), Canada community-dwelling women aged ≥70 years with wet AMD (n = 114) had a significantly greater number of falls and almost twice the risk of injurious falls compared to women of the same age from that community without the condition who had recent normal eye exam (n = 132). A mean of 0.37 injurious falls per person-year were experienced among wet AMD participants, compared to 0.16 injurious falls per person-year among non-wet AMD participants ($p = 0.006$). The age-adjusted incidence rate for injurious falls, for individuals with wet AMD was 1.77 (95% CI 1.07 to 3.02) times higher than in those without the condition.

In a Nigerian study to determine ocular morbidity associated with age-related macular degeneration in the Nigerian population (N = 256), 34 patients (13.3%) were bilaterally blind and 130 (50.8%) had bilateral visual impairment. Of the blind patients 13 (38.3%) had wet AMD and 6 (17.7%) had geographic atrophy. The authors concluded that AMD was the cause of blindness in 7.4% of the patient population (10).

Demographic profile of target population

The target population as studied by some investigators is subjects 40 years of age and older with rates of disease increasing with increasing age (5, 22, 23).

Ethnic variations have been described suggesting a higher prevalence among whites (24). Age-related macular degeneration is also more prevalent in older women compared to older men (5, 25).

On average, people with AMD are more likely to be elderly white women with hypertension, diabetes, or history of MI compared to people without the condition (12). In the large non-interventional study (NIS) OCEAN, in which patients treated with ranibizumab in a real-world setting are being observed in Germany (N = 5,606 overall), the cohort of subjects with wet AMD (n = 3,614) had a mean age of 77.9 ± 8.2 years, 61.2% were females, 22.3% had a medical history of arterial hypertension, 5.5% of MI, 4.0% of stroke or apoplexy, and 0.1% of transient ischemic attack (TIA) (26). A similar demographic structure was found in a retrospective, comparative, non-randomized cohort study based on patients' real-world data from electronic medical record databases in Australia and the United Kingdom (UK). The mean age in the Australian (N = 570) and UK cohort (N = 2,755) was 78.5 ± 6.8 and 78.0 ± 8.1 years, respectively, and 57.8% and 63.7%, respectively, were women (27).

SI.2.2 Central retinal vein occlusion (CRVO)

Characteristics of target indication

Abruptly decreased vision and a "blood and thunder" retina are classic signs of CRVO, a retinal vascular disease first described by Leibreich in 1855 and Michel in 1878. Dilated tortuous retinal veins, optic disc hyperaemia and oedema, 360-degree intraretinal haemorrhages, and often massive central oedema lead to an abrupt decrease in visual acuity (28).

Central retinal vein occlusion (CRVO) is an important cause of moderate to severe visual loss in older persons (29) and a serious risk factor for macular edema in CRVO (30). The pathogenesis of macular edema in CRVO remains uncertain but is likely multifactorial (31). Thrombosis of the central retinal vein results in venous stasis, leading to disc swelling, diffuse nerve fibre layer and pre-retinal haemorrhage, macular edema and cotton wool spots. There are two types of CRVO: non-ischemic and ischemic. The former has a better prognosis than the latter, which is often complicated by iris neovascularization and neovascular glaucoma. Usually CRVO occurs in the elderly with a peak of incidence in the sixth to seventh decade and is frequently associated with systemic vascular conditions including atherosclerosis, diabetes, and hypertension (31, 32).

Results of a small study (n = 30) by Turello *et al.* 2010 (33) showed that 84.2% of patients over 50 years and 90.9% of patients under 50 years with CRVO were found to have one or more haemostasis-related risk factors. Other small studies could not consistently confirm an important role of impaired haemostasis as a major systemic risk factor for RVO (34, 35). However, in patients without acquired risk factors, screening analyses for thrombophilia were recommended (36). To date, classic systemic risk factors that are commonly considered to be the cause of retinal vein occlusion (RVO, central and branch) are: smoking, diabetes mellitus and arterial hypertension.

A longitudinal study aimed to identify risk factors associated with CRVO among 1,302 managed care enrollees (from 2001 to 2009) ≥55 years of age. Cox regression analysis was used to determine the hazard of CRVO. After adjustment for known confounders, blacks had a 58% increased risk of CRVO compared with whites (HR, 1.58; 95% CI, 1.25–1.99), and women had a 25% decreased risk of CRVO compared with men (HR, 0.75; 95% CI, 0.66– 0.85) (37).

In a population-based, cross-sectional study to evaluate the prevalence and associated factors of retinal vein occlusion in the Korean National Health and Nutritional Examination Survey

(2008-2012), the following risk factors were found to be significantly associated with any RVO (i.e., CRVO or BRVO) in multivariate logistic regression analyses after adjusting for all potential factors: advanced age (OR = 1.72, 95%-CI: [1.27; 2.34]), hypertension (OR = 2.56, 95%-CI: [1.31; 5.08]), history of stroke (OR = 2.08, 95%-CI: [1.01; 4.45]), and hyper-cholesterolemia (OR = 1.84, 95%-CI: [1.01; 3.35]) (38).

Incidence of target indication

Central retinal vein occlusion (CRVO) remains a common cause of unilateral visual loss (39). After diabetic retinopathy, retinal vein occlusions, both branch and central, are the second most common cause of visual loss from retinal vascular disorders (40).

Based on the 2008 world population, and on the prevalence rates ranging from 0.1% to 0.5% of the middle aged to older groups (32), (41), it was estimated, that 2.5 million adults were affected by CRVO worldwide (42).

In the Wisconsin Beaver Dam Eye Study in the US (4,926 residents, 43 to 84 years of age at baseline from 1990 to 1995), the 5-year cumulative incidence of CRVO was 0.2% (32) and the 15-year cumulative incidences was 0.5% (43). The incidence increased with age affecting 1.3% of those aged 65 to 74 years or older at Baseline (43).

In Australia, the 10-year cumulative incidence reported by the Blue Mountain Eye Study (44), 3,654 Australian residents 49 years of age and older from 1992 to 2004) for CRVO was 0.4%, which is similar to the cumulative incidence reported in the Beaver Dam Eye Study.

Based on the before-mentioned 2 studies, Petrella *et.al.* estimated the incidence of CRVO to be 0.04%/year in adults aged ≥45 years in Caucasian populations (45).

The 9-year cumulative incidence (1998-2007) of CRVO in a Japanese population was 0.3% and it significantly increased with increasing age (46).

Prevalence of target indication

In the combined populations of the Atherosclerosis Risk in Communities Study (n = 12,642; mean age, 60 years) and the Cardiovascular Health Study (n = 2,824; mean age, 79 years), the prevalence of retinal vein occlusion was 0.3% (n = 39) (47).

Combined individual-level data from 15 major population-based studies around the world estimated the prevalence of CRVO. Overall, the authors collated data for 68,751 participants from 15 studies from the US, Europe, Asia, and Australia. Of these participants, 43.7% were male, 48.4% were white, 27.1% were Asian, 17.2% were Hispanic, and 7.2% were black. The age- and sex-standardized prevalence (per 1,000 persons) was 0.65 in the pooled analysis. The standardized prevalence rates for CRVO in individual studies varied from 0.04 per 1,000 in the Cardiovascular Health Study (CHS) to 1.59 per 1,000 in the Blue Mountains Eye Study (42).

A longitudinal study aimed at determining the incidence of CRVO among managed-care enrollees (from 2001 to 2009) ≥55 years of age. Of 494,165 enrollees, 1,302 (0.26%) were diagnosed with CRVO over 5.4 ± 1.8 years (37).

In the Hisayama study (N = 1,775) of Japanese people 40 years of age and older, the prevalence of CRVO was 2 per 1,000 people (48).

In a population-based, cross-sectional study to evaluate the prevalence and associated factors of retinal vein occlusion in the Korean National Health and Nutritional Examination Survey

(2008–2012), the crude prevalence (expressed as weighted estimate in %) of CRVO among the 25,765 evaluable participants with ophthalmic examination was <0.1% (38).

Mortality in target indication

In some clinical studies, overall mortality and cardiovascular mortality in CRVO patients have been reported to be similar to patients from the general US population without the condition (49, 50). A pooled data analysis from two US population-based cohort studies, the Beaver Dam Eye and the Blue Mountains Eye Study, evaluated cardiovascular and cerebrovascular mortality in patients with and without RVO (central or branch) (51). After adjusting for age, gender, body mass index, hypertension, diabetes, smoking, glaucoma, and study site, RVO was not associated with cardiovascular-related mortality (Hazard ratio [HR] 1.2, 95% CI 0.8 to 1.8) or cerebrovascular-related mortality (HR 0.9, 95% CI 0.4 to 2.1) among participants of all ages. However, in persons under 70 years of age, baseline RVO was associated with higher cardiovascular mortality (HR 2.5; 95% CI 1.2–5.2).

Potential health risk

Central retinal vein occlusion (CRVO) may lead to moderate to severe vision loss (32) and with it to reduced quality of life and risks of injuries. A study which utilized the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) found that patients with CRVO had a clinically relevant decrease in their vision-related quality of life as they scored significantly lower than patients without ocular disease (52). Responses correlated most strongly with visual acuity in the better-seeing eye, the number of systemic medical conditions and patients' opinions about their general health.

Demographic profile of target population

CRVO frequency is commonly similar in men and women and occurs for the most part in persons over the age of 65 years (32, 42).

In the large NIS OCEAN, in which patients treated with ranibizumab in a real-world setting are being observed in Germany (N = 5,606 overall), the cohort of subjects with CRVO (n = 121) had a mean age of 70.3 ± 11.5 years, and 52.9% of CRVO subjects were females (26).

The findings from the Hisayama study (48) suggest that the prevalence of RVO (central and branch) is higher in Japanese than in other Asians or Caucasians.

SI.2.3 Branch retinal vein occlusion (BRVO)

Characteristics of target indication

Branch retinal vein occlusion (BRVO) is a venous occlusion that can occur in any of the branches of the central retinal vein and is considered to be the most common form of retinal vein occlusions (RVOs) (53). In BRVO, abnormal arteriovenous crossing with vein compression, degenerative changes of the vessel wall and abnormal haematological factors constitute the primary mechanism of vessel occlusion. The first case of BRVO was described by Leber in 1877 (54). BRVO is classified according to its anatomical location either as major, when one of the major branch veins draining one of the retinal quadrants is involved, or as macular, when a small venous vessel draining a specific sector of the macula is occluded (55). In the superotemporal quadrant the incidence of BRVO is higher as compared to the other quadrants. A tendency to a greater number of arteriovenous (AV) crossing at the site has been suggested to be causative (53). In 66% of eyes with BRVO, there is occlusion of the

major branch in the superotemporal quadrant followed by 22%–43% of eyes with occlusion of the major branch in the inferotemporal quadrant (56).

Generally, risk factors for BRVO are consistent with those identified for CRVO (see also section on CRVO above). Risk factors for BRVO are eyes with focal retinal arteriolar narrowing or glaucoma history, a history of smoking, migraine headaches, asthma and increase in systolic blood pressure (57), as well as, hyperlipidaemia, diabetes mellitus, thrombophilia, hypercoagulation, systemic vasculitis, and inflammatory diseases (53). Hypertension and atherosclerotic cardiovascular disease have been postulated to cause retinal arteriosclerotic changes, especially at the arteriovenous crossings, resulting in RVO through endothelial cell damage and thrombosis (58). Arteriosclerosis resulting in arteriolar insufficiency has been described as a possible underlying etiologic factor resulting in BRVO (57, 59).

Incidence of target indication

The Beaver Dam Eye study (Wisconsin United States of America [USA]) (57) was a population-based (age 43-86 years) study where BRVO and CRVO were detected (if present) at baseline in 1988-90 (n = 4,068) and at three 5-year follow-up examinations (ending in 2005), by grading 30°colour fundus photographs.

The 5-year incidence of BRVO in the Beaver Dam eye study was 0.6% (6/1,000). The incidence by age group was:

Age 43-54: 0.2% (2/1,000)

Age 55-64: 0.5% (5/1,000)

Age 65-74: 1.3% (13/1,000)

Age 75-86: 0.9% (9/1,000) (32).

The 15-year cumulative incidence of BRVO was 18 per 1,000 (1.8%, 95% CI, 1.4%-2.2%) and varied with age reaching the highest rates (2.9%) at ages 65-74 years. The frequencies were similar in men and women (age-adjusted frequencies, 1.5% *vs.* 2.1%, respectively, p = 0.55).

The 15 years incidence (accounting for competing risk of death) by age groups was:

Age 43-54: 1% (10/1,000)

Age 55-64: 1.5% (15/1,000)

Age 65-74: 2.9% (29/1,000)

Age 75-86: 2.3% (23/1,000) (57).

In right eyes as compared with left eyes, the overall 15-year cumulative incidence was similar (1.0% *vs*. 0.9%, respectively; p = 0.70) (57).

The Blue Mountain Eye Study (Australia) was a population-based cohort study of a suburban Australian population of ages 49 years and older at baseline (1992-94). The surviving baseline participants were invited to attend follow-up examinations after 5 years (1997-1999) and after 10 years (2002-2004). The 10-year cumulative incidence of BRVO was 1.2% (60).

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Prevalence of target indication

A recent meta-analysis (42) pooled data from 15 studies totaling 68,751 participants (age range 30-101 years) from several countries. The age- and sex-standardized prevalence of BRVO in 11 studies that assessed ≥2 fundus fields of both eyes (n = 49,869) was 4.4 per 1,000 people with a range between 0.26 and 6.85 per 1,000 people. The age and sex standardized prevalence of BRVO by the 15 individual studies representing over 8 countries is displayed in following Table SI.1.

Table SI.1: Age- and Sex-Standardized Prevalence a of BRVO from 15 studies participating in a meta-analysis (adapted from Rogers *et al.* (42))

	Eyes	Total Population	BRVO prevalence
Overall results			
All (15 studies)	Any	68,721	3.77 (3.08–4.46)
All (11 studies)	Both	49,839	4.42 (3.65–5.19)
Men (15 studies)	Any	30,329	3.19 (2.66–3.71) [b]
Women (15 studies)	Any	38,392	4.33 (3.07–5.60) [b]
Men (11 studies)	Both	22,181	3.76 (3.11–4.40) [b]
Women (11 studies)	Both	27,658	5.07 (3.69–6.45) [b]
By study			
ARIC (USA)	1 eye	12,604	0.45 (0.24–0.65)
BDES (USA)	Both	4,792	2.82 (1.65–4.00)
Beijing Eye Study (China)	Both	4,335	4.67 (2.48–6.85)
BMES (Australia)	Both	3,525	5.63 (3.94–7.32)
CHS (USA)	1 eye	2,824	0.26 (0.07–0.45)
EUREYE Study (Europe)	Both	4,753	1.48 (0.91–2.05)
Funagata Study (Japan)	1 eye	1,502	3.87 (0.13–7.61)
Handan Eye Study (China)	Both	6,716	6.16 (4.30–8.01)
Hisayama Study (Japan)	Both	1,775	9.32 (5.96–12.67)
LALES (USA)	Both	6,011	6.02 (4.31–7.73)
MESA (USA)	Both	6,132	2.87 (1.56–4.19)
Proyecto VER study (USA)	Both	2,908	6.85 (4.89–8.81)
Rotterdam Study (The Netherlands)	Both	6,418	1.60 (0.98–2.22)
Shihpai Eye Study (Taiwan)	Both	1,058	3.45 (1.72–5.18)
SiMES (Singapore)	Both	3,265	2.82 (1.46-4.19)

ARIC = Atherosclerosis Risk in Communities Study; BDES = Beaver Damn Eye Study; BMES = Blue Mountains Eye Study; BRVO = branch retinal vein occlusion; CHS = Cardiovascular Health Study; LALES = Los Angeles Latino Eye; SiMES = Singapore Malay Eye Study; VER = Vision Evaluation and Research.
[a]: Prevalence per 1,000 adults. Prevalence has been directly age- and sex-standardized to the 2008 world population aged ≥30 years (population data extracted from International Data Base, Total Midyear Population for the World: 1950-2050 [http://www.census.gov/ipc/www/idb/region.php; Accessed July 7, 2009]).
[b]: Denotes sex-specific estimates of prevalence, which are directly age standardized using the method and population as above.

In a population-based, cross-sectional study to evaluate the prevalence and associated factors of retinal vein occlusion in the Korean National Health and Nutritional Examination Survey (from 2008 to 2012) (38), the crude prevalence (expressed as weighted estimate in %) of

BRVO among the 25,765 evaluable participants with ophthalmic examination was 0.6 ± 0.1% overall and increased with age (see Table SI.2).

Table SI.2: Prevalence of BRVO in a nationwide, population-based, cross-sectional study in South Korea

Age group (years)	Crude prevalence[a]
19–29	<0.1 (1)
30–39	<0.1 (3)
40–49	0.3 ± 0.1 (13)
50–59	0.8 ± 0.2 (35)
60–69	1.4 ± 0.2 (63)
70–79	2.5 ± 0.3 (71)
80+	2.1 ± 0.7 (11)

[a]: Expressed as weighted estimate (%) (95% confidence interval, standard error [%]).
Source: Table 1 in (38)

Mortality in target indication

In a prospective study in Denmark (61) to assess BRVO as a prognostic marker of mortality, cases of BRVO were identified from a background population of 5.4 million and compared for risk of mortality with the non-BRVO segment of this population. Standardized mortality rates were calculated.

A total of 329 BRVO patients (173 women, 156 men) born between 1902 and 1956 were identified. They were 39 to 91 years old when diagnosed between 1973 and 1998. Follow-up was concluded on 08 JUL 2004, when 144 deaths were recorded among the BRVO patients (74 women, 70 men), compared with an expected number of 145.5 deaths in the background population. The standardized mortality rate was 0.99 (95%-CI: 0.84-1.16). Thus, the overall mortality rate of the BRVO population was almost identical to the background population. Stratified analyses revealed no significant effect of age, gender, or time of diagnosis (61).

The study investigators noted that an association between BRVO and cardiovascular/cerebrovascular risk factors has previously been documented in cross-sectional studies. The outcome in this longitudinal study may have been influenced by interventions instituted after the diagnosis of BRVO was made and by preferential survival before the diagnosis of BRVO of the more fit patients with the necessary precursor condition of having arteriovenous nicking, which is more prevalent in subjects with diabetes and hypertension (61).

A Danish case-control study (62) with prospective follow-up data from Danish national registries covering 80% of the Danish population (4.4 million) was performed to study BRVO comorbidities. A total of 1,168 patients with photographically verified branch retinal vein occlusion and 116,800 controls aged ≥40 years when the occlusion was diagnosed in the corresponding case were selected. The mortality hazard ratio adjusted for sex and year of diagnosis and with age as the underlying time scale, was similar in cases and controls (hazard ratio 0.94, 0.85 to 1.05; p = 0.30).

Potential health risk

BRVO is a component of retinal vein occlusion, which is the second most common retinal vascular disorder after diabetic retinopathy and is considered to be an important cause of visual loss (63).

Most BRVO cases (particularly major BRVO) result in retinal ischemia, predominantly affecting macular retinal ganglion cells, which are most vulnerable to ischemic damage, and pigmentary degeneration and/or epiretinal membrane that may develop in the foveal region secondary to prolonged macular edema (64).

Complications of BRVO include macular edema, ischemic maculopathy, retinal neovascularization, macroaneurysmal formation, retinal telangiectasia, retinal detachment, and vitreous haemorrhage (53, 56, 65, 66). The most common complications are macular edema, followed by retinal neovascularization, vitreous haemorrhage, or retinal detachment (53).

The average reduction in visual acuity for ischemic BRVO is 20/50 and for non-ischemic BRVO it is 20/60. In the retina, acute BRVO presents with flame-shaped haemorrhages, dot and blot haemorrhages, cotton wool spots, hard exudates, oedema, and dilated tortuous veins in the affected eye. In the chronic phase after absorption of intraretinal haemorrhage, morphological signs are more subtle and include capillary non-perfusion, dilatation of capillaries, microaneurysms, telangiectatic vessels, and collateral vessel formation, in addition to the previously mentioned complications (53).

A Danish case control study found that after a BRVO diagnosis, patients had an increased risk of developing arterial hypertension (incidence rate ratio 1.37, 95% CI: 1.15 to 1.57), diabetes (1.51, 1.17 to 2.04), congestive heart failure (1.41, 1.12 to 1.68), and cerebrovascular disease (1.49, 1.27 to 1.76) compared to the non-BRVO reference group (62).

Demographic profile of target population

Branch retinal vein occlusion (BRVO) affects most frequently patients at the age of 50 years and older, and the sex distribution is similar or includes a slightly higher female population (42, 53, 57).

In population-based research that studied BRVO, the racial distribution, BRVO prevalence, and population mean age was as summarized in Table SI.3.

Table SI.3: Overview of racial distribution, BRVO prevalence, and population mean age in population-based research that studied BRVO

Country/ Study	Ethnicity of Population	Prevalence (per 1,000 persons)	Mean age (years)
USA			
The Atherosclerosis Risk in Communities (ARIC)	77% White 23% Black	0.45	59.9
Beaver Dam Eye Study (BDES)	100% White	2.82	62.1
Cardiovascular Health Study (CHS)	83% White, 17% Black	0.26	78.7
Proyecto VER Study	100% Hispanic	6.85	56.9
Los Angeles Latino Eye (LALES)	100% Hispanic	6.02	54.9
Europe			
European Eye (EUREYE) study	100% White	1.48	72.7
Rotterdam study	98% White 1% Asian	1.60	69.0
Asia- Pacific			
Australia - Blue Mountain Eye Study (BMES)	99% White	5.63	66.2
China - Beijing Eye Study	100% Asian	4.67	56.2
China - Handan Eye Study:	100% Asian	6.16	52
Taiwan – Shihpai Eye Study	100% Asian	3.45	71.8
Singapore – Singapore Malay Eye Study (SiMES)	100% Asian	2.82	58.7
Japan - Funagata study	100% Asian	3.87	60.0
Hisayama Study	100% Asian	9.32	61.9

Overall, the prevalence findings of these studies suggested that BRVO occurs more frequently and possibly at younger age among Asians and Hispanics compared to Whites.

A retrospective study of 95 patients with retinal vein occlusion was carried out to determine the clinical presentation and pattern of distribution of the condition in the local Malaysian population. There was no significant difference in the sex distribution of the subjects. When comparing racial distribution between BRVO and CRVO patients, in the BRVO group, 40% were Indians, 29% Malays, and 31% Chinese. For CRVO in contrast, the Indians made up only 20% of the cases, the Malays 38% and the Chinese 43% (67).

In the large NIS OCEAN, in which patients treated with ranibizumab in a real-world setting are being observed in Germany (N = 5,606 overall), the cohort of subjects with BRVO (n = 204) had a mean age of 71.2 ± 10.0 years, and 58.3% of BRVO subjects were females (26).

SI.2.4 Myopic choroidal neovascularization (myopic CNV)

Characteristics of target indication

Choroidal neovascularization (CNV) is the most common vision-threatening complication of high myopia. The exact pathogenesis of myopic CNV remains unclear (68). In myopic populations, elongation of the eyeball and mechanical stress in the eye may induce choroidal

ischemia followed by atrophy of the retinal pigment epithelium (RPE) and overlying retina and subsequent growth factor release (69). These changes may lead to the formation of breaks in Bruch's membrane (lacquer cracks), RPE atrophy, and subsequent CNV formation (70). Lacquer cracks and chorioretinal atrophic areas are predictive of an unfavourable course in pathologic myopia and are associated with macular atrophy and CNV (71). Blood vessels from the underlying choriocapillaris may grow through the ruptured Bruch´s membrane and under the retina. The appearance of lacquer cracks and the presence of high levels of vascular endothelial growth factor (VEGF) and low levels of pigment epithelium-derived factor (PEDF) (72), are probably involved in the development of myopic CNV (70).

Myopic CNV usually appears at an earlier age than that associated with age-related macular degeneration (AMD) and the diameter of the lesion is usually smaller; however, myopic CNV is subfoveal in up to 89% of cases (70).

Myopic CNV can be classified into two groups: Type 1 is formed by well delineated lesions with early hyperfluorescence and little leakage in late phases of the angiogram. Type 2 is formed by lesions with early hyperfluorescence and leakage causing a neuroepithelial detachment (70).

Incidence of target indication

Although a number of epidemiology studies in general and high myopia (> minus 5, > minus 6 or > minus 8 dioptres) are available, little is known regarding the prevalence or incidence of pathologic myopia.

Among Caucasians in Australia and the United States, approximately 20% of the population has (simple) myopia. In many Asian countries, however, the incidence exceeds 20%. In the Tajimi Study (Sawada *et al.* 2008, (73)), myopia among Asians was found to be roughly 2.5 times greater than among Caucasians, and the incidence of high myopia, defined as > minus 6 dioptres, is approximately 2.3 greater.

Ohno-Matsui reviewed the medical records of 218 consecutive Japanese patients (325 eyes) with myopic fundus changes in the macula. During an average follow-up of 130 months of the 325 highly myopic eyes, 33 eyes (10.2%) developed myopic CNV. The incidence was higher (34.8%) among the fellow eyes of patients with pre-existing CNV than among eyes of patients without pre-existing CNV (6.1%). Choroidal neovascularization (CNV) developed in 3.7% of patients with diffuse chorioretinal atrophy, in 20.0% with patchy atrophy, and in 29.4% with lacquer cracks (74).

In a retrospective cohort study using data from an administrative claims database in Taiwan (JAN 2009 to DEC 2011), the cumulative annual incidence of myopic CNV rose from 11.9/100,000 (95%-CI: [11.4; 12.4]) in 2010 to 12.5/100,000 (95%-CI: [12.0; 13.0]) in 2011 (75).

Prevalence of target indication

Choroidal neovascularization (CNV) is the most common vision threatening complication of high myopia (68). The prevalence of choroidal neovascularization in people with highly myopic eyes was estimated at 5% of eyes (69, 70).

In a cohort examined by Lai *et al.* in 2008 (76), 11 % of highly myopic asymptomatic eyes with ≤-minus6 D were found to have posterior pole lesions, and more than 50% had peripheral retinal lesions. In France, a retrospective study of 363 patients under 50 years of

age who were referred to a tertiary care ophthalmology department found that 62% of CNV was secondary to pathologic myopia (77).

A retrospective cohort study using data from an administrative claims database in Taiwan (JAN 2009 to DEC 2011) (75) reported the prevalence of myopic CNV to be 0.017% (n = 9,068 myopic CNV patients identified over a total of 15,011.98 person-years of follow-up).

Mortality in target indication

No information was identified.

Potential health risk

The long-term prognosis for natural progression of myopic CNV over time is extremely poor. It is believed that, after the onset of CNV, chorioretinal atrophy expands outward from around the periphery of the CNV in the process of gradual shrinkage of the CNV, and that this is the primary cause of the decline in visual acuity and progression of central scotoma (78). Yoshida *et al.* found that approximately 90% of their patients had a visual acuity of 20/200 or less after 5 years, and almost all (96.3%) had a visual acuity of 20/200 after 10 years (79).

Degenerative myopia is estimated to be the seventh most common cause of blindness in adults in the US, is present in about 0.5% of the general population in Europe, and is estimated to represent 2% of all types of myopia (80). Caution should be exercised in interpreting these figures, however, as they date from the last century, and more recent publications are not available.

Myopic CNV usually appears at an earlier age than that associated with age-related macular degeneration (AMD) and the diameter of the lesion is usually smaller (70, 81). Serous retinal detachment is a risk as well with associated haemorrhages (81).

It has been estimated that 36% to 82% of eyes with CNV show lacquer cracks (69, 82).

Demographic profile of target population

Myopic CNV affects both men and women and occurs in young adults as well as those over 50 years of age.

In various studies of myopic CNV the population age ranged between 12 and 93 years and was younger on average compared to AMD populations (83). In the Japanese study by Yoshida *et al.*, the age of the patient population ranged from 7 to 82 years (mean 48.3 [SD 14.8]) (79). In a retrospective cohort study using data from an administrative claims database in Taiwan (JAN 2009 to DEC 2011; n = 9,068 myopic CNV patients identified) the mean age was 52.6 ± 16.5 years, and 39.0% were male (75).

CNV occurs in approximately 5% of eyes with pathologic myopia. Ethnic origin seems to influence the likelihood of developing pathologic myopia, with prevalence being higher in Asian populations and lower in African and Pacific island groups (83, 84). There is strong evidence that pathologic myopia has a genetic factor, based on studies in twins and in families with pathologic myopia. Pathologic myopia appears to be a multi-factorial and polygenic disorder that is genetically heterogeneous. The simultaneous development of CNV in both eyes is uncommon (83).

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SI.2.5 Diabetic macular edema (DME)

Characteristics of target indication

Diabetic macular edema is the result of retinal microvascular changes that occur in patients with diabetes mellitus. Thickening of the basement membrane and reduction in the number of pericytes is believed to lead to increased permeability and incompetence of retinal vasculature. This compromise of the blood-retinal barrier leads to leakage of plasma constituents into the surrounding retina, resulting in retinal oedema and vision loss. The hypoxic state achieved through this mechanism can also stimulate the production of vascular endothelial growth factor (VEGF) (85, 86). The role of VEGF appears to be central, since it increases microvascular permeability (87, 88).

The ETDRS group defined DME, based on stereoscopic fundus photography, as an increase in retinal thickness at or within 1 disk diameter of the foveal centre. This increase in thickness may be focal or diffuse, and hard exudates or macular cysts may or may not be present as well (ETDRS Group 1985). The term "clinically significant macular edema" (CSME) was introduced to characterize the severity of disease, and for treatment guidelines. Clinically significant macular edema meets at least 1 of the following 3 criteria: retinal thickening at or within 500 μm from the centre of the macula; hard exudates at or within 500 μm from the center of the macula associated with thickening of the adjacent retina; an area or areas of retinal thickening at least 1 disk area in size, at least part of which is within 1 disk diameter of the centre of the macula (89).

Incidence of target indication-

USA:

The 25-year cumulative incidence of DME in people with type I diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) was 29% (90). The 10-year incidence of DME in the WESDR was 20.1% in type I diabetics; 25.4% in insulin-treated type II diabetics, and 13.9% in non-insulin treated type II diabetics (91).

The 4-year incidence of DME in the Los Angeles Latino Eye Study was 5.4% (38/699) (92).

European Union (EU) and USA:

In a review of the literature, Chen *et al.* 2010 (93) provided a figure describing the increasing incidence of DME and CSDME over time in diabetic patients (see following figure). This information indicates a considerably higher DME risk in the US compared to EU countries, which continued to increase over time from the diagnosis of diabetes. The incidence rates of DME/CSDME in the overall diabetic population by reported countries were:

Sweden 1999 (94): 1-year CSDME: 2.3%

UK 2002 (95): 2-year CSDME: 4.79%

Spain 2007 (96): 15-year DME (type 1 diabetics): 20.5%

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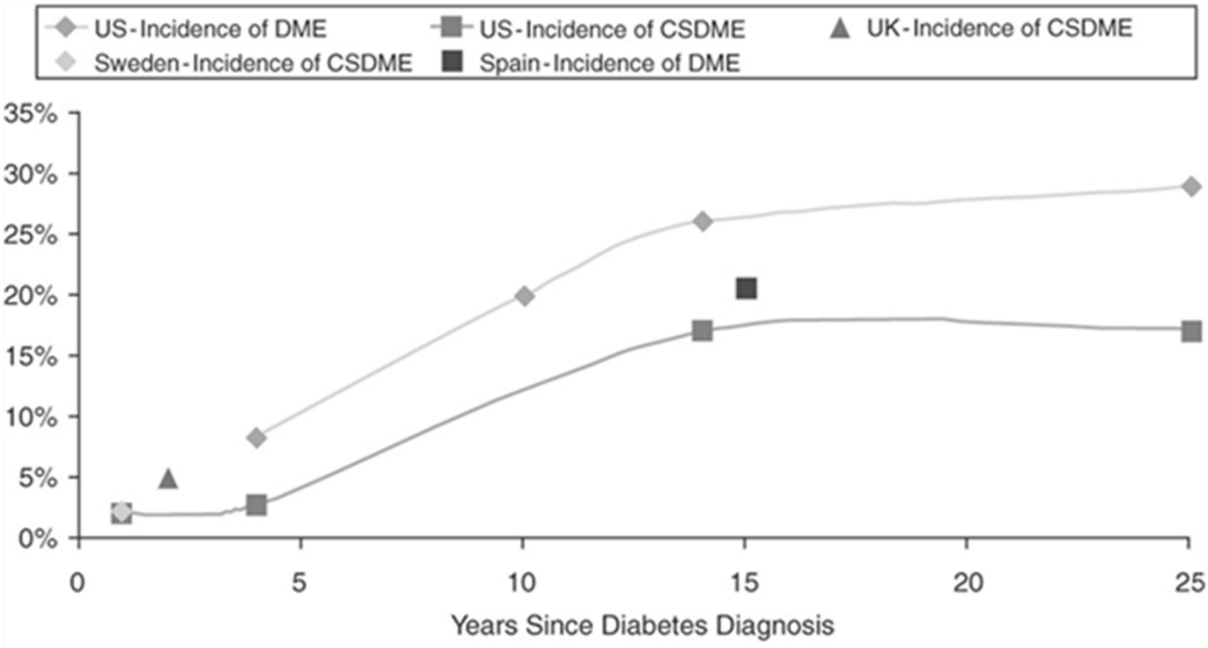
Figure SI.1: Incidence of diabetic macular edema (DME) and clinically significant diabetic macular edema (CSDME) in the USA and European countries as reported by Chen *et al.* 2010 (93)



CSDME: clinically significant diabetic macular edema; DME: diabetic macular edema

Source: 12,14,24-26,29-31

There seems to be a decrease in the annual incidence of DME and CSDME over time in some countries. In WESDR, the annual incidence of DME was found to be lower in the last follow-up period compared with earlier follow-up periods (2.3% from 1980–2 to 1984–6, 2.1% from 1984–6 to 1990–2, 2.3% from 1990–2 to 1994–6, and 0.9% from 1994–6 to 2005-7) (90). The authors attributed the decline to better glycaemic control (i.e., decreasing glycosylated haemoglobin), decreasing mean arterial blood pressure level, and earlier treatment of hypertension. A clinic-based study in Denmark also showed a decline in the incidence of DME in patients over time. The incidence after 15 years of diabetes duration was 11% and 12% for patients diagnosed in 1965–1969 and 1970–1974, respectively, while only 5% for patients diagnosed in 1975–1979 (90).

Prevalence of target indication

In 2010, of an estimated 285 million people worldwide with diabetes, over one-third had signs of diabetic retinopathy (DR), and a third of these are afflicted with vision-threatening retinopathy, defined as severe non-proliferative DR or diabetic macular edema (DME) (97).

The global prevalence of diabetes for all age groups is expected to increase from 2.8% in 2000 to 4.4% in 2030. The total number of people with diabetes is predicted to rise to 300 million by the year 2025, with the most significant increases in developing countries, due to population growth, aging, obesity and sedentary lifestyles (98).

The prevalence of DME is strongly related to the duration of diabetes. In the USA, an estimated 29% of adults with diabetes have DR and 3% have DME (99). In a cross-sectional study of 778 individuals with ages 45 to 85 years with diabetes, participating in the Multi-Ethnic Study of Atherosclerosis (MESA) (100), the prevalence of any retinopathy was 33.2% and macular edema 9.0%. When looking at racial distribution, the prevalence of

macular edema was significantly higher in Blacks (11.1%) and Hispanics (10.7%) than in Whites (2.7%) and Chinese (8.9%) (p = 0.007). Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (101) showed that after 15 years of known diabetes, the prevalence of DME was 18% in patients with type I diabetes, 20% in patients with type II diabetes who are taking insulin, and 12% in patients with type II diabetes who do not take insulin.

Outside of the USA, rates in diabetic populations have been reported as follows:

Spain: A population-based study of 8,187 type II diabetes and 488 type I diabetes patients in Spain in 2008 reported a yearly prevalence of 5.7% for macular edema in type I diabetes and 6.4% in type II diabetes (102).

India: The overall prevalence of macular edema in a population-based cross-sectional study (Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics, (103) was 31.76% (95%-CI: 26.04 – 37.47). The prevalence of macular edema was higher in persons with known diabetes than in those with newly diagnosed diabetes (32.9% *vs.* 13.3%).

Australia: In a population-based study of 2,177 diabetic adults aged ≥25 years in 42 randomly selected areas of Australia, 15.3% had retinopathy, and diabetic macular edema was present in 1.2% of these patients with retinopathy (n = 4) (104).

South Asia: In a community-based cross-sectional study (2009) involving 10 general practices; 1,035 patients with type 2 diabetes were studied: 421 of South Asian and 614 of white European ethnicity. The prevalence of DME was 12% (105, 106).

Rural China: In a cross-sectional study of 6,830 Han Chinese aged 30 years and older from 13 villages, 387 participants (6.9%) were diagnosed with diabetes mellitus. The overall prevalence of macular edema in the diabetic population was 5.2% and of CSDME 3.5% (107).

A pooled analysis of 35 studies (1980–2008) (97) provided data from 22,896 individuals with diabetes. The overall prevalence for DME was 6.81% (6.74–6.89). Studies from the USA, Australia, Europe, and Asia were included. In the pooled data, 52% were female, 44.4% were Caucasian, 30.9% were Asian, 13.9% were Hispanic, and 8.9% were African American. The mean age was 58.1 years (range 3–97), median diabetes duration was 7.9 years (interquartile range [IQR] 3–16). The prevalence of DME in the different studies ranged between 54% (49%, 59%) in the ARIC study (USA) and 15.19% (14.17%, 16.21%) in the EDC study (USA).

The World Health Organization estimates that 346 million people worldwide have diabetes, and this is expected to rise as the number of people with diabetes has doubled over the last 3 decades (108). Diabetic retinopathy (DR) is the most common microvascular complication of diabetes and is a major cause of visual impairment (109-112). In the US, it is estimated that about 28% of subjects 40 years and older with diabetes have DR, and 4.4% have vision-threatening DR (99). Outside the US, the estimates of diabetic patients who have DR range from 18% (India) to almost 50% in western European countries (103, 112, 113). The rate of vision-threatening DR outside the US ranges from 5.3% to 10% (113, 114).

Mortality in target indication

A 20-years follow-up of the Wisconsin Epidemiologic Study of Diabetic Retinopathy, WESDR (115) showed that clinically significant DME decreased survival in people with older onset (diagnosed at age >30) diabetes mellitus (hazard ratio [HR] 1.27, 95%-CI 1.01 to

1.61) compared to people in the older age group with diabetes but without clinically significant macular edema. Clinically significant DME in WESDR was also associated with increased all-cause and ischemic heart disease mortality in older-onset diabetic patients (HR, 1.55; 95%-CI, 1.25-1.92; and HR, 1.56; 95%-CI, 1.15–2.13, respectively) compared to people in the older age group with diabetes but without clinically significant macular edema, when adjusting for age and gender. After controlling for other risk factors, the association remained significant for ischemic heart disease mortality (HR, 1.58; 95% CI, 1.07–2.35; p = 0.02) among those taking insulin.

In the Early Treatment Diabetic Retinopathy Study (ETDRS) (116), type I and type II diabetic retinopathy patients had an increased risk for all-cause mortality compared to none/mild non-proliferative diabetic retinopathy patients, mostly due to cardiovascular disease (55%-56%). A multivariable analysis controlling for demographic, cardiovascular, and insulin intake variables, still showed increased mortality in diabetics due to macrovascular disease, proteinuria, increased serum creatinine, ulceration, amputation, and reduced visual acuity.

Potential health risk

In the WESDR study, clinically significant DME was associated with higher risk of ischemic heart disease in people with older onset diabetes who were taking insulin (HR 1.58, 95% CI 1.07 to 2.35). Stroke and ischemic heart disease were not significantly associated with this condition in those not talking insulin (115). Also, in the WESDR, univariate analysis showed that the incidence of DME was associated with male sex, more severe diabetic retinopathy, higher glycosylated haemoglobin, proteinuria, higher systolic and diastolic blood pressure, and more pack-years of cigarette smoking. Multivariate analyses showed that the incidence of DME was related to higher baseline glycosylated haemoglobin (HR per 1% 1.17; 95% CI, 1.10–1.25; p = 0.001) and higher systolic blood pressure (HR per 10 mmHg 1.15; 95% CI, 1.04–1.26; p = 0.004) and marginally to proteinuria (HR 1.43; 95% CI, 0.99–2.08; p = 0.06) (90).

A clinic-based study (Schepens Eye research Institute, Harvard, USA) (117) investigated the systemic and ocular factors associated with diffuse macular edema in patients with diabetic retinopathy (DR) in 160 DR patients. The risk of developing diffuse macular edema was 3.2 times greater in patients with high blood pressure (HBP) (95% confidence interval [CI], 1.5 to 6.9). Patients with cardiovascular disease (CVD) had a higher prevalence of diffuse (58.0%) than focal (26.0%) or no maculopathy (16.0%) (p = 0.01). The odds for developing diffuse macular edema were 3.4 times greater in patients with vitreomacular adhesion (95%-CI, 1.15 to 13.30) than in those with complete posterior vitreoretinal attachment or vitreoretinal separation. The odds for development of diffuse macular edema were 7.7 times greater (95%-CI, 3.12 to 19.12) in patients with proliferative DR (PDR) in comparison with those with non-PDR (NPDR).

Demographic profile of target population

The target population is adults with type I or type II diabetes who have developed DME as a sequelae of diabetic retinopathy. Racial variations exist: In the third National Health and Nutrition Examination Survey in the USA, the prevalence of diabetic retinopathy was 46% higher in blacks and 84% higher in Mexican Americans than in Whites with diabetes (118).

In the large NIS OCEAN, in which patients treated with ranibizumab in a real-world setting are being observed in Germany (N = 5,606 overall), the cohort of subjects with DME

(n = 1,211) had a mean age of 67.6 ± 10.9 years, and 41.9% of DME subjects were female. The majority of subjects (77.3%) suffered from T2DM; 9.6% had a medical history of T1DM (26).

In the WESDR, univariate analyses found that the incidence of DME was associated with male sex, more severe diabetic retinopathy, higher glycosylated haemoglobin, proteinuria, higher systolic and diastolic blood pressure, and more pack-years of cigarette smoking. Multivariate analyses showed that the incidence of DME was related to higher baseline glycosylated haemoglobin (HR per 1% 1.17; 95%-CI, 1.10–1.25; p = 0.001) and higher systolic blood pressure (HR per 10 mmHg 1.15; 95%-CI, 1.04–1.26; p = 0.004) and marginally to proteinuria (HR 1.43; 95% CI, 0.99–2.08; p = 0.06) (90).

SI.2.6 Retinopathy of prematurity (ROP)

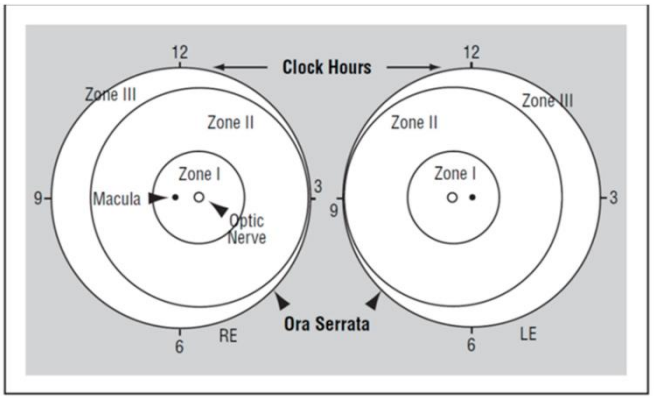
Characteristics of target indication

Retinopathy of prematurity (ROP) is a condition characterized by the cessation of eye development and disrupted neurovascular growth of the retina (119). It primarily affects preterm infants born at gestational age (GA) below 32 weeks and with very low birth weight (VLBW), i.e., ≤1,500g, and leads to an increased risk of visual impairment and blindness. Retinopathy of Prematurity (ROP) occurs in two phases. In phase I of ROP, the period from birth until about postmenstrual age (PMA) 30 weeks, retinal vascularization is inhibited because of hyperoxia and loss of the nutrients and growth factors provided at the maternal-foetal interface. Suppression of blood vessel growth and hypoxia occurs as the poorly vascularized retina matures and metabolic demand increases. Phase II results from prolonged hypoxia in the retina, which stimulates retinal neovascularization through increased expression of oxygen-regulated factors such as erythropoietin (EPO) and vascular endothelial growth factor (VEGF). Proliferation of new blood vessels that poorly perfuse the retina and are leaky leads to fibrous scar formation and retinal detachment (119).

Retinopathy of Prematurity (ROP) is described in a standardized manner using the International Classification of Retinopathy of Prematurity (ICROP) system (120). This method gives information on the location of retinal involvement (zone I – central circle, zone II – mid-peripheral ring, or zone III – peripheral ring), the extent of circumferential disease (in number of clock hours), as illustrated in Figure SI.-2, the severity of the disease (from stage 1 through 5, depending on the morphological appearance), and the presence of Plus disease (venous dilatation and arteriolar tortuosity of the posterior retinal vessels in at least 2 quadrants and indicating more aggressive course at any stage). A subtype called aggressive posterior ROP (AP-ROP) is an uncommon, rapidly progressing, severe form of ROP, characterized by posterior location, prominence of Plus disease, with extremely intense vascular activation and shows fast progression over a few days to advanced stages if untreated. AP-ROP is typically seen in zone I but may occur in posterior zone II (120, 121). ROP has also been divided into “threshold” (defined as 5 contiguous or 8 total clock hours of stage 3 in zone I or zone II with plus disease) and “prethreshold” disease (defined as any ROP in zone I that was less than threshold, or in zone II stage 2 with plus disease, or zone II stage 3 disease without plus disease, or zone II stage 3 with plus disease but fewer than five contiguous or eight cumulative clock hours) to guide treatment decisions (121). Recently, in the Early Treatment of Retinopathy of Prematurity Randomized Trial (ETROP), researchers redefined the indications for treatment and the terms “pre-threshold ROP” and “threshold

ROP", they have been replaced with "type 1 ROP" (aggressive, treatment requiring) and "type 2 ROP" (more indolent, less aggressive), respectively (122).

Figure SI.-2: Zones of retinal disease in retinopathy of prematurity



RE: right eye; LE: left eye

Prevalence of target indication

Prevalence estimates of ROP from population-based studies vary among countries even if similar neonatal intensive care facilities are available. This variation might be partially accounted for by differences in the proportion of infants at high risk of ROP who survive when born at an early gestational age (GA); in Sweden 11.5% of survivors were born in weeks 22-23, compared with 0%-6% in other studies (119). The estimated worldwide number of preterm infants developing ROP in 2010 was 184,700 (uncertainty range 169,600 – 214,500); severe ROP requiring treatment was 53,800 (28,800 – 85,000); blindness due to ROP was 20,000 (15,500 – 27,200); and mild or moderate visual impairment due to ROP was 12,300 (8,300 – 18,400) (123). Observed variations in reported rates of ROP may be explained by differences in quality of care i.e., wide variations in reported rates seen in NICUs, even in high income countries including varying approaches oxygen delivery and monitoring (123).

Retinopathy of Prematurity (ROP) screening coverage and screening criteria also vary among countries further contributing to different estimates. In most countries preterm infants with birth weight (BW) < 1,500 grams or GA < 32 weeks are screened for ROP (Sweden and Netherlands GA 29 weeks; Canada, USA and UK with GA 30 weeks; Germany 31 weeks) (124). Selected infants with higher BW or GA may also undergo screening if considered high risk by the clinician, including requiring cardiorespiratory support, hypotension requiring inotropic treatment, receiving oxygen supplementation for more than a few days or receiving oxygen without saturation monitoring (121, 122). Screening ultimately aims at prompt case detection and optimal treatment for ROP, thereby reducing the severity and overall burden of childhood blindness (125).

Incidence of target indication

About 10% to 11% of newborn infants are born preterm (<37 GA weeks) (119, 126). In Europe this proportion varies among countries from 5.4 % to 12% in 2015 (127). Among premature infants screened for ROP, the incidence of ROP ranges from 25.2% to 36%, with the rate increasing with decreasing preterm infant GA and BW (123).The wide range in incidence of any ROP, severe ROP (sROP) and treated ROP reported in different studies (Table SI.4) is likely due to differences in GA of infant populations, premature survival rates,

availability of neonatal care (119) and ascertainment bias, due to subjective interpretation of the retina and differences in clinical practice across countries (128). Among the 37,653 premature infants <27 weeks GA screened for ROP in the International Network for Evaluating Outcomes (iNeo), the rates of ROP ranged from 25.2% to 91%, and treatment varied between 4.3% and 30.4% in the 10 participating countries (128). Pooled analyses from 80 studies reporting on population-based incidence of ROP from 2000 to 2010 found that 21.8% (95% CI: 16.6–27.0%) of all survivors <32 week GA in countries with neonatal mortality rate (NMR) < 5, and 36.5% (95% CI: 31.8–41.4%) in countries with NMR ≥ 5 developed some degree of ROP. These results suggest that the incidence of ROP is higher in low-middle income countries, than in countries with better neonatal care (123).

Table SI.4: Incidence (%) of ROP, severe ROP (sROP), and infants receiving treatment for ROP[a]

Study Description	Cohort Criteria	Infants Screened	% ROP [a]	% sROP[a]	% treated[a]
CRYO-ROP 1986-1987(129)	BW < 1,251 g	4,099	65.8	27.1	N/A
ETROP 2000-2002 (130)	BW < 1,251 g	6,998	68.0	36.9	N/A
US NY Hospital Discharges 1996-2000(131)	BW < 1,500 g	10,596	20.31	N/A	2.15
Sweden SWEDROP 2008-2015 (132)	GA < 31 weeks	5,734	31.9	10.8	5.7
Germany NICUs 2001-2007 (133)	GA < 32 weeks or BW < 1,501 g or GA < 36 weeks and artificial oxygen ventilation for > 3 days	1,222	27.5	N/A	3.43
EuroNeoStat 2004 (134)	BW < 1,501 g or GA < 32 weeks	1,900	24.5	5.5	2.3
Japan NICU 2009-2011 (135)	GA <28 weeks	51	70.6	18	15.7
Global meta-analysis 2010 (123)	GA < 32 weeks	149,900[b]	21.81	4.2	3.67
IQTIG Germany 2010-2017 (124)	BW < 1,500 g	52,461	28.7	N/A	2.9
Swiss NeoNetwork 2006-2015 (136)	GA < 32 weeks	6472	9.3	1.8	1.2
South Korea 2007-2018 (137)	GA < 37 weeks	161,984	29.8	N/A	2.95

[a]: out of the screened patients
[b]: Estimation from Global Meta-Analysis model
BW = Birth Weight; GA = Gestational Age, ROP = Retinopathy Of Prematurity, < = Less than, > = More than, N/A= Not Applicable

Mortality

Neonates born very preterm (<32 weeks GA) and VLBW (BW <1,500 g) are at increased risk for mortality and life-long disability (128). The survival of preterm infants improves as gestational age increases. As showed in TableSI.5, there has been noticeable improvement in

the survival of extremely premature infants since the 1990s. The continuous increase in the survival of the immature infants might contribute to the increasing incidence of ROP (and of the frequency of treatment)(132). In an analysis using the SwissNeoNet registry, mortality rate dropped from 100% at 22 weeks GA to below 10% on premature infants 27 weeks GA and older (136). In the iNeo collaboration the overall mortality rate of very preterm and very low birth weight infants before discharge was 10% (5% in Japan; between 6% and 10% in Canada, Australia/New Zealand, Sweden, Switzerland, and the UKNC; 14% in Israel; and 17% in Spain) between 2007 and 2010 (128). The variation in mortality across countries could be the result of organization of perinatal health care delivery, population characteristics, case definitions, ascertainment, data quality and reliability, and health care processes involved.

TableSI.5: Survival rates of Preterm infants at discharge

Study	GA 22w	GA 23w	GA 24w	GA 25w	GA 26w	GA 27w
Draper UK (1994-1997), (138)	2%	6%	16%	33%	54%	N/A
Markestad Norway (1999-2000), (139)	0%	26%	55%	77%	84%	N/A
NICDH US (2003-2007), (140)	6%	26%	55%	72%	84%	88%
EpiCure UK (2006) (141)	2%	19%	40%	66%	77%	N/A
Swiss NeoNetwork (2006-2015), (136)	0%	6.7%	40.4%	64.2%	82.8%	89.3%
Epipage 2 FR (2011), (142)	0%	1%	31.2%	59.1%	75.3%	82.3%

GA = Gestational Age, w = Week

Potential health risk

ROP is the most common avoidable cause of childhood blindness globally (143). The prevalence of blindness caused by severe ROP in developed nations ranges between 3%-13% and in various moderately developed nations estimates are >20% (144, 145). Approximately 400-600 cases of blindness due to severe ROP are estimated to occur in the United States each year (119, 146). Complications of ROP involve visual disorders including strabismus, amblyopia, high refractive errors and cataracts. If left untreated, severe ROP can lead to increased risk of myopia, retinal detachment, long-term visual impairment, and blindness (119). However, approximately 90% of infants with ROP have mild forms that regress without treatment. Most non-proliferative ROP regresses without treatment; nevertheless even non-proliferative disease is associated with visual deficits since preterm birth itself has lasting effects on the developing visual system (119). Severe ROP in very low-birth-weight neonates is associated with increased risk of nonvisual impairment at age of 5 years, including motor impairment, cognitive impairment, and severe hearing loss (147).

Demographic profile

ROP most frequently affects premature infants with extremely low BW and with GA < 28 weeks (119, 146). Some studies have reported a lower risk of severe ROP in premature infants of African descent compared with other ethnic groups, and a higher risk in those of south Asian descent (123, 148). An analysis conducted in the iNeo collaboration among 48,087 premature infants with 24 to 27 weeks found that male sex, lower GA, lower BW, and delivery by caesarean section were associated with the occurrence of severe ROP requiring treatment, whereas the use of antenatal corticosteroids and multiple births were not (128). Other risk factors for ROP include severe respiratory distress syndrome, anaemia, neonatal sepsis, thrombocytopenia, multiple blood transfusions and apnoea (149).

Furthermore, being small for gestational age (weight below the 10th percentile for the GA) or having low weight gain proportion (i.e., weight gain less than 50% of the birth weight in the first 6 weeks of life) are also associated with ROP (149-151).

SI.3 Concomitant medication(s) in the target population

SI.3.1 Wet age-related macular degeneration (wet AMD)

Eylea 40 mg/mL (2 mg dose) is approved in the EU and US for the treatment of wet AMD Therapeutic options apart from Eylea to treat wet AMD include other IVT anti-VEGF therapies such as Macugen® (pegaptanib), Lucentis® (ranibizumab; approved), conbercept (approved in the People's Republic of China), or bevacizumab (currently off-label), Beovu® (brolucizumab, approved), Vabysmo® (faricimab, approved in US, Japan, EU, Australia, Canada and UK in 2022), Susvimo® (ranibizumab port delivery system, approved in US, Australia and UK, MAA under assessment by European Medicine Agency [EMA]) and photodynamic therapy in combination with verteporfin as photosensitizer. To date, intravitreal injections of anti-VEGF drugs have been the gold standard for the treatment of CNV secondary to AMD (152).

Eylea is administered as monotherapy; no systematic experience in terms of possible interactions with these alternative treatment approaches is currently available.

SI.3.2 Central retinal vein occlusion (CRVO)

Eylea 40 mg/ml (2 mg dose) is approved in the EU and US for the treatment of macular edema following RVO (including CRVO). Other therapeutic options besides Eylea to treat the macula oedema caused by CRVO include other IVT anti-VEGF therapies such as Lucentis® (ranibizumab; approved), or bevacizumab (currently off-label), IVT-applied corticosteroids such as dexamethasone (Ozurdex®) or triamcinolone acetate (Triesence®, Trivaris®), and panretinal photocoagulation (in the event of disease progression to anterior segment neovascularization).

Eylea is administered as monotherapy; no systematic experience in terms of possible interactions with these alternative treatment approaches is currently available.

SI.3.3 Branch retinal vein occlusion (BRVO)

Over the last three decades three main treatment options for macular edema secondary to BRVO have been developed:

Macular grid laser photocoagulation is considered to be the standard of care in BRVO since the mid 80’s (63). Although grid laser photocoagulation showed benefits in a sizeable proportion of patients with perfused BRVO, in some patients poor vision persisted despite treatment (153). One principal concern with laser photocoagulation is, that the laser would cause sudden damage of the retina through coagulation, which would be an important factor for permanent VA reduction. So especially in the presence of macular ischemia, effects of grid laser photocoagulation may be limited (153). The relatively low frequency of vision gain and delayed vision improvement following grid laser photocoagulation for BRVO, has prompted interest in other treatment modalities (for an overview see below and (154)).

Two different glucocorticoid drugs have been studied following intravitreal (IVT) administration, (preservative-free) triamcinolone acetonide and, more recently, dexamethasone implants (Ozurdex®). For IVT triamcinolone acetonide results of the

SCORE study (155) suggest that for macular edema secondary to BRVO it is not more effective than the use of macular grid laser photocoagulation alone. A combination treatment showed a higher risk of adverse events and is therefore not recommended. The authors of the SCORE study group concluded that grid laser photocoagulation would still be the standard of care for macular edema secondary to BRVO. The sustained-release IVT dexamethasone implant (Ozurdex®) received approvals for the treatment of macular edema secondary to RVO from the US FDA in 2009 and in the EU in 2010. Two pivotal studies included a total subgroup of 291 BRVO eyes. In the 0.7 mg group of Ozurdex® the proportion of BRVO patients with VA gain ≥15 letters was 24% (0.7 mg dose group) at Day 90 compared to 15% in the sham control. This result was only statistically significant up to Day 90 of the study. At Day 180 the difference in the proportion of the 15-letter gainers was no longer statistically significant between groups. IVT dexamethasone is contraindicated in patients with glaucoma. Use of corticosteroids including Ozurdex® may produce posterior subcapsular cataracts, increased eye pressure, glaucoma, and may increase the risk of secondary eye infections due to bacteria, fungi, or viruses.

Numerous case series and uncontrolled studies have shown that IVT injections of anti-VEGF agents (bevacizumab and ranibizumab) can improve visual acuity (VA) and reduce retinal oedema in patients with both BRVO and CRVO (30, 154, 156, 157). A well-controlled study (BRAVO) of IVT ranibizumab has provided the first pivotal evidence that inhibition of VEGF is effective in the treatment of visual impairment due to macular edema secondary to BRVO (158, 159). Lucentis® (ranibizumab) was approved for the treatment of macular edema following RVO by US FDA in 2010 and by European Commission in 2011.

Eylea 40 mg/mL (2 mg dose) has been approved in the EU and US for the treatment of macular edema following RVO.

SI.3.4 Myopic choroidal neovascularization (myopic CNV)

Until recently, treatment modalities were limited to thermal laser photocoagulation for extrafoveal CNV and photodynamic therapy for juxtafoveal and subfoveal CNV (68, 83), (160), and possibly surgery (83). Both these modalities primarily aim at prevention of further visual loss with no improvement in vision (i.e., maintenance of vision) (70). Novel inhibitors of VEGF may now successfully restore visual acuity to some extent in patients with subfoveal myopic CNV (70, 83).

To date, Eylea 40 mg/mL with a dose of 2 mg (by European Commission), ranibizumab (by US FDA/EC) are approved anti-VEGF agents for the treatment of myopic CNV. The recommended dose for Eylea is a single IVT injection of 2 mg. Additional doses should be administered only if visual and anatomic outcomes indicate that the disease persists. Recurrences are treated like a new manifestation of the disease.

SI.3.5 Diabetic macular edema (DME)

Standard treatments for DME include focal/grid laser photocoagulation, IVT steroids, and vitrectomy for selected cases and advanced stages of DME. The disadvantage of laser photocoagulation and vitrectomy is the limited number of patients showing significant visual improvement. Many patients still lose VA despite these procedures, and in some cases, vision is further compromised as a result of these interventions. More recently, anti-VEGF compounds have been used in the treatment of DME. The effectiveness of anti-VEGF agents

for the treatment of DME was demonstrated in several clinical studies. Based on the data from the pivotal Phase III studies RISE and RIDE (161), the Phase II study RESOLVE (162), and the pivotal Phase III study RESTORE (163), ranibizumab was approved in the EU and in the USA for the treatment of DME in 2011 and 2012, respectively.

Additionally, ranibizumab with prompt or deferred laser treatment demonstrated superior efficacy compared to laser alone in a large randomized clinical trial sponsored by The Diabetic Retinopathy Clinical Research Network. At Year 1, the mean change in BCVA letter score was statistically superior for the ranibizumab + prompt laser group (+9 letters) and the ranibizumab + deferred laser group (+9 letters) compared with the laser group (+3 letters). A significantly greater proportion of patients gained ≥15 letters for the ranibizumab + prompt laser group (29.0%) and the ranibizumab + deferred laser group (26.7%) compared with the laser group (14.2%). The mean central retinal thickness was significantly reduced from baseline for the ranibizumab + prompt laser group (-112 µm) and the ranibizumab + deferred laser group (-111 µm) compared with the laser group (‑79 µm). There were also significantly greater proportions of eyes with ≥2-step improvement in the Diabetic Retinopathy Severity Scale for the ranibizumab + prompt laser group (20.9%) and the ranibizumab + deferred laser group (21.4%) compared with the laser group (6.2%). There were 3 injection-related cases of infectious endophthalmitis in the ranibizumab-treated groups. Elevation of IOP was reported more frequently in eyes in the triamcinolone + prompt laser group (50%) than in the ranibizumab (9%) or sham (11%) groups (164).

The favorable results for ranibizumab plus prompt or deferred laser were sustained through the second and third years of the study, which constitutes the extent of the currently available evidence (165, 166).

Eylea 40 mg/mL (2 mg dose) has been approved in the EU and US for treatment of DME. The recommended dose for Eylea 40 mg/mL is 2 mg aflibercept administered by IVT monthly (once every 4 weeks) for the first 5 consecutive doses, followed by one injection every 2 months (8 weeks).

Beovu® (brolucizumab) and Vabysmo® (faricimab) have been approved in the EU for the treatment of DME.

SI.3.6 Retinopathy of prematurity (ROP)

Treatment of ROP is based on the principle of retinal ablation. Treatment is directed to the avascular part of the retina with the goal of decreasing the production of angiogenic growth factors. Treatment modalities for established ROP range from transpupillary laser photocoagulation or cryotherapy to vitreoretinal surgery for advanced stages in subjects who develop retinal detachment. Both laser and cryotherapy are performed only on infants with advanced ROP, particularly stage 3 with “plus disease”, whereby laser coagulation is less prone to severe complications and considered standard of care. In the later stages of ROP, surgical options include scleral buckle (usually performed on infants with stage 4 or 5) and vitrectomy (performed only at stage 5).

Intravitreal injections of anti-VEGF agents are also used in select cases (earlier disease stages with involvement of the central retina). Ranibizumab is currently approved in Europe for the treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) disease. Further therapeutic approaches

aim to prevent the progression of ROP to stages requiring treatment (e.g., propranolol, dietary supplementation with fatty acids).

The presence of "plus disease" in zones I or II indicates that treatment, rather than observation, is appropriate. Treatment should be initiated within 72 hours for findings that indicate Type 1 ROP (122).

SI.4 Important co-morbidities found in the target population

SI.4.1 Wet age-related macular degeneration (wet AMD)

Important co-morbidities in the AMD population include glaucoma, cataract, stroke, hypertension, and hyperlipidaemia. In a case control study of 26,057 wet AMD patients and an equal number of controls from the Medicare population, wet AMD subjects had at least 20% higher odds for hypertension, hypercholesterolemia, emphysema, chronic obstructive pulmonary disease, atherosclerosis, arthritis, coronary heart disease, cataract, glaucoma, and myopia (167).

In a combined cross-sectional and cohort study of 1,519,086 Medicare enrolees identified between 2000 and 2003, the prevalences of hypertension, diabetes, and history of MI were 75%, 33%, and 5%, respectively, in the wet AMD group. In contrast, they were 73%, 27%, and 4.68% in the non-wet AMD group, and 65%, 25%, and 4.54% in the non-AMD group ($p < 0.01$ for comparing the prevalence in wet And non-wet AMD versus non-wet AMD groups) (12).

A study to determine the incidence, pattern and ocular morbidity associated with age-related macular degeneration (AMD) at the Guinness Eye Centre Onitsha Nigeria examined 256 AMD patients of all types. Systemic co-morbidities were hypertension and diabetes; the main ocular co-morbidities were cataract and glaucoma (10).

A 2011 German publication hypothesized the following: "Oxidative Stress at the retinal level is the common pathway in the development of AMD and cataract. AMD and cataract are not two independent processes. Cataract is a self-defence reaction of the retina to reduce oxidative stress and retinal damage" (168).

While in a German study of 45 wet AMD patients, who were injected with anti-VEGF treatment, no history of glaucoma was detected (169), another study of intraocular pressure (IOP) post anti-VEGF agents in wet AMD patients found the following: Of the 215 eyes receiving injections with bevacizumab and/or ranibizumab, 6% (n = 13) had sustained IOP elevation requiring medical or laser interventions. Of the eyes receiving only bevacizumab, 9.9% (10/101) had sustained elevated IOP, while 3.1% (3/96) of eyes receiving only ranibizumab experienced increases ($p = 0.049$). Patients with pre-existing glaucoma experienced higher rates of elevated IOP when compared with patients without pre-existing glaucoma (33% *vs*. 3.1% respectively; $p < 0.001$). The glaucoma subgroup had a lower median number of injections (6; interquartile range 5-10) compared with the non-glaucoma group (9.5; interquartile range 6-13.7; $p = 0.031$) (170).

In a rural Italian community, 210 patients (79%) 65 year of age and older participated in a study of risk factors for AMD and age-related maculopathy. Older age ($p = 0.014$), prior cataract surgery ($p <0.001$) and hypertension history ($p = 0.005$) were associated with the two conditions (171).

Stroke is also considered an important co-morbidity in the AMD patient population. A 5-year population-based follow-up study in Taiwan reported that wet AMD is associated with a higher risk of stroke in patients 65 years of age and older compared to a same age control group. The adjusted hazard ratio for stroke during the follow-up period was 2.21 (p = 0.001) (172).

An Australian study followed participants for cardiovascular disease mortality. Of 3,654 baseline participants (1992-1994) aged 49+ years, 2,335 were re-examined after 5 years and 1,952 after 10 years. Retinal photographs were graded using the Wisconsin System. History and physical examination provided data on possible risk factors. Deaths and cause of death were confirmed by data linkage with the Australian National Death Index. Among persons aged <75 years at baseline, early AMD predicted a doubling of cardiovascular mortality (RR, 2.32; 95% confidence interval (CI), 1.03 to 5.19), over the next decade, after controlling for traditional cardiovascular risk factors. Late AMD predicted 5-fold higher cardiovascular mortality (RR, 5.57; 95% CI, 1.35 to 22.99) and 10-fold higher stroke mortality (RR, 10.21; 95% CI, 2.39 to 43.60) after adjusting for age and sex only. These associations were not present when persons older than 75 were included (173).

In a study to investigate whether AMD is associated with the development of ischemic and haemorrhagic stroke among elderly Americans, Medicare data were utilized. Baseline demographic variables and chronic conditions (AMD and type, history of MI, stroke, hypertension, and diabetes) were defined based on the occurrence of relevant ICD-9 codes in relevant diagnosis fields of the baseline Medicare Data. A total of 215,900 persons who had a diagnosis of MI or stroke during baseline period were excluded to form a cohort of 1,303,186 individuals who were free of major cardio-cerebral vascular disease (CVD) at baseline. The prevalence of AMD was 10.6%, with 19.7% being wet AMD and 80.3% being non-wet AMD. Baseline age, gender, race, hypertension, and diabetes adjusted 2-year incident odds ratios and 95% confidence interval of stroke associated with AMD were 1.31 (1.26, 1.36) for wet AMD, 1.18 (1.15, 1.21) for non-wet AMD, and 1.21 (1.18, 1.23) for either neovascular or non-wet AMD. The conclusion was that the findings are suggestive of an association between AMD, especially wet AMD, and incident stroke, independently of demographic factors and co-morbidity (174).

In the Women's Health Initiative Sight Examination (WHISE) study, on the other hand, stroke was not found to be a risk factor for AMD. A total of 4,288 women aged 63 years and older participated. Prevalence of any AMD was 21.4% (n = 919). Of those with AMD, 5.8% (n = 53) had signs of exudative AMD (n = 39) or pure geographic atrophy (n = 14), limiting the power to examine associations. Significant associations between late AMD and CVD risk factors were (odds ratio [OR], 95% CI) older age (1.19, 1.13 to 1.27, p< 0001), more pack years smoked (1.02 per pack-year smoked, 1.003 to 1.03, p = 0.01), systolic blood pressure (0.84 per 10 mmHg, 0.71 to 0.995, p = 0.04), report of taking calcium channel blockers (2.49, 1.21 to 5.12, p = 0.04), self-reported history of diabetes (2.00, 1.01 to 3.96, p = 0.05), and greater body mass index (1.05 per 1 kg/m2, 1.001 to 1.10, p = 0.05). History of MI, stroke, use of statins, or white blood cell count was not associated with AMD (175).

A report from a case series in Frankfurt, Germany, indicated that AMD patients who took anticoagulants and antiplatelet agents tended to develop large subretinal haemorrhages compared to non-AMD patients. Moreover, arterial hypertension was reported to be a strong risk factor for large subretinal haemorrhages in AMD patients receiving anticoagulants or antiplatelet agents (176).

The AMD patient population has shown higher odds of hyperlipidaemia than the general population (167). The Beaver Dam Offspring Study (32) reported that older age, male sex, more pack-years of cigarettes smoked, higher serum high-density lipoprotein cholesterol level and hearing impairment were associated with early AMD.

The association between arteriosclerosis and AMD was studied in a cross-sectional study with 730 patients from the Munster age and retina study (MARS) which examines patients in the age range 60 to 80 years who were referred by ophthalmologists from the Muenster area. Patients with narrow angle glaucoma were excluded. All patients underwent a standardized ophthalmoscopic examination and were classified into four groups: without AMD (n = 190), with unilateral or bilateral early forms of AMD (n = 340), with unilateral late forms of AMD (n = 139) and with bilateral late forms of AMD (n = 50). The mean age was 72 years, 58% were women and the sex distribution within groups did not differ significantly. Risk factors for arteriosclerosis such as diabetes, body-mass-index and hypertension did not differ significantly. The number of smokers increased significantly with the severity of AMD ($p = 0.02$). Associations with lipids were examined, adjusting for age and sex, and showed significant decrease of HDL ($p = 0.087$) and significant increases of the HDL/LDL quotient ($p = 0.0007$). The non-fasting triglyceride values ($p = 0.0058$) correlated with the severity of AMD. The conclusions was that there was a highly significant, direct association of indicators of dyslipidaemia such as increasing HDL/LDL quotient and decreasing HDL with increasing severity of AMD (177).

SI.4.2 Central retinal vein occlusion (CRVO)

A clinic-based case control study compared 408 patients with CRVO aged 21 years and older and 566 controls that were seen between 01 JAN 1990, and 31 DEC 2001 to determine risk factors for CRVO. An increased risk of CRVO was found in patients with systemic hypertension, but odds ratios were greater for older patients. Risk of CRVO also increases with hypercoagulability, diabetes mellitus, kidney disease, and glaucoma (178).

A population-based, cross-sectional study of 6,147 participants (whites, blacks, Hispanics, Chinese) from 6 US communities compared people with RVO (central and branch) to those without RVO. Independent risk factors associated with RVO were hypertension (OR 2.06, 95% CI 1.18 to 3.59), hypertriglyceridemia (OR 1.98, 95% CI 1.10 to 3.56), renal dysfunction (OR 1.85, 95% CI 1.01 to 3.39), presence of retinal arteriovenous nicking (OR 4.01, 95% CI 2.06 to 7.81) and focal arteriolar narrowing (OR 4.38, 95% CI 1.44 to 13.34) (179).

In a study comparing 117 patients (61 males, 56 females; mean age 51 ± 13 years) with a history of RVO (62 CRVO, 48 BRVO, 7 both) to 202 age- and sex-matched control subjects, arterial hypertension was significantly more frequent in the RVO (central and branch) patients than in the control group (64.9% versus 28.2%, adjusted OR 4.5, 95% CI 2.4 to 7.9, $p = 0.0001$). Diabetes was significantly more frequent as well (17.9% versus 7.9%, $p = 0.05$) (180).

A longitudinal study aimed to identify risk factors associated with CRVO among 1,302 managed care enrolees (from 2001 to 2009) ≥55 years. Cox regression analysis was used to determine the hazard of CRVO.

After adjustment for known confounders, a diagnosis of stroke increased the hazard of CRVO by 44% (HR, 1.44; 95% CI, 1.23–1.68), and hypercoagulable state was associated with a 145% increased CRVO risk (HR, 2.45; 95% CI, 1.40–4.28). Individuals with end-organ

damage from hypertension or diabetes mellitus had a 92% (HR, 1.92; 95% CI, 1.52–2.42) and 53% (HR, 1.53; 95% CI, 1.28–1.84) increased risk of CRVO, respectively, relative to those without these conditions (37).

A Medline literature review of RVO publications specified the following co-morbidities for CRVO: poor visual acuity at diagnosis, and presence of macular edema (which resolves in 30% of non-ischemic CRVO eyes and in up to 73% of ischemic CRVO eyes). Cardiovascular disease was indicated in association with RVO (181).

SI.4.3 Branch retinal vein occlusion (BRVO)

Cardiovascular diseases are important co-morbidities in people with BRVO. A meta-analysis of several BRVO studies showed that, in patients with BRVO, the odds for hypertension were 3.0 (95%-CI: 2.0–4.4), for hyperlipidaemia 2.3 (95%-CI: 1.5–3.5), and for diabetes mellitus 1.1 (95%-CI: 0.8–1.5) compared to non-BRVO controls (182). Kaderli *et al.* (183) found that arterial stiffness as measured by pulse wave velocity and aortic distensibility was abnormal in BRVO patients, in comparison with both healthy and hypertensive controls.

A retrospective case–control study of 60 patients younger than 50 years indicated that hypertension, hyperlipidaemia, and body mass index were more prevalent in this patient group compared to controls (184). History of asthma and of migraine showed also increased odds for the development of BRVO (Odds ratio 2.00 and 2.73, respectively) (57). Glaucoma is among the ocular comorbid conditions in BRVO populations (53).

A Danish case-control study (62) with prospective follow-up data from Danish national registries covering 80% of the Danish population (4.4 million) was performed to study BRVO comorbidities. A total of 1,168 patients with photographically verified BRVO and 116,800 controls aged ≥40 years when the occlusion was diagnosed in the corresponding case were selected. Risk factors present 1 year before the diagnosis of BRVO included peripheral artery disease (odds ratio 1.83, 95%-CI: 1.14 - 2.95), diabetes (1.74, CI: 1.40 to 2.17), cardiovascular disease (2.07, CI: 1.79-2.40), and arterial hypertension (2.16, CI: 1.86 to 2.51). After the diagnosis, patients had an increased risk of developing arterial hypertension (incidence rate ratio 1.37, 95%-CI: 1.15 to 1.57), diabetes (1.51, 1.17 to 2.04), congestive heart failure (1.41, 1.12 to 1.68), and cerebrovascular disease (1.49, 1.27 to 1.76). The study conclusion was that diabetes, hypertension, and peripheral artery disease were associated with an increased risk of developing BRVO. BRVO was also associated with subsequently developing hypertension, diabetes, congestive heart failure, and cerebrovascular disease. These results fit the assumption that BRVO is a consequence of arterial thickening and that the arteriovenous crossing signs that precede it can be hallmarks of arterial disease (62).

SI.4.4 Myopic choroidal neovascularization (myopic CNV)

Evidence suggest that eyes with myopic CNV tend to have an early stabilization of vision followed by gradual and progressive decrease in visual acuity (VA) over time primarily due to the development of chorioretinal atrophy around regressed CNV (68).

It has been estimated that 36% to 82% of the eyes with CNV show lacquer cracks while the latter’s frequency among highly myopic eyes without CNV is considerably lower (0.6%) (70).

A retrospective study of (any) CNV patients younger than 50 years of age, who had been referred to a tertiary care ophthalmology department, was performed in Western Europe. CNV was associated with high myopia in 225 (62%) patients, pseudo-presumed ocular

histoplasmosis syndrome in 42 (12%), angioid streaks in 17 (5%), and hereditary or traumatic or inflammatory disorders in 16 (4%) (77).

SI.4.5 Diabetic macular edema (DME)

Diabetes is a leading cause of mortality and reduced life expectancy in the western world (185). In the USA it is ranked as the 6th leading cause of death accounting for over 71,000 deaths per year (116).

Diabetic retinopathy is the leading cause of vision loss in people 20 to 74 years of age in the developed world (118, 186) and macular involvement is the major cause of visual loss in patients with DR (117, 187).

A study investigated the systemic and ocular factors associated with diffuse macular edema in 160 patients with diabetic retinopathy (DR). The risk of developing diffuse macular edema was 3.2 times greater in patients with high blood pressure (95% CI, 1.5 to 6.9). Patients with cardiovascular disease had a higher prevalence of diffuse (58.0%) than focal (26.0%) or no maculopathy (16.0%) (p = 0.01). The odds for developing diffuse macular edema were 3.4 times greater in patients with vitreomacular adhesion (95%-CI, 1.15 to 13.30) than in those with complete posterior vitreoretinal attachment or vitreoretinal separation. The odds for development of diffuse macular edema were 7.7 times greater (95%-CI, 3.12 to 19.12) in patients with proliferative DR (PDR), respectively, in comparison with those with non-PDR (117).

SI.4.6 Retinopathy of prematurity (ROP)

Retinopathy of Prematurity (ROP) often occurs in conjunction with other neonatal morbidities such as neurological dysfunction, poor brain growth, necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH) and bronchopulmonary dysplasia (BPD) (119). Preterm infants born at a very low GA are more susceptible having two or more comorbidities compared to older premature infants, and are more likely to develop severe forms of disease (188). Table SI.6 provides information on the proportion of patients with various comorbidities by GA from a Swiss neonatal registry (136). In a US NICHD (National Institute of Child Health and Human Development) survey, a high proportion of preterm infants born at a GA <27 weeks (n = 8,515) had significant comorbidities: 93% respiratory distress syndrome (RDS), 68% BPD, 59% any ROP, 46% patent ductus arteriosus (PDA), 36% late onset sepsis, 16% severe IVH (grade >2), 16% severe ROP, and 11% NEC (140). Data from a German retrospective cohort suggest that comorbidities also occur more frequently among low BW infants with ROP (stage 1 to 5) than among those without ROP (Table SI.7) (189).

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Table SI.6: ROP comorbidities stratified by gestational age (GA)

SwissNeoNet Registry	23w	24w	25w	26w	27w	28w	29w	30w	31w
Number of infants	238	411	495	644	730	877	1,075	1,407	1,815
Sepsis (%)[a]	16.7	29.8	28.4	25.2	17.2	10.7	7.6	4.2	3.5
NEC (%)[a]	11.1	8	4.1	4	3.1	3.2	2.1	1.7	0.9
Severe IVH (%)[a]	36.1	21.5	20	11.3	9.8	4.2	3.8	2.8	1.6
BPD (%)[b]	50	45.5	32.7	23.8	17	10.9	6.5	3.6	2.2

BPD = Bronchopulmonary Dysplasia; IVH = Intraventricular Hemorrhage; NEC = Necrotizing Enterocolitis; ROP = Retinopathy of Prematurity; w = Weeks.
[a]: Proportion of admitted infants.
[b]: Proportion of infants discharges.

Table SI.7: Percent of ROP and non-ROP infants with comorbidities

German Retrospective Study Infants with BW ≤ 1,500 g	No ROP (n=257)	Any ROP (n=145)
Respiratory distress syndrome	30.8	53.1
Bronchopulmonary dysplasia	8.95	37.2
Patent ductus arteriosus	16.3	42.1
Intraventricular haemorrhage	14.4	35.9
Necrotizing enterocolitis	3.89	2.75
Pneumonia	21.4	23.4
Pneumothorax	8.56	10.3
Sepsis	20.2	36.5

BW = Birth Weight; ROP = Retinopathy of Prematurity

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Part II – Module SII: Non-Clinical Part of the Safety Specification

PART II Module SII: Non-Clinical Part of the Safety Specification

Introduction

A comprehensive toxicology and safety pharmacology program was conducted to support the clinical use as well as marketing authorization of aflibercept. The monkey was identified as the only relevant species for repeated-dose studies with intravitreal (IVT) administration. This module summarizes the relevant non-clinical findings for the 2 mg and 8 mg applications. As an overall conclusion, none of the non-clinical findings are considered a safety concern for aflibercept requiring risk management activities other than information *via* the suggested label.

SII.1 Key Safety findings (from non-clinical studies) and relevance to human usage

Table SII.1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
• Potential to impair fertility. • Potential to be embryo-fetotoxic.	*Results from animal studies with high systemic exposure indicate that aflibercept can impair male and female fertility. Such effects are not expected after ocular administration with very low systemic exposure.* *Although the systemic exposure after ocular administration is very low, aflibercept should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.* *Aflibercept is not recommended in women of childbearing potential not using contraception.* *Appropriate contraception during the treatment and for at least 3 months after the last administration of aflibercept 2 mg or 4 months after the last administration of 8 mg has to be indicated for women who could possibly become pregnant.* *The malformations and variations observed after systemic treatment with aflibercept in the embryo-foetal development studies occur early in organogenesis and are not expected to occur after IVT administration of aflibercept in preterm infants with ROP, as the major organ systems affected are already fully developed in this population.*

Repeat-dose toxicity

Repeated monthly IVT administration of aflibercept to monkeys for up to 8 months with the 2 mg aflibercept formulation (with bilateral doses of 0.5, 2 and 4 mg/eye) and up to 6 months in a bridging study with the 8 mg aflibercept formulation (with bilateral doses of 4 and 7 mg/eye) was not associated with ocular effects considered adverse. Based on the difference in vitreous volume between monkeys and humans (2 mL in monkey *vs.* 4 mL in humans), the dose used in the monkey eye corresponds to a doubled dose in the adult human eye (i.e., the dose of 4 mg/monkey eye, corresponds to the clinical dose of 8 mg/adult human eye). Ocular

findings were limited to inflammation that was generally mild and reversed completely or mostly by 4-weeks post-dose.

Erosions and ulcerations of the respiratory epithelium of the nasal turbinates were observed in individual animals treated at and above the clinical dose of 2 mg/eye in the 8-month study on the 2 mg aflibercept formulation and with mostly low severity at the end of the dosing period. Although these lesions had not completely resolved after recovery, data indicate reversibility after the treatment free 4-month recovery period.

Similar to that, microscopic findings at terminal necropsy in the 6-month IVT bridging study on the 8 mg aflibercept formulation were limited to erosion and/or ulceration, squamous metaplasia, and minimal haemorrhage of the respiratory epithelium in the nasal turbinates in animals administered aflibercept at 4 or 7 mg/eye. At the dose of 4 mg/monkey eye, which - based on differences in vitreous volume - corresponds to the clinical dose of 8 mg/adult human eye, the findings of the respiratory epithelium of the nasal turbinates were mostly mild and reversible. At recovery sacrifice, no nasal turbinate ulceration was noted for animals administered aflibercept. The incidence and severity of lesions at the end of the 3-month recovery phase were lower compared with the terminal sacrifices at the end of the treatment period consistent with recovery. Similar nasal turbinate findings were also observed in two other arms of this study with repeated IVT administration of aflibercept 8 mg in different formulations for 3-months.

An additional 3-month repeat-dose IVT toxicology study using clinically relevant high dose aflibercept formulation enriched with 6% and 10% high molecular weight species was conducted to support the specification of aflibercept 8 mg. This study demonstrated ocular tolerability and did not reveal any nasal turbinate findings at the administered bilateral dose of 5.6 mg/eye. In contrast to all other IVT studies in monkeys, in which a dose volume of 50 µL/eye was injected, only 40 µL/eye was administered in the current study. Assessing adverse events in clinical trials on adult patients including a sub-study of one of the pivotal Phase III studies (VIEW 2), serial nasal endoscopy and ears/nose/throat (ENT) specialist examinations of patients treated with 2 mg aflibercept per eye did not reveal any occurrence of these findings following repeated IVT dosing of aflibercept. In the PULSAR (nAMD Phase 3), CANDELA (nAMD Phase 2), and PHOTON (DME Phase 2/3) studies, an analysis of treatment emergent adverse events of nasomucosal findings was conducted with no indication of a safety signal in the 8 mg aflibercept groups compared to 2 mg (Module 2.7.4). The lack of a safety signal following IVT administration of 2 mg (as the comparator group) in these studies is consistent with all prior clinical trials and post-marketing safety experience with aflibercept 2 mg.

Since preterm infants with ROP have lower safety margins and could be more sensitive than adult patients with regard to changes of the nasal epithelium after IVT treatment with aflibercept, monitoring for nasal bleeding was included in the Phase III Study 20090 (FIREFLEYE). No cases of nasal bleeding were observed in this study in ROP patients treated with Aflibercept.

The target-organ toxicities observed after systemic administration of aflibercept occurred at exposures well in excess of the exposures achieved after IVT administration in adult patients and are, therefore, not considered relevant for the intravitreal use of aflibercept in this patient population. The above clinical data of the ENT sub-study resolved the possibly remaining concerns for adult patients. Target organs, which appeared already at the LOAEL of the

studies with systemic administration were especially the kidneys, the growth plates of the bones, and the nasal cavities/sinuses. Due to the above-mentioned reasons, the Phase III Study 20090 (FIREFLEYE) in premature infants with ROP included monitoring for nasal bleeding, proteinuria and growth. No effects on these parameters were observed. Since the development of many organ systems, such as the kidney or the skeleton, continues in a preterm infant, growth and development of ROP patients enrolled in the clinical study are monitored for a prolonged follow-up period to 5 years of age by enrolment into a long-term follow-up study (FIREFLEYE NEXT, extension study 20275).

Reproductive and developmental toxicity

Effects on male and female fertility were assessed as part of the 6-month studies in monkeys with weekly intravenous (IV) administration of aflibercept at doses ranging from 3 to 30 mg/kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. Based on maximum concentration (C_{max}) and area under the concentration time curve (AUC) for free aflibercept observed at the 3 mg/kg IV dose in monkeys, the systemic exposures were approximately 4,900-fold (in terms of C_{max}) and 1,500-fold higher (in terms of AUC), respectively, than the exposures observed in adult patients after unilateral IVT administration of 2 mg/eye, and approximately 606-fold and 91-fold higher, respectively, than the population PK-estimated exposures in adult patients after unilateral IVT administration of 8 mg/eye. They are, therefore, considered not relevant for the intravitreal use of aflibercept. All changes were reversible.

No changes to reproductive organs were observed after IVT administration of aflibercept in monkeys.

Based on its mechanism of action, aflibercept is expected to affect embryo-foetal development. This was shown in an embryo-foetal development study in pregnant rabbits with IV administration (3 to 60 mg/kg). At 60 mg/kg foetal resorptions, pregnancy disruptions and numerous foetal (external, visceral and skeletal) malformations were observed. The maternal "No Observed Adverse Effect Level" (NOAEL) was the dose of 3 mg/kg, whereas the developmental NOAEL was not identified, since at 3 mg/kg still signs of embryo-foetal toxicity were observed.

At the lowest dose of 3 mg/kg, systemic exposures of free aflibercept were approximately 600- to 2,000-fold in excess of the maximum human exposure in adult patients after a unilateral IVT administration of 2 mg/eye as well as approximately 364- to 40-fold in excess of the population PK-estimated human exposure in adult patients after a unilateral IVT administration of 8 mg/eye (based on C_{max} and AUC, respectively).

In a combined early embryonic/embryo-foetal development study with aflibercept in pregnant rabbits with subcutaneous (s.c.) administration (0.1 to 1 mg/kg) starting at gestation day (GD) 1, no influence on maternal toxicity, gestation rate, post-implantation loss, placental weight, placental appearance, foetal sex distribution, or foetal weight was observed at all doses tested. The overall rate of cardiac ventricular septal defects (with/without malformation of major vessels), and skeletal malformations was slightly higher in aflibercept treated than control animals but showed no clear dose-dependency. A “spina bifida”" was seen in a single foetus from each of 2 different dams that received 0.1 mg/kg during gestation. A “meningocele” was seen in 1 foetus from a single dam that received 1.0 mg/kg during

gestation. Based on the results of this study, the maternal NOAEL was considered to be 1 mg/kg.

The developmental NOAEL was not identified. Comparison of the systemic exposures observed in this study with population PK-estimated mean exposures in adult patients indicate an exposure margin of approximately 10-fold following a unilateral 2 mg/eye dose or 0.9-fold following a unilateral 8 mg/eye dose, respectively, (based on mean AUC for free aflibercept).

These data support that treatment with aflibercept is not recommended during pregnancy unless the potential benefit outweighs the potential risk to the foetus. Likewise, aflibercept is not recommended in women of childbearing potential not using contraception.

The malformations and variations observed in the embryo-foetal development studies on aflibercept develop early in organogenesis whilst in preterm infants with ROP, development of the affected organ systems is already completed. Therefore, similar effects are not expected to occur after IVT treatment of these patients with aflibercept. Overall, from these data, there were no undue risks identified for the IVT treatment of premature infants presenting with ROP.

Organ toxicity (Nephro-/Hepatotoxicity)

No signals indicating a potential for nephro- or hepatotoxicity were observed following intravitreal administration in any of the studies conducted on the 2 mg aflibercept formulation as well as on the 8 mg aflibercept formulation.

Genotoxicity

In accordance with International Council for Harmonisation (ICH) guideline S6, no genotoxicity studies were conducted. Since aflibercept is a large biotechnology-derived molecule, it is not expected to interact directly with deoxyribonucleic acid (DNA) or other chromosomal material.

Carcinogenicity

No studies explicitly targeting carcinogenicity were conducted. Based on studies performed so far, there is no evidence that aflibercept (or other VEGF-inhibitory compounds) act as growth factors or are immunosuppressive. Therefore, currently there is no reason to suspect that aflibercept has a tumorigenic potential.

General safety pharmacology/Drug interactions

Effects of aflibercept on blood pressure and wound healing were only observed following systemic administration. Exposures after systemic administration were substantially above those following IVT injection. Therefore, IVT administration of aflibercept is not expected to exert appreciable effects on VEGF-mediated processes outside of the eye of adult patients. Since safety margins are low in preterm infants for blood pressure increases, blood pressure measurements were included in the Phase III Study 20090 (FIREFLEYE). Analyses showed that plasma aflibercept concentrations were not related to changes in systolic or diastolic blood pressure.

In the CANDELA Phase II and PULSAR/PHOTON Phase III studies, no clinically meaningful changes in blood pressure were observed with the treatment of 8 mg aflibercept.

Since no overlapping substrate specificity in the metabolism of aflibercept and potentially co-administered small molecule drugs has to be expected, no drug interaction studies have been performed.

Conclusions on non-clinical safety data

The following conclusions can be derived from the non-clinical data outlined above:

No important identified risks (confirmed by clinical data) were identified.

The non-clinical safety studies performed in monkeys and rabbits with systemic administration of aflibercept, suggest a potential of aflibercept to impair fertility and to exert embryo-fetotoxic effects. However, the systemic exposure to free aflibercept in the IV monkey study investigating fertility was distinctly higher than the exposure observed in adult patients following unilateral intravitreal injection of 2 mg or the population PK-estimated exposure following unilateral intravitreal injection of 8 mg/eye. Overall, aflibercept should not be administered during pregnancy, unless the potential benefit outweighs the potential risk to the foetus, and aflibercept is not recommended in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose of 2 mg/eye or 4 months after the last dose of 8 mg/eye. Clinical data on this issue are currently not available. The occurrence of embryo-fetotoxicity (regarded as important potential risk) is an objective of routine pharmacovigilance monitoring. The effects on the developing embryo/foetus observed in the embryo-foetal development studies occur early in organogenesis. They are not expected to occur after IVT administration of aflibercept in preterm infants with ROP, as major organogenesis is already complete in this population.

Erosions and ulcerations of the respiratory epithelium of the nasal turbinates, which were observed in monkeys in repeat-dose IVT studies with the 2 mg aflibercept as well as with 8 mg aflibercept formulations and treatment durations from 3 to 8 months, occurred from bilateral doses of 2 mg/eye and at a dose volume of 50 µL/eye. In contrast, no nasal turbinate findings were seen in another 3-month IVT study on the 8 mg aflibercept formulation with enhanced impurity levels after application of 5.6 mg/eye at a dose volume of 40 µL/eye and higher systemic exposure than in the other IVT studies (C_{max}: 20 *vs.* 6- 11 µg/mL, $AUC_{(028\ days)}$: more than 5,000 µg·h/mL *vs.* 2,000 to 3,400 µg·h/mL). These data suggest that local exposure to aflibercept, i.e., leakage of aflibercept formulation after administration of higher dose volumes from 50 µL/eye onwards from the injection canal *via* the nasolacrimal duct, might lead to nasomucosal changes in monkeys, while this is not observed after injection of 40 µL/eye. Based on difference in vitreous volume between monkey and human (2 mL in monkey *vs.* 4 mL in humans) it can be expected that an application volume of 80 µL per eye will be tolerated without remarkable leakage from the injection site after IVT dosing in human patients, thus covering the clinically used dose volume of 70 µL/eye for aflibercept 8 mg. This fits to the fact that nasomucosal lesions were also not confirmed in a targeted sub-study within the clinical Phase III study VIEW 2 with a dose of 2 mg/eye and a dose volume of 50 µL/eye. In the PULSAR (nAMD Phase 3), CANDELA (nAMD Phase 2), and PHOTON (DME Phase 2/3) studies, an analysis of treatment emergent adverse events of nasomucosal findings was conducted with no indication of a safety signal in the 8 mg aflibercept groups compared to 2 mg (Module 2.7.4). The lack of safety signal following IVT administration of 2 mg (as the comparator group) in these studies is consistent with all

prior clinical trials and post-marketing safety experience with aflibercept 2 mg. In the Phase III Study 20090 (FIREFLEYE) in preterm infants with ROP, monitoring for nasal bleeding was included, since this patient population could be more sensitive with regard to changes of the nasal epithelium after IVT treatment with aflibercept and has a higher systemic exposure than adults. Again, no cases of nasal bleeding were observed in this study.

Due to the low systemic exposure following the IVT route of administration, aflibercept is generally not expected to exert appreciable effects on VEGF-mediated processes outside of the eye. To confirm this also in preterm infants with ROP, target organs like the kidneys, growth plates of the bones, and the nasal cavities/sinuses, which appeared already at the LOAEL of the toxicological studies with systemic administration were included in the monitoring of the Phase III Study 20090 (FIREFLEYE). No cases of nasal bleeding, proteinuria and no effects on growth were observed in this study. Since the development of organ systems such as the kidney or the skeleton continues in a preterm infant, growth and development of ROP patients enrolled in the clinical study will be monitored through 5 years of age in a long-term follow-up study (FIREFLEYE NEXT, extension study 20275).

No signs of hepatotoxicity or nephrotoxicity were observed in the nonclinical toxicology program.

Studies focusing on genotoxicity, carcinogenicity, or drug interactions were not performed, since such endpoints are not applicable to the drug or are not relevant for IVT treatment.

Blood pressure increases were observed after systemic administration of aflibercept in safety pharmacology studies in rodents. Since safety margins are low for this parameter in preterm infants, blood pressure was monitored in the Phase III Study 20090 (FIREFLEYE). No correlation between change in blood pressure and concentrations of free aflibercept was observed in this study.

In the 8 mg aflibercept CANDELA Phase II study no nasal mucosal adverse events were reported. Similarly, in the Phase III studies PULSAR/PHOTON no signal pertinent to nasal erosions/ulcerations were observed through week 48 under 8 mg aflibercept therapy.

Currently, there is no need for additional non-clinical investigations or research activities.

PART II: Module SIII: Clinical Trial Exposure

SIII.1 Brief overview of development

Eylea (international non-proprietary name: aflibercept) was developed by Bayer AG and Regeneron Pharmaceuticals, Inc., as an effective treatment for a number of ophthalmologic conditions.

SIII.1.1 Development in the indication "wet age-related macular degeneration (wet AMD)"

SIII.1.1.1 Wet AMD (Eylea 40 mg/mL, 2 mg dose)

The initial clinical development program for the indication neovascular (wet) age-related macular degeneration (AMD) consisted of 4 studies.

In 2005, the clinical development program was initiated by Regeneron Pharmaceuticals, Inc. with the start of the Phase-1 study VGFT-OD-0502 (SN 14395). This study provided the first evidence of a dose-response in the bioeffects of intravitreally (IVT) administered Eylea and indicated that single doses of less than 0.5 mg Eylea were associated with sub-optimal effects. At higher single doses, however, Eylea was associated with improvements in visual acuity and improvements in morphologic characteristics of the choroidal neovascularization (CNV) lesion. These improvements, which were evident for at least 1 month after a single injection, provided the first evidence of the durability of the effect of IVT Eylea in subjects with wet AMD.

In Phase-2 study VGFT-OD-0508 (SN 14394), which assessed 0.5 mg and 2 mg Eylea administered monthly or every 12 weeks and 4 mg Eylea administered every 12 weeks, all treatment groups experienced improvements in visual acuity as early as Week 1 and these improvements were maintained through Week 12 (the assessment of the primary efficacy endpoint). The improvement in visual acuity was maintained during Weeks 16 through 52 with an average of only 2 additional doses during this time. These results and the time course of improvements suggested that initiating treatment with 3 monthly injections was associated with a better outcome than a single injection of either 2 mg or 0.5 mg. In addition, the improvements in visual acuity were similar in all treatment groups at Week 8, suggesting that, in principle, the effects of Eylea may be maintained over an 8-week dosing interval without compromising efficacy. In the subsequent flexible-dosing phase of the study, when criteria-based dosing allowed for prolonged dosing intervals (i.e., subjects were only retreated if one or more of the protocol-specified retreatment criteria was met and there was no limit to how long a subject could go between treatments) the 0.5 mg dose did not perform as well as the 2 mg dose.

The dosing rationale for the Phase-3 studies was based on the improvements in best-corrected visual acuity (BCVA) seen in VGFT-OD-0508 (SN 14394) and the improvements in morphologic endpoints as assessed by optical coherence tomography (OCT) and fluorescein angiography (FA). The two pivotal studies (VIEW 1 [1y] and VIEW 2 [1y]) compared 0.5 mg and 2 mg Eylea dosed monthly and 2 mg Eylea dosed every two months (after an initial three-monthly injections) to ranibizumab 0.5 mg dose monthly. The rationale for including 2 mg Eylea dosed every two months was based on the observation from VGFT- OD- 0508 (SN 14394) that, at Week 8, improvements in visual acuity after a single 2 mg dose were similar to those obtained with 2 mg dosed monthly, suggesting that a longer and less

burdensome dosing interval (i.e., every 8 weeks) may be possible without sacrificing efficacy. In Year 2, the mandatory dosing interval was extended to 12 weeks, but subjects were allowed to receive injections more often, if certain re-treatment criteria were fulfilled (the treatment scheme in Year 2 is referred to as "modified quarterly dosing").

In the pivotal studies (VIEW 1 [1y] and VIEW 2 [1y]), the primary endpoint, proportion of subjects maintaining vision at Week 52, was met for all Eylea treatment regimens, was duplicated in both pivotal studies and the integrated analysis (1y) of the data from the pivotal studies, and established the non-inferiority of Eylea to ranibizumab (at a pre-specified 10% margin). The statistical test sequence employed in the two pivotal studies showed confirmatory results with very narrow confidence intervals.

In conclusion, administration of 2 mg Eylea administered every two months produced essentially the same efficacy results as monthly dosing of 2 mg Eylea or monthly dosing of 0.5 mg ranibizumab in subjects with wet AMD. In particular, this was clearly apparent in terms of the primary and clinically most important measure in the pivotal Phase-3 studies, visual acuity.

The efficacy and safety results from the pivotal Phase-3 studies showed that with 2 mg Eylea dosed every two months, subjects with wet AMD can undergo less frequent intravitreal injections, which are associated with certain risks, without sacrificing efficacy. While it cannot be excluded that a more frequent dosing with 2 mg Eylea could lead to even better results in some subjects, the vast majority of clinical subjects receiving 2 mg Eylea every two months, after three initial monthly doses, showed robustly good and durable improvements in vision as well as morphologic characteristics of the CNV lesion.

The results in Year 2 of the studies showed that the improvements achieved after 1 year of treatment were largely maintained on modified quarterly dosing with Eylea, particularly in those subjects continuing an exclusively proactive treatment. The latter were those just receiving the mandatory 3 injections over the course of Year 2.

Therefore, it can be concluded, that the benefits, in particular the possibility of prolonged, proactive dosing intervals of 8 weeks (or even longer, as suggested by the large proportion of subjects who were exclusively treated at intervals of 12 weeks in Year 2 of the pivotal studies) of a Eylea therapy, clearly outweigh potential risks arising from its use. Overall, the dosing experience in Year 1 and Year 2 of the pivotal studies suggested that Eylea treatment should be initiated with 1 injection per month for 3 consecutive months, followed by one injection every 2 months. After the first 12 months of treatment, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections.

Based on these results and the favourable benefit/risk balance, the US Food and Drug Administration (FDA) was the first health authority to approve Eylea for the indication of wet AMD on 18 NOV 2011; EU approval was granted on 22 NOV 2012.

Patients originally enrolled in VIEW 1 who completed the core study period of 96 weeks had the opportunity to continue (or start) treatment with Eylea 2 mg in the open-label extension

study VGFT-OD-0910 (SN 14832). A total of 320 out of 323 enrolled[1] patients from VIEW 1 received extension treatment in the study eye at individual injection intervals ranging from 4 to 12 weeks for an additional mean treatment duration of 25.8 months (range: 1 to 41 months). In conclusion, visual acuity as measured by BCVA was largely maintained with repeated long-term treatment, and treatment with Eylea was generally safe and well tolerated. No new safety signals were observed in this long-term extension study.

An additional AMD study was SIGHT (SN 13406), a randomized, double-masked, photodynamic therapy-controlled Phase III study of the efficacy, safety, and tolerability of IVT VEGF Trap-Eye in Chinese subjects with wet AMD. In addition to the exposure data, the safety results observed in the VIEW 1 extension study and in SIGHT were also considered in this RMP version.

Another additional study included in this RMP version is ALTAIR (SN 17668). This randomized, open-label Phase IV study assessed the efficacy and safety of intravitreal administration of aflibercept with two different approaches of Treat and Extend dosing regimen in Japanese subjects with wet AMD for up to 2 years; the 1-year data are considered for this RMP version.

SIII.1.1.2 Wet AMD (Eylea 114.3 mg/mL, 8 mg dose)

The clinical development program for the 8 mg (High Dose, HD) aflibercept dose in the indication wet AMD consists of 2 studies:

A randomized, single-masked, active-controlled Phase II study CANDELA was conducted. The primary objectives of the study were to determine the safety of 8 mg aflibercept injection and to determine if 8 mg aflibercept provided greater intraocular pharmacodynamic effect and/or longer duration of action compared to 2 mg intravitreal aflibercept injection. Fifty-three patients were randomized to receive 2 mg intravitreal aflibercept (IAI group) and 53 to receive 8 mg intravitreal aflibercept (high dose group, HD group). Overall, the mean (SD) duration of treatment in the study eye was 36.9 (7.77) weeks in the IAI group and 37.7 (4.52) weeks in the HD group. Results of the CANDELA study showed that:

- A numerically higher proportion of participants in the HD group compared with IAI group showed improvement in anatomical outcomes (dryness in centre subfield, dry macula, absence of subretinal fluid in the centre subfield and in the macula) at week 16 and 44.
- A numerically higher improvement in BCVA was observed in the HD group when compared with the IAI group. A numerically higher proportion of participants in the HD group achieved a clinically meaningful BCVA gain of ≥ 10 letters and ≥ 15 letters from baseline.
- The HD group showed a numerically greater median reduction in central retinal thickness when compared with the IAI group at weeks 16 and 44.
- The HD group showed numerically greater reduction in total lesion size and choroidal neovascularisation size at Week 44.

[1] Please note: Three subjects enrolled in the VIEW 1 extension study received Eylea 2 mg at Week 96 in the original VIEW 1 study (not counted for the VIEW 1 study exposure) but did not receive further treatment in the extension study. These 3 patients are considered for the safety analyses in the VIEW 1 extension study, and the 3 active injections at Week 96 are considered for the calculation of the AMD and overall exposure across studies.

- Treatment with IAI and HD was well-tolerated and both the ocular and systemic safety profile of HD and IAI were similar. No new safety signals were identified.

The Phase III randomized, double-masked, active-controlled study PULSAR week 96 results are displayed in this RMP. The primary objective at week 48 was to determine if treatment with 8 mg aflibercept at intervals of 12 or 16 weeks provides non-inferior BCVA change compared to 2 mg aflibercept every 8 weeks in participants with wet AMD.

- 336 patients were randomized to receive 2 mg intravitreal aflibercept every 8 weeks (2q8) after 3 initial injections at 4-week intervals
- 335 patients to receive 8 mg intravitreal aflibercept every 12 weeks (HDq12) after 3 initial injections at 4-week intervals
- 338 patients to receive 8 mg intravitreal aflibercept every 16 weeks (HDq16) after 3 initial injections at 4-week intervals

During the first year, all patients in the HD groups could qualify for interval shortening based on protocol specified dose regimen modification (DRM) criteria beginning at week 16 (patients in the HDq12 group could be shortened to 8 weeks and patients in the HDq16 group could be shortened to 12 or 8 weeks). The minimum interval allowed between injections was 8 weeks, which was considered a rescue regimen for patients unable to tolerate a dosing interval greater than every 8 weeks. During the second year, patients could also qualify for interval shortening or interval extension by 4-week increments, based on protocol specified DRM criteria. Patients randomized to 2q8 remained on a fixed Q8 dosing regimen through week 96 (i.e., did not have modifications of their treatment intervals regardless of the outcomes of the DRM assessments).

For the primary endpoint, the week 48 data of the PULSAR study showed non-inferiority of the 8 mg doses, HDq12 and HDq16, versus the treatment with the comparator 2q8. The following overall conclusions were made:

- Treatment with HD aflibercept at intervals of 12 or 16 weeks provided non-inferior increases in BCVA from baseline at Week 48 compared to treatment with 2 mg aflibercept every 8 weeks.
- Treatment with HD aflibercept was superior to treatment with 2 mg aflibercept in that 11.7% points more participants in the combined All HD group (combined HDq12+HDq16) than in the 2q8 group had no IRF and no SRF in central subfield at Week 16.
- The non-inferior visual acuity outcomes in the HDq12 and HDq16 groups compared to 2q8 were achieved with the majority of participants remaining on their randomized treatment interval: 79% and 77%, respectively. This led to a clinically meaningful reduction in the number of injections over 48 weeks compared to treatment with 2 mg aflibercept every 8 weeks.
- Overall, 83% of participants in all HD group were able to be maintained on a dosing interval of 12 weeks or longer with 8 mg aflibercept treatment, while 17% of participants did require shortening of the dosing interval to 2q8.
- Immunogenicity was low across all treatment groups. None of the ADA positive samples were found to be positive in the Neutralizing (NAb) assay.

- Review of the safety data did not reveal any new signals or adverse trends in the HD (8 mg dose) aflibercept groups compared to the 2 mg group. No new adverse drug reactions were identified. The ocular and systemic safety profile of aflibercept HD was consistent with the established safety profile of aflibercept 2 mg.

All week 48 efficacy variables were analyzed descriptively at week 96, as applicable. For change from baseline in BCVA measured by ETDRS letter score at week 96, HDq12 and HDq16 treatment groups both met the non-inferiority criteria that had been specified for the primary endpoint at week 48 when compared to the 2q8 treatment group. Through week 96, 75.3% of completers in the HDq12 group and 70.2% of completers in the HDq16 group maintained their randomized treatment interval. The analysis of the key secondary endpoint at week 96 was numerically higher in the HDq12 group compared to the 2q8 and the HDq16 groups. In addition, 37.8% and 48.6% of patients in the HDq12 and HDq16 groups, respectively, were maintained and extended to an interval of 20 weeks or longer (without having their interval shortened at any time), and 40.5% and 53.1% of patients in the HDq12 and HDq16 groups respectively, were assigned to a last intended dosing interval of ≥ 20-week interval through week 96. The analysis of the key secondary endpoint (no IRF and no SRF) at week 96 was numerically higher in the HDq12 group compared to the 2q8 and the HDq16 groups.

Based on these results and the favourable benefit/risk profile, the US Food and Drug Administration (FDA) was the first health authority to approve Eylea 114.3 mg/mL for the indication of wet AMD on 18 AUG 2023; EU approval was granted on 05 JAN 2024.

SIII.1.2 Development in the indication "macular edema secondary to central retinal vein occlusion (CRVO)" (Eylea 40mg/mL, 2 mg dose)

The clinical development program for the indication “macular edema secondary to central retinal vein occlusion (CRVO)” comprised two pivotal Phase III studies, each comparing 2 mg Eylea IVT injections every 4 weeks (2Q4) for 20 weeks with sham injections every 4 weeks. Eligible subjects in both studies were randomized using a ratio of 3: 2 (Eylea:sham), with stratification by geographic region and baseline BCVA.

In the first 24-week period of both studies (i.e., Week 0 to Week 20), subjects received either 2 mg Eylea IVT injections every 4 weeks (2Q4), or sham injections every 4 weeks. The sham injection was performed by pressing a syringe barrel with no active drug to the conjunctival surface (without a needle or intraocular penetration).

In the next 28-week period (Week 24 through Week 52), subjects in both studies were evaluated monthly. In the COPERNICUS study, subjects in both treatment groups were eligible to receive either Eylea 2 mg IVT injections as clinically needed (PRN), according to protocol-defined retreatment criteria, or sham injections. In the GALILEO study, subjects in the Eylea group received either Eylea 2 mg IVT injections PRN, according to protocol-defined retreatment criteria, or sham injections. Subjects in the sham group continued to receive only sham injections.

Starting at Week 52, all subjects in the COPERNICUS study were eligible to continue in a 1-year PRN extension. Subjects were evaluated quarterly to receive 2 mg Eylea IVT injections according to the re-treatment criteria. Sham injections were not given during this period. If, in the investigator’s opinion, subjects required more frequent dosing, they may have been dosed as frequently as every 4 weeks.

Starting at Week 52, all subjects in the GALILEO study were eligible to continue in a 6-month PRN extension, with follow-up visits every 8 weeks through Week 76. In the Eylea treatment group, subjects received either 2 mg Eylea IVT injections or sham injections, according to the retreatment criteria. In the sham group, subjects received 2 mg Eylea at Week 52 unless the masked investigator decided for medical reasons that study drug treatment was not in the best interest of the subject. If Eylea was not administered at this visit, the subject received sham treatment. At Weeks 60 and 68, subjects in the sham group received either Eylea or sham treatment depending on the same retreatment criteria used from Week 24 in the Eylea treatment group. No treatments were administered at Week 76.

All subjects were eligible to receive panretinal photocoagulation (PRP) at any time during the study if they progressed to clinically significant ocular neovascularization.

The primary efficacy variable in both studies was the proportion of subjects who gained 15 letters or more of BCVA (using the ETDRS protocol) over baseline at Week 24. The primary efficacy variable was supported by secondary efficacy variables of change in BCVA from baseline to Week 24, change in CRT from baseline to Week 24, proportion of subjects progressing to any neovascularization by Week 24, and change in NEI VFQ-25 total scores from baseline to Week 24. Tertiary variables were assessed at the 52-week endpoint. Efficacy variables were assessed for each study individually (i.e., COPERNICUS and GALILEO) and in an integrated analysis of the pooled 6-month data from the two Phase-3 studies.

In both studies, Eylea administered 2Q4 was shown to be superior to sham treatment with regard to the proportion who gained ≥ 15 letters of vision during the first 24 weeks of treatment. In addition, all other efficacy results (i.e., secondary and tertiary) showed robust benefits. The results of the individual studies and the integrated analysis were consistent over all parameters investigated and confirmed the superiority of Eylea for improving visual acuity over observation alone in subjects with macular edema (ME) secondary to CRVO.

This clinical effect was largely sustained on continued active treatment with Eylea with less frequent PRN dosing up to Week 52 and a significant benefit of treatment was still shown at Week 76 (in GALILEO) or Week 100 (in COPERNICUS). However, the switch from proactive, fixed dosing at Week 24 to reactive PRN dosing gradually led to a mean loss up to approximately 1 line of BCVA. Moreover, the loss was accelerated when the monitoring interval was extended from 4 up to 12 weeks after the first year, suggesting that a proactive regimen might be more adequate to maintain achieved gains. Similar results were seen with most of the other efficacy measures.

Subgroup analyses showed that there are no restrictions regarding efficacy of Eylea in relation to organ function such as renal impairment, liver function, or diabetes status.

Overall, IVT injections of Eylea were safe and well tolerated. Differences seen in the incidence of some disease-related adverse events between the 2Q4 and PRN dosing phases may represent a de-stabilization of the disease with reactive PRN dosing that was well controlled with the proactive fixed-dosing regimen.

Based on these results and the favourable benefit/risk balance, the US Food and Drug Administration (FDA) was the first health authority to approve Eylea for the indication CRVO on 21 SEP 2012. In Europe, Eylea was approved by the EMA in the CRVO indication on 26 AUG 2013. In Japan, treatment of CRVO with Eylea was approved by the Japanese Ministry of Health, Labour and Welfare (MHLW) in NOV 2013.

EYLEA®
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EU Risk Management Plan
Part II – Module SIII: Clinical Trial Exposure

SIII.1.3 Development in the indication "macular edema secondary to branch retinal vein occlusion (BRVO)" (Eylea 40 mg/mL, 2 mg dose)

The BRVO clinical development program was initiated by Regeneron Pharmaceuticals, Inc., building directly from the clinical development program of the approved indications AMD and CRVO (see aforementioned considerations). The design of the Phase III BRVO development program was based on advice given at several scientific advice meetings/letters with CHMP and FDA.

The clinical development program for BRVO consisted of one pivotal Phase III study (SN 15432, VGFTe RVO-1027, VIBRANT). VIBRANT was a randomized, double-masked, active controlled 52-week study of the efficacy, safety, and tolerability of repeated IVT administration of VEGF Trap-Eye compared with grid laser photocoagulation in subjects with macular edema secondary to BRVO. A total of 183 patients were randomized and exposed to study treatment (91 in the Eylea group and 92 in the laser group). The study was conducted by Regeneron Pharmaceuticals, Inc. in North America (USA, Canada) and Japan. The primary endpoint was the proportion of subjects who gained at least 15 letters in BCVA from baseline to Week 24. Study treatment (up to 48 weeks, followed by a 4 week observation period) was completed with LPLV on 10 MAR 2014.

Week 24 analyses showed that 53% of patients who received Eylea 2Q4 gained at least 15 letters in vision from Baseline at Week 24, compared to 27% of patients who received standard-of-care treatment with macular grid laser (primary endpoint; p <0.001). At Week 24, patients who received Eylea 2Q4 achieved a 17.0 letter mean improvement over Baseline in BCVA (a secondary endpoint) compared to a 6.9 letter mean improvement in patients who received laser (p <0.0001).

The final study data observed at Week 52 showed that the efficacy achieved at Week 24 (time of primary endpoint assessment) was maintained through Week 52, even with the treatment interval increased from monthly to every 8 weeks during the second study half: Subjects in the Eylea 2 mg group still demonstrated a nominally significant improvement in mean change in BCVA over subjects in the Laser+Eylea 2 mg group[2] from Baseline to Week 52 (mean change of 17.1 *vs*. 12.2 letters, LS mean change difference 5.2 letters, 95%- CI: [1.7; 8.7], p=0.0035; FAS Last-Observation-Carried-Forward [LOCF]), treatment initiated with Eylea provided a higher proportion of subjects with an increase of ≥15 letters in BCVA at Week 52 compared to Laser + Eylea treatment (57.1% *vs*. 41.1%, adjusted difference 16.2%, 95%-CI: [2.0; 30.5], p = 0.0296; FAS LOCF), and Eylea led to a mean reduction in CRT, which was greater than Laser+Eylea 2 mg at Week 52 (mean change of -283.9 *vs*. -249.3 microns, LS mean change difference -29.5 microns, 95%- CI: [-54.7; -4.4], p=0.0218; FAS LOCF). The subjects in the Laser+Eylea 2 mg group, who were not exposed to Eylea through Week 20, benefitted from the rescue treatment option with VEGF Trap-Eye (beginning at Week 24, if pre-specified eligibility criteria were met) by gaining approximately 5 letters in BCVA (1 line of vision) from Week 24 to Week 52.

Overall, the incidence of ocular TEAEs in the study eye through Week 52 was similar between the 2 groups (47.8% in the Laser+Eylea 2 mg group and 49.5% in the Eylea 2 mg group). Likewise, the incidence of non-ocular TEAEs was similar between groups (68.5%

[2] Patients randomized to initial laser treatment had the opportunity to be treated with Eylea from Week 24 onwards (i.e., after the evaluation for the primary endpoint), if pre-specified eligibility criteria were met.

Laser+Eylea 2 mg and 67.0% Eylea 2 mg). The most common ocular TEAEs (≥5%) in the study eye were "conjunctival hemorrhage" (15.2% in the Laser+Eylea 2 mg group and 24.2% in the Eylea 2 mg group; this difference was due to the lower number of penetrating injections in the Laser+Eylea 2 mg group), "eye pain" (7.6% Laser+Eylea 2 mg and 5.5% Eylea 2 mg), and "eye irritation" (1.1% Laser+Eylea 2 mg and 7.7% Eylea 2 mg). Other individual ocular TEAEs in the study eye were low and mostly balanced between treatment groups. Treatment-emergent ocular AEs considered by the investigator to be related to the injection procedure in the study eye occurred with a higher frequency in the Eylea 2 mg group (29.7%) than in the Laser+Eylea 2 mg group (19.6%). Also, this difference was probably due to the lower number of penetrating injections in the Laser+Eylea 2 mg group. The incidence of SAEs through Week 52 was slightly higher in the Eylea group (10.9% on Laser+Eylea 2 mg and 15.4% on Eylea 2 mg). Only one study subject (in the Eylea 2 mg group) experienced an ocular SAE in the study eye ("traumatic cataract", which was considered injection-related). No drug-related SAEs were reported. Through Week 52, 2 study subjects experienced an adjudicated Anti-Platelet Trialists Collaboration (APTC) event (both patients were in the Laser+Eylea 2 mg group; "cerebrovascular accident" occurred prior to any Eylea rescue and "myocardial infarction" occurred after first Eylea exposure) and there was one death (this patient, randomized to the Laser+Eylea 2 mg group, died from pneumonia prior to any Eylea rescue). Overall, the observed safety profile trough Week 52 was as expected and in line with the Week 24 safety results. Eylea was generally well-tolerated with a favourable ocular and systemic safety profile after 52 weeks of treatment in this population of subjects with BRVO.

Based on the favourable Week 24 results that were used for the submission of a supplemental Biologics License Application, Eylea was approved for the treatment of BRVO patients by the FDA on 06 OCT 2014, and in the EU on 25 FEB 2015.

SIII.1.4 Development in the indication "choroidal neovascularization secondary to pathologic myopia" (myopic CNV) (Eylea 40 mg/mL, 2 mg dose)

The clinical development program for the indication "choroidal neovascularization secondary to pathologic myopia" consisted of one pivotal Phase III study comparing a single 2 mg Eylea IVT injection followed by additional injections up to every 4 weeks in case of recurring or persisting CNV with sham. Eligible patients were randomized in a ratio of 3:1 (Eylea:sham).

In the first 24-week period of the study, patients received either one mandatory 2 mg Eylea IVT injection at Baseline followed by sham injections every 4 weeks, which could be replaced by additional active injections in case of recurring or persisting CNV, or sham injections every 4 weeks only. Sham injections were performed by pressing a syringe barrel with no active drug to the conjunctival surface (without a needle or intraocular penetration).

In the next study period (Week 24 through Week 44), patients in both treatment arms (i.e., including the patients who were previously treated with sham) were allowed to receive active Eylea 2 mg treatment in the case of recurring or persisting CNV; otherwise, sham injections were administered for masking purposes. Initially, all patients in the sham group received one mandatory active injection at Week 24. Patients were evaluated monthly until Week 48.

The primary efficacy variable was the change in BCVA as assessed following the ETDRS protocol from Baseline to Week 24. The primary efficacy variable was supported by one confirmatory secondary efficacy variable of proportion of patients who gain ≥15 letters in both treatment groups.

Exploratory secondary variables included the proportion of patients who gain or lose certain amounts of letters of BCVA, the change in central retinal thickness assessed on OCT, the change in total CNV lesion size, and leakage as assessed by FA, as well as vision-related Quality of life (QoL) as assessed by NEI-VFQ-25 and general health as assessed by ED-5D.

The primary and secondary efficacy analyses performed at Week 24 demonstrated superiority of Eylea over sham (i.e., no active intervention) in the treatment of myopic CNV. Clinically meaningful improvements compared to sham (with nominal p-values <0.05) were observed in all functional (BCVA) and morphological (CRT, CNV lesion size, leakage area) variables as well as in the NEI VFQ-25 total score. In contrast, the baseline disease conditions in the untreated sham group on average continued to persist, or even had deteriorated by Week 24. Beyond Week 24, the mean change in BCVA was maintained and even slightly increased until Week 48 in the Eylea 2 mg group; exploratory analyses of additional morphological and functional outcomes showed consistent improvements up to Week 48. In the Sham + Eylea 2 mg group, the mandatory start of active treatment with Eylea 2 mg as from Week 24 also resulted in clinically meaningful improvement in all efficacy variables up to Week 48. However, the magnitude of change did not reach the same level as in those patients treated with Eylea from the beginning of the study.

Overall, IVT injections of Eylea were safe and well tolerated through Week 48 in either treatment group. No patient died during the course of the study; the overall rate of treatment-emergent SAEs from Baseline through Week 48 was low with 8 study patients involved (6.6%; N = 122). In the Sham + Eylea 2 mg group, the only SAE (PT: "VA reduced" in one patient [3.2%; N=31]) occurred in the study eye and was considered unrelated to treatment or injection. In the Eylea 2 mg group, 7 patients (7.7%; N = 91) experienced a treatment-emergent SAE, including 3 patients (3.3%) with ocular and 4 patients (4.4%) with non-ocular treatment-emergent SAEs. Only one ocular treatment-emergent SAE (1.1%) occurred in the study eye, a macular hole that was regarded as related to study drug (and injection procedure and study procedure as well). All non-ocular treatment-emergent SAEs were classified as not related to study drug, study procedure, or injection. Only one non-ocular treatment-emergent SAE, a cerebral haemorrhage in the Eylea 2 mg group (1.1%), was classified as an APTC event by the masked Adjudication Committee. Some small differences between treatment groups in the incidence of non-ocular TEAEs were deemed attributable to the 3:1 randomization leading to uneven group sizes.

Based on the favourable benefit/risk balance observed at Week 24, the data obtained from the 15170 study (MYRROR) were submitted in Japan for market approval by PMDA in DEC 2013, and in SEP 2014 the approval for treatment of myopic CNV was received from MHLW. In the EU, Eylea was approved for the treatment of myopic CNV on 28 OCT 2015.

SIII.1.5 Development in the indication "diabetic macular edema" (DME)

SIII.1.5.1 DME (Eylea 40 mg/mL, 2 mg dose)

The clinical development program for the 2 mg dose in the indication "diabetic macular edema (DME)" is comprised of 4 studies.

In 2006, the clinical development program was initiated by Regeneron Pharmaceuticals, Inc. with the start of the Phase I study VGFT-OD-0512. In this safety and tolerability study of IVT administered VEGF Trap-Eye in 5 patients with DME, a single 4 mg IVT dose of VEGF Trap-Eye was well tolerated. No dose-limiting toxicity was observed. Ocular adverse events

(AEs) were mild, and none of the AEs were considered to be related to the study medication. No patient had detectible anti-VEGF Trap-Eye antibodies. Excess retinal thickness (ERT) and total macular volume decreased, and VA improved relative to baseline values.

In the Phase II, double-masked, randomized, controlled study DA VINCI (VGFT-OD-0706) of the safety, tolerability and biological effect of repeated IVT administration of VEGF Trap-Eye in patients with clinically significant DME, 2 doses of IVT administered VEGF Trap-Eye (0.5 and 2 mg) at 3 different dosing schedules (every 4 and 8 weeks, PRN) were compared to macular laser photocoagulation. A total of 221 subjects were randomized and 219 treated. Treatment with VEGF Trap-Eye was superior to laser therapy for the treatment of DME over 24 weeks and 52 weeks. At Week 24, treatment with VEGF Trap-Eye resulted in statistically significantly better mean best corrected visual acuity (BCVA) outcomes (gain of +8.5 to +11.4 letters), and greater mean reductions in retinal thickness (- 127.3 μm to - 194.5 μm) compared to the laser arm (gain of 2.5 letters and reduction of - 67.9 μm, respectively). At Week 52, treatment with VEGF Trap-Eye continued to show greater mean BCVA outcomes (gain of +9.7 to +13.1 letters) and greater mean reductions in retinal thickness (-165.4 μm to -227.4 μm) compared to the laser arm (- 1.3 letters and - 58.4 μm, respectively).

Considering data from the AMD program and from the DA VINCI study, the dose advanced into the Phase III DME program (VIVID-DME and VISTA-DME) was 2 mg, and the dose regimens were every 4 weeks, and every 8 weeks (after 5 initial monthly doses). Although the DA VINCI study was not designed to distinguish among treatment groups, it was noted that a greater proportion of patients lost vision from baseline at Week 52 in the 0.5 mg group as opposed to the 2Q4 group. This further supported the decision to move forward with the 2 mg dose in DME, evaluating 2Q4 and 2Q8 regimens. The additional dose group studied in the DA VINCI study was 2 mg PRN, in which patients received as needed dosing after 3 initial monthly doses, but were required to be monitored on a monthly basis through Week 52. The 2Q8 and 2PRN groups ended up receiving a similar number of injections and had similar visual acuity and anatomic outcomes. In practice, the 2Q8 regimen would result in a lower burden of monitoring, and therefore the 2Q8 regimen was considered more practical than the 2PRN regimen. In addition, every 8-week dosing paradigm has an advantage over the PRN dosing regimen in that treatment is delivered on a proactive basis and not in response to recurrence of disease. Therefore, it was decided not to move forward with the PRN dosing regimen in the Phase III DME program. Fluctuations in the 2Q8 group in CRT after the Q8 interval began led to the inclusion of an additional monthly dose in the Phase III DME program. This was done in an attempt to enhance the maintenance of CRT reduction once the maximum decrease in CRT was attained and augment the improvement in BCVA over the Q8 treatment interval. The addition of an extra dose (at Week 12) deferred the start of the first Q8 interval from week 8 to week 16, resulting in 5 initial monthly doses.

A total of 872 patients were randomized and 865 patients (=SAF) treated in the pivotal Phase III DME studies VIVID-DME (404 subjects) and VISTA-DME (461 subjects). Consistently in both studies, Eylea administered 2Q4 and 2Q8 was shown to be superior to laser treatment with regard to the pre-specified primary efficacy analysis, i.e., the change from baseline in mean ETDRS letter score at Week 52, analysed for the FAS using the LOCF approach. All supportive sensitivity analyses conducted to assess the robustness of these results confirmed the findings of the primary analysis. Also, in the analyses of the secondary efficacy variables the results for all visual acuity and anatomic efficacy variables supported

the conclusion drawn from the primary variable that treatment with 2 mg Eylea once every 4 weeks or once every 8 weeks following 5 initial monthly doses is superior to laser treatment.

Results through Week 100 (2-year analysis) and through Week 148 (3-year analysis) of the studies supported the primary, secondary, and additional endpoints analysed at Week 52 and showed that the effects of treatment with Eylea were maintained in all VA and anatomic endpoints.

The pooled safety analysis of the pivotal Phase III studies through Week 148 showed that Eylea was generally well tolerated.

The overall TEAE rate was without any notable difference compared to the laser treatment. However, since in the laser group, 85% of patients received additional or PRN treatment with VTE, the comparison of AE occurrence between laser and the VTE combined group is of limited value and conclusions should be drawn with caution in the outer years of the studies.

There were no differences compared to laser photocoagulation in the incidence of ocular or non-ocular TEAEs which raise safety concerns, e.g., the differences in drug-related non-ocular/ocular TEAEs, injection procedure-related ocular TEAEs, and non-ocular serious TEAEs.

In general, TEAEs consistent with the injection procedure were more common in the Eylea groups, whereas TEAEs consistent with disease worsening were more common in the laser group.

The most common ocular TEAEs in the study eye were "conjunctival haemorrhage", "cataract", and "eye pain". Most ocular TEAEs had a mild or moderate intensity; few were severe in intensity or were serious. The most common non-ocular TEAEs were "hypertension", "nasopharyngitis", "urinary tract infection", and "anaemia". In general, the frequencies of these events were similar between the Eylea groups and the laser group. Most non-ocular TEAEs had a maximum intensity of mild or moderate. The overall frequency of treatment-emergent APTC events was low and within the expected range in the DME population (22 patients [7.7%] in the laser group, 31 patients [10.7%] in the 2Q4 group, and 21patients [7.3%] in the 2Q8 group). Any deaths through Week 148 were reported in 8 subjects (2.8%) in the laser group, 19 subjects (6.5%) in the 2Q4 group, and 13 subjects (4.5%) in the 2Q8 group. The causes of the deaths were consistent with the demographics and predisposition of the population being studied. No new ADRs were reported in the DME studies compared with those reported in the AMD studies in the initial marketing authorization application or the CRVO studies in the first supplemental authorization application.

Based on the week 52/week 100 results and the favourable benefit/risk balance, Eylea was approved in the US (JUL 2014) and EU (AUG 2014) for the indication DME.

Two further completed DME studies are considered in this RMP version for the calculation of exposure and the assessment of safety of Eylea in DME patients: VIVID-JAPAN (SN: 15657) was an open-label, single-arm Phase III study in 72 evaluable Japanese DME patients, who were treated with Eylea 2Q8 after 5 initial doses at monthly intervals through Week 48. The other study, VIVID-EAST (SN 15161), was a randomized controlled Phase III study over one year in mostly Asian patients with the same design as in the first year of the pivotal Phase III studies (VIVID-DME and VISTA-DME). In both studies, the safety and efficacy results at

Week 52 were generally consistent with those observed after one year in the pivotal Phase III studies.

SIII.1.5.2 DME (Eylea 114.3 mg/mL, 8 mg dose)

The development of the 8 mg application of aflibercept included a Phase II/III study:

The randomized, double-masked, active-controlled Phase II/III PHOTON study week 96 results are displayed in this RMP. The primary objective at week 48 of this study was to determine if treatment with 8 mg aflibercept at intervals of 12 or 16 weeks provides noninferior BCVA compared to 2 mg aflibercept dosed every 8 weeks. Secondary objectives are to determine the effect of 8 mg versus 2 mg aflibercept on anatomic and other visual measures of response, to evaluate the safety, immunogenicity, and pharmacokinetics of 8 mg aflibercept.

Patients were randomized to one of the following groups:

- 2 mg intravitreal aflibercept every 8 weeks (2q8) after 5 initial injections at 4-week intervals
- 8 mg intravitreal aflibercept every 12 weeks (HDq12) after 3 initial injections at 4-week intervals
- 8 mg intravitreal aflibercept every 16 weeks (HDq16) after 3 initial injections at 4-week intervals

During the first year, all patients in the HD groups could qualify for interval shortening based on protocol specified DRM criteria beginning at week 16 (patients in the HDq12 group could be shortened to 8 weeks and patients in the HDq16 group could be shortened to 12 or 8 weeks). The minimum interval allowed between injections was 8 weeks, which was considered a rescue regimen for patients unable to tolerate a dosing interval greater than every 8 weeks. During the second year, patients could also qualify for interval shortening or interval extension by 4-week increments, based on protocol specified DRM criteria. Patients randomized to 2q8 remained on a fixed Q8 dosing regimen through week 96 (i.e., did not have modifications of their treatment intervals regardless of the outcomes of the DRM assessments).

Week 48 results of the PHOTON study were based on 167 patients in the 2Q8 group, 328 patients in the HDq12 group, and 163 patients in the HDq16 group (these patients were valid for both the SAF and FAS analyses). The primary endpoint analysis (i.e., change from baseline in BCVA as measured by ETDRS letter score) at Week 48 showed that the primary efficacy endpoint was met: Both HD groups demonstrated non-inferiority to 2Q8 using the non-inferiority (NI) margin of 4 letters with LS mean change from baseline in BCVA of 8.10 letters (HDq12) and 7.23 letters (HDq16), respectively versus 8.67 letters in the 2Q8 group. Treatment differences (CI) were -0.57 (-2.26, 1.13) and -1.44 (-3.27, 0.39) for HDq12 and HDq16, respectively compared to 2Q8. The robustness of these results for the primary endpoint were supported by the sensitivity analyses, including analysis of the primary efficacy endpoint in the PPS.

The key secondary efficacy endpoint was the proportion of participants with a ≥2 step improvement in DRSS score at week 48. This treatment goal was achieved in 90/310 patients (29.0%) in the HDq12 group, 30/153 patients (19.6%) in the HDq16 group, and 42/158 patients (26.6%) in the 2Q8 group. The NI margin was prespecified at 15%. While that

margin was met for HDQ12 *vs*. 2Q8 (the adjusted difference [95%-CI] In CMH-weighted estimates was 1.98% [-6.61; 10.57]; i.e., even a 10% NI margin was met), HDq16 *vs*. 2Q8 failed to show non-inferiority, since the adjusted treatment difference was -7.52% with an accompanying 95%-CI of [-16.88; 1.84]. However, the HDq16 group had more participants with moderate to mild (level 43 or better) retinopathy at baseline with the majority of participants in all treatment groups having a baseline DRSS score of level 35. The descriptive analyses of the additional secondary endpoints evaluated at Week 48 suggested similar outcomes on treatment with 8 mg compared to 2Q8.

All week 48 efficacy variables were analyzed descriptively at week 96, as applicable. For change from baseline in BCVA measured by ETDRS letter score at week 96, HDq12 and HDq16 treatment groups both met the non-inferiority criteria that had been specified for the primary endpoint at week 48 when compared to the 2q8 treatment group. Through week 96, 87.5% of completers in the HDq12 group and 83.5% of completers in the HDq16 group, maintained their randomized treatment interval. Results for the proportion of participants with a ≥ 2-step improvement in DRSS score at week 96 were consistent with results at week 48 and the HDq12 (33.9%) group met the non-inferiority criterion established for week 48 compared to the 2q8 (31.0%) group; however, also consistent with week 48, the HDq16 (22.2%) group did not meet these criteria. In addition, 42.2% and 45.3% of patients in the HDq12 and HDq16 groups, respectively, were maintained and extended to an interval of 20 weeks, and 43.0% and 46.8% of patients in the HDq12 and HDq16 groups respectively, were assigned to a last intended dosing interval of ≥ 20-week interval through week 96.

Overall, treatment with HD aflibercept at intervals of 12 or 16 weeks provided non-inferior BCVA compared to 2 mg aflibercept dosed every 8 weeks. Treatment with 8 mg was well-tolerated and both the ocular and systemic safety profile of 8 mg was similar to 2 mg. No new safety signals were identified.

Based on these results and the favourable benefit/risk profile, the US Food and Drug Administration (FDA) was the first health authority to approve Eylea 114.3 mg/mL for the indication of wet AMD on 18 AUG 2023; EU approval was granted on 05 JAN 2024

SIII.1.6 Development in the indication “retinopathy of prematurity” (ROP), (Eylea 40mg/mL, 0.4 mg dose)

The clinical development program with intravitreal aflibercept (EYLEA) for the treatment of ROP was designed to collect prospective, randomized, controlled data for EYLEA in the vulnerable population of preterm infants in medical need due to a severe, vision-threatening disease requiring timely and adequate treatment. This clinical development program consisted of one completed pivotal Phase III study 20090 (FIREFLEYE) and the ongoing Phase IIIb Study 20275 (FIREFLEYE NEXT, extension study).

The FIREFLEYE study was an open-label, randomized, two–arm, controlled Phase III study to assess the efficacy, safety, and tolerability of IVT aflibercept compared to laser photocoagulation in patients with ROP. Subjects were randomized 2:1 to receive treatment with an IVT injection of aflibercept 0.4 mg/0.01 mL or laser photocoagulation. Study duration was at least 24 weeks in the study protocol.

One or both eyes could be treated according to the investigator’s assessment of the study’s eligibility criteria. Retreatment(s) with the subject’s randomized treatment, or rescue

treatment (laser for the aflibercept arm; aflibercept for the laser arm) were allowed if the specified criteria are met during the 23-week treatment period.

A total of 121 subjects were screened and 118 subjects were randomized, 75 to aflibercept and 43 to the laser arm. Five subjects randomized to the laser treatment arm were withdrawn before treatment was administered. Therefore, 75 (100%) subjects were treated with aflibercept and 38 (88.4%) with laser. All 113 treated subjects (75 in aflibercept and 38 in laser treatment arm) were considered valid for both efficacy (FAS) and the safety (SAF) analyses. A majority of subjects in both treatment arms were bilaterally treated (71 [94.7%] in the aflibercept arm and 34 [79.1%] in the laser arm).

The number of male subjects (54.7%) was slightly higher than female subjects (45.3%) in the aflibercept treatment arm (whereas it was equally distributed in the laser treatment arm, 50% males, 50% females). The majority of subjects were White (73.5%), while 23.0% were Asian (of which 14.2% were from Japan). At the time of treatment, the mean chronological age was 10.3 weeks and the mean body weight was 1965.3 g (mean weight at the time of birth: 862.1 g).

The primary efficacy outcome for this study was to evaluate the proportion of subjects with absence of active ROP and unfavourable structural outcomes at 24 weeks after starting study treatment. Using a Bayesian model, the estimated response probability (median of the posterior distribution) for meeting the response criterion “absence of active ROP and unfavourable structural outcomes at 24 weeks” was 85.5% in the aflibercept treatment arm and 82.1% for the laser treatment arm. As the 90% credible interval for the treatment difference does not exclude -5%, non-inferiority of aflibercept compared to laser treatment (pre-defined success criterion) could not be concluded, although the aflibercept arm numerically showed slightly better outcomes.

As a secondary efficacy endpoint, requirement for intervention with a second treatment modality from baseline to week 24 was evaluated. A second treatment modality for ROP was either rescue treatment as defined in the protocol or any other surgical or nonsurgical treatment for ROP (e.g., IVT anti-VEGF injection, ablative laser therapy, cryotherapy, or vitrectomy) after study start. Using a Bayesian model, the estimated median response probability for subjects requiring an intervention with a second modality from baseline until Week 24 was 7.2% in the aflibercept arm and 9.6% in the laser arm.

The proportion of subjects with ocular AEs and TEAEs in the study eye was overall comparable in the two treatment arms (aflibercept: 38.7%; laser: 36.8%). The most frequent ocular TEAEs by MedDRA PT in treated eyes (>5% in either treatment arm) were *retinal haemorrhage* (aflibercept 6.7% *vs.* laser 13.2%), *retinal detachment* (aflibercept 5.3% *vs* laser 5.3%), *conjunctival haemorrhage* (aflibercept 5.3% *vs.* laser 0%), and *eyelid oedema* (aflibercept 2.7%; laser 7.9%) in the *eye disorders* SOC; and *conjunctivitis* (aflibercept 4.0%, laser 10.5%) in the *infections and infestations* SOC.

The proportion of subjects reported with ocular SAEs was 13.3% for aflibercept and 7.9% for laser, and for ocular TESAEs 8.0% and 7.9%, respectively. Non-ocular (systemic) TEAEs were more pronounced in the laser treatment arm (aflibercept 52.0% *vs.* laser 63.2%) and reflect the underlying prematurity of the study population with typical comorbidities in both treatment arms. The proportion of subjects reported with systemic SAEs was 24.0% for aflibercept *vs.* 36.8% for laser, and the proportion of subjects with systemic TESAEs was 6.7% for aflibercept and 18.4% for laser. There were 3 subjects in the aflibercept treatment

arm with a fatal outcome due to AEs which occurred in context of complications of the underlying prematurity related comorbidities, assessed as unrelated to the study treatment.

Overall, the safety data in FIREFLEYE is consistent with the established safety profile of Eylea and no new safety concern has been identified.

The data from the 6-month Phase 3 Study FIREFLEYE suggest a favourable benefit-risk profile for IVT aflibercept in the treatment of premature infants with severe ROP.

All treated patients from Study 20090 must be offered participation in a follow-up study 20275 (FIREFLEYE NEXT, Phase IIIb extension study) until they are 5 years of age to assess long-term ocular effects, clinical and neurodevelopmental outcomes. Subjects will be followed until the age of 5 years, when detailed assessment of visual function and overall development becomes feasible and stable. This study is ongoing and the interim safety data are considered for this RMP version.

SIII.2 Clinical Trial Exposure

SIII.2.1 Introduction and overview of studies considered for the calculation of exposure

Clinical trial exposure showing the overall number of patients by study, by treatment duration, dose, number of injections, demographics, age, gender, ethnicity, and special populations are shown in Table SIII.1 through Table SIII.38. The overall clinical exposure includes data from treated subjects in 11 Phase I-IV studies in wet AMD (including the 2 mg and 8 mg doses), 2 Phase III studies in CRVO, the single BRVO Phase III study, the single-Phase III study in myopic CNV, 7 Phase I-III studies in DME (including the 2 mg and 8 mg doses), and the single Phase III study in ROP.

Exposure data in special populations are exclusively shown for the 2 pivotal randomized Phase III wet AMD studies (VIEW 1 and 2), the 2 Phase III CRVO studies (GALILEO and COPERNICUS), the Phase III BRVO study (VIBRANT), the Phase III trial in myopic CNV (MYRROR), the 2 controlled Phase III DME studies (VIVID-DME and VISTA-DME), the Phase III ROP study (FIREFLEYE), and the two 8 mg aflibercept AMD studies (CANDELA and PULSAR) and the 8 mg aflibercept DME (PHOTON) study.

A summary of patient exposure to Eylea IVT injections for wet AMD, CRVO, BRVO, myopic CNV, DME, and ROP in the various clinical trials is provided in Table SIII.1. This table includes the number of patients who switched from one dose to another one within the same study according to protocol, or with enrolment into a follow-up long-term safety study (i.e., VGFT-OD-0702). In addition, this table includes patients that were treated in the 8 mg aflibercept wet AMD (CANDELA and PULSAR) and 8 mg aflibercept DME (PHOTON) studies.

In the 11 Phase I-IV wet AMD studies, 2 Phase III CRVO studies, one Phase III BRVO study, one Phase III myopic CNV study, 7 Phase I-III DME studies, and one Phase III ROP study, a total of 11,186 patients have been enrolled; with 6,487 thereof having received Eylea injections at various doses of 0.4 mg for preterm infants, ≤1 mg, 2 mg, 4 mg, or 8 mg in adult patients (see Table SIII.1). For this clinical trial exposure overview, the wet AMD Phase I-II studies, final 96 weeks data from the VIEW 1 and 2 studies, the final data from the VIEW 1 extension study VGFT-OD-0910, the final data from the completed Phase I/II extension study

VGFT-OD-0702, the final 1-year data from the completed SIGHT study[3], as well as the 44-week data from the CANDELA Phase II 8 mg aflibercept study and the 96-week data from the PULSAR Phase III 8 mg aflibercept study were considered. For CRVO, the final 76 and 100 weeks data from the Phase III CRVO studies (GALILEO and COPERNICUS trials, respectively) were considered. For BRVO, the final study data of VIBRANT up to Week 52 are included. The myopic CNV indication is represented by final 48 weeks data of the Phase III MYRROR study. For DME, final data of the following studies are considered: Phase I study VGFT-OD-0512, Phase II study DAVINCI, single-arm, open-label Phase III study VIVID-JAPAN, pivotal Phase III studies VIVID-DME and VISTA-DME, and Phase III study VIVID-EAST. Additionally, the 96 8-week data from the PHOTON Phase II/III 8 mg aflibercept study are presented. For ROP the Phase III FIREFLEYE study data was considered.

SIII.2.1.1 Brief description of wet AMD studies

A total of 6,903 patients were enrolled and 3,787 patients exposed to Eylea in the Phase I-IV wet AMD studies (see Table SIII.1):

VGFT-OD-0502 was a Phase I study, with 3 parts (A, B and C), of single IVT injections of up to 4 mg of Eylea in patients with wet AMD (12-week active observation, 1 year follow-up).

VGFT-OD-0508 (CLEAR-IT) was a Phase II study of repeated IVT injections of doses of up to 4 mg per injection in patients with wet AMD (12-week fixed dosing every 4 weeks (Q4) or Q12, followed by 52 weeks with dosing as needed).

VGFT-OD-0603 was a Phase I study of repeated IVT injections of 4 mg per dose in patients with wet AMD (8 weeks for first 3 doses, up to 9 months, if treatment was required thereafter).

VGFT-OD-0605 (VIEW 1) was a randomized, controlled Phase III study of repeated IVTinjections of 0.5 mg and 2 mg Eylea versus ranibizumab for 2 years in patients with wet AMD.

VGFT-OD-0910 [SN 14832] was an open-label extension study (sponsored by Regeneron Pharmaceuticals, Inc.) subsequent to VIEW 1 in order to enable patients who had completed 2 years of treatment in VIEW 1 to continue (or to initiate) therapy with Eylea 2 mg, for an additional mean treatment duration of approximately 110 weeks. A total of 320 patients completed VIEW 1 and were subsequently treated with Eylea in the study eye (2 mg at individual intervals ranging from 4 to 12 weeks) during the extension study (69 patients from the former ranibizumab group and 87/92/72 patients from the former Eylea 0.5 Q4/2Q4/2Q8 treatment groups). Three subjects enrolled in the VIEW 1 extension study received Eylea 2 mg at Week 96 in the original VIEW 1 study (not counted for the VIEW 1 study exposure) but did not receive further treatment in the extension study. These 3 patients are considered for the safety analyses in the VIEW 1 extension study (increased SAF: 323, i.e., 69 and 87/95/72 per treatment group), and the 3 active injections at Week 96 are considered for the calculation of the AMD and overall exposure across studies. Exposure data from VIEW 1 and the extension study were pooled for the description of exposure in VIEW 1 (see Table SIII.1).

[3] Please note that the SIGHT study, which is included in the calculation of clinical trial exposure, is not part of the EU submission as it solely relates to Chinese patients with AMD.

311523/91689 (VIEW 2) was a randomized, controlled Phase III study of repeated IVT injections of 0.5 mg and 2 mg Eylea versus ranibizumab for 2 years in patients with wet AMD.

VGFT-OD-0702 was a randomized, single-masked, long-term, safety, and tolerability study of IVT Eylea in Subjects with wet AMD. Subjects enrolled in the original studies VGFT-OD-0502, VGFT-OD-0508, or VGFT-OD-00603 continued to receive Eylea in this study with a follow up period of up to 3 years. A total of 157 patients were enrolled and 149 patients randomized (50 to the vial group and 99 to the PFS group). Patients in study VGFT-OD-0702 are counted once for the exposure tables below and are included in exposure data of their initial study assignment.

SIGHT (SN 13406) was a randomized, double-masked, photodynamic therapy-controlled Phase III study of the efficacy, safety, and tolerability of VEGF Trap-Eye in Chinese subjects with wet AMD. The primary endpoint (mean change in BCVA) was assessed at 28 weeks, while the study had a total follow-up of 52 weeks. The study had 2 treatment arms. Patients in the Eylea arm were treated with 2 mg Eylea every 4 weeks for the first 3 months, thereafter every 8 weeks until the end of the trial. Subjects in the PDT group underwent one PDT procedure at Baseline and then additional procedures as indicated according to local clinical practice and the clinical judgment of the investigator. These subjects crossed over to active VEGF Trap-Eye treatment after the primary efficacy assessments at Week 28. Thus, the Eylea exposure is calculated based on the 229 patients initially randomized to Eylea plus 70 patients of the original PDT group who were switched to Eylea after Week 28 (i.e., 299 patients in total).

ALTAIR (SN 17668) was a randomized, open-label phase IV study evaluating the efficacy and safety of repeated doses of intravitreal aflibercept with variable treatment intervals in Japanese subjects with wet AMD for up to 2 years. The Treat and Extend regimen was a dosing strategy where the injection interval could be gradually extended as long as functional and anatomic stability of a patient was maintained. The interval could also be shortened if the physician saw deterioration of the patient´s condition. After a run-in phase consisting of 3 monthly doses and a 4th dose given after 8 weeks, 247 patients were randomly assigned to one of the two treatment arms of the study. Depending on various adjustment criteria, the dose regimen was shortened or extended per individual patient for 2 or 4 weeks (124 subjects in the 2-week [2W] adjustment group, 123 subjects in the 4-week [4W] adjustment group, and 7 subjects failed to be randomized). The 1-year data from both of these groups are considered for this RMP version. The ALTAIR study can help guide physicians in optimizing individual treatment while minimizing over- and under-treatment.

All Eylea 40 mg/mL (2 mg dose) data concerned with wet AMD utilized in this RMP (other than in this exposure module) are mainly based on the final global integrated analysis of the final 96 weeks dataset of the VIEW 1 and 2 studies; safety results from the VIEW 1 extension study VGFT-OD-0910 as well as from SIGHT and ALTAIR are reported separately.

Two 8 mg aflibercept AMD studies CANDELA and PULSAR were conducted and are described below.

CANDELA (VGFTe-HD-AMD-1905, SN 21086) was a randomized, single-masked, active-controlled Phase II study sponsored by Bayer AG’s license partner and Marketing Authorization Holder (MAH) in the USA Regeneron Pharmaceuticals INC. A total of 106 eligible patients was randomized into 2 groups in a 1:1 ratio. One group received 2 mg

aflibercept and the other 8 mg aflibercept. Aflibercept was administered intravitreally monthly for 3 initial injections at baseline, week 4 and week 8, followed by additional doses at weeks 20 and 32. At weeks 24, 28, 36 and 40 patients were evaluated and given a dose (at their randomized dose level) if defined retreatment criteria were met. The primary safety analysis took place at week 20, with exploratory endpoints evaluated at week 20 and week 44. The study was completed.

PULSAR (SN 20968) is a randomized, double-masked, active-controlled Phase III study sponsored by Bayer AG. 1011 participants were randomly assigned in a 1:1:1 ratio into one of three parallel groups. One group received 2 mg aflibercept every 8 weeks, one group received 8 mg aflibercept every 12 weeks and the third group received 8 mg aflibercept every 16 weeks (each group after 3 initial monthly injections). During the first year, all patients in the HD groups could qualify for interval shortening based on protocol specified dose regimen modification (DRM) criteria beginning at week 16 (patients in the HDq12 group could be shortened to 8 weeks and patients in the HDq16 group could be shortened to 12 or 8 weeks). The minimum interval allowed between injections was 8 weeks, which was considered a rescue regimen for patients unable to tolerate a dosing interval greater than every 8 weeks. During the second year, patients could also qualify for interval shortening or interval extension by 4-week increments, based on protocol specified DRM criteria. Patients randomized to 2q8 remained on a fixed Q8 dosing regimen through week 96 (ie, did not have modifications of their treatment intervals regardless of the outcomes of the DRM assessments). The primary endpoint was change from baseline in BCVA measured by ETDRS letter score at week 48. Week 96 exposure and safety data of the PULSAR study is included in this RMP.

The two 8 mg aflibercept wet AMD studies CANDELA and PULSAR are integrated in the exposure analyses provided in this module.

Wet AMD and DME safety data of the 8 mg aflibercept program are integrated and the pooled wet AMD/DME 8 mg aflibercept safety data (CANDELA week 44/PHOTON week 96/PULSAR week 96) are displayed in the respective risk sections of this RMP.

SIII.2.1.2 Brief description of CRVO studies

During the 76/100 weeks duration of the 2 Phase III CRVO studies, a total of 513 patients were enrolled, of these, 317 patients received Eylea injections (see Table SIII.1).

VGFT-OD-0819 (COPERNICUS) was a randomized, double masked, controlled Phase III study of the efficacy, safety, and tolerability of repeated IVT administration of Eylea in subjects with macular edema secondary to CRVO. In the first 6-months, subjects received either 2 mg Eylea every 4 weeks (Eylea 2Q4) for 20 weeks, or sham injections every 4 weeks for 20 weeks. In the second 6-month period (Week 24 through Week 52), subjects were evaluated every 4 weeks and received either Eylea 2 mg injections or sham injections in accordance with protocol-defined re-treatment criteria. Thus, patients randomized to only receive sham through Week 20 were able to receive active Eylea 2 mg injections from Week 24 to Week 52 if they met re-treatment criteria. In COPERNICUS, starting at Week 52, all subjects were eligible to receive treatment with Eylea to Week 100 in an unmasked 1-year extension phase comprising "as-needed" (PRN) treatment. In this phase of the study, subjects were evaluated quarterly (i.e., every 3 months) and received 2 mg Eylea IVT according to the study re-treatment criteria. No sham injections were performed during this phase.

Study No. 14130 (GALILEO) was a randomized, double-masked, sham-controlled Phase III study of the efficacy, safety, and tolerability of repeated IVT administration of Eylea in subjects with macular edema secondary to CRVO. In the first 6-months, subjects received either 2 mg Eylea every 4 weeks (Eylea 2Q4) for 20 weeks, or sham injections every 4 weeks for 20 weeks. Starting Week 24 through Week 52, subjects in the Eylea group received either Eylea 2 mg injections or sham injections according to protocol-defined re-treatment criteria, while subjects in the sham group continued to receive only sham injections until Week 52. In GALILEO, starting at Week 52, all subjects were eligible to receive treatment with Eylea/sham to Week 76 in a masked 6-month PRN extension phase. In this phase of the study, subjects were evaluated every 8 weeks and received either 2 mg Eylea IVT or sham injections according to the study re-treatment criteria.

In this RMP version, the final data up to Week 76 (GALILEO) and Week 100 (COPERNICUS) from both of the above CRVO studies is included.

SIII.2.1.3 Brief description of BRVO study

VIBRANT (SN 15432, VGFTe RVO-1027) was a randomized, double-masked, active controlled 52-week study to investigate the efficacy, safety, and tolerability of repeated IVT administration of Eylea compared with grid laser photocoagulation in subjects with macular edema secondary to BRVO. Macular grid laser photocoagulation was chosen as comparator treatment, because at the time of inception of VIBRANT in 2012 it could be regarded as representative standard of care treatment in macular edema secondary to BRVO. A total of 183 patients (281 enrolled) were randomized: 91 patients to treatment with Eylea and 92 patients to treatment with laser (see Table SIII.1). Study treatment in the 2 treatment arms was scheduled as follows:

Eylea arm: Patients received Eylea 2 mg every 4 weeks (2Q4) through (including) Week 24, then every 8 weeks (2Q8) through Week 48. Sham IVT injections were administered every 8 weeks starting from Week 28, alternating with Eylea injections every 8 weeks, through Week 44. The last active injection with Eylea was on Week 48. Patients in the Eylea group also received one sham laser treatment on Day 1. Rescue treatment with active laser in this group was possible, if patients meet the pre-defined laser rescue treatment criteria at Week 36.

Laser arm: Patients received grid laser photocoagulation treatment at Day 1, and sham IVT injections every 4 weeks from Day 1 through Week 48. Rescue treatment with laser was possible from Week 12 onwards (minimum intervals of 12 weeks from previous laser treatment) in those patients who met the pre-specified rescue treatment criteria. Patients in the laser arm became generally eligible for rescue treatment with Eylea beginning at Week 24. This rescue treatment had to be started with 3 initial active injections every 4 weeks, followed by 2 mg injections every 8 weeks.

In this RMP version, the final study data up to Week 52 (last active treatment on Week 48) are included. A total of 67 patients randomized to the laser arm additionally received rescue treatment with Eylea from Week 24 onwards, thus a total of 158 patients were exposed to Eylea in the VIBRANT study.

SIII.2.1.4 Brief description of myopic CNV study

Study No. 15170 (MYRROR) was a Phase III, multicenter, randomized, double-masked, sham-controlled study of the efficacy, safety, and tolerability of Eylea in patients with

choroidal neovascularization secondary to pathologic myopia. In the first 24-week period of the study, patients received either one mandatory 2 mg Eylea IVT injection at Baseline followed by sham injections every 4 weeks, which could be replaced by additional active injections in case of recurring or persisting CNV, or sham injections every 4 weeks only. In the next study period (Week 24 through Week 44), patients in both treatment arms (i.e., incl. patients in the sham group) were allowed to receive Eylea treatment in case of recurring or persisting CNV. Initially, all patients in the sham group received one mandatory active injection at Week 24. Patients continued to be evaluated monthly until Week 48 (the last active injection could be administered at Week 44). Overall, a total of 122 patients were randomized; of these, 91 received Eylea injections before completion of the primary endpoint assessment at Week 24, while 31 patients were randomized to sham treatment. 25 original sham patients actually received at least one active injection with Eylea at Week 24, thus the number of patients exposed to Eylea in the MYRROR study accumulated to 116 patients in total (see Table SIII.1).

In this RMP version, the final study data through Week 48 are presented.

SIII.2.1.5 Brief description of DME studies

A total of 3,195 patients were enrolled and 2,030 patients exposed to Eylea in the DME studies (see Table SIII.1).

VGFT-OD-0512 (SN: 14805) was a Phase I, single dose study to assess the safety and tolerability of IVT administered VEGF Trap-Eye in 5 patients with DME, who were exposed to a single 4 mg IVT dose of VEGF Trap-Eye.

VGFT-OD-0706 (DA VINCI; SN: 13336) was a randomized, double-masked, controlled Phase II study of the safety, tolerability, and biological effect of repeated IVT administration of VEGF Trap-Eye in subjects with DME with central involvement, and a BCVA of 20/40 to 20/320 (letter score of 73 to 24). A total of 221 patients were enrolled and 219 treated in the United States, Canada, and Austria. End of treatment was at Week 52 (followed by a safety observation phase up to Week 76). Subjects were randomized to 1 of the following 5 treatment groups:

- VEGF Trap-Eye 0.5 mg every 4 weeks (0.5q4) to week 52,
- VEGF Trap-Eye 2 mg every 4 weeks (2q4) to week 52,
- VEGF Trap-Eye 2 mg every 8 weeks (2q8) after 3 monthly loading doses, with sham injections at alternating visits, to week 52,
- VEGF Trap-Eye 2 mg PRN after 3 monthly loading doses, according to the VEGF Trap-Eye re-treatment criteria, with sham injections at visits at which VEGF Trap-Eye re-treatment criteria were not met, and
- Laser photocoagulation, using the modified ETDRS technique at week 1, and 1 week after visits at which patients met laser re-treatment criteria, to week 52; sham injections every 4 weeks at each study visit; laser re-treatment was permitted no more than once every 16 weeks ± 3 days.

VGFT-OD-1009 (VISTA-DME) was a 3-year, randomized, double-masked, active-controlled, multicenter Phase III clinical trial of the efficacy and safety of repeated doses of IVT VEGF Trap-Eye in subjects with DME with central involvement, and a BCVA of 20/40 to 20/320

(letter score of 73 to 24). In VISTA-DME, a total of 461 subjects (SAF) were treated in the US. [4]

BAY 86-5321/91745 (VIVID-DME) was a 3-year, randomized, double-masked, active-controlled, multicenter Phase III clinical trial of the efficacy and safety of repeated doses of IVT VEGF Trap-Eye in subjects with DME with central involvement, and a BCVA of 20/40 to 20/320 (letter score of 73 to 24). In VIVID-DME, a total of 404 subjects (SAF) were treated in European countries, Australia, and Japan. VISTA-DME and VIVID-DME had nearly identical overall study designs and are described together, unless otherwise indicated. Patients in either study were randomized to 1 of the following 3 treatment groups:

- VEGF Trap-Eye 2 mg every 4 weeks (2Q4) to Week 144,
- VEGF Trap-Eye 2 mg every 8 weeks (2Q8) after 5 monthly loading doses, with sham injections at alternating visits, to Week 144,
- Laser photocoagulation through week 144.
- Subjects in the VEGF Trap-Eye groups received sham laser at baseline and at visits at which subjects met the criteria for laser re-treatment (no more often than every 12 weeks). Subjects in all groups were assessed for additional treatment (i.e., VEGF Trap-Eye for the laser subjects and laser for the VEGF Trap-Eye subjects) for inadequate responders at each visit starting with week 24. Additional treatment was to be administered if either of the criteria were met:
- A loss of ≥15 letters from the best previous BCVA score due to DME with current BCVA score not better than baseline,
- A loss of ≥10 letters at 2 consecutive visits at least 7 days apart from the best previous BCVA score due to DME with current BCVA score not better than baseline.
- During Year 3, subjects randomized to the laser group who did not meet the criteria for additional treatment previously could receive VEGF Trap-Eye as needed (PRN) according to the VEGF Trap Eye re-treatment criteria from Week 100 to Week 144. The primary efficacy endpoint in both studies was the change in ETDRS letter score from baseline to week 52. Efficacy (visual function) was assessed using the ETDRS protocol at 4 meters at each study visit. Other measures of efficacy included change in CRT as measured by OCT, improvement in ETDRS Diabetic Retinopathy Severity Scale (DRSS) using fundus photography and fluorescein angiography (FA), and questionnaires to examine vision-related quality of life. Overall safety was assessed by monitoring/evaluation of treatment emergent adverse events (TEAEs), physical examinations, electrocardiograms, vital signs, and clinical safety laboratory tests. Ocular safety was assessed by ophthalmic examinations (slit lamp biomicroscopy, indirect ophthalmoscopy, intraocular pressure, OCT), and FP and FA. Last study assessment was on Week 148.

  Fellow eye treatment for DME with anti-VEGF agents was allowed in both Phase III studies. In VIVID-DME, standard of care was used (including ranibizumab or

[4] As per amendment No. 4, patients completing Visit 39 (Week 148) in VISTA-DME were allowed to receive further treatment extension with Eylea until the planned date for the last on-study patient to complete Visit 39 (NOV 2014) in order to avoid a potential treatment gap between study end and availability of commercial Eylea. However, the exposure and safety analyses in VISTA-DME are aligned with VIVID-DME and thus limited to the last core study visit (i.e., Week 148).

bevacizumab; licensed treatment preferred). In VISTA DME, VEGF Trap-Eye was provided and required as fellow eye treatment; (although ranibizumab could be used. used if VEGF Trap-Eye was unavailable due to logistical reasons).

BAY 86-5321/15161 (VIVID-EAST) was designed similarly to VIVID-DME and VISTA-DME and was conducted in 25 centres in China, Hong Kong, Republic of Korea, and the Russian Federation. Eligible patients were randomized to the laser group (N=124), the Eylea 2Q4 group (N=127), or the Eylea 2Q8 group (N=127). Patients in the laser group were treated with laser photocoagulation at baseline and from week 12 onwards, if laser re-treatment criteria were met. Patients in the Eylea 2Q4 group received Eylea 2 mg at monthly intervals continuously through Week 48, and patients in the Eylea 2Q8 group received Eylea 2 mg every 2 months following 5 initial injections at monthly intervals (i.e., from Baseline to including Week 16) through Week 48. Additional treatment (with Eylea in the laser group or with laser in the Eylea groups) was permitted from Week 24 onwards. The final study assessments were performed at Week 52.

BAY 86-5321/15657 (VIVID-JAPAN) was an open-label, Phase III study evaluating the safety and tolerability of repeated doses of IVT VEGF Trap-Eye in 73 Japanese patients with DME (SAF: 72 patients, since one treated patient withdrew informed consent and thus was excluded from the SAF). As with the randomized Phase III studies in the 2Q8 group, all patients in VIVID-JAPAN were treated in an open-label fashion with Eylea every 2 months (2Q8) after 5 initial doses at monthly intervals (i.e., 2Q4 up to Week 16). Last treatment was on Week 48; the final endpoint assessments were performed at Week 52. No additional treatment of the study eye with laser was permitted. Fellow eye treatment was allowed as per local standard of care/medical routine. Systemic concentrations of free and bound VEGF Trap were measured at pre-defined time points during the study period.

In this RMP version, the exposure data of the aforementioned 6 Phase I-III studies are used for the description of clinical trial exposure. Safety data of 2 mg aflibercept in DME are primarily derived from the pooled data set of the pivotal studies VIVID-DME and VISTA-DME through Week 148, while complementary safety results from VIVID-JAPAN and VIVID-EAST are described separately.

Moreover, this RMP version includes the 96-week results from the Phase II/III study PHOTON (VGFTe-HD-DME-1934, SN 21091), in which the aflibercept 8 mg dose was investigated for treatment of DME. This study is a randomized, double-masked and active-controlled study. Patients were randomized into one of three parallel treatment groups (1:2:1 ratio). One group received 2 mg aflibercept every 8 weeks following 5 initial monthly doses, one group received 8 mg aflibercept every 12 weeks following 3 initial monthly doses and the third group received 8 mg aflibercept every 16 weeks following 3 initial monthly injections. The primary endpoint was the change from baseline in BCVA at week 48. During the first year, all patients in the HD groups could qualify for interval shortening based on protocol specified DRM criteria beginning at week 16 (patients in the HDq12 group could be shortened to 8 weeks and patients in the HDq16 group could be shortened to 12 or 8 weeks). The minimum interval allowed between injections was 8 weeks, which was considered a rescue regimen for patients unable to tolerate a dosing interval greater than every 8 weeks. During the second year, patients could also qualify for interval shortening or interval extension by 4-week increments, based on protocol specified DRM criteria. Patients randomized to 2q8 remained on a fixed Q8 dosing regimen through week 96 (ie, did not have

modifications of their treatment intervals regardless of the outcomes of the DRM assessments).

Week 96 exposure and safety data of the PHOTON study is included in this RMP.

DME and wet AMD safety data of the 8 mg aflibercept development program were integrated and the 96week pooled wet AMD/DME safety data (CANDELA/PHOTON/PULSAR) are displayed in the respective risks sections of this RMP.

SIII.2.1.6 Brief description of ROP studies

FIREFLEYE (SN 20090) was a Phase 3, multicenter, open-label, randomized, two arm, controlled study to assess the efficacy, safety, and tolerability of IVT aflibercept compared to laser photocoagulation in subjects with ROP. The study consisted of a screening phase followed by a baseline visit when subjects were randomized either to aflibercept or laser (ratio: 2:1), followed by a 23-week treatment period, which equals a 24-week total study duration.

Male and female treatment-naïve, preterm (gestational age at birth ≤32 weeks) or very low birthweight preterm infants (≤1,500 g) who weighed at least 800 g at baseline, with ROP classified in at least one eye as Zone I stage 1 plus, 2 plus, 3 non-plus or plus, or Zone II stage 2 plus or 3 plus, or aggressive posterior ROP (AP-ROP) according to the International Classification for ROP (ICROP) were enrolled.

One or both eyes were treated based on the study eligibility criteria as assessed by the investigator. Subjects were also allowed to be retreated or administered rescue treatment (laser for the aflibercept arm; aflibercept for the laser arm) if protocol-specified criteria were met during the treatment period. Patients receiving rescue treatment were counted as non-responders and were considered as missing for the primary endpoint but were to be followed to assess the efficacy and safety outcomes after rescue treatment.

The primary efficacy endpoint was the *proportion of subjects with absence of active ROP and unfavourable structural outcomes at 24 weeks after starting study treatment* based on investigator's assessment.

Key secondary efficacy endpoints addressing the primary objective were subjects with requirement for intervention with a second treatment from baseline to Week 24 and subjects with recurrence of ROP from baseline to Week 24, which were also analysed using a similar Bayesian statistical model as for the primary endpoint.

In this study, a total of 113 subjects, 75 in the aflibercept treatment arm and 38 in the laser treatment arm were treated.

FIREFLEYE NEXT (SN 20275) is a Phase IIIb extension study which follows up on ocular, neurodevelopmental and overall clinical outcomes until 5 years of age (when detailed assessment of visual function and overall development becomes feasible and table). No study treatment is administered. In case treatment is required, subjects will be able to receive any treatment modality according to the local standard of care. Of the 113 patients treated in FIREFLEYE, 100 patients have transitioned to FIREFLEYE NEXT, 3 patients died during FIREFLEYE and for 10 patients participation was declined.

In this RMP version, the final study data up to week 24 of FIREFLEYE are included. A total of 4 patients randomized to the laser arm additionally received rescue treatment with Eylea, thus a total of 79 patients were exposed to Eylea in the FIREFLEYE study. Safety results

from the FIREFLEYE NEXT extension study are reported separately (i.e., all subjects who entered the extension study as of 29 MAR 2021 were included in this interim analysis; n=90 in total with n=29 patients previously treated with laser and n=61 treated previously with aflibercept in the pivotal FIREFLEYE study).

SIII.2.2 Tabulated overview of exposure across of all studies

Considering the 6,487 subjects who had received at least one dose of Eylea in all wet AMD (2 mg and 8 mg doses), CRVO, BRVO, myopic CNV, DME (2 mg and 8 mg doses), and ROP studies, the clinical trial exposure was as displayed in Table SIII.1.

Table SIII.1: No. of subjects who were exposed to Eylea in the wet AMD, CRVO, BRVO, myopic CNV, DME and ROP studies (all enrolled subjects)

Study identifier	N enrolled	N not randomized	N randomized	Treatment group [a]	No. in SAF
Total	11,186	3,831	7,355	**VTE total**	**6,487**
				VTE 0.4 mg	79
				VTE ≤1 mg	738
				VTE 2 mg	4,555
				VTE 4 mg	93
				VTE 8 mg	1,217
Wet AMD					
VGFT-OD-0508	299	140	159	**VTE total**	**157**
(SN 14394)				VTE ≤1 mg	64
->VGFT-OD-0702				VTE 2 mg	117
				VTE 4 mg	31
VGFT-OD-0502[b]	91	40	51	**VTE total**	**49**
(SN 14395)				VTE ≤1 mg	29
->VGFT-OD-0702				VTE 2 mg	22
				VTE 4 mg	37
VGFT-OD-0603	30	10	20	**VTE total**	**20**
(SN 14396)				VTE 2 mg	14
≥*VGFT-OD-0702*				VTE 4 mg	20
311523 (VIEW 2)	2,031	791	1,240	**VTE total**	**913**
				VTE ≤1 mg	297
				VTE 2 mg	616
311561 (VIEW 1)	2,073	856	1,217	**VTE total**	**980**
(VGFT-OD-0605)				VTE ≤1 mg	304
≥SN 14832 (extension study VGFT-OD-0910)				VTE 2 mg	763
SIGHT	451	147	304	**VTE total**	**299**
(SN 13406)				VTE 2 mg	299
ALTAIR (1 year)	288	41	247	**VTE total**	**254**
(SN 17668)				VTE 2 mg	254

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Table SIII.1: No. of subjects who were exposed to Eylea in the wet AMD, CRVO, BRVO, myopic CNV, DME and ROP studies (all enrolled subjects)

Study identifier	N enrolled	N not randomized	N randomized	Treatment group [a]	No. in SAF
VGFTe-HD-AMD-1905	245	139	106	**VTE total**	**106**
(CANDELA)				VTE 2 mg	53
				VTE 8 mg	53
SN20968	1,395	383	1,012	**VTE total**	**1,009**
(PULSAR)				VTE 2 mg	336
				VTE 8 mg	673
				VTE total[c]	***3,787***
CRVO					
14130	240	63	177	**VTE total**	**146**
(GALILEO)				VTE 2 mg	146
14232	273	85	188	**VTE total**	**171**
(COPERNICUS)				VTE 2 mg	171
				CRVO VTE total[c]	***317***
BRVO					
15432 (VGFTe-RVO-1027) (VIBRANT)	281	98	183	**VTE total**	**158**
				VTE 2 mg	158
				BRVO VTE total[c]	**158**
myopic CNV					
15170 (MYRROR)	173	51	122	**VTE total**	**116**
				VTE 2 mg	116
				myopic CNV VTE total[c]	**116**
DME					
VGFT-OD-0512	11	6	5	**VTE total**	**5**
(Phase I)				VTE 4 mg	5
VGFT-OD-0706	284	64	220	**VTE total**	**175**
(SN 13336)				VTE ≤1 mg	44
(DA VINCI)				VTE 2 mg	131
91745	604	198	406	**VTE total**	**380**
(VIVID-DME)				VTE 2 mg	380
VGFT-OD-1009	687	221	466	**VTE total**	**441**
(VISTA-DME)				VTE 2 mg	441
15657[d]	100	27	73	**VTE total**	**72**
(VIVID-JAPAN)				VTE 2 mg	72
15161	539	158	381	**VTE total**	**299**
(VIVID-EAST)				VTE 2 mg	299
VGFTe-HD-DME-1934	970	310	660	**VTE total**	**658**

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Table SIII.1: No. of subjects who were exposed to Eylea in the wet AMD, CRVO, BRVO, myopic CNV, DME and ROP studies (all enrolled subjects)

Study identifier	N enrolled	N not randomized	N randomized	Treatment group [a]	No. in SAF
(PHOTON)				VTE 2 mg	167
				VTE 8 mg	491
				DME VTE total[c]	***2,030***
			ROP		
20090	121	3	118	**VTE total**	79
(FIREFLEYE)				VTE 0.4 mg	79
				ROP VTE total[e]	***79***

VTE = VEGF-Trap Eye (Eylea)
a: Subjects may have received more than one dose. These subjects are considered for each dose, but once for VTE total.
[b]: SN 14395 (VGFT-OD-502): Part B is excluded from analysis.
[c]: VTE total per indication added by author.
[d]: Please note that one randomized and treated patient was excluded from the SAF because of his/her withdrawal of informed consent.
e: Subjects who were treated with laser and additionally with VTE 0.4 mg pediatric are considered in VTE 0.4 mg and VTE total.
Source: Integrated Analysis – Pool 3 RMP exposure / AMD 2 mg (up to year 3) + AMD 8 mg (w44/96), CRVO 2 mg (w76/100), BRVO 2 mg (1y), DME 2 mg (3y) + DME 8 mg (w96), mCNV 2 mg (w48), ROP 0.4 mg (w24/27); Table 1/1, Table 1/2, Table 1/3 and Table 1/4

SIII.2.3 Duration of exposure (patient months)

SIII.2.3.1 Indication: Wet AMD

Subject exposure per treatment duration as well as the total cumulative exposure (expressed as patient months) is shown for the wet AMD indication in Table SIII.2. The actual minimum dose applied per single injection was 0.5 mg (shown as ≤1 mg), and the maximum dose was 8 mg. Total exposure for all wet AMD subjects was 77,756 patient months.

Table SIII.2: Clinical trial exposure by treatment duration - Indication: wet AMD (SAF)

Treatment group	Duration of exposure	Patients	Person time (months)
IAI ≤1 mg	At least one dose	694	
	At least 1 month	658	
	At least 3 months	648	
	At least 6 months	622	
	At least 12 months	574	
	At least 18 months	515	11056
	Total person time	**694**	**12483**
IAI 2 mg	At least one dose	2,474	
	At least 1 month	2,438	
	At least 3 months	2,411	
	At least 6 months	2282	
	At least 12 months	1989	
	At least 18 months	1577	40842

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Table SIII.2: Clinical trial exposure by treatment duration - Indication: wet AMD (SAF)

Treatment group	Duration of exposure	Patients	Person time (months)
	Total person time	**2474**	**49954**
IAI 4 mg	At least one dose	88	
	At least 1 month	78	
	At least 3 months	71	
	At least 6 months	56	
	At least 12 months	11	141
	Total person time	**88**	**669**
IAI 8 mg	At least one dose	726	
	At least 1 month	721	
	At least 3 months	712	
	At least 6 months	700	
	At least 12 months	626	
	At least 18 months	599	13407
	Total person time	**726**	**14543**
IAI total	At least one dose	3787	
	At least 1 month	3736	
	At least 3 months	3683	
	At least 6 months	3519	
	At least 12 months	3106	
	At least 18 months	2639	66545
	Total person time	**3787**	**77756**

1 month = 30 days.
Subjects receiving at least one active IAI injection (pure or in combination) are displayed, subjects treated with sham or comparator including laser only are not displayed.
Subjects who were treated with sham or comparator and additionally with IAI 2 mg were considered in IAI 2 mg and IAI total.
Subjects may have received more than one dose. These subjects are considered for each dose, but once for IAI total.
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SIII.2.3.2 Indication: CRVO

Subject exposure per treatment duration as well as the total exposure in months is shown for the CRVO indication (GALILEO and COPERNICUS) in Table SIII.3. All subjects exposed to Eylea were treated with the 2 mg dose per injection. The total exposure in the CRVO indication was 4,962 patient months.

Table SIII.3: Clinical trial exposure by treatment duration - Indication: CRVO (SAF)

Treatment Group	Duration of exposure	Total patients (N)	Total patient time (months)
Eylea 2 mg	At least 1 dose	317	
(=Total)	At least 1 month	315	
	At least 3 months	304	
	At least 6 months	258	
	At least 12 months	246	
	At least 18 months	106	
	Cumulative exposure	**317**	**4,962**

Note: 1 month = 30 days
Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y); Table 1.2/3b

SIII.2.3.3 Indication: BRVO

Subject exposure per treatment duration as well as the total exposure in months is shown for the BRVO indication in Table SIII.4. All 158 subjects exposed to Eylea were treated with the 2 mg dose per injection. The total exposure to Eylea in the BRVO indication was 1,421 patient months.

Table SIII.4: Clinical trial exposure by treatment duration - Indication: BRVO (SAF)

Treatment Group	Duration of exposure	Total patients (N)	Total patient time (months)
Eylea 2 mg	At least 1 dose	158	
(=Total)	At least 1 month	156	
	At least 3 months	151	
	At least 6 months	132	
	At least ~~6~~12 months	62	
	Cumulative exposure	**158**	**1,421**

Note: 1 month = 30 days.
Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y); Table 1.2/3e

SIII.2.3.4 Indication: Myopic CNV

The final patient exposure per treatment duration as well as the total exposure in months is shown for the myopic CNV indication (MYRROR) through Week 48 in Table SIII.5. A total of 25 patients in the sham group received at least one active Eylea injection from Week 24 onwards; the exposure, however, was less extensive than in the Eylea 2 mg group, since the potential treatment duration was shorter. Overall, a total of 116 patients were exposed to Eylea in the MYRROR study through Week 48 and the cumulative exposure duration was 1,079 patient months.

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Table SIII.5: Clinical trial exposure by treatment duration - Indication: myopic CNV (SAF)

Treatment Group	Duration of exposure	Total patients (N)	Total patient time (months)
Sham + Eylea 2 mg	At least 1 dose	25	
	At least 1 month	25	
	At least 3 months	24	
	At least 6 months	1	
	Cumulative exposure	**25**	**139**
Eylea 2 mg	At least 1 dose	91	
	At least 1 month	89	
	At least 3 months	87	
	At least 6 months	83	
	Cumulative exposure	**91**	**940**
Eylea Total	At least 1 dose	116	
	At least 1 month	114	
	At least 3 months	111	
	At least 6 months	84	
	Cumulative exposure	**116**	**1,079**

Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y); Table 1.2/3c

SIII.2.3.5 Indication: DME

Subject exposure per treatment duration as well as the total exposure in months is shown for the DME indication in Table SIII.6. The total exposure in the DME indication (N=2,030) was 40,954 patient months.

Table SIII.6: Clinical trial exposure by treatment duration - Indication: DME (SAF)

Treatment group	Duration of exposure	Patients	Person time (months)
IAI <= 1 mg	At least one dose	44	
	At least 1 month	44	
	At least 3 months	43	
	At least 6 months	41	
	At least 12 months	37	455
	Total person time	**44**	**505**
IAI 2 mg	At least one dose	1490	
	At least 1 month	1469	
	At least 3 months	1443	
	At least 6 months	1393	
	At least 12 months	1165	
	At least 18 months	726	22219
	Total person time	**1490**	**30363**
IAI 4 mg	At least one dose	5	5

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Table SIII.6: Clinical trial exposure by treatment duration - Indication: DME (SAF)

Treatment group	Duration of exposure	Patients	Person time (months)
	Total person time	**5**	**5**
IAI 8 mg	At least one dose	491	
	At least 1 month	488	
	At least 3 months	478	
	At least 6 months	463	
	At least 12 months	446	
	At least 18 months	418	9401
	Total person time	**491**	**10082**
IAI total	At least one dose	2030	
	At least 1 month	2001	
	At least 3 months	1964	
	At least 6 months	1897	
	At least 12 months	1648	
	At least 18 months	1144	31619
	Total person time	**2030**	**40954**

1 month = 30 days.
Subjects receiving at least one active IAI injection (pure or in combination) are displayed, subjects treated with sham or comparator including laser only are not displayed.
Subjects who were treated with sham or comparator and additionally with IAI 2 mg were considered in IAI 2 mg and IAI total.
Subjects may have received more than one dose. These subjects are considered for each dose, but once for IAI total.
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SIII.2.3.6 Indication: ROP

Subject exposure per treatment duration as well as the total exposure in months is shown for the ROP indication in Table SIII.7. The total exposure in the ROP indication (N=79) was 106 patient months.

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Table SIII.7: Clinical trial exposure by treatment duration - Indication: ROP (SAF)

Treatment Group	Duration of exposure	Total patients (N)	Total patient time (months)
Eylea 0.4 mg	At least 1 dose	79	
(=Total)	At least 1 month	14	
	At least 3 months	10	38
	Cumulative exposure	**79**	**106**

Note: 1 month = 30 days. Total patients include 4 patients from the laser group who received Eylea as rescue therapy.
Subjects receiving at least one active VTE injection (pure or in combination) are displayed, subjects treated with comparator are not displayed.
Subjects who were treated with comparator and additionally with VTE 0.4 mg were considered in VTE 0.4 mg and VTE total.
Subjects may have received more than one dose. These subjects are considered for each dose, but once for VTE total.
Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y) + ROP (w24/27); Table 1.2/1f

SIII.2.3.7 All indications combined

The cumulative exposure in the wet AMD Phase I-IV studies (2 mg and 8 mg doses), CRVO Phase III studies, BRVO Phase III study, myopic CNV Phase III study, DME Phase I-III studies (2 mg and 8 mg doses), and ROP Phase III study was 126,278 patient months (see Table SIII.8.

Table SIII.8: Clinical trial exposure by treatment duration in wet AMD, CRVO, BRVO, myopic CNV, DME, and ROP (SAF)

Treatment group	Duration of exposure	Patients	Person time (months)
IAI 0.4 mg pediatric	At least one dose	79	
	At least 1 month	14	
	At least 3 months	10	38
	Total person time	**79**	**106**
IAI <= 1 mg	At least one dose	738	
	At least 1 month	702	
	At least 3 months	691	
	At least 6 months	663	
	At least 12 months	611	
	At least 18 months	515	11,056
	Total person time	**738**	**12,988**
IAI 2 mg	At least one dose	4,555	
	At least 1 month	4,492	
	At least 3 months	4,420	
	At least 6 months	4,149	
	At least 12 months	3,462	
	At least 18 months	2,409	65,372
	Total person time	**4,555**	**87,778**
IAI 4 mg	At least one dose	93	

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Table SIII.8: Clinical trial exposure by treatment duration in wet AMD, CRVO, BRVO, myopic CNV, DME, and ROP (SAF)

Treatment group	Duration of exposure	Patients	Person time (months)
	At least 1 month	78	
	At least 3 months	71	
	At least 6 months	56	
	At least 12 months	11	141
	Total person time	**93**	**673**
IAI 8 mg	At least one dose	1,217	
	At least 1 month	1,209	
	At least 3 months	1,190	
	At least 6 months	1,163	
	At least 12 months	1,072	
	At least 18 months	1,017	22,808
	Total person time	**1,217**	**24,624**
IAI total	At least one dose	6,487	
	At least 1 month	6,336	
	At least 3 months	6,223	
	At least 6 months	5,890	
	At least 12 months	5,062	
	At least 18 months	3,889	100,476
	Total person time	**6,487**	**126,278**

1 month = 30 days.
Subjects receiving at least one active IAI injection (pure or in combination) are displayed, subjects treated with sham or comparator including laser only are not displayed.
Subjects who were treated with sham or comparator and additionally with IAI 2 mg were considered in IAI 2 mg and IAI total.
Subjects may have received more than one dose. These subjects are considered for each dose, but once for IAI total.
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SIII.2.4 Number of active injections

SIII.2.4.1 Indication: Wet AMD

A total of 46,853 Eylea injections were administered to a total of 3,787 wet AMD subjects (see Table SIII.9).

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Table SIII.9: Summary statistics for number of injections among wet AMD subjects (excluding sham injections, SAF)

	IAI ≤1 mg N=694 (100%)	IAI 2 mg N=2474 (100%)	IAI 4 mg N=88 (100%)	IAI 8 mg N=726 (100%)	IAI total N=3787 (100%)
Number of injections (excl sham)					
1	36 (5.19%)	39 (1.58%)	11 (12.50%)	4 (0.55%)	50 (1.32%)
2	17 (2.45%)	25 (1.01%)	16 (18.18%)	3 (0.41%)	48 (1.27%)
3	8 (1.15%)	30 (1.21%)	13 (14.77%)	12 (1.65%)	43 (1.14%)
4	12 (1.73%)	52 (2.10%)	15 (17.05%)	18 (2.48%)	82 (2.17%)
5	20 (2.88%)	138 (5.58%)	13 (14.77%)	41 (5.65%)	189 (4.99%)
6	12 (1.73%)	95 (3.84%)	11 (12.50%)	24 (3.31%)	117 (3.09%)
7	9 (1.30%)	134 (5.42%)	4 (4.55%)	136 (18.73%)	274 (7.24%)
8	9 (1.30%)	346 (13.99%)	3 (3.41%)	136 (18.73%)	483 (12.75%)
9	5 (0.72%)	38 (1.54%)	1 (1.14%)	185 (25.48%)	218 (5.76%)
10	7 (1.01%)	73 (2.95%)	0	69 (9.50%)	142 (3.75%)
11	7 (1.01%)	223 (9.01%)	0	37 (5.10%)	269 (7.10%)
12	7 (1.01%)	153 (6.18%)	1 (1.14%)	33 (4.55%)	195 (5.15%)
13	13 (1.87%)	327 (13.22%)	0	27 (3.72%)	363 (9.59%)
14	20 (2.88%)	59 (2.38%)	0	0	75 (1.98%)
15	47 (6.77%)	72 (2.91%)	0	0	114 (3.01%)
16	192 (27.67%)	251 (10.15%)	0	0	408 (10.77%)
17	99 (14.27%)	111 (4.49%)	0	0	186 (4.91%)
18	54 (7.78%)	58 (2.34%)	0	0	98 (2.59%)
19	38 (5.48%)	33 (1.33%)	0	0	67 (1.77%)
20 - 24	81 (11.67%)	99 (4.00%)	0	0	178 (4.70%)
>= 25	1 (0.14%)	118 (4.77%)	0	0	187 (4.94%)
Number of injections (excl sham)					
n	694	2474	88	725	3786
nmiss	0	0	0	1	1
Sum	10128	30363	346	6016	46853
Mean (SD)	14.6 (5.7)	12.3 (6.5)	3.9 (2.2)	8.3 (2.2)	12.4 (6.7)
Median	16.0	12.0	4.0	8.0	11.0
Q1, Q3	14.0, 18.0	8.0, 16.0	2.0, 5.0	7.0, 9.0	8.0, 16.0
Min, Max	1, 25	1, 61	1, 12	1, 13	1, 61

Subjects receiving at least one active IAI injection (pure or in combination) are displayed, subjects treated with sham or comparator including laser only are not displayed.
Subjects who were treated with sham or comparator and additionally with IAI 2 mg are considered in IAI 2 mg and IAI total.
Subjects may have received more than one dose. These subjects are considered for each dose, but once for IAI total.
Optional injections at Week 96 are counted for VIEW 1 subjects who continued in the VIEW 1 extension study.
Only study eye injections are considered.
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SIII.2.4.2 Indication: CRVO

A total of 2,728 active Eylea injections were administered to 317 subjects during the 2 Phase III CRVO studies; the maximum number of injections (in one subject) was 21 (see Table SIII.10).

Table SIII.10: Summary statistics for number of injections among CRVO subjects (excluding sham injections, SAF)

	Sham Injection	Eylea 2 mg	Eylea Total
Denominator (N)	142	317	317
Number of injections (n, %)			
0	142 (100.0)	0	0
1	0	17 (5.4)	17 (5.4)
2	0	26 (8.2)	26 (8.2)
3	0	22 (6.9)	22 (6.9)
4	0	3 (0.9)	3 (0.9)
5	0	10 (3.2)	10 (3.2)
6	0	24 (7.6)	24 (7.6)
7	0	20 (6.3)	20 (6.3)
8	0	21 (6.6)	21 (6.6)
9	0	29 (9.1)	29 (9.1)
10	0	32 (10.1)	32 (10.1)
11	0	31 (9.8)	31 (9.8)
12	0	19 (6.0)	19 (6.0)
13	0	17 (5.4)	17 (5.4)
14	0	16 (5.0)	16 (5.0)
15	0	15 (4.7)	15 (4.7)
16	0	6 (1.9)	6 (1.9)
17	0	3 (0.9)	3 (0.9)
18	0	4 (1.3)	4 (1.3)
19	0	1 (0.3)	1 (0.3)
20-24	0	1 (0.3)	1 (0.3)
Mean number of injections			
No. of patients	142	317	317
Sum of injections	0	2,728	2,728
Mean ± STD	0.0	8.6 ± 4.4	8.6 ± 4.4
Range	0-0	1-21	1-21

Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y); Table 1.1/5b

SIII.2.4.3 Indication: BRVO

A total of 1,115 active Eylea injections were administered to the 158 patients exposed to Eylea (91 patients in the original Eylea 2 mg group and, now additionally including, 67 patients randomized to the Laser + Eylea 2 mg group who had received 295 active

injections from Week 24 onwards). The maximum number of injections in the studied period was 10 injections as defined per study protocol for the study's fixed dose regimen in the Eylea group (see Table SIII.11).

Table SIII.11: Summary statistics for number of active injections in the BRVO study VIBRANT through Week 52 (excluding sham injections, SAF)

	Laser+Eylea	Eylea 2 mg	Eylea total
Denominator (N)	N=92	N=91	N=158
Number of active injections (n, %)			
0	25 (27.2)	0	0
1	2 (2.2)	1 (1.1)	2 (1.3)
2	3 (3.3)	2 (2.2)	4 (2.5)
3	5 (5.4)	2 (2.2)	7 (4.4)
4	13 (14.1)	1 (1.1)	15 (9.5)
5	44 (47.8)	2 (2.2)	45 (28.5)
6	0	4 (4.4)	2 (1.3)
7	0	5 (5.5)	4 (2.5)
8	0	21 (23.1)	5 (3.2)
9	0	53 (58.2)	21 (13.3)
10	0	0	53 (33.5)
Mean number of active injections			
N patients	67	91	158
Sum of injections	295	820	1,115
Mean ± STD	4.4 ± 1.0	9.0 ± 1.8	7.1 ± 2.7
Median	5.0	10.0	7.5
Range	1-5	2-10	1-10

Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y); Table 1.1/5e

SIII.2.4.4 Indication: Myopic CNV

By Week 48, the 91 patients randomized to the Eylea group in the myopic CNV study MYRROR have received a total of 380 active injections, while 25 of the 31 patients randomized to the Sham+Eylea 2 mg group were treated with a sum of 94 active injections (see Table SIII.12). Overall, the 116 patients exposed to Eylea were treated with 4.1 ± 2.8 injections on average; the maximum possible number per patient was 12 injections (Baseline through Week 44 at monthly intervals).

Table SIII.12: Summary statistics for number of injections among myopic CNV patients (excluding sham injections, SAF)

	Sham+Eylea 2 mg	Eylea 2 mg	Eylea total
Denominator (N)	31	91	116
Number of injections (n, %)			
0	6 (19.4)	0	0
1	2 (6.5)	14 (15.4)	16 (13.8)

Table SIII.12: Summary statistics for number of injections among myopic CNV patients (excluding sham injections, SAF)

	Sham+Eylea 2 mg	Eylea 2 mg	Eylea total
2	6 (19.4)	14 (15.4)	20 (17.2)
3	6 (19.4)	26 (28.6)	32 (27.6)
4	2 (6.5)	11 (12.1)	13 (11.2)
5	0	3 (3.3)	3 (2.6)
6	9 (29.0)	5 (5.5)	14 (12.1)
7	0	3 (3.3)	3 (2.6)
8	0	5 (5.5)	5 (4.3)
9	0	3 (3.3)	3 (2.6)
11	0	1 (1.1)	1 (0.9)
12	0	6 (6.6)	6 (5.2)
Mean number of injections			
No. of patients	25	91	116
Sum of injections	94	380	474
Mean ± STD	3.8 ± 1.9	4.2 ± 3.1	4.1 ± 2.8
Range	1-6	1-12	1-12

Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y); Table 1.1/5c

SIII.2.4.5 Indication: DME

The 2,030 subjects who were treated with at least one active injection with Eylea in the 7 DME studies have received a total of 27,914 active injections, with a mean number of 13.8 ± 9.2 injections (see Table SIII.13).

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Table SIII.13: Summary statistics for number of injections among DME subjects (excluding sham injections, SAF)

	IAI <= 1 mg N=44 (100%)	IAI 2 mg N=1490 (100%)	IAI 4 mg N=5 (100%)	IAI 8 mg N=491 (100%)	IAI total N=2030 (100%)
Number of injections (excl sham)					
1	0	25 (1.68%)	5 (100.00%)	3(0.61%)	33 (1.63%)
2	1 (2.27%)	25 (1.68%)	0	8 (1.63%)	34 (1.67%)
3	0	34 (2.28%)	0	14 (2.85%)	48 (2.36%)
4	2 (4.55%)	30 (2.01%)	0	12 (2.44%)	44 (2.17%)
5	0	38 (2.55%)	0	9 (1.83%)	47 (2.32%)
6	0	55 (3.69%)	0	18 (3.67%)	73 (3.60%)
7	0	45 (3.02%)	0	63 (12.83%)	108 (5.32%)
8	0	67 (4.50%)	0	92 (18.74%)	159 (7.83%)
9	0	195 (13.09%)	0	166 (33.81%)	361 (17.78%)
10	4 (9.09%)	25 (1.68%)	0	76 (15.48%)	105 (5.17%)
11	2 (4.55%)	41 (2.75%)	0	9 (1.83%)	52 (2.56%)
12	11 (25.00%)	60 (4.03%)	0	14 (2.85%)	85 (4.19%)
13	24 (54.55%)	157 (10.54%)	0	7 (1.43%)	188 (9.26%)
14	0	142 (9.53%)	0	0	142 (7.00%)
15	0	15 (1.01%)	0	0	15 (0.74%)
16	0	26 (1.74%)	0	0	26 (1.28%)
17	0	20 (1.34%)	0	0	20 (0.99%)
18	0	34 (2.28%)	0	0	34 (1.67%)
19	0	13 (0.87%)	0	0	13 (0.64%)
20 - 24	0	209 (14.03%)	0	0	209 (10.30%)
>= 25	0	234 (15.70%)	0	0	234 (11.53%)
Number of injections (excl sham)					
n	44	1,490	5	491	2,030
nmiss	0	0	0	0	0
Sum	516	23,342	5	4,051	27,914
Mean (SD)	11.7(2.5%)	15.7 (9.9%)	1.0 (0.0%)	8.3 (2.1%)	13.8 (9.2%)
Median	13.0	13.0	1.0	9.0	11.0
Q1, Q3	12.0,13.0	9.0, 21.0	1.0, 1.0	7.0, 9.0	8.0, 17.0
Min, Max	2, 13	1, 41	1, 1	1, 13	1, 41

Subjects receiving at least one active IAI injection (pure or in combination) are displayed, subjects treated with sham or comparator including laser only are not displayed.
Subjects who were treated with sham or comparator and additionally with IAI 2 mg are considered in IAI 2 mg and IAI total.
Subjects may have received more than one dose. These subjects are considered for each dose, but once for IAI total.
Optional injections at Week 96 are counted for VIEW 1 subjects who continued in the VIEW 1 extension study.
Only study eye injections are considered.
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SIII.2.4.6 Indication: ROP

The 79 subjects who were treated with at least one active injection per eye with Eylea in the ROP study have received a total of 181 active injections, with a mean number of 2.3 ± 0.8 injections. The maximum number of Eylea injections per subject was 4 (2 treatments per eye) (see Table SIII.14).

Table SIII.14: Summary statistics for number of injections among ROP patients (excluding sham injections, SAF)

	Laser	Eylea 0.4 mg[a]	Eylea total
Denominator (N)	38	79	79
Number of injections (n, %)			
0	34 (89.5)	0	0
1	0	4 (5.1)	4 (5.1)
2	3 (7.9)	58 (73.4)	58 (73.4)
3	1 (2.6)	7 (8.9)	7 (8.9)
4	0	10 (12.7)	10 (12.7)
Mean number of injections			
No. of patients	4	79	79
Sum of injections	9	181	181
Mean ± STD	2.3 ± 0.5	2.3 ± 0.8	2.3 ± 0.8
Range	2-3	1-4	1-4

a: This column includes all patients treated with Eylea and is therefore identical with the Eylea total column.
Note: Total patients include 4 patients from the laser group who received Eylea as rescue therapy.
Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y) + ROP (w24/27); Table 1.1/3f

SIII.2.4.7 All indications combined

Overall, 79,265 Eylea injections were administered to a total of 6,487 subjects (all studies in wet AMD, CRVO, BRVO, myopic CNV, DME, or ROP); the maximum number of injections administered to a patient was 61 injections (see Table SIII.15).

Table SIII.15: Summary statistics for number of injections among wet AMD, CRVO, BRVO, myopic CNV, DME, and ROP patients (excluding sham injections, SAF)

	IAI 0.4 mg pediatric N=79 (100%)	IAI ≤ 1 mg N=738 (100%)	IAI 2 mg N=4,555 (100%)	IAI 4 mg N=93 (100%)	IAI 8 mg N=1,217 (100%)	IAI total N=6,487 (100%)
Number of injections (excl. sham)						
1	4 (5.06%)	36 (4.88%)	99 (2.17%)	16 (17.20%)	7 (0.58%)	122 (1.88%)
2	58 (73.42%)	18 (2.44%)	100 (2.20%)	16 (17.20%)	11 (0.90%)	190 (2.93%)
3	7 (8.86%)	8 (1.08%)	125 (2.74%)	13 (13.98%)	26 (2.14%)	159 (2.45%)
4	10 (12.66%)	14 (1.90%)	113 (2.48%)	15 (16.13%)	30 (2.47%)	167 (2.57%)
5	0	20 (2.71%)	234 (5.14%)	13 (13.98%)	50 (4.11%)	294 (4.53%)
6	0	12 (1.63%)	190 (4.17%)	11 (11.83%)	42 (3.45%)	230 (3.55%)
7	0	9 (1.22%)	206 (4.52%)	4 (4.30%)	199 (16.35%)	409 (6.30%)

Table SIII.15: Summary statistics for number of injections among wet AMD, CRVO, BRVO, myopic CNV, DME, and ROP patients (excluding sham injections, SAF)

	IAI 0.4 mg pediatric N=79 (100%)	IAI ≤ 1 mg N=738 (100%)	IAI 2 mg N=4,555 (100%)	IAI 4 mg N=93 (100%)	IAI 8 mg N=1,217 (100%)	IAI total N=6,487 (100%)
8	0	9 (1.22%)	444 (9.75%)	3 (3.23%)	228(18.73%)	673(10.37%)
9	0	5(0.68%)	286 (6.28%)	1 (1.08%)	351 (28.84%)	632 (9.74%)
10	0	11 (1.49%)	183 (4.02%)	0	145 (11.91%)	332 (5.12%)
11	0	9 (1.22%)	296 (6.50%)	0	46 (3.78%)	353 (5.44%)
12	0	18 (2.44%)	238 (5.23%)	1 (1.08%)	47 (3.86%)	305 (4.70%)
13	0	37 (5.01%)	501 (11.00%)	0	34 (2.79%)	568 (8.76%)
14	0	20 (2.71%)	217 (4.76%)	0	0	233 (3.59%)
15	0	47 (6.37%)	102 (2.24%)	0	0	144 (2.22%)
16	0	192 (26.02%)	283 (6.21%)	0	0	440 (6.78%)
17	0	99 (13.41%)	134 (2.94%)	0	0	209 (3.22%)
18	0	54 (7.32%)	96 (2.11%)	0	0	136 (2.10%)
19	0	38 (5.15%)	47 (1.03%)	0	0	81 (1.25%)
20 - 24	0	81 (10.98%)	309 (6.78%)	0	0	388 (5.98%)
>= 25	0	1 (0.14%)	352 (7.73%)	0	0	421 (6.49%)
Number of injections (excl sham)						
n	79	738	4555	93	1216	6486
nmiss	0	0	0	0	1	1
Sum	181	10644	58022	351	10067	79265
Mean (SD)	2.3 (0.8)	14.4 (5.6)	12.7 (8.0)	3.8 (2.2)	8.3 (2.1)	12.2 (7.6)
Median	2.0	16.0	12.0	4.0	9.0	11.0
Q1, Q3	2.0, 2.0	13.0, 17.0	8.0, 16.0	2.0, 5.0	7.0, 9.0	8.0,16.0
Min, Max	1, 4	1, 25	1, 61	1, 12	1, 13	1, 61

Subjects receiving at least one active IAI injection (pure or in combination) are displayed, subjects treated with sham or co mparator including laser only are not displayed.
Subjects who were treated with sham or comparator and additionally with IAI 2 mg are considered in IAI 2 mg and IAI tot al.
Subjects may have received more than one dose. These subjects are considered for each dose, but once for IAI total.
Optional injections at Week 96 are counted for VIEW 1 subjects who continued in the VIEW 1 extension study.
Only study eye injections are considered.
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SIII.2.5 Duration of exposure (in patient months) by age, sex, and ethnicity

SIII.2.5.1 Indication: Wet AMD

Table SIII.16 presents the allocation to treatment groups of all subjects who were included in the Phase I-IV AMD trials, separated by sex, age category, and race.

Generally, there were slightly more female than male subjects treated with Eylea (53.4% *vs.* 46.6%). As there were more studies performed in the EU and in the USA than in other countries, the majority of subjects in all dose groups receiving Eylea injection were

White (71.3%), followed by Asians (26.3%). The majority of subjects receiving Eylea injections were ≥75 years of age in all dose groups (56.0%), followed by the age group ≥65 to <75 years of age (30.5%).

Overall, the subgroup analyses did not point to a specific risk on treatment with Eylea in any of the analysed subgroups.

Table SIII.16: Number of subjects by treatment group and sex, age, and race in AMD Phase I-IV studies (SAF)

	IAI ≤1 mg N=694 n (%)	IAI 2 mg N=2,474 n (%)	IAI 4 mg N=88 n (%)	IAI 8 mg N=726 n (%)	IAI Total N=3,787 n (%)
Sex					
Females	376 (54.2)	1,311 (53.0)	54 (61.4)	392 (54.0)	2,021 (53.4)
Males	318 (45.8)	1,163 (47.0)	34 (38.6)	334 (46.0)	1,766 (46.6)
Age group (years)					
≥1 to <65	67 (9.7)	379 (15.3)	4 (4.5)	72 (9.9)	510 (13.5)
≥ 65 to <75	167 (24.1)	729 (29.5)	23 (26.1)	277 (38.2)	1,155 (30.5)
≥75	460 (66.3)	1,366 (55.2)	61 (69.3)	377 (51.9)	2,122 (56.0)
Race					
American Indian or Alaska native	2 (0.3)	3 (0.1)	0	0	5 (0.1)
Asian	67 (9.7)	783 (31.6)	0	151 (20.8)	997 (26.3)
Black or African American	1 (0.1)	6 (0.2)	2 (2.3)	2 (0.3)	11 (0.3)
Multiple	0	1 (<0.1)	0	1 (0.1)	2 (<0.1)
Native Hawaiian or other pacific islander	0	1 (<0.1)	0	1 (0.1)	2 (<0.1)
Other	0	1 (<0.1)	0	0	1 (<0.1)
Not reported	18 (2.6)	47 (1.9)	0	3 (0.4)	68 (1.8)
White	606 (87.3)	1,632 (66.0)	86 (97.7)	568 (78.2)	2,701 (71.3)

IAI=Intravitreal Aflibercept Injection
Due to different study designs, subjects may have been exposed to more than 1 dosage.
Source: Integrated Analysis Pool 3 RMP: wet AMD 2 mg (up to year 3) + wet AMD 8 mg (w44/48) + CRVO 2 mg (w76/100) + mCNV 2 mg (w48) + DME 2 mg (3y) + DME 8 mg (w48) + BRVO 2 mg (1y) + ROP 0.4 mg (w24/27), Table 1/6

Table SIII.17 summarizes the duration of exposure (patient months) in wet AMD by demographic subgroups.

Table SIII.17: Clinical trial exposure (duration in patient months) by demographic subgroups sex, age categories, and ethnicity in wet AMD subjects (SAF)

Treatment group	Subgroup		Patients	Person time (months)
IAI ≤ 1 mg	Age group	≥:1 to <65	67	1,280

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Table SIII.17: Clinical trial exposure (duration in patient months) by demographic subgroups sex, age categories, and ethnicity in wet AMD subjects (SAF)

Treatment group	Subgroup		Patients	Person time (months)
		≥:65 to <75	167	3,039
		≥:75	460	8,165
	Sex	Male	318	5,848
		Female	376	6,636
	Race	White	606	10,819
		Black or African American	1	17
		Asian	67	1,293
		American Indian or Alaska Native	2	41
		Not Reported	18	313
IAI 2 mg	Age group	≥1 to <65	379	6,387
		≥65 to <75	729	14,158
		≥75	1,366	29,409
	Sex	Male	1,163	21,765
		Female	1,311	28,189
	Race	White	1,632	38,278
		Black or African American	6	132
		Asian	783	10,489
		American Indian or Alaska Native	3	62
		Native Hawaiian or Other Pacific Islander	1	15
		Not Reported	47	949
		Other	1	9
		Multiple	1	21
IAI 4 mg	Age group	≥1 to <65	4	29
		≥65 to <75	23	183
		≥75	61	456
	Sex	Male	34	245
		Female	54	424
	Race	White	86	666
		Black or African American	2	3
IAI 8 mg	Age group	≥1 to <65	72	1,507
		≥65 to <75	277	5,746
		≥75	377	7,290
	Sex	Male	334	6,625
		Female	392	7,918
	Race	White	568	11,287
		Black or African American	2	45

Table SIII.17: Clinical trial exposure (duration in patient months) by demographic subgroups sex, age categories, and ethnicity in wet AMD subjects (SAF)

Treatment group	Subgroup		Patients	Person time (months)
		Asian	151	3,113
		Native Hawaiian or Other Pacific Islander	1	9
		Not Reported	3	67
		Multiple	1	23
IAI total	Age group	≥1 to <65	510	9,209
		≥65 to <75	1,155	23,143
		≥75	2,122	45,404
	Sex	Male	1,766	34,529
		Female	2,021	43,227
	Race	White	2,701	61,149
		Black or African American	11	196
		Asian	997	14,904
		American Indian or Alaska Native	5	103
		Native Hawaiian or Other Pacific Islander	2	24
		Not Reported	68	1,329
		Other	1	9
		Multiple	2	43

1 month = 30 days.
Subjects receiving at least one active IAI injection (pure or in combination) are displayed, subjects treated with sham or comparator including laser only are not displayed.
Subjects who were treated with sham or comparator and additionally with IAI 2 mg were considered in IAI 2 mg and IAI t otal.
Subjects may have received more than one dose. These subjects are considered for each dose, but once for IAI total.
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SIII.2.5.2 Indication: CRVO

Table SIII.18 presents the subjects who were treated with Eylea in the 2 Phase III CRVO trials, separated by sex, age category, and race.

Slightly more men than women were included in the Eylea total group (56.5% *vs*. 43.5%). As seen in the wet AMD studies, the majority of subjects treated with Eylea were White (76.0%). In contrast to the more age-related condition of wet AMD, the CRVO subjects treated with Eylea were obviously younger than wet AMD subjects: Almost half of the subjects in the Eylea total group (45.7%) were younger than 65 years (wet AMD: 10.4%), whilst 21.5% were at the age of 75 years or older (wet AMD: 63.6%).

Again, no specific risk regarding Eylea injection was identified for CRVO subjects in any of the analysed subgroup.

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Table SIII.18: Number of subjects treated with Eylea by sex, age, and race in the 2 CRVO Phase III studies (SAF)

	Eylea 2 mg (=Eylea total) N=317 N (%)
Sex	
Females	138 (43.5)
Males	179 (56.5)
Age group (years)	
<65	145 (45.7)
≥ 65 to <75	104 (32.8)
≥75	68 (21.5)
Race	
American Indian or Alaska native	2 (0.6)
Asian	42 (13.2)
Black or African American	10 (3.2)
Multiple	17 (5.4)
Not reported	5 (1.6)
White	241 (76.0)

Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y); Table 1.2/2b

Table SIII.19 summarizes the duration of exposure (patient months) in CRVO subjects by demographic subgroups.

Table SIII.19: Clinical trial exposure (duration in patient months) by demographic subgroups sex, age categories, and ethnicity in CRVO subjects (SAF)

		No. of subjects	Patient time (months)
Sex by age groups			
Males	<65 years	95	1,470
	≥65 - <75 years	55	825
	≥75 years	29	504
Females	<65 years	50	787
	≥65 - <75 years	49	766
	≥75 years	39	611
Sex [a]			
Males		179	2,799
Females		138	2,164
Age groups [a]			
<65 years		145	2,257
≥65 - <75 years		104	1,591
≥75 years		68	1,115

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Table SIII.19: Clinical trial exposure (duration in patient months) by demographic subgroups sex, age categories, and ethnicity in CRVO subjects (SAF)

	No. of subjects	Patient time (months)
Ethnicity		
White	241	3,811
Black or African American	10	175
Asian	42	552
American Indian or Alaska native	2	45
Not reported	5	53
Multiple	17	326

[a]: Calculated by author based on the "sex by age" results
Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y); Table 1.2/4b

An additional analysis was run to determine the age distribution among the 156 women who participated in the 2 CRVO studies (additionally including 204 males [mean age: 63.6 ± 14.7 years], 360 study subjects in total). Applying a threshold age of <55 years, a total of 23 women (14.7% of the 156 enrolled women) seemed to have been of childbearing potential in the CRVO studies (see Table SIII.20).

Table SIII.20: Age distribution among women enrolled in the CRVO studies (SAF)

	Sham[d] N=68	Sham + PRN[c] N=74	Eylea 2Q4+PRN[b] N=218	Total[a] N=360
Mean age (years)				
Mean ± STD	66.2 ± 11.6	72.1 ± 13.4	66.1 ± 10.3	67.5 ± 11.5
Median (Range)	68.0 (41-87)	76.0 (32-88)	66.0 (39-85)	68.5 (32-88)
	Age categories for the subgroup of women (N=156)			
Age groups (years)				
	N=31 (100.0)	*N=35 (100.0)*	*N=90 (100.0)*	*N=156 (100.0)*
<45 (n, %)	1 (3.2)	2 (5.7)	3 (3.3)	6 (3.8)
≥45-<50 (n, %)	2 (6.5)	1 (2.9)	4 (4.4)	7 (4.5)
≥50-<55 (n, %)	3 (9.7)	1 (2.9)	6 (6.7)	10 (6.4)
≥55 (n, %)	25 (80.6)	31 (88.6)	77 (85.6)	133 (85.3)
Age decades (years)				
	N=31 (100.0)	*N=35 (100.0)*	*N=90 (100.0)*	*N=156 (100.0)*
20-29 (n, %)	0	0	0	0
30-39 (n, %)	0	1 (2.9)	1 (1.1)	2 (1.3)
40-49 (n, %)	3 (9.7)	2 (5.7)	6 (6.7)	11 (7.1)
50-59 (n, %)	6 (19.4)	2 (5.7)	12 (13.3)	20 (12.8)
60-69 (n, %)	7 (22.6)	6 (17.1)	35 (38.9)	48 (30.8)
70-79 (n, %)	12 (38.7)	12 (34.3)	26 (28.9)	50 (32.1)
80-89 (n, %)	3 (9.7)	12 (34.3)	10 (11.1)	25 (16.0)

Please note that the treatment group designation in this table differs from the remaining tables in this module:
[a]: Total: All study subjects.
[b]: Eylea 2Q4 + PRN: Subjects who were initially treated with Eylea 2Q4 followed by PRN injections in both studies.

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Table SIII.20: Age distribution among women enrolled in the CRVO studies (SAF)

	Sham[d] N=68	Sham + PRN[c] N=74	Eylea 2Q4+PRN[b] N=218	Total[a] N=360
Mean age (years)				
Mean ± STD	66.2 ± 11.6	72.1 ± 13.4	66.1 ± 10.3	67.5 ± 11.5
Median (Range)	68.0 (41-87)	76.0 (32-88)	66.0 (39-85)	68.5 (32-88)
Age categories for the subgroup of women (N=156)				

[c]: Sham + PRN (COPERNICUS): Subjects with sham injections from Day 1 to Week 20 followed by Eylea 2 mg PRN from Week 24 onwards.
[d]: Sham + PRN (GALILEO): Subjects with sham injections from Day 1 to Week 48 followed by Eylea 2 mg PRN from Week 52 onwards.
STD=Standard deviation.
Source: IA Pool 1 CRVO (Week 76/100), Response to rapporteur questions, Table 1.1/1.

SIII.2.5.3 Indication: BRVO

Table SIII.21 presents the 158 subjects who were treated with Eylea in the Phase III BRVO study VIBRANT separated by sex, age category, and race.

The proportions of men and women treated with Eylea were similar, 44.9% of patients were younger than 65 years, and 73.4% were White. Generally, the BRVO patient characteristics were similar to those observed in the CRVO population.

No specific risk regarding Eylea injection was identified for BRVO subjects in any of the analysed subgroup.

Table SIII.21: Number of subjects treated with Eylea by sex, age, and race in the BRVO Phase III study (SAF)

	Eylea 2 mg (=Eylea total) N=158 n (%)
Sex	
Females	72 (45.6)
Males	86 (54.4)
Age group (years)	
<65	71 (44.9)
≥ 65 to <75	53 (33.5)
≥75	34 (21.5)
Race	
Native Hawaiian or other Pacific Islander	1 (0.6)
Asian	19 (12.0)
Black or African American	17 (10.8)
White	116 (73.4)
Not reported	5 (3.2)

Source: I Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y); Table 1.2/2e

Table SIII.22 summarizes the duration of exposure (patient months) in BRVO subjects by demographic subgroups.

Table SIII.22: Clinical trial exposure (duration in patient months) by demographic subgroups sex, age categories, and ethnicity in BRVO subjects (SAF)

		No. of subjects	Patient time (months)
Sex by age groups			
Males	<65 years	41	338
	≥65 - <75 years	29	254
	≥75 years	16	149
Females	<65 years	30	269
	≥65 - <75 years	24	228
	≥75 years	18	183
Sex [a]			
Males		86	741
Females		72	680
Age groups [a]			
<65 years		71	607
≥65 - <75 years		53	482
≥75 years		34	332
Ethnicity			
White		116	1,070
Black or African American		17	131
Asian		19	181
Native Hawaiian or other Pacific Islander		1	12
Not reported		5	26

[a]: Calculated by author based on the "sex by age" results.
Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y); Table 1.2/4e

SIII.2.5.4 Indication: Myopic CNV

Table SIII.23 shows the MYRROR study patients separated by sex, age category, and race. All enrolled patients in this study were Asians, and clearly more females than males were treated in the Eylea total group (75.0% *vs*. 25.0%). In this indication - and in contrast to wet AMD or CRVO, where less than half of the patients were <65 years of age -, the majority of patients were younger than 65 years (65.5%), while only 9.5% were 75 years or older in the Eylea total group.

No specific risks associated with Eylea were identified in any of the analyzed subgroups through study end at Week 48.

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Table SIII.23: Number of patients treated with Eylea by sex, age, and race in the myopic CNV Phase III study (SAF)

	Sham+Eylea 2 mg N=31 n (%)	Eylea 2 mg N=91 n (%)	Eylea total N=116 n (%)
Sex			
Females	27 (87.1)	65 (71.4)	87 (75.0)
Males	4 (12.9)	26 (28.6)	29 (25.0)
Age group (years)			
<65	22 (71.0)	58 (63.7)	76 (65.5)
≥ 65 to <75	7 (22.6)	24 (26.4)	29 (25.0)
≥75	2 (6.5)	9 (9.9)	11 (9.5)
Race			
Asian	31 (100.0)	91 (100.0)	116 (100.0)

Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y); Table 1.2/2c

Table SIII.24 summarizes the duration of exposure (patient months) in the 116 myopic CNV patients treated with Eylea by demographic subgroups.

Table SIII.24: Clinical trial exposure (duration in patient months) by demographic subgroups sex, age categories, and ethnicity in myopic CNV patients (SAF)

		No. of patients	Patient time (months)
Sex by age groups			
	<65 years	22	213
Males	≥65 - <75 years	5	51
	≥75 years	2	22
	<65 years	54	478
Females	≥65 - <75 years	24	234
	≥75 years	9	81
Sex [a]			
Males		29	286
Females		87	793
Age groups [a]			
<65 years		76	691
≥65 - <75 years		29	285
≥75 years		11	103
Ethnic origin			
Asian		116	1,079

[a]: Calculated by author based on the "sex by age" results
Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y); Table 1.2/4c

Also, in the myopic CNV population the proportion of females of childbearing potential was evaluated (see Table SIII.25). Given the same age threshold as used for the CRVO population to assume a childbearing potential (i.e., <55 years), a total of 30 women (32.6%) of the

92 females enrolled in MYRROR were of childbearing potential in the myopic CNV study. This proportion was about twice as high as in the CRVO studies.

Table SIII.25: Number of patients treated with Eylea by sex and age in the myopic CNV Phase III study (SAF)

	Sham+Eylea 2 mg	Eylea 2 mg	All patients
Females			
Age (years)			
N	27	65	92
Mean ± STD	59.3 ± 11.7	59.4 ± 13.2	59.4 ± 12.7
Median (min:max)	63.0 (27:82)	63.0 (27:82)	63.0 (27:82)
Age categories (n, %)			
N	27	65	92
<45 years	3 (11.1)	10 (15.4)	13 (14.1)
≥45-<55 years	5 (18.5)	12 (18.5)	17 (18.5)
≥55-<65 years	10 (37.0)	17 (26.2)	27 (29.3)
≥65-<75 years	7 (25.9)	19 (29.2)	26 (28.3)
≥75 years	2 (7.4)	7 (10.8)	9 (9.8)
Males			
Age (years)			
N	4	26	30
Mean ± STD	45.3 ± 6.8	55.8 ± 14.8	54.4 ± 14.4
Median (min:max)	46.0 (38:51)	61.0 (32:83)	51.0 (32:83)
Age categories (n, %)			
N	4	26	30
<45 years	2 (50.0)	7 (26.9)	9 (30.0)
≥45-<55 years	2 (50.0)	5 (19.2)	7 (23.3)
≥55-<65 years	0	7 (26.9)	7 (23.3)
≥65-<75 years	0	5 (19.2)	5 (16.7)
≥75 years	0	2 (7.7)	2 (6.7)

Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y); Table 1.1/1

SIII.2.5.5 Indication: DME

Table SIII.26 shows the 2,030 subjects, who were treated with Eylea in the Phase I-III DME studies separated by sex, age category, and race. The majority of exposed DME subjects were White (65.6%), and more men than women were included (57.7% *vs*. 42.3%). 58.4% of the DME subjects were ≥1 to <65 years of age, while 8.7% were 75 years or older.

So far, no specific risk associated with Eylea has been identified for DME in any of the analysed subgroups.

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Table SIII.26: Number of subjects by treatment group and sex, age, and race in DME Phase I-III studies (SAF)

	Eylea ≤1 mg N=44 n (%)	Eylea 2 mg N=1,490 n (%)	Eylea 4 mg N=5 n (%)	Eylea 8 mg N=491 n (%)	Eylea Total N=2,030 n (%)
Sex					
Females	20 (45.5)	653 (43.8)	3 (60.0)	182 (37.1)	858 (42.3)
Males	24 (54.5)	837 (56.2)	2 (40.0)	309 (62.9)	1,172 (57.7)
Age group (years)					
≥1 to <65	24 (54.5)	882 (59.2)	3 (60.0)	277 (56.4)	1,186 (58.4)
≥ 65 to <75	16 (36.4)	486 (32.6)	1 (20.0)	164 (33.4)	667 (32.9)
≥75	4 (9.1)	122 (8.2)	1 (20.0)	50 (10.2)	177 (8.7)
Race					
American Indian or Alaska native	0	2 (0.1)	0	2 (0.4)	4 (0.2)
Asian	0	464 (31.1)	0	71 (14.5)	535 (26.4)
Black or African American	3 (6.8)	74 (5.0)	2 (40.0)	44 (9.0)	123 (6.1)
Multiple	0	2 (0.1)	0	1 (0.2)	3 (0.1)
Native Hawaiian or other pacific islander	0	4 (0.3)	0	1 (0.2)	5 (0.2)
Other		4 (0.3)	0	7 (1.4)	11 (0.5)
Not reported	0	12 (0.8)	0	6 (1.2)	18 (0.9)
White	41 (93.2)	928 (62.3)	3 (60.0)	359 (73.1)	1,331 (65.6)

Source: Integrated Analysis Pool 3 RMP wet AMD 2 mg (up to year 3) + wet AMD 8 mg (w44/48) + CRVO 2 mg (w76/100) + mCNV 2 mg (w48) + DME 2 mg (3y) + DME 8 mg (w48) + BRVO 2 mg (1y) + ROP 0.4 mg (w24/27), Table 1/6

The age distribution among the 364 females who were enrolled in the pivotal randomized, controlled DME Phase III studies VISTA-DME and VIVID-DME (N=865 in SAF) is summarized in Table SIII.27 (please note that the treatment groups reflect the originally randomized treatment arm). Based on the previously mentioned threshold of <55 years, a total of 44/364 women (12.1%) were of childbearing potential in these 2 studies. This figure was similar to that observed among the females with CRVO.

Table SIII.27: Age distribution among women enrolled in the pivotal Phase III DME studies VIVID-DME and VISTA-DME (SAF)

	Laser N=123	Eylea 2Q4 N=121	Eylea 2Q8 N=120	2Q4 + 2Q8 N=241	Total N=364
Mean age (years)					
Mean ± STD	62.8 ± 8.3	63.5 ± 9.6	64.7 ± 9.0	64.1 ± 9.3	63.6 ± 9.0
Median (Range)	62.0 (37-81)	64.0 (26-83)	66.0 (33-86)	65.0 (26-86)	64.0 (26-86)
Age groups (years)					
<45 (n, %)	3 (2.4)	4 (3.3)	3 (2.5)	7 (2.9)	10 (2.7)
≥45-<55 (n, %)	12 (9.8)	12 (9.9)	10 (8.3)	22 (9.1)	34 (9.3)
≥55-<65 (n, %)	58 (47.2)	49 (40.5)	42 (35.0)	91 (37.8)	149 (40.9)
≥65-<75 (n, %)	37 (30.1)	43 (35.5)	50 (41.7)	93 (38.6)	130 (35.7)
≥75 (n, %)	13 (10.6)	13 (10.7)	15 (12.5)	28 (11.6)	41 (11.3)

Please note that the treatment group designation in this table differs from the remaining tables in this module, since the original randomization groups are shown (i.e., females in the laser group also might have received Eylea).
STD=Standard deviation.
Source: Integrated Analysis - Pool 1 Week 52 ISS; Table 14.1.1/1

Table SIII.28 summarizes the duration of exposure (patient months) in the 2,030 DME subjects treated with active Eylea at least once by demographic subgroups.

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Table SIII.28: Clinical trial exposure (duration in patient months) by demographic subgroups sex, age categories, and ethnic origin in DME subjects (SAF)

Treatment group	Subgroup		Patients	Person time (months)
IAI <= 1 mg	Age group	>=1 to <65	24	274
		>=65 to <75	16	186
		>=75	4	45
	Sex	Male	24	263
		Female	20	243
	Race	White	41	468
		Black or African American	3	37
IAI 2 mg	Age group	>=1 to <65	882	17498
		>=65 to <75	486	10404
		>=75	122	2461
	Sex	Male	837	17009
		Female	653	13354
	Race	White	928	21443
		Black or African American	74	1680
		Asian	464	6693
		American Indian or Alaska Native	2	35
		Native Hawaiian or Other Pacific Islander	4	90
		Not Reported	12	310
		Other	4	87
		Multiple	2	25
IAI 4 mg	Age group	>=1 to <65	3	3
		>=65 to <75	1	1
		>=75	1	1
	Sex	Male	2	2
		Female	3	3
	Race	White	3	3
		Black or African American	2	2
IAI 8 mg	Age group	>=1 to <65	277	5771
		>=65 to <75	164	3304
		>=75	50	1007
	Sex	Male	309	6313
		Female	182	3768
	Race	White	359	7332
		Black or African American	44	870
		Asian	71	1551

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Table SIII.28: Clinical trial exposure (duration in patient months) by demographic subgroups sex, age categories, and ethnic origin in DME subjects (SAF)

Treatment group	Subgroup		Patients	Person time (months)
		American Indian or Alaska Native	2	46
		Native Hawaiian or Other Pacific Islander	1	22
		Not Reported	6	106
		Other	7	132
		Multiple	1	22
IAI total	Age group	>=1 to <65	1186	23546
		>=65 to <75	667	13895
		>=75	177	3513
	Sex	Male	1172	23587
		Female	858	17367
	Race	White	1331	29247
		Black or African American	123	2589
		Asian	535	8244
		American Indian or Alaska Native	4	81
		Native Hawaiian or Other Pacific Islander	5	113
		Not Reported	18	415
		Other	11	219
		Multiple	3	47

1 month = 30 days.
Subjects receiving at least one active IAI injection (pure or in combination) are displayed, subjects treated with sham or comparator including laser only are not displayed.
Subjects who were treated with sham or comparator and additionally with IAI 2 mg were considered in IAI 2 mg and IAI t otal.
Subjects may have received more than one dose. These subjects are considered for each dose, but once for IAI total.
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SIII.2.5.6 Indication: ROP

Table SIII.29 shows the ROP study patients separated by sex and race. Most of the enrolled patients in this study were White (74.7%) followed by Asian race (21.5%). There were slightly more males than females treated in the Eylea group (54.4% *vs.* 45.6%), whereas it was equally distributed in the laser treatment arm, 50% males, 50% females.

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Table SIII.29: Number of patients treated with Eylea by sex, age, and race in the ROP Phase III study (SAF)

	Laser N=38 n (%)	Eylea 0.4 mg[a] N=79 n (%)	Eylea total N=79 n (%)
Sex			
Males	19 (50.0)	43 (54.4)	43 (54.4)
Females	19 (50.0)	36 (45.6)	36 (45.6)
***Age (years):* <1**	38 (100.0)	79 (100.0)	79 (100.0)
Race			
White	28 (73.7)	59 (74.7)	59 (74.7)
Black or African American	0	2 (2.5)	2 (2.5)
Asian	9 (23.7)	17 (21.5)	17 (21.5)
American Indian or Alaska native	1 (2.6)	0	0
Multiple	0	1 (1.3)	1 (1.3)

[a]: This column includes all patients treated with Eylea and is therefore identical with the Eylea total column.
Subjects randomized to laser and receiving at least one active VTE injection are considered in laser and Eylea total columns.
Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y) + ROP (w24/27); Table 1.1/4f

Table SIII.30 summarizes the duration of exposure (patient months) in ROP by demographic subgroups. An additional analysis was run to determine the age distribution among the preterm infants. Most preterm infants (n=48) were between ≥24th - <27th gestational week.

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Table SIII.30: Clinical trial exposure (duration in patient months) by demographic subgroups sex, age categories, and ethnicity in ROP patients (SAF)

		No. of patients	Patient time (months)
Sex by age groups[a]			
	<24	2	2
Males	≥24 - <27	22	33
	≥27 - <32	19	24
	<24	2	6
Females	≥24 - <27	26	31
	≥27 - <32	8	11
Sex[b]			
Males		43	59
Females		36	48
Age groups[b]			
<1 year		79	107
Ethnic origin			
White		59	69
Black or African American		2	2
Asian		17	34
Multiple		1	1

[a]: Age subgroup is based on gestational age at birth (weeks).
[b]: Calculated by author based on the "sex by age" results and absolute months
VTE total: all subjects who received VTE 0.4 mg including subjects randomized to laser and receiving VTE 0.4 mg as rescue treatment
Source: Integrated Analysis Pool 1 RMP: ROP 20090 (w24/27); Table 1.1/4
Source: Integrated Analysis Pool 3 RMP: AMD (up to year 3) + CRVO (w76/100) + BRVO (1y) + mCNV (w48) + DME (3y) + ROP (w24/27); Table 1.2/2f

SIII.2.5.7 All indications combined

Finally, Table SIII.31 summarizes the allocation to treatment with Eylea (2 mg and 8 mg doses) in all subjects who were included in the Phase I-IV wet AMD trials, the Phase III CRVO trials, the Phase III BRVO trial, the Phase III myopic CNV trial, the Phase I-III DME trials, and the Phase III ROP trial separated by sex, age category, and race. In this large patient population consisting of 6,487 patients, 50.5% were males, 68.6% were White, 37.2% were aged 75 years or older, and 1.2% were preterm infants.

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Table SIII.31: Number of subjects by treatment group and sex, age, and race in wet AMD Phase I-IV studies, CRVO Phase III studies, BRVO Phase III study, myopic CNV Phase III study, DME Phase I-III studies, and ROP Phase III study (SAF)

	IAI 0.4 mg N=79 n (%)	IAI ≤1 mg N=738 n (%)	IAI 2 mg N=4,555 n (%)	IAI 4 mg N=93 n (%)	IAI 8 mg N=1,217 n (%)	IAI total N=6,487 n (%)
Sex						
Males	43 (54.4)	342 (46.3)	2,294 (50.4)	36 (38.7)	643 (52.8)	3,275 (50.5)
Females	36 (45.6)	396 (53.7)	2,261 (49.6)	57 (61.3)	574 (47.2)	3,212 (49.5)
Age group (years)						
<1	79 (100.0)	0	0	0		79 (1.2)
≥1 to <65	0	91 (12.3)	1,553 (34.1)	7 (7.5)	349 (28.7)	1,988 (30.6)
≥ 65 to <75	0	183 (24.8)	1,401 (30.85)	24 (25.8)	441 (36.2)	2,008 (31.0)
≥75	0	464 (62.9)	1,601 (35.1)	62 (66.7)	427 (35.1)	2,412 (37.2)
Race						
White	59 (74.7)	647 (87.7)	2,917 (64.0)	89 (95.7)	927 (76.2	4,448 (68.6)
Black or African American	2 (2.5)	4 (0.5)	107 (2.3)	4 (4.3)	46 (3.8)	163 (2.5)
Asian	17 (21.5)	67 (9.1)	1,424 (31.3)	0	222 (18.2)	1,726 (26.6)
American Indian or Alaska native	0	2 (0.3)	7 (0.2)	0	2 (0.2)	11 (0.2)
Native Hawaiian or other pacific islander	0	0	6 (0.1)	0	2 (0.2)	8 (0.1)
Other	0	0	5 (0.1)	0	7 (0.6)	12 (0.2)
Not reported	0	18 (2.4)	69 (1.5)	0	9 (0.7)	96 (1.5)
Multiple	1 (1.3)	0	20 (0.4)	0	2 (0.2)	23 (0.4)

IAI=Intravitreal Aflibercept Injection
Note: Due to different study designs, subjects may have been exposed to more than 1 dosage. For ROP, total patients include 4 patients from the laser group who received Eylea as rescue therapy.
Subjects receiving at least one active VTE injection (pure or in combination) are displayed, subjects treated with sham or comparator including laser only are not displayed.
Subjects who were treated with sham or comparator and additionally with VTE 2.0 mg or VTE 0.4 mg were considered in VTE 2.0 mg or VTE 0.4 mg and VTE total.
Subjects may have received more than one dose. These subjects are considered for each dose, but once for VTE total.
Source: Integrated Analysis - Pool 3 RMP exposure / wet AMD 2 mg (up to year 3) + wet AMD 8 mg (w44/48) + CRVO 2 mg (w76/100) + mCNV 2 mg (w48) + DME 2 mg (3y) + DME 8 mg (w48) + BRVO 2 mg (1y) + ROP 0.4 mg (w24/27), Table 1/5

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Table SIII.32 summarizes the duration of exposure (patient months) in all subjects with wet AMD, CRVO, BRVO, myopic CNV, DME, or ROP by demographic subgroups (2 mg and 8 mg doses).

Table SIII.32: Clinical trial exposure (duration in patient months) by demographic subgroups sex, age categories, and race in wet AMD, CRVO, BRVO, myopic CNV, DME, and ROP subjects (SAF)

Treatment group	Subgroup		Patients	Person time (months)
IAI 0.4 mg pediatric	Age group	<1	79	106
	Sex	Male	43	58
		Female	36	48
	Race	White	59	69
		Black or African American	2	2
		Asian	17	34
		Multiple	1	1
IAI <= 1 mg	Age group	>=1 to <65	91	1554
		>=65 to <75	183	3225
		>=75	464	8209
	Sex	Male	342	6110
		Female	396	6878
	Race	White	647	11287
		Black or African American	4	53
		Asian	67	1293
		American Indian or Alaska Native	2	41
		Not Reported	18	313
IAI 2 mg	Age group	>=1 to <65	1553	27439
		>=65 to <75	1401	26918
		>=75	1601	33420
	Sex	Male	2294	42600
		Female	2261	45179
	Race	White	2917	64602
		Black or African American	107	2118
		Asian	1424	18995
		American Indian or Alaska Native	7	142
		Native Hawaiian or Other Pacific Islander	6	117
		Not Reported	69	1337
		Other	5	95
		Multiple	20	371
IAI 4 mg	Age group	>=1 to <65	7	32

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Table SIII.32: Clinical trial exposure (duration in patient months) by demographic subgroups sex, age categories, and race in wet AMD, CRVO, BRVO, myopic CNV, DME, and ROP subjects (SAF)

Treatment group	Subgroup		Patients	Person time (months)
		>=65 to <75	24	184
		>=75	62	457
	Sex	Male	36	247
		Female	57	427
	Race	White	89	669
		Black or African American	4	5
IAI 8 mg	Age group	>=1 to <65	349	7278
		>=65 to <75	441	9050
		>=75	427	8296
	Sex	Male	643	12938
		Female	574	11686
	Race	White	927	18619
		Black or African American	46	915
		Asian	222	4663
		American Indian or Alaska Native	2	46
		Native Hawaiian or Other Pacific Islander	2	31
		Not Reported	9	173
		Other	7	132
		Multiple	2	45
IAI total	Age group	<1	79	106
		>=1 to <65	1988	36310
		>=65 to <75	2008	39395
		>=75	2412	50467
	Sex	Male	3275	62000
		Female	3212	64279
	Race	White	4448	95346
		Black or African American	163	3093
		Asian	1726	24994
		American Indian or Alaska Native	11	229
		Native Hawaiian or Other Pacific Islander	8	148
		Not Reported	96	1823
		Other	12	228

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Table SIII.32: Clinical trial exposure (duration in patient months) by demographic subgroups sex, age categories, and race in wet AMD, CRVO, BRVO, myopic CNV, DME, and ROP subjects (SAF)

Treatment group	Subgroup		Patients	Person time (months)
		Multiple	23	417

1 month = 30 days.
Subjects receiving at least one active IAI injection (pure or in combination) are displayed, subjects treated with sham or comparator including laser only are not displayed.
Subjects who were treated with sham or comparator and additionally with IAI 2 mg were considered in IAI 2 mg and IAI t otal.
Subjects may have received more than one dose. These subjects are considered for each dose, but once for IAI total.
Bayer: /var/swan/root/bhc/865321/ia/stat/main04/prod/analysis/pgms/t_adex_exp_rmp_p3_eu.sas 06SEP2023 14:57
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SIII.2.6 Exposure in special populations

Data on special populations are shown for the 2 Phase III wet AMD studies (VIEW 1 and 2), the 2 Phase III CRVO studies (GALILEO and COPERNICUS), the Phase III BRVO study (VIBRANT), the Phase III myopic CNV study (MYRROR), the pivotal Phase III DME studies VIVID-DME and VISTA-DME, the Phase III ROP study (FIREFLEYE), the Phase II/III 8 mg wet AMD studies (CANDELA and PULSAR) and the Phase II/III 8 mg DME study (PHOTON). This subsection presents the number of subjects by dose group (treatment group) and special population subgroup in order to provide an overview of the distribution of the exposed study subjects among the pre-defined subgroups.

Generally, 6 special population subgroups were identified by medical history, i.e., diabetes mellitus, hypertension, cerebrovascular disease (e.g., CVA/stroke), ischemic heart disease (e.g., myocardial infarction), history of renal impairment, and history of hepatic impairment. The percentages are related to the number of patients who received the respective dose of Eylea in the respective Phase III studies.

SIII.2.6.1 Indication: Wet AMD

As regards the wet AMD indication, a total of 1,824 patients with exposure to Eylea constituted the 96 weeks-safety population in the 2 pivotal Phase III studies in wet AMD (VIEW 1 and VIEW 2). Table SIII.33 shows the number of patients with a medical history of diabetes mellitus, hypertension, cerebrovascular disease (e.g., CVA/stroke), ischemic heart disease (e.g., myocardial infarction), hepatic and renal impairment by dose group. There were no significant safety issues revealed during exposure of special populations to Eylea injection in the wet AMD Phase III studies.

Table SIII.33: Clinical trial exposure by special populations in the 0.5/2 mg pivotal wet AMD Phase III studies VIEW 1 and VIEW 2 (SAF)

	Eylea 2Q4 N=613 n (%)	**Eylea 0.5Q4 N=601 n (%)**	**Eylea 2Q8 N=610 n (%)**	**Eylea total N=1,824 n (%)**
Mild renal impairment	222 (36.2)	207 (34.4)	215 (35.2)	644 (35.3)
Moderate renal impairment	132 (21.5)	117 (19.5)	132 (21.6)	381 (20.9)
Severe renal impairment	12 (2.0)	34 (5.7)	20 (3.3)	66 (3.6)
Hepatic impairment	15 (2.4)	20 (3.3)	20 (3.3)	55 (3.0)

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Table SIII.33: Clinical trial exposure by special populations in the 0.5/2 mg pivotal wet AMD Phase III studies VIEW 1 and VIEW 2 (SAF)

	Eylea 2Q4 N=613 n (%)	Eylea 0.5Q4 N=601 n (%)	Eylea 2Q8 N=610 n (%)	Eylea total N=1,824 n (%)
Diabetes mellitus	71 (11.6)	78 (13.0)	76 (12.5)	225 (12.3)
Arterial hypertension	320 (52.2)	352 (58.6)	340 (55.7)	1,012 (55.5)
Cerebrovascular disease (e.g., CVA/stroke)	44 (7.2)	62 (10.3)	39 (6.4)	145 (7.9)
Ischemic heart disease (e.g., myocardial infarction)	98 (16.0)	104 (17.3)	112 (18.4)	314 (17.2)

Mild renal impairment: creatinine clearance >50 to 80 mL/min.
Moderate renal impairment: creatinine clearance >30 to 50 mL/min.
Severe renal impairment: creatinine clearance ≤30 mL/min, or requirement for dialysis.
Source: Integrated Analysis – Pool 1, 96 weeks analysis, RMP Exposure, Table 1.1/2a (selected subgroups)

A total of 726 patients with exposure to 8 mg aflibercept constituted the 44/48 week-safety population in the 2 Phase II/III studies in wet AMD (CANDELA and PULSAR). Table SIII.34 shows the number of patients with a medical history of diabetes mellitus, hypertension, cerebrovascular disease (e.g., CVA/stroke), ischemic heart disease (e.g., myocardial infarction), hepatic and renal impairment by dose group. No safety signals were identified in these subgroups.

Table SIII.34: Clinical trial exposure by special populations in the 8 mg wet AMD Phase II study CANDELA and Phase III study PULSAR (SAF)

	2 mg N=389 n (%)	HDq12 N=388 n (%)	HDq16 N=338 n (%)	HD total N=726 n (%)
Mild renal impairment	191 (49.1)	191 (49.2)	151 (44.7)	342 (47.1)
Moderate renal impairment	53 (13.6)	58 (14.9)	56 (16.6)	114 (15.7)
Severe renal impairment	3 (0.8)	4 (1.0)	3 (0.9)	7 (1.0)
Hepatic impairment	15 (3.9)	20 (5.2)	15 (4.4)	35 (4.8)
Diabetes mellitus	58 (14.9)	68 (17.5)	60 (17.8)	128 (17.6)
Arterial hypertension	237 (60.9)	248 (63.9)	219 (64.8)	467 (64.3)
Cerebrovascular disease (e.g., CVA/stroke)	38 (9.8)	35 (9.0)	28 (8.3)	63 (8.7)
Ischemic heart disease (e.g., myocardial infarction)	50 (12.9)	63 (16.2)	38 (11.2)	101 (13.9)

Mild renal impairment: creatinine clearance >50 to 80 mL/min.
Moderate renal impairment: creatinine clearance >30 to 50 mL/min.
Severe renal impairment: creatinine clearance ≤30 mL/min, or requirement for dialysis.
2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
HD total: HDq12 and Hdq16 combined.
Source: Integrated Analysis – Pool 1, 48 weeks analysis, AMD 8 mg (w44/48); Table 1/3

SIII.2.6.2 Indication: CRVO

A total of 317 subjects constituted the pooled Phase III CRVO safety population exposed to Eylea (either from the beginning or following sham treatment). Table SIII.35 shows the number of patients with a medical history of diabetes mellitus, hypertension, cerebrovascular disease (e.g., CVA/stroke), ischemic heart disease (e.g., myocardial infarction), hepatic and renal impairment by dose groups. There were no significant safety issues revealed during exposure of special populations to Eylea injections in the CRVO Phase III studies.

Table SIII.35: Clinical trial exposure by special populations in the pivotal CRVO Phase III studies (SAF)

	2Q4 + PRN N=218 n (%)	Sham [a] N=142 n (%)	PRN [b] N=99 n (%)	Eylea total [c] N=317 n (%)
Mild renal impairment	75 (34.4)	42 (29.6)	30 (30.3)	105 (33.1)
Moderate renal impairment	19 (8.7)	24 (16.9)	15 (15.2)	34 (10.7)
Severe renal impairment	4 (1.8)	4 (2.8)	3 (3.0)	7 (2.2)
Hepatic impairment	8 (3.7)	4 (2.8)	2 (2.0)	10 (3.2)
Diabetes mellitus	47 (21.6)	22 (15.5)	17 (17.2)	64 (20.2)
Arterial hypertension	120 (55.0)	82 (57.7)	58 (58.6)	178 (56.2)
Cerebrovascular disease (e.g., CVA/stroke)	12 (5.5)	7 (4.9)	3 (3.0)	15 (4.7)
Ischemic heart disease (e.g., myocardial infarction)	20 (9.2)	16 (11.3)	12 (12.1)	32 (10.1)

Mild renal impairment: creatinine clearance >50 to 80 mL/min.
Moderate renal impairment: creatinine clearance >30 to 50 mL/min.
Severe renal impairment: creatinine clearance ≤30 mL/min, or requirement for dialysis.
[a]: Sham (without or before 1st PRN): includes all subjects receiving at least one sham injection and considers time period up to 1st active PRN injection.
[b]: PRN (following sham, after 1st PRN): includes all subjects receiving at least one active PRN injection and considers time period from 1st active PRN injection onwards. All subjects of PRN (following sham, after 1st PRN) group are also included in Sham (without or before 1st PRN) group, but with a different observation period.
[c]: Eylea total: Eylea 2Q4 + PRN and PRN (following sham, after 1st PRN) combined.
Source: Integrated Analysis – Pool 1 CRVO, RMP, Table 1.1/2

SIII.2.6.3 Indication: BRVO

The BRVO safety population consisted of 183 patients, with 158 patients exposed to Eylea. Table SIII.36 shows the number of patients with a medical history of diabetes mellitus, hypertension, cerebrovascular disease (e.g., CVA/stroke), ischemic heart disease (e.g., myocardial infarction), hepatic and renal impairment by randomized treatment group. Generally, there were no significant safety issues revealed during the exposure of special populations to Eylea injections in the BRVO Phase III study.

Table SIII.36: Clinical trial exposure by special populations in the pivotal BRVO Phase III study (SAF)

	Laser+Eylea 2mg N=92 n (%)	Eylea 2 mg N=91 n (%)	Eylea total N=158 n (%)
Mild renal impairment	22 (23.9)	26 (28.6)	41 (25.9)
Moderate renal impairment	3 (3.3)	8 (8.8)	11 (7.0)

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Table SIII.36: Clinical trial exposure by special populations in the pivotal BRVO Phase III study (SAF)

	Laser+Eylea 2mg N=92 n (%)	Eylea 2 mg N=91 n (%)	Eylea total N=158 n (%)
Severe renal impairment	2 (2.2)	1 (1.1)	3 (1.9)
Hepatic impairment	4 (4.3)	2 (2.2)	4 (2.5)
Diabetes mellitus	26 (28.3)	16 (17.6)	35 (22.2)
Arterial hypertension	76 (82.6)	66 (72.5)	122 (77.2)
Cerebrovascular disease (e.g., CVA/stroke)	5 (5.4)	8 (8.8)	13 (8.2)
Ischemic heart disease (e.g., MI)	13 (14.1)	7 (7.7)	16 (10.1)

Mild renal impairment: creatinine clearance >50 to 80 mL/min.
Moderate renal impairment: creatinine clearance >30 to 50 mL/min.
Severe renal impairment: creatinine clearance ≤30 mL/min, or requirement for dialysis.
Source: Integrated Analysis BRVO RMP Pool 1 (1y), Table 1.2/2e

SIII.2.6.4 Indication: Myopic CNV

Table SIII.37 shows the number of patients with a medical history of diabetes mellitus, hypertension, cerebrovascular disease (e.g., CVA/stroke), ischemic heart disease (e.g., myocardial infarction), hepatic and renal impairment by randomized treatment group and in the group of the 116 myopic CNV patients who were exposed to Eylea in the MYRROR study. Overall, there were no significant safety issues observed during exposure of special populations to Eylea injections in that myopic CNV study.

Table SIII.37: Clinical trial exposure by special populations in the pivotal myopic CNV Phase III study (SAF)

	Sham+Eylea 2 mg N=31 n (%)	Eylea 2 mg N=91 n (%)	Eylea total N=116 n (%)
Mild renal impairment	13 (41.9)	47 (51.6)	57 (49.1)
Moderate renal impairment	1 (3.2)	10 (11.0)	11 (9.5)
Severe renal impairment	0	0	0
Hepatic impairment	0	8 (8.8)	8 (6.9)
Diabetes mellitus	1 (3.2)	6 (6.6)	7 (6.0)
Arterial hypertension	5 (16.1)	29 (31.9)	33 (28.4)
Cerebrovascular disease (e.g., CVA/stroke)	1 (3.2)	4 (4.4)	5 (4.3)
Ischemic heart disease (e.g., myocardial infarction)	0	4 (4.4)	4 (3.4)

Mild renal impairment: creatinine clearance >50 to 80 mL/min.
Moderate renal impairment: creatinine clearance >30 to 50 mL/min.
Severe renal impairment: creatinine clearance ≤30 mL/min, or requirement for dialysis
Source: Integrated Analysis Pool 1 mCNV (48 weeks), Table 1.2/2c

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SIII.2.6.5 Indication: DME

Table SIII.38 shows the number of subjects with a medical history of hypertension, cerebrovascular disease (e.g., CVA/stroke), ischemic heart disease (e.g., myocardial infarction), hepatic and renal impairment in the DME subjects enrolled in the randomized, controlled Phase III studies VIVID-DME and VISTA-DME. Inherently, all enrolled patients suffered from diabetes mellitus. By Week 148, there were no significant safety issues observed during exposure of special populations to Eylea injections in the DME studies.

Table SIII.38: Clinical trial exposure by special populations in the pivotal randomized, controlled DME Phase III studies (SAF)

	Laser[a] N=287 n (%)	Eylea 2Q4[b] N=291 n (%)	Eylea 2Q8[b] N=287 n (%)	2Q4 + 2Q8[b] N=578 n (%)	Eylea Total[c] N=821 n (%)
Mild renal impairment	92 (32.1)	84 (28.9)	81 (28.2)	165 (28.5)	241 (29.4)
Moderate renal impairment	24 (8.4)	32 (11.0)	30 (10.5)	62 (10.7)	81 (9.9)
Severe renal impairment	4 (1.4)	10 (3.4)	7 (2.4)	17 (2.9)	20 (2.4)
Hepatic impairment	11 (3.8)	13 (4.5)	14 (4.9)	27 (4.7)	37 (4.5)
Arterial hypertension	227 (79.1)	224 (77.0)	235 (81.9)	459 (79.4)	650 (79.2)
Cerebrovascular disease (e.g., CVA/stroke)	30 (10.5)	35 (12.0)	33 (11.5)	68 (11.8)	92 (11.2)
Ischemic heart disease (e.g., myocardial infarction)	66 (23.0)	60 (20.6)	63 (22.0)	123 (21.3)	177 (21.6)

Mild renal impairment: creatinine clearance >50 to 80 mL/min.
Moderate renal impairment: creatinine clearance >30 to 50 mL/min.
Severe renal impairment: creatinine clearance ≤30 mL/min, or requirement for dialysis
[a]: All subjects randomized to initial treatment with active laser.
[b]: All subjects randomized to initial treatment with Eylea (2Q4 and 2Q8, respectively).
[c]: All subjects from any treatment group (incl. laser group) who received at least one active Eylea injection from Baseline through Week 144.
Source: Integrated Analysis - Pool 1 DME (3y) RMP Table 1.2/2d

Table SIII.39 shows the number of subjects with a medical history of hypertension, cerebrovascular disease (e.g., CVA/stroke), ischemic heart disease (e.g., myocardial infarction), hepatic and renal impairment in the DME subjects enrolled in the 8 mg Phase II/III study PHOTON. No safety signals were identified in these subgroups.

Table SIII.39: Clinical trial exposure by special populations in the 8 mg DME Phase II/III study PHOTON (SAF)

2 mg N=167 n (%)	HDq12 N=328 n (%)	HDq16 N=163 n (%)	HD total N=491 n (%)	
Mild renal impairment	37 (22.2)	72 (22.0)	38 (23.3)	110 (22.4)
Moderate renal impairment	13 (7.8)	22 (6.7)	8 (4.9)	30 (6.1)
Severe renal impairment	4 (2.4)	11 (3.4)	5 (3.1)	16 (3.3)
Hepatic impairment	4 (2.4)	12 (3.7)	4 (2.5)	16 (3.3)
Diabetes mellitus	167 (100.0)	328 (100.0)	162 (99.4)	490 (99.8)

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Table SIII.39: Clinical trial exposure by special populations in the 8 mg DME Phase II/III study PHOTON (SAF)

2 mg N=167 n (%)	HDq12 N=328 n (%)	HDq16 N=163 n (%)	HD total N=491 n (%)	
Arterial hypertension	130 (77.8)	254 (77.4)	130 (79.8)	384 (78.2)
Cerebrovascular disease (e.g., CVA/stroke)	19 (11.4)	21 (6.4)	10 (6.1)	31 (6.3)
Ischemic heart disease (e.g., myocardial infarction)	28 (16.8)	64 (19.5)	22 (13.5)	86 (17.5)

HD= High Dose (8 mg Aflibercept)
Mild renal impairment: creatinine clearance >50 to 80 mL/min.
Moderate renal impairment: creatinine clearance >30 to 50 mL/min.
Severe renal impairment: creatinine clearance ≤30 mL/min, or requirement for dialysis.
2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
HD total: HDq12 and Hdq16 combined.
Source: Integrated Analysis – Pool 1, 48 weeks analysis, DME 8 mg (w48); Table 1/3

SIII.2.6.6 Indication: ROP

Table SIII.40 shows the number of patients with a medical history of diabetes mellitus, hypertension, cerebrovascular disease (e.g., CVA/stroke), ischemic heart disease (e.g., myocardial infarction), hepatic and renal impairment by treatment group and in the group of the 79 ROP patients who were exposed to Eylea in the FIREFLEYE study. More than 60% of the preterm infants suffered from mild to moderate renal impairment, more than 50% from hepatic impairment, and more than 40% from cerebrovascular disease.

Table SIII.40: Clinical trial exposure by special populations in the ROP Phase III study (SAF)

	Laser N=38 n (%)	Eylea 0.4 mg N=75 n (%)	Eylea total N=79 n (%)
Mild renal impairment	15 (39.5)	25 (33.3)	26 (32.9)
Moderate renal impairment	8 (21.1)	21 (28.0)	22 (27.8)
Severe renal impairment	1 (2.6)	2 (2.7)	2 (2.5)
Hepatic impairment	16 (42.1)	41 (54.7)	42 (53.2)
Diabetes mellitus	0	0	0
Arterial hypertension	0	3 (4.0)	3 (3.8)
Cerebrovascular disease (e.g., CVA/stroke)	17 (44.7)	31 (41.3)	34 (43.0)
Ischemic heart disease (e.g., myocardial infarction)	0	0	0

Note: Total patients include 4 patients from the laser group who received Eylea as rescue therapy.
Mild renal impairment: creatinine clearance >50 to 80 mL/min.
Moderate renal impairment: creatinine clearance >30 to 50 mL/min.
Severe renal impairment: creatinine clearance ≤30 mL/min, or requirement for dialysis
Eylea total: all subjects who received VTE 0.4 mg including subjects randomized to laser and receiving VTE 0.4 mg as rescue treatment
Source: Integrated Analysis Pool 1 ROP 20090, Table 1.1/2

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SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Program

Table SIV.1a: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information (Eylea 40 mg/mL, 2 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Prior/concomitant treatments for underlying condition			
<u>AMD & CRVO & mCNV & DME</u> • Prior or concomitant treatment with other investigational agents. • Prior or concomitant treatment with anti-VEGF therapy (DME: within the last 3 months prior to treatment start; previous treatment with anti-angiogenic drugs in either eye (pegaptanib sodium, bevacizumab, ranibizumab etc.)). • Prior treatment with intraocular and/or systemic steroids (AMD & CRVO & mCNV). • Intraocular or periocular corticosteroids in the study eye within 120 days (DME). • Prior surgery in the study eye for the relative indication including vitrectomy (AMD & CRVO & mCNV). • Radiation and laser including PDT (AMD & CRVO & mCNV). • Laser photocoagulation (panretinal or macular) in the study eye within 90 days (DME). • More than 2 previous macular laser treatments in the study eye or, in the opinion of the investigator, the subject has no potential to benefit from laser treatments (e.g., if too	The exclusion criteria for prior or concomitant treatment and prior surgery or radiation including laser coagulation and PDT were contained in a similar form in all Eylea studies. These were technical exclusion criteria for the reduction of confounding factor impact on efficacy measurements and were not based on safety concerns.	No	Concomitant use of different anti-VEGF therapies and other therapies for wet AMD, CRVO, BRVO, myopic CNV, and DME is no longer considered missing information as no additional activities are conducted (EMA request: procedure: EMEA/H/C/002392/II/0075. According to current Eylea 2 mg Summary of Product Characteristics (SmPC): "No interaction studies have been performed. Adjunctive use of verteporfin photodynamic therapy (PDT) and Eylea has not been studied, therefore, a safety profile is not established."

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Table SIV.1a: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information (Eylea 40 mg/mL, 2 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
many laser treatments were applied in the past) (DME). • History of vitreoretinal surgery and/or including scleral buckling in the study eye (DME). • Active proliferative diabetic retinopathy (PDR) in the study eye with the exception of inactive, regressed PDR. <u>BRVO</u> • Previous treatment of the study eye with scatter or panretinal laser photocoagulation, sector laser photocoagulation, or macular grid laser photocoagulation. • Concomitant ocular or systemic administration of drugs that could interfere with or potentiate the mechanism of action of VEGF Trap-Eye. • Previous use of intraocular corticosteroids or anti-angiogenic drugs in the study eye (pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) • Use of periocular corticosteroids in the study eye within 3 months before day 1. • Use of intraocular or periocular corticosteroids or anti-angiogenic drugs in the fellow eye within 3 months before day 1 (pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.). • Previous administration of systemic anti-angiogenic medications.			

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Table SIV.1a: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information (Eylea 40 mg/mL, 2 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
ROP			
• Previous exposure to any IVT or systemic anti-VEGF agent, including maternal exposure during pregnancy and/or during breastfeeding		No	Concomitant use of different anti-VEGF therapies is no longer considered missing information as no additional activities are conducted (EMA request: procedure: EMEA/H/C/002392/II/0075)
• Postnatal treatment with oral or intravenous corticosteroids at an equivalent dose of prednisone ≥1 mg/kg/day for >2 weeks within 14 days of the first study intervention		No	Use of prior corticosteroids excluded for technical reasons in order to reduce the impact of potentially confounding factors for safety measurements such as increased risk of ocular and systemic infections due to potentially immunosuppressive effects of postnatal use of systemic steroids, or of other systemic conditions (such as worsening of gastrointestinal ulcer).
• Previous surgical or nonsurgical treatment for ROP (IVT anti-VEGF injection, ablative laser therapy, cryotherapy, and vitrectomy).		No	Concomitant use of different anti-VEGF therapies and other therapies are no longer considered missing information for Eylea.
Concomitant systemic disease or history thereof			
• Current treatment of a serious systemic infection (CRVO, BRVO, & DME).	Severe systemic disease (including severe systemic infection) was excluded in all Eylea trials for technical reasons in order to reduce the impact of potentially confounding factors for safety measurements.	No	No rationale from available data and information that treatment should be considered as missing information under these conditions. Not considered as relevant for the safety profile. According to SmPC: “There is only limited experience in the treatment of subjects with DME due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy. Eylea has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of
AMD & CRVO & mCNV & DME			
• Metabolic dysfunction, uncontrolled hypertension, uncontrolled diabetes mellitus (DME studies: defined as HbA1c >12%), cerebrovascular disease, myocardial infarction, renal failure.			
• Clinical or lab finding contraindicating use of investigational drugs (DME: or might affect interpretation of study results).			

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Table SIV.1a: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information (Eylea 40 mg/mL, 2 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
BRVO • Uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg while subject is sitting). • Uncontrolled diabetes mellitus, as defined by HbA1c >12%. • History of either cerebral vascular accident (and)/or myocardial infarction within 180 days (6 months) prior to Day 1. • Renal failure requiring dialysis or renal transplant. • History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug, might affect interpretation of the results of the study, or renders the subject at high risk for treatment complications.			treatment with Eylea in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.”
ROP • Known or suspected chromosomal abnormality, genetic disorder or syndrome		No	Severe systemic disease excluded in all Eylea trials for technical reasons in order to reduce the impact of potentially confounding factors for safety measurements; not considered relevant for safety profile.
• Clinically significant neurological disease (e.g., intraventricular haemorrhage grade 3 or higher, periventricular leukomalacia, congenital brain lesions significantly impairing optic nerve function, severe hydrocephalus with significantly increased intracranial pressure).		No	Severe systemic disease excluded in all Eylea trials for technical reasons in order to reduce the impact of potentially confounding factors for safety measurements; not considered relevant for safety profile.

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Table SIV.1a: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information (Eylea 40 mg/mL, 2 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
	Concomitant ocular disease or history thereof		
• Uncontrolled glaucoma (AMD & CRVO & mCNV). • Uncontrolled glaucoma in the study eye (patient who has had filtration surgery in the past, or likely to need filtration surgery in the future) (DME). • Intraocular pressure (IOP) ≥25 mmHg in the study eye (DME). • Uncontrolled glaucoma defined as intraocular pressure (IOP) ≥25 mmHg in the study eye, or previous filtration surgery in either the study eye or the fellow eye (BRVO).	Technical exclusion criteria in all studies for the sake of feasibility of safety and efficacy assessments, particularly imaging.	No	Use of Eylea in patients with uncontrolled glaucoma is no longer considered missing information as no additional activities are conducted (EMA request: procedure: EMEA/H/C/002392/II/0075) According to SmPC: "Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with Eylea. Special precaution is needed in patients with poorly controlled glaucoma (do not inject Eylea while the intraocular pressure is ≥30 mmHg). In all cases both the intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately.
• Aphakia or pseudophakia (AMD & CRVO & mCNV & DME) • Aphakia or absence of the posterior capsule in the study eye (BRVO). • History of corneal transplant of corneal dystrophy in the study eye (AMD & CRVO & mCNV). • Significant media opacities including cataract (AMD & CRVO & mCNV). • Cataract surgery within 90 days before Day 1 (DME).	Technical exclusion criteria in all studies for the sake of feasibility of safety and efficacy assessments, particularly imaging.	No	No rationale from available data and information that treatment should be considered as missing information under these conditions. Not considered as relevant for the safety profile. No rationale for further warnings or contraindication.
• Myopia of a spherical equivalent prior to any possible refractive or cataract surgery of ≥ 8 dioptres (CRVO & DME). • Presence of scleromalacia (AMD & CRVO & mCNV).	Technical exclusion criterion. High myopia may negatively affect the quality of OCT imaging and was therefore excluded for study purposes. Additionally, highly myopic eyes have a		

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Table SIV.1a: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information (Eylea 40 mg/mL, 2 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
• Prior trabeculectomy or other filtration surgery in the study eye (AMD & CRVO & mCNV). • Ocular inflammation including trace or above in the study eye (DME). • Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye (DME). • History of idiopathic or autoimmune uveitis in the study eye (DME) or in either eye (BRVO) • Ocular conditions with a poorer prognosis in the fellow eye than in the study eye (DME).	different anatomy, which may interfere with study procedures and interpretation of results.		
• Only one functional eye even if that eye is otherwise eligible for the study (AMD, CRVO, BRVO, mCNV, and DME). • Ocular conditions with a poorer prognosis in the fellow eye than in the study eye (AMD, CRVO & DME).	Technical exclusion criterion for clinical studies; as long as beneficial effects are not proven, the only remaining functional eye should not be exposed to experimental drug.		
<u>ROP</u> • Presence of active ocular infection within 5 days of the first treatment.		No	Local infectious ocular disease excluded for technical reasons in order to reduce the impact of potentially confounding factors for safety measurements, active infection is contraindicated; IOI/endophthalmitis is known risk for IVT.
Other neovascular disorder			
<u>AMD</u> • History or clinical evidence of diabetic retinopathy, DME, or any other retinal vascular disease other than AMD. • Any concurrent intraocular conditions in the study eye that could require either medical or surgical	Technical exclusion criteria to reduce the impact of confounding factors on safety measurements. No safety concern was anticipated.	No	No rationale from available data and information that treatment should be considered as missing information under these conditions. Not considered as relevant for the safety profile. Contrarily, benefit is to be expected for the patient should

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Table SIV.1a: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information (Eylea 40 mg/mL, 2 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
intervention during the study period or could increase the risk to the subject safety of which otherwise may interfere with evaluation of efficacy and safety. • Presence of other causes of CNV in the study eye. <u>CRVO & BRVO</u> • Decrease in BCVA due to causes other than CRVO, history or presence of AMD, DME, or diabetic retinopathy. • Concurrent disease in the study eye that could compromise VA or require medical or surgical intervention during the study period, inability to obtain fundus photographs or FA. • Spherical equivalent of the refractive error in the study eye of more than -8 Dpt. (CRVO) • History or presence of AMD (dry or wet form) that was considered by the investigator to affect significantly the subject's central vision; DME, or diabetic retinopathy, defined with/as more than one microaneurysm outside the area of the vein occlusion in diabetic subjects in either the study eye or (anywhere in the retina of) the fellow eye. • Concurrent disease in the study eye that could compromise VA or require medical or surgical intervention during the study period. • Any ocular disorder in the study eye that, in the opinion of the investigator, may have confounded the			any of these conditions co-occur.

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Table SIV.1a: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information (Eylea 40 mg/mL, 2 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
interpretation of the study results. • Inability to obtain fundus photographs or fluorescein angiograms of sufficient quality to be analysed by the study site. <u>mCNV</u> • History or presence of CNV with an origin other than pathologic myopia. <u>DME</u> • Concurrent disease in the study eye, other than DME, that could compromise VA, require medical or surgical intervention during the study period, or could confound interpretation of the results (including retinal vascular occlusion, retinal detachment, macular hole, or choroidal neovascularization of any cause).			
Complications of the underlying disease			
<u>AMD</u> • Subretinal haemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. • Scar or fibrosis making up >50% of the total lesion in the study eye. • Scar, fibrosis or atrophy involving the centre of the fovea in the study eye. • Presence of retinal pigment epithelial tears or rips involving the macula in the study eye. • Total lesion size >12 disc areas including blood, scars and neovascularization as assessed by FA in the study eye. • History of any vitreous haemorrhage within	Technical exclusion criteria in AMD studies to reduce the impact of confounding factors on the efficacy and/or safety measurements or for interference with study procedures (imaging).	No	Sub/intraretinal haemorrhage is caused primarily by AMD. It should therefore not be regarded as missing information in the clinical setting. Contrarily, patients with subretinal haemorrhage are probably those with a high need to be treated to prevent further bleeds. No rationale from available data and information that any of these conditions should be considered as missing information. According to SmPC: "Wet AMD is characterised by pathological choroidal neovascularisation (CNV). Leakage of blood and fluid from CNV may cause retinal thickening or oedema and/or sub-/intra-retinal

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Table SIV.1a: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information (Eylea 40 mg/mL, 2 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
4 weeks prior to Visit 1 in the study eye. • History of retinal detachment or treatment or surgery for retinal detachment in the study eye. • Any history of macular hole of stage 2 and above in the study eye.			haemorrhage, resulting in loss of visual acuity". No concern referring to any specific safety aspect was detected.
<u>CRVO & BRVO</u> • Structural damage to the centre of the macula in either the study eye or the fellow eye that was considered to be likely to preclude improvement in visual acuity following the resolution of macular edema. • Vitreomacular traction or epiretinal membrane in either the study eye or the fellow eye, which was evident biomicroscopically or on OCT and was considered by the investigator to affect significantly the subject´s central vision. • Iris neovascularization, vitreous haemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in either the study eye or the fellow eye.	Technical exclusion criteria in the CRVO/BRVO studies to reduce the impact of confounding factors on the efficacy and/or safety measurements or for interference with study procedures (imaging).	No	No rationale from available data and information that any of these conditions should be considered as missing information regarding treatment with Eylea. Not considered as relevant for the safety profile.
• Current bilateral manifestation of RVO.	Technical exclusion criterion in the RVO studies to exclude the confounding effect of need for bilateral treatment in a subset of study subjects.	No	Bilateral treatment with anti-VEGF treatments is not considered missing information for Eylea 2 mg
<u>BRVO</u> • Insufficient clearing of macular haemorrhage that would prevent the patient from receiving laser treatment safely on day 1.	Technical exclusion criteria in BRVO study to include patients eligible for laser treatment. No relation to treatment with Eylea.	No	No rationale from available data and information that any of these conditions should be considered as missing information regarding treatment with Eylea. Not

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Table SIV.1a: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information (Eylea 40 mg/mL, 2 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
• Cataract surgery in the study eye within 3 months, yttrium-aluminum-garnet laser capsulotomy within the past 2 months, or any other intraocular surgery within 3 months before day 1.			considered as relevant for the safety profile.
<u>mCNV</u> • Greatest linear dimension of the lesion in the study eye is greater than 12 disc areas. • Recurrent mCNV in the study eye. • Significant scarring or atrophy in the fovea that indicates substantial irreversible vision loss in the study eye. • Vitreomacular traction of traction retinal detachment, epiretinal membrane in either eye as evident biomicroscopically or on OCT that is considered by the investigator to affect significantly central vision.	Technical exclusion criteria in the mCNV study to reduce the impact of confounding factors on the efficacy and/or safety measurements or for interference with study procedures (imaging).		No rationale from available data and information that any of these conditions should be considered as missing information regarding treatment with Eylea. Not considered as relevant for the safety profile.
<u>DME</u> • Current iris neovascularization, vitreous haemorrhage, or tractional retinal detachment in the study eye. • Ocular media of insufficient quality to obtain fundus and OCT images. • Pre-retinal fibrosis involving the macula in the study eye. • Aphakia in the study eye. • Yttrium-aluminium-garnet (YAG) capsulotomy in the study eye within 30 days before Day 1. • Any other intraocular surgery within 90 days before Day 1 in the study eye.	Technical exclusion criteria in DME studies. Would have impact on feasibility of study procedures (particularly imaging methods) for safety and efficacy assessments. No safety concern was anticipated.		No rationale from available data and information that any of these conditions should be considered as missing information regarding treatment with Eylea. Not considered as relevant for the safety profile.

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Table SIV.1a: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information (Eylea 40 mg/mL, 2 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
• Structural damage to the centre of the macula in the study eye that is likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia or organized hard exudates. • Vitreomacular traction or epiretinal membrane in the study eye evident biomicroscopically or on OCT that is thought to affect central vision.			
Pregnancy			
<u>AMD & CRVO & BRVO & mCNV & DME</u> • Females who are pregnant, breastfeeding, or of childbearing potential, unwilling to practice adequate contraception throughout the study and at least 3 months after the last intravitreal injection of aflibercept (including males in DME, BRVO and mCNV studies, unless vasectomized). Adequate contraceptive measures include oral contraceptives (stable use for 2 or more cycles prior to screening), intrauterine devices, hormonal injections, hormonal implants, bilateral tubal ligation, vasectomy, condom or diaphragm plus either contraceptive sponge, foam or jelly.	Technical exclusion criterion to avoid potential fetotoxicity.	Yes (use in breastfeeding women)	This issue is covered in label (SmPC) per the following paragraphs: "Although the systemic exposure after ocular administration is very low, Eylea should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus". "Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept." “Embryo-feto-toxicity” is included in this RMP as important potential risk. "There are no data on the use of aflibercept in pregnant women. Studies in animals have shown embryo-foetal toxicity." No rationale from available data and information that treatment should be considered as missing

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Table SIV.1a: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information (Eylea 40 mg/mL, 2 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
			information under these conditions.
	Other		
<u>AMD & CRVO & mCNV & DME</u> • Known serious allergy to the fluorescein sodium for injection in angiography. • AMD only: Any history of allergy to povidone iodine. <u>BRVO</u> History of allergy to fluorescein used in fluorescein angiography. Patients with a history of allergy to povidone iodine who were unwilling to allow use of alternate options for povidone iodine in study procedures. Participation in an investigational study within 30 days prior to initial screening visit that involved treatment with any drug (excluding vitamins and minerals) or device. • CRVO only: Disease duration >9 months from the date of diagnosis. • DME only: Administration of systemic anti-angiogenic agents within 180 days before Day 1.	Technical exclusion criteria as such allergies were not compatible with study procedures Technical exclusion criteria to reduce the impact of confounding factors on the efficacy and/or safety measurements	No	No rationale from available data and information that any of these conditions should be considered as missing information regarding treatment with Eylea. Not considered as relevant for the safety profile.
<u>ROP</u> Inclusion of preterm infants with weight at baseline (day of treatment) ≥ 800 g (i.e., those with <800g were excluded).		No	Severe systemic disease excluded in all Eylea trials for technical reasons in order to reduce the impact of potentially confounding factors for safety measurements; not considered relevant for safety profile; to prevent/reduce the risk of any potential systemic effects based on allometric modeling and preclinical data (including multiples of exposures).

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Table SIV.1b: Exclusion criteria in the pivotal studies across the development program which are not proposed to be considered as missing information (Eylea 114.3 mg/mL, 8 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Prior/concomitant treatments for underlying condition			
Wet AMD & DME • Prior or concomitant treatment with other investigational agents (e.g., with anti-angiopoietin/anti-VEGF bispecific monoclonal antibodies). • Prior or concomitant treatment with anti-VEGF therapy. • IVT implant, gene therapy, or cell therapy at any time. • Previous use of ocular corticosteroids in the study eye within 16 weeks (112 days) of the screening visit, or IVT implants at any time • Laser photocoagulation (panretinal or macular) in the study eye (within 90 days for AMD), within 84 days for DME). • History of vitreoretinal surgery and/or including scleral buckling in the study eye. • Any intraocular surgery (within 90 days for AMD, within 84 days for DME) before the screening visit. • Active proliferative diabetic retinopathy (PDR) in the study eye.	The exclusion criteria for prior or concomitant treatment and prior surgery or laser coagulation were contained in a similar form in all Eylea studies. These were technical exclusion criteria for the reduction of confounding factor impact on efficacy measurements and were not based on safety concerns.	No	No rationale from available data and information that treatment should be considered as relevant missing information under these conditions.
Concomitant systemic disease or history thereof			
Wet AMD & DME • Uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg). • DME: uncontrolled diabetes mellitus (DME studies: defined as HbA1c >12%) • History of cerebral vascular accident or myocardial infarction within 24 weeks	Severe systemic disease was excluded in all Eylea trials for technical reasons in order to reduce the impact of potentially confounding factors for safety measurements.	No	No rationale from available data and information that treatment should be considered as missing information under these conditions requiring additional activities. According to SmPC: "There is only limited experience in the treatment of subjects with DME due to type I diabetes

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Table SIV.1b: Exclusion criteria in the pivotal studies across the development program which are not proposed to be considered as missing information (Eylea 114.3 mg/mL, 8 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
(168 days) before screening visit • Renal failure requiring dialysis or renal transplant. • History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use an investigational drug, might affect interpretation of the results of the study, or renders the subject at high risk for treatment complications.			or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy. Eylea has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with Eylea in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients." "Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. There are limited data on safety in the treatment of patients with nAMD or DME with a history of stroke or transient ischaemic attacks or myocardial infarction within the last 6 months. Caution should be exercised when treating such patients."
Concomitant ocular disease or history thereof			
<u>AMD & DME</u> • AMD: Uncontrolled glaucoma (defined as IOP >25 mmHg despite treatment with anti-glaucoma medication) in the study eye. • Intraocular pressure (IOP) ≥25 mmHg in the study eye (DME).	Technical exclusion criteria in all studies for the sake of feasibility of safety assessments.	No	Not considered missing information requiring additional activities. According to SmPC: "Transient increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with Eylea. Special precaution is needed in patients with poorly

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Table SIV.1b: Exclusion criteria in the pivotal studies across the development program which are not proposed to be considered as missing information (Eylea 114.3 mg/mL, 8 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
			controlled glaucoma (do not inject Eylea while the intraocular pressure is ≥30 mmHg). In all cases both the intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately."
• wet AMD: Aphakia, or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium-aluminum-garnet [YAG] posterior capsulotomy performed more than 4 weeks (30 days) before screening), in the study eye. • History of corneal transplant for corneal dystrophy in the study eye • Significant media opacities including cataract. • Cataract surgery within 90 days before Day 1.	Technical exclusion criteria in all studies for the sake of feasibility of safety and efficacy assessments, particularly imaging.	No	No rationale from available data and information that treatment should be considered as missing information under these conditions. No rationale for further warnings or contraindication.
• Myopia of a spherical equivalent prior to any possible refractive or cataract surgery of ≥ 8 dioptres. • History of glaucoma filtration surgery in the past, or likely to need filtration surgery in the future in the study eye • Any intraocular inflammation/infection in either eye within 12 weeks (84 days) of the screening visit. • Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye. • History of idiopathic or autoimmune uveitis in the study eye.	Technical exclusion criterion. High myopia may negatively affect the quality of OCT imaging and was therefore excluded for study purposes. Additionally, highly myopic eyes have a different anatomy, which may interfere with study procedures and interpretation of results.		

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Table SIV.1b: Exclusion criteria in the pivotal studies across the development program which are not proposed to be considered as missing information (Eylea 114.3 mg/mL, 8 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
• Ocular conditions with a poorer prognosis in the fellow eye than in the study eye. • Only one functional eye even if that eye is otherwise eligible for the study	Technical exclusion criterion for clinical studies; as long as beneficial effects are not proven, the only remaining functional eye should not be exposed to experimental drug.		
Other neovascular disorder			
Wet AMD • History or clinical evidence of diabetic retinopathy, DME, or any other retinal vascular disease other than AMD. • Presence of other causes of CNV in the study eye. DME • Evidence of macular edema due to any cause other than diabetes mellitus in either eye. • Active proliferative diabetic retinopathy in the study eye	Technical exclusion criteria to reduce the impact of confounding factors on the efficacy and/or safety measurements. No safety concern was anticipated.	No	No rationale from available data and information that treatment should be considered as missing information under these conditions. 8 mg Eylea studies were performed in wet AMD and DME indications separately.
Complications of the underlying ocular disease			
Wet AMD • Subretinal haemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. • Scar or fibrosis making up >50% of the total lesion in the study eye. • Scar, fibrosis or atrophy involving the centre of the fovea in the study eye. • Presence of retinal pigment epithelial tears or rips	Technical exclusion criteria in AMD studies to reduce the impact of confounding factors on the efficacy and/or safety measurements or for interference with study procedures (imaging).	No	Sub/intraretinal haemorrhage is caused primarily by wet AMD. It should therefore not be regarded as missing information in the clinical setting. Contrarily, patients with subretinal haemorrhage are probably those with a high need to be treated to prevent further bleeds. No rationale from available data and information that any of these conditions should be considered as missing information.

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Table SIV.1b: Exclusion criteria in the pivotal studies across the development program which are not proposed to be considered as missing information (Eylea 114.3 mg/mL, 8 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
involving the macula in the study eye. • Total lesion size >12 disc areas including blood, scars and neovascularization as assessed by FA in the study eye. • Vitreomacular traction or epiretinal membrane in the study eye evident on biomicroscopy or OCT that is thought to affect central vision. • Any history of macular hole of stage 2 and above in the study eye. • Structural damage to the centre of the macula in the study eye that is likely to preclude improvement in BCVA following the resolution of retinal fluid including but not limited to, atrophy of the retinal pigment epithelium, subretinal fibrosis or scar or significant macular ischemia.			According to SmPC: "Wet AMD is characterized by pathological choroidal neovascularization (CNV). Leakage of blood and fluid from CNV may cause retinal oedema and/or sub-/intra-retinal haemorrhage, resulting in loss of visual acuity". No concern referring to any specific safety aspect was detected.

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Table SIV.1b: Exclusion criteria in the pivotal studies across the development program which are not proposed to be considered as missing information (Eylea 114.3 mg/mL, 8 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
DME			
• Current iris neovascularization, vitreous haemorrhage, or tractional retinal detachment in the study eye. • Ocular media of insufficient quality to obtain fundus and OCT images. • Pre-retinal fibrosis involving the macula in the study eye. • Structural damage to the centre of the macula in the study eye that is likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia or organized hard exudates. • Vitreomacular traction or epiretinal membrane in the study eye evident biomicroscopically or on OCT that is thought to affect central vision.	Technical exclusion criteria in DME studies. Would have impact on feasibility of study procedures (particularly imaging methods) for safety and efficacy assessments. No safety concern was anticipated.	No	No rationale from available data and information that any of these conditions should be considered as missing information regarding treatment with Eylea 114.3 mg/mL (8 mg dose). Not considered as relevant for the safety profile.
Pregnancy			
Wet AMD & DME			
• Men or women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 3 months after the last dose.	Technical exclusion criterion to avoid potential fetotoxicity.	No	This issue is covered in label (SmPC) per the following paragraphs: "Eylea should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus". "Women of childbearing potential have to use effective contraception during treatment and for at least 4 months after the last intravitreal injection of aflibercept."

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Table SIV.1b: Exclusion criteria in the pivotal studies across the development program which are not proposed to be considered as missing information (Eylea 114.3 mg/mL, 8 mg dose)

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
			"There are limited data on the use of aflibercept in pregnant women. Studies in animals have shown reproductive toxicity." No rationale from available data and information that treatment should be considered as missing information under these conditions.
Other			
Wet AMD & DME			
• Allergy or hypersensitivity to any of the compounds/excipients in the study interventions formulations	Technical exclusion criteria as such allergies were not compatible with study procedures	No	No rationale from available data and information that any of these conditions should be considered as missing information regarding treatment with 8 mg Eylea. It is constitutes a contraindication for 8 mg Eylea.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

Table SIV.2a: Limitations of ADR detection common to 2 mg Eylea clinical trial development program

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	Total exposure during the wet AMD (Phase I-IV), central retinal vein occlusion (CRVO; Phase III), branch retinal vein occlusion (BRVO; Phase III), diabetic macular edema (DME; Phase I-III) studies, myopic CNV (Phase III) studies, and retinopathy of prematurity (ROP; Phase III): • 4,714 patients exposed to Eylea (2,672 with wet AMD, 317 with CRVO, 158 with BRVO, 116 with myopic CNV, 1,372 with DME, and 79 with ROP). • Total number of Eylea injections administered:	Rare adverse drug reactions detected during the clinical development program for 2 mg Eylea (in wet AMD, CRVO, BRVO, myopic CNV, and DME patients) were eye disorders such as traumatic cataract, vitritis, and hypopyon. Based on the experience from the long exposure during the clinical development of Eylea, it is unlikely that a rare adverse reaction will impact the benefit/risk balance of Eylea in the target population. Furthermore, there now is a 10-

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Table SIV.2a: Limitations of ADR detection common to 2 mg Eylea clinical trial development program

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
	62,734 (36,525 for wet AMD, 2,728 for CRVO, 1,115 for BRVO, 474 for myopic CNV, 21,711 for DME, and 181 for ROP). The majority of patients were treated for 1 to <3 years in the clinical trial program.	year post-marketing experience with 2 mg Eylea and no new rare adverse drug reactions have been identified.
Due to prolonged exposure	See above	See above
Which have a long latency	See above	See above
Due to cumulative effects	Aflibercept is slowly absorbed from the eye into the systemic circulation after intravitreal administration and is predominately observed in the systemic circulation as an inactive stable complex with VEGF. As with other large proteins, both free and bound aflibercept are expected to be cleared by proteolytic catabolism.	It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than a 100-fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF (2.91 µg/mL) in a study of healthy volunteers. Adverse events due to cumulative effects are not anticipated.

Table SIV.2b: Limitations of ADR detection common to the 8 mg Eylea clinical trial development program

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	Total exposure during the wet AMD (Phase II/III), and diabetic macular edema (DME; Phase III) studies: • 1,217 patients exposed to Eylea 8 mg (726 with wet AMD and 491 with DME). • Total number of Eylea 8 mg injections administered: 6,676 (3,994 for wet AMD and 2,682 for DME). Study data for week 48 are available, the studies are ongoing.	Rare adverse drug reactions detected during the clinical development program for Eylea 8 mg (in wet AMD [including PCV], and DME patients) were eye disorders such as uveitis, iridocyclitis, and eyelid oedema. In the 8 mg clinical trial program the safety profile of 2 mg and 8 mg Eylea was similar. No new safety concerns or new ADRs were identified for 8 mg aflibercept. The studies are ongoing. Based on the broad clinical trial and 10 year post-marketing experience with 2 mg Eylea no new rare ADRs with relevant impact on the benefit-risk balance are expected for 8 mg Eylea.

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Table SIV.2b: Limitations of ADR detection common to the 8 mg Eylea clinical trial development program

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Due to prolonged exposure	The Phase III studies of 8 mg aflibercept in wet AMD/DME are ongoing.	The safety profile of 2 mg and 8 mg aflibercept is considered similar. For the 2 mg formulation a comprehensive clinical trial program was conducted, plus there is a long-standing post-marketing experience over more than 10 years. To date, no specific safety concerns are expected due to prolonged use.
Which have a long latency	See above	See above
Due to cumulative effects	Aflibercept is slowly absorbed from the eye into the systemic circulation after intravitreal administration and is predominately observed in the systemic circulation as an inactive stable complex with VEGF. Aflibercept is expected to undergo elimination through both target-mediated disposition *via* binding to free endogenous VEGF and metabolism *via* proteolysis. The median time to reach non-quantifiable concentrations of free aflibercept in plasma for 8 mg administered intravitreally was 3.5 weeks.	It is estimated that after intravitreal administration of 8 mg to patients, the mean maximum plasma concentration of free aflibercept is more than a 9-fold lower than the concentration of aflibercept re-quired to half-maximally bind systemic VEGF (2.91 µg/mL) in a study of healthy volunteers. Adverse events due to cumulative effects are not anticipated.

SIV.3 Limitations in Respect to Populations Typically under-represented in Clinical Trial Development Programs

SIV.3.1 Children

The safety and efficacy of Eylea in children and adolescents below 18 years of age for indications other than ROP have not been studied (0.4 mg Eylea was investigated in the indication ROP). There is no relevant use of Eylea in the paediatric population for the indications of wet AMD, CRVO, BRVO, DME and myopic CNV.

SIV.3.2 Elderly

2 mg Aflibercept Development Program:

In the wet AMD studies VIEW 1 and VIEW2, more than half of the patients exposed to Eylea (57.7%) were ≥75 years old and 27.3% were aged between 65 and 74 years. Therefore, there is a high percentage of elderly in the clinical study program.

More than half of the patients enrolled in both Phase III CRVO studies were ≥65 years (54.3%). 45.7% of the CRVO patients were below 65 years of age. Mean age of patients at enrolment was 64.0 years, with individual patients' ages ranging from 22 to 89 years.

In the Phase III BRVO study VIBRANT, 44.9% of the 158 Eylea-exposed patients were younger than 65 years, 33.5% were aged between 65 to 74 years, and 21.5% were aged 75 years or older.

In the myopic CNV study, 65.5% of the 116 subjects exposed to Eylea (SAF) were at the age of <65 years, 25.0% were aged between 65 and 74 years, and 9.5% were ≥75 years.

In the Phase I-III DME studies, 32.7% of the 1,372 subjects exposed to Eylea were at the age of ≥65 to <75 years, and 7.7% were ≥75 years. Due to the relatively small number of DME patients aged 75 years or older, a statement was included in the Summary of Product Characteristics (SmPC) that there is limited experience in patients older than 75 years with DME.

The distribution of the age groups is summarized by indication (excluding ROP) and in total in Table SIV.3. Overall, approximately one-third each of all exposed patients (N=4,635) belonged to one of the 3 age groups <65 years (32.4% of patients), ≥65 to <75 years (29.9%), and ≥75 years (37.6%).

Table SIV.3: 2 mg Eylea – Development Program: No. of patients by age in Phase I-III AMD studies, Phase III CRVO studies, Phase III BRVO study, Phase III myopic CNV study, and Phase I-III DME studies (SAF)

Eylea-exposed patients (Eylea total) in clinical studies on:						
Age Group [years]	**AMD (N=2,672) n (%)**	**CRVO (N=317) n (%)**	**BRVO (N=158) n (%)**	**mCNV (N=116) n (%)**	**DME (N=1,372) n (%)**	**All (N=4,635) n (%)**
<65	395 (14.8)	145 (45.7)	71 (44.9)	76 (65.5)	817 (59.5)	1,504 (32.4)
≥65 to <75	752 (28.1)	104 (32.8)	53 (33.5)	29 (25.0)	449 (32.7)	1,387 (29.9)
≥75	1,525 (57.1)	68 (21.5)	34 (21.5)	11 (9.5)	106 (7.7)	1,744 (37.6)

Source: Integrated Analysis Pool 3 - RMP: AMD (up to year 3), CRVO (w76/100), BRVO (1y), DME (3y), mCNV (1y); Table 1.2/2

8 mg Aflibercept Development Program:

In the 8 mg wet AMD studies CANDELA and PULSAR, half of the patients exposed to aflibercept 8 mg dose (51.9%) were ≥75 years old and 38.2% were aged between 65 and 74 years, only 9.9% were younger than 65 years.

In the Phase II/III DME 8 mg study PHOTON, 33.4% of the 491 subjects exposed to aflibercept 8 mg dose were at the age of ≥65 to <75 years, and 10.2% were ≥75 years.

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Table SIV.4: No. of patients by age in Phase II/III AMD studies (CANDELA, PULSAR), and Phase II/III DME study (PHOTON, SAF) – 8 mg

Eylea-exposed patients (Eylea total) in clinical studies on:				
Age Group [years]	**AMD (CANDELA + PULSAR)**		**DME (PHOTON)**	
	2 mg (N=389) n (%)	**All HD (N=726) n (%)**	**2 mg (N=167) n (%)**	**All HD (N=491) n (%)**
≥1 to <65	49 (12.6)	72 (9.9)	92 (55.1)	277 (56.4)
≥65 to <75	142 (36.5)	277 (38.2)	54 (32.3)	164 (33.4)
≥75	198 (50.9)	377 (51.9)	21 (12.6)	50 (10.2)

Source: Integrated Analysis – Pool 1, 48 weeks analysis, AMD 8 mg (w44/48) + DME 8 mg (w48); Table 1/3
HD= High Dose (8mg aflibercept)

SIV.3.3 Pregnant or breast-feeding women

Pregnancy and lactation constituted exclusion criteria in all clinical trials. There are no adequate and well-controlled studies in pregnant women.

So far, 8 cases of pregnancy were reported from 2 mg aflibercept clinical studies (direct exposure or exposure through male partner; see Part II Module SVII, Section SVII.3.1.14 and 12 cases of pregnancy in female patients treated in the post-marketing setting until 15 SEP 2017 (Part II Module SVII, Section SVII.3.1.14). These few cases did not suggest that treatment with Eylea might be associated with relevant embryo-fetotoxic effects.

To date, no pregnancy occurred in the 8 mg aflibercept development program.

SIV.3.4 Patients with a medical history of hepatic impairment

No specific studies have been performed in patients with hepatic disorders.

Patients with hepatic disorders were not excluded in the clinical study program.

After intravitreal administration of a maximum of 2 mg per dose, plasma concentrations of free aflibercept are negligibly low compared with those after subcutaneous and intravenous administration. Concentrations of bound aflibercept were also very low. In addition, the active moiety in aflibercept is a large protein. The metabolism and excretion of such molecules is generally by means other than the renal or hepatic pathways. It was therefore not considered necessary to conduct special clinical studies in patients with hepatic impairment.

No PK analyses were performed in VIEW 1, and no specific PK analysis in patients with a medical history of hepatic impairment was performed in the wet AMD study VIEW 2.

In SIGHT (SN 311523), there were only 4 subjects with a medical history of hepatic impairment compared with 195 subjects with no hepatic impairment, with mean values for free (adjusted bound) VTE of 22.85 (160.25) and 10.69 (147.79) µg/L, respectively. The difference in free VTE was attributed to high variability and the small number of subjects in the hepatic impairment group. Overall, the data did not provide any indication for a clinically relevant difference in free or adjusted bound VTE concentrations detected in subjects with different hepatic impairment status.

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In the ALTAIR study (SN 17668), 17 subjects had a medical history of hepatic impairment compared to 237 subjects with no hepatic impairment. No pharmacokinetic analyses were performed in the frame of this study.

Pharmacokinetic analysis of patients in the GALILEO study (study 14130, Bayer AG study) at Week 12, revealed no differences with respect to plasma concentrations of active drug after intravitreal administration every 4 weeks. It must be considered that the sub-group of subjects with a medical history of hepatic impairment included only one to two subjects across all weeks. No pharmacokinetic analyses were done in the COPERNICUS study (study run by Regeneron Pharmaceuticals, Inc.).

Pharmacokinetic analysis of patients in the VIBRANT study (study VGFTe-RVO-1027-BA01V1, study run by Regeneron Pharmaceuticals, Inc.) revealed no differences with respect to plasma concentrations of active drug after intravitreal administration every 4 weeks through Week 24 (no PK sampling time points were planned after Week 24). It must be considered that the sub-group of subjects with a medical history of hepatic impairment included only one subject.

Similarly, pharmacokinetic analyses of patients in the myopic CNV study (MYRROR) up to Week 24 showed that the systemic exposure to free and bound VEGF Trap was low. The exploratory sub-group analyses did not reveal any relevant influence of hepatic function on the plasma concentration of adjusted bound VEGF Trap. However, it must be considered that the subgroup of patients with a medical history of hepatic impairment included only 7 patients at Week 12 (compared to 53 without medical history of hepatic impairment) and 5 patients at Week 24 (compared to 27 without a medical history of hepatic impairment). For free VEGF Trap, the concentrations measured for the subgroup analyses were below the limit of quantification, therefore definitive conclusions regarding the effect of the covariate factors on systemic exposures to free VEGF Trap could not be drawn. The final analyses at Week 48 did not result in new or unexpected findings compared to Week 24.

In the VIVID-DME study (SN 91745, Bayer AG study), analysis of patients with a medical history of hepatic impairment at Week 0, Day 2-4, Week 24, and Week 52 revealed no influence of a medical history of hepatic impairment on plasma concentrations of free VEGF Trap. For adjusted bound VEGF Trap, a medical history of hepatic impairment showed a slight trend towards lower plasma concentrations with increasing level of impairment. However, the number of patients with liver dysfunction was very low (n=7) compared to patients without (n=118). In addition, plasma concentration ranges overlapped considerably. Therefore, these differences were not considered to be clinically relevant. No PK analyses were performed after the first year of the study.

No pharmacokinetic analysis was done in the VISTA-DME study (study run by Regeneron Pharmaceuticals, Inc.) or in the VIVID-EAST study (study run by Bayer AG). In the Phase III open-label DME study VIVID-JAPAN, exploratory subgroup analyses revealed no clinically relevant effects on free and bound VEGF Trap plasma concentrations with respect to medical history of hepatic impairment.

No specific PK analysis in patients with a medical history of hepatic impairment was performed in the ROP study FIREFLEYE.

No special studies in patients with renal impairment or hepatic impairment have been conducted with aflibercept 8 mg. Population pharmacokinetic analysis revealed that mild

hepatic impairment had no influence on systemic exposures to aflibercept compared to patients with normal hepatic function.

SIV.3.5 Patients with renal impairment

No specific studies have been performed in patients with renal disorders. Patients enrolled in the clinical studies were classified according to their baseline creatinine clearance values in one of the 4 groups:

- Creatinine clearance >80 mL/min (normal renal function),
- Creatinine clearance >50-80 mL/min (mild renal impairment),
- Creatinine clearance >30-50 mL/min (moderate renal impairment),
- Creatinine clearance ≤30 mL/min or requiring dialysis (severe renal impairment).

No PK analyses were performed in VIEW 1. Pharmacokinetic analysis of patients in the VIEW 2 study, of which 40% had a medical history of renal impairment (24% mild, 15% moderate, and 1% severe), revealed no differences with respect to plasma concentrations of active drug after intravitreal administration every 4 or 8 weeks. After intravitreal administration of a maximum of 2 mg per dose, plasma concentrations of free aflibercept were negligibly low compared with those after subcutaneous and intravenous administration. Concentrations of bound aflibercept were also very low. In addition, the active moiety in aflibercept is a large protein. The metabolism and excretion of such molecules is generally by means other than the renal or hepatic pathways. It was therefore not considered necessary to conduct special clinical studies in patients with renal disorders.

In SIGHT (SN 311523), the number of subjects in each creatinine clearance subgroup decreased from normal and mild renal impairment groups (89 subjects in the >80 mL/min group and 93 subjects in the >50-80 mL/min group) to moderate and severe renal impairment groups (12 subjects in the >30-50 mL/min group, and 1 subject in the ≤30 mL/min group). There was no quantifiable free VTE concentration in the one severe renal impairment subject. Overall, there was no difference in free or adjusted bound VTE concentrations detected in subjects with different renal function.

No PK analyses were performed in the ALTAIR study (SN 17668).

Pharmacokinetic analysis of patients in the GALILEO study (study 14130, Bayer AG study) at Week 12, of which 43% had a medical history of renal impairment (39% mild and 4% moderate), revealed no differences with respect to plasma concentrations of active drug after intravitreal administration every 4 weeks. No pharmacokinetic analyses were done in the COPERNICUS study (study run by Regeneron Pharmaceuticals, Inc.).

Pharmacokinetic analysis of patients in the VIBRANT study (study VGFTe-RVO-1027-BA01V1, study run by Regeneron Pharmaceuticals, Inc.) revealed no differences with respect to plasma concentrations of active drug after intravitreal administration every 4 weeks through Week 24 (no PK sampling time points were planned after Week 24). It must be considered that the sub-group of subjects with a medical history of renal impairment included 3 subjects with moderate (>30-50mL/min) and 11 subjects with mild (>50-80 mL/min) renal impairment.

In the Phase III myopic CNV MYRROR study, 63% of patients treated with VEGF Trap had a medical history of renal impairment (52% mild and 11% moderate; solely defined through baseline creatinine clearance values of >50-80 mL/min and >30-50 mL/min, respectively).

Pharmacokinetic analyses of patients in MYRROR up to Week 48 revealed no specific influence of medical history of renal impairment on the pharmacokinetics of bound VEGF Trap.

In the VIVID-DME study (SN: 91745, Bayer AG study), analysis of patients with a medical history of renal impairment at Week 0, Day 2-4, Week 24, and Week 52 revealed no influence of renal impairment on plasma concentrations of free VEGF Trap. For (the pharmacologically inactive) adjusted bound VEGF Trap, a slight trend towards higher plasma concentrations with increasing level of impairment was shown. However, the number of patients with renal dysfunction decreased from more than 60 (>80 mL/min creatinine clearance) to 1 (<30 mL/min creatinine clearance). In addition, plasma concentration ranges overlapped considerably. Therefore, these differences were not considered to be clinically relevant. No further PK samples were taken after the first year of the study.

No pharmacokinetic analysis was done in the VISTA study (study run by Regeneron Pharmaceuticals, Inc.) or in the VIVID-EAST study (study run by Bayer AG).

In the Phase III open-label DME study VIVID-JAPAN, renal function was assessed by calculated CL_{CR} and divided into 4 subgroups. The mean of free VEGF Trap concentrations slightly increased with decreasing CL_{CR}. However, taking into account the absolute values, large variability, and very low number of patients in the lowest CL_{CR} (≤30 mL/min) group, these differences appeared to be small and clinically not relevant. For the pharmacologically inactive adjusted bound VEGF Trap, there was no clear trend seen in plasma concentrations across the different CL_{CR} groups. Subjects in the >80 mL/min CL_{CR} group had a lower mean compared to subjects with CL_{CR} values ≤80 mL/min. However, the ranges of all CR_{CL} groups overlapped considerably and in 3 out of the 4 groups the maximum concentrations of adjusted bound VEGF Trap did no exceed the LLOQ (lower limit of quantitation) by more than 4.5-fold (except CL_{CR} >50-80 mL/min group where it exceeded the LLOQ by 19-fold).

No specific PK analysis in patients with a medical history of renal impairment was performed in the ROP study FIREFLEYE.

No specific studies in patients with renal impairment have been conducted with 8mg aflibercept. Population pharmacokinetic analysis revealed that systemic exposures to aflibercept in patients with mild to severe renal impairment were similar to those with normal renal function.

SIV.3.6 Patients with other relevant co-morbidity

Not applicable.

SIV.3.7 Patients with a disease severity different from the inclusion criteria in the clinical trial population

Not applicable.

SIV.3.8 Sub-populations carrying known and relevant polymorphisms

Not applicable.

SIV.3.9 Patients of different racial and/or ethnic origin

The VIEW 1 and VIEW 2 studies (Phase III wet AMD trials) were conducted in a total of 28 countries including North and South America, Europe and Asia Pacific. Study populations

included Caucasian, Asian, Hispanic, and Black patients. The Phase III AMD study SIGHT was performed among 304 Chinese patients.

The Phase III CRVO trial COPERNICUS was conducted at 61 sites in the USA, Canada, Colombia, Israel and India. The GALILEO study was conducted at 63 sites in Europe and the Asia Pacific region.

The Phase III BRVO study VIBRANT was conducted at 58 sites in the USA, Canada, and Japan.

Only Asian patients were randomized and treated in the Phase III myopic CNV study MYRROR (90 patients in Japan and 32 patients in other Asian countries [Taiwan, South Korea, Hong Kong, and Singapore]).

The Phase III DME study VISTA-DME was performed in the USA, while the Phase III DME study VIVID-DME was conducted in various European countries, Japan, and Australia. Only Japanese patients were included in the open-label Phase III DME study VIVID-JAPAN (72 patients in the SAF). In the Phase III DME study VIVID-EAST, most of the patients were enrolled in China (approximately 80%), while the remaining patients were enrolled in Russia and other Asia-Pacific countries.

The Phase III ROP study FIREFLEYE was conducted in a total of 27 countries including Europe, Asia Pacific, and South America.

Overall, patients of various different racial and/or ethnic origins were exposed to Eylea 40 mg/mL (2 mg dose) in the development programs; the majority of exposed patients, however, were White (66.0%; see Table SIV.5).

Table SIV.5: No. of patients by race in Phase I-III AMD studies, Phase III CRVO studies, Phase III BRVO study, Phase III myopic CNV study, Phase I-III DME studies, and Phase III ROP study (SAF) – Eylea 40 mg/mL (2 mg dose) development

Eylea-exposed patients (Eylea total) in clinical studies on:							
Race	**AMD (N=2,672) n (%)**	**CRVO (N=317) n (%)**	**BRVO (N=158) n (%)**	**mCNV (N=116) n (%)**	**DME (N=1,372) n (%)**	**ROP (N=79) n (%)**	**All trials (N=4,714) n (%)**
American Indian or Alaska Native	4 (0.1)	2 (0.6)	0	0	2 (0.1)	0	8 (0.2)
Asian	763 (28.6)	42 (13.2)	19 (12.0)	116 (100)	434 (31.6)	17 (21.5)	1,391 (29.5)
Black or African American	7 (0.3)	10 (3.2)	17 (10.8)	0	61 (4.4)	2 (2.5)	97 (2.1)
Multiple	1 (<0.1)	17 (5.4)	0	0	2 (0.1)	1 (1.3)	21 (0.4)
Native Hawaiian or other Pacific Islander	1 (<0.1)	0	1 (0.6)	0	4 (0.3)	0	6 (0.1)
Not reported	63 (2.4)	5 (1.6)	5 (3.2)	0	9 (0.7)	0	82 (1.7)

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Table SIV.5: No. of patients by race in Phase I-III AMD studies, Phase III CRVO studies, Phase III BRVO study, Phase III myopic CNV study, Phase I-III DME studies, and Phase III ROP study (SAF) – Eylea 40 mg/mL (2 mg dose) development

Eylea-exposed patients (Eylea total) in clinical studies on:							
Race	**AMD (N=2,672) n (%)**	**CRVO (N=317) n (%)**	**BRVO (N=158) n (%)**	**mCNV (N=116) n (%)**	**DME (N=1,372) n (%)**	**ROP (N=79) n (%)**	**All trials (N=4,714) n (%)**
White	1,833 (68.6)	241 (76.0)	116 (73.4)	0	860 (62.7)	59 (74.7)	3,109 (66.0)

Note: Total patients include 4 patients from the laser group who received Eylea as rescue therapy.
Subjects receiving at least one active VTE injection (pure or in combination) are displayed, subjects treated with sham or comparator including laser only are not displayed.
Subjects who were treated with sham or comparator and additionally with VTE 2.0 mg or VTE 0.4 mg were considered in VTE 2.0 mg or VTE 0.4 mg and VTE total.
Subjects may have received more than one dose. These subjects are considered for each dose, but once for VTE total.
Source: Integrated Analysis Pool 3 - RMP: AMD (up to year 3), CRVO (w76/100), BRVO (1y), DME (3y), mCNV (1y), ROP (w24/27); Table 1.1/4 and 1.1/4a-f

Overall, patients of various different racial and/or ethnic origins were exposed to Eylea 114.3 mg/mL (8 mg dose) in the development program; the majority of exposed patients were White in both indications (wet AMD/2 mg: 77.1%, wet AMD/8 mg: 78.2%; DME/2 mg: 67.1%, DME/8 mg: 73.1%%; see Table SIV.6). No safety signal was identified for specific ethnicities.

Table SIV.6: No. of patients by race in Phase II and III wet AMD studies (CANDELA, PULSAR), Phase II/III DME (PHOTON) study (SAF) – Eylea 114.3 mg/mL (8 mg dose) development

Eylea-exposed patients (Eylea total) in clinical studies on:				
Race	**AMD (CANDELA+PULSAR)**		**DME (PHOTON)**	
	2 mg (N=389) n (%)	**All HD (N=726) n (%)**	**2 mg (N=167) n (%)**	**All HD (N=491) n (%)**
American Indian or Alaska Native	1 (0.3)	0	0	2 (0.4)
Asian	83 (21.3)	151 (20.8)	30 (18.0)	71 (14.5)
Black or African American	2 (0.5)	2 (0.3)	18 (10.8)	44 (9.0)
Multiple	0	1 (0.1)	0	1 (0.2)
Native Hawaiian or other Pacific Islander	0	1 (0.1)	0	1 (0.2)
Other	1 (0.3)	0	4 (2.4)	7 (1.4)
Not reported	2 (0.5)	3 (0.4)	3 (1.8)	6 (1.2)
White	300 (77.1)	568 (78.2)	112 (67.1)	359 (73.1)

HD = High Dose (8mg Aflibercept)
2 mg: Aflibercept 2 mg regardless of injection schedule.
All HD: HDq12 and HDq16 combined.
Source: Integrated Analysis – Pool 1, 48 weeks analysis, AMD 8 mg (w44/48) + DME 8 mg (w48); Table 1/3

SIV.3.10 Conclusion on the populations not studied and other limitations of the clinical trial development program

As Eylea belongs to the class of anti-VEGF therapies, which are potentially teratogenic, embryo-fetotoxicity has been identified as an important potential risk. No additional safety concerns were identified in this section.

PART II Module SV: Post-authorisation Experience

SV.1 Post-authorisation Exposure

SV.1.1 Method used to Calculate Exposure

The patient exposure displayed in this RMP (expressed as patient years [PYs]) was estimated based on the number of sold/distributed Eylea vials/PFS during the reporting period and the presumed underlying prevalence and treatment schedules of the approved Eylea indications wet AMD, CRVO, BRVO and DME. The following assumptions were made:

- wet AMD: 52% of Eylea-treated patients will have AMD and receive 7 vials/PFS per year,
- CRVO: 6% of Eylea-treated patients will have CRVO and receive 6 vials/PFS per year,
- DME: 26% of Eylea-treated patients will have DME and receive 8 vials/PFS per year,
- BRVO: 13% of Eylea-treated patients will have BRVO and receive 6 vials/PFS per year,
- Myopic CNV: 3% of Eylea-treated patients will have myopic CNV and receive 1 vial/PFS per year.

The resulting formula for the calculation of total PYs is:

$$\text{Total no. of vials and PFS} / ((0.52 \times 7) + (0.06 \times 6) + (0.26 \times 8) + (0.13 \times 6) + (0.03 \times 1)) = \text{Total no. of vials and PFS} / 6.89$$

and the PYs per indication were calculated as 52%, 6%, 26%, 13%, and 3% from the total PYs for wet AMD, CRVO, DME, BRVO, and myopic CNV, respectively.

This mode of calculation for PYs is considered rather conservative, because patients treated under usual care conditions might receive fewer injections than required per label, meaning that the true number of patient years (i.e., number of treated patients) could be even higher than calculated (which would further decrease the estimated incidence rates of post-marketing safety events related to PYs).

SV.1.2 Exposure

A total of 59,495,014 units (vial/PFS) were sold world-wide by 31 OCT 2022, resulting in an estimated overall exposure of 8,634,980 patient years across all 5 indications based on the aforementioned formula.

Table SV.1: Post-marketing exposure by indication - data lock point 31 OCT 2022

Indication	Cumulative no. of units sold	Estimated Exposure (patient years)					
		AMD	CRVO	BRVO	DME	mCNV	TOTAL
Total	**59,495,014**	**4,490,190**	**518,099**	**1,122,547**	**2,245,095**	**259,049**	**8,634,980**

PART II Module SVI: Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No potential for misuse or illegal purposes is currently anticipated with the use of Eylea.

PART II Module SVII: Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Introductory note: Please note that the contents of the previous Eylea EU-RMP (Version 24.0) have been transferred into the new EU-RMP template. Therefore, this section does not describe the situation at the time of the initial approval of 2 mg Eylea, as this information is outdated (initial EU approval was on 22 NOV 2012). Instead, both the definitions of safety concerns and the adverse drug reaction table valid at the time of the first drug renewal procedure (EMEA/H/C/002392//R/0033) have been used for the current presentation of safety concerns according to the new template. This section will now be locked after RMP approval and any future changes presented in Section SVII.2.

This section SVII.1 reflects the ADR frequencies as observed during the development of Eylea 40 mg/mL (2 mg dose). The conclusion on "Risks not considered important for Inclusion in the List of Safety Concerns in the RMP" (below SVII.1.), "Risks considered important for Inclusion in the List of Safety Concerns in the RMP" (SVII.1.2), are also applicable to Eylea 114.3 mg/mL, 8 mg dose.

SVII.1.1 Risks not considered important for Inclusion in the List of Safety Concerns in the RMP

Adverse drug reactions seen in Eylea 40 mg/mL (2 mg dose development) phase III studies

The following treatment-emergent drug reactions (reported in patients in Eylea Phase III studies) are included in the current SmPC (version JUL 2017, MedDRA preferred term level):

Very common: Visual acuity reduced, conjunctival haemorrhage, eye pain.

Common: Retinal pigment epithelial tear, detachment of retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract, cataract cortical, cataract nuclear, cataract subcapsular, corneal erosion, corneal abrasion, intraocular pressure increased, vision blurred, vitreous floaters, vitreous detachment, injection site pain, foreign body sensation in eyes, lacrimation increased, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival hyperaemia, ocular hyperaemia.

Uncommon: Hypersensitivity, endophthalmitis, retinal detachment, retinal tear, iritis, uveitis, iridocyclitis, lenticular opacities, corneal epithelium defect, injection site irritation, abnormal sensation in eye, eyelid irritation, anterior chamber flare, corneal oedema.

Rare: Blindness, cataract traumatic, vitritis, hypopyon.

The conditions, which are regarded as important identified or potential risks (either as single preferred term event term or by term grouping) are underlined in the preceding listing. The remaining risks are not regarded as important for the following reasons A to C:

A) Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Visual acuity reduced (very common), vision blurred (common).
  Comment: This functional loss is mainly considered to occur as a result of the underlying ocular disease. It may represent a symptom of an injection related event

such as intraocular inflammation/infection or retinal tear/detachment. These complications pose important identified risk in the EU RMP.

- Conjunctival haemorrhage (very common), conjunctival hyperaemia (common), ocular hyperaemia (common), vitreous haemorrhage (common), vitreous floaters (common), eye pain (very common), injection site pain (common), injection site haemorrhage (common), injection site irritation (uncommon), lacrimation increased (common), foreign body sensation in eyes (common), abnormal sensation in eye (uncommon), eyelid irritation (uncommon).
  Comment: These are local events likely caused by the intraocular injection procedure, which are usually mild and fully reversible in nature. It is expected that Health Care Professionals (HCPs) are well familiar with these concomitant adverse effects of the IVT injection.

B) Known risks that do not impact the risk-benefit profile (in relation to the severity of the indication treated):

- Detachment of retinal pigment epithelium (common), retinal degeneration (common), vitreous detachment (common), corneal erosion (common), corneal abrasion (common), punctate keratitis (common), corneal epithelium defect (uncommon).
  Comment: These events are likely procedure-related (however, “detachment of retinal pigment epithelium” and “retinal degeneration” could also be promoted by underlying disease) and may result in longer-term complaints. However, no severe sequelae are expected, and these events are not assumed to impair the positive risk/benefit profile of Eylea. It is expected that HCPs are well familiar with these potential adverse effects of the IVT injection.

C) Adverse reactions 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:

- Blindness (rare).
  Comment: This event is rare and may also occur as a result of the underlying disease.

Reasons for considering other risks not important (incl. class effects)

Potential risk: Sustained intraocular pressure.

Issue: A persistent ocular hypertension (OHT) has been observed after intravitreal injection of VEGF inhibitors (ranibizumab, bevacizumab) (170, 190-192), leading to an assumed class effect of “sustained” IOP increase. The incidence of sustained OHT after intraocular administration of these VEGF inhibitors ranged between 3.1% and 11.9% in studies with 96 - 512 treated eyes (170, 190). Two hypotheses have been described for the underlying mechanism of chronic OHT:

1) The anti-VEGF antibodies (= high molecular proteins) may accumulate in the aqueous outflow channels including the trabecular meshwork or Schlemm´s canal and obstruct aqueous outflow (193).

2) Immunological reactions and low-grade inflammation post-injection may be an additional mechanism leading to IOP elevations (170, 194).

Both effects may be amplified by the quality of the injected VEGF inhibitor: aggregation of the antibody to higher molecular structures may enhance the obstruction of the outflow system. Also, contaminants such as silicone oil from the syringe barrel or rubber stopper may block the outflow system or induce subclinical inflammation (191, 195, 196).

Comment: A transient increase of IOP, which is often observed after intravitreal injection of fluids, is considered an important identified risk of IVT Eylea administration. It is attributed to an increase in vitreous volume (volume effect), which is compensated within 0.5 to 1 hours after injection, so that IOP normalizes back to baseline values (195, 197). Therefore, the volume effect is not responsible for a chronic elevation of IOP. Thorough monitoring of mean values over time for pre-injection IOP in the clinical Phase III Eylea trials indicated the there is no trend towards sustained IOP increase on treatment with Eylea. Therefore, the assumed class effect of "sustained" IOP increase is not regarded as an important risk of treatment with Eylea.

SVII.1.2 Risks considered important for Inclusion in the List of Safety Concerns in the RMP

An overview of the important identified risks of Eylea is provided in Table SVII.1.

Table SVII.1: Overview of important identified risks

Important identified risk	Risk-benefit impact
Endophthalmitis (likely infectious origin)	Endophthalmitis is an intraocular infection and may occur as a result of an infection with microorganisms, either through direct traumatic injury of the eye (exogenous infection) or through spreading of microorganisms from other areas of the body (endogenous infection). In cases of inflammation where no pathogens can be identified (no/negative culture growth of microorganisms observed), the condition may be characterized as "sterile endophthalmitis" or "non-infectious endophthalmitis". Because of the risk of severe vision loss, treatment should be initiated as soon as possible, and, depending on cause and severity, may consist of topical and intravitreal application of antibiotics, corticosteroids, and surgical removal of matter and infected structures (drainage, vitrectomy). The risk of endophthalmitis (and other intraocular infections) cannot be completely excluded but minimized through strict aseptic and sterile conditions when administering Eylea. Only experienced and appropriately trained ophthalmologists should be charged with the injections, and patients should report any signs or symptoms of intraocular inflammation (e.g., visual acuity decreased, pain, photophobia, or redness) as soon as possible in order to enable the treating physician to introduce appropriate countermeasures in due time. Educational material is provided i.a., to promote optimal administration technique. The proportion of Eylea-exposed adult patients who experienced endophthalmitis in the study eye in the clinical studies with Eylea was low (range from 0% to 0.9% in the VIEW 1 extension study); endophthalmitis is regarded as an uncommon ADR. Endophthalmitis cases (and other cases of intraocular inflammation) reported in post-marketing setting are subject to additional follow-up using specific

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Table SVII.1: Overview of important identified risks

Important identified risk	Risk-benefit impact
	questionnaires. Currently, the risk-benefit in terms of endophthalmitis is considered favourable for Eylea.
Intraocular inflammation	Intraocular inflammations (other than endophthalmitis) are inflammations of defined structures of the inner eye (e.g., iritis, uveitis, iridocyclitis). Aside from endophthalmitis/intraocular inflammations with an infectious origin, there are also inflammations where no pathogens can be identified (either no culture performed or negative culture growth), the condition may be characterized as "sterile" inflammatory condition. The cause of a sterile inflammation, independently of the administered drug, remains uncertain, and a multifactorial origin cannot be discarded. An intraocular inflammation generally constitutes a serious condition, which may lead to generalized eye inflammation and risk of blindness. Treatment should be initialized as soon as possible, and, depending on cause and severity, may consist of topical and intravitreal application of antibiotics, corticosteroids, and surgical removal of matter and infected structures (drainage, vitrectomy). The risk of intraocular infections can be minimized through strict aseptic and sterile conditions when administering Eylea (see endophthalmitis). The proportion of Eylea-exposed adult patients who experienced intraocular inflammation (grouped term) in the study eye in the clinical studies with Eylea ranged from 0% to 2.6% (VIEW 1 & 2 AMD studies). Single preferred terms events associated with intraocular inflammation are considered uncommon ADRs (e.g., iritis, uveitis, iridocyclitis) or rate ADRs (vitritis, hypopyon). Endophthalmitis and other cases of intraocular inflammation reported in post-marketing setting are subject to additional follow-up using specific questionnaires. Currently, the risk-benefit in terms of intraocular inflammation is considered favourable for Eylea.
Transient intraocular pressure increase	Chronically elevated intraocular pressure is a major risk factor for a condition called "glaucoma", which is characterized by a loss of nerve fibres in the optic nerve with the subsequent risk of blindness. However, many different factors may be responsible for the development of glaucoma, and increased intraocular pressure is not a mandatory prerequisite for the development of glaucoma (e.g., normal-tension glaucoma). Transient IOP increase following IVT injection is a well-known side effect of any IVT administration of liquids used for drug dissolution, but this condition is limited and usually resolved once the surplus fluid has been resorbed from the inner eye. The proportion of Eylea-exposed adult patients who experienced an increase in intraocular pressure (grouped term) in the study eye in the clinical studies with Eylea ranged from 2.8% (VIVID-JAPAN DME study) to 13.6% (CRVO studies GALILEO & COPERNICUS), but the vast majority of these events were resolved. Systematic measurements of IOP during the course of the clinical studies did not indicate a trend

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Table SVII.1: Overview of important identified risks

Important identified risk	Risk-benefit impact
	towards sustained IOP increase. "Intraocular pressure increased" (single preferred term) is considered a common ADR. Transient intraocular pressure increase reported in post-marketing setting are subject to additional follow-up using specific questionnaires. Currently, the risk-benefit in terms of transient IOP increase is considered favourable for Eylea.
Retinal pigment epithelial (RPE) tears	The retinal pigment epithelium is the outer layer of the retina, and tears in that layer may occur secondary to AMD, following intravitreal injections, or for unknown reasons. These tears may be self-sealing or may require sealing by laser coagulation. In clinical trials up to 1.9% of patients with underlying wet AMD who were treated with Eylea developed RPE tear, while none of the patients treated for other Eylea indications (CRVO, BRVO, myopic CNV, DME) had developed RPE tear. RPE tear is considered a common ADR. However, the total incidence of RPE tears with Eylea in the AMD Phase III trials was in line with the known background incidences from literature; and the absence of RPE tear in the clinical studies investigating the non-AMD indications of Eylea suggests that RPE tear development caused by IVT treatment with Eylea is rather unlikely. Currently, the risk-benefit in terms of RPE tear is considered favourable for Eylea.
Retinal tear / detachment	Retinal tear/detachment is characterized by separation of the retina from its attachment to the underlying tissues. Most retinal detachments are a result of a retinal break, hole, or tear. Retinal tear/detachment usually constitutes an ophthalmological emergency that requires medical intervention, including sealing and/or re-attachment of the retinal lesion through laser photocoagulation or freezing (cryotherapy). The risk can be reduced by performing a proper IVT injection technique IVT procedure using a correct angle of the needle while injecting. The proportion of Eylea-exposed adult patients who experienced retinal tear/detachment in the study eye in the clinical studies with Eylea ranged from 0% to 1.5% (VIEW 1 extension study). Retinal tear/detachment is considered an uncommon ADR. Currently, the risk-benefit in terms of retinal tear/detachment is considered favourable for Eylea.
Cataract (especially of traumatic origin)	Cataract (clouding of lens) may occur spontaneously (particularly in the elderly), as a side effect of certain drugs, or following outside influences such as irradiation or mechanical injury (traumatic cataract). Thus, the needle injury required to inject Eylea through the lens into the eyeball could cause such a traumatic cataract. However, by correct IVT procedure and a correct angle of the needle while injecting, the risk of cataract development can be minimized. The proportion of Eylea-exposed adult patients who experienced traumatic cataract in the study eye in the clinical studies with Eylea ranged from 0% to 2.8% (VIVID-DME &

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Table SVII.1: Overview of important identified risks

Important identified risk	Risk-benefit impact
	VISTA-DME). Various forms of cataract (cortical, nuclear, subcapsular) are considered common ADRs; traumatic cataract is regarded as a rare ADR. There is currently no evidence that the occurrence of a traumatic cataract is increased on treatment with Eylea. However, as this might be a hypothetical result of the lens perforation, it has been included as important identified risk. Currently, the risk-benefit in terms of cataract development is considered favourable for Eylea.
Hypersensitivity and immunogenicity	VEGF-Trap Eye is a foreign protein to the patient and, as such, may generate allergic reactions or may prompt the immune system to react by formation of specific antibodies, which in turn may cause immunologic reactions or attenuate the drug effects. Therefore, both hypersensitivity and immunogenicity are considered important identified risks of treatment with Eylea. Patients with known hypersensitivity to Eylea or to any of its excipients must not be treated with Eylea. The proportion of Eylea-exposed adult patients who experienced any potential hypersensitivity events in the clinical studies (grouped term) with Eylea ranged from 0% to 5.2% (VIEW 1 & VIEW 2). Hypersensitivity is considered an uncommon ADR. Since Eylea is injected locally into the eye, the systemic exposure to Eylea is very small. Furthermore, immunogenicity to Eylea appears to be very low and there is no evidence that it impacts the safety or efficacy of Eylea. Currently, the risk-benefit in terms of hypersensitivity / immunogenicity is considered favourable for Eylea.

Table SVII.2 summarizes the identified potential risks of Eylea. This group mainly includes the class effects known from systematically administered VEGF inhibitors as well as off-label use and medication error.

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Table SVII.2: Overview of important potential risks

Important potential risk	Risk-benefit impact
Arterial thromboembolic events (ATEs), including non-MI ATEs and cardiovascular ischemic events	Intravenous injections of anti-VEGF agents at high doses used to treat cancer are known to be associated with an increased occurrence of arterial thromboembolic events (ATEs). Since Eylea is administered in very small doses directly into the eye, the risk of developing such systemic adverse events is considered very low. However, since Eylea belongs to the class of anti-VEGF therapies, arterial thromboembolic events are considered an important potential risk. The targeted analysis of adjudicated ATE according to the definitions provided by the Anti-Platelet Trialists' Collaboration (APTC) during the clinical development program is highly expressive, since the ATE terms are clearly defined and adjudicated by an independent data review committee. Consistently, the analyses in the AMD, CRVO, BRVO, myopic CNV, and DME studies did not show meaningful differences between Eylea and the respective parallel control groups. No dose-dependent trends could be observed in ATE incidences, and incidences were generally low. So far, there is no relevant indication that treatment with Eylea might be associated with an increased risk of arterial thromboembolic events. Systemic pharmacodynamic effects, including the development of ATEs, are deemed unlikely. ATE cases reported in post-marketing setting are subject to additional follow-up using specific questionnaires.
Venous thromboembolic events	Venous thromboembolic events have been associated with intravenous injection of anti-VEGF therapies at the doses used for cancer treatment. As with the remaining potential systemic class effect risks, the low incidence and the absence of dose dependency in the Phase III AMD, CRVO, BRVO, myopic CNV, and DME studies support that Eylea is unlikely to cause venous thromboembolic events.
Hypertension	Arterial hypertension has been associated with intravenous injection of anti-VEGF therapies at the doses used for cancer treatment. So far, there is no evidence that the very small doses of Eylea that are injected into the eye are associated with an increased risk of hypertension. Following IVT administration of aflibercept at the doses studied, free aflibercept is not present at sufficient plasma concentrations (or for a sufficient length of time) to induce meaningful reductions in available systemic active endogenous free VEGF. Importantly, aflibercept did not accumulate in plasma after IVT administration every 4 weeks (VIEW 2). A contributory role of Eylea to an increase in blood pressure is considered unlikely. Hypertension cases reported in post-marketing setting are subject to additional follow-up using specific questionnaires.

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Table SVII.2: Overview of important potential risks

Important potential risk	Risk-benefit impact
Proteinuria	Proteinuria is associated with intravenous injection of anti-VEGF therapies at the doses used for cancer treatment. The incidence of treatment-emergent proteinuria was low in patients treated with Eylea in the clinical development program and showed no dose dependency. There is no evidence that the very small doses of Eylea that are injected into the eye are associated with an increased risk of proteinuria.
Non-ocular haemorrhage	Non-ocular bleedings are associated with intravenous injection of anti-VEGF therapies at the doses used for cancer treatment. The similar event rates in the Eylea groups compared to the respective parallel groups (i.e., ranibizumab, sham, or laser) as well as the absence of any dose-response relationship among Eylea-treated patients in the Phase III AMD, CRVO, BRVO, myopic CNV, and DME studies suggest that Eylea is unlikely to cause non-ocular (systemic) haemorrhages.
Medication error	There is an excess volume in the marketed vial which exceeds the recommended net dose of 2 mg Eylea per injection. Thus, injection of more than the approved volume results in overdose. However, this numerical overdose is limited, and the drug will be administered only by qualified physicians (not by patients), and this reduces the risk of inappropriate dosing and administration as well. No clinically meaningful events of overdose have been reported so far (neither in clinical trials nor in usual care). Nevertheless, it was decided to consider "medication error " a potential risk of treatment, which is, however, completely avoidable by proper adherence to the dosing recommendations.
Off-label use and misuse	As with other drugs, Eylea might be intentionally used other than recommended, or in clinical conditions outside the approved indications. Eylea does not have any dependence potential. Since the clinical experience with Eylea in such off-label use is limited (in particular in terms of efficacy and safety), any case of off-label use is currently considered an important potential risk. In addition, intentional off-label use in the context of multiple use of single use product (vial splitting) has been observed with Eylea. The Eylea vial is approved for single eye use only.
Embryo-fetotoxicity	As angiogenesis is a critical component of embryonic and foetal development, inhibition of angiogenesis following systemic administration of anti-VEGF therapies might result in adverse effects on pregnancy. The current experience with IVT-administered anti-VEGF therapies in pregnancy is sparse (single cases reported only) and thus inconclusive. However, early loss of pregnancy after IVT bevacizumab injection has been reported in a very few instances (198). Therefore, particular attention is paid to that safety issue. No cases of embryo-fetotoxicity were reported during the clinical development program; however, pregnant females were excluded from clinical study participation. Current post-marketing surveillance data do not suggest an increased risk of embryo-fetotoxicity on treatment with Eylea.

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Table SVII.2: Overview of important potential risks

Important potential risk	Risk-benefit impact
Retinal haemorrhage	Many ocular diseases, including wet AMD, CRVO, BRVO, or DME may lead to retinal bleeding. However, since rare cases of retinal haemorrhages were reported to be related to IVT treatment with anti-VEGF therapies, this condition is also considered an important potential risk.

Table SVII.3 provides an overview of the missing information for Eylea.

Table SVII.3: Overview of missing information

Missing information	Risk-benefit impact
Use of Eylea in patients with uncontrolled glaucoma	Eylea has not been studied in patients with uncontrolled glaucoma, and it is possible that the additional volume load and secondary transient increase in intraocular pressure caused by the IVT injection might be especially detrimental in those patients with uncontrolled glaucoma. The currently available data do not allow a final judgment of this theoretical concern. No additional Pharmacovigilance (PV) activities are currently warranted.
Concomitant use of different anti-VEGF therapies and other therapies for wet AMD, CRVO, BRVO, myopic CNV, and DME (including bilateral anti-VEGF therapy).	Under real-world conditions patients may be simultaneously treated with numerous drugs, which might result in interferences that have never been evaluated in clinical studies. Thus, there is a certain probability that Eylea will be administered in combination (or in close temporal sequence) with other anti-VEGF therapies or other treatments for wet AMD, CRVO, BRVO, myopic CNV, and DME. The potential interferences and consequences of such combinations cannot be assessed at the moment; no additional PV activities are currently warranted.
Long-term safety beyond 2 years	The clinical studies, which provided the basis for the approval of Eylea, did not cover a treatment period of longer than 2 years. However, since patients in the post-authorization phase are likely to be treated for longer than 2 years, it would be reasonable to systematically collect safety data beyond 2 years in order to assess the long-term safety of Eylea more appropriately. Sufficiently comprehensive data on the long-term safety of Eylea beyond the 2 years of administration is currently not available; no additional PV activities are currently warranted.
Posology utilized in marketed use	Dose recommendations are provided by the marketing authorization holder in the package insert and other documents. However, physicians might choose a different dosage, based on their expert medical opinion. It is useful for the marketing authorization holder to receive information about these intentional deviations from the recommended dosage in order to be better aware of how the mediation is being used in practice. Currently, there is insufficient information about the posology actually being used by physicians in clinical practice. Two post-authorization efficacy studies (PAES) are currently being conducted in order to evaluate the effects of an “treat and extend” regimen *vs*. a fixed treatment regimen in patients with AMD and

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Table SVII.3: Overview of missing information

Missing information	Risk-benefit impact
	DME, respectively (Studies BAY 86-5321/16598 and BAY 86-5321/17613, respectively).
Long-term safety of aflibercept in preterm infants with ROP	The current knowledge about potential long-term effects of aflibercept IVT treatment in preterm infants with ROP is lacking and current safety profile is based on the 6-months pivotal study FIREFLEYE. An extension study FIREFLEYE NEXT (20275) has been set-up to evaluate the long-term outcomes up to 5 years of chronological age of patients who received treatment for ROP in study FIREFLEYE (20090). This study is ongoing and follows up on ocular, neurodevelopmental and overall clinical outcomes until 5 years of age when detailed assessment of visual function and overall development becomes more feasible.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Changes since last RMP:

Overall, following the review of the 44/96-week data of the 8 mg studies CANDELA, PULSAR and PHOTON no new safety concerns were identified.

Changes/decisions made in previous RMPs:

Patients in the CANDELA and PHOTON studies were allowed to be treated with 2 mg aflibercept in the fellow eye. Patients in the wet AMD PULSAR study were allowed to be treated with 2 mg aflibercept or other anti-VEGFs in the non-study eye. The review of safety data in bilaterally treated patients with 8 mg in study and 2 mg in the fellow eye did not result in a new safety concern. As bilateral treatment with Eylea 114.3 mg/mL (8 mg dose) per eye has not been studied during the pre-authorization phase “Exposure with bilateral 8 mg aflibercept therapy” was added as Missing Information. The safety associated with 8 mg aflibercept bilateral administration will be monitored in the PSUR.

Based on the cumulative review of the proteinuria cases and the use of Eylea as displayed in PSUR#7, the Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur concluded that “proteinuria” could be removed from the important potential risk list and the topic could be monitored through routine pharmacovigilance activities.

After a cumulative review of all cases received during the period covered by PSUR#9 (from 01 DEC 2018 to 30 NOV 2019) (Procedure no.: EMEA/H/C/PSUSA/00010020/201911), the PRAC Rapporteur recommended to include the AE “retinal haemorrhage” in the SmPC Section 4.8 under “Eye disorder” and delete it as important identified risk.

In Procedure No. EMEA/H/C/002392/II/0075 the PRAC recommended to shorten the list of safety concerns by removing some identified and potential risks not associated with additional risk minimisation measures such as retinal tear/detachment, hypersensitivity and immunology, arterial thromboembolic events, venous thromboembolic events, hypertension and non-ocular haemorrhage. These safety concerns will continue to be addressed in subsequent PSURs. Furthermore, PRAC requested to have the following Missing Information topics removed from the EU RMP due to lack of additional Pharmacovigilance (PV)

activities: Use of Eylea® in patients with uncontrolled glaucoma, Concomitant use of different anti-VEGF therapies and other therapies for wet AMD, CRVO and DME (including bilateral treatment with anti- VEGFs), Long term safety beyond 2 years.

Following completion of studies VIOLET and AZURE removal of "Posology utilized in marketed use" as a missing information was requested in procedure No. EMEA-H-C-002392-II-0076.

One new safety concern was identified regarding missing information long-term safety of aflibercept in preterm infants with ROP.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Overview of data sources (clinical studies and post-marketing data)

Overview of clinical studies

Important identified and potential risks were determined considering the safety data of Eylea 40 mg/mL (0.4/2 mg dose) in the following studies:

- Pooled data of the pivotal Phase III AMD randomized controlled studies VIEW 1 and VIEW 2 (96 weeks),
- Open-label VIEW 1 extension study (VGFT-OD-0910),
- Phase III AMD randomized controlled study SIGHT (52 weeks),
- Phase IV AMD study ALTAIR (52 weeks),
- Pooled data of the Phase III CRVO randomized controlled studies GALILEO and COPERNICUS (76/100 weeks),
- Phase III BRVO randomized controlled study VIBRANT (52 weeks),
- Phase III myopic CNV randomized controlled study MYRROR (48 weeks),
- Pooled data of the pivotal Phase III DME randomized controlled studies VIVID-DME and VISTA-DME (148 weeks),
- Randomized, controlled Phase III DME study VIVID-EAST (52 weeks),
- Single-arm, open-label study Phase III DME study VIVID-JAPAN (52 weeks).
- Randomized, open-label, two-arm, controlled Phase III ROP study FIREFLEYE (24 weeks) and it´s extension study FIREFLEYE NEXT.

In addition, important identified and potential risks were determined considering the safety data of 114.3 mg/mL (8 mg dose) aflibercept in the following studies:

- Randomized, controlled Phase II wet AMD study CANDELA,
- Randomized, controlled Phase III wet AMD study PULSAR,
- Randomized, controlled Phase II/III DME study PHOTON.

Safety data per identified/potential risk derived from the Eylea 114.3 mg/mL (8 mg dose) development program is shown pooled across the indications (wet AMD/DME (pool: 44/96 weeks data for CANDELA/PULSAR/PHOTON). Pooling is considered meaningful based on similar study designs, same competitor, and an overall similar safety profile of wet AMD and DME.

The presented figures represent crude incidences from the data, regardless of the investigator's causality attribution. The study designs are outlined in the following sections.

Eylea 40 mg/mL (0.5/2 mg doses) studies in wet AMD

For AMD, pooled data (**VIEW 1 [VGFT-OD-0605] and VIEW 2 [SN 91689] studies**) from baseline through 96 weeks[5] are primarily presented. In Year 1 of the studies, patients received fixed-dose treatment with ranibizumab 0.5 mg every 4 weeks (RQ4), VEGF Trap-Eye 0.5 mg every 4 weeks (0.5Q4), VEGF Trap-Eye 2 mg every 4 weeks (2Q4), and VEGF Trap-Eye 2 mg every 8 weeks (2Q8). The original dose of Year 1 (i.e., 0.5 or 2.0 mg per injection) was maintained in Year 2 of the studies, but the treatment intervals could be extended to 12 weeks at maximum according to pre-specified re-treatment criteria (modified quarterly dosing). The safety data of the 1,824 SAF patients treated in VIEW 1 and VIEW 2 are presented by randomized treatment group at Baseline, i.e., RQ4 (N=595), VTE 0.5Q4 (N=601), VTE 2Q4 (N=613), and VTE 2Q8 (N=610).

VIEW 1 patients of any randomized treatment group who had completed the 96 weeks of the core study had the opportunity to start or continue treatment with Eylea 2 mg in the open-label, multi-dose VIEW 1 extension study (VGFT-OD-0910) conducted in order to assess the long-term safety and tolerability of Eylea. During the course of the study, patients were randomized in a 1:1:1 ratio to 3 treatment groups which differed in the packaging or sterilization techniques of Eylea 2 mg (i.e., vials, or one of the externally sterilized prefilled syringes [ethylene oxide, ETO, or hydrogen peroxide, VHP]) in order to investigate the safety profile of the different product configurations and external sterilization techniques. Eylea 2 mg was to be administered no more frequently than every 4 weeks and no less frequently than every 12 weeks (later on amended in the US to 8 weeks). A total of 323 VIEW 1 completers were enrolled in VGFT-OD-0910, 320 received study drug treatment in the extension phase with Eylea in the study eye (69 from the original RQ4 group, 87 from the original 0.5Q4 group, and 92 and 72 from the original 2Q4 and 2Q8 groups, respectively), and 281 were randomized to the different product specifications (93 to vials, 94 to ETO, and 94 to VHP). Three of the 323 subjects enrolled in the VIEW 1 extension study were last treated with Eylea 2 mg at Week 96 of the core VIEW 1 study (all 3 were randomized in the 2Q4 group) but did not receive treatment in the extension phase. These patients were nevertheless included in the safety set of the VIEW 1 extension study, as they had received Eylea at Week 96 of the VIEW 1 core study and thus were exposed to Eylea.

The mean treatment duration in VGFT-OD-0910 (excluding the core study period of 96 weeks) for all enrolled extension study patients (N=323) was 110.4 weeks. The safety data presented in this module are based on the safety events occurring during the extension period in the 323 patients (SAF) who were exposed to Eylea in the extension period (referred to as "Eylea total group"). Two additional analysis groups were defined, with

i) patients who had been treated with ranibizumab in the preceding core study period (N=69; designated as "ranibizumab group" in the tables and "former ranibizumab group" in the running text), and

[5] Patients in VIEW 2 who received their last study injection on Week 92 were to be followed up to Week 100 according to regulatory obligations. For the sake of straightforwardness, the duration of observation in both VIEW 1 and VIEW is designated as 96 weeks (although some patients in VIEW 2 were observed for up to 100 weeks).

ii) patients who had been treated with Eylea at any dose (i.e., 0.5Q4, 2Q4, or 2Q8) already during the core study period (N=254; designated as "Eylea combined group" in the tables and "former Eylea groups" in the running text).

This separation was deemed reasonable, because only the 254 patients from the original Eylea groups were on true long-term treatment with Eylea (i.e., beyond 96 weeks of treatment, for up to approximately 5 years in total). In the 320 subjects who also received treatment in the study extension period, a total of 7,215 injections were administered in the study eye from the original baseline in VIEW 1 through the end of the extension period (range: 12 to 61 injections), and the overall mean treatment duration was 48.9 ± 9.8 months (range: 23 to 64 months).

SIGHT (SN 13406) was a randomized, double-masked, photodynamic therapy-controlled Phase III study in order to evaluate the efficacy, safety, and tolerability of Eylea in Chinese subjects with wet AMD. A total of 304 patients were randomized in a 3:1 ratio to treatment with Eylea 2 mg (N=228) or control treatment with PDT (N=76). Primary efficacy assessments were performed at Week 28. Patients in the Eylea 2 mg group received the first 3 IVT injections with Eylea every 4 weeks (i.e., at Baseline, Week 4 and Week 8) and subsequently every 8 weeks until Week 48 (i.e., at Weeks 16, 24, 32, 40, and 48). At Weeks 28 and 36, sham injections were additionally required. Patients in the PDT control group received one PDT procedure at baseline and were allowed to undergo additional PDT procedures through Week 28 as indicated according to local clinical practice and the clinical judgment of the investigator. Sham injections were administered in order to maintain the blind (while patients in the Eylea group underwent a sham PDT procedure at baseline and additional sham PDT procedures as indicated according to local clinical practice and the clinical judgment of the investigator). At Week 28, after all variables for the primary efficacy endpoint had been assessed and the data recorded, subjects in the PDT group were to receive one injection with Eylea 2 mg and subsequent injections with Eylea 2 mg at Weeks 32, 36, 40, and 48. Actually, 71 out of the 76 patients randomized to the PDT control group were exposed to Eylea. Safety data are presented for the entire study period through Week 52 by randomized treatment group (N=76 and 288, respectively) and additionally in the Eylea total group that includes all study patients who were exposed to Eylea (N=299; only AEs occurring during or after the first Eylea exposure are counted in the 71 original PDT patients who received Eylea from Week 28 onwards).

ALTAIR (SN17668) was a randomized, open-label phase 4 study evaluating the efficacy and safety of repeated doses of intravitreal aflibercept with variable treatment intervals in Japanese subjects with neovascular age-related macular degeneration. Eligible subjects received an IVT injection of aflibercept at every scheduled treatment visit. After completion of treatment at Week 16, the timing of the subsequent treatment visits was determined at the previous treatment visit by the treating physician based on the criteria of the Treat and Extend regimen. Subjects who had completed the run-in phase were randomly assigned to one of the two treatment arms of the study (2-week [2W] adjustment group or 4-week [4W] adjustment group) in 1:1 ratio at Week 16. A total of 247 patients were randomized, 7 patients were treated but not randomized.

2W adjustment group (N=124): Aflibercept IVT injection at Week 0, Week 4, Week 8 and Week 16, followed by the variable treatment intervals based on the criteria of the Treat and Extend regimen.

If the study eye of a subject met the respective criteria for shortening or extension, length of either extension or shortening of the treatment interval was 2 weeks from the last interval, respectively.

4W adjustment group (N=123): Aflibercept IVT injection at Week 0, Week 4, Week 8 and Week 16, followed by the variable treatment intervals based on the criteria of the Treat and Extend regimen.

Shortening of interval: If the study eye of a subject met the criteria for shortening, the treatment interval was shortened by 2 weeks. However, if the last treatment interval of a subject had been extended by 4 weeks from the second last interval, the treatment interval was shortened by 4 weeks.

Extension: If the study eye of a subject met the criteria for extension, length of extension of the treatment interval was 4 weeks. However, when a subject had a history of receiving treatment with interval shortened by 4 weeks during this study, the length of the extension was 2 weeks.

Subjects were evaluated at Week 52 and Week 96, regardless of treatment schedule. In study eyes, only the study drug was administered while fellow eyes could receive any domestically approved treatments. If a subject was judged to need any extra treatment in the study eye either using study drug or non-study treatment, the subject terminated the study. Ophthalmic evaluations were done at every treatment and evaluation visits other than visit for safety follow-up using visual acuity test with ETDRS score, slit lamp and indirect ophthalmoscopy, and optical coherence tomography (OCT). Fundus photography (FP), FA and indocyanine green angiography (ICGA) were conducted at visit for screening, Week 52 and Week 96. In addition to these ophthalmic evaluations, general evaluation and vital sign assessment in subjects were used for safety evaluation methods. Aflibercept was administered every 4 weeks until Week 8 (Run-in phase). Subjects who completed the Run-in phase were randomly assigned to one of the two treatment arms of the study (2W adjustment group or 4W adjustment group) in 1:1 ratio at Week 16. After the IVT injection at Week 16, treatment was followed by a Treat and Extend regimen with variable treatment intervals up to Week 96 (Treatment phase). During Week 16 to Week 96, treatment interval between two injections must not be less than 8 weeks and must not be more than 16 weeks.

Eylea 114.3 mg/mL (8 mg dose) studies in wet AMD

CANDELA (VGFTe-HD-AMD-1905, SN 21086) was a randomized, single-masked, active-controlled Phase II study. The primary objectives of the study were to determine the safety of 8 mg aflibercept injection and to determine if 8 mg aflibercept provided greater intraocular pharmacodynamic effect and/or longer duration of action compared to 2 mg intravitreal aflibercept injection. The co-primary endpoints were: Safety, which was evaluated by assessment of treatment-emergent adverse events and serious adverse events through week 4 and the proportion of patients without retinal fluid in the centre subfield at week 20. A total of 106 eligible patients were randomized into 2 groups in a 1:1 ratio. One group received 2 mg aflibercept and the other 8 mg aflibercept. The latter was administered intravitreally monthly for 3 initial injections at baseline, week 4 and week 8, followed by additional doses at weeks 20 and 32. At weeks 24, 28, 36 and 40 patients were evaluated and given a dose (at their randomized dose level) if defined retreatment criteria were met. The duration of the study for a patient was approximately 44 weeks, excluding the screening period. The primary safety analysis took place at week 20, with exploratory endpoints evaluated at week 20 and week 44.

PULSAR (SN 20968) is a Phase III randomized, double-masked, active-controlled study. The primary objective was to determine if treatment with 8 mg aflibercept at intervals of 12 or 16 weeks provides non-inferior BCVA change compared to 2 mg aflibercept (administered every 8 weeks, after 3 initial monthly doses). Secondary objectives are to determine the effect of 8 mg aflibercept on other visual and anatomic outcomes (change of BCVA at week 60, proportion of patients with no intraretinal fluid and no subretinal fluid in the central subfield at week 16, proportion of patients gaining at least 15 letters in BCVA from baseline at week 48, proportion of patients achieving an ETDRS letter score of at least 69 at week 48, change in neovascularization size from baseline to week 48, change in total lesion area from baseline to week 48, proportion of patients with no intraretinal fluid and no subretinal fluid in the center subfield at week 48, change from baseline in central subfield retinal thickness at week 48). Further secondary objectives were to assess the efficacy of 8 mg versus 2 mg aflibercept of the vision-related quality of life, the safety of aflibercept, the pharmacokinetics and immunogenicity of aflibercept. The application scheme for aflibercept in the three treatment groups in the first year was:

- 2q8: 2 mg aflibercept administered every 8 weeks after 3 initial monthly doses
- HDq12: 8 mg aflibercept administered every 12 weeks after 3 initial monthly doses
- HDq16: 8 mg aflibercept administered every 16 weeks after 3 initial monthly doses

CRVO studies

In the Phase III CRVO study **COPERNICUS (VGFT-OD-0819)**, patients received either Eylea or sham (2Q4) in the first 6 months (Week 24); in the second 6 months sham patients were able to receive active treatment depending on re-treatment criteria defined in the protocol. All subjects were allowed to continue PRN treatment through Year 2 (Week 100).

In the Phase III CRVO study **GALILEO (SN 14130)**, patients were treated either with Eylea or sham up to 52 weeks. During the 52 weeks study duration, sham patients were not foreseen to be treated with Eylea but could be treated with Eylea from Week 52 to Week 76.

The pooled safety data of the 2 CRVO studies are shown for the entire study period from Baseline to Week 76/100 (the study period was 76 weeks in GALILEO and 100 weeks in COPERNICUS). Treatment groups for data presentation are based on original randomization, i.e., 142 patients randomized to sham with subsequent PRN treatment and 218 patients randomized to Eylea 2Q4 with subsequent PRN treatment. In addition, AEs in all patients from either randomization group who received at least one active injection with Eylea are summarized from the day when the first injection was administered (N=317; i.e., excluding the 43 patients of the sham-PRN group who never received Eylea, referred to as "Eylea total group").

BRVO study

VIBRANT (VGFTe RVO-1027) was a randomized, double-masked, active controlled 52-week study to evaluate the efficacy, safety, and tolerability of repeated IVT administration of Eylea compared with grid laser photocoagulation in subjects with macular edema secondary to BRVO. A total of 183 patients were randomized and exposed to study treatment (91 in the Eylea group and 92 in the laser group). The study was conducted by Regeneron Pharmaceuticals, Inc. in North America (USA, Canada) and Japan. Patients in the Eylea group received Eylea 2Q4 through (including) Week 24, then 2Q8 through Week 48. Sham IVT injections were administered every 8 weeks starting from Week 28, alternating with Eylea

injections every 8 weeks, through Week 44. The last active injection with Eylea was on Week 48. Patients in the Eylea group also received one sham laser treatment on Day 1. Rescue treatment with active laser in this group was possible, if patients had met the pre-defined criteria at Week 36. Patients randomized to the laser group received grid laser photocoagulation treatment at Day 1, and sham IVT injections every 4 weeks from Day 1 through Week 48. Rescue treatment with laser was possible from Week 12 onwards (minimum intervals of 12 weeks from previous laser treatment) in those patients who had met the pre-specified criteria. Patients in the laser arm could become eligible for rescue treatment with Eylea beginning at Week 24. In this case, they were to receive 3 initial Eylea 2 mg injections every 4 weeks, followed by injections every 8 weeks. Safety data are presented in this RMP version for the final Week 52 study data as per randomized treatment group, i.e., based on the 91 patients in the VTE 2 mg group and the 92 patients in the Laser+VTE 2 mg group (i.e., patients randomized to initial treatment with laser through Week 20 and the option for Eylea rescue therapy beginning at Week 24). In addition, the Eylea total group (N=158) includes all patients who had received Eylea at least once (i.e., in addition to patients from the Eylea treatment group, the 67 patients in the Laser+VTE 2 mg group who had received rescue treatment with Eylea beginning at Week 24). In this group, all adverse events occurring after the first Eylea injection are counted.

Myopic CNV study

In the multi-center, randomized, double-masked, sham-controlled, Phase III myopic CNV study **MYRROR (SN 5170)**, a total of 122 Asian subjects with active subfoveal or juxtafoveal CNV secondary to pathologic myopia were randomized to receive either Eylea 2 mg or sham injection. The primary efficacy endpoint (mean change in BCVA) was evaluated after 24 weeks of treatment (injections from baseline through Week 20). In this study period, subjects in the Eylea group (N=91) received an active injection at Baseline and were then assessed at regular intervals of 4 weeks for the need of a repeated injection based on pre-defined re-treatment criteria (i.e., in case of recurring or persisting CNV). If no active injection was required, these subjects received a sham-injection. In the sham group (N=31), subjects underwent the same study-related procedures, but were solely treated with sham injections.

After the primary endpoint assessment at Week 24, all patients randomized to sham who continued the study (N=25) received one mandatory injection with active Eylea and continued treatment in the same way as in the Eylea 2 mg group, i.e., active injections, when pre-specified retreatment criteria were met, or a sham injection otherwise. Patients were still monitored at monthly intervals; the last active injection could be given at Week 44, and the final study assessments were performed at Week 48.

This RMP version includes the final MYRROR study results through Week 48. Safety results of the MYRROR are presented for treatment groups as randomized (i.e., Sham+Eylea 2 mg group [N=31] *vs*. Eylea 2 mg group [N=91]) and additionally for all patients who were treated with active Eylea at least once during the study period (Eylea total group [N=116]).

Eylea 40 mg/mL (2 mg dose) DME studies

VIVID-DME (SN 91745) and **VISTA-DME (VGFT-OD-1009)** were both 3 year, randomized, double-masked, active-controlled, multi-center, Phase III studies of the efficacy and safety of repeated doses of Eylea in subjects with DME with central involvement. In VIVID-DME, a total of 404 subjects (SAF) were treated in European countries, Australia, and

Japan. In VISTA-DME, a total of 461 subjects (SAF) were treated in the US. [6] The studies had nearly identical overall study designs and are described together unless otherwise indicated.

Patients were randomized to 1 of the following 3 treatment groups: Eylea 2Q4 to Week 148, Eylea 2Q8 (after 5 initial monthly doses), with sham injections at alternating visits, to Week 148, or laser photocoagulation through Week 148 plus sham injection. Subjects in the Eylea groups received sham laser at Baseline and at visits, at which subjects met the criteria for laser re-treatment (no more often than every 12 weeks). The last administration of study treatment in all treatment groups was at Week 144.

Subjects in all groups were assessed for additional treatment (i.e., "rescue" treatment with Eylea for the laser subjects, and laser for the Eylea subjects) for inadequate responders at each visit starting at Week 24. Additional treatment was to be administered if pre-specified criteria were met.

During Year 3, subjects randomized to the laser group who did not meet the criteria for additional treatment previously were allowed to receive Eylea as needed (PRN) according to the Eylea re-treatment criteria from Week 100 through the end of the study (Week 144).

Fellow eye treatment for DME with anti-VEGF agents was allowed in both studies. In VIVID-DME, standard of care was used (including ranibizumab or bevacizumab; licensed treatment preferred). In VISTA-DME, VEGF Trap-Eye was provided and required as fellow eye treatment (although ranibizumab could be used, if VEGF Trap-Eye was unavailable due to logistical reasons).

The primary efficacy endpoint in both studies was the change in ETDRS letter score from Baseline to Week 52. In this RMP version, the final safety-related results through Week 148 are reported. The pooled DME safety results from VIVID-DME and VISTA-DME are presented with tabulated summaries using the following patient groups:

- Laser group (active control): All patients in the SAF randomized to initial treatment with laser. All treatment-emergent AEs up to study end (Week 148) are considered for the analysis.
- VTE 2Q4 group: All patients in the SAF randomized to initial treatment with 2 mg VEGF Trap-Eye every 4 weeks. All treatment-emergent AEs up to study end (Week 148) are considered for the analysis.
- VTE 2Q8 group: All patients in the SAF randomized to initial treatment with 2 mg VEGF Trap-Eye every 4 weeks until Week 16 (i.e., a total of 5 initial monthly doses) and subsequent dosing intervals of 8 weeks (2Q8). All treatment-emergent AEs up to study end (Week 148) are considered for the analysis.
- VTE total (Eylea total group): All subjects (including patients randomized to the laser group) who have received at least one active Eylea injection in the study eye by Week 144. Considered are all treatment-emergent events that started after first study eye exposure to Eylea up to Week 148.

[6] As per amendment No. 4, patients completing Visit 39 (Week 148) in VISTA-DME were allowed to receive further treatment extension with Eylea until the planned date for the last on-study patient to complete Visit 39 (NOV 2014) in order to avoid a potential treatment gap between study end and availability of commercial Eylea. However, the exposure and safety analyses in VISTA-DME are aligned with VIVID-DME and thus limited to the last core study visit (i.e., Week 148).

For the interpretation of the DME safety results based on these groups, it should be considered that:

- Patients in all randomized treatment groups were allowed to receive fellow eye treatment with Eylea or other anti-VEGF therapies (this should be particularly considered for the assessment of potential systemic adverse events),
- Patients in the laser group were allowed to receive additional treatment of the study eye with Eylea from Week 24 onwards or Eylea PRN (if-re-treatment criteria were met and no additional treatment with Eylea was previously started) in the third year of the study (actually, 243 subjects in the laser group have received at least one additional or PRN treatment with Eylea by Week 144),
- Patients in either Eylea group were allowed to receive additional treatment of the study eye with active laser from Week 24 onwards (actually, 17 subjects in the 2Q4 group and 32 subjects in the 2Q8 group have received at least one additional treatment with active laser by Week 144), and
- The group of subjects included in the VTE total group consisted of the 578 subjects who were enrolled in the Eylea groups plus the 243 subjects the laser group who had received additional (rescue) treatment with VTE in the study eye for varying amounts of time, depending upon when they met the criteria for additional treatment or PRN treatment with VTE (possible in Year 3). In these patients, TEAEs occurring at or after the first exposure to Eylea are considered.

The study design of **VIVID-EAST (SN 15161)** was very similar to the designs of the pivotal studies VIVID-DME and VISTA-DME in the first year, and was conducted in China, Hong Kong, Republic of Korea, and the Russian Federation. The primary efficacy variable was the change from baseline in BCVA in ETDRS letter score at week 52. A total of 378 SAF patients were randomized to treatment with laser photocoagulation (N=124), the Eylea 2Q4 (N=127), or Eylea 2Q8 (N=127). Laser patients were treated with laser photocoagulation at baseline and from week 12 onwards, if laser-re-treatment criteria were met. Patients in the Eylea 2Q4 group received Eylea 2 mg at monthly intervals continuously through Week 48, and patients in the Eylea 2Q8 group received Eylea 2 mg every 2 months following 5 initial injections at monthly intervals (i.e., from Baseline to including Week 16) through Week 48. As with the pivotal studies, additional treatment with Eylea in the laser group (or with laser in the Eylea groups) was permitted from Week 24 onwards in the case that pre-defined additional treatment criteria were met. The last study treatment was administered on Week 48; final study assessments were performed at Week 52. The safety data are presented by randomized treatment group, and in the Eylea total group considering all TEAEs that occurred at or after the first administration of Eylea (N=299; i.e., the 254 patients initially randomized to Eylea treatment plus 45 laser group patients who received Eylea as additional treatment during the course of the study at Week 24 at the earliest). Generally, the aforementioned considerations about the interpretation of the safety data in the pivotal DME studies do also apply to VIVID-EAST.

VIVID-JAPAN (SN 15657) was a 1-year, open-label Phase III study performed in Japan with a treatment schedule that was generally similar to the 2Q8 arm in the randomized, controlled studies, i.e., all subjects were treated (in an open-label fashion) with Eylea 2 mg every 2 months (2Q8) after 5 initial doses at monthly intervals (i.e., 2Q4 up to Week 16). Last treatment was on Week 48; the final endpoint assessments were performed at Week 52. No additional treatment of the study eye with laser was permitted. Fellow eye treatment was

allowed as per local standard of care/medical routine. Study assessments included effectiveness and safety of treatment as well as PK analyses. The safety analyses were performed without further stratification in a total of 72 subjects (one of the 73 enrolled and treated patient was excluded from the SAF because he/she withdrew consent).

Eylea 114.3 mg/mL (8 mg dose) DME studies

PHOTON (VGFTe-HD-DME-1934, SN 21091) is a randomized, double-masked, active-controlled Phase II/III study. The primary objective of this study was to determine if treatment with 8 mg aflibercept at intervals of 12 or 16 weeks provides noninferior BCVA compared to 2 mg aflibercept dosed every 8 weeks. Secondary objectives are to determine the effect of 8 mg versus 2 mg aflibercept on anatomic and other visual measures of response, to evaluate the safety, immunogenicity, and pharmacokinetics of 8 mg aflibercept. This study includes three randomization arms (1:2:1 ratio). One group receives 2 mg aflibercept every 8 weeks following 5 initial monthly doses, one group receives 8 mg aflibercept every 12 weeks following 3 initial monthly doses and the third group receives 8 mg aflibercept every 16 weeks following 3 initial monthly injections. The application scheme for aflibercept in the first study year with three treatment arms was:

- 2q8: 2 mg aflibercept every 8 weeks, following 5 initial doses
- HDq12: 8 mg aflibercept every 12 weeks, following 3 initial monthly doses
- HDq16: 8 mg aflibercept every 16 weeks, following 3 initial monthly doses

ROP studies

FIREFLEYE (SN 20090) was a Phase III, multicenter, open-label, randomized, two arm, controlled study to assess the efficacy, safety, and tolerability of IVT 0.4 mg aflibercept compared to laser photocoagulation in preterm infants with ROP. The study consisted of a screening phase followed by a baseline visit when subjects were randomized either to aflibercept or laser (ratio: 2:1), followed by a 23-week treatment period, which equals a 24 week total study duration. One or both eyes were treated based on the study eligibility criteria as assessed by the investigator. Subjects were also allowed to be retreated or administered rescue treatment (laser for the aflibercept arm; aflibercept for the laser arm). The primary efficacy endpoint was the proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment based on investigator's assessment. Key secondary efficacy endpoints addressing the primary objective were subjects with requirement for intervention with a second treatment from baseline to Week 24 and subjects with recurrence of ROP from baseline to Week 24, which were also analysed using a similar Bayesian statistical model as for the primary endpoint. A total of 118 subjects were randomized, 75 to aflibercept and 38 to the laser arm. This RMP version includes the final FIREFLEYE study results through Week 24. Safety results of the FIREFLEYE study are presented for treatment groups as randomized (i.e., Eylea 0.4 mg group [N=75] *vs*. Laser group [N=38]) and additionally for all patients who were treated with Eylea at least once during the study period (Eylea total group [N=79; i.e., the 75 patients initially randomized to Eylea treatment plus 4 laser group patients who received Eylea as rescue treatment during the course of the study].

FIREFLEYE NEXT (SN 20275) is a Phase IIIb study which follows up on ocular, neurodevelopmental and overall clinical outcomes until 5 years of age. All patients treated in the FIREFLEYE study were offered participation.

EYLEA®
(Aflibercept)
EU Risk Management Plan
Part II – Module SVII: Identified and Potential Risks

Post-marketing data

In addition to the clinical study data, the post-marketing cases for the important identified and potential risks, cumulating from market launch through cut-off date 15 SEP 2017, are provided (MedDRA version 20.0). These cases include spontaneously reported cases and cases from non-interventional studies (incl. solicited sources such patient support programs and market research programs), both medically confirmed and non-confirmed cases, and both valid and invalid cases (i.e., one case might include more than one patient).
Invalid/incomplete cases in Bayer's Global Pharmacovigilance Safety Database are defined as cases where at least one of the 4 minimal criteria is not fulfilled. These 4 minimal criteria are: i) identifiable patient, ii) identifiable reporter, iii) suspect Bayer product (in development or marketed drug/device), and iv) an adverse event. Adverse events can include reports of lack of drug effect, medication error, overdose, drug abuse, drug misuse, drug dependency, occupational exposure, pre-existing condition improved, off-label use, drug exposure *via* mother/father without adverse event and incident reports for medical devices. Reports which fulfil at least the two criteria "adverse event" and "suspect BHC medical product" according to the above definitions are recorded and fully processed in the MAH's database. These cases are marked as invalid cases in the Global Pharmacovigilance Safety Database.

Evidence sources and strength of evidence

The evidence sources for the evaluation of identified and potential risks are

- Clinical trial data:

  Wet AMD (Eylea 40 mg/mL, 0.5/2 mg doses): 96 weeks dataset of the two Phase III studies VIEW 1 and VIEW 2,

  Wet AMD (Eylea 40 mg/mL, 0.5/2 mg doses): Final dataset of the VIEW 1 extension study VGFT-OD-0910,

  Wet AMD (Eylea 40 mg/mL, 2 mg dose): 52 weeks data set of the SIGHT study,

  Wet AMD (Eylea 40 mg/mL, 2 mg dose): 52 weeks data set of the ALTAIR study,

  CRVO (Eylea 40 mg/mL, 2 mg dose): 76/100 weeks datasets of the two Phase III studies COPERNICUS and GALILEO,

  BRVO (Eylea 40 mg/mL, 2 mg dose): 52 weeks dataset of the Phase III study VIBRANT,

  Myopic CNV (Eylea 40 mg/mL, 2 mg dose): 48 weeks dataset of the Phase III study MYRROR,

  DME (Eylea 40 mg/mL, 2 mg dose): 148 weeks datasets of the two Phase III studies VIVID- and VISTA-DME,

  DME (Eylea 40 mg/mL, 2 mg dose): 52 weeks dataset of the VIVID-EAST study,

  DME (Eylea 40 mg/mL, 2 mg dose): 52 weeks dataset of the VIVID-JAPAN study,

  ROP (Eylea 40 mg/mL, 0.4 mg dose): 24 week dataset of the Phase III FIREFLEYE study and interim safety data of the extension study FIREFLEYE NEXT.

  AMD and DME (Eylea 114.3 mg/mL, 8 mg dose): Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (48 weeks), and the DME PHOTON study (48 weeks).

- Post-marketing data (pharmacovigilance database; cut-off date 15 SEP 2017).
- Background incidence/prevalence: see embedded references.

Thus, the evidence is primarily based on randomized controlled clinical trials, which are considered highly evident sources. Complementary information is provided by post-marketing surveillance.

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

SVII.3.1.1 Identified risk: Endophthalmitis (likely infectious origin)

Potential mechanisms

The intravitreal injection procedure can implant pathogens into the eye if there is a break in sterile technique. Source of pathogenic agents is in most cases the patient's conjunctival bacterial flora.

Evidence source(s) and strength of evidence

Main reason for considering endophthalmitis as an important identified risk

Inflammation of the inner structures of the eye (in particular the vitreous body, which fills the globe) may occur as a result of an infection with microorganisms, either through direct traumatic injury of the eye (exogenous infection) or through spreading of microorganisms from other areas of the body (endogenous infection). This pathogen-caused inner eye (intraocular) infection is called endophthalmitis. In cases of inflammation where no pathogens can be identified (no/negative culture growth of microorganisms observed), the condition may be characterized as "sterile endophthalmitis" or "non-infectious endophthalmitis".

Because of the risk of severe vision loss, treatment should be initiated as soon as possible, and, depending on cause and severity, may consist of topical and intravitreal application of antibiotics, corticosteroids, and surgical removal of matter and infected structures (drainage, vitrectomy). The proportion of Eylea-exposed adult patients who experienced endophthalmitis in the study eye in the clinical studies with Eylea ranged from 0% to 0.9% (VIEW 1 extension study).

Evidence sources: refer to the linked subsection.

MedDRA search terms (version 19.1 for adult clinical 2 mg studies, version 20.0 for PM data and version 23.1 for ROP studies in preterm infants; version 25.0 for 8 mg dose in wet AMD and DME):

Preferred terms included in search: Candida endophthalmitis, endophthalmitis, eye infection, eye infection bacterial, eye infection chlamydial, eye infection fungal, eye infection intraocular, eye infection staphylococcal, infectious iridocyclitis, infective iritis, infective uveitis, mycotic endophthalmitis, and necrotising retinitis.

Characterization of the risk

Frequency

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg doses) - Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

The overall 96-week incidence of endophthalmitis (likely infectious origin, hereinafter referred to simply as endophthalmitis) was 0.3% and 1.0% in the combined Eylea and in the ranibizumab group, respectively (see Table SVII.4 below).

Table SVII.4: Number of subjects with endophthalmitis in the study eye (grouped term and included preferred terms) in randomized Phase III wet AMD studies from baseline through Week 96 (Pool 1, SAF)

MedDRA 19.1	Ranibizumab		Eylea		
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
Endophthalmitis	6 (1.0)	4 (0.7)	1 (0.2)	0	5 (0.3)
Included preferred terms					
Endophthalmitis	5 (0.8)	4 (0.7)	1 (0.2)	0	5 (0.3)
Eye infection	1 (0.2)	0	0	0	0

Q4 = every 4 weeks, Q8 = every 8 weeks
Note: All reported events were considered serious (see Table 1.3/4a); the Eylea-treated patients were completely recovered by the end of the study, 4 patients in the ranibizumab group were completely recovered and one was recovered with sequelae (Table 1.3/3a).
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.1/1

The incidence of endophthalmitis in the Eylea treatment arms was very low (0.3%), which is below the incidence reported in the literature for IVT administration of VEGF inhibitors (1.0% to 1.1%; see background incidence/prevalence information).

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg doses) - VIEW 1 long-term extension study

Three patients (one in the former randomized ranibizumab group [1.4%] and 2 in the former randomized Eylea groups [0.8%] experienced endophthalmitis in the study eye during the extension study period (Table SVII.5). There were no meaningful differences compared with the frequency of endophthalmitis reported from the pivotal AMD trials through Week 96 (see preceding Table SVII.4).

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Table SVII.5: Number of subjects with endophthalmitis (likely infectious origin) in the study eye (grouped term and included preferred terms) in the Phase III VIEW 1 extension study in AMD (SAF; all subjects treated with VTE in the extension phase, treatment groups are displayed according to original randomization in VIEW 1)

MedDRA 19.1	*Ranibizumab 0.5Q4* [a] *n (%)*	*Eylea combined* [b] *n (%)*	Eylea Total [c] n (%)
Number of subjects	69	254	323
Grouped term			
Endophthalmitis	1 (1.4)	2 (0.8)	3 (0.9)
Included preferred terms			
Endophthalmitis	1 (1.4)	2 (0.8)	3 (0.9)

[a]: Patients who were randomized to treatment with ranibizumab in the VIEW 1 core study.
[b]: Patients who were randomized to treatment with Eylea (0.5Q4, 2Q4, or 2Q8) in the VIEW 1 core study.
[c]: All patients who were treated with Eylea in the extension study period. Only AEs occurring after the first active Eylea injection were counted.
Note: Events that occurred in the VIEW 1 core study are not considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.2/1

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial SIGHT (52 weeks)

No events pertaining to the group of endophthalmitis in the study eye were reported during the course of the SIGHT study.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial ALTAIR (52 weeks)

No events pertaining to the group of endophthalmitis in the study eye were reported during the course of the ALTAIR study.

CRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

One case of endophthalmitis (0.3% of Eylea-treated patients) in the study eye was reported from the pooled CRVO studies (see Table SVII.6 below). No endophthalmitis events were reported during sham treatment.

Table SVII.6: Number of subjects with endophthalmitis (likely infectious origin) in the study eye (grouped term and included preferred terms) in the Phase III CRVO studies from baseline through Week 76/100 (Pool 1, SAF)

MedDRA 19.1	Sham + PRN n (%)	VTE 2Q4 + PRN n (%)	Eylea total [a] n (%)
Number of subjects	142	218	317
Grouped term			
Endophthalmitis	0	1 (0.5)	1 (0.3)
Included preferred terms			
Endophthalmitis	0	1 (0.5)	1 (0.3)

[a]: All patients exposed to Eylea. All TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (CRVO), Table 1.3.1/1

BRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIBRANT (52 weeks)

No cases of endophthalmitis in the study eye were reported through Week 52 in the BRVO study VIBRANT.

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial MYRROR (48 weeks)

No cases of endophthalmitis were reported in the MYRROR study through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose) - Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

Three cases of endophthalmitis were reported through Week 148 (2 patients in the 2Q4 group and one patient in the 2Q8 group; see Table SVII.7).

Table SVII.7: Number of subjects with endophthalmitis in the study eye (grouped term and included preferred terms) in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Endophthalmitis	0	2 (0.7)	1 (0.3)	3 (0.4)
Included preferred terms				
Endophthalmitis	0	2 (0.7)	1 (0.3)	3 (0.4)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis - EU-RMP Pool 1 (DME), Table 1.5.1/1

DME (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIVID-EAST (52 weeks)

No events pertaining to the group of endophthalmitis in the study eye were reported in the VIVID-EAST study.

DME (Eylea 40 mg/mL, 2 mg dose) - Open-label Clinical Trial VIVID-JAPAN (52 weeks)

No cases of endophthalmitis in the study eye were reported in the VIVID-JAPAN study.

ROP (Eylea 40 mg/mL, 0.4 mg dose) - Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

No events pertaining to the group of endophthalmitis in the Eylea-exposed eye were reported in the FIREFLEYE or the FIREFLEYE NEXT study.

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose) - Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (96 weeks), and the DME PHOTON study (96 weeks):

Through week 96, two patients treated with 2 mg Eylea experienced an endophthalmitis. There were no endophthalmitis cases in 8 mg aflibercept treated patients.

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Table SVII.8: Number of subjects with endophthalmitis (likely infectious origin) in the study eye (grouped term and included preferred terms) in the Phase II CANDELA study and Phase III PULSAR study in wet AMD and in the Phase III PHOTON study in DME (SAF)

MedDRA 26.0	*2 mg* *n (%)*	*HDq12* *n (%)*	*HDq16* *n (%)*	HD Total n (%)
Number of subjects	556	716	501	1,217
Grouped term				
Endophthalmitis	2 (0.4)	0	0	0
Included preferred terms				
Endophthalmitis	2 (0.4)	0	0	0

Adverse events are sorted by alphabetical order of the MedDRA classification.
A subject is counted only once within each safety topic and preferred term.
2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
All HD: HDq12 and HDq16 combined.

Post-Marketing Data

A total of 844 cases (including 880 events) belonging to the endophthalmitis group were reported by cut-off date 15 SEP 2017 (see Table SVII.9).

An individual case review of the endophthalmitis cases was performed in order to check whether the diagnosis of endophthalmitis was substantiated by direct evidence of pathogens detected through e.g., tap culture. This review showed that in 232 of the 844 endophthalmitis cases (i.e., 27.5% based on all 844 cases or 66.9% based on the 347 cases with a documented test result) pathogen were identified. In the remaining cases, the samples were negative (115 cases), tests were performed but no outcomes provided (57 cases), or tests not reported/not performed (440 cases).

Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period until 30 SEP 2017, the reporting rate of endophthalmitis cases (N=844) was 0.05 cases per 1,000 sold vials (0.005%) and 0.36 cases per 1,000 patient years (0.036%), respectively. The incidence reported thus far during post-authorization use is within the reported incidence reported in the literature with the IVT injection of anti-VEGF agents and other drugs (see sections on incidence and prevalence).

Table SVII.9: Number of post-marketing events "endophthalmitis" by 15 SEP 2017

Group: Endophthalmitis		***844 cases***	
Grouped preferred terms[a]:	**Non-serious**	**Serious**	**All**
Endophthalmitis	2	752	754
Eye infection	27	57	84
Eye infection bacterial	1	15	16
Eye infection staphylococcal	0	13	13
Eye infection intraocular	0	8	8
Necrotising retinitis	0	4	4
Infective uveitis	0	1	1
Total number of events	**30**	**850**	**880**

Source: Global Pharmacovigilance Safety Database

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Table SVII.9: Number of post-marketing events "endophthalmitis" by 15 SEP 2017

Group: Endophthalmitis		*844 cases*	
Grouped preferred terms[a]:	**Non-serious**	**Serious**	**All**

[a]: MedDRA Version 20.0. Figures are event-based, i.e., more than one preferred term event per reported case is possible. Included are both medically confirmed and non-medically confirmed events.

Seriousness/outcomes

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) - Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

All PT "endophthalmitis" events reported in the 5 patients treated with ranibizumab and in the 5 patients treated with Eylea were considered serious, while the single event "eye infection" in the ranibizumab group was non-serious.

All events of endophthalmitis in the Eylea-treated patients were completely resolved by the end of the study. In the ranibizumab group, 5 cases were resolved and one case (PT: "Endophthalmitis") was resolved with sequelae.

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg doses) - VIEW 1 long-term extension study

All 3 reported endophthalmitis cases were considered serious. Two cases were resolved, in the remaining case (one patient [0.4%] in the former randomized Eylea groups; N=254) the outcome was "recovered/resolved with sequelae".

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial SIGHT (52 weeks)

No events pertaining to the group of endophthalmitis in the study eye were reported during the course of the SIGHT study.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial ALTAIR (52 weeks)

No events pertaining to the group of endophthalmitis in the study eye were reported during the course of the ALTAIR study.

CRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

The only reported event of endophthalmitis (in the Eylea 2Q4+PRN group) was considered serious and the patient completely recovered by the end of the study.

BRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIBRANT (52 weeks)

No cases of endophthalmitis in the study eye were reported through Week 52 in the BRVO study VIBRANT.

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial MYRROR (48 weeks)

No endophthalmitis cases were reported in the MYRROR study through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose) - Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

All 3 endophthalmitis events (occurring in 3 patients through Week 148) were regarded as serious; all 3 patients recovered (see Table SVII.10).

Table SVII.10: Number of subjects with endophthalmitis in the study eye by outcome in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Endophthalmitis	0	2 (0.7)	1 (0.3)	3 (0.4)
Outcome				
Recovered/resolved	0	2 (0.7)	1 (0.3)	3 (0.4)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis - EU-RMP Pool 1 (DME), Table 1.5.1/3

DME (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIVID-EAST (52 weeks)

No events pertaining to the group of endophthalmitis in the study eye were reported in VIVID-EAST.

DME (Eylea 40 mg/mL, 2 mg dose) - Open-label Clinical Trial VIVID-JAPAN (52 weeks)

No cases of endophthalmitis in the study eye were reported in the VIVID-JAPAN study.

ROP (Eylea 40 mg/mL, 0.4 mg dose) - Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

No events pertaining to the group of endophthalmitis in the Eylea-exposed eye were reported in the FIREFLEYE or the FIREFLEYE NEXT study.

AMD and DME (Eylea 114.3 mg/mL, 8 mg dose) - Pooled data sets from the AMD CANDELA study (44 weeks), the AMD PULSAR study (96weeks), and the DME PHOTON study (96 weeks):

Out of 2 events of endophthalmitis in patients treated with 2 mg Eylea, one event was reported as serious.

One patient with endophthalmitis recovered and one did not recover at the time of the reporting.

No cases of endophthalmitis in the study eye were reported through Week 96 in the 8 mg arms of the CANDELA, PULSAR or PHOTON studies.

Post-marketing Data

Almost all of the 844 reported endophthalmitis events were serious (850 events; see previous post-marketing table on endophthalmitis).

Reported outcomes were "recovered/resolved" in 206 events, "recovering/resolving" in 99 events, "recovered/resolved with sequelae" in 28 events, and "not recovered/not resolved" in 105 events (missing or unknown outcomes in the remaining 442 events).

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Severity and nature of risk

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) - Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

Four out of the 5 endophthalmitis cases were classified as severe in the combined Eylea group (see Table SVII.11 below), and 4 out of 6 cases were severe in the ranibizumab group.

Out of 5 cases with reported endophthalmitis in Eylea-treated patients, 3 were identified as culture-positive endophthalmitis.

Table SVII.11: Number of subjects with grouped term endophthalmitis by maximum severity in randomized Phase III wet AMD studies from baseline through Week 96 (Pool 1, SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
Endophthalmitis	6 (1.0)	4 (0.7)	1 (0.2)	0	5 (0.3)
Maximum severity					
Mild	1 (0.2)	0	0	0	0
Moderate	1 (0.2)	0	1 (0.2)	0	1 (<0.1)
Severe	4 (0.7)	4 (0.7)	0	0	4 (0.2)

Q4 = every 4 weeks, Q8 = every 8 weeks
Note: At each level of subject summarization (Safety topic/PT), a subject is classified according to the maximum intensity, if the subject reported one or more events. At each level of subject summarization, a subject is counted only once.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.1/2

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg doses) - VIEW 1 long-term extension study

The severity of the 3 reported endophthalmitis cases (all were serious) was moderate in 2 cases and severe in the remaining case (one patient [0.4%] in the former Eylea groups; N=254).

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial SIGHT (52 weeks)

No events pertaining to the group of endophthalmitis in the study eye were reported during the course of the SIGHT study.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial ALTAIR (52 weeks)

No events pertaining to the group of endophthalmitis in the study eye were reported during the course of the ALTAIR study.

CRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

Endophthalmitis was reported in one subject in the Eylea group and was classified as of "severe" nature. The vitreous culture was positive for coagulase-negative Staphylococcus.

BRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIBRANT (52 weeks)

No cases of endophthalmitis in the study eye were reported through Week 52 in the BRVO study VIBRANT.

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial MYRROR (48 weeks)

No endophthalmitis cases were reported in the MYRROR study through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose) - Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

Two of the 3 reported endophthalmitis events were severe and one event was moderate (see Table SVII.12).

Table SVII.12: Number of subjects with endophthalmitis in the study eye by maximum severity in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Endophthalmitis	0	2 (0.7)	1 (0.3)	3 (0.4)
Maximum severity				
Mild	0	0	0	0
Moderate	0	1 (0.3)	0	1 (0.1)
Severe	0	1 (0.3)	1 (0.3)	2 (0.2)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis - EU-RMP Pool 1 (DME), Table 1.5.1/2

DME (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIVID-EAST (52 weeks)

No events pertaining to the group of endophthalmitis in the study eye were reported in VIVID-EAST.

DME (Eylea 40 mg/mL, 2 mg dose) - Open-label Clinical Trial VIVID-JAPAN (52 weeks)

No cases of endophthalmitis in the study eye were reported in the VIVID-JAPAN study.

ROP (Eylea 40 mg/mL, 0.4 mg dose) - Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

No events pertaining to the group of endophthalmitis in the Eylea-exposed eye were reported in of the FIREFLEYE or the FIREFLEYE NEXT study.

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose) - Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (96 weeks), and the DME PHOTON study (96 weeks):

Of the 2 endophthalmitis cases reported, one event was mild and the second was reported as severe in nature.

Post-marketing Data

Event severity is not routinely recorded on the post-marketing case report forms.

Background incidence/prevalence

Incidence of endophthalmitis after IVT anti-VEGF injections

A systematic review of 278 publications was published in 2011 to identify adverse events associated with anti-VEGF injections. Endophthalmitis was reported with incidence rates below or equal to 0.04 (95% CI: 0.02–0.08), 0.05 (95% CI: 0.03–0.10) per 100 injections for ranibizumab and bevacizumab[7], respectively (199). Another systematic review identified 5 controlled trials that evaluated the efficacy or safety of administration of anti-VEGF agents compared with conventional therapy in 383 preterm infants with ROP; no cases of endophthalmitis were reported (200).

Reports from wet AMD studies

The Phase III trials for ranibizumab (Lucentis®) – ranibizumab for wet AMD (MARINA) and ranibizumab versus verteporfin for wet AMD (ANCHOR) – demonstrated a low rate of endophthalmitis. At 96 sites in the US, of the 716 patients enrolled in the 2-year MARINA study, 478 patients received 0.3 mg or 0.5 mg ranibizumab and 238 patients received sham injection. The endophthalmitis rate was 1.0% (5 of 477 patients), or, alternatively, a rate per injection of 0.05% (5 of 10,443 total injections) (201). Similar incidence rates of 1.1% (3 of 277 patients or of 0.05% per injection (3 of 5,921) were reported in the ANCHOR study where 5,921 injections of ranibizumab were administered. In this study 423 patients were randomized 1:1:1 in 83 international sites to verteporfin photodynamic therapy (PDT) plus monthly sham intraocular injection (n=143) or to sham verteporfin PDT plus monthly IVT ranibizumab (0.3 mg or 0.5 mg) injection (140 each in the 2 ranibizumab groups) (28). A review of safety data performed by Mitchell *et al.* reported that 3,252 patients in ANCHOR, MARINA, PIER, and SAILOR study received over 28,500 IVT ranibizumab injections. The overall rate of endophthalmitis in these studies was 0.05% per injection (41).

In the United Kingdom (UK) a 12-month prospective, double masked, multicentre, randomized controlled trial (ABC Trial) enrolled 131 patients (mean age 81) from 3 centres with wet AMD to receive IVT bevacizumab (1.25 mg, 3 loading injections at 6-week intervals followed by further treatment if required at 6-week intervals, n=65) or the standard treatment available at the start of the trial (PDT with verteporfin for predominantly classic type wet AMD, n=16, or IVT pegaptanib, n=38, or sham treatment, n=12, for occult or minimally classic type AMD). There were no cases of endophthalmitis (202).

In 2 Phase III multicentre trials (VISION I and II trial), which evaluated 2 years of therapy with pegaptanib sodium injection for wet AMD, a total of 7,545 IVT pegaptanib sodium injections and 2,557 sham injections were administered. A total of 1,190 patients were randomized to receive 0.3 mg, 1 mg, or 3 mg of pegaptanib sodium by intravitreous injection or sham injection every 6 weeks. The reported endophthalmitis incidence per injection was 0.16%. Most of the cases (75%) resulted from violations of the injection preparation protocol and the rate dropped to 0.07% in the 2nd year after reinforced aseptic procedure (203). During the 3rd year of the VISION trials 422 patients received 3,227 pegaptanib injections and the endophthalmitis rate per injection was 0.06% (204).

[7] Please note that bevacizumab is not approved for treatment of ocular disorders and no formal PV system has been established in ophthalmological use. Thus, published data on bevacizumab might be limited.

No cases of endophthalmitis or intraocular inflammation were reported in the randomized controlled wet AMD-PCV studies LAPTOP over 12 months (205) or EVEREST study over 6 months (206).

Reports from CRVO studies

A Phase III, prospective, randomized, sham controlled, double masked, multicenter clinical trial of ranibizumab injection in patients with macular edema secondary to CRVO (CRUISE Study) enrolled 392 patients to monthly IVT injections of 0.3 mg or 0.5 mg of ranibizumab (n=262) or sham (n=130) injections. The 6-month primary end point results reported no events of endophthalmitis (207), as did the 12-month primary end point results (208). The total number of injections was not published.

A dose-ranging, double-masked, multicenter, sham controlled, Phase II trial included 98 subjects with CRVO of ≤6 months duration and assigned them (1:1:1) to receive pegaptanib sodium (0.3 mg and 1 mg, n=33 each) or sham (n=32) injections every 6 weeks for 24 weeks. This study was conducted in practitioners' offices and clinics in Australia, France, Germany, Israel, Spain, and the US. No subject developed endophthalmitis (209). The total number of injections has not been published.

Reports from BRVO studies

The Pan American Collaborative Retina Study Group conducted an interventional, retrospective, comparative multicenter study with 63 patients (63 eyes) with macular edema secondary to BRVO that were treated primarily with IVT bevacizumab. Patients were recruited at 8 institutions in Costa Rica, Venezuela, Puerto Rico, Brazil, Peru, Mexico, Argentina, and Spain and had at least 24 months of follow-up. During the 24 months, there were 138 injections recorded in the 1.25 mg dose group and 109 injections in the 2.5 mg dose group. There were no cases of endophthalmitis (210).

In a randomized controlled trial (211) of intravitreal 0.5-ranibizumab injection versus standard grid lase for macular edema following BRVO, there were no events of endophthalmitis, during the 12-month-long treatment period. A total of 36 patients with vision loss in one eye attributable to macular edema were included in the study.

In a randomized controlled clinical trial (BRAVO) to the assess 12-month efficacy and safety of intraocular injections of 0.3 mg (n=134) or 0.5 mg ranibizumab (n=131) *vs.* sham treatment (n=132) in patients with macular edema secondary to BRVO (n=397) (159), one case of endophthalmitis was reported in the ranibizumab 0.5 mg treatment group (n=131, incidence 0.8%). The follow-up study (HORIZON) on ranibizumab for macular edema due to RVO reported no cases of endophthalmitis (in BRVO or CRVO) during the 12 months follow-up period (212).

The SCORE-BRVO study compared the efficacy and safety of 1 mg and 4 mg doses of intravitreal triamcinolone with standard of care (grid photocoagulation in eyes without dense macular haemorrhage and deferral of photocoagulation until haemorrhage cleared in eyes with dense macular haemorrhage) for eyes with vision loss associated with macular edema secondary to BRVO. A total of 411 participants were randomized and followed for 12 months. Through month 12, there were neither reports of infectious endophthalmitis in the standard of care group (n=137) nor in the 1 mg triamcinolone group (n=136), but one case (incidence =0.7%) was reported in the 4 mg triamcinolone group (n=138) 3 days after the third injection (155).

In Russo *et al.* 2009 (bevacizumab compared with macular laser grid photocoagulation in a randomized, controlled study, in 30 consecutive eyes with macular edema in BRVO), no cases of endophthalmitis were reported (213).

Parodi *et al*. (214), compared the effectiveness of sub-threshold grid laser treatment (SGLT) with infrared micropulse diode laser alone (n=13) or in combination with intravitreal triamcinolone injection (n=11) in BRVO patients. No endophthalmitis events were observed during the 12 months follow-up study period.

In Donati *et al*. (215) evaluating in an open-label study the long-term efficacy of intravitreal bevacizumab (IVB) versus combined IVB and macular grid laser photocoagulation for the treatment of macular edema secondary to BRVO, no sterile or infectious endophthalmitis events were observed.

Reports from myopic CNV studies

In a case series, records of 35 consecutive patients who were treated with intravitreal injection of bevacizumab from 18 DEC 2008, through 20 JAN 2009 were reviewed. Of the 35 patients, five developed severe intraocular inflammation. There were three patients with myopic CNV, of whom one developed the condition. It was a 49-year-old woman who received one intravitreal bevacizumab injection and symptoms were identified four days after the injection. All five cases were culture negative (216).

In a Japanese study, bevacizumab was aliquotted into smaller doses (5 mg/0.2 mL x 20). Intravitreal bevacizumab (1.25 mg/0.05 mL) was injected into nineteen eyes of fifteen patients, two of whom (three eyes) had myopic CNV. Ocular inflammation occurred in 14 eyes of 11 patients, including both of the myopic CNV patients (male age 61, female age 82 in both eyes). Both myopic CNV patients required pars planta vitrectomy (217).

No cases of endophthalmitis were reported through Month 12 in the myopic CNV study RADIANCE (218).

Reports from DME studies

A 12-month, randomized, sham controlled, double-masked, multicenter Phase II study of safety and efficacy of ranibizumab in DME with centre involvement (RESOLVE Study) enrolled 151 subjects to either ranibizumab (0.3 mg, n=51; or 0.5 mg, n =51) or sham treatment (n=49). Two cases of endophthalmitis were reported in the ranibizumab treatment group (2%) and no cases in the sham group (162). The total number of injections was not published.

Two 24 month, parallel, methodologically identical, randomized, multi-center, double-masked, sham injection-controlled, Phase III studies (RISE and RIDE) to evaluate efficacy and safety of intravitreal ranibizumab in DME. In RISE, 377 patients were randomized to either ranibizumab (n=125 to 0.3mg and n=125 to 0.5mg) or sham injection (n=127) out of which one case of endophthalmitis occurred in the 0.3mg ranibizumab treatment group (0.8%) and no case of endophthalmitis in 0.5mg ranibizumab and sham group. Total number of injections in sham group was 2,461, 0.3mg ranibizumab was 2,682 and 0.5mg ranibizumab was 2,628 in RISE study. In RIDE, 382 patients were randomized to either ranibizumab (n=125 to 0.3 mg and n=127 to 0.5 mg) or sham injection (n=130) out of which one case of endophthalmitis occurred in the 0.3mg ranibizumab treatment group (0.8%), two cases of endophthalmitis in 0.5mg ranibizumab treatment group (1.6%) and no

cases in sham group. Total number of injections in the sham group was 2,647, 0.3 mg ranibizumab was 2,560 and 0.5 mg ranibizumab was 2714 in the RIDE study (161).

A 12-month, randomized, laser controlled, double masked, multicenter Phase III study to demonstrate superiority of ranibizumab 0.5 mg monotherapy or combined with laser over laser alone in DME patients (RESTORE study). 345 patients were randomized to ranibizumab + sham laser (n = 116), ranibizumab + laser (n = 118), or sham injections + laser (n = 111). No cases of endophthalmitis were reported in any treatment arms. Total number of injections in ranibizumab + sham laser was 800, ranibizumab + laser was 816 and sham injections + laser were 802 (163).

A 6-month phase 2 randomized, multicenter clinical trial of intravitreal bevacizumab for DME conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net) at 36 clinical sites in the US reported one case of injection-related endophthalmitis out of 185 injections. In this study 121 patients (109 eligible for analysis) have been randomly assigned to one of five groups: focal photocoagulation at baseline (n=19), intravitreal injection of 1.25 mg bevacizumab at baseline and 6 weeks (n=22), intravitreal injection of 2.5 mg bevacizumab at baseline and 6 weeks (n=24), intravitreal injection of 1.25 mg bevacizumab at baseline and sham injection at 6 weeks (n=22), or intravitreal injection of 1.25 mg bevacizumab at baseline and 6 weeks with photocoagulation at 3 weeks (n=22) (219).

In a Phase II randomized double-masked, sham controlled, trial of pegaptanib sodium for DME one case of endophthalmitis out of a total of 652 injections in 128 pegaptanib subjects occurred. The occurrence rate of endophthalmitis was 0.15% per injection or 0.8% per subject assigned to a pegaptanib group. No subject developed endophthalmitis in the sham group (n=42). This 36-week trial enrolled 172 patients with DME from 39 US sites (220).

Reports from ROP studies

Among 143 premature infants included in a prospective, controlled, randomized, stratified, multicenter trial to assess intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3+ (i.e., stage 3 with plus disease) ROP (BEAT-ROP), there were no cases of endophthalmitis reported (221). Two other clinical trials evaluated 79 and 50 infants with ROP randomized to bevacizumab/ranibizumab or in to laser therapy reported no cases of endophthalmitis (222, 223).

Impact on individual patient

Endophthalmitis can cause permanent loss of vision if it is not diagnosed at an early stage and appropriately treated. Vision loss as such constitutes a substantial burden for the involved subject.

Risk factors and risk groups

Improper aseptic technique increases the risk of intraocular inflammation.

Preventability

The risk of intraocular inflammation, especially if caused by pathogens, cannot be completely excluded, but may be minimized. In the scope of intravitreal injections of drugs for treatment of wet AMD, CRVO, BRVO, myopic CNV, DME (by which pathogens might be inadvertently carried into the inner eye) or ROP, it is absolutely crucial to work under strict

aseptic and sterile conditions. Thus, only experienced and appropriately trained ophthalmologists should be charged with the injections.

Moreover, patients should report to their doctors any signs or symptoms of intraocular inflammation (e.g., visual acuity decreased, pain, photophobia, or redness) in order to enable the treating physician to introduce appropriate countermeasures in due time.

Impact on the risk-benefit balance of the product

An educational program is performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks. The effectiveness of this program was verified with a post authorization safety study (SN 16526). Furthermore, a specific questionnaire is used to gain more knowledge about this risk.

This important identified risk does not have an impact on the positive risk-benefit balance of Eylea.

Public health impact

Severe intraocular infection/inflammation such as endophthalmitis can cause permanent loss of vision, if it is not rapidly diagnosed and appropriately treated. This condition is likely to impact the ability to work and to increase the dependency on caregivers.

SVII.3.1.2 Identified risk: Intraocular inflammation

Potential mechanism

In a certain percentage the intraocular inflammation is culture negative. However, there are some difficulties in the definition and diagnosis of "sterile" endophthalmitis or intraocular inflammation. Many infectious cases are not diagnosed as such as no tap is performed, or tap is performed, but culture is false negative. Vice versa, true sterile cases may be false positive in culture (e.g., due to contamination of the medium) and thus misdiagnosed as infectious.

The aetiology of sterile intraocular inflammations, independently of the administered drug, remains uncertain, and a multifactorial origin has been proposed. Needle trauma *per se* might cause a certain inflammatory reaction. Inflammation secondary both to IVT triamcinolone acetonide and to IVT bevacizumab (or other anti-VEGF agents) that manifest with acute and painless vision loss is usually interpreted as being primarily toxic and sterile. In these patients, visual acuity improves progressively as the intraocular inflammation reduces without any specific treatment. However, since there remains a substantial uncertainty on origin, the complication is often treated - on top of steroids and NSAID - like an acute (infectious) endophthalmitis with antibiotics because of the devastating visual prognosis of this intraocular infection in the absence of antibiotic therapy (224).

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Evidence source(s) and strength of evidence

Main reason for considering intraocular inflammation as an important identified risk:

Next to endophthalmitis/intraocular inflammations with an infectious origin, there are inflammations where no pathogens can be identified (either no culture performed or negative culture growth), the condition may be characterized as "sterile" inflammatory condition.

The cause of a sterile inflammation, independently of the administered drug, remains uncertain, and a multifactorial origin cannot be discarded. An intraocular inflammation generally constitutes a serious condition, which may lead to generalized eye inflammation and risk of blindness. Treatment should be initialized as soon as possible, and, depending on cause and severity, may consist of topical and intravitreal application of antibiotics, corticosteroids, and surgical removal of matter and infected structures (drainage, vitrectomy). The proportion of Eylea-exposed adult patients who experienced intraocular inflammation in the study eye in the clinical studies with Eylea ranged from 0% to 2.6% (VIEW 1 & 2 AMD 2 mg studies).

Evidence sources: refer to the linked subsection.

MedDRA search terms (version 19.1 for adult clinical 2 mg dose studies, version 20.0 for PM data and version 23.1 for ROP studies in preterm infants, version 25.0 for 8 mg dose in wet AMD and DME):

Preferred terms included in search: Anterior chamber cell, anterior chamber fibrin, anterior chamber flare, anterior chamber inflammation, aqueous fibrin, autoimmune uveitis, chorioretinitis, choroiditis, cyclitis, eye inflammation, hypopyon, iridocyclitis, iritis, non-infectious endophthalmitis, non-infective chorioretinitis, pseudoendophthalmitis, uveitis, vitreal cells, vitreous fibrin, and vitritis.

Characterization of the risk

Frequency

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg doses) - Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

The incidence of intraocular inflammation in the study eye over 96 weeks in the AMD studies VIEW 1 and VIEW 2 was 2.6% and 3.9% in the combined Eylea and in the ranibizumab group, respectively (see Table SVII.13 below).

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Table SVII.13: Number of subjects with intraocular inflammation in the study eye (grouped term and included preferred terms) in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	0.5 mg Q4 n (%)	0.5 mg Q4 n (%)	2.0 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	601	613	610	1,824
Grouped term					
Intraocular inflammation	23 (3.9)	18 (3.0)	15 (2.4)	13 (2.1)	46 (2.5)
Included preferred terms					
Anterior chamber cell	7 (1.2)	9 (1.5)	8 (1.3)	5 (0.8)	22 (1.2)
Anterior chamber flare	9 (1.5)	4 (0.7)	3 (0.5)	5 (0.8)	12 (0.7)
Aqueous fibrin	1 (0.2)	0	0	0	0
Eye inflammation	0	0	1 (0.2)	0	1 (<0.1)
Hypopyon	2 (0.3)	1 (0.2)	0	0	1 (<0.1)
Iridocyclitis	0	2 (0.3)	1 (0.2)	1 (0.2)	4 (0.2)
Iritis	3 (0.5)	1 (0.2)	0	1 (0.2)	2 (0.1)
Non-infectious endophthalmitis	1 (0.2)	0	0	0	0
Uveitis	0	1 (0.2)	1 (0.2)	0	2 (0.1)
Vitreal cells	9 (1.5)	9 (1.5)	6 (1.0)	4 (0.7)	19 (1.0)
Vitritis	1 (0.2)	1 (0.2)	1 (0.2)	0	2 (0.1)

Q4 = every 4 weeks, Q8 = every 8 weeks
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.1/1

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) - VIEW 1 long-term extension study

Intraocular inflammation in the study eye during the extension period occurred in 6 patients in the former randomized Eylea groups (2.4% or 1.9% based on all treated patients; Table SVII.14). There were no meaningful differences compared with the frequency of intraocular inflammation reported from the pivotal AMD trials through Week 96 (see preceding Table SVII.13).

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Table SVII.14: Number of subjects with intraocular inflammation in the study eye (grouped term and included preferred terms) in the Phase III VIEW 1 extension study in AMD (SAF; all subjects treated with VTE in the extension phase, treatment groups are displayed according to original randomization in VIEW 1)

MedDRA 19.1	*Ranibizumab 0.5Q4* [a] *n (%)*	*Eylea combined* [b] *n (%)*	Eylea Total [c] n (%)
Number of subjects	69	254	323
Grouped term			
Intraocular inflammation	0	6 (2.4)	6 (1.9)
Included preferred terms			
Anterior chamber cell	0	3 (1.2)	3 (0.9)
Anterior chamber flare	0	1 (0.4)	1 (0.3)
Chorioretinitis	0	1 (0.4)	1 (0.3)
Eye inflammation	0	1 (0.4)	1 (0.3)
Iridocyclitis	0	1 (0.4)	1 (0.3)
Uveitis	0	1 (0.4)	1 (0.3)
Vitreal cells	0	2 (0.8)	2 (0.6)
Vitritis	0	1 (0.4)	1 (0.3)

a: Patients who were randomized to treatment with ranibizumab in the VIEW 1 core study.
b: Patients who were randomized to treatment with Eylea (0.5Q4, 2Q4, or 2Q8) in the VIEW 1 core study.
c: All patients who were treated with Eylea in the extension study period. Only AEs occurring after the first active Eylea injection were counted.
Note: Events that occurred in the VIEW 1 core study are not considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.2/1

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial SIGHT (52 weeks)

Cases of intraocular inflammation were infrequent in the SIGHT study, since only one patient in the Eylea 2Q8 group with "vitreal cells" was reported (0.3% of all patients exposed to Eylea; see Table SVII.15).

Table SVII.15: Number of subjects with intraocular inflammation in the study eye (grouped term and included preferred terms) in the Phase III AMD study SIGHT from baseline through Week 52 (SAF)

MedDRA 19.1	PDT + VTE 2mg [a] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	76	228	299
Grouped term			
Intraocular inflammation	0	1 (0.4)	1 (0.3)
Included preferred terms			
Vitreal cells	0	1 (0.4)	1 (0.3)

a: PDT + sham injections until Wk. 24, afterwards VTE 2 mg at Wks. 28, 32, 36, 40, and 48.
b: First 3 injections with VTE 2Q4, followed by VTE 2Q8 until Wk. 48 (sham PDT until Wk. 24).
c: All patients exposed to Eylea. Only TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.3/1

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial ALTAIR (52 weeks)

No events pertaining to the group of intraocular inflammations (excluding likely infectious origin) in the study eye were reported during the course of the ALTAIR study.

CRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

A total of 7 patients (5 [1.6%] of them on treatment with Eylea) experienced at least one event of IOI in the pooled CRVO studies (see Table SVII.16 below). In view of the small absolute number of events, no meaningful differences were observed between the 2 randomized treatment groups.

Table SVII.16: Number of subjects with intraocular inflammation in the study eye (grouped term and included preferred terms) in the Phase III CRVO studies from baseline through Week 76/100 (SAF)

MedDRA 19.1	Sham + PRN n (%)	VTE 2Q4 + PRN n (%)	Eylea total [a] n (%)
Number of subjects	142	218	317
Grouped term			
Intraocular inflammation	4 (2.8)	3 (1.4)	5 (1.6)
Included preferred terms			
Iridocyclitis	0	1 (0.5)	1 (0.3)
Iritis	3 (2.1)	0	1 (0.3)
Vitreal cells	1 (0.7)	2 (0.9)	3 (0.9)

[a]: All patients exposed to Eylea. All TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (CRVO), Table 1.3.1/1

BRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIBRANT (52 weeks)

One patient experienced intraocular inflammation events in the Phase III study VIBRANT through Week 52: Two events (preferred term: "vitreal cells") occurred in this patient in the Laser+VTE 2 mg group (1.1%; N=92), who was also included in the Eylea total group (0.6%; N=158). The 2 events were mild, non-serious, and resolved.

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial MYRROR (48 weeks)

There was only one patient with intraocular inflammation reported in the MYRROR study through Week 48. This patient was treated in the Eylea 2 mg group (1.1% [N=91] or 0.9% related to N=116 [Eylea total group]). The underlying event (PT: Anterior chamber cell) was non-serious, had a mild severity, and was resolved.

DME (Eylea 40 mg/mL, 2 mg dose) - Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

The proportion of patients with IOI in the 2 randomized Phase III DME studies up to Week 148 was 1.0% in the laser group and 2.4% in the Eylea total group (see Table SVII.17 below).

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Table SVII.17: Number of subjects with intraocular inflammation in the study eye (grouped term and included preferred terms) in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser[a] n (%)	VTE 2Q4[b] n (%)	VTE 2Q8[b] n (%)	VTE total[c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Intraocular inflammation	3 (1.0)	13 (4.5)	7 (2.4)	20 (2.4)
Included preferred terms				
Anterior chamber cell	0	3 (1.0)	1 (0.3)	4 (0.5)
Anterior chamber flare	1 (0.3)	1 (0.3)	2 (0.7)	3 (0.4)
Anterior chamber inflammation	0	2 (0.7)	3 (1.0)	5 (0.6)
Eye inflammation	0	3 (1.0)	1 (0.3)	4 (0.5)
Hypopyon	0	0	1 (0.3)	1 (0.1)
Iridocyclitis	0	2 (0.7)	1 (0.3)	3 (0.4)
Iritis	1 (0.3)	1 (0.3)	0	1 (0.1)
Uveitis	0	1 (0.3)	1 (0.3)	2 (0.2)
Vitreal cells	1 (0.3)	1 (0.3)	2 (0.7)	3 (0.4)
Vitritis	0	0	1 (0.3)	1 (0.1)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis - EU-RMP Pool 1 (DME), Table 1.5.1/1

DME (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIVID-EAST (52 weeks)

No events pertaining to the group of other intraocular inflammation in the study eye were reported in the VIVID-EAST study.

DME (Eylea 40 mg/mL, 2 mg dose) - Open-label Clinical Trial VIVID-JAPAN (52 weeks)

In the open-label study VIVID-Japan, one patient was reported to have experienced one intraocular inflammation event (non-serious, mild, and resolved "iritis").

ROP (Eylea 40 mg/mL, 0.4 mg dose) - Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

No events pertaining to the group of intraocular inflammation in the Eylea-exposed eye were reported in the FIREFLEYE or the FIREFLEYE NEXT study.

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose) - Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (96 weeks), and the DME PHOTON study (96 weeks):

A total of 16 patients (1.3%) on treatment with Eylea 114.3 mg/mL (8 mg dose) experienced at least one event of IOI in the pooled 8 mg studies (wet AMD and DME, see Table SVII.18 below). No meaningful differences were observed between the 2 mg dose and 8 mg dose treatment groups.

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Table SVII.18: Number of subjects with intraocular inflammation in the study eye (grouped term and included preferred terms) in the Phase II CANDELA study and Phase III PULSAR study in wet AMD and in the Phase III PHOTON study in DME (SAF)

MedDRA 25.0	*2 mg* *n (%)*	*HDq12* *n (%)*	*HDq16* *n (%)*	HD Total n (%)
Number of subjects	556	716	501	1,217
Grouped term Intraocular inflammation	8 (1.4%)	12 (1.7%)	4 (0.8%)	16 (1.3%)
Included preferred terms				
Anterior chamber cell	1 (0.2%)	2 (0.3%)	0	2 (0.2%)
Chorioretinitis	0	1 (0.1%)	0	1 (<0.1%)
Eye inflammation	1 (0.2%)	0	0	0
Hypopyon	1 (0.2%)	0	0	0
Iridocyclitis	2 (0.4%)	0	4 (0.8%)	4 (0.3%)
Iritis	0	3 (0.4%)	0	3 (0.2%)
Uveitis	2 (0.4%)	2 (0.3%)	0	2 (0.2%)
Vitreal cells	2 (0.4%)	2 (0.3%)	0	2 (0.2%)
Vitritis	0	2 (0.3%)	0	2 (0.2%)
Anterior chamber cell	1 (0.2%)	2 (0.3%)	0	2 (0.2%)

2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
HD total: HDq12 and HDq16 combined.
Source: Integrated Analysis – Pool 1, 96 weeks analysis, AMD 8 mg (w44/96) + DME 8 mg (w96); Table 3.1/17

Post-Marketing Data

A total of 1,047 cases (including 1,277 events) with IOI terms were reported in the post-marketing environment until 15 SEP 2017 (see following Table SVII.19). The most commonly reported preferred term events (>100 events) were “eye inflammation” (299 events), “non-infectious endophthalmitis” (295 events), “uveitis” (177 events), and “vitritis” (176 events).

Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period until 30 SEP 2017, the reporting rate of IOI cases (N = 1,047) was 0.07 cases per 1,000 sold vials (0.007%) and 0.45 cases per 1,000 patient years (0.045%), respectively. The incidence reported thus far during post-authorization use is within the

reported incidence reported in the literature with the IVT injection of anti-VEGF agents and other drugs (see subsequent sections on background incidence and prevalence).

Table SVII.19: Number of post-marketing events"intraocular inflammation" by 15 SEP 2017

Group: Intraocular inflammation	***1,047 cases***		
Grouped preferred terms[a]:	**Non-serious**	**Serious**	**All**
Eye inflammation	212	87	299
Non-infectious endophthalmitis	5	290	295
Uveitis	2	175	177
Vitritis	20	156	176
Hypopyon	61	25	86
Iritis	38	16	54
Anterior chamber cell	36	7	43
Anterior chamber inflammation	8	35	43
Iridocyclitis	5	37	42
Pseudoendophthalmitis	0	18	18
Vitreal cells	14	4	18
Chorioretinitis	0	11	11
Anterior chamber flare	6	1	7
Anterior chamber fibrin	3	1	4
Vitreous fibrin	1	1	2
Aqueous fibrin	0	1	1
Cyclitis	0	1	1
Total number of events	**411**	**866**	**1,277**

Source: Global Pharmacovigilance Safety Database
[a]: MedDRA Version 20.0. Figures are event-based, i.e., more than one preferred term event per reported case is possible. Included are both medically confirmed and non-medically confirmed events.

Seriousness/outcomes

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg doses) - Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

Serious IOIs were reported in one patient in the ranibizumab group (resolved non-infectious endophthalmitis; 0.2%) and in one patient in the Eylea 2Q8 group (resolved iridocyclitis; <0.1% of all Eylea-treated patients).

Event outcomes are described in the following Table SVII.20. In 38 patients (2.1%) in the Eylea total group the events were resolved, while 7 patients (0.4%) experienced events that were not resolved (one patient with anterior chamber cell, one patient with anterior chamber flare, 4 patients with vitreal cells, and one patient with vitritis).

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Table SVII.20: Number of subjects with intraocular inflammation in the study eye by outcome in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	0.5 mg Q4 n (%)	0.5 mg Q4 n (%)	2.0 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	601	613	610	1,824
Grouped term					
Intraocular inflammation	23 (3.9)	18 (3.0)	15 (2.4)	13 (2.1)	46 (2.5)
Outcome					
Recovered/resolved	14 (2.4)	14 (2.3)	11 (1.8)	13 (2.1)	38 (2.1)
Recovering/resolving	1 (0.2)	0	1 (0.2)	0	1 (<0.1)
Unknown	2 (0.3)	0	0	0	0
Not recovered/resolved	6 (1.0)	4 (0.7)	3 (0.5)	0	7 (0.4)

Q4 = every 4 weeks, Q8 = every 8 weeks
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.1/4

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) - VIEW 1 long-term extension study

None of the reported intraocular inflammation events were regarded as serious.

One event (PT: vitreal cells) remained unresolved, while the other events were reported to be resolved (see Table SVII.21).

Table SVII.21: Number of subjects with intraocular inflammation in the study eye by outcome in the Phase III VIEW 1 extension study in AMD (SAF; all subjects treated with VTE in the extension phase, treatment groups are displayed according to original randomization in VIEW 1)

MedDRA 19.1	*Ranibizumab 0.5Q4* [a] *n (%)*	*Eylea combined* [b] *n (%)*	Eylea Total [c] n (%)
Number of subjects	69	254	323
Grouped term			
Intraocular inflammation	0	6 (2.4)	6 (1.9)
Outcome			
Recovered/resolved	0	5 (2.0)	5 (1.5)
Not recovered/resolved	0	1 (0.4)	1 (0.3)

[a]: Patients who were randomized to treatment with ranibizumab in the VIEW 1 core study.
[b]: Patients who were randomized to treatment with Eylea (0.5Q4, 2Q4, or 2Q8) in the VIEW 1 core study.
[c]: All patients who were treated with Eylea in the extension study period. Only AEs occurring after the first active Eylea injection were counted.
Note: Events that occurred in the VIEW 1 core study are not considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.2/4

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial SIGHT (52 weeks)

The only reported event of intraocular inflammation in the SIGHT study ("vitreal cells" in one patient in the Eylea 2Q8 group) was non-serious and resolved.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial ALTAIR (52 weeks)

No events pertaining to the group of intraocular inflammations (excluding likely infectious origin) in the study eye were reported during the course of the ALTAIR study.

CRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

None of the reported IOI events were considered serious. All patients with reports (4 [2.8%] in the Sham+PRN group and 3 [1.4%] in the Eylea 2Q4+PRN group) recovered from their other ocular inflammation events.

BRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIBRANT (52 weeks)

Two IOI events (preferred term: "vitreal cells") occurred in one patient in the Laser+VTE 2 mg group (1.1%; N=92), who was also included in the Eylea total group (0.6%; N=158). Both events were mild, non-serious, and resolved.

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial MYRROR (48 weeks)

There was only one patient with intraocular inflammation reported in the MYRROR study through Week 48. This patient was treated in the Eylea 2 mg group (1.1% [N=91] or 0.9% related to N=116 [Eylea total group]). The underlying event (PT: Anterior chamber cell) was non-serious, had a mild severity, and was resolved.

DME (Eylea 40 mg/mL, 2 mg dose) - Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

None of the reported intraocular inflammation events in the DME studies up to Week 148 were rated as serious. Event outcomes are provided in the Table SVII.22. In 3 patients, the IOI remained unresolved (see following table; "anterior chamber flare" in one patient in the laser group, "vitreal cells" in another patient in the laser group, and "uveitis" in one patient in the 2Q8 group).

Table SVII.22: Number of subjects with intraocular inflammation in the study eye by outcome in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Intraocular inflammation	3 (1.0)	13 (4.5)	7 (2.4)	20 (2.4)
Outcome				
Recovered / resolved	1 (0.3)	13 (4.5)	6 (2.1)	19 (2.3)
Not recovered / not resolved	2 (0.7)	0	1 (0.3)	1 (0.1)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis - EU-RMP Pool 1 (DME), Table 1.5.1/3

DME (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIVID-EAST (52 weeks)

No events pertaining to the group of other intraocular inflammation in the study eye were reported in the VIVID-EAST study.

DME (Eylea 40 mg/mL, 2 mg dose) - Open-label Clinical Trial VIVID-JAPAN (52 weeks)

In the open-label study VIVID-JAPAN, one patient was reported to have experienced an intraocular inflammation event (non-serious, mild, and resolved "iritis").

ROP (Eylea 40 mg/mL, 0.4 mg dose) - Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

No events pertaining to the group of intraocular inflammation in the Eylea-exposed eye were reported in the FIREFLEYE or the FIREFLEYE NEXT study.

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose) - Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (96 weeks), and the DME PHOTON study (96 weeks):

There were no serious intraocular inflammations reported.

Event outcomes are provided in Table SVII.23. In 7 out of 8 patients in the 2 mg dose treatment group and 11 out of 16 patients in the 8 mg treatment group outcome were reported as “recovered/recovering”. Events in 4 patients treated with 8 mg aflibercept had not resolved at time of the report. No meaningful differences were seen between the 2 mg and the 8 mg dose treatment groups regarding the outcome.

Table SVII.23: Number of subjects with intraocular inflammation in the study eye by outcome in the Phase II CANDELA study and Phase III PULSAR study in wet AMD, and in the Phase III PHOTON study in DME (SAF)

MedDRA 25.0	***2 mg*** ***n (%)***	***HDq12*** ***n (%)***	***HDq16*** ***n (%)***	**HD Total** **n (%)**
Number of subjects	556	716	501	1,217
Grouped term Intraocular inflammation	8 (1.4%)	12 (1.7%)	4 (0.8%)	16 (1.3%)
Outcome				
Recovered/resolved	7 (1.3%)	8 (1.1%)	2 (0.4%)	10 (0.8%)
Recovering/resolving	0	1 (0.1%)	0	1 (<0.1%)
Unknown	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)
Not recovered/not resolved	0	3 (0.4%)	1 (0.2%)	4 (0.3%)

2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
HD total: HDq12 and HDq16 combined.
Source: Integrated Analysis – Pool 1, 96 weeks analysis, AMD 8 mg (w44/96) + DME 8 mg (w96); Table 3.1/57

Post-marketing Data

A total of 866 of the 1,277 reported IOI events were regarded as serious (see previous post-marketing table on IOI events).

Reported outcomes were "recovered/resolved" in 520 events, "recovering/resolving" in 129 events, "recovered/resolved with sequelae" in 7 events, and "not recovered/not resolved" in 100 events (missing or unknown outcomes in the remaining 521 events).

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Severity and nature of risk

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) - Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

Most of the reported events in the ranibizumab group and the Eylea total group had a maximum intensity assessed as "mild" (Table SVII.24). No severe IOIs were reported in the Eylea groups; the 2 severe events reported in 2 patients in the ranibizumab group were hypopyon and non-infectious endophthalmitis.

Table SVII.24: Number of subjects with intraocular inflammation in the study eye by maximum severity in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	0.5 mg Q4 n (%)	0.5 mg Q4 n (%)	2.0 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	601	613	610	1,824
Grouped term					
Intraocular inflammation	23 (3.9)	18 (3.0)	15 (2.4)	13 (2.1)	46 (2.5)
Maximum severity					
Mild	17 (2.9)	17 (2.8)	14 (2.3)	11 (1.8)	42 (2.3)
Moderate	4 (0.7)	1 (0.2)	1 (0.2)	2 (0.3)	4 (0.2)
Severe	2 (0.3)	0	0	0	0

Q4 = every 4 weeks, Q8 = every 8 weeks
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.1/2

Wet AMD (Eylea 40 mg/mL, 0,5/2 mg dose) - VIEW 1 long-term extension study

None of the intraocular inflammation events occurring during the VIEW 1 extension period were assessed as severe (see Table SVII.25).

Table SVII.25: Number of subjects with intraocular inflammation in the study eye by maximum severity in the Phase III VIEW 1 extension study in AMD (SAF; all subjects treated with VTE in the extension phase, treatment groups are displayed according to original randomization in VIEW 1)

MedDRA 19.1	*Ranibizumab 0.5Q4* [a] *n (%)*	*Eylea combined* [b] *n (%)*	Eylea Total [c] n (%)
Number of subjects	69	254	323
Grouped term			
Intraocular inflammation	0	6 (2.4)	6 (1.9)
Maximum severity			
Mild	0	2 (0.8)	2 (0.6)
Moderate	0	4 (1.6)	4 (1.2)
Severe	0	0	0

[a]: Patients who were randomized to treatment with ranibizumab in the VIEW 1 core study.
[b]: Patients who were randomized to treatment with Eylea (0.5Q4, 2Q4, or 2Q8) in the VIEW 1 core study.
[c]: All patients who were treated with Eylea in the extension study period. Only AEs occurring after the first active Eylea injection were counted.
Note: Events that occurred in the VIEW 1 core study are not considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.2/2

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial SIGHT (52 weeks)

The only reported event of intraocular inflammation in the SIGHT study (non-serious and resolved "vitreal cells" in one patient in the Eylea 2Q8 group) had a mild intensity.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial ALTAIR (52 weeks)

No events pertaining to the group of intraocular inflammations (excluding likely infectious origin) in the study eye were reported during the course of the ALTAIR study.

CRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

All IOI events were regarded as "mild" in the CRVO studies.

BRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIBRANT (52 weeks)

Two IOI events (preferred term: "vitreal cells") occurred in one patient in the Laser+VTE 2 mg group (1.1%; N=92), who was also included in the Eylea total group (0.6%; N=158). Both events were mild, non-serious, and resolved.

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial MYRROR (48 weeks)

There was only one patient with intraocular inflammation reported in the MYRROR study through Week 48. This patient was treated in the Eylea 2 mg group (1.1% [N=91] or 0.9% related to N=116 [Eylea total group]). The underlying event (PT: Anterior chamber cell) was non-serious, had a mild severity, and was resolved.

DME (Eylea 40 mg/mL, 2 mg dose) - Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

One event in one patient in the 2Q8 group (non-serious, resolved hypopyon) was regarded as severe.

Table SVII.26: Number of subjects with intraocular inflammation in the study eye by maximum severity in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Intraocular inflammation	3 (1.0)	13 (4.5)	7 (2.4)	20 (2.4)
Maximum severity				
Mild	3 (1.0)	10 (3.4)	5 (1.7)	15 (1.8)
Moderate	0	3 (1.0)	1 (0.3)	4 (0.5)
Severe	0	0	1 (0.3)	1 (0.1)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148. Please see also Section 3.1.6 for a more detailed description of the scheduled treatment regimens in each randomization group, including additional / PRN treatment in the study eye, and fellow eye treatment.
Table Source: Integrated Analysis - EU-RMP Pool 1 (DME), Table 1.5.1/2

DME (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIVID-EAST (52 weeks)

No events pertaining to the group of other intraocular inflammation in the study eye were reported in the VIVID-EAST study.

DME (Eylea 40 mg/mL, 2 mg dose) - Open-label Clinical Trial VIVID-JAPAN (52 weeks)

In open-label study VIVID-JAPAN, one patient was reported to have experienced an intraocular inflammation event (non-serious, mild, and resolved "iritis").

ROP (Eylea 40 mg/mL, 0.4 mg dose) - Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

No events pertaining to the group of intraocular inflammation in the Eylea-exposed eye were reported in the FIREFLEYE or the FIREFLEYE NEXT study.

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose) - Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (96 weeks), and the DME PHOTON study (96 weeks):

None of the intraocular inflammation events occurring during the 96-weeks 8 mg dose studies was of “severe” intensity (see Table SVII.27). In the 2 mg dose treatment group, 7 out of 8 patients had mild events. In the 8 mg dose treatment group, 12 patients had mild and 4 patients had moderate events.

Table SVII.27: Number of subjects with intraocular inflammation in the study eye by maximum intensity in the Phase II CANDELA study and Phase III PULSAR study in wet AMD, and in the Phase III PHOTON study in DME (SAF)

MedDRA 25.0	*2 mg* *n (%)*	*HDq12* *n (%)*	*HDq16* *n (%)*	HD Total n (%)
Number of subjects	556	716	501	1,217
Grouped term				
Intraocular inflammation	8 (1.4%)	12 (1.7%)	4 (0.8%)	16 (1.3%)
uMaximum intensity				
Mild	7 (1.3%)	9 (1.3%)	3 (0.6%)	12 (1.0%)
Moderate	1 (0.2%)	3 (0.4%)	1 (0.2%)	4 (0.3%)

2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
HD total: HDq12 and HDq16 combined.
Source: Integrated Analysis – Pool 1, 48 weeks analysis, AMD 8 mg (w44/96) + DME 8 mg (w96); Table 3.1/30

Post-marketing Data

Event severity is not routinely recorded on the post-marketing case report forms.

Background incidence/prevalence

Post-injection, sterile intraocular inflammation is a known risk following intravitreal injections of anti-VEGFs and for other intravitreally applied drugs.[8]

[8] Please consider methodological limitations described in the subsequent section "potential mechanisms".

Incidence rates reported in the literature can vary from 0.02% to 0.3% and have been reported to often occur in clusters. In the largest retrospective case series reported to date, Moshfeghi *et al*. described 12 cases (11 patients) out of 60,322 anti-VEGF injections (bevacizumab n=7; ranibizumab n=5) that developed post-injection inflammation (0.02% per injection) (225). Day *et al*. conducted a retrospective, longitudinal case-control study using the Medicare 5% claims database. Based on an evaluation of 40,903 intravitreal injections of anti-VEGF agents in wet AMD, an endophthalmitis rate of 0.09% (37 cases) and a uveitis rate of 0.11% (45 cases) were reported (226). Chong *et al*. reported 44 cases of sterile inflammation after intravitreal injection of bevacizumab (0.27% of 16,166 injections). Seventeen inflammatory reactions were clustered around specific dates, which suggests a possible relation to drug preparation, though a specific cause remains unclear (227).

In Ness *et al*., a cluster of 10 cases of "toxic vitritis" developed after intravitreal injection of bevacizumab - 6 patients were culture-negative and the remaining 4 were not cultured. The authors attributed these cases to a toxic reaction from the syringe brand used. No further cases occurred after changing to another brand of syringe (228).

Roth *et al*. described a cluster of 7 patients out of 104 who developed culture negative endophthalmitis, following triamcinolone injection for macula oedema. All 7 cases experienced painless, but severe inflammation within 2 days of intravitreal injection (229).

Reports from wet AMD, CRVO, BRVO, myopic CNV, DME, and ROP studies

Please see the remarks for previous risk "endophthalmitis".

Impact on individual patient

Severe intraocular infection/inflammation can cause permanent loss of vision, if it is not diagnosed at an early stage and appropriately treated. Vision loss as such constitutes a substantial burden for the involved subject.

Risk factors and risk groups

Improper aseptic technique increases the risk of intraocular inflammation.

Preventability

Measures other than aseptic injection techniques to prevent infectious reactions are not known to minimize the risk of IOI. It is crucial to work under strict aseptic and sterile conditions.

Thus, only experienced and appropriately trained ophthalmologists should be charged with the injection procedure.

Moreover, patients should report to their doctors any signs or symptoms of intraocular inflammation (e.g., visual acuity decreased, pain, photophobia, or redness) as soon as possible in order to enable the treating physician to introduce appropriate countermeasures in due time.

Impact on risk-benefit balance of the product

An educational program is performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks. The effectiveness of this program was verified with a post authorization safety study (SN 16526). Furthermore, a specific questionnaire is used to gain more knowledge about this risk.

This important identified risk does not have an impact on the positive risk-benefit balance of Eylea.

Public health impact

Severe intraocular infection/inflammation can cause permanent loss of vision, if it is not rapidly diagnosed and appropriately treated. This condition is likely to impact the ability to work and to increase the dependency on caregivers.

SVII.3.1.3 Identified risk: Transient intraocular pressure increase

Introductory note:

The subsequent analyses are based on the frequency of adverse events coded to the MedDRA preferred terms "intraocular pressure increased" or "ocular hypertension". Inherently, the combined term "intraocular pressure (IOP) increase" does not include information about the duration/persistence of the events. Therefore, the outcome of the adverse events should also be taken into consideration in order to evaluate the occurrence of transient (i.e., "resolved") events of increased intraocular pressure.

Potential mechanisms

Transient IOP increase is attributed to an increase in vitreous volume (volume effect).

Evidence source(s) and strength of evidence

Main reason for considering transient intraocular pressure increase as an important identified risk:

Due to the filling of the eye-ball with liquids (i.e., aqueous and vitreous humour), there is an inherent pressure in the eye, which is measured in the same unit as the blood pressure is (i.e., in millimetre Mercury; mmHg). Normal pressure in the inner eye is approximately 10-21 mmHg. Elevated eye pressure is a major risk factor for a condition called "glaucoma", which is characterized by a loss of nerve fibres in the optic nerve with the subsequent risk of blindness. However, many different factors may be responsible for the development of glaucoma, and increased intraocular pressure is not a mandatory prerequisite for the development of glaucoma (e.g., the condition of normal-tension glaucoma is well-known). In the scope of intravitreal injections, it is easily comprehensible that the volume load caused by the application of the drug, which is dissolved in a certain amount of injection liquid, will lead to a transient increase of intraocular pressure at least until the surplus fluid will have been resorbed from the inner eye.

The proportion of Eylea-exposed adult patients who experienced an increase in intraocular pressure in the study eye in the clinical studies with Eylea ranged from 2.8% (VIVID-JAPAN DME study) to 13.6% (CRVO studies GALILEO & COPERNICUS).

Evidence sources: refer to the linked subsection.

MedDRA search terms (version 19.1 for adult 2 mg clinical studies, version 20.0 for PM data and version 23.1 for ROP studies in preterm infants, version 25.0 for 8 mg dose in wet AMD and DME):

Preferred terms included in search: Intraocular pressure increased, ocular hypertension.

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Characterization of the risk

Frequency

Wet AMD (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

AEs of increased IOP in the study eye occurred in 66 patients (11.1%) who were treated with ranibizumab, compared to 142 patients (7.8%) in the combined group of patients treated with Eylea during the 96 weeks treatment period in the VIEW 1 and VIEW 2 studies (see Table SVII.28).

Table SVII.28: Number of subjects with increased intraocular pressure in the study eye (grouped term and included preferred terms) in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
IOP increase	66 (11.1)	50 (8.2)	41 (6.8)	51 (8.4)	142 (7.8)
Included preferred terms					
IOP increased	64 (10.8)	48 (7.8)	37 (6.2)	47 (7.7)	132 (7.2)
Ocular hypertension	4 (0.7)	3 (0.5)	5 (0.8)	4 (0.7)	12 (0.7)

IOP=Intraocular pressure, Q4 = every 4 weeks, Q8 = every 8 weeks
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.1/1

Wet AMD (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - VIEW 1 long-term extension study

In total 16 patients (all in the former Eylea groups [6.3%]) experienced an adverse event related to increased intraocular pressure (Table SVII.29). There were no meaningful differences compared with the frequency of IOP increase reported from the pivotal AMD trials through Week 96 (see preceding Table SVII.28).

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Table SVII.29: Number of subjects with increased intraocular pressure in the study eye (grouped term and included preferred terms) in the Phase III VIEW 1 extension study in AMD (SAF; all subjects treated with VTE in the extension phase, treatment groups are displayed according to original randomization in VIEW 1)

MedDRA 19.1	*Ranibizumab 0.5Q4* [a] *n (%)*	*Eylea combined* [b] *n (%)*	Eylea Total [c] n (%)
Number of subjects	69	254	323
Grouped term			
IOP increase	0	16 (6.3)	16 (5.0)
Included preferred terms	0		
IOP increased	0	12 (4.7)	12 (3.7)
Ocular hypertension	0	4 (1.6)	4 (1.2)

[a]: Patients who were randomized to treatment with ranibizumab in the VIEW 1 core study.
[b]: Patients who were randomized to treatment with Eylea (0.5Q4, 2Q4, or 2Q8) in the VIEW 1 core study.
[c]: All patients who were treated with Eylea in the extension study period. Only AEs occurring after the first active Eylea injection were counted.
Note: Events that occurred in the VIEW 1 core study are not considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.2/1

Wet AMD (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Clinical Trial SIGHT (52 weeks)

IOP increase in the study eye was reported in 2 patients (2.6%) in the PDT+VTE 2 mg group *vs*. 15 patients (6.6%) in the VTE 2Q8 group (17 patients [5.7%] in the Eylea total group; see Table SVII.30). Thus, all reported cases of IOP increase occurred on treatment with Eylea.

Table SVII.30: Number of subjects with increased intraocular pressure in the study eye (grouped term and included preferred terms) in the Phase III AMD study SIGHT from baseline through Week 52 (SAF)

MedDRA 19.1	PDT + VTE 2mg [a] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	76	228	299
Grouped term			
IOP increase	2 (2.6)	15 (6.6)	17 (5.7)
Included preferred terms			
Intraocular pressure increased	1 (1.3)	12 (5.3)	13 (4.3)
Ocular hypertension	1 (1.3)	4 (1.8)	5 (1.7)

[a]: PDT + sham injections until Wk. 24, afterwards VTE 2 mg at Wks. 28, 32, 36, 40, and 48.
[b]: First 3 injections with VTE 2Q4, followed by VTE 2Q8 until Wk. 48 (sham PDT until Wk. 24).
[c]: All patients exposed to Eylea. Only TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.3/1

Wet AMD (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Clinical Trial ALTAIR (52 weeks)

No events pertaining to the group of intraocular pressure increase in the study eye were reported during the course of the ALTAIR study.

CRVO (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

A total of 43 subjects (13.6%) experienced at least one adverse event of increased intraocular pressure in the study eye from baseline through Week 76/100 on treatment with Eylea (see Table SVII.31). No meaningful differences were observed between the 2 randomized treatment groups.

Table SVII.31: Number of subjects with increased intraocular pressure in the study eye (grouped term and included preferred terms) in the Phase III CRVO studies from baseline through Week 76/100 (SAF)

MedDRA 19.1	Sham + PRN n (%)	VTE 2Q4 + PRN n (%)	Eylea total [a] n (%)
Number of subjects	142	218	317
Grouped term			
IOP increase	19 (13.4)	34 (5.6)	43 (13.6)
Included preferred terms			
IOP increased	17 (12.0)	32 (14.7)	41 (12.9)
Ocular hypertension	2 (1.4)	4 (1.8)	4 (1.3)

IOP=Intraocular pressure
[a]: All patients exposed to Eylea. All TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (CRVO), Table 1.3.1/1

BRVO (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Clinical Trial VIBRANT (52 weeks)

Four patients (4.4%) in the VTE 2 mg group and one patient (1.1%) in the Laser+VTE 2 mg group experienced at least one event of IOP increase through Week 52 in the VIBRANT study. This small difference was regarded as not clinically meaningful. The incidence in the Eylea total group was 3.2% (see Table SVII.32).

Table SVII.32: Number of subjects with increased intraocular pressure in the study eye (grouped term and included preferred terms) in the Phase III BRVO study from baseline through Week 52 (SAF)

MedDRA 19.1	Laser+VTE 2 mg n (%)	VTE 2 mg n (%)	Eylea total [a] n (%)
Number of subjects	92	91	158
Grouped term			
IOP increase	1 (1.1)	4 (4.4)	5 (3.2)
Included preferred terms			
IOP increased	1 (1.1)	4 (4.4)	5 (3.2)

IOP=Intraocular pressure
[a]: All patients exposed to Eylea. All TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (BRVO), Table 1.4.1/1

Myopic CNV (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Clinical Trial MYRROR (48 weeks)

No adverse events of increased intraocular pressure in the study eye were reported in the period from baseline through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

The incidence of the adverse events related to "intraocular pressure increased" in the study eye through Week 148 was 8.0% of patients in the laser group, 18.2% of patients in the Eylea 2Q4 group, and 10.8% of patients in the Eylea 2Q8 group (Table SVII.33). Thus, the incidence was numerically slightly higher in the Eylea groups compared to the laser group, which is consistent with the procedure-related effects of IVT Eylea administration. Among all patients who had received Eylea at least once (Eylea total group), the frequency of the AEs related to "intraocular pressure increased" after treatment initiation with Eylea was 12.2%.

Table SVII.33: Number of subjects with increased intraocular pressure in the study eye (grouped term and included preferred terms) in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Increased IOP	23 (8.0)	53 (18.2)	31 (10.8)	100 (12.2)
Included preferred terms				
IOP increased	20 (7.0)	42 (14.4)	27 (9.4)	82 (10.0)
Ocular hypertension	4 (1.4)	13 (4.5)	4 (1.4)	20 (2.4)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis - EU-RMP Pool 1 (DME), Table 1.5.1/1

DME (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Clinical Trial VIVID-EAST (52 weeks)

Increased IOP occurred in 4 patients (3.2%) in the laser group, 4 patients (3.1%) in the 2Q4 group, and 6 patients (4.7%) in the 2Q8 group (11 patients [3.7%] in the Eylea total group; Table SVII.34).

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Table SVII.34: Number of subjects with increased intraocular pressure in the study eye (grouped term and included preferred terms) in the Phase III DME study VIVID-EAST from baseline through Week 52 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	N=124	N=127	N=127	N=299
Grouped term				
Increased IOP	4 (3.2)	4 (3.1)	6 (4.7)	11 (3.7)
Included preferred terms				
IOP increased	4 (3.2)	4 (3.1)	4 (3.1)	9 (3.0)
Ocular hypertension	0	0	3 (2.4)	3 (1.0)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=45 exposed to Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 52.
Table Source: Integrated Analysis - EU-RMP Pool 1 (DME), Table 1.5.3/1

DME (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Open-label Clinical Trial VIVID-JAPAN (52 weeks)

In the open-label Phase III study VIVID-JAPAN, a total of 2 subjects (2.8% of the 72 SAF subjects) experienced at least one treatment-emergent adverse event of "intraocular pressure increased" in the study eye through Week 52.

ROP (Eylea 40 mg/mL, 0.4 mg dose, injection volume: 10 µL) - Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

In the open-label Phase III study FIREFLEYE, a total of 3 subjects (3.8% of the 79 SAF subjects; no case reported in the FIREFLEYE NEXT study) experienced at least one treatment-emergent adverse event of "intraocular pressure increased" (see Table SVII.35).

Table SVII.35: Number of subjects with increased intraocular pressure in the study eye (grouped term and included preferred terms) in the Phase III FIREFLEYE study (SAF)

MedDRA 23.1	Laser n (%)	VTE 0.4 mg n (%)	VTE total[a] n (%)
Number of subjects	38	75	79
Grouped term			
IOP increased	0	3 (4.0)	3 (3.8)
Included preferred terms			
IOP increased	0	3 (4.0)	3 (3.8)

IOP=Intraocular pressure
[a]: VTE total includes all subjects who received VTE 0.4 mg including subjects randomized to laser and receiving VTE 0.4 mg as rescue treatment. All non-ocular adverse events after first VTE treatment in any eye and all ocular adverse events after first VTE treatment in the eye where the event occurred are considered.
Table Source: Integrated Analysis - EU-RMP ROP submission Pool 1 (ROP 20090), Table 1.2/1

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose, injection volume: 70 µL) - Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (96 weeks), and the DME PHOTON study (96 weeks): A total of 44 subjects (3.6%) experienced at least one adverse event of increased intraocular pressure in the study eye from

baseline through Week 96 on treatment with the aflibercept 8 mg dose (see Table SVII.36). For comparison, in the 2 mg dose treatment group 20 patients (3.6%) experienced at least one increased IOP event. No meaningful differences were observed between the 2 mg dose and the 8 mg dose treatment groups.

Table SVII.36: Number of subjects with increased intraocular pressure in the study eye (grouped term and included preferred terms) in the Phase II CANDELA study and Phase III PULSAR study in wet AMD and in the Phase III PHOTON study in DME (SAF)

MedDRA 25.0	*2 mg* *n (%)*	*HDq12* *n (%)*	*HDq16* *n (%)*	HD Total n (%)
Number of subjects	556	716	501	1,217
Grouped term Intraocular pressure increased	20 (3.6%)	28 (3.9%)	16 (3.2%)	44 (3.6%)
Included preferred terms				
Intraocular pressure increased	17 (3.1%)	21 (2.9%)	13 (2.6%)	34 (2.8%)
Ocular hypertension	3 (0.5%)	8 (1.1%)	4 (0.8%)	12 (1.0%)

2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
HD total: HDq12 and HDq16 combined.
Source: Integrated Analysis – Pool 1, 96 weeks analysis, AMD 8 mg (w44/96) + DME 8 mg (w96); Table 3.1/3

Post-marketing Data

By 15 SEP 2017, a total of 250 cases with 260 events pertaining to the grouping "increased ocular pressure" were reported in the pharmacovigilance database (Table SVII.37).

Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period until 30 SEP 2017, the reporting rate of cases associated with IOP increase (N=250) was 0.02 cases per 1,000 sold vials (0.002%) and 0.11 cases per 1,000 patient years (0.011%), respectively.

Table SVII.37: Number of post-marketing events of increased intraocular pressure by 15 SEP 2017

Group: IOP increase	***250 cases***		
Grouped preferred terms [a]:	**Non-serious**	**Serious**	**All**
Intraocular pressure increased	143	95	238
Ocular hypertension	11	11	22
Total number of events	**154**	**106**	**260**

Source: Global Pharmacovigilance Safety Database
[a]: MedDRA Version 20.0. Figures are event-based, i.e., more than one preferred term event per reported case is possible. Included are both medically confirmed and non-medically confirmed events.

Seriousness/outcomes

Wet AMD (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

There were few serious cases of the AE IOP increase; thus, the frequency was low and very similar across all treatment groups (0.2% in the combined Eylea group; Table SVII.38).

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Table SVII.38: Number of subjects with serious increased intraocular pressure in the study eye (grouped term and included preferred terms) in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
IOP increase	1 (0.2)	0	1 (0.2)	2 (0.3)	3 (0.2)
Included preferred terms					
IOP increased	1 (0.2)	0	1 (0.2)	2 (0.3)	3 (0.2)

IOP=Intraocular pressure, Q4 = every 4 weeks, Q8 = every 8 weeks
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.1/4

In the vast majority of patients across all treatment groups, the reported IOP increase was only transient and was resolved (Table SVII.39).

Table SVII.39: Number of subjects with increased intraocular pressure in the study eye by outcome in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
IOP increase	66 (11.1)	50 (8.2)	41 (6.8)	51 (8.4)	142 (7.8)
Outcome					
Recovered/resolved	52 (8.7)	44 (7.2)	37 (6.2)	43 (7.0)	124 (6.8)
Recovering/resolving	3 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)
Unknown	3 (0.5)	1 (0.2)	0	0	1 (<0.1)
Not recovered / not resolved	8 (1.3)	4 (0.7)	3 (0.5)	7 (1.1)	14 (0.8)

IOP=Intraocular pressure, Q4 = every 4 weeks, Q8 = every 8 weeks
Note: For each subject, only the adverse event with the worst outcome is counted within each safety topic class and overall.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.1/3

Wet AMD (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - VIEW 1 long-term extension study

One event in one patient was serious (0.4% of patients in the former Eylea groups [N = 254]; PT: intraocular pressure increased). This event was also regarded as severe; the event outcome was "recovered/resolved".

Overall, most of the events (in 12 patients) were resolved, while in 4 patients the events remained unresolved (Table SVII.40).

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Table SVII.40: Number of subjects with increased intraocular pressure in the study eye by outcome in the Phase III VIEW 1 extension study in AMD (SAF; all subjects treated with VTE in the extension phase, treatment groups are displayed according to original randomization in VIEW 1)

MedDRA 19.1	*Ranibizumab 0.5Q4* [a] *n (%)*	*Eylea combined* [b] *n (%)*	Eylea Total [c] n (%)
Number of subjects	69	254	323
Grouped term			
IOP increase	0	16 (6.3)	16 (5.0)
Outcome			
Recovered/resolved	0	12 (4.7)	12 (3.7)
Not recovered/resolved	0	4 (1.6)	4 (1.2)

[a]: Patients who were randomized to treatment with ranibizumab in the VIEW 1 core study.
[b]: Patients who were randomized to treatment with Eylea (0.5Q4, 2Q4, or 2Q8) in the VIEW 1 core study.
[c]: All patients who were treated with Eylea in the extension study period. Only AEs occurring after the first active Eylea injection were counted.
Note: Events that occurred in the VIEW 1 core study are not considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.2/3

Wet AMD (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Clinical Trial SIGHT (52 weeks)

All reported cases of increased IOP in the study eye (see preceding frequency table) were non-serious (and mild), and all 17 involved patients recovered.

Wet AMD (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Clinical Trial ALTAIR (52 weeks)

No events pertaining to the group of intraocular pressure increase in the study eye were reported during the course of the ALTAIR study.

CRVO (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

No IOP events were considered serious in the CRVO trials. Of the 43 subjects with an AE of increased IOP in the Eylea total group, 31 were recovered, whilst 11 subjects remained not recovered (missing information in one patient, Table SVII.41).

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Table SVII.41: Number of subjects with increased intraocular pressure in the study eye by outcome in the Phase III CRVO studies from baseline through Week 76/100 (SAF)

MedDRA 19.1	Sham + PRN n (%)	VTE 2Q4 + PRN n (%)	Eylea total [a] n (%)
Number of subjects	142	218	317
Grouped term			
IOP increase	19 (13.4)	34 (15.6)	43 (13.6)
Outcome			
Recovered/resolved	13 (9.2)	26 (11.9)	31 (9.8)
Unknown	0	1 (0.5)	1 (0.3)
Not recovered/resolved	6 (4.2)	7 (3.2)	11 (3.5)

IOP=Intraocular pressure
[a]: All patients exposed to Eylea. All TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (CRVO), Table 1.3.1/3

BRVO (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Clinical Trial VIBRANT (52 weeks)

None of the reported IOP events were considered serious. Four of the affected patients recovered and one event was assessed as recovering/resolving (see Table SVII.42).

Table SVII.42: Number of subjects with increased intraocular pressure in the study eye by outcome in the Phase III BRVO study from baseline through Week 52 (SAF)

MedDRA 19.1	Laser+VTE 2 mg n (%)	VTE 2 mg n (%)	Eylea total [a] n (%)
Number of subjects	92	91	158
Grouped term			
IOP increase	1 (1.1)	4 (4.4)	5 (3.2)
Outcome			
Recovered/resolved	1 (1.1)	3 (3.3)	4 (2.5)
Recovering/resolving	0	1 (1.1)	1 (0.6)

IOP=Intraocular pressure
[a]: All patients exposed to Eylea. All TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (BRVO), Table 1.4.1/3

Myopic CNV (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Clinical Trial MYRROR (48 weeks)

No adverse events of increased intraocular pressure in the study eye were reported in the period from baseline through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

Only one event of increased intraocular pressure was considered serious in the pivotal DME trials through Week 148. This event occurred post-injection in one patient in the Eylea 2Q8 group (0.1% of the 821 patients who had received Eylea at least once).

The outcome of the reported events is summarized in the following Table SVII.43. The IOP increase was "resolved" (88 subjects) in the majority of the 100 subjects in the total Eylea

group, whereas 8 patients did not recover. Overall, most of the reported adverse events of intraocular pressure increase were obviously transient.

Table SVII.43: Number of subjects with increased intraocular pressure in the study eye by outcome in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
IOP increase	23 (8.0)	53 (18.2)	31 (10.8)	100 (12.2)
Outcome				
Recovered/resolved	20 (7.0)	45 (15.5)	27 (9.4)	88 (10.7)
Recovering/resolving	0	2 (0.7)	2 (0.7)	4 (0.5)
Not recovered/not resolved	3 (1.0)	6 (2.1)	2 (0.7)	8 (1.0)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis - EU-RMP Pool 1 (DME), Table 1.5.1/3

DME (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Clinical Trial VIVID-EAST (52 weeks)

All reported cases of increased IOP in the study eye were regarded as non-serious. Two patients did not recover (both in the laser group and not treated with Eylea); in the remaining patients the IOP events were resolved (Table SVII.44).

Table SVII.44: Number of subjects with increased intraocular pressure in the study eye by outcome in the Phase III DME study VIVID-EAST from baseline through Week 52 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	N=124	N=127	N=127	N=299
Grouped term				
IOP increase	4 (3.2)	4 (3.1)	6 (4.7)	11 (3.7)
Outcome				
Recovered / resolved	2 (1.6)	4 (3.1)	6 (4.7)	11 (3.7)
Not recovered / not resolved	2 (1.6)	0	0	0

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=45 exposed to Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 52.
Table Source: Integrated Analysis - EU-RMP Pool 1 (DME), Table 1.5.3/3

DME (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) - Open-label Clinical Trial VIVID-JAPAN (52 weeks)

In the open-label Phase III study VIVID-JAPAN, both events of "intraocular pressure increased" in the study eye were regarded as mild and non-serious. The outcome was "recovered/resolved" in one case and "recovering/resolving" in the other case.

ROP (Eylea 40 mg/mL, 0.4 mg dose, injection volume: 10 µL) - Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

Out of the 3 cases reported in the FIREFLEYE study (no case reported in the FIREFLEYE NEXT study) 2 cases of increased IOP in the study eye were regarded as non-serious and one as serious (reported in the VTE 0.4 mg pediatric group and related to an inadvertent overdosing). All patients did recover (Table SVII.45):

Table SVII.45: Number of subjects with increased intraocular pressure in the study eye by outcome in the Phase III FIREFLEYE study (SAF)

MedDRA 23.1	Laser n (%)	VTE 0.4 mg n (%)	VTE total[a] n (%)
Number of subjects	38	75	79
Grouped term			
IOP increase	0	3 (4.0)	3 (3.8)
Outcome			
Recovered/resolved	0	3 (4.0)	3 (3.8)

IOP=Intraocular pressure
[a]: VTE total includes all subjects who received VTE 0.4 mg including subjects randomized to laser and receiving VTE 0.4 mg as rescue treatment. All non-ocular adverse events after first VTE treatment in any eye and all ocular adverse events after first VTE treatment in the eye where the event occurred are considered.
Table Source: Integrated Analysis - EU-RMP ROP submission Pool 1 (ROP20090), Table 1.2/3

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose, injection volume: 70 µL) - Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (96 weeks), and the DME PHOTON study (96 weeks):

Three patients experienced serious IOP events in the 8 mg dose trials (all in the HDq12 treatment group, 2 events were considered as medically important and 1 event required prolonged hospitalization). Of the 44 subjects with an AE of increased IOP in the aflibercept 8 mg dose total group, 37 patients were recovered/recovering, whilst 4 subjects remained not recovered (0.3%, missing information in 3 patients, Table SVII.46). Of the 20 subjects with an AE of increased IOP in the aflibercept 2 mg dose group, 18 patients were recovered/recovering, whilst 1 subject remained not recovered (0.2%, missing information in 1 patients). No meaningful differences were detected between the 2 mg and the 8 mg dose treatment groups.

Table SVII.46: Number of subjects with increased intraocular pressure in the study eye by outcome in the Phase II CANDELA study and Phase III PULSAR study in wet AMD and in the Phase III PHOTON study in DME (SAF)

MedDRA 25.0	*2 mg* n (%)	*HDq12* n (%)	*HDq16* n (%)	HD Total n (%)
Number of subjects	556	716	501	1,217
Grouped term				
Intraocular pressure increased	20 (3.6%)	28 (3.9%)	16 (3.2%)	44 (3.6%)
Outcome				
Recovered/resolved	16 (2.9%)	21 (2.9%)	14 (2.8%)	35 (2.9%)
Recovering/resolving	2 (0.4%)	1 (0.1%)	1 (0.2%)	2 (0.2%)
Unknown	1 (0.2%)	3 (0.4%)	0	3 (0.2%)
Not recovered/not resolved	1 (0.2%)	3 (0.4%)	1 (0.2%)	4 (0.3%)

2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
HD total: HDq12 and HDq16 combined.
Source: Integrated Analysis – Pool 1, 48 weeks analysis, AMD 8 mg (w44/96) + DME 8 mg (w96); Table 3.1/43

Post-marketing Data

A total of 106 out of the 260 reported events of increased IOP were regarded as serious (see previous post-marketing table on IOP events).

Reported outcomes were “recovered/resolved” in 88 events, “recovering/resolving” in 31 events, and “not recovered/not resolved” in 28 events (missing or unknown outcomes in the remaining 113 events).

Severity and nature of risk

Wet AMD (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) – Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

The majority of the cases of increased IOP were of mild severity across all treatment groups (Table SVII.47). There were few cases of severely increased IOP, accounting for 0.3% of all patients in both the ranibizumab and the combined Eylea group.

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Table SVII.47: Number of subjects with increased intraocular pressure in the study eye by maximum severity in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
IOP increase	66 (11.1)	50 (8.2)	41 (6.8)	51 (8.4)	142 (7.8)
Maximum severity					
Mild	51 (8.6)	42 (6.9)	31 (5.2)	37 (6.1)	110 (6.0)
Moderate	13 (2.2)	8 (1.3)	7 (1.2)	12 (2.0)	27 (1.5)
Severe	2 (0.3)	0	3 (0.5)	2 (0.3)	5 (0.3)

IOP=Intraocular pressure, Q4 = every 4 weeks, Q8 = every 8 weeks
Note: Note: At each level of subject summarization (Safety topic/PT), a subject is classified according to the maximum intensity, if the subject reported one or more events. At each level of subject summarization, a subject is counted only once.
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.1/2

AMD (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) – VIEW 1 long-term extension study

Most of the events occurring during the extension period were mild or moderate; in 2 patients (0.8% in the former randomized Eylea groups) were regarded as severe (Table SVII.48).

Table SVII.48: Number of subjects with increased intraocular pressure in the study eye by maximum severity in the Phase III VIEW 1 extension study in AMD (SAF; all subjects treated with VTE in the extension phase, treatment groups are displayed according to original randomization in VIEW 1)

MedDRA 19.1	*Ranibizumab 0.5Q4* [a] *n (%)*	*Eylea combined* [b] *n (%)*	Eylea Total [c] n (%)
Number of subjects	69	254	323
Grouped term			
IOP increase	0	16 (6.3)	16 (5.0)
Maximum severity			
Mild	0	6 (2.4)	6 (1.9)
Moderate		8 (3.1)	8 (2.5)
Severe	0	2 (0.8)	2 (0.6)

[a]: Patients who were randomized to treatment with ranibizumab in the VIEW 1 core study.
[b]: Patients who were randomized to treatment with Eylea (0.5Q4, 2Q4, or 2Q8) in the VIEW 1 core study.
[c]: All patients who were treated with Eylea in the extension study period. Only Aes occurring after the first active Eylea injection were counted.
Note: Events that occurred in the VIEW 1 core study are not considered.
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.2/2

AMD (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) – Clinical Trial SIGHT (52 weeks)

All reported cases of increased IOP in the study eye (see preceding frequency table) were mild (and non-serious and resolved).

AMD (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) – Clinical Trial ALTAIR (52 weeks)

No events pertaining to the group of intraocular pressure increase in the study eye were reported during the course of the ALTAIR study.

CRVO (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) – Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

Most of the reported events of increased intraocular pressure were mild; only one case (on sham treatment, the event [PT: intraocular pressure increased] was not counted in the Eylea total group) was regarded as severe (Table SVII.49). No severe events associated with IOP increase occurred on treatment with Eylea.

Table SVII.49: Number of subjects with increased intraocular pressure in the study eye by maximum severity in the Phase III CRVO studies from baseline through Week 76/100 (SAF)

MedDRA 19.1	Sham + PRN n (%)	VTE 2Q4 + PRN n (%)	Eylea total [a] n (%)
Number of subjects	142	218	317
Grouped term			
IOP increase	19 (13.4)	34 (15.6)	43 (13.6)
Maximum severity			
Mild	17 (12.0)	27 (12.4)	36 (11.4)
Moderate	1 (0.7)	7 (3.2)	7 (2.2)
Severe	1 (0.7)	0	0

IOP=Intraocular pressure
[a]: All patients exposed to Eylea. All TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis – EU-RMP Pool 1 (CRVO), Table 1.3.1/2

BRVO (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) – Clinical Trial VIBRANT (52 weeks)

None of the reported IOP events were regarded as serious; most of them had a “mild” intensity (Table SVII.50).

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Table SVII.50: Number of subjects with increased intraocular pressure in the study eye by maximum severity in the Phase III BRVO study from baseline through Week 52 (SAF)

MedDRA 19.1	Laser+VTE 2 mg n (%)	VTE 2 mg n (%)	Eylea total [a] n (%)
Number of subjects	92	91	158
Grouped term			
IOP increase	1 (1.1)	4 (4.4)	5 (3.2)
Maximum severity			
Mild	1 (1.1)	3 (3.3)	4 (2.5)
Moderate	0	1 (1.1)	1 (0.6)

IOP=Intraocular pressure
[a]: All patients exposed to Eylea. All TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis – EU-RMP Pool 1 (BRVO), Table 1.4.1/2

Myopic CNV (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) – Clinical Trial MYRROR (48 weeks)

No adverse events of increased intraocular pressure in the study eye were reported in the period from baseline through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) – Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

With the exception of one severe event in the Eylea 2Q4 group, all remaining events were regarded as mild (73/100 patients in the Eylea total group) or moderate (26/100 patients in the Eylea total group; Table SVII.51).

Table SVII.51: Number of subjects with increased intraocular pressure in the study eye by maximum severity in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
IOP increase	23 (8.0)	53 (18.2)	31 (10.8)	100 (12.2)
Maximum severity				
Mild	17 (5.9)	35 (12.0)	25 (8.7)	73 (8.9)
Moderate	6 (2.1)	17 (5.8)	6 (2.1)	26 (3.2)
Severe	0	1 (0.3)	0	1 (0.1)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all Aes which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis – EU-RMP Pool 1 (DME), Table 1.5.1/2

DME (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) – Clinical Trial VIVID-EAST (52 weeks)

In the Eylea total group, the reported IOP events were “mild” in 9 of the 11 involved patients, and “moderate” and “severe”, respectively, in the remaining 2 patients (Table SVII.52).

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Table SVII.52: Number of subjects with increased intraocular pressure in the study eye by maximum severity in the Phase III DME study VIVID-EAST from baseline through Week 52 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	N=124	N=127	N=127	N=299
Grouped term				
IOP increase	4 (3.2)	4 (3.1)	6 (4.7)	11 (3.7)
Maximum severity				
Mild	3 (2.4)	4 (3.1)	4 (3.1)	9 (3.0)
Moderate	0	0	1 (0.8)	1 (0.3)
Severe	1 (0.8)	0	1 (0.8)	1 (0.3)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=45 exposed to Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 52.
Table Source: Integrated Analysis – EU-RMP Pool 1 (DME), Table 1.5.3/2

DME (Eylea 40 mg/mL, 2 mg dose, injection volume: 50 µL) – Open-label Clinical Trial VIVID-JAPAN (52 weeks)

Both events of "intraocular pressure increased" in the study eye were regarded as mild (and non-serious).

ROP (Eylea 40 mg/mL, 0.4 mg dose, injection volume: 10 µL) – Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

Out of the 3 cases reported in the FIREFLEYE study (no case reported in the FIREFLEYE NEXT study) two cases of increased IOP in the study eye were regarded as mild and one as moderate (Table SVII.53).

Table SVII.53: Number of subjects with increased intraocular pressure in the study eye by maximum severity in the Phase III FIREFLEYE study (SAF)

MedDRA 23.1	Laser n (%)	VTE 0.4 mg n (%)	VTE total [a] n (%)
Number of subjects	38	75	79
Grouped term			
IOP increase	0	3 (4.0)	3 (3.8)
Maximum severity			
Mild	0	2 (2.7)	2 (2.5)
Moderate	0	1 (1.3)	1 (1.3)

IOP=Intraocular pressure
[a]: VTE total includes all subjects who received VTE 0.4 mg including subjects randomized to laser and receiving VTE 0.4 mg as rescue treatment. All non-ocular adverse events after first VTE treatment in any eye and all ocular adverse events after first VTE treatment in the eye where the event occurred are considered.
Table Source: Integrated Analysis – EU-RMP ROP submission Pool 1 (ROP 20090), Table 1.2/2

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose, injection volume: 70 µL) – Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (96 weeks), and the DME PHOTON study (96 weeks):

In the majority of patients with increased IOP severity was "mild" across all treatment groups (Table SVII.54, 2 mg: 3.1%, HDq12: 2.7%, HDq16: 3.0%). There was 1 patient with severely increased IOP, accounting for <0.1% of all patients in aflibercept 8 mg dose total treatment group.

Table SVII.54: Number of subjects with increased intraocular pressure in the study eye by maximum severity in the Phase II CANDELA study and Phase III PULSAR study in wet AMD and in the Phase III PHOTON study in DME (SAF)

MedDRA 25.0	*2 mg* *n (%)*	*HDq12* *n (%)*	*HDq16* *n (%)*	HD Total n (%)
Number of subjects	556	716	501	1,217
Grouped term Intraocular pressure increased	20 (3.6%)	28 (3.9%)	16 (3.2%)	44 (3.6%)
Maximum severity				
Mild	17 (3.1%)	19 (2.7%)	15 (3.0%)	34 (2.8%)
Moderate	3 (0.5%)	8 (1.1%)	1 (0.2%)	9 (0.7%)
Severe	0	1 (0.1%)	0	1 (<0.1%)

2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
HD total: HDq12 and HDq16 combined.
Source: Integrated Analysis – Pool 1, 48 weeks analysis, AMD 8 mg (w44/48) + DME 8 mg (w48); Table 3.1/19

Post-marketing Data

Event severity is not routinely recorded on the post-marketing case report forms.

Background incidence/prevalence

AMD/CRVO

No publications on transient intraocular pressure increase due to study disease were identified.

BRVO

In the following three out of five clinical trials involving BRVO subjects no intra-ocular pressure (IOP) increase was reported:

Campochiaro *et al*. 2010 (158) (ranibizumab 0.3 mg or 0.5 mg *vs*. sham treatment), Russo *et al*. 2009 (213) (Bevacizumab compared with macular laser grid photocoagulation), and Donati *et al*. 2012 (215) (combined intravitreal bevacizumab and grid laser photocoagulation).

In SCORE–BRVO 2009 (155) (intravitreal triamcinolone *vs*. standard of care), IOP increase requiring medication was observed in 2%, 8%, and 41% in the standard of care group, 1 mg triamcinolone group, and 4 mg triamcinolone group, respectively. IOP >10 mmHg was observed in the 4 mg triamcinolone group (36%) compared with the 1 mg triamcinolone (9%) and standard of care (3%) group.

Parodi *et al*. 2008 (214) (intravitreal triamcinolone acetonide combined with sub-threshold grid laser treatment compared to simple laser grid) described an increase in IOP in 54% of the 24 study patients, which required treatment.

Myopic CNV

A prospective study (Gharbiya *et al*. 2009) to evaluate the short-term efficacy and safety of intravitreal bevacizumab for the treatment of myopic CNV was conducted in Italy on 20 patients. At month 12 follow-up, no significant intraocular pressure (IOP) changes in the treated eyes were observed: mean IOP values (± SD) at baseline and at month 12 were respectively 14.2 (± 2.21) mmHg and 13.75 (± 2.46) mmHg (p = 0.35) (230).

An open-label study (Ikuno *et al*. 2010) to compare the long-term visual and anatomic outcome of treatment with photodynamic therapy or intravitreal bevacizumab for myopic CNV was conducted on 31 eyes of Japanese women. No transient IOP increase was reported (231).

Another retrospective study of 63 patients conducted in Japan by the same investigator (Ikuno *et al*. 2009) aimed at assessing the potential effect of intravitreal bevacizumab on retinal function and anatomic recovery in eyes with myopic CNV. No IOP increase was reported (232).

In a prospective study (Osaka University) to compare the visual outcomes of intravitreal bevacizumab and sub-Tenon triamcinolone acetonide (TA) for choroidal neovascularization attributable to myopic CNV, 53 patients participated. In the sub-Tenon TA group, 3 eyes (15%) had an IOP of more than 21 mmHg that was managed with antiglaucoma medications (233).

DME

In a Phase III controlled study, 197 patients with diabetic macular edema were randomized to receive a fluocinolone 0.5 mg implant, or standard of care (macular grid laser/observation). Glaucoma was reported in 9% of patients treated with the fluocinolone implant and in 0% of patients treated with photocoagulation. The study did not describe transient IOP increases (234).

A Korean study compared the efficacy of posterior sub-Tenon's capsule triamcinolone acetonide injection combined with modified grid macular photocoagulation (PSTI + MP) with intravitreal triamcinolone acetonide (IVTA) injection in the treatment of diffuse DME. Forty eyes of 33 patients with diffuse DME were randomly allocated to either treatment. IOP was measured using a Goldman applanation tonometer. Between-group comparisons revealed significant differences in mean IOP changes at 1 month and 3 months ($p = 0.006$, $p = 0.026$, respectively). Three of 20 (15%) eyes in the IVTA group developed IOP elevation which exceeded 21 mmHg; and this was controlled with topical anti-glaucomatous agents. The 3 eyes with elevated IOP belonged to three different patients. No eye that received a posterior sub-Tenon injection developed increased IOP exceeding 21 mmHg (235).

Two 24 month, parallel, methodologically identical, randomized, multicenter, double-masked, sham injection-controlled, Phase III studies (RISE and RIDE) to evaluate efficacy and safety of intravitreal ranibizumab in DME. In RISE, 377 patients were randomized to either ranibizumab (n=125 to 0.3 mg and n = 125 to 0.5 mg) or sham injection (n = 127) out of which no case of increased IOP was reported in RISE study. In RIDE, 382 patients were randomized to either ranibizumab (n=125 to 0.3mg and n=127 to 0.5 mg) or sham injection (n=130) out of which one case of increased IOP occurred in the 0.5mg ranibizumab treatment group (0.8%) and no case of increased IOP was reported in 0.3mg ranibizumab and sham

group. The study did not specify if the increase in IOP was transient, but the event was considered a serious adverse event (161).

A 12-month, randomized, sham controlled, double-masked, multicenter Phase II study of safety and efficacy of ranibizumab in DME with centre involvement (RESOLVE Study) enrolled 151 subjects to either ranibizumab (0.3 to 0.6 mg, n=51; or 0.5 to 1mg, n=51) or sham treatment (n=49). Six cases of transient IOP increase were reported in 0.3 to 0.6mg ranibizumab treatment group (11.8%) and 15 cases of transient IOP increase were reported in 0.5 to 1mg ranibizumab treatment group (29.4%) and one case of transient IOP increase in sham group (2%) (162).

A 12-month, randomized, laser controlled, double masked, multicenter Phase III study to demonstrate superiority of ranibizumab 0.5 mg monotherapy or combined with laser over laser alone in DME patients (RESTORE study). 345 patients were randomized to ranibizumab + sham laser (n=116), ranibizumab + laser (n = 118), or sham injections + laser (n=111). One patient each in ranibizumab arms experienced IOP increase and none in sham group. Both cases of IOP resolved on their own and investigator related it to the injection procedure and not to the drug (163).

ROP

No publications of clinical studies reporting transient intraocular pressure increase among premature infants with ROP were found.

Impact of individual patient

Transient IOP increase is usually a mild reaction which is compensated within 0.5 – 1 hours after injection so that IOP normalizes back to baseline values. Patients recovered without sequelae (195, 197).

Risk factors and risk groups

Patients with glaucoma.

Increased intraocular pressure is a known adverse drug reaction on treatment with intravitreal corticosteroids.

Preventability

Intraocular pressure should be checked after each injection. As the transient increase of eye pressure is an inherent result of the procedure-related volume load in the scope of intravitreal injections, there is no reasonable chance to avoid this effect. However, this effect is usually transient, and there is no robust evidence so far that pressure increases following intravitreal injections (even after multiple injections) could become durable or may lead to clinically relevant glaucoma.

Impact on the risk-benefit balance of the product

An educational program is performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks. The effectiveness of this program was verified with a post authorization safety study (SN 16526). Furthermore, a specific questionnaire is used to gain more knowledge about this risk.

This important identified risk does not have an impact on the positive risk-benefit balance of Eylea.

Public health impact

Due to the transient and usually mild nature of the condition, no impact of this safety concern on public health issues is expected.

SVII.3.1.4 Identified risk: Retinal pigment epithelial tear

Potential mechanisms

Development of RPE tears after anti-VEGF intravitreal injection has been attributed to a decline in intercellular adherence, thereby increasing susceptibility to tearing of the RPE layer (236).

Evidence source(s) and strength of evidence

Main reason for considering retinal pigment epithelial tear as an important identified risk:

The retinal pigment epithelium is the outer layer of the retina. Tears in that layer may occur secondary to AMD, following intravitreal injections, or for unknown reasons. These tears may be self-sealing or may require sealing by laser coagulation.

In clinical trials up to 1.9% of patients with underlying wet AMD who were treated with Eylea developed a tear of the outer layer of the retina, whilst none of the patients with underlying CRVO, BRVO, myopic CNV, or DME developed a tear of the outer layer of the retina.

Evidence sources: refer to the linked subsection.

MedDRA search terms (version 19.1 for adult 2 mg clinical studies, version 20.0 for PM data and version 23.1 for ROP studies in preterm infants, version 25.0 for 8 mg dose in wet AMD and DME):

Preferred term: Retinal pigment epithelial tear.

Characterization of the risk

Frequency

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg doses) – Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

Retinal pigment epithelial (RPE) tears occurred in 1.9% of all patients treated with Eylea, compared to 1.5% of patients in the ranibizumab group (see Table SVII.55).

Table SVII.55: Number of subjects with retinal pigment epithelium tears in the study eye in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Preferred term					
RPE tear	9 (1.5)	5 (0.8)	10 (1.7)	20 (3.3)	35 (1.9)

Q4 = every 4 weeks, Q8 = every 8 weeks
Note: No grouping of preferred terms was performed.
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.1/1

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) – VIEW 1 long-term extension study

Two patients (0.6% of all 323 patients treated with Eylea) experienced RPE tears in the study eye during the extension period (one patient in former randomized ranibizumab group [1.4%] and one patient in former randomized Eylea groups [0.4%]). There were no meaningful differences compared with the frequency of RPE tears reported from the pivotal AMD trials through Week 96 (see preceding Table SVII.55).

Wet AMD (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial SIGHT (52 weeks)

Cases of RPE tears were infrequent in the SIGHT study, since only one patient in the Eylea 2Q8 group was involved (0.4% based on 228 patients randomized to the 2Q8 group or 0.3% based on the 299 Eylea-exposed patients). This event was mild, non-serious, and not resolved.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial ALTAIR (52 weeks)

Cases of RPE tears were infrequent in the ALTAIR study, since only 3 patients in the 2W adjustment group experienced RPE tears (2.4% based on 124 patients randomized to the 2W adjustment group or 1.2% based on the 254 Eylea-exposed patients).

CRVO (Eylea 40 mg/mL, 2 mg dose) – Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

No cases of RPE tears were reported in the CRVO trials.

BRVO (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial VIBRANT (52 weeks)

No cases of RPE tears were reported in the BRVO study VIBRANT through Week 52.

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial MYRROR (48 weeks)

No cases of RPE tears were reported in the period from baseline through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose) – Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

Please note that RPE tears is a phenomenon that occurs particularly in AMD patients. However, it has been included as important identified risk, since the RMP covers all indications. As with CRVO, BRVO, and myopic CNV, no cases of RPE tears in the study eye were reported in the DME trials through Week 148.

DME (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial VIVID-EAST (52 weeks)

No cases of RPE tears in the study eye were reported in VIVID-EAST.

DME (Eylea 40 mg/mL, 2 mg dose) – Open-label Clinical Trial VIVID-JAPAN (52 weeks)

No cases of RPE tears in the study eye were reported in VIVID-JAPAN.

ROP (Eylea 40 mg/mL, 0.4 mg dose) – Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

No events pertaining to the group of retinal pigment epithelial tear in the Eylea-exposed eye were reported in the FIREFLEYE or the FIREFLEYE NEXT study.

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose) – Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (96 weeks), and the DME PHOTON study (96 weeks):

In both, the 2 mg and the 8 mg dose treatment groups retinal pigment epithelial (RPE) tears occurred in 0.7% of patients (see Table SVII.56).

Table SVII.56: Number of subjects with retinal pigment epithelial tears in the study eye (grouped term and included preferred terms) in the Phase II CANDELA study and Phase III PULSAR study in wet AMD and in the Phase III PHOTON study in DME (SAF)

MedDRA 25.0	*2 mg* *n (%)*	*HDq12* *n (%)*	*HDq16* *n (%)*	HD Total n (%)
Number of subjects	556	716	501	1,217
Grouped term				
Retinal pigment epithelial tear	4 (0.7)	6 (0.8)	3 (0.6)	9 (0.7)
Included preferred terms				
Retinal pigment epithelial tear	4 (0.7)	6 (0.8)	3 (0.6)	9 (0.7)

2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
HD total: HDq12 and HDq16 combined.
Source: Integrated Analysis – Pool 1, 96 weeks analysis, AMD 8 mg (w44/96) + DME 8 mg (w96); Table 3.1/5

Post-marketing Data

As of 15 SEP 2017, a total of 159 cases (with 163 events) with RPE tear were reported in the pharmacovigilance database. All but 10 events were considered serious.

Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period until 30 SEP 2017, the reporting rate of “RPE tear” cases (N=159) was 0.01 cases per 1,000 sold vials (0.001%) and 0.07 cases per 1,000 patient years (0.007%), respectively.

Seriousness/outcomes

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) – Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

The rate of patients with serious treatment-emergent RPE tears was 0.2% in both the ranibizumab and the combined Eylea group (corresponding to one patient treated with ranibizumab and 4 patients treated with Eylea) (Table SVII.57).

Table SVII.57: Number of subjects with serious retinal pigment epithelium tears in the study eye in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Preferred term					
RPE tear	1 (0.2)	0	1 (0.2)	3 (0.5)	4 (0.2)

Q4 = every 4 weeks, Q8 = every 8 weeks
Note: No grouping of preferred terms was performed.
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.1/4

RPE tears remained unresolved until the end of the study in the majority of affected patients in any treatment group (Table SVII.58).

Table SVII.58: Number of subjects with retinal pigment epithelium tears by outcome in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Preferred term					
RPE tear	9 (1.5)	5 (0.8)	10 (1.7)	20 (3.3)	35 (1.9)
Outcome					
Recovered/resolved	1 (0.2)	0	0	4 (0.7)	4 (0.2)
Recovering/resolving	1 (0.2)	0	0	0	0
Recovered/resolved with sequelae	1 (0.2)	0	1 (0.2)	1 (0.2)	2 (0.1)
Unknown	0	1 (0.2)	0	0	1 (<0.1)
Not recovered / not resolved	6 (1.0)	4 (0.7)	9 (1.5)	15 (2.5)	28 (1.5)

Q4 = every 4 weeks, Q8 = every 8 weeks
Note: For each subject, only the adverse event with the worst outcome is counted within each safety topic class and overall.
Note: No grouping of preferred terms was performed.
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.1/3

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) – VIEW 1 long-term extension study

Two patients (0.6% of all 323 patients treated with Eylea) experienced RPE tears in the study eye during the extension period (one patient in former randomized ranibizumab group [1.4%] and one patient in former randomized Eylea groups [0.4%]). Both events were non-serious and mild, but the patients were not recovered from that event.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial SIGHT (52 weeks)

The only reported event of RPE tears (occurring in one patient in the Eylea 2Q8 group) was non-serious, mild, and not resolved.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial ALTAIR (52 weeks)

3 cases of RPE tears were reported (occurring in the 2W adjustment group), in 2 of them the outcome was unknown, in one case not recovered. None of these cases was serious.

CRVO (Eylea 40 mg/mL, 2 mg dose) – Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

No cases of RPE tears were reported in the CRVO trials.

BRVO (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial VIBRANT (52 weeks)

No cases of RPE tears were reported in the BRVO study VIBRANT through Week 52.

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial MYRROR (48 weeks)

No cases of RPE tears were reported in the period from baseline through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose) – Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

No cases of RPE tears in the study eye were reported in the DME trials through Week 148.

DME (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial VIVID-EAST (52 weeks)

No cases of RPE tears in the study eye were reported in VIVID-EAST.

DME (Eylea 40 mg/mL, 2 mg dose) – Open-label Clinical Trial VIVID-JAPAN (52 weeks)

No cases of RPE tears in the study eye were reported in VIVID-JAPAN.

ROP (Eylea 40 mg/mL, 0.4 mg dose) – Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

No cases of RPE tears in the Eylea-exposed eye were reported in the FIREFLEYE or the FIREFLEYE NEXT study.

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose) – Pooled data sets from the AMD CANDELA study (44 weeks), the AMD PULSAR study (96 weeks), and the DME PHOTON study (96 weeks):

There were no serious reports of RPE tears.

RPE tears remained unresolved up to week 96 of the study in the majority of affected patients in the 8 mg dose treatment total group (8 out of 9 patients, 0.7%, Table SVII.59). Regarding the 2 mg dose treatment group, in 0.2% outcome was reported as “resolving” and in 0.5% “not resolved”. No meaningful differences were detected between the 2 mg and the 8 mg dose. In none of the patients, the events were assessed as serious.

Table SVII.59: Number of subjects with retinal pigment epithelial tears in the study eye by outcome in the Phase II CANDELA study and Phase III PULSAR study in wet AMD and in the Phase III PHOTON study in DME (SAF)

MedDRA 25.0	***2 mg*** ***n (%)***	***HDq12*** ***n (%)***	***HDq16*** ***n (%)***	**HD Total** **n (%)**
Number of subjects	556	716	501	1,217
Grouped term				
Retinal pigment epithelial tear	4 (0.7)	6 (0.8)	3 (0.6)	9 (0.7)

Table SVII.59: Number of subjects with retinal pigment epithelial tears in the study eye by outcome in the Phase II CANDELA study and Phase III PULSAR study in wet AMD and in the Phase III PHOTON study in DME (SAF)

MedDRA 25.0	*2 mg* *n (%)*	*HDq12* *n (%)*	*HDq16* *n (%)*	HD Total n (%)
Outcome				
Recovering/resolving	1 (0.2%)	0	0	0
Recovered/resolved with sequelae	0	0	1 (0.2%)	1 (<0.1%)
Not recovered/not resolved	3 (0.5%)	6 (0.8%)	2 (0.4%)	8 (0.7%)

2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
HD total: HDq12 and HDq16 combined.
Source: Integrated Analysis – Pool 1, 96 weeks analysis, AMD 8 mg (w44/96) + DME 8 mg (w96); Table 3.1/45

Post-marketing Data

Ten of the 148 reported events of RPE tears were considered non-serious, whilst 153 events were serious.

Reported outcomes were “recovered/resolved” in 8 events, “recovering/resolving” in 8 events, “recovered/resolved with sequelae” in 10 events, and “not recovered/not resolved” in 77 events (missing or unknown outcomes in the remaining 60 events).

Severity and nature of risk

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) – Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

Except for 2 patients with severe events (one patient each on ranibizumab or Eylea), RPE tears were of mild or moderate intensity (Table SVII.60).

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Table SVII.60: Number of subjects with retinal pigment epithelium tears by maximum severity in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Preferred term					
RPE tears	9 (1.5)	5 (0.8)	10 (1.7)	20 (3.3)	35 (1.9)
Maximum severity					
Mild	4 (0.7)	4 (0.7)	3 (0.5)	8 (1.3)	15 (0.8)
Moderate	4 (0.7)	1 (0.2)	7 (1.2)	11 (1.8)	19 (1.0)
Severe	1 (0.2)	0	0	1 (0.2)	1 (<0.1)

Q4 = every 4 weeks, Q8 = every 8 weeks
Note: At each level of subject summarization (Safety topic/PT), a subject is classified according to the maximum intensity, if the subject reported one or more events. At each level of subject summarization, a subject is counted only once.
Note: No grouping of preferred terms was performed.
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.1/2

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) – VIEW 1 long-term extension study

Two patients (0.6% of all 323 patients treated with Eylea) experienced RPE tears in the study eye during the extension period (one patient in former randomized ranibizumab group [1.4%] and one patient in former randomized Eylea groups [0.4%]). Both events were non-serious and mild.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial SIGHT (52 weeks)

The only reported event of RPE tears (occurring in one patient in the Eylea 2Q8 group) was mild (and non-serious, not resolved).

Wet AMD (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial ALTAIR (52 weeks)

3 cases of RPE tears were reported (occurring in the 2W adjustment group), 2 of them were mild and one case was moderate.

CRVO (Eylea 40 mg/mL, 2 mg dose) – Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

No cases of RPE tears were reported in the CRVO trials.

BRVO (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial VIBRANT (52 weeks)

No cases of RPE tears were reported in the BRVO study VIBRANT through Week 52.

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial MYRROR (48 weeks)

No cases of RPE tears were reported in the period from baseline through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose) – Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

No cases of RPE tears in the study eye were reported in the pivotal DME trials.

DME (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial VIVID-EAST (52 weeks)

No cases of RPE tears in the study eye were reported in VIVID-EAST.

DME (Eylea 40 mg/mL, 2 mg dose) – Open-label Clinical Trial VIVID-JAPAN (52 weeks)

No cases of RPE tears in the study eye were reported in VIVID-JAPAN.

ROP (Eylea 40 mg/mL, 0.4 mg dose) – Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

No cases of RPE tears in the Eylea-exposed eye were reported in the FIREFLEYE or the FIREFLEYE NEXT study.

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose) – Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (96 weeks), and the DME PHOTON study (96 weeks).

For 9 patients (0.7%) RPE tears were reported in the 8 mg dose treatment groups, in 4 of them intensity was “mild” and in 5 of them of “moderate”. Four patients (0.7%) with RPE tears were reported in the 2 mg dose treatment group, in 3 of them intensity was “mild” and 1 had “moderate” intensity (Table SVII.61). No meaningful differences were detected between the 2 mg and the 8 mg dose treatment groups.

Table SVII.61: Number of subjects with retinal pigment epithelial tears in the study eye by maximum severity in the Phase II CANDELA study and Phase III PULSAR study in wet AMD and in the Phase III PHOTON study in DME (SAF)

MedDRA 25.0	*2 mg* *n (%)*	*HDq12* *n (%)*	*HDq16* *n (%)*	HD Total n (%)
Number of subjects	556	716	501	1,217
Grouped term				
Retinal pigment epithelial tear	4 (0.7)	6 (0.8)	3 (0.6)	9 (0.7)
Maximum severity				
Mild	3 (0.5)	4 (0.6)	0	4 (0.3)
Moderate	1 (0.2)	2 (0.3)	3 (0.6)	5 (0.4)

2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
HD total: HDq12 and HDq16 combined.
Source: Integrated Analysis – Pool 1, 96 weeks analysis, AMD 8 mg (w44/96) + DME 8 mg (w96); Table 3.1/25

Post-marketing Data

Event severity is not routinely recorded on the post-marketing case report forms.

Background incidence/prevalence

Wet AMD:

RPE tears have been reported in patients with wet AMD in the absence of treatment, particularly when a pigment epithelial detachment (PED) is present. Incidence rates for spontaneous RPE tears ranged between 2%-6% of eyes with AMD (237-239) and between 10%-25% in eyes with AMD and pigment epithelial detachments (PED) (239). The most important predisposing risk factor appears to be PED size as measured by basal diameter (238) and vertical height (17, 237). Also, eyes with serious RPE detachment appear to be more vulnerable to RPE tears (240).

CRVO:

No data identified.

BRVO:

No findings were identified. All reviewed BRVO studies did not report any RPE tears.

Myopic CNV:

In the Osaka University study, 114 of the 707 participants were myopic CNV patients. There were no reports of RPE tears among them (241).

In a consecutive prospective study to determine the efficacy and safety of intravitreal bevacizumab in the treatment of CNV secondary to pathological myopia 17 patients participated. During a six months follow-up one RPE tear was reported after the first injection (242).

No findings of RPE tears were reported in the two studies by Ikuno *et al*. (231, 232) and Gharbiya *et al*. 2009 (230), and the rest of the reviewed publications.

DME:

No data identified.

ROP:

No data identified.

Additional considerations on RPE tears as class effect:

RPE tears have also been reported following treatment of the neovascularization, regardless of whether the treatment was delivered intravitreally (pegaptanib sodium, bevacizumab, ranibizumab) or through other means (argon or krypton laser photocoagulation, transpupillary thermotherapy, photodynamic therapy with verteporfin) (193, 196, 243-252).

Development of RPE tears after anti-VEGF intravitreal injection has been attributed to a decline in intercellular adherence, thereby increasing susceptibility to tearing of the RPE layer (236).

The incidence of RPE tears during ranibizumab treatment was 0.4% (201).

Salz *et al*. (239) concluded in their review that the overall incidence of RPE tears in eyes with wet AMD was similar regardless of whether an anti-VEGF agent was used, and that patients receiving anti-VEGF therapy were more likely to develop a tear earlier than untreated patients, most probably related to the accelerated involution induced by VEGF inhibition.

According to Chang and Seraf (238), all cases of RPE tear associated with anti-VEGF treatment occurred in the setting of wet AMD. Information on RPE in the CRVO population from the published literature is scarce. Below are some findings:

Data from a study of 707 patients (1,300 injections) who visited Osaka University Hospital, Japan, and received one or repeated IVT injections of bevacizumab were reviewed. Each patient was followed for AEs for two months post injections. No cases of RPE were reported among the 88 CRVO/BRVO patients. The one reported case of RPE occurred in a patient with AMD (241).

Overall, the total incidence of RPE tears with Eylea in the AMD Phase III trials was in line with the known background incidences from literature; no RPE tears occurred in the CRVO/BRVO studies, in the myopic CNV study, or in the DME studies through Week 148. The promotion of RPE tear development by IVT treatment with Eylea is, therefore, deemed unlikely.

Impact on individual patients

RPE tears may lead to a loss of vision (and thus to legal blindness).

Risk factors and risk groups

Wet AMD with pigment epithelial detachment; treatment of neovascularization.

Preventability

The underlying mechanisms resulting in RPE tears following intravitreal injection are not yet understood and thus, no preventive measure are currently known.

Impact on risk-benefit balance of the product

An educational program is performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks. The effectiveness of this program was verified with a post authorization safety study (SN 16526).

This important identified risk does not have an impact on the positive risk-benefit balance of Eylea.

Public health impact

The potential public health impact of this safety concern is considered to be low, due to the low frequency of serious or severe events in clinical trials.

SVII.3.1.5 Identified risk: Cataract (especially of traumatic origin)

Potential mechanisms

Related to IVT procedure.

Evidence source(s) and strength of evidence

Main reason for considering cataract (especially of traumatic origin) as an important identified risk:

Generally, clouding of the usually clear eye lens is called a cataract. Cataract may occur spontaneously (particularly in the elderly), as a side effect of certain drugs, or following outside influences such as irradiation or mechanical injury (traumatic cataract).

If the needle used to inject Eylea touched the lens in the patient’s eye this could cause such a traumatic cataract. There is currently no evidence that the occurrence of a traumatic cataract is increased on treatment with Eylea. However, as this might be a hypothetical result of the lens perforation, it has been included as potential important risk.

The proportion of Eylea-exposed adult patients who experienced traumatic cataract in the study eye in the clinical studies with Eylea ranged from 0% to 2.8% (VIVID-DME & VISTA-DME).

Evidence sources: refer to the linked subsection.

MedDRA search terms (version 19.1 for adult clinical 2 mg studies, version 20.0 for PM data and version 23.1 for ROP studies in preterm infants, version 25.0 for 8 mg dose in wet AMD and DME):

Preferred terms included in search: Atopic cataract, cataract, cataract cortical, cataract diabetic, cataract nuclear, cataract operation, cataract subcapsular, cataract traumatic, intraocular lens implant, lens capsulotomy, lens discolouration, lens extraction, lenticular injury, lenticular opacities, lenticular operation, posterior lens capsulotomy, radiation cataract, and toxic cataract.

Due to a MedDRA update and additions of PTs considered in a Bayer MedDRA Labeling Group the following PT was also considered in the retrieval for the 8 mg studies: PT posterior capsule opacification.

Characterization of the risk:

Frequency

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) – Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

All cataracts:

The 96 weeks overall cataract incidence including all terms from the search strategy was 12.8% of patients in the combined Eylea group and 10.4% in the ranibizumab group regardless of association to the injection-procedure (Table SVII.62). This incidence of cataracts is in line with background incidences as derived from literature and as seen in control arms from clinical trials with other anti-VEGF therapies (see background incidences below).

Table SVII.62: Number of subjects with cataract in the study eye (grouped term and included preferred terms) in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
Cataract	62 (10.4)	86 (14.0)	72 (12.0)	75 (12.3)	233 (12.8)
Included preferred terms					
Cataract					
Cataract cortical	37 (6.2)	53 (8.6)	51 (8.5)	40 (6.6)	144 (7.9)
Cataract nuclear	7 (1.2)	4 (0.7)	1 (0.2)	11 (1.8)	16 (0.9)
Cataract operation	15 (2.5)	16 (2.6)	13 (2.2)	12 (2.0)	41 (2.2)
Cataract subcapsular	0	1 (0.2)	0	1 (0.2)	2 (0.1)
Intraocular lens implant	5 (0.8)	10 (1.6)	11 (1.8)	12 (2.0)	33 (1.8)
Lenticular opacities	1 (0.2)	2 (0.3)	0	1 (0.2)	3 (0.2)
Lens capsulotomy	1 (0.2)	5 (0.8)	2 (0.3)	7 (1.1)	14 (0.8)
	0	1 (0.2)	0	0	1 (<0.1)

Q4 = every 4 weeks, Q8 = every 8 weeks
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.1/1

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Injection-related (traumatic) cataracts:

In total 0.8% of patients treated with Eylea showed cataracts which were assessed as related to the IVT injection procedure based on the investigators' assessment and thus may be considered of traumatic origin (Table SVII.63). The incidence of such cataracts was 0.5% in the ranibizumab group.

Table SVII.63: Number of subjects with injection-related cataract in the study eye (grouped term and included preferred terms) in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
Cataract	3 (0.5)	6 (1.0)	5 (0.8)	3 (0.5)	14 (0.8)
Included preferred terms					
Cataract	2 (0.3)	3 (0.5)	3 (0.5)	3 (0.5)	9 (0.5)
Cataract cortical	1 (0.2)	0	0	0	0
Cataract nuclear	0	2 (0.3)	1 (0.2)	0	3 (0.2)
Cataract subcapsular	0	1 (0.2)	1 (0.2)	0	2 (0.1)
Lenticular opacities	0	1 (0.2)	0	0	1 (<0.1)

Q4 = every 4 weeks, Q8 = every 8 weeks
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.1/1

A study comparing different IVT administered drugs suggested that the occurrence of traumatic cataract events is statistically independent of the injected drug, and patients' age (253). The 96 weeks incidence of 0.8% of traumatic cataract is in a similar range of incidences derived from other studies which ranged from 0.2% to 0.6% of patients experiencing traumatic cataracts (254), see also the section on background incidence and prevalence.

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg doses) – VIEW 1 long-term extension study

All cataracts:

Cataracts in the study eye during the extension period occurred in 45 patients (8 patients [11.6%] in the former randomized ranibizumab group and 37 patients [14.6%] in the former randomized Eylea groups; Table SVII.64). There were no meaningful differences compared with the frequency of any cataract reported from the pivotal AMD trials through Week 96 (12.8%).

Table SVII.64: Number of subjects with cataract in the study eye (grouped term and included preferred terms) in the Phase III VIEW 1 extension study in AMD (SAF; all subjects treated with VTE in the extension phase, treatment groups are displayed according to original randomization in VIEW 1)

MedDRA 19.1	*Ranibizumab 0.5Q4* [a] *n (%)*	*Eylea combined* [b] *n (%)*	Eylea Total [c] n (%)
Number of subjects	69	254	323
Grouped term	8 (11.6)	37 (14.6)	45 (13.9)

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Table SVII.64: Number of subjects with cataract in the study eye (grouped term and included preferred terms) in the Phase III VIEW 1 extension study in AMD (SAF; all subjects treated with VTE in the extension phase, treatment groups are displayed according to original randomization in VIEW 1)

MedDRA 19.1	*Ranibizumab 0.5Q4* [a] *n (%)*	*Eylea combined* [b] *n (%)*	Eylea Total [c] n (%)
Cataract			
Included preferred terms			
Cataract	4 (5.8)	14 (5.5)	18 (5.6)
Cataract cortical	1 (1.4)	0	1 (0.3)
Cataract nuclear	1 (1.4)	13 (5.1)	14 (4.3)
Cataract subcapsular	1 (1.4)	12 (4.7)	13 (4.0)
Intraocular lens implant	1 (1.4)	1 (0.4)	2 (0.6)
Lenticular opacities	0	1 (0.4)	1 (0.3)

[a]: Patients who were randomized to treatment with ranibizumab in the VIEW 1 core study.
[b]: Patients who were randomized to treatment with Eylea (0.5Q4, 2Q4, or 2Q8) in the VIEW 1 core study.
[C]: All patients who were treated with Eylea in the extension study period. Only AEs occurring after the first active Eylea injection were counted.
Note: Events that occurred in the VIEW 1 core study are not considered.
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.2/1

Injection-related (traumatic) cataracts:

No injection-related cataracts were reported during the extension period.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial SIGHT (52 weeks)

All cataracts:

Any cataracts in the study eye were reported in 3 patients (3.9%) in the PDT+VTE 2 mg group and in 10 patients (4.4%) in the VTE 2Q8 group (12 patients [4.0%] in the Eylea total group; see Table SVII.65).

Table SVII.65: Number of subjects with any cataract in the study eye (grouped term and included preferred terms) in the Phase III AMD study SIGHT from baseline through Week 52 (SAF)

MedDRA 19.1	PDT + VTE 2mg [a] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	76	228	299
Grouped term			
Cataract	3 (3.9)	10 (4.4)	12 (4.0)
Included preferred terms			
Cataract	1 (1.3)	2 (0.9)	3 (1.0)
Cataract cortical	0	3 (1.3)	3 (1.0)
Lenticular opacities	2 (2.6)	5 (2.2)	6 (2.0)

[a]: PDT + sham injections until Wk. 24, afterwards VTE 2 mg at Wks. 28, 32, 36, 40, and 48.
[b]: First 3 injections with VTE 2Q4, followed by VTE 2Q8 until Wk. 48 (sham PDT until Wk. 24).
[c]: All patients exposed to Eylea. Only TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.3/1

Injection-related (traumatic) cataracts:

Injection-related cataracts in the study eye were reported in one patient (1.3%) in the PDT+VTE 2 mg group and in 2 patients (0.9%) in the VTE 2Q8 group (3 patients [1.0%] in the Eylea total group; see Table SVII.66). Thus, the rate of traumatic cataract was small and similar in the 2 treatment groups.

Table SVII.66: Number of subjects with injection-related (traumatic) cataract in the study eye (grouped term and included preferred terms) in the Phase III AMD study SIGHT from baseline through Week 52 (SAF)

MedDRA 19.1	PDT + VTE 2mg [a] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	76	228	299
Grouped term			
Injection-related cataract	1 (1.3)	2 (0.9)	3 (1.0)
Included preferred terms			
Cataract	1 (1.3)	2 (0.9)	3 (1.0)

[a]: PDT + sham injections until Wk. 24, afterwards VTE 2 mg at Wks. 28, 32, 36, 40, and 48.
[b]: First 3 injections with VTE 2Q4, followed by VTE 2Q8 until Wk. 48 (sham PDT until Wk. 24).
[c]: All patients exposed to Eylea. Only TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.3/1

Wet AMD (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial ALTAIR (52 weeks)

All cataracts:

Cases of cataract were infrequent in the ALTAIR study, since only 2 patients in the 2W adjustment group and 1 patient in the 4W adjustment group experienced such events (1.6% based on 124 patients randomized to the 2W adjustment group or 0.8% based on 123 patients randomized to the 4W adjustment group or 1.2% based on the 254 Eylea-exposed patients).

Injection-related cataracts:

No injection-related cataracts were reported in ALTAIR through week 52.

CRVO (Eylea 40 mg/mL, 2 mg dose) – Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

All cataracts:

Cataracts in the study eye occurred in 7.6% of patients on Eylea treatment (24 patients, Table SVII.67). The incidence was higher in the Eylea 2Q4+PRN group than in the Sham+PRN group (9.2% *vs*. 4.9%) but, in view of the small absolute number of events, no clinically meaningful differences were observed between the 2 randomized treatment groups.

Table SVII.67: Number of subjects with cataract in the study eye (grouped term and included preferred terms) in the Phase III CRVO studies from baseline through Week 76/100 (SAF)

MedDRA 19.1	Sham + PRN n (%)	VTE 2Q4 + PRN n (%)	Eylea total [a] n (%)
Number of subjects	142	218	317
Grouped term			
Cataract	7 (4.9)	20 (9.2)	24 (7.6)
Included preferred terms			
Cataract	5 (3.5)	11 (5.0)	14 (4.4)
Cataract nuclear	1 (0.7)	4 (1.8)	5 (1.6)
Cataract subcapsular	0	1 (0.5)	1 (0.3)
Lenticular opacities	1 (0.7)	4 (1.8)	4 (1.3)

[a]: All patients exposed to Eylea. All TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis – EU-RMP Pool 1 (CRVO), Table 1.3.1/1

Injection-related (traumatic) cataracts:

Only one patient in the CRVO studies (in the Eylea 2Q4+PRN group) experienced an injection-related cataract in the study eye (PT: Cataract).

BRVO (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial VIBRANT (52 weeks)

All cataracts:

Seven patients in the VTE 2 mg group (7.7%) *vs.* no patient in the Laser+VTE 2 mg group experienced at least one event of any cataract (Table SVII.68).

Table SVII.68: Number of subjects with cataract in the study eye (grouped term and included preferred terms) in the Phase III BRVO study from baseline through Week 52 (SAF)

MedDRA 19.1	Laser+VTE 2 mg n (%)	VTE 2 mg n (%)	Eylea total[a] n (%)
Number of subjects	92	91	158
Grouped term			
Cataract	0	7 (7.7)	7 (4.4)
Included preferred terms			
Cataract	0	3 (3.3)	3 (1.9)
Cataract cortical	0	2 (2.2)	2 (1.3)
Cataract subcapsular	0	1 (1.1)	1 (1.1)
Cataract traumatic	0	1 (1.1)	1 (1.1)

[a]: All patients exposed to Eylea. All TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis – EU-RMP Pool 1 (BRVO), Table 1.4.1/1

Injection-related (traumatic) cataracts:

One case of cataract (preferred term: “cataract traumatic”) was regarded as injection-related (i.e., traumatic). This event occurred in the VTE 2 mg group.

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial MYRROR (48 weeks)

All cataracts:

There was only one patient with cataract reported in the MYRROR study through Week 48. This patient was treated in the Eylea 2 mg group (1.1% [N=91] or 0.9% related to N=116 [Eylea total group]). The underlying event (PT: Cataract subcapsular) was non-serious and had a mild severity but was not resolved.

Injection-related (traumatic) cataracts:

No injection-related (i.e., traumatic) cataracts were reported in MYRROR through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose) – Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

All cataracts:

The proportions of patients with any cataract through Week 148 were 23.3% in the laser group, 30.2% in the 2Q4 group, 23,3% in the 2Q8 group, and 22.9% among the 821 study patients who were exposed to Eylea at least once (Table SVII.69).

Table SVII.69: Number of subjects with any cataract in the study eye (grouped term and included preferred terms) in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Cataract	67 (23.3)	88 (30.2)	67 (23.3)	188 (22.9)
Included preferred terms				
Cataract	38 (13.2)	56 (19.2)	44 (15.3)	121 (14.7)
Cataract cortical	12 (4.2)	9 (3.1)	12 (4.2)	27 (3.3)
Cataract nuclear	11 (3.8)	11 (3.8)	8 (2.8)	22 (2.7)
Cataract operation	2 (0.7)	2 (0.7)	1 (0.3)	5 (0.6)
Cataract subcapsular	12 (4.2)	23 (7.9)	15 (5.2)	43 (5.2)
Intraocular lens implant	1 (0.3)	0	0	1 (0.1)
Lenticular opacities	4 (1.4)	5 (1.7)	1 (0.3)	8 (1.0)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis – EU-RMP Pool 1 (DME), Table 1.5.1/1

Injection-related (traumatic) cataracts:

The incidence of injection-related (i.e., traumatic) cataracts through Week 148 was slightly smaller in the laser group than in the Eylea 2Q4 and 2Q8 groups (1.0% *vs*. 4.5% and 2.4%, respectively; Table SVII.70).

Table SVII.70: Number of subjects with injection-related (traumatic) cataract in the study eye (grouped term and included preferred terms) in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Injection-related cataract	3 (1.0)	13 (4.5)	7 (2.4)	23 (2.8)
Included preferred terms				
Cataract	3 (1.0)	6 (2.1)	6 (2.1)	15 (1.8)
Cataract cortical	0	1 (0.3)	1 (0.3)	2 (0.2)
Cataract subcapsular	0	6 (2.1)	1 (0.3)	7 (0.9)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis – EU-RMP Pool 1 (DME), Table 1.5.1/1

DME (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial VIVID-EAST (52 weeks)

All cataracts:

Any cataracts in the study eye were reported in 10 patients (8.1%) in the laser group, 3 patients (2.4%) in the 2Q4 group, 2 patients (1.6%) in the 2Q8 group, and 6 patients (2.0%) in the Eylea total group (Table SVII.71). Thus, cataract cases occurred more frequently in the laser group than in the Eylea groups.

Table SVII.71: Number of subjects with any cataract in the study eye (grouped term and included preferred terms) in the Phase III DME study VIVID-EAST from baseline through Week 52 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	N=124	N=127	N=127	N=299
Grouped term				
Cataract	10 (8.1)	3 (2.4)	2 (1.6)	6 (2.0)
Included preferred terms				
Cataract	3 (2.4)	1 (0.8)	1 (0.8)	3 (1.0)
Cataract cortical	5 (4.0)	0	1 (0.8)	1 (0.3)
Cataract nuclear	0	1 (0.8)	0	1 (0.3)
Cataract subcapsular	1 (0.8)	1 (0.8)	0	1 (0.3)
Lenticular opacities	1 (0.8)	0	0	0

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=45 exposed to Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 52.
Table Source: Integrated Analysis – EU-RMP Pool 1 (DME), Table 1.5.3/1.

Injection-related (traumatic) cataracts:

No cases of injection-related cataract in the study eye were reported in the VIVID-EAST study.

DME (Eylea 40 mg/mL, 2 mg dose) – Open-label Clinical Trial VIVID-JAPAN (52 weeks)

All cataracts:

In the open-label Phase III study VIVID-JAPAN, one patient (1.4% of the 72 subjects included in the SAF) experienced one treatment-emergent adverse event of cataract in the study eye through Week 52. This event was non-serious, but severe and non-resolved.

Injection-related (traumatic) cataracts:

No injection-related (traumatic cataracts) were reported in the open-label Phase III study VIVID-JAPAN.ROP (Eylea 40 mg/mL, 0.4 mg dose) – Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

All cataracts:

In the open-label Phase III study FIREFLEYE, a total of 2 subjects (2.5% of the 79 SAF subjects, no case reported in the FIREFLEYE NEXT study) experienced any treatment-emergent adverse event of “cataract” (Table SVII.72).

Table SVII.72: Number of subjects with any cataract in the study eye (grouped term and included preferred terms) in the Phase III FIREFLEYE study (SAF)

MedDRA 23.1	Laser n (%)	VTE 0.4 mg n (%)	VTE total [a] n (%)
Number of subjects	38	75	79
Grouped term			
Cataract	1 (2.6)	1 (1.3)	2 (2.5)
Included preferred terms			
Cataract	1 (2.6)	0	1 (1.3)
Lenticular opacities	0	1 (1.3)	1 (1.3)

[a]: VTE total includes all subjects who received VTE 0.4 mg including subjects randomized to laser and receiving VTE 0.4 mg as rescue treatment.
Table Source: Integrated Analysis – EU-RMP ROP submission Pool 1 (ROP 20090), Table 1.2/1

No cataracts were reported in the Phase IIIb study FIREFLEYE NEXT (interim data).

Injection-related (traumatic) cataracts:

No injection-related (i.e., traumatic) cataracts were reported in the Phase III study FIREFLEYE or the Phase IIIb study FIREFLEYE NEXT.

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose) – Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (96 weeks), and the DME PHOTON study (96 weeks):

All cataracts:

Any cataracts in the study eye were reported in 133 patients (10.9%) in the 8 mg dose treatment group and in 51 patients (9.2%) in the 2 mg dose treatment group (see Table SVII.73).

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Table SVII.73: Number of subjects with any cataract in the study eye (grouped term and included preferred terms) in the Phase II CANDELA study and Phase III PULSAR study in wet AMD and in the Phase III PHOTON study in DME (SAF)

MedDRA 26.0	*2 mg* *n (%)*	*HDq12* *n (%)*	*HDq16* *n (%)*	HD Total n (%)
Number of subjects	556	716	501	1,217
Grouped term Cataract	51 (9.2%)	71 (9.9%)	62 (12.4%)	133 (10.9%)
Included preferred terms				
Cataract	28 (5.0%)	49 (6.8%)	51 (10.2%)	100 (8.2%)
Cataract cortical	3 (0.5%)	4 (0.6%)	1 (0.2%)	5 (0.4%)
Cataract nuclear	7 (1.3%)	5 (0.7%)	2 (0.4%)	7 (0.6%)
Cataract operation	1 (0.2%)	0	0	0
Cataract subcapsular	9 (1.6%)	10 (1.4%)	1(0.2%)	11 (0.9%)
Lenticular opacities	1 (0.2%)	1 (0.1%)	0	1 (<0.1%)
Posterior capsule opacification	5 (0.9%)	7 (1.0%)	9 (1.8%)	16 (1.3%)
Cataract	28 (5.0%)	49 (6.8%)	51 (10.2%)	100 (8.2%)
Cataract cortical	3 (0.5%)	4 (0.6%)	1 (0.2%)	5 (0.4%)

2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
HD total: HDq12 and HDq16 combined.
Source: Integrated Analysis – Pool 1, 96 weeks analysis, AMD 8 mg (w44/96) + DME 8 mg (w96); Table 3.1/1

Injection-related (traumatic) cataracts:

Three patients (0.2%) treated with aflibercept 8 mg dose showed a cataract which was assessed as related to the IVT injection procedure based on the investigators' assessment and thus may be considered of traumatic origin. The incidence of such cataracts was 0.2% (1 patient) in the aflibercept 2 mg dose treatment group.

Post-marketing Data

As of 15 SEP 2017, a total of 713 cases (including 786 events) with any cataract were reported.

Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period until 30 SEP 2017, the reporting rate of "cataract" cases (N=713) was 0.04 cases per 1,000 sold vials (0.004%) and 0.31 cases per 1,000 patient years (0.031%), respectively.

Table SVII.74: Number of post-marketing events "cataract" by 15 SEP 2017

Group: Cataract	*713 cases*		
Grouped preferred terms[a]:	**Non-serious**	**Serious**	**All**
Cataract	125	427	552
Cataract operation	4	184	188
Intraocular lens implant	0	20	20
Cataract traumatic	0	6	6
Cataract nuclear	1	3	4
Cataract subcapsular	1	3	4
Lenticular opacities	2	1	3
Lens capsulotomy	0	3	3
Lenticular injury	1	1	2
Lens extraction	0	2	2
Lens discolouration	1	0	1
Lenticular operation	0	1	1
Total number of events	**135**	**651**	**786**

Source: Global Pharmacovigilance Safety Database
a: MedDRA Version 20.0. Figures are event-based, i.e., more than one preferred term event per reported case is possible. Included are both medically confirmed and non-medically confirmed events.

Seriousness/outcomes

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg doses) – Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

All cataracts:

Serious cataracts were reported in 2 patients (0.3%) on treatment with ranibizumab and 14 patients (0.8%) on treatment with Eylea (Table SVII.75).

Table SVII.75: Number of subjects with serious cataract in the study eye (grouped term and included preferred terms) in randomized Phase III wet AMD studies from baseline through Week 96 (Pool 1, SAF)

MedDRA 19.1	**Ranibizumab**	**Eylea**			
	Q4 n (%)	**2 mg Q4 n (%)**	**0.5 mg Q4 n (%)**	**2 mg Q8 n (%)**	**Total n (%)**
Number of subjects	595	613	601	610	1,824
Grouped term					
Cataract	2 (0.3)	6 (1.0)	4 (0.7)	4 (0.7)	14 (0.8)
Included preferred terms					
Cataract	1 (0.2)	4 (0.7)	3 (0.5)	4 (0.7)	11 (0.6)
Cataract cortical	1 (0.2)	0	0	0	0
Cataract nuclear	0	1 (0.2)	1 (0.2)	0	2 (0.1)
Cataract subcapsular	0	1 (0.2)	0	0	1 (<0.1)

Q4 = every 4 weeks, Q8 = every 8 weeks
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.1/4

The event outcomes of all cataracts are summarized in the following Table SVII.76. In 40 patients (6.7%) in the ranibizumab group and 152 patients (8.3%) in the Eylea total group the cataract events were not resolved.

Table SVII.76: Number of subjects with cataract in the study eye by outcome in randomized Phase III wet AMD studies from baseline through Week 96 (Pool 1, SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
Cataract	62 (10.4)	86 (14.0)	72 (12.0)	75 (12.3)	233 (12.8)
Outcomes					
Recovered/resolved	14 (2.4)	22 (3.6)	17 (2.8)	21 (3.4)	60 (3.3)
Recovering/resolving	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.3)	4 (0.2)
Recovered/resolved with sequelae	2 (0.3)	1 (0.2)	0	1 (0.2)	2 (0.1)
Unknown	5 (0.8)	4 (0.7)	5 (0.8)	6 (1.0)	15 (0.8)
Not recovered / not resolved	40 (6.7)	58 (9.5)	49 (8.2)	45 (7.4)	152 (8.3)

Q4 = every 4 weeks, Q8 = every 8 weeks
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.1/3

Injection-related (traumatic) cataracts:

In 0.2% of patients treated with Eylea (3 patients), the injection-related cataracts were considered serious (Table SVII.77).

Table SVII.77: Number of subjects with serious injection-related cataract in the study eye in the randomized Phase III wet AMD studies from baseline through Week 96 (Pool 1, SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
Cataract	2 (0.3)	2 (0.4)	0	1 (0.2)	3 (0.2)
Included preferred terms					
Cataract	1 (0.2)	2 (0.3)	0	1 (0.2)	3 (0.2)
Cataract cortical	1 (0.2)	0	0	0	0

Q4 = every 4 weeks, Q8 = every 8 weeks
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.1/4

Among the 14 Eylea-treated patients with injection-related cataract, 8 patients were recovered, while 6 patients remained not recovered (Table SVII.78).

Table SVII.78: Number of subjects with injection-related cataract in the study eye by outcome in randomized Phase III wet AMD studies from baseline through Week 96 (Pool 1, SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
Cataract	3 (0.5)	6 (1.0)	5 (0.8)	3 (0.5)	14 (0.8)
Outcome					
Recovered/resolved	2 (0.3)	3 (0.5)	2 (0.3)	3 (0.5)	8 (0.4)
Not recovered / not resolved	1 (0.2)	3 (0.5)	3 (0.5)	0	6 (0.3)

Q4 = every 4 weeks, Q8 = every 8 weeks
Note: For each subject, only the adverse event with the worst outcome is counted within each safety topic class and overall.
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.1/3

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) – VIEW 1 long-term extension study

All cataracts:

One cataract event occurring in the extension period (in one patient of the former randomized Eylea groups [0.4%], PT: "cataract") was regarded as serious (this patient recovered from the event).

Cataract event outcomes in the Eylea total group were "resolved" and "not resolved" in similar proportions (23 and 22 patients, respectively; Table SVII.79).

Table SVII.79: Number of subjects with cataract in the study eye by outcome in the Phase III VIEW 1 extension study in AMD (SAF; all subjects treated with VTE in the extension phase, treatment groups are displayed according to original randomization in VIEW 1)

MedDRA 19.1	*Ranibizumab 0.5Q4* [a] *n (%)*	*Eylea combined* [b] *n (%)*	Eylea Total [c] n (%)
Number of subjects	69	254	323
Grouped term			
Cataract	8 (11.6)	37 (14.6)	45 (13.9)
Outcome			
Recovered/resolved	6 (8.7)	17 (6.7)	23 (7.1)
Not recovered/resolved	2 (2.9)	20 (7.9)	22 (6.8)

[a]: Patients who were randomized to treatment with ranibizumab in the VIEW 1 core study.
[b]: Patients who were randomized to treatment with Eylea (0.5Q4, 2Q4, or 2Q8) in the VIEW 1 core study.
[c]: All patients who were treated with Eylea in the extension study period. Only AEs occurring after the first active Eylea injection were counted.
Note: Events that occurred in the VIEW 1 core study are not considered.
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.2/3

Injection-related (traumatic) cataracts:

No injection-related cataracts were reported during the extension period.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial SIGHT (52 weeks)

All cataracts:

Only one cataract (also considered injection-related) was regarded as serious. This event occurred in one patient in the PDT+VTE 2 mg group after start of Eylea (1.3% based on the number of patients in the PDT+VTE 2 mg group or 0.3% based on all 299 exposed patients).

In 8 of the 12 patients with any cataract the event outcome was “not recovered”, while in 2 and one patients the outcome was “recovering” and “recovered”, respectively (Table SVII.80).

Table SVII.80: Number of subjects with any cataract in the study eye by outcome in the Phase III AMD study SIGHT from baseline through Week 52 (SAF)

MedDRA 19.1	PDT + VTE 2mg [a] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	76	228	299
Grouped term			
Cataract	3 (3.9)	10 (4.4)	12 (4.0)
Outcome			
Recovered / resolved	1 (1.3)	1 (0.4)	2 (0.7)
Recovering / resolving	0	2 (0.9)	2 (0.7)
Not recovered / not resolved	2 (2.6)	7 (3.1)	8 (2.7)

[a]: PDT + sham injections until Wk. 24, afterwards VTE 2 mg at Wks. 28, 32, 36, 40, and 48.
[b]: First 3 injections with VTE 2Q4, followed by VTE 2Q8 until Wk. 48 (sham PDT until Wk. 24).
[c]: All patients exposed to Eylea. Only TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.3/3

Injection-related (traumatic) cataracts:

One injection-related cataract was regarded as serious. This event occurred in the patient in the PDT+VTE 2 mg group after start of Eylea (1.3% based on the number of patients in the PDT+VTE 2 mg group or 0.3% based on all 299 exposed patients).

Outcomes of injection-related cataracts were “not recovered”, “recovering”, and “recovered” in one patient each (Table SVII.81).

Table SVII.81: Number of subjects with injection-related cataract in the study eye by outcome in the Phase III AMD study SIGHT from baseline through Week 52 (SAF)

MedDRA 19.1	PDT + VTE 2mg [a] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	76	228	299
Grouped term			
Injection-related cataract	1 (1.3)	2 (0.9)	3 (1.0)
Outcome			
Recovered / resolved	0	1 (0.4)	1 (0.3)
Recovering / resolving	0	1 (0.4)	1 (0.3)
Not recovered / not resolved	1 (1.3)	0	1 (0.3)

[a]: PDT + sham injections until Wk. 24, afterwards VTE 2 mg at Wks. 28, 32, 36, 40, and 48.
[b]: First 3 injections with VTE 2Q4, followed by VTE 2Q8 until Wk. 48 (sham PDT until Wk. 24).
[c]: All patients exposed to Eylea. Only TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.1.3/3

Wet AMD (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial ALTAIR (52 weeks)

3 cases of cataracts were reported (2 occurring in the 2W adjustment group and 1 in the 4W adjustment group), none of the cases was serious. Outcome for these cases was reported as unknown. CRVO (Eylea 40 mg/mL, 2 mg dose) – Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

All cataracts:

In 5 patients (4 in the Eylea 2Q4+PRN group and one in the sham group on treatment with Eylea) the reported cataract was regarded as serious (1.6% of patients in the Eylea total group; Table SVII.82).

Table SVII.82: Number of subjects with serious cataract in the study eye (grouped term and included preferred terms) in the Phase III CRVO studies from baseline through Week 76/100 (SAF)

MedDRA 19.1	Sham + PRN n (%)	VTE 2Q4 + PRN n (%)	Eylea total [a] n (%)
Number of subjects	142	218	317
Grouped term			
Cataract	1 (0.7)	4 (1.8)	5 (1.6)
Included preferred terms			
Cataract	1 (0.7)	4 (1.8)	5 (1.6)

[a]: All patients exposed to Eylea. All TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis – EU-RMP Pool 1 (CRVO), Table 1.3.1/4

In 16 patients in the total Eylea group (5.0%) the cataract was not resolved, see Table SVII.83.

Table SVII.83: Number of subjects with cataract in the study eye by outcome in the Phase III CRVO studies from baseline through Week 76/100 (SAF)

MedDRA 19.1	Sham + PRN n (%)	VTE 2Q4 + PRN n (%)	Eylea total [a] n (%)
Number of subjects	142	218	317
Grouped term			
Cataract	4 (4.9)	20 (9.2)	24 (7.6)
Outcome			
Recovered/resolved	3 (2.1)	4 (1.8)	7 (2.2)
Recovering/resolving	2 (1.4)	1 (0.5)	1 (0.3)
Not recovered/not resolved	2 (1.4)	15 (6.9)	16 (5.0)

[a]: All patients exposed to Eylea. All TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis – EU-RMP Pool 1 (CRVO), Table 1.3.1/3

Injection-related (traumatic) cataracts:

Only one patient in the CRVO studies (in the Eylea 2Q4+PRN group) experienced an injection-related cataract in the study eye (PT: Cataract). This event was considered serious and was not resolved.

BRVO (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial VIBRANT (52 weeks)

All cataracts:

A serious cataract was reported in one patient in the VTE 2 mg group (1.1% based on 91 patients, or 0.6% based on all 158 subjects exposed to Eylea). This serious event (PT: traumatic cataract) was regarded as injection-related (see description in text next paragraph).

Injection-related (traumatic) cataracts:

The only injection-related cataract reported by Week 52 (occurring in the Eylea group) was considered serious (severe intensity, resolved).

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial MYRROR (48 weeks)

All cataracts:

The only reported case of cataract (occurring in the Eylea 2 mg group) was non-serious; the outcome was “not recovered/not resolved”.

Injection-related (traumatic) cataracts:

No injection-related (i.e., traumatic) cataracts were reported in MYRROR through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose) – Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

All cataracts:

Serious cataracts in the study eye were reported in 4 patients in the laser group (1.4%), 11 patients in the Eylea 2Q4 group (3.8%), 9 patients in the Eylea 2Q8 group (3.1%) and 23 patients in the Eylea total group (2.8%; Table SVII.84).

Table SVII.84: Number of subjects with any serious cataract in the study eye (grouped term and included preferred terms) in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Cataract	4 (1.4)	11 (3.8)	9 (3.1)	23 (2.8)
Included preferred terms				
Cataract	1 (0.3)	9 (3.1)	6 (2.1)	15 (1.8)
Cataract operation	2 (0.7)	2 (0.7)	1 (0.3)	5 (0.6)
Cataract subcapsular	1 (0.3)	0	2 (0.7)	3 (0.4)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis – EU-RMP Pool 1 (DME), Table 1.5.1/4

The event outcome for all cataracts in the study eye through Week 148 is summarized in the following table. The proportions of patients with resolved *vs*. unresolved cataracts were similar in the Eylea total group (9.7% *vs*. 11.8%; Table SVII.85).

Table SVII.85: Number of subjects with any cataract in the study eye by outcome in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Cataract	67 (23.3)	88 (30.2)	67 (23.3)	188 (22.9)
Outcome				
Recovered / resolved	29 (10.1)	35 (12.0)	31 (10.8)	80 (9.7)
Recovering / resolving	3 (1.0)	3 (1.0)	4 (1.4)	9 (1.1)
Recovered / resolved with sequelae	0	0	1 (0.3)	1 (0.1)
Unknown	1 (0.3)	0	0	1 (0.1)
Not recovered / not resolved	34 (11.8)	50 (17.2)	31 (10.8)	97 (11.8)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis – EU-RMP Pool 1 (AMD), Table 1.5.1/3

Injection-related (traumatic) cataracts:

Serious injection-related cataracts were reported in 2 patients in the 2Q4 group and 3 patients in the 2Q8 group (Table SVII.86).

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Table SVII.86: Number of subjects with serious injection-related (traumatic) cataract in the study eye (grouped term and included preferred terms) in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Injection-related cataract	0	2 (0.7)	3 (1.0)	5 (0.6)
Included preferred terms				
Cataract	0	2 (0.7)	2 (0.7)	4 (0.5)
Cataract subcapsular	0	0	1 (0.3)	1 (0.1)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis – EU-RMP Pool 1 (DME), Table 1.5.1/4

As with any cataracts, also the proportions of patients with resolved *vs*. unresolved injection-related cataract were similar in the Eylea total group (1.5% *vs*. 1.2%; Table SVII.87).

Table SVII.87: Number of subjects with injection-related (traumatic) cataract in the study eye by outcome in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Injection-related cataract	3 (1.0)	13 (4.5)	7 (2.4)	23 (2.8)
Outcome				
Recovered / resolved	2 (0.7)	7 (2.4)	3 (1.0)	12 (1.5)
Recovering / resolving	1 (0.3)	0	0	1 (0.1)
Not recovered / not resolved	0	6 (2.1)	4 (1.4)	10 (1.2)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis – EU-RMP Pool 1 (DME), Table 1.5.1/3

DME (Eylea 40 mg/mL, 2 mg dose) – Clinical Trial VIVID-EAST (52 weeks)

All cataracts:

One cataract case (occurring in one patient in the 2Q4 group) was regarded as serious.

Three of the 6 patients with any cataract in the study eye in the Eylea total group did not recover, while 3 recovered or were recovering (Table SVII.88).

Table SVII.88: Number of subjects with any cataract in the study eye by outcome in the Phase III DME study VIVID-EAST from baseline through Week 52 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	N=124	N=127	N=127	N=299
Grouped term				
Cataract	10 (8.1)	3 (2.4)	2 (1.6)	6 (2.0)
Outcome				
Recovered / resolved	1 (0.8)	1 (0.8)	0	2 (0.7)
Recovering / resolving	0	0	1 (0.8)	1 (0.3)
Not recovered / not resolved	9 (7.3)	2 (1.6)	1 (0.8)	3 (1.0)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=45 exposed to Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 52.
Table Source: Integrated Analysis – EU-RMP Pool 1 (DME), Table 1.5.3/3

Injection-related (traumatic) cataracts:

No cases of injection-related cataract in the study eye were reported in the VIVID-EAST study.

DME (Eylea 40 mg/mL, 2 mg dose) – Open-label Clinical Trial VIVID-JAPAN (52 weeks)

All cataracts:

The only reported event of cataract was non-serious, severe, and not resolved.

Injection-related (traumatic) cataracts:

No injection-related cataracts were reported in VIVID-JAPAN.ROP (Eylea 40 mg/mL, 0.4 mg dose) – Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

In the open-label Phase III study FIREFLEYE none of the 2 cases was regarded as serious (no case reported in the FIREFLEYE NEXT study). Reported event outcomes in the Eylea total group were “recovered/resolved” in 1/2 patients and “not recovered / not resolved” in 1/2 patients (Table SVII.89).

Table SVII.89: Number of subjects with cataract in the study eye by outcome in the Phase III FIREFLEYE study (SAF)

MedDRA 23.1	Laser n (%)	VTE 0.4 mg n (%)	VTE total[a] n (%)
Number of subjects	38	75	79
Grouped term			
Cataract	1 (2.6%)	1 (1.3%)	2 (2.5%)
Outcome			
Recovered / resolved	0	1 (1.3%)	1 (1.3%)
Not recovered / not resolved	1 (2.6%)	0	1 (1.3%)

[a]: VTE total includes all subjects who received VTE 0.4 mg including subjects randomized to laser and receiving VTE 0.4 mg as rescue treatment.
Table Source: Integrated Analysis – EU-RMP ROP submission Pool 1 (ROP 20090), Table 1.2/3

Injection-related (traumatic) cataracts:

No injection-related (traumatic) cataracts were reported in the Phase III study FIREFLEYE or the Phase IIIb study FIREFLEYE NEXT.

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose) – Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (96 weeks), and the DME PHOTON study (96 weeks):

All cataracts:

Seven patients (0.6%) treated with 8mg aflibercept and 1 patient (0.2%) treated with 2 mg aflibercept experienced a serious cataract.

The event outcomes of all cataracts are summarized in the following Table SVII.90. In 60 patients (4.9%%) in the aflibercept 8 mg dose treatment groups and 25 patients (4.5%) in the aflibercept 2 mg dose treatment group the cataract events were resolved/resolving; the simlar percentages were detected for the outcome “not recovered”. In some patients outcome was reported as “unknown” (2 mg: 6patients, 1.1%; HDq12: 11 patients, 1.5%; HDq16: 8 patients, 1.6%) at the time of this report (week 96). Serious cataracts were reported in 7 patients (0.6%) on treatment with aflibercept 8 mg dose and in one patient (0.2%) treated with 2 mg aflibercept.No meaningful differences were observed between the 2 mg and the 8 mg dose treatment groups.

Table SVII.90: Number of subjects with any cataract in the study eye by outcome in the Phase II CANDELA study and Phase III PULSAR study in wet AMD and in the Phase III PHOTON study in DME (SAF)

MedDRA 25.0	*2 mg* n (%)	*HDq12* n (%)	*HDq16* n (%)	HD Total n (%)
Number of subjects	556	716	501	1,217
Grouped term Cataract	51 (9.2%)	71 (9.9%)	62 (12.4%)	133 (10.9%)
Outcome				
Recovered/resolved	21 (3.8%)	27 (3.8%)	25 (5.0%)	52 (4.3%)
Recovering/resolving	3 (0.5%)	3 (0.4%)	4 (0.8%)	7 (0.6%)
Recovered/resolved with sequele	1 (0.2%)	1 (0.1%)	0	1 (<0.1%)
Unknown	6 (1.1%)	11 (1.5%)	8 (1.6%)	19 (1.6%)
Not recovered/not resolved	20 (3.6%)	29 (4.1%)	25 (5.0%)	54 (4.4%)

2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
HD total: HDq12 and HDq16 combined.
Source: Integrated Analysis – Pool 1, 48 weeks analysis, AMD 8 mg (w44/48) + DME 8 mg (w48); Table 3.1/33

Injection-related (traumatic) cataracts:

Three patients (0.2%) treated with aflibercept 8 mg dose and one patient (0.2%) treated with aflibercept 2 mg dose experienced an injection-related cataract in the study eye. One of them was considered serious (HDq12). Outcome was reported as “not recovered” in the aflibercept 2 mg dose treatment group and as “not recovered” in one patient and “recovered” in 2 patients of the aflibercept 8 mg dose treatment group.

Post-marketing Data

Most of the 786 reported cataract events were serious (651 events), while 135 events were non-serious (see previous post-marketing table on cataract events).

Reported outcomes were "recovered/resolved" in 159 events, "recovering/resolving" in 95 events, "recovered/resolved with sequelae" in 2 events, and "not recovered/not resolved" in 165 events (missing or unknown outcomes in the remaining 365 events).

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Severity and nature of risk

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg doses) - Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

All cataracts:

Similar to the incidence of serious cataracts, "severe" cataracts were reported in one patient (0.2%) on treatment with ranibizumab and 14 patients (0.8%) on treatment with Eylea (Table SVII.91). Thus, most of the events in either treatment group were mild or moderate.

Table SVII.91: Number of subjects with cataract in the study eye by maximum severity in randomized Phase III wet AMD studies from baseline through Week 96 (Pool 1, SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
Cataract	62 (10.4)	86 (14.0)	72 (12.0)	75 (12.3)	233 (12.8)
Maximum severity					
Missing	0	0	0	1 (0.2)	1 (<0.1)
Mild	33 (5.5)	47 (7.7)	42 (7.0)	33 (5.4)	122 (6.7)
Moderate	28 (4.7)	32 (5.2)	27 (4.5)	37 (6.1)	96 (5.3)
Severe	1 (0.2)	7 (1.1)	3 (0.5)	4 (0.7)	14 (0.8)

Q4 = every 4 weeks, Q8 = every 8 weeks
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.1/2

Injection-related (traumatic) cataracts:

As shown in Table SVII.92 below, the majority of IVT-associated cataracts occurring in the Eylea total group were either mild or moderate in severity.

Table SVII.92: Number of subjects with injection-related cataract in the study eye by maximum severity in randomized Phase III wet AMD studies from baseline through Week 96 (Pool 1, SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
Cataract	3 (0.5)	6 (1.0)	5 (0.8)	3 (0.5)	14 (0.8)
Maximum severity					
Mild	2 (0.3)	3 (0.5)	3 (0.5)	0	6 (0.3)
Moderate	1 (0.2)	2 (0.1)	2 (0.3)	2 (0.3)	6 (0.3)
Severe	0	1 (0.2)	0	1 (0.2)	2 (0.1)

Q4 = every 4 weeks, Q8 = every 8 weeks
Note: At each level of subject summarization (Safety topic/PT), a subject is classified according to the maximum intensity, if the subject reported one or more events. At each level of subject summarization, a subject is counted only once.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.1/2

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Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) - VIEW 1 long-term extension study

All cataracts:

Three cataract events (all occurring in the former randomized Eylea groups) were regarded as severe (Table SVII.93).

Table SVII.93: Number of subjects with cataract in the study eye by maximum severity in the Phase III VIEW 1 extension study in AMD (SAF; all subjects treated with VTE in the extension phase, treatment groups are displayed according to original randomization in VIEW 1)

MedDRA 19.1	*Ranibizumab 0.5Q4*[a] *n (%)*	*Eylea combine* [b] *n (%)*	Eylea Total[c] n (%)
Number of subjects	69	254	323
Grouped term			
Cataract	8 (11.6)	37 (14.6)	45 (13.9)
Maximum severity			
Mild	4 (5.8)	21 (8.3)	25 (7.7)
Moderate	4 (5.8)	13 (5.1)	17 (5.3)
Severe	0	3 (1.2)	3 (0.9)

[a]: Patients who were randomized to treatment with ranibizumab in the VIEW 1 core study.
[b]: Patients who were randomized to treatment with Eylea (0.5Q4, 2Q4, or 2Q8) in the VIEW 1 core study.
[c]: All patients who were treated with Eylea in the extension study period. Only AEs occurring after the first active Eylea injection were counted.
Note: Events that occurred in the VIEW 1 core study are not considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.2/2

Injection-related (traumatic) cataracts:

No injection-related cataracts were reported during the extension period.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial SIGHT (52 weeks)

All cataracts:

No severe cataracts were reported during the 52 weeks' period of the SIGHT study, and most of them were mild (in 10/12 patients; Table SVII.94).

Table SVII.94: Number of subjects with any cataract in the study eye by maximum severity in the Phase III AMD study SIGHT from baseline through Week 52 (SAF)

MedDRA 19.1	PDT + VTE 2mg[a] n (%)	VTE 2Q8[b] n (%)	VTE total[c] n (%)
Number of subjects	76	228	299
Grouped term			
Cataract	3 (3.9)	10 (4.4)	12 (4.0)
Maximum severity			
Mild	2 (2.6)	9 (3.9)	10 (3.3)

Table SVII.94: Number of subjects with any cataract in the study eye by maximum severity in the Phase III AMD study SIGHT from baseline through Week 52 (SAF)

MedDRA 19.1	PDT + VTE 2mg[a] n (%)	VTE 2Q8[b] n (%)	VTE total[c] n (%)
Moderate	1 (1.3)	1 (0.4)	2 (0.7)
Severe	0	0	0

[a]: PDT + sham injections until Wk. 24, afterwards VTE 2 mg at Wks. 28, 32, 36, 40, and 48.
[b]: First 3 injections with VTE 2Q4, followed by VTE 2Q8 until Wk. 48 (sham PDT until Wk. 24).
[c]: All patients exposed to Eylea. Only TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.3/2

Injection-related cataracts

The injection-related cataracts were moderate in 2 patients and mild in one patient (Table SVII.95).

Table SVII.95: Number of subjects with injection-related cataract in the study eye by maximum severity in the Phase III AMD study SIGHT from baseline through Week 52 (SAF)

MedDRA 19.1	PDT + VTE 2mg [a] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	76	228	299
Grouped term			
Injection-related cataract	1 (1.3)	2 (0.9)	3 (1.0)
Maximum severity			
Mild	0	1 (0.4)	1 (0.3)
Moderate	1 (1.3)	1 (0.4)	2 (0.7)
Severe	0	0	0

[a]: PDT + sham injections until Wk. 24, afterwards VTE 2 mg at Wks. 28, 32, 36, 40, and 48.
[b]: First 3 injections with VTE 2Q4, followed by VTE 2Q8 until Wk. 48 (sham PDT until Wk. 24).
[c]: All patients exposed to Eylea. Only TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.3/2

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial ALTAIR (52 weeks)

3 cases of cataracts were reported (2 occurring in the 2W adjustment group and 1 in the 4W adjustment group); all 3 cases were regarded as “mild”.CRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

All cataracts:

Most cataracts were of mild or moderate intensity, whereas 2 patients (0.6%) in the Eylea total group experienced severe cataracts (Table SVII.96).

Table SVII.96: Number of subjects with cataract in the study eye by maximum severity in the Phase III CRVO studies from baseline through Week 76/100 (Pool 1, SAF)

MedDRA 19.1	Sham + PRN n (%)	VTE 2Q4 + PRN n (%)	Eylea total [a] n (%)
Number of subjects	142	218	317
Grouped term			
Cataract	4 (4.9)	20 (9.2)	24 (7.6)
Maximum severity			
Mild	4 (2.8)	13 (6.0)	15 (4.7)
Moderate	2 (1.4)	6 (2.8)	7 (2.2)
Severe	1 (0.7)	1 (0.5)	2 (0.6)

[a]: All patients exposed to Eylea. All TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.3.1/2

Injection-related (traumatic) cataracts:

The only reported injection-related cataract in the CRVO studies (Eylea total group) was regarded as severe.

BRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIBRANT (52 weeks)

All cataracts:

The reported cataracts in the study eye were mild in 4 patients, moderate in 2 patients, and severe in one patient (Table SVII.97).

Table SVII.97: Number of subjects with cataract in the study eye by maximum severity in the Phase III BRVO study from baseline through Week 52 (SAF)

MedDRA 19.1	Laser+VTE 2 mg n (%)	VTE 2 mg n (%)	Eylea total [a] n (%)
Number of subjects	92	91	158
Grouped term			
Cataract	0	7 (7.7)	7 (4.4)
Maximum severity			
Mild	0	4 (4.4)	4 (2.5)
Moderate	0	2 (2.2)	2 (1.3)
Severe	0	1 (1.1)	1 (0.6)

[a]: All patients exposed to Eylea. All TEAEs occurring after first exposure are considered.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.4.1/1

Injection-related (traumatic) cataracts:

The only injection-related cataract reported by Week 52 (occurring in the VTE 2 mg group) was considered severe (serious event, resolved).

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial MYRROR (48 weeks)

All cataracts:

The only reported case of cataract (occurring in the Eylea 2 mg group) had a mild severity.

Injection-related (traumatic) cataracts:

No injection-related (i.e., traumatic) cataracts were reported in MYRROR through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose) - Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

All cataracts:

Severe cataracts were reported in 10 patients in the Eylea total group (1.2%; Table SVII.98).

Table SVII.98: Number of subjects with any cataract in the study eye by maximum severity in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser [a] n (%)	VTE 2Q4 [b] n (%)	VTE 2Q8 [b] n (%)	VTE total [c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Cataract	67 (23.3)	88 (30.2)	67 (23.3)	188 (22.9)
Maximum severity				
Mild	45 (15.7)	48 (16.5)	36 (12.5)	103 (12.5)
Moderate	21 (7.3)	34 (11.7)	28 (9.8)	75 (9.1)
Severe	1 (0.3)	6 (2.1)	3 (1.0)	10 (1.2)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis - EU-RMP Pool 1 (DME), Table 1.5.1/2

Injection-related (traumatic) cataracts:

Two of the injection-related cataracts (one case each occurring in the 2Q4 and 2Q8 group) were regarded as severe (Table SVII.99).

Table SVII.99: Number of subjects with injection-related (traumatic) cataract in the study eye by maximum severity in the pivotal Phase III DME studies from baseline through Week 148 (SAF)

MedDRA 19.1	Laser[a] n (%)	VTE 2Q4[b] n (%)	VTE 2Q8[b] n (%)	VTE total[c] n (%)
Number of subjects	287	291	287	821
Grouped term				
Injection-related cataract	3 (1.0)	13 (4.5)	7 (2.4)	23 (2.8)
Maximum severity				
Mild	0	4 (1.4)	2 (0.7)	6 (0.7)
Moderate	3 (1.0)	8 (2.7)	4 (1.4)	15 (1.8)
Severe	0	1 (0.3)	1 (0.3)	2 (0.2)

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=243 exposed to additional/PRN treatment with Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 148.
Table Source: Integrated Analysis - EU-RMP Pool 1 (DME), Table 1.5.1/2

DME (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIVID-EAST (52 weeks)

All cataracts:

No severe cataracts were reported during the 52 weeks' period of the VIVID-EAST study, and most of the events were mild (in 4 of 6 involved patients in the Eylea total group; Table SVII.100).

Table SVII.100: Number of subjects with any cataract in the study eye by maximum severity in the Phase III DME study VIVID-EAST from baseline through Week 52 (SAF)

MedDRA 19.1	Laser[a] n (%)	VTE 2Q4[b] n (%)	VTE 2Q8[b] n (%)	VTE total[c] n (%)
Number of subjects	N=124	N=127	N=127	N=299
Grouped term				
Cataract	10 (8.1)	3 (2.4)	2 (1.6)	6 (2.0)
Maximum severity				
Mild	9 (7.3)	2 (1.6)	2 (1.6)	4 (1.3)
Moderate	1 (0.8)	1 (0.8)	0	2 (0.7)
Severe	0	0	0	0

[a]: All subjects randomized to initial study eye treatment with active laser.
[b]: All subjects randomized to initial study eye treatment with Eylea (VTE 2Q4 or 2Q8).
[c]: All subjects from any treatment group (incl. laser group; N=45 exposed to Eylea) who received at least one active Eylea injection in the study eye; counting all AEs which started during or after the first Eylea injection in the study eye through Week 52.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.5.3/2

Injection-related cataracts:

No cases of injection-related cataract in the study eye were reported in the VIVID-EAST study.

DME (Eylea 40 mg/mL, 2 mg dose) - Open-label Clinical Trial VIVID-JAPAN (52 weeks)

All cataracts:

The only reported cataract case in VIVID-JAPAN was non-serious, severe, and non-resolved.

Injection-related cataracts:

No injection-related cataracts were reported in VIVID-JAPAN.ROP (Eylea 40 mg/mL, 0.4 mg dose) -Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

The two reported cataracts in the study eye were of moderate severity (no case reported in the FIREFLEYE NEXT study, Table SVII.101).

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Table SVII.101: Number of subjects with any cataract in the study eye by maximum severity in the Phase III FIREFLEYE study (SAF)

MedDRA 23.1	Laser n (%)	VTE 0.4 mg n (%)	VTE total [a] n (%)
Number of subjects	38	75	79
Grouped term			
Cataract	1 (2.6)	1 (1.3)	2 (2.5)
Maximum severity			
Moderate	1 (2.6)	1 (1.3)	2 (2.5)

[a]: VTE total includes all subjects who received VTE 0.4 mg including subjects randomized to laser and receiving VTE 0.4 mg as rescue treatment.
Table Source: Integrated Analysis - EU-RMP ROP submission Pool 1 (ROP 20090), Table 1.2/2

Injection-related (traumatic) cataracts:

No injection-related (traumatic) cataracts were reported in the Phase III study FIREFLEYE or the Phase IIIb study FIREFLEYE NEXT.

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose) - Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (96weeks), and the DME PHOTON study (96 weeks):

All cataracts:

"Severe" cataracts were reported in one patient (0.2%) on treatment with aflibercept 2 mg and in 3 patients (0.2%) on treatment with aflibercept 8 mg (Table SVII.102). Thus, in most of the patients in either treatment group, intensity was “mild” or “moderate”.

Table SVII.102: Number of subjects with any cataract in the study eye by maximum severity in the Phase II CANDELA study and Phase III PULSAR study in wet AMD and in the Phase III PHOTON study in DME (SAF)

MedDRA 25.0	*2 mg* n (%)	*HDq12* n (%)	*HDq16* n (%)	HD Total n (%)
Number of subjects	556	716	501	1,217
Grouped term				
Cataract	21 (3.8)	26 (3.6)	27 (5.4)	53 (4.4)
Maximum severity				
Mild	29 (5.2%)	50 (7.0%)	37 (7.4%)	87 (7.1%)
Moderate	21 (3.8%)	19 (2.7%)	24 (4.8%)	43 (3.5%)
Severe	1 (0.2%)	2 (0.3%)	1 (0.2%)	3 (0.2%)

2 mg: Aflibercept 2 mg regardless of injection schedule.
HDq12: Aflibercept 8 mg administered every 12 weeks or every 12 weeks + PRN after loading phase.
HDq16: Aflibercept 8 mg administered every 16 weeks after loading phase.
HD total: HDq12 and HDq16 combined.
Source: Integrated Analysis – Pool 1, 48 weeks analysis, AMD 8 mg (w44/48) + DME 8 mg (w48); Table 3.1/17

Injection-related (traumatic) cataracts:

Three of the injection-related cataracts (1 patient in the 2 mg dose treatment group and 2 patients in the HDq16 dose treatment group) were regarded as "mild". One injection related cataract in HDq12 was moderate in nature.

Post-marketing Data

Event severity is not routinely recorded on the post-marketing case report forms.

Background incidence/prevalence

Historically, traumatic cataract (TC) has been reported in patients receiving IVT injections, but limited information is available about cataract development or progression after intravitreal injection of VEGF inhibitors. In addition, due to differences in the way cataract and/or "traumatic cataract" have been defined or reported in such studies, the direct comparison of some reported rates could be difficult. Special attention should be given to the type of cataract the reported rates represent.

Several studies involving intravitreal injection (including ranibizumab, pegaptanib sodium, and triamcinolone acetonide) reported no findings of traumatic cataract (165, 255-258).

Still, a limited number of reports revealed of low frequency of traumatic cataract associated with intravitreal injections of bevacizumab, ranibizumab, or triamcinolone (203, 251, 253, 254, 259, 260). Holz *et al*. specified 1 TC out of 513 patients (0.2%), Sorensen and Kemp reported one TC out of 647 eyes, and Jonas *et al*. reported that three eyes out of 5,403 injections (two in bevacizumab and one in triamcinolone acetonide) showed "progressive cataract" in a case series (253, 254, 260). The VISION study reported 5 TC events in 892 subjects (0.07%/injection) exposed to pegaptanib (203).

AMD:

In two double-blind placebo-controlled Pegaptanib trials involving 1208 patients, about 1% of patients developed cataract (261).

CRVO:

Several cohort and randomized studies on CRVO patients treated with different modalities reported information on traumatic cataract as an event to be noted:

A multicenter randomized, sham injection-controlled trial to assess the efficacy and safety of intraocular injections of 0.3 mg or 0.5 mg ranibizumab in patients with macular edema after CRVO. A total of 392 patients participated. At the end of 6 months the numbers of cataract cases were: 0/129 for sham, 2/132 (1.6%) for the 0.3 mg treatment group and 2/129 (1.6%) for the 0.5 mg group (207). At the end of 12 months follow-up of this study there were 7/131 cases (5.3%) of cataract in the sham group, 6/134 (4.5%) in the 0.3 mg group, and 8/130 (6.2%) in the 0.5 mg group (208).

BRVO:

A prospective, randomized, dose-finding study was performed to assess the efficacy and safety of IVT pegaptanib sodium for macular edema secondary to BRVO. Twenty subjects from three clinical practices in the United States with BRVO of more than 1 month and fewer than 6 months' duration were randomized 3:1 to IVT injections of pegaptanib 0.3 or 1 mg at Baseline and at weeks 6 and 12 with subsequent injections at 6-week intervals at investigator discretion until week 48. No cases of traumatic cataract were observed (258).

No other traumatic cataract events have been mentioned in the BRVO studies that have been reviewed.

Myopic CNV:

No data were identified.

DME:

A Korean study compared the efficacy of posterior sub-Tenon's capsule triamcinolone acetonide injection combined with modified grid macular photocoagulation (PSTI + MP) with intravitreal triamcinolone acetonide (IVTA) injection in the treatment of diffuse diabetic macular edema (DME). Forty eyes of 33 patients with diffuse DME were randomly allocated to either treatment. Examinations were carried out at baseline and also at 1 month, 3 months and 6 months after treatment.

The average increases in cataract grading (based on the Lens Opacities Classification System III (LOCS III), compared to baseline values, were 0.62 ± 0.81 (mean ± SD) in the PSTI + MP group and 1.54 ± 1.33 in the IVTA group; the latter being significantly higher than the former (p = 0.043, Student’s t-test). Significant cataract progression that necessitated cataract surgery was noted in 1 of 13 (7.7%) phakic eyes in the IVTA group, but in none of the eyes treated with posterior sub-Tenon injections (235).

In a Phase III controlled study, 197 patients with diabetic macular edema were randomized to receive a fluocinolone 0.5mg implant, or standard of care (macular grid laser/observation). Among phakic patients, cataract developed in 43.1% of patients treated with the fluocinolone implant and in 7.3% of patients treated with standard of care based on 34-week data. Patients in this trial will be followed for an additional 2.5 years (234).

The randomized trial of the Diabetic Retinopathy Clinical Research Group evaluated Ranibizumab *vs*. triamcinolone for treatment of DME. The two year cumulative cataract surgery events in the triamcinolone + prompt laser group was considerably higher (59%) than the rates for the sham + prompt laser group or the ranibizumab groups (14% and 14%, respectively; P<0.001 for both comparisons) (164).

ROP:

Three randomized trials reported the outcome cataract using eyes as the denominator (221-223). Of these, two trials did not report any case of cataract in either of the groups ((222, 223). The BEAT-ROP trial did not find any significant difference in the incidence of lens opacity requiring cataract removal between the two groups (RR 0.15, 95% CI 0.01 to 2.79) (221).

Impact on individual patient

Development of cataract may impair vision and thus may require cataract surgery in order to remove the lens opacification.

Risk factors and risk groups

Cataract is a known adverse drug reaction on treatment with IVT corticosteroids.

Preventability

By correct IVT procedure and a correct angle of the needle while injecting a cataract could be prevented. This is common knowledge of injecting physicians.

Impact on risk-benefit balance of the product

An educational program is performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks. The effectiveness of this program was verified with a post authorization safety study (SN 16526).

This important identified risk does not have an impact on the positive risk-benefit balance of Eylea.

Public health impact:

Patients experiencing (traumatic) cataract may require cataract surgery.

SVII.3.1.6 Potential risk: Medication errors

Potential mechanism

Not applicable.

Evidence source(s) and strength of evidence

Main reason for considering medication error as an important potential risk:

- Two milligram (2 mg) aflibercept is provided in a vial or a pre-filled syringe with a dose line. In both vial and PFS presentations, excess volume is to be expelled during the priming step before injecting the recommended dose. Thus, injecting the entire volume of the pre-filled syringe/vial would result in overdose. However, this numerical overdose is limited, and the drug will be administered only by qualified physicians (not by patients), and this reduces the risk of inappropriate dosing and administration as well. Proper adherence to the instructions for use when using the PFS/vial is key to avoid overdosing.
- Eight milligram (8mg) aflibercept is provided in a vial or a pre-filled syringe with a dosing device (OcuClick®). Both formats need to undergo priming steps before the injection.
- Eylea is available in two different formulations and dosages: 2 mg and 8 mg. To avoid medication error with mix-up of the two different versions, each part of the packaging material will include clear differentiation for each strength (see below section in preventability).

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Evidence sources: refer to the linked subsection.

MedDRA search terms (version 19.1 for adult clinical 2 mg studies, version 20.0 for PM data and version 23.1 for ROP studies in preterm infants, version 25.0 for 8 mg dose in wet AMD and DME):

Search is performed using the MedDRA SMQ: "Medication errors".

Characterization of the risk

Frequency

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) - Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

Through the 2-year period in the Phase III AMD studies, 10 cases of overdose in 36,203 injections (including 9,810 ranibizumab injections) have been reported. Two overdose reports were with ranibizumab (0.02% of injections) and 8 with Eylea (0.03% of injections). In one case, 10-fold the dose and volume of the study drug was administered. Three of the patients experienced a transient increase of IOP. The IOP increase was probably associated with the larger volume administered. In the other cases, no AEs occurred. All patients recovered without sequelae. (Note: not all of above occurrences necessarily reported PTs pertaining to medication error).

PTs pertaining to medication error occurred in 4 patients (0.7%) who were treated with ranibizumab, compared to 5 patients (0.3%) in the combined group of patients on treatment with Eylea (Table SVII.103).

Table SVII.103: Number of subjects with medication errors (grouped term and included preferred terms) in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
Medication error and misuse	4 (0.7)	2 (0.3)	1 (0.2)	2 (0.3)	5 (0.3) [a]
Included preferred terms					
Drug administration error	0	0	0	1 (0.2)	1 (<0.1)
Incorrect dose administered	1 (0.2)	0	0	0	0
Overdose	3 (0.5)	2 (0.3)	1 (0.2)	1 (0.2)	4 (0.2)

Q4 = every 4 weeks, Q8 = every 8 weeks
[a]: In 4 additional cases, overdose has not been reported as event, but as explanation for the event IOP increase.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.1/1

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) - VIEW 1 long-term extension study

No cases of medication error were reported in the VIEW 1 extension study period.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial SIGHT (52 weeks)

No cases of medication error were reported during the course of the SIGHT study.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial ALTAIR (52 weeks). No cases of medication error were reported during the course of the ALTAIR study.

CRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

No cases of medication error were reported in the Phase III CRVO studies.

BRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIBRANT (52 weeks)

No cases of medication error were reported in the Phase III BRVO study.

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial MYRROR (48 weeks)

No cases of medication error were reported in the MYRROR study through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose) - Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

One case of medication error and was reported in the DME studies through Week 148, but this event occurring in the Eylea 2Q4 group (serious, severe and resolved; PT: "accidental overdose") was not associated with Eylea treatment, but with an unintentional overdose of concomitantly administered tramadol (for restless leg syndrome) in a 72-year-old Caucasian male (Subject No. 774-008 in study VGFT-OD-1009 [VISTA-DME]).

DME (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIVID-EAST (52 weeks)

No cases of medication error were reported in VIVID-EAST.

DME (Eylea 40 mg/mL, 2 mg dose) - Open-label Clinical Trial VIVID-JAPAN (52 weeks)

No cases of medication error were reported in VIVID-JAPAN.ROP (Eylea 40 mg/mL, 0.4 mg dose) - Clinical Trial FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

In the open-label Phase III study FIREFLEYE, 2 subjects in the VTE total group (2.5% of the 79 SAF subjects, no case reported in the FIREFLEYE NEXT study) experienced a treatment-emergent adverse event of "medication error" (Table SVII.104). One patient was inadvertently overdosed with 4 mg aflibercept on the firstly injected right eye and reported adverse events (intraocular pressure increased, corneal oedema) showed spontaneous and complete regression. The remaining patient was treated bilaterally with Eylea using the same Eylea vial with no further events reported.

Table SVII.104: Number of subjects with medication errors (grouped term and included preferred terms) in the Phase III FIREFLEYE study (SAF)

MedDRA 23.1	Laser n (%)	VTE 0.4 mg n (%)	VTE total [a] n (%)
Number of subjects	38	75	79
Grouped term			
Medication error	0	2 (2.7%)	2 (2.5%)
Included preferred terms			
Multiple use of single-use product	0	1 (1.3%)	1 (1.3%)
Overdose	0	1 (1.3%)	1 (1.3%)

[a]: VTE total includes all subjects who received VTE 0.4 mg including subjects randomized to laser and receiving VTE 0.4 mg as rescue treatment. All non-ocular adverse events after first VTE treatment in any eye and all ocular adverse events after first VTE treatment in the eye where the event occurred are considered.
Table Source: Integrated Analysis - EU-RMP ROP submission Pool 1 (ROP 20090), Table 1.2/1

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose, injection volume: 70 µL) - Pooled data sets from the AMD CANDELA study (44 weeks), the AMD PULSAR study (96 weeks), and the DME PHOTON study (96weeks):

Two cases of medication error were reported in the 8 mg dose studies CANDELA, PULSAR or PHOTON, both in HDq12. One referred to a defibrillator malfunction and the second to an unspecified “injury associated with device, left foot”. Both were mild, non-serious and not related to aflibercept or its injection procedure.

Post-Marketing Data

By 15 SEP 2017, a total of 3,245 cases of medication error were reported with 3,577 events. The 5 most frequently reported preferred term events were “inappropriate schedule of drug administration” (1,476 events), “drug dose omission” (583 events), “product use issue” (523 events), “multiple use of single-use product” (263 events), and “product use in unapproved indication” (172 events).

Vial/dose fractioning (coded to PT “multiple use of single-use product”) is a common practice in some countries, and it might be supported by some health insurances. This PT was reported in 263 cases (with 263 events) and more than half of these cases (138 cases) were invalid, while 125 cases were valid. Most of the valid cases were associated with intraocular inflammations/infections which is an established and labelled ADR of the Eylea injection. For these cases it remains unknown whether the procedure of vial splitting contributed to the development of an intraocular infection. Overall, no increase in reporting rates for reported intraocular inflammations/infections was observed over the years worldwide, and to date, the reported number of cases with vial fractioning is considered low.

In view of the large number of vials sold by 15 SEP 2017 (almost 16 million), there is no indication that medication errors might be a relevant issue of treatment with Eylea in routine care. Numerically, the reporting rate of cases with medication error (N=3,245) was 0.20 cases per 1,000 sold vials (0.020%) and 1.40 cases per 1,000 patient years of exposure (0.140%), respectively.

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Table SVII.105: Number of post-marketing events "medication error" by 15 SEP 2017

Group: Medication error	***3,245 cases***		
Grouped preferred terms [a]:	**Non-serious**	**Serious**	**All**
Inappropriate schedule of drug administration	1,466	1	1,467
Drug dose omission	580	3	583
Product use issue	519	4	523
Multiple use of single-use product	240	23	263
Product use in unapproved indication	172	0	172
Incorrect drug administration duration	100	0	100
Inappropriate prescribing	77	0	77
Injury associated with device	53	3	56
Drug prescribing error	43	0	43
Wrong technique in product usage process	34	4	38
Incorrect dosage administered	36	0	36
Incorrect product storage	27	0	27
Poor quality drug administered	23	0	23
Needle issue	20	1	21
Drug administration error	17	2	19
Syringe issue	15	1	16
Drug administered at inappropriate site	13	0	13
Underdose	11	0	11
Wrong drug administered	9	1	10
Occupational exposure to product	9	0	9
Accidental exposure to product	8	0	8
Product preparation error	5	3	8
Expired product administered	5	0	5
Inadequate aseptic technique in use of product	2	3	5
Incorrect dose administered	5	0	5
Incorrect route of drug administration	5	0	5
Labelled drug-drug interaction medication error	2	2	4
Medication error	4	0	4
Overdose	4	0	4
Drug administered to patient of inappropriate age	3	0	3
Drug dispensing error	3	0	3
Accidental underdose	2	0	2
Medication monitoring error	1	1	2
Booster dose missed	1	0	1
Circumstance or information capable of leading to medication error	1	0	1
Device use error	1	0	1
Documented hypersensitivity to administered product	1	0	1

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Table SVII.105: Number of post-marketing events "medication error" by 15 SEP 2017

Group: Medication error	*3,245 cases*		
Grouped preferred terms [a]:	**Non-serious**	**Serious**	**All**
Extra dose administered	1	0	1
Incorrect dose administered by device	1	0	1
Product use complaint	1	0	1
Unintentional use for unapproved indication	1	0	1
Device malfunction	1	0	1
Product expiration date issue	1	0	1
Product lot number issue	1	0	1
Communication issue	1	0	1
Total number of events	**3,525**	**52**	**3,577**

Source: Global Pharmacovigilance Safety Database
a: MedDRA Version 20.0. Figures are event-based, i.e., more than one preferred term event per reported case is possible. Included are both medically confirmed and non-medically confirmed events.

Seriousness/outcomes

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg doses) - Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

All cases of medication error in the Eylea groups were regarded as non-serious, and all events were completely resolved. In the ranibizumab group, one case (incorrect dose administered; reason for seriousness not reported) was regarded as serious; all events (including the SAE) were completely resolved.

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) - VIEW 1 long-term extension study

No cases of medication error were reported in the VIEW 1 extension study period.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial SIGHT (52 weeks)

No cases of medication error were reported during the course of the SIGHT study.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial ALTAIR (52 weeks)

No cases of medication error were reported during the course of the ALTAIR study. CRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

No cases of medication error were reported in the Phase III CRVO studies.

BRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIBRANT (52 weeks)

No cases of medication error were reported in the Phase III BRVO study.

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial MYRROR (48 weeks)

No cases of medication error were reported in the MYRROR study through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose) - Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

The only reported case of medication error through Week 148 (PT: "accidental overdose") was not associated with Eylea treatment, but with an unintentional overdose of concomitantly administered tramadol. This event was serious and severe; the patient recovered.

DME (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIVID-EAST (52 weeks)

No cases of medication error were reported in VIVID-EAST.

DME (Eylea 40 mg/mL, 2 mg dose) - Open-label Clinical Trial VIVID-JAPAN (52 weeks)

No cases of medication error were reported in VIVID-JAPAN.ROP (Eylea 40 mg/mL, 0.4 mg dose) - Clinical Trials FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

In the FIREFLEYE study (no case reported in the FIREFLEYE NEXT study) 1 case of medication error in the VTE total group was documented as non-serious and one as serious (“overdose”), both events were completely resolved.

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose, injection volume: 70 µL) - Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (96 weeks), and the DME PHOTON study (96 weeks):

The 2 reported cases pertaining to medication error (defibrillator malfunction and unspecified “injury associated with device, left foot” were non-serious and resolved/were resolving.

Post-marketing Data

A few of the reported medication error cases were considered serious (49 cases [1.5% of all 3,245 cases] with 52 events [1.5% of all 3,577 events]; see previous post-marketing table).

For most of the 3,577 cases, the event outcome was unknown or not reported (3,283 events). Specified event outcomes were “recovered/resolved” (159 events), “recovering/resolving” (21 events), “recovered/resolved with sequelae” (one event), and “not recovered/not resolved” (113 events).

Severity and nature of risk

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) - Pivotal Clinical Trials VIEW 1 and VIEW 2 (pooled data, 96 weeks)

Medication error events occurring on treatment with Eylea were of moderate intensity in 3 cases (missing severity in the remaining 2 cases; Table SVII.106). In the ranibizumab group, the serious adverse event (incorrect dose administered) was of severe intensity; one case was moderate, and the remaining 2 cases were mild.

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Table SVII.106: Number of subjects with medication error by maximum severity in randomized Phase III wet AMD studies from baseline through Week 96 (SAF)

MedDRA 19.1	Ranibizumab	Eylea			
	Q4 n (%)	2 mg Q4 n (%)	0.5 mg Q4 n (%)	2 mg Q8 n (%)	Total n (%)
Number of subjects	595	613	601	610	1,824
Grouped term					
Medication error and misuse	4 (0.7)	2 (0.3)	1 (0.2)	2 (0.3)	5 (0.3)
Maximum severity					
Missing	0	1 (0.2)	0	1 (0.2)	2 (0.1)
Mild	2 (0.3)	0	0	0	0
Moderate	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)
Severe	1 (0.2)	0	0	0	0

Q4 = every 4 weeks, Q8 = every 8 weeks
Note: At each level of subject summarization (Safety topic/PT), a subject is classified according to the maximum intensity, if the subject reported one or more events. At each level of subject summarization, a subject is counted only once.
Table Source: Integrated Analysis - EU-RMP Pool 1 (AMD), Table 1.1.1/2

Wet AMD (Eylea 40 mg/mL, 0.5/2 mg dose) - VIEW 1 long-term extension study

No cases of medication error were reported in the VIEW 1 extension study period.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial SIGHT (52 weeks)

No cases of medication error were reported during the course of the SIGHT study.

Wet AMD (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial ALTAIR (52 weeks)

No cases of medication error were reported during the course of the ALTAIR study. CRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trials COPERNICUS and GALILEO (pooled data, 76/100 weeks)

No cases of medication error were reported in the Phase III CRVO studies.

BRVO (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIBRANT (52 weeks)

No cases of medication error were reported in the Phase III BRVO study.

Myopic CNV (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial MYRROR (48 weeks)

No cases of medication error were reported in the MYRROR study through Week 48.

DME (Eylea 40 mg/mL, 2 mg dose) - Pivotal Clinical Trials VIVID-DME and VISTA-DME (pooled data, 148 weeks)

The only reported case of medication error through Week 148 (PT: "accidental overdose") was not associated with Eylea treatment, but with an unintentional overdose of concomitantly administered tramadol. This event was serious and severe; the patient recovered.

DME (Eylea 40 mg/mL, 2 mg dose) - Clinical Trial VIVID-EAST (52 weeks)

No cases of medication error were reported in VIVID-EAST.

DME (Eylea 40 mg/mL, 2 mg dose) - Open-label Clinical Trial VIVID-JAPAN (52 weeks)

No cases of medication error were reported in VIVID-JAPAN.ROP (Eylea 40 mg/mL, 0.4 mg dose) - Clinical Trial FIREFLEYE (24 weeks) and FIREFLEYE NEXT (interim data)

The severity of both cases of medication error in the FIREFLEYE study (no case reported in the FIREFLEYE NEXT study) was assessed as moderate.

Wet AMD and DME (Eylea 114.3 mg/mL, 8 mg dose, injection volume: 70 µL) - Pooled data sets from the wet AMD CANDELA study (44 weeks), the wet AMD PULSAR study (48 weeks), and the DME PHOTON study (48 weeks):

No patients with medication error were reported in the 8 mg dose studies CANDELA, PULSAR or PHOTON.

Post-marketing Data

Event severity is not routinely recorded on the post-marketing case report forms.

Background incidence/prevalence

Not applicable.

Impact on individual patient

There is no life-threatening potential when Eylea is administered by an incorrect route.

Risk factors and risk groups

Not applicable.

Preventability

Instructions on the correct drug preparation and administration will be given in the SmPCs and the educational program in order to minimize the risk of accidental medication errors.

Proper preparation of the injection with the 2 mg/8 mg Eylea PFS and for 2mg/8 mg Eylea vial according to the Instruction for Use is key in mitigating medication errors including overdose.

Eylea is available in two different formulations and dosages: 2 mg and 8 mg. To avoid medication error with mix-up of the two different versions, each part of the packaging material will include clear differentiation for each strengths as depicted below:

For the outer carton: The below differentiations items are included that would enable differentiation on each panels of the box:

- different colour of the triangle in the upper right corner
- different colour for ‘eye’-logo
- different coloured background
- strengths for 8 mg is highlighted with a coloured background

For the immediate packaging – vial:

- different colour of the plastic cap
- on the label, strength for 8 mg is highlighted with a coloured background

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Impact on risk-benefit balance of the product

An educational program is performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks. The effectiveness of this program was verified with a post authorization safety study (SN 16526).

This important potential risk does not have an impact on the positive risk-benefit balance of Eylea.

Public health impact

There is no life-threatening potential when Eylea is administered by an incorrect route.

SVII.3.1.7 Potential risk: Off-label use and misuse

Potential mechanism

Not applicable

Evidence of source(s) and strength of evidence

Main reason for considering off-label use and misuse as an important potential risk:

As with other drugs, Eylea might be intentionally used other than recommended, or in clinical conditions outside the approved indications (so-called off-label use). Since the clinical experience with Eylea in such off-label use will be limited (in particular in terms of efficacy and safety), any case of off-label use will be considered a potential risk. Since Eylea has no dependence potential, the risk of misuse is regarded as very low.

Evidence sources: refer to the linked subsection.

MedDRA search terms (version 19.1 for adult clinical 2 mg studies, version 20.0 for PM data and version 23.1 for ROP studies in preterm infants, version 25.0 for 8 mg dose in wet AMD and DME):

Preferred term included in search: Off-label use, intentional device misuse, intentional overdose, and intentional product misuse.

Characterization of the risk

Frequency:

Phase III-IV clinical 2 mg studies (AMD, CRVO, BRVO, myopic CNV, DME, and ROP)

There were no reports of off-label use or misuse in the herein reported Phase III-IV trials in wet AMD, CRVO, BRVO, myopic CNV, DME, and ROP.

There were no reports of off-label use or misuse in the Phase II-III clinical studies (wet AMD and DME) for the 8 mg dose of aflibercept.

Post-Marketing Data

Cases of off-label use were identified based on a concept that considered events of intentional drug use outside of the authorized product information in therapeutic intention as reported by HCP (or HCP involved). Preferred terms included in that safety topic were “off label use”, “intentional device misuse”, “intentional overdose”, and “intentional product misuse”.

By 15 SEP 2017, there were 1,846 recorded cases (including 1,925 events) of off-label use and misuse (Table SVII.107). Considering the sales figures and the estimated cumulative

patient exposure in the post-marketing period until 30 SEP 2017, the reporting rate of off-label cases (N=1,846) was 0.12 cases per 1,000 sold vials (0.012%) and 0.80 cases per 1,000 patient years (0.080%), respectively.

Table SVII.107: Number of post-marketing events "off-label use and misuse" by 15 SEP 2017

Group: Off-label use and misuse	*1,846 cases*		
Grouped preferred terms [a]:	**Non-serious**	**Serious**	**All**
Off label use	1,904	10	1,914
Intentional product misuse	11	0	11
Total number of events	**1,915**	**10**	**1,925**

Source: Global Pharmacovigilance Safety Database
a: MedDRA Version 20.0. Figures are event-based, i.e., more than one preferred term event per reported case is possible. Included are both medically confirmed and non-medically confirmed events.

A review of these cases suggested that many cases of off-label use and misuse occurred within a labelled indication and were solely associated with deviations from the labelled treatment schedule or were used for indications that were not yet approved locally at the time of their use (but were approved elsewhere). For a high-level check of the treatment indication, the data base field “product indication preferred term” was screened.

Conditions associated with AMD (AMD not further specified) were reported as indication in 586 cases, explicitly wet AMD in 546 cases, any diabetic conditions in 624 cases, and retinal vein occlusion in 32 cases (multiple specifications per patient were possible). CNV not associated with one of these 3 conditions was reported in 83 cases; in 217 cases, no indication at all was provided.

The cases of off-label use and misuse were specifically screened for off-label treatment indications associated with glaucoma, diabetic retinopathy, polypoidal choroidal vasculopathy (PCV), pigment epithelium detachment (PED), and retinopathy of prematurity (ROP).

The indication "glaucoma" was reported in 9 cases; in 4 cases the pathogenesis as “neovascular/neovascularization” glaucoma was explicitly mentioned in the corresponding product reported indication terms.

No other adverse events (including those potentially indicating acute issues with high IOP) were reported in these 9 cases (apart from the events “visual impairment” and “drug ineffective” in one case).

The indication "diabetic retinopathy" (coded to PT “diabetic retinopathy”) was reported in 27 cases.

The indication "PCV" (coded to PT “Polypoidal choroidal vasculopathy”) was reported in 7 cases.

The indication "PED" (coded to PTs: Detachment of [macular] retinal pigment epithelium) was reported in 6 cases.

The indication "ROP" (coded to PT: “Retinopathy of prematurity”) was reported in 8 cases.

Administration of Eylea in paediatric patients <18 years was reported in 12 cases.

None of these 12 cases was associated with adverse events.

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Seriousness/outcomes

Phase III-IV clinical studies (AMD, CRVO, BRVO, myopic CNV, DME, and ROP)

Not applicable, since no related events were reported (including Phase II-III clinical studies [wet AMD and DME] for the 8 mg dose of Eylea).

Post-marketing Data

In 10 cases the off-label use was regarded as serious. These included the following events (events are as reported term):

1) Off-label use event as reported term: “Receiving treatment with EYLEA therapy for blood behind the right eye (OD)”. Product indication (coded to PT): “Eye haemorrhage”. Reason for seriousness: Medically significant. Outcome: Unknown.
2) Off-label use event as reported term: “Eylea was used for retinopathy of prematurity”. Product indication (coded to PT): “Retinopathy of prematurity”. Reason for seriousness: Hospitalization. Outcome: Not reported.
3) Off-label use event as reported term: “Eylea was used without loading phases (off label use)”. Product indication (coded to PT): “neovascular AMD”. Reason for seriousness: Disability. Outcome: Not reported.
4) Off-label use event as reported term: “EYLEA indication for use reported as "anaemia, unspecified"”. Product indication (coded to PT): “Anaemia”. Reason for seriousness: Hospitalized/Medically Significant. Outcome: Not recovered/not resolved.
5) Off-label use event as reported term: “Eylea in CNV of unknown origin (possibly retinopathia centralis serosa) (off-label)”. Product indication (coded to PT): “CNV, chorioretinopathy”. Reason for seriousness: Medically significant. Outcome: Not reported.
6) Off-label use event as reported term: “Used Eylea for stroke in left eye causing vison problems”. Product indication (coded to PT): “Visual impairment”. Reason for seriousness: Medically significant. Outcome: Unknown.
7) Off-label use event as reported term: “Indication for Eylea; retinal macroaneurysm and retinal haemorrhage”. Product indication (coded to PT): “Retinal haemorrhage” and “retinal aneurysm”. Reason for seriousness: Medically significant. Outcome: Unknown.
8) Off-label use event as reported term: “Indication for use iridoschisis”. Product indication (coded to PT): “Iridoschisis”. Reason for seriousness: Medically significant. Outcome: Unknown.
9) Off-label use event as reported term: “Indication, malignant neoplasm of prostate”. Product indication (coded to PT): “Prostate cancer”. Reason for seriousness: Medically significant. Outcome: Unknown.
10) Off-label use event as reported term: “Eylea used for retina separation in the right eye, left “eye is bad” (off label use)”. Product indication (coded to PT): “Retinoschisis” and “eye disorder”. Reason for seriousness: Disability/ medically significant. Outcome: Unknown.

Generally, an outcome for the 1,925 events of off-label use and misuse was provided only for 113 events: "recovered/resolved" in 19 events, "recovering/resolving" in 15 events, and "not

recovered/not resolved" in 79 events; the outcomes for the remaining 1,812 events were unknown or missing.

Severity and nature of risk

Phase III-IV clinical studies (AMD, CRVO, BRVO, myopic CNV, DME, and ROP)

Not applicable, since no related events were reported (including Phase II-III clinical studies [wet AMD and DME] for the 8 mg dose of Eylea).

Post-marketing Data

Event severity is not routinely recorded on the post-marketing case report forms.

Background incidence/prevalence:

Not applicable.

Impact on individual patient

Not applicable.

Risk factors and risk groups

Not applicable.

Preventability

Eylea is being studied in many conditions for which off-label use might be considered.

Off-label ophthalmic use has been reported with currently marketed VEGF inhibitors, e.g., for bevacizumab for the treatment of wet AMD (262) or DME (263, 264). Off-label use of ranibizumab has been reported for ophthalmic diseases other than wet AMD such as DME (265) or retinal vein occlusion (266) before market authorization was granted in the respective indications. There are also reports on off-label use of bevacizumab and ranibizumab in rarer diseases such as myopic CNV (in countries where myopic CNV is not labelled), or retinopathy of prematurity (265), reviewed in article by Andreoli and Miller (267). In general, as for the majority of possible indications for anti-VEGF therapy approved medications are available, the potential for off-label use is considered minimal. Additionally, non-approved indications are currently being investigated in various studies to establish safety and efficacy in these therapeutic areas.

Most neovascular and VEGF dependent retina diseases including particularly AMD are diseases of the adult. Therefore, the potential for off-label use in the paediatric population is expected to be very limited due to the nature of paediatric ophthalmic diseases. However, there might be exceptions to be considered, as reviewed in article by Andreoli and Miller (267). In some rare cases, diabetic retinopathy may occur in adolescents. Some ophthalmologists tend to use off-label anti-VEGF drugs in this disease instead of the approved therapy. Myopic CNV, CRVO, and BRVO may also very rarely occur in adolescents and may be treated off-label with any IVT anti-VEGF drug, including Eylea. Eylea may be also used to treat some cases of retinopathy of prematurity (268). The number of such cases is considered very low and their care is provided by paediatric ophthalmologists who are tertiary care based and experienced in the care of these infants.

Intentional misuse, as such, is difficult to prevent because of the user's deliberate decision to deviate from the provided instructions. However, there is no known dependence potential of Eylea.

Impact of risk-benefit balance of the product

An educational program is performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks. The effectiveness of this program was verified with a post authorization safety study (SN 16526).

This important potential risk does not have an impact on the positive risk-benefit balance of Eylea.

Public health impact

Not applicable.

SVII.3.1.8Potential risk: Embryo-fetotoxicity

Potential mechanism

An embryo-foetal toxicity study was performed in the rabbit with IV dosing of aflibercept at doses which provided systemic exposures over 670-fold higher than that observed with IVT dosing using the clinical dose of 2 mg. The study identified dose-related increases in foetal resorptions, pregnancy disruptions and numerous foetal (external, visceral and skeletal) malformations. These effects were thought to be due to the antiangiogenic effect of aflibercept. For more details see **Part II Module SII**.

Evidence source(s) and strength of evidence

Main reason for considering embryo-fetotoxicity as an important potential risk:

Testing of Eylea in animals was performed as a standard part of the development of Eylea. It was noted that Eylea given in extremely high doses to animals (by far exceeding the doses which would be given to humans) might have an adverse influence on prenatal development (i.e., during the embryonic or foetal development period; so-called embryo-fetotoxicity). Therefore, embryo-fetotoxicity is regarded as a potential risk of treatment with Eylea. However, Eylea is injected locally and at a dose that is distinctively lower than the exposure in animals under which the critical events were observed. So far, there is no relevant indication that treatment with Eylea might be associated with embryo-fetotoxicity.

Evidence sources: refer to the linked subsection.

MedDRA search terms (version 19.1 for clinical 2 mg aflibercept studies and version 20.0 for PM data, version 25.0 for 8 mg aflibercept dose in wet AMD and DME):

SMQ search:

- Congenital, familial and genetic disorders,
- Termination of pregnancy and risk of abortion,
- Foetal disorders.

In addition, all cases associated with the PT “Pregnancy” are routinely checked in order to ensure appropriate and complete follow-up of any pregnancy.

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Characterization of the risk

Frequency

Phase I-IV clinical studies

Currently, there are 8 cases of pregnancy reported from clinical studies by 15 SEP 2017 (direct exposure or exposure through male partner):

1) Male; PTs: i) "syncope", ii) "drug exposure *via* father/no adverse event". This patient was treated in CRVO study 14130 (GALILEO) and actively exposed to Eylea. Follow-up for another adverse event (syncope) revealed that the patient's partner had become pregnant.Further follow-up revealed that an abortion had been electively performed on an unknown date, since the subject and his partner did not want the pregnancy.

2) Female; PT: drug exposure *via* father/no adverse event. This case was entered as a result of the previous case report (this woman was the pregnant partner of the aforementioned GALILEO study patient). The patient had a history of one pregnancy and one induced abortion. No contraceptives or an intra-uterine device, but only a condom had been used. The patient was exposed to study drug (VEGF trap eye or sham) *via* her partner during her pregnancy which was confirmed by Human chorionic gonadotropin (HCG) test and an ultrasonography. No adverse event was reported. The patient performed an elective abortion on an unknown date, since the subject and her partner did not want the pregnancy. No medical reason in the mother or in the foetus was reported.

3) Female; PT: Pregnancy. This patient was enrolled in study No. 15161 (VIVID-EAST). The patient started Eylea or sham laser, one time for 4 weeks at an unspecified dose for DME. The patient's previous contraception was condoms; she had not had previous pregnancies. On an unspecified date the patient experienced pregnancy. The pregnancy was confirmed with HCG pregnancy test and ultrasonography. At 2 to 3 weeks abortion was done due to the patient's decision. Action taken with aflibercept was not reported.

4): This case number refers to a female who was treated in the VISTA-DME study. The patient had a medical history of diabetes mellitus type I, stage IV kidney disease, hypertension, hyperthyroidism, hyperphosphatemia, and hypercholesterolemia. This patient became pregnant during the study treatment period (PT: Maternal exposure during pregnancy [non-serious; resolved]) and subsequently experienced preeclampsia (PT: Pre-eclampsia [serious; resolved]) requiring premature delivery of twins (PT: premature delivers [serious; resolved]). The patient had received 36 study treatments of masked VTE or laser to the study eye and 6 open-label study treatments to the fellow eye. Actually, the patient was randomized to treatment assignment with VTE 2Q8 (unmasked information) and exposed to study medication.The pregnancy was confirmed (pregnancy duration 5-6 weeks; pregnant with twins). Afterwards, the study site contacted the patient on a monthly basis. The patient was found to be 23 weeks pregnant with no previous complications during her pregnancy.

The patient was admitted to the hospital due to high blood pressure and possible preeclampsia. The patient's blood pressure was stabilized, and she was discharged from the hospital. The patient was re-admitted to the hospital due to due to elevated blood pressures at home with nausea, vomiting and shortness of breath. Upon admission, patient's shortness of breath worsened with IV fluids (given for treatment of dehydration) and a chest x-ray revealed developing pulmonary oedema while echocardiogram results were normal. She was started on IV Lasix (furosemide). Due to non-reassuring foetal tracings and the inability to

stabilize the patient's condition, an emergency Caesarean section was performed on the same day. After delivery, the patient was stable and transferred to the ICU. A chest x-ray revealed pulmonary oedema. Progressive worsening of renal function had been seen during her pregnancy from baseline creatinine 2.6 to 3.7 *[mg/dL]* and worsening nephrotic range proteinuria of close to 11 grams. The patient was relatively stable on 2 litres of oxygen with a persisting cough. Post-operatively, she experienced decompensated heart failure with anasarca and pulmonary oedema in the setting of Stage IV-V kidney disease from her diabetes. IV Lasix was replaced with a Bumex (bumetanide) drip. The patient's condition was stable, and she was discharged from the hospital. She is continuing to follow-up with her endocrinologist and nephrologist.
According to the investigator, the event of preeclampsia was severe in severity and not related to the study drug or study procedure. The alternative explanation for the event was reported as an underlying/concomitant illness, specifically the patient’s medical history of high blood pressure and kidney disease. Consistently, the Sponsor considered the event of preeclampsia not related to the study drug or study procedure.

5) This case number refers to female Baby A (PT: premature baby [serious]) of the aforementioned female. Baby A was potentially exposed to VTE *in utero*. The mother had been hospitalized for an emergency Caesarean section on the same day due to the babies' heart rates decreasing and her high blood pressure and preeclampsia. Baby A was female with weight 1 lb. 5 ounces, length 12 inches, and she was immediately transported to the neonatal intensive care unit (NICU). Diagnoses made upon NICU admission were feeding problems in newborn (<28 days), hyponatremia (<125 *mmol/L*), respiratory distress syndrome, apnoea of prematurity, apnoea (drug treated), chronic lung disease (CLD) at 28 days, patent ductus arteriosus (PDA), anaemia birth (HCT <40%), jaundice due to prematurity, rule out sepsis, anaemia of prematurity, germinal matrix bleed (grade 1), retinopathy of prematurity grade 1 or 2, and fractures of tibia/fibula on right. Besides numerous other measures, such as parenteral nutrition and ventilation, blood cell transfusions were received. A head ultrasound revealed a right-sided grade 1 intracranial haemorrhage with no ventriculomegaly. Haemorrhage was stable and continued resolving. An echocardiogram was performed. Both left atrium and left ventricle chamber size were enlarged. There was a patent foramen ovale with left to right flow and a large patent ductus arteriosus. Shunt flow was left to right. PDA was small to moderate with continuous left to right flow (35 mmHg) and no suggestion of PPHN. Patent Ductus Arteriosus (PDA) continued to decreaseand there was a small aortopulmonary collateral which was not significant. Baby A passed ALGO hearing screen bilaterally. An X-ray of the right lower extremity showed essentially complete interval healing of previously described fractures of the distal tibia and fibula with no new fractures identified. Baby A was cared for in the NICU for a total of 128 days and was discharged to home. Since discharge, Baby A was home with mother doing well.
According to the investigator, the event of premature birth was severe in severity and not related to the study drug or study procedure. The alternative explanation for the event was reported as an underlying/concomitant illness, specifically the mother’s medical history of high blood pressure and kidney disease. Accordingly, the Sponsor considered the event of premature birth not related to the study drug or study procedure, and most likely secondary to underlying/concomitant illness, specifically the mother's medical history.

6): This case number refers to male Baby B (PT: premature baby [serious]) of the aforementioned female. Baby B was potentially exposed to VTE in utero. The mother had been hospitalized for an emergency Caesarean section on the same day due to the babies'

heart rates decreasing and her high blood pressure and preeclampsia. Baby B was male weight 1 pound (lb) 4 ounces, and length 11.5 inches, and he was immediately transported to the NICU. Diagnoses made upon NICU admission were hypocalcaemia (<7.0, units and range not provided), hyponatremia (<125, units and range not provided), feeding problems in a newborn, inguinal hernia, respiratory distress syndrome, apnoea of prematurity, drug treated apnoea, pneumothorax on left, pulmonary interstitial emphysema, chronic lung disease (CLD) at 28 days, patent ductus arteriosus, jaundice due to prematurity, thrombocytopenia (platelets <100,000, units and range not provided), neutropenia (ANC <1,000, units and range not provided), sepsis ruled out and sepsis suspected, retinopathy of prematurity (ROP) (grade 1 or 2), ROP (zone 2, stage 3), and extreme prematurity. Besides numerous other measures, such as parenteral nutrition, ventilation, and antibiotic treatment, Baby B received phototherapy for 4 days, red blood cell transfusions, and was treated with erythropoietin. Echocardiogram performed showed a patent foramen ovale with left to right flow and a large patent ductus arteriosus, shunt flow left to right. Echocardiogram showed no patent ductus arteriosus. Flow was seen into the ampulla, but flow was not seen through the ductus into the pulmonary artery. No intracranial haemorrhage or ventriculomegaly was noted in the head ultrasound. Baby B received ibuprofen for treatment of patent ductus arteriosus, and hydrocortisone for hypotension. An Electrocardiogram (ECG) was done. Arrhythmia was noted previously. Electroencephalography (EEG) was normal on unspecified date. Haematocrit was 33.8%. Laser therapy was performed for ROP grade 1 or 2. Retinopathy of Prematurity (ROP) regressed in both eyes (OU) following laser treatment. Baby B passed ALGO hearing screen bilaterally. Head ultrasound continued to be normal. Like his sister, Baby B was cared for in the ICN for a total of 128 days and was discharged to home. Since discharge, Baby B was home with mother doing well. According to the investigator, the event of premature birth was severe in severity and not related to the study drug or study procedure. The alternative explanation for the event was reported as an underlying/concomitant illness, specifically the mother's medical history of high blood pressure and kidney disease. Accordingly, the Sponsor considered the event of premature birth not related to the study drug or study procedure, and most likely secondary to underlying/concomitant illness, specifically the mother's medical history.

7): This female was treated in the scope of an investigator sponsored study (ISS) (SN 17216 [CLARITY] - Clinical Efficacy and Mechanistic Evaluation of Aflibercept for Proliferative Diabetic Retinopathy Eylea therapy was started. and about 1 months and 12 days later pregnancy was confirmed. Eylea was discontinued. Pregnancy was ongoing at the time of the report; no further information available.

8): This female with proliferative diabetic retinopathy was treated in the scope of an investigator sponsored study (ISS) (SN 17216). She received 4 Eylea injections. The pregnancy was confirmed about 9 days after the last injection Thus, one Eylea injection during pregnancy was administered. The patient had 2 previous pregnancies. The first one was medically terminated due to the child’s abnormal brain development. In the second pregnancy, patient delivered a male healthy baby. The patient’s current child was born; mother and baby were reported as doing well.

9): This is a report of “drug exposure via mother” in a neonate female, related to the aforementioned caseThe mother was enrolled in ISS no. 17216 (title: “clinical efficacy and mechanistic evaluation of aflibercept for proliferative diabetic retinopathy”). The female baby was exposed to study drug aflibercept during her mother's pregnancy (*via* transplacental). The

baby was also exposed (*via* transplacental) to concomitant drugs used by her mother during pregnancy: Novorapid (insulin aspart), Lantus (insulin glargine), Sertraline (sertraline), Chloramphenicol (chloramphenicol), and Optive (optive). The last dose of study drug given prior to pregnancy. The child was born and delivered *via* caesarean section (elective). No antenatal problems were observed. The female baby had a body weight of 2,900 g. She had neonatal jaundice and was submitted to phototherapy. She was kept nil by mouth as she had bilious aspirate. No other concerns occurred. Mother and baby were reported as doing well; event outcome was "recovered".

10): This is a clinical study case report received from an investigator which refers to a female patient who was enrolled in an investigator sponsored study (CLARITY) and experienced pregnancy, caesarean section, and diabetic ketoacidosis. The patient started study drug for proliferative diabetic retinopathy. On an unspecified date the patient experienced pregnancy. Thepatient experienced diabetic ketoacidosis; the outcome was recovered. The patient was seen and diagnosed with foetal growth restriction/intrauterine growth restriction (requiring Caesarean section) and foetal sublingual cyst (reported as symptom). The seriousness was due to required inpatient hospitalization. The estimated foetal weight was 5th centile with small reduction in growth velocity. Severity was severe and patient required Caesarean section.

Follow-up showed the following additional information: The antenatal problems were poor glycaemic control, nephropathy with oedema to knees and intra uterine growth retardation. Previous pregnancy history were spontaneous vaginal delivery with 5 children, one caesarean section with intrauterine death still birth with foetal distress, and one miscarriage (gestation of 12 weeks). The patient did not know she was pregnant until she was 18 weeks pregnant. Her first ultrasound confirmed pregnancy. Impression of foetal growth retardation was only made on the ultrasound scan, not before that. Patient remained inpatient from 15 JAN 2016 for course of (unspecified) steroids, but after ultrasound scan decision for caesarean section was made. Other diagnosis were type I diabetes, diabetic neuropathy, known smoker, impaired glycaemic control with hospital admission for hypoglycaemia and diabetic ketoacidosis. The mode of delivery caesarean section. The male neonate was delivered (no birth weight was reported). Patient was inpatient one week post-caesarean section with oedema to lower abdomen and limbs and thrombocytosis. Ultrasound resulted in no intra-abdominal collection.

11): This is the child case associated with above case. The patient experienced "foetal growth restriction/ intrauterine growth retardation" and "foetal sublingual cyst", and therefore the patient was hospitalized. The investigator reported that the patient's mother was seen at hospital and was diagnosed with foetal growth restriction. The estimated foetal weight was on the fifth centile with small reduction in growth velocity which needed a caesarean section. According to the investigator the event "foetal growth restriction/intrauterine growth retardation" and the event "foetal sublingual cyst", both became serious (hospitalization). The outcome of the 2 events was reported as not resolved. The investigator considered the events "foetal growth restriction/intrauterine growth retardation" and "foetal sublingual cyst" as severe in severity and not related to study drug. Follow-up information showed that the sublingual cyst (cyst size 12.1x12.2x13 mm) was diagnosed through ultrasound. The size of the cyst remained static. No further information was provided.

12): This is a clinical study case which refers to a female patient of unspecified age whose partner, an adult male patient of unspecified age, was involved in an ISS (SN 17216; CLARITY). The patient's partner became pregnant. No information given on patient's past drugs and concurrent conditions. The patient did not take any regular medication. The

patient's historical condition included childhood asthma. Past pregnancy history included female baby., with 3.8 kg at birth, mode of delivery: forceps. Postnatal problems included baby tachycardia for 48 hours (special care baby unit) resolved fully, no explained cause found. The patient (study participant) started study drug. On an unspecified date the patient's partner became pregnant.

13): This case was reported astudy (VGFT-OD-1329: Treatment for Central-Involved Diabetic Macular edema in Eyes with Very Good Visual Acuity) and refers to a female patient of unknown age who became pregnant during the study. The patient received first dose of Eylea on an unknown date. The total number of doses the patient received prior to the onset of the event was not provided. Study drug was discontinued as a result of the pregnancy. The patient became pregnant on an unknown dateNo additional details are currently provided.

There were no reports of pregnancies in the Phase II-III clinical studies (wet AMD and DME, e.g., CANDELA, PULSAR, PHOTON) for the 8 mg dose of aflibercept.

Post-Marketing Data

As of 15 SEP 2017, 12 pregnancy cases were reported in the in the post-marketing setting outside a clinical study setting:

1): Reported PT: "Abortion missed". The patient's medical history included 8 pregnancies with 5 healthy children and 2 spontaneous abortions. No information was given on patient's drug history and concurrent conditions. The current conception was spontaneous; the patient had consumed wine until Gestational Week (GW) 4. About 3 weeks after the last menstrual period the patient received Eylea at an unknown dosage regimen for CRVO and another dose of Eylea (aflibercept) was received in the month thereafter (i.e., GW 2+6 days and approximately GW 8+2days). Ultrasound examinations were normal until a missed abortion occurring in GW 8. Although the patient's history of 2 spontaneous abortions and her age are known risk factors and might alternatively explain the event, the company assessment considered that the causality between the reported event and Eylea cannot be completely excluded.

2):Reported PTs: “Off label use” (verbatim: Eylea in CNV of unknown origin [possibly retinopathia centralis] [off-label]), “detachment of retinal pigment epithelium”, and “exposure during breast feeding”. No information was given on patient's history and past drugs. Her CNV was possibly due to a retinopathia centralis serosa. On an unspecified date the patient started Eylea at an unspecified dose for CNV. It was unknown whether Eylea was used previously. On an unspecified date after two successful Eylea administrations, the patient developed detachment of RPE, and she received administrations after that event. It was also reported that the patient became pregnant on an unspecified date; the temporal relationship to drug administration was unclear. Further follow-up information revealed that Eylea was administered during the breastfeeding period, not during pregnancy. No further information was provided.

3): Reported PT: “Maternal exposure during pregnancy”. The patient's past medical history included diabetes mellitus, stage 2 kidney disease, polycystic ovarian syndrome, hypertension, diabetic gastropathy, neuropathy, elevated liver function tests diagnosed as hepatitis, and panic attacks. Concomitant medications included Novolog, labetalol, Xanax, unspecified cholesterol medication, and vitamin D. Treatment with Eylea for macular edema and diabetic retinopathy, intravitreal injection monthly (unspecified dose), was initiated About 4-5 months later the patient determined she was pregnant and Eylea was discontinued.

Trimester of exposure began in first trimester (calculated from due date). The patient was seeing a high-risk obstetric gynaecologist every 2 weeks. At the time of initial reporting, all ultrasounds were normal, and no amniocentesis was performed. The outcome of the pregnancy is currently unknown.

4): Reported PTs: “Maternal exposure before pregnancy”, “abortion spontaneous”, and “product use issue” (verbatim: received the second Eylea injection with more than one month of interval). The patient had 3 pregnancies, one full-term birth and 2 stillbirths. There were no problems in the previous completed pregnancy. No information was given on patient's history, past drugs, concomitant medication and concurrent conditions. It was unknown whether Eylea was used previously. The patient received a total of 2 Eylea injections for DME, at 0.05 mL IVT, the patient got pregnant 3 weeks after the last Eylea injection, and the ophthalmologist stopped injecting Eylea after the knowledge of the pregnancy. Pregnancy was confirmed by HCG (pregnancy test) and ultrasonography. A spontaneous abortion occurred, and the child had a stillbirth of unknown origin Patient had no problems in previous pregnancy. This event was not related to Eylea according to physician because patient already had several miscarriages before. Despite follow-up attempts, no further information was received.

5)female of unknown age; reported PTs: “Prolonged pregnancy” and “off label use” (verbatim: receiving Eylea injections for retinal artery occlusion/thrombosis). The patient's medical history and concomitant medications were not provided. Treatment with Eylea for retinal artery occlusion/thrombosis was initiated on an unknown date (dosing and frequency not specified). On an unknown date, the patient experienced prolonged pregnancy (verbatim event: “was 10 months pregnant”). The event outcome and action taken with Eylea were unknown. At the time of the current report no further information was available.

6): Reported PT: “Maternal exposure during pregnancy”. The patient’s medical history included 2 previous pregnancies. The patient was diagnosed with RVO in the right eye following her second pregnancy. Concomitant medication was not reported. Treatment with Eylea was initiated on an unknown date and administered every 6 weeks (dosing not reported). The patient had received an unknown number of injections. On an unknown date, the patient became pregnant, and at the time of this most recent report she was in the first trimester. No additional information was provided.

7): Reported PTs: “Diabetes mellitus inadequate control” (verbatim: rebalancing diabetes), “abortion spontaneous” (verbatim: stopped pregnancy [miscarriage]), and “maternal exposure during pregnancy”. This patient started unilateral treatment with Eylea 2 mg q8w. About 6 months later the dose was changed to injection in both eyes, and further treatments at the same dose were continued. Pregnancy was confirmed by β-HCG test and ultrasound examination. Thus, the patient received Eylea during the first trimester of pregnancy. The patient experienced serious diabetes mellitus (seriousness criterion: hospitalization) and the patient experienced spontaneous abortion (seriousness criterion: medically significant). The investigator did not provide a causality assessment, and no further information is available. The MH considered the events “diabetes mellitus inadequate control” and “abortion spontaneous” unrelated to Eylea, since there is no increased risk of systemic effects following IVT administration of Eylea, and pregnancy *per se* may unbalance diabetes in patients with previous diabetes.

8): Reported PT: “Maternal exposure during pregnancy” (verbatim: 5 weeks pregnant at the time of the injection). On an unknown date, the patient started Eylea 40 mg/mL bilaterally for treatment of DME (dose, frequency and total number of injections not reported). The patient's

last menstrual period was on an unknown date; the patient received Eylea beginning at Week 5 of the pregnancy with a potential foetal exposure during the first trimester of pregnancy. No further information is currently available.

9): Reported PTs: "Maternal exposure during pregnancy", "stillbirth". This female patient was involved in a patient support program. The patient received Eylea for diabetic retinopathy. Concurrent conditions included pericardial effusion, pleural effusion, and water retention. On an unknown date, the patient started diuretics at an unspecified dose and frequency., One day after starting and 1 day after the last dose of Eylea, the patient experienced malaise. The patient experienced respiratory disorder. On an unknown date, the patient experienced cardiac failure, renal disorder, abnormal weight loss, and abnormal weight gain. The patient experienced stillbirth. Last menstrual period and estimated date of delivery were not provided; according to the patient she had not been pregnant before. Eylea treatment was not changed.

10) Reported PT: "Maternal exposure during pregnancy". This prospective pregnancy case was reported by an ophthalmologist and described drug exposure during pregnancy in a female patient (gravida 1, para 0), who received Eylea solution for injection for myopic CNV. The patient had no previous pregnancies. The patient experienced maternal exposure during pregnancy. On an unknown date, the patient started Eylea 2 mg at an unspecified frequency. Last menstrual period and estimated date of delivery were not provided. The patient received Eylea beginning at week 1 of the pregnancy with a potential foetal exposure during the first trimester of pregnancy. The reporter commented: At the time of the initial report the patient was in the 7th week of pregnancy with no findings. No further information is currently available.

11) Female of unknown age reported PT: "Maternal exposure during pregnancy". This female (gravida 1) patient was involved in a company-sponsored observational study to assess the effectiveness of Eylea in routine clinical practice in patients with visual impairment due to DME (protocol No. 18058. The patient's concurrent conditions included chronic fatigue syndrome, hypertension, and depression. Concomitant products included bisoprolol, ramipril and venlafaxine. The patient started Eylea 2 mg at an unspecified frequency. Further 4 treatments were administered at the same dose. On an unknown date, the patient experienced maternal exposure during pregnancy. Pregnancy was verified by HCG test. The patient had received Eylea during the first trimester of pregnancy.

12) Female of unknown age reported PT: "Maternal exposure during pregnancy". This prospective pregnancy case was reported by a physician and describes the occurrence of exposure during pregnancy in an adult female patient who received Eylea for treatment of DME. On an unknown date, the patient started Eylea at an unspecified dose and frequency. On an unknown date, the patient experienced exposure during pregnancy. Last menstrual period and estimated date of delivery were not provided. No further information is currently available.

Conclusion

Overall, these few pregnancy cases currently reported both in clinical studies and in post-marketing use do not give any rise to assume that treatment with Eylea might be associated with relevant embryo-fetotoxic effects.

Seriousness/outcomes

See individual case reports described above.

There were no reports of pregnancies in the Phase II-III clinical studies (wet AMD and DME, e.g., CANDELA, PULSAR, PHOTON) for the 8 mg dose of aflibercept.

Severity and nature of risk

See individual case reports described above.

There were no reports of pregnancies in the Phase II-III clinical studies (wet AMD and DME, e.g., CANDELA, PULSAR, PHOTON) for the 8 mg dose of aflibercept.

Background incidence/prevalence

See individual case reports described above. Not applicable for ROP.

There were no reports of pregnancies in the Phase II-III clinical studies (wet AMD and DME, e.g., CANDELA, PULSAR, PHOTON) for the 8 mg dose of aflibercept.

Impact on individual patient

Based on currently available non-clinical data, no individual impact in terms of risk to the treated population is apparent.

Risk factor and risk groups

Patients at risk are women of childbearing potential.

Preventability

Treatment with Eylea is not recommended during pregnancy, unless the potential benefit outweighs the potential risk to the foetus.

Impact on risk-benefit balance of the product

An educational program is performed as an additional risk minimization measure to raise patients´ and physicians´ awareness on identified and potential risks. The effectiveness of this program was verified with a post authorization safety study (SN 16526).

This important potential risk does not have an impact on the positive risk-benefit balance of Eylea.

Public health impact

Based on currently available non-clinical data, no public health impact in terms of risk to the treated population is apparent.

SVII.3.2 Presentation of the Missing Information

SVII.3.2.1Long-term safety of aflibercept in preterm infants with ROP

Evidence source:

The current knowledge about potential long-term effects of aflibercept IVT treatment in preterm infants with ROP is lacking and current safety profile is based on the 6-months pivotal study FIREFLEYE.

Population in need of further characterization:

A Phase IIIb study FIREFLEYE NEXT is currently performed to evaluate the long-term safety in preterm infants until 5 years of age. This extension study has been set-up to evaluate the long-term outcomes up to 5 years of chronological age of patients who received treatment

for ROP in study FIREFLEYE (20090). This study is ongoing and follows up on ocular, neurodevelopmental and overall clinical outcomes until 5 years of age when detailed assessment of visual function and overall development becomes feasible and stable.

SVII.3.2.2 Exposure with bilateral 8 mg dose aflibercept therapy

Evidence source:

Aflibercept 8 mg studies allowed for concurrent dosing of 8 mg in the study eye and 2 mg aflibercept or other anti-VEGFs in the fellow eye. Safety data from patients treated with 8 mg in the study eye and 2 mg aflibercept/other anti-VEGFs in the fellow eye did not reveal a new safety concern.

Need for further characterization:

The safety associated with 8 mg aflibercept bilateral administration will be monitored in the PSUR.

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Part II – Modules SVIII: Summary of the Safety Concerns

PART II Module SVIII: Summary of the Safety Concerns

The safety concerns (important identified risks, important potential risks, missing information) as identified in previous Modules SII, SIV, SVI, and SVII of Part II are summarized in the following Table SVIII.1. Pharmacovigilance actions associated with these safety concerns are provided in PART III: Pharmacovigilance Plan

Table SVIII.1: Summary of safety concerns

Important identified risks	• Endophthalmitis (likely infectious origin) • Intraocular inflammation • Transient intraocular pressure increase • Retinal pigment epithelial tears • Cataract (especially of traumatic origin)
Important potential risks	• Medication errors • Off-label use and misuse • Embryo-fetotoxicity
Missing information	• Long-term safety of aflibercept in preterm infants with ROP • Exposure with bilateral 8 mg aflibercept therapy

See **Part III** for planned actions.

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Part III: Pharmacovigilance Plan (including post-authorization safety studies)

PART III: Pharmacovigilance Plan

III.1 Routine Pharmacovigilance Activities

III.1.1 Specific Adverse Reaction Follow-up Questionnaires for safety concerns

In order to optimize the data collection for defined medical conditions, specific follow-up questionnaires will be used for endophthalmitis/intraocular inflammation, and IOP increases with the 2 mg Eylea PFS (see **Annex 4**). These specific questionnaires will be used to follow-up on any post-marketing or study reports causing suspicion of these events in order to standardize and increase the completeness of reports.

The questionnaire for endophthalmitis/intraocular inflammation was updated to include the ROP indication and 0.4 mg dose recommended for ROP as well as the 8 mg dosage for the wet AMD/DME indications (see updated questionnaire in **Annex 4**).

The questionnaire for IOP increase was developed following the early launch observation of IOP increase with the 2 mg PFS usage. It continues to be distributed for this 2mg PFS format specifically.

Upon marketing authorisation approval, the questionnaires will include the 8mg Eylea PFS format and will be added to Annex 4 with the next EU RMP:

Table Part III.1: Routine PV activities/questionnaires

Important identified risk		
Routine PV activities beyond adverse reactions reporting and signal detection	**Objectives**	**Important identified risk**
Specific questionnaire to be used for any post-marketing or study reports suspicious for endophthalmitis and intraocular inflammation (see **Annex 4.1**).	Specific questionnaire to obtain comprehensive and standardized follow-up information about cases suspicious for endophthalmitis and intraocular inflammation.	Endophthalmitis (likely infectious origin) and intraocular inflammation.
Specific questionnaire to be used for any post-marketing or study report related to IOP increase following the use of the Bayer Eylea 2 mg PFS (see **Annex 4.2**).	Specific questionnaire to obtain comprehensive and standardized follow-up information related to intraocular pressure increase following the use of the Bayer Eylea pre-filled syringe.	Transient intraocular pressure increase

III.1.2 Other Forms of Routine Pharmacovigilance Activities for safety concerns

No other forms of Routine Pharmacovigilance Activities beyond adverse reaction reporting, signal detection and the ones described above will be implemented for Eylea.

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Part III: Pharmacovigilance Plan (including post-authorization safety studies)

III.2 Additional Pharmacovigilance Activities

FIREFLEYE NEXT study 20275, an extension study to evaluate the long-term outcomes of subjects who received treatment for retinopathy of prematurity in the FIREFLEYE Study 20090 (Category 3)

Study short name and title:

Study no. BAY 86-5321/20275: Extension study to evaluate the long-term outcomes of subjects treated in Study 20090

Rationale and study objectives:

The purpose of the current study is to primarily collect the missing data of the potential long-term effects after treatment with aflibercept and laser. Subjects will be followed up to 5 years of chronological age, which will enable a detailed assessment of visual function and overall development.

The primary study objective is to evaluate long-term safety outcomes and visual function of subjects included in Study 20090 for treatment for ROP.

The secondary study objective is to describe the visual function and overall development of subjects included in Study 20090 for treatment for ROP.

Study design:

This is a Phase 3b, multicenter study to assess the long-term outcomes of subjects previously diagnosed with ROP who were treated in Study 20090. No study treatment is defined to be administered during this study. The study interventions being assessed were administered in Study 20090 (aflibercept and/or laser photocoagulation). Any potential non-study treatments are to be decided by the treating physician, according to local standards of care.

The screening/baseline visit (Visit 1a) of Study 20275 can be conducted concomitantly with the Week 24 visit or the last follow-up visit of Study 20090, whichever is later, or at a later point between this date and before the subject is 13 months of chronological age. Visit 1b will be scheduled when the subject is 40 weeks of chronological age (-7 days / +14 days). Additional visits will be scheduled according to the subject's yearly birthday, with the last visit at the subject's 5th birthday (the visit window for Visit 2 is ± 1 month and for Visits 3-6 is -1 month / +3 months). Visit 1a can be combined with Visit 1b or Visit 2. If Visit 1a takes place after the subject is 40 weeks of chronological age, then Visit 1b is no longer applicable.

Best-corrected visual acuity and overall ophthalmological development will be evaluated. Safety will be assessed by monitoring and evaluation of adverse events, physical examinations, and vital signs. Neurodevelopment will be assessed by hearing tests and developmental scales.

Milestones:

Final protocol version: 27 NOV 2019

Planned LPLV: OCT 2025

Planned submission of interim data:

- 2-year of age data in Q2 2023
- 3-year of age data in 2024

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- 4-year of age data in 2025

Planned submission of final data: 2026

III.3 Summary Table of Additional Pharmacovigilance Activities

The studies/activities beyond the routine pharmacovigilance activities are summarized in Table Part III.2.

Table Part III.2: On-going and planned additional PV activities

Study Status	Objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional Pharmacovigilance (PhV) activity (to address specific safety concerns or to measure effectiveness of risk minimization measures).				
Review safety outcomes of FIREFLEYE NEXT study BAY 86-5321/20275: An extension study to evaluate the long-term outcomes of subjects who received treatment for retinopathy of prematurity in Study 20090 Status: Ongoing	• Primary study objective: To evaluate long-term safety outcomes and visual function of subjects included in Study 20090 for treatment for retinopathy of prematurity (ROP) • Secondary study objective: To describe the visual function and overall development of subjects included in Study 20090 for treatment for ROP	• The purpose of the current study is to collect the missing data of the potential long-term effects after treatment with aflibercept and laser. Subjects will be followed up to 5 years of chronological age, which will enable a detailed assessment of visual function and overall development.	Protocol finalized (27 NOV 2019) LPLV: planned for OCT 2025	Interim study report: • 2-year of age data in Q2 2023 • 3-year of age data in 2024, • 4-year of age data in 2025 Final study report 2026

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Part III: Pharmacovigilance Plan (including post-authorization safety studies)

Table Part III.2: On-going and planned additional PV activities

Study Status	Objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional Pharmacovigilance (PhV) activity (to address specific safety concerns or to measure effectiveness of risk minimization measures).				

Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations.
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimization measures).

PART IV: Plans for Post-authorization Efficacy Studies

There are no planned or ongoing post authorization efficacy studies.

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Part V – Risk Minimisation Measures

PART V: Risk Minimization Measures

Risk Minimization Plan

The following tables provide, per safety concern, an overview of the applied routine and additional risk minimization measures (quoted SmPC text parts are taken from the EU-SmPC).

V.1 Routine Risk Minimization Measures

Table Part V.1: Description of routine risk minimization measures by safety concern for Eylea 40 mg/mL (0.4/2 mg dose) and Eylea 114.3 mg/mL (8 mg dose)

Safety concern	Routine risk minimization activities
Endophthalmitis (likely infectious origin)	**Routine risk communication:** 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) Package Leaflet section 2 (What you need to know before you are given Eylea) Package Leaflet section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.2 (Posology and method of administration): A comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • SmPC Section 4.2 (Posology and method of administration) and Package Leaflet section 2 (What you need to know before you are given Eylea): Suggestive symptoms of endophthalmitis are mentioned. • *"Ocular or periocular infection"* and *"active severe intraocular inflammation"* are listed in SmPC Section 4.3 (Contraindications) and Package Leaflet section 2 (What you need to know before you are given Eylea). • SmPC Section 4.4 (Special warnings and precautions for use): Instructions for aseptic injection techniques, monitoring and instructions of patients are mentioned. • Package Leaflet section 2 (What you need to know before you are given Eylea): Description of symptoms potentially indicative of endophthalmitis is given. • For the treatment of babies born prematurely with retinopathy of prematurity (ROP) a separate package leaflet instruction is available (Information for guardians of babies born prematurely): Package Leaflet section 2 (What you need to know before the baby is given Eylea): Description of symptoms potentially indicative of endophthalmitis is given. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections.
Intraocular inflammation	**Routine risk communication:** SmPC section 4.2 (Posology and method of administration)

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Table Part V.1: Description of routine risk minimization measures by safety concern for Eylea 40 mg/mL (0.4/2 mg dose) and Eylea 114.3 mg/mL (8 mg dose)

Safety concern	Routine risk minimization activities
	SmPC section 4.3 (Contraindications) SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) Package Leaflet section 2 (What you need to know before you are given Eylea) Package Leaflet section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • In SmPC Section 4.2 (Posology and method of administration), a comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • "Ocular or periocular infection" and "active severe intraocular inflammation" are listed in SmPC Section 4.3 (Contraindications) and Package Leaflet section 2 (What you need to know before you are given Eylea). • SmPC Section 4.4 (Special warnings and precautions for use): Instructions for aseptic injection techniques, monitoring and instructions of patients are given. • SmPC Section 4.4 (Special warnings and precautions for use): Potential for immunogenicity with Eylea is mentioned (see Section 4.8). Monitoring of symptoms is advised. • Package Leaflet section 2 (What you need to know before you are given Eylea): Description, monitoring and early treatment of symptoms are mentioned. • Package Leaflet section 3 (How you will be given Eylea): Description on pre-injection use of disinfectant for cleaning measures provided. • For the treatment of babies born prematurely with retinopathy of prematurity (ROP) a separate package leaflet instruction is available (Information for guardians of babies born prematurely): Package Leaflet section 2 (What you need to know before the baby is given Eylea): Description, monitoring and early treatment of symptoms are mentioned. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections.
Transient intraocular pressure increase	**Routine risk communication:** SmPC section 4.2 (Posology and method of administration) SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) SmPC section 4.9 (Overdose) Package Leaflet section 2 (What you need to know before you are given Eylea) Package Leaflet section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • In SmPC Section 4.2 (Posology and method of administration), a

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Table Part V.1: Description of routine risk minimization measures by safety concern for Eylea 40 mg/mL (0.4/2 mg dose) and Eylea 114.3 mg/mL (8 mg dose)

Safety concern	Routine risk minimization activities
	comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • SmPC Section 4.2 (Method of administration): Appropriate monitoring for elevation in intraocular pressure is mentioned. Special precaution in patients with poorly controlled glaucoma is mentioned. • SmPC Section 4.4 (Special warnings and precautions for use): Excess volume from the 2 mg Eylea pre-filled syringe/vial must be expelled/discarded prior to administration. • Package Leaflet section 2 (What you need to know before you are given Eylea): Injections with Eylea may cause an increase in eye pressure. • For the treatment of babies born prematurely with retinopathy of prematurity (ROP) a separate package leaflet instruction is available (Information for guardians of babies born prematurely): Package Leaflet section 2 (What you need to know before the baby is given Eylea): Potential increase in eye pressure and its monitoring is mentioned. • SmPC Section 4.9 (Overdose): Effect of overdosing, monitoring and treatment of intraocular pressure by the physician are mentioned. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections.
Retinal pigment epithelial tears	**Routine risk communication:** SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) Package Leaflet section 2 (What you need to know before you are given Eylea) Package Leaflet section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4 (Special warnings and precautions for use): A description of risk factors is given for retinal pigment epithelial tear (RPE tear) in wet AMD patients and advice to be cautious when initiating Eylea therapy in patients with this risk factor. • Package Leaflet section 2 (What you need to know before you are given Eylea): Check of risk factors for retinal tear/detachment, RPE tear/detachment by the physician is mentioned. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections.
Cataract (especially of traumatic origin)	**Routine risk communication:** SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) Package Leaflet section 2 (What you need to know before you are given Eylea)

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Table Part V.1: Description of routine risk minimization measures by safety concern for Eylea 40 mg/mL (0.4/2 mg dose) and Eylea 114.3 mg/mL (8 mg dose)

Safety concern	Routine risk minimization activities
	Package Leaflet section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.2 (Posology and method of administration), a comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • SmPC Section 4.4 (Special warnings and precautions for use): Instructions for aseptic injection techniques, monitoring and instructions for patients are mentioned. • Package Leaflet section 2 (What you need to know before you are given Eylea): Description, monitoring and early treatment of symptoms are mentioned. • Package Leaflet section 3 (How you will be given Eylea): "Before the injection your doctor will use a disinfectant eyewash to clean your eye carefully to prevent infection." **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections.
Medication errors	**Routine risk communication:** SmPC section 4.2 (Posology and methods of administration) SmPC section 4.9 (Overdose) Package Leaflet section 1 (What Eylea is and what it is used for) Package Leaflet section 3 (How you will be given Eylea) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.2 (Posology and methods of administration) and Package Leaflet section 'information intended for Health Care Professionals (HCPs) only': Verbal instruction is provided for the handling of the pre-filled syringe/vial in order to minimize the risk of drug administration error. • SmPC Section 4.9 (Overdose): Association between overdose and IOP increase is mentioned. • SmPC Section 6.6 (Special precautions for disposal and other handling) and Package Leaflet section 'information intended for HCPs only': Instruction for the use of the pre-filled syringe in the paediatric and adult population is provided. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections. To enhance differentiation and to avoid medication error with Eylea 2 mg versus Eylea 8 mg the outer packages/boxes have different coloured appearance highlighting the different concentrations. In addition, the vial cap has a different colour.

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Table Part V.1: Description of routine risk minimization measures by safety concern for Eylea 40 mg/mL (0.4/2 mg dose) and Eylea 114.3 mg/mL (8 mg dose)

Safety concern	Routine risk minimization activities
Off-label use and misuse	**Routine risk communication:** SmPC section 4.1 (Therapeutic indications) Package Leaflet section 1 (What Eylea is and what it is used for) Package Leaflet section 3 (How you will be given Eylea) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Contraindications are listed in SmPC Section 4.3 (Contraindications) and Package Leaflet section 2 (What you need to know before you are given Eylea) • Conditions in which treatment should be withheld/discontinued/not recommended are included in the SmPC section 4.4 and Package Leaflet section 2 (What you need to know before you are given Eylea) • Conditions of use in pregnancy and breastfeeding are included in the SmPC section 4.6 and Package Leaflet section 2 (What you need to know before you are given Eylea) **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections.
Embryo-fetotoxicity	**Routine risk communication:** SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.6 (Fertility, pregnancy and lactation) SmPC section 5.3 (Preclinical safety data) Package Leaflet section 2 (What you need to know before you are given Eylea) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.4 (Special warnings and precautions for use) and Package Leaflet section 2 (What you need to know before you are given Eylea: Instructions for pregnancy and women of childbearing potential are mentioned. • SmPC Section 4.6 (Fertility, pregnancy and lactation): Instructions for pregnancy and women of childbearing potential are mentioned. • Package Leaflet section 2 (What you need to know before you are given Eylea): Instructions for pregnancy and women of childbearing potential are mentioned. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections
Long-term safety of aflibercept in preterm infants with ROP	**Routine risk communication:** SmPC section 4.4 and 4.8 (Undesirable effects)

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Table Part V.1: Description of routine risk minimization measures by safety concern for Eylea 40 mg/mL (0.4/2 mg dose) and Eylea 114.3 mg/mL (8 mg dose)

Safety concern	Routine risk minimization activities
Exposure with bilateral 8 mg aflibercept therapy	**Routine risk communication:** SmPC section 4.4 Description that bilateral Eylea 114.3 mg/mL has not been studied. SmPC section 5.1 To indicate allowance regarding fellow eye treatment in the wet AMD/DME 8 mg aflibercept studies it is clarified that patients with bilateral disease were solely eligible to receive aflibercept 2 mg treatment or another anti-VEGF medicinal product in their fellow eye.

V.2 Additional Risk Minimization Measures

V.2.1 Educational program

Besides routine risk minimization activities (SmPC and patient information), additional activity, specifically an educational program, is considered to be necessary for the important identified risks of endophthalmitis (likely infectious origin), intraocular inflammation, transient intraocular pressure increase, retinal pigment epithelium tears (adult population), and cataract (especially of traumatic origin), as well as for the important potential risk of medication errors, off-label use and misuse, embryo-fetotoxicity (adult population), the preparation and handling of the 2mg Eylea PFS with the paediatric dosing device (ROP indication). Generally, the educational material covers the indications wet AMD, CRVO, BRVO, myopic CNV, DME, and ROP.

The Educational Material will cover all approved dosages (0.4 mg/2 mg/8 mg) and approved formats (2 mg/8 mg aflibercept PFS, 2 mg/8 mg aflibercept vial).

Following the assessment (EMEA/H/C/002392/II/0039) of the post authorization study 16526 (Evaluation of Physician and Patient Knowledge of Safety and Safe Use Information for Aflibercept in Europe), the MAH has updated and re-distributed the educational materials according to the PRAC Type II variation assessment report received on 08 FEB 2018. The updated Educational Material for HCPs include highlighted information regarding treatment of women of child-bearing potential, information on the injection procedure with respect to unnecessary dilation of the eye, with the need for vision and intraocular pressure evaluation after the injection as well as potential for medication misuse, particularly re-use of the vial (see EU RMP Part III). The protocol for the follow-up survey (study 20285) was submitted to EMA for review on 25 JUN 2018 and approved on 28 FEB 2019. The study was conducted between OCT 2019 and APR 2020 and the study results were submitted in OCT 2020.

V.2.1.1. Objectives and rationale for the additional risk minimization activity

To inform patients and physicians about risks in order to minimize their occurrence and consequences in routine care, to include guidance on the IVT injection procedure including the usage of the 2 mg Eylea PFS together with the paediatric dosing device to train physicians in order to minimize injection-related adverse reactions.

Educational material also includes guidance on the IVT injection procedure to re-train physicians in order to minimize injection-related adverse reactions (adult population). The following risks are addressed in the Educational Material: endophthalmitis/intraocular

inflammation, transient intraocular pressure increase, RPE tear (adult population), cataract, medication error, off label use and misuse, and embryo-fetotoxicity (adult population).

V.2.1.2. Target audience and planned distribution path

The target audience are HCPs specialized in intravitreal injections of anti-VEGF agents as well as patients to be treated. The key messages of the educational materials (provided in Part VII Annex 6) will be distributed as paper version and/or through a digital communication method (digital platform) to the target audience(s). The feasibility and implementation of the planned distribution path will be agreed upon with and after liaising with the national health authorities in the EU member states, as requested per GVP Module XVI addendum.

V.2.1.3. Plans to evaluate the effectiveness of the interventions and criteria for success

Based on PRAC recommendations following assessment of the Post-authorization Safety Study (PASS) study 16526 (Evaluation of Physician and Patient Knowledge of Safety and Safe Use Information for Aflibercept in Europe) a new follow-up survey for physicians with revised Educational Material was mandated (see EU RMP Part III). The protocol for the follow-up survey was submitted to EMA for review on 25 JUN 2018 and approved on 28 FEB 2019. The study was conducted between OCT 2019 and APR 2020 and study results submitted in OCT 2020.

The following criteria for judging the success of the proposed risk minimization measures were applied:

- Proportion of physicians who have received the education materials.
- Level of physicians' knowledge and understanding of the updated educational material (i.e., underline information on treatment of women of child-bearing potential, information on the injection procedure with respect to unnecessary dilation of the eye, vision and intraocular pressure evaluation after injection and on potential medication misuse, particularly inadvertent reuse of the vial).

For the ROP indication, the following criteria for judging the success of the proposed risk minimization measures are applied:

- Proportion of physicians who have received the educational materials.

V.2.2 Removal of additional risk minimization activities

Not applicable.

V.3 Summary of Risk Minimization Measures

Table Part V.2: Summary table of pharmacovigilance activities and risk minimization activities by safety concern for Eylea 40 mg/mL (0.4/2 mg doses) and Eylea 114.3 mg/mL (8 mg dose)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Endophthalmitis (likely infectious origin)	**Routine risk minimization measures:** SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet (for adults and babies born prematurely) section 2, 3, and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific questionnaire to be used for any post-marketing or study reports suspicious

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimization activities by safety concern for Eylea 40 mg/mL (0.4/2 mg doses) and Eylea 114.3 mg/mL (8 mg dose)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (adult indications) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, for adult indications: patient guide “Your guide to Eylea”, and its audio version).	for endophthalmitis and intraocular inflammation (see **Annex 4.1**). **Additional pharmacovigilance activities:** None
Intraocular inflammation	**Routine risk minimization measures:** SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet (for adults and babies born prematurely) section 2, 3, and 4 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (adult indications) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, for adult indications: patient guide “Your guide to Eylea”, and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific questionnaire to be used for any post-marketing or study reports suspicious for endophthalmitis and intraocular inflammation (see **Annex 4.1**). **Additional pharmacovigilance activities:** None
Transient intraocular pressure increase	**Routine risk minimization measures:** SmPC sections 4.2, 4.4, 4.8, and 4.9 Package Leaflet (for adults and babies born prematurely) sections 2 and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimization activities by safety concern for Eylea 40 mg/mL (0.4/2 mg doses) and Eylea 114.3 mg/mL (8 mg dose)

Safety concern	Risk minimization measures	Pharmacovigilance activities
		Specific questionnaire to be used for any post-marketing or study report regarding IOP increase following the use of the Bayer Eylea pre-filled syringe.
	Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections	
	Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (adult indications) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, for adult indications: patient guide “Your guide to Eylea”, and its audio version).	**Additional pharmacovigilance activities:** None
Retinal pigment epithelial tears	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 Package Leaflet sections 2 and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable.
	Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections	**Additional pharmacovigilance activities:** None
	Additional risk minimization measures: Educational program for adults: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video, patient guide “Your guide to Eylea”, and its audio version).	
Cataract (especially of traumatic origin)	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 and 4.8 Package Leaflet sections 2, 3, and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable.

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimization activities by safety concern for Eylea 40 mg/mL (0.4/2 mg doses) and Eylea 114.3 mg/mL (8 mg dose)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (adult indications) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, for adult indications: patient guide “Your guide to Eylea”, and its audio version).	**Additional pharmacovigilance activities:** None
Medication errors	**Routine risk minimization measures:** SmPC sections 4.2, 4.9, and 6.6 Package Leaflet sections 1 and 3 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections. Packing differentiation Eylea 40 mg/ml versus Eylea 114.3 mg/ml. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise physicians' awareness on medication error (prescriber guide and video; in addition, for adult indications: patient guide “Your guide to Eylea”, and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable. **Additional pharmacovigilance activities:** None

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimization activities by safety concern for Eylea 40 mg/mL (0.4/2 mg doses) and Eylea 114.3 mg/mL (8 mg dose)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Off-label use and misuse	**Routine risk minimization measures:** SmPC sections 4.1, 4.3, 4.4, and 4.6 Package Leaflet sections 1, 2, and 3 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' (adult indications) and physicians' awareness on off-label use (prescriber guide and video; in addition, for adult indications: patient guide “Your guide to Eylea”, and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable. **Additional pharmacovigilance activities:** None
Embryo-fetotoxicity	**Routine risk minimization measures:** SmPC sections 4.4, 4.6, and 5.3 Package Leaflet section 2 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program for adults: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on the potential risk of embryo-toxicity and to underline information on treatment of women of child-bearing potential, and the need for appropriate contraception in women of childbearing potential (prescriber guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable. **Additional pharmacovigilance activities:** None

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Table Part V.2: Summary table of pharmacovigilance activities and risk minimization activities by safety concern for Eylea 40 mg/mL (0.4/2 mg doses) and Eylea 114.3 mg/mL (8 mg dose)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	and video, patient guide "Your guide to Eylea", and its audio version).	
Long-term safety of aflibercept in preterm infants within ROP	**Routine risk minimization measures:** SmPC section 4.4 and 4.8 **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable. **Additional pharmacovigilance activities:** FIREFLEYE NEXT Phase IIIb study
Exposure with bilateral 8 mg aflibercept therapy	**Routine risk minimization measures:** SmPC section 4.4/5.1	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** The safety associated with 8 mg aflibercept bilateral administration will be monitored in the PSUR. **Additional pharmacovigilance activities:** Not applicable.

PART VI: Summary of Activities in the Risk Management Plan by Product

This is a summary of the EU risk management plan (RMP) for Eylea 40 mg/mL (2 mg dose), Eylea 40 mg/mL (0.4 mg dose), and Eylea 114.3 mg/mL (8 mg dose). The RMP details important risks of Eylea, how these risks can be minimized, and how more information will be obtained about Eylea's risks and uncertainties (missing information).

Eylea's 40 mg/mL (0.4/2 mg dose) and Eylea 114.3 mg/mL (8 mg dose) summary of product characteristics (SmPC) and their package leaflets give essential information to healthcare professionals and patients on how Eylea should be used.

This summary of the RMP for Eylea 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 Eylea's RMP.

I The Medicine and what it is used for

Eylea 40 mg/mL (2 mg dose) is indicated for adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to macular edema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular edema (DME), and visual impairment due to myopic choroidal neovascularization (myopic CNV; see SmPC for the full indication).

Eylea 114.3 mg/mL (8 mg dose) is indicated for the treatment of wet AMD and DME (see SmPC for the full indication).

It contains aflibercept as the active substance and it is given by intravitreal injection. The following pharmaceutical forms are currently available:

- Eylea 40 mg/mL (2 mg dose): Solution for injection in a vial. One vial contains 4 mg aflibercept in 100 microliters in iso-osmotic solution. Delivers a single dose of 2 mg/0.05 mL.
- Eylea 40 mg/mL (2 mg dose): Solution for injection in a pre-filled syringe. One pre-filled syringe contains 3.6 mg aflibercept in 90 microliters in iso-osmotic solution. Delivers a single dose of 2 mg/0.05 mL.
- Eylea 114.3 mg/mL (8 mg dose): Solution for injection in a vial. One vial contains 11.4 mg aflibercept in 100 microlitres in iso-osmotic solution. Delivers a single dose of 8 mg/0.07 mL.
- Eylea 114.3 mg/mL (8 mg dose): Solution for injection in a pre-filled syringe. One PFS contains 21 mg aflibercept in 0.184 mL in iso-osmotic solution. Delivers a single dose of 8 mg/0.07 mL.

In addition, Eylea 40 mg/mL is indicated in premature infants for the treatment of retinopathy of prematurity (ROP). The dosing device PICLEO in combination with the 2mg Eylea pre-filled syringe and a low dead space needle are used for administration of a single dose of 0.4 mg aflibercept (equivalent to 0.01 mL solution for injection).

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Further information about the evaluation of Eylea's benefits can be found in Eylea's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/eylea).

II Risks Associated with the Medicine and Activities to Minimize or further Characterize the Risks

Important risks of Eylea together with measures to minimize such risks and the proposed studies for learning more about Eylea'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 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 Eylea, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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

II.A List of Important Risks and Missing Information

Important risks of Eylea 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 Eylea. 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 on 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).

Table Part VI.1: Summary of safety concerns

Important identified risks	• Endophthalmitis (likely infectious origin) • Intraocular inflammation • Transient intraocular pressure increase • Retinal pigment epithelial tears • Cataract (especially of traumatic origin)
Important potential risks	• Medication errors • Off-label use and misuse

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Table Part VI.1: Summary of safety concerns

	• Embryo-fetotoxicity
Missing information	• Long-term safety of aflibercept in preterm infants with ROP • Exposure with bilateral 8 mg aflibercept therapy

II.B Summary of Important Risks Eylea 40 mg/mL (0.4/2 mg doses) and Eylea 114.3 mg/mL (8 mg dose)

Important identified risk: Endophthalmitis (likely infectious origin)	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. The intravitreal injection procedure can implant pathogens into the eye if there is a break in sterile technique. Source of pathogenic agents is in most cases the patient's conjunctival bacterial flora.
Risk factors and risk groups	Improper aseptic technique increases the risk of intraocular inflammation.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet (for adults and babies born prematurely) sections 2, 3, and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (for adults) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, for adult indications patient guide "Your guide to Eylea", and its audio version).

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Important identified risk: Intraocular inflammation	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. Post-injection, sterile intraocular inflammation is a known risk following intravitreal injections of anti-VEGFs and for other intravitreally applied drugs.
Risk factors and risk groups	Improper aseptic technique increases the risk of intraocular inflammation.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet (for adults and babies born prematurely) section 2, 3 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (for adults) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition for adult indications patient guide “Your guide to Eylea”, and its audio version).

Important identified risk: Transient intraocular pressure increase	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. Transient IOP increase is attributed to an increase in vitreous volume after Eylea injection (volume effect).
Risk factors and risk groups	Patients with glaucoma. Increased intraocular pressure is a known adverse drug reaction on treatment with intravitreal corticosteroids.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections 4.2, 4.4, 4.8, and 4.9 Package Leaflet (for adults and babies born prematurely) sections 2 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (for adults) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, for adult indications patient guide “Your guide to Eylea”, and its audio version).

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Important identified risk: Retinal pigment epithelial tears	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. Development of RPE tears after anti-VEGF intravitreal injection has been attributed to a decline in intercellular adherence, thereby increasing susceptibility to tearing of the RPE layer particularly in patients with wet AMD.
Risk factors and risk groups	Wet AMD with pigment epithelial detachment; treatment of neovascularization.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 Package Leaflet sections 2 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program for adults: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video, in addition for adult indications patient guide “Your guide to Eylea”, and its audio version).

Important identified risk: Cataract (especially of traumatic origin)	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. Related to IVT procedure.
Risk factors and risk groups	Cataract is a known adverse drug reaction on treatment with IVT corticosteroids.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections 4.2, 4.4, and 4.8 Package Leaflet sections 2, 3, and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ (for adults) and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition for adult indications patient guide “Your guide to Eylea”, and its audio version).

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Important potential risk: Medication errors	
Evidence for linking the risk to the medicine	Although 2 mg Eylea is provided in a pre-filled syringe, there is an excess volume which exceeds the recommended net dose of 2 mg Eylea per injection. The drug will be administered only by qualified physicians (not by patients), and this reduces the risk of inappropriate dosing and administration as well. Proper adherence to the instructions for adequate PFS preparation and use minimizes medication errors.
Risk factors and risk groups	Not applicable
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.9 and 6.6 Package Leaflet section 1 and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise physicians' awareness on medication error (prescriber guide and video; in addition, for adult indications patient guide “Your guide to Eylea”, and its audio version).

Important potential risk: Off-label use and misuse	
Evidence for linking the risk to the medicine	As with other drugs, Eylea might be intentionally used other than recommended, or in clinical conditions outside the approved indications (so-called off-label use). Since the clinical experience with Eylea in such off-label use will be limited (in particular in terms of efficacy and safety), any case of off-label use will be considered a potential risk. Since Eylea has no dependence potential, the risk of misuse is regarded as very low.
Risk factors and risk groups	Not applicable
Risk minimization measures	Routine risk minimization measures: SmPC section 4.1, 4.3, 4.4 and 4.6 Package Leaflet sections 1, 2 and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' (for adults) and physicians' awareness on off-label use (prescriber guide and video; in addition for adult indications patient guide “Your guide to Eylea”, and its audio version).

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Important potential risk: Embryo-fetotoxicity	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. An embryo-foetal toxicity study was performed in the rabbit with IV dosing of aflibercept at doses which provided systemic exposures over 670-fold higher than that observed with IVT dosing using the clinical dose of 2 mg. The study identified dose-related increases in foetal resorptions, pregnancy disruptions and numerous foetal (external, visceral and skeletal) malformations. These effects were thought to be due to the antiangiogenic effect of aflibercept.
Risk factors and risk groups	Patients at risk are women of childbearing potential.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4, 4.6 and 5.3 Package Leaflet section 2 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Eylea must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimization measures: Educational program for adults: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on the potential risk of embryo-toxicity and to underline information on treatment of women of child-bearing potential, and the need for appropriate contraception in women of childbearing potential (prescriber guide and video, patient guide “Your guide to Eylea”, and its audio version).

Missing information: Long-term safety of aflibercept in preterm infants with ROP	
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 and 4.8 Additional risk minimization measures: None
Missing information: Exposure with bilateral 8 mg aflibercept therapy	
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 and 5.1 Additional risk minimization measures: None

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II.C Post-authorization Development Plan

II.C.1 Studies which are conditions of the Marketing Authorization

No Category 1 studies are currently planned or ongoing which are the requisites of market authorization.

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

One Category 3 study (FIREFLEYE NEXT Phase IIIb study) is currently ongoing as additional pharmacovigilance activity to evaluate long-term safety of aflibercept (0.4 mg) in preterm infants with ROP.

PART VII: Annexes

Table of Content

Annex 4 – Specific adverse event follow-up forms

Upon marketing authorization of the Eylea 114.3 mg/mL (8 mg dose) PFS, the questionnaires will include the 8mg PFS format. The updated and valid questionnaires will be added to the next EU RMP update.

Table of Content

Annex 4.1 QUESTIONNAIRE Endophthalmitis and intraocular inflammation (IOI) following the use of Bayer Eylea 40 mg/ml (0.4/2 mg dose) and Eylea 114.3 mg/ml (8 mg dose)

Aflibercept (Vials/PFS) Questionnaire - Intraocular Inflammation/Endophthalmitis

RESET FORM

SECTION I- REFERENCE ID			
BAYER CASE ID:		STUDY ID:	PATIENT ID:
SECTION II- REPORTER/PATIENT INFORMATION			
REPORTER: ◯ Physician ◯ Nurse ◯ Other (specify):			
REPORTER CONTACT INFORMATION			
Name:			
Institution/Practice Name:			
Phone:		Fax:	
Address:			
Email:			
PATIENT INFORMATION:			
Age: (at onset of the event)	Age group:	Gender: male ◯ female ◯	Weight: unit: Height: unit:
SECTION III- PRODUCT INFORMATION (Eylea)			
Therapy date: (dd/mm/yyyy): ☐ ongoing		Number of Eylea doses before the event:	
Indication:		If other indication, specify:	
Eye injected /dose: OS: ☐ 0.4 mg ☐ 2 mg ☐ 8 mg		OD: ☐ 0.4 mg ☐ 2 mg ☐ 8 mg	

Vial	PFS (Pre-filled syringe) For ROP only: PFS in combination with Picleo pediatric dosing device (PDD)
Lot/Batch number: OS: _____ Expiry date: OD: _____ Expiry date:	PFS Lot/Batch number: OS: _____ OD: _____ Expiry date OS: _____ OD: _____ For ROP only: PDD Lot/Batch number: OS: _____ OD: _____ Expiry date: OS: _____ OD: _____
Was the same vial used for more than one patient? ◯ Yes ◯ No If yes, did an event occur in other patients? ◯ Yes ◯ No If yes, how many?	Was the same PFS used for more than one patient? ◯ Yes ◯ No If yes, did an event occur in another patient? ◯ Yes ◯ No If yes, how many?
Was the vial aliquoted in several syringes? ◯ Yes ◯ No Was the vial multipunctured? ◯ Yes ◯ No Was the supplied filter needle used? ◯ Yes ◯ No ◯ Unknown	Was the same PDD used for more than one patient? ◯ Yes ◯ No If yes, did an event occur in another patient? ◯ Yes ◯ No If yes, how many? _____
Date of injection preparation (dd/mm/yyyy): Time of injection preparation (hh:mm):	Date of injection preparation (dd/mm/yyyy): Time of injection preparation (hh:mm):
What was used for injection? Injection needle Batch No: Brand of the needle: OS_____,OD_____ Syringe (Luer lock: ☐ yes ☐ no) ◯ Glass ◯ Plastic Batch No: Brand of the syringe: OS_____, OD _____	What was used for injection? Injection needle Batch No:_____ Brand of injection needle, if known: OS_____, OD_____

Annex 4.1 QUESTIONNAIRE Endophthalmitis and intraocular inflammation (IOI) following the use of Bayer Eylea 40 mg/ml (0.4/2 mg dose) and Eylea 114.3 mg/ml (8 mg dose)

Aflibercept (Vials/PFS) Questionnaire - Intraocular Inflammation/Endophtalmitis

Vial	PFS (Pre-filled syringe) For ROP only: Picleo pediatric dosing device (PDD)
Where was the syringe for injection prepared? ◯ Off-site pharmacy ◯ On-site pharmacy ◯ Treatment/Examining room	**Was the PFS/PDD stored according to the instructions for storage provided by the Manufacturer?** ☐ Yes ☐ No **If No, please explain deviation of storage condition**
If prepared in pharmacy, provide the name and contact details:	
How many hours did the prepared syringe stay at room temperature prior to administration?	

SECTION IV- ADVERSE EVENT INFORMATION

Event *(as reported term)*	**Start date** *(dd/mm/yyyy)* **Start time** *(hh:mm)*	**or how much time after injection did the event occur** *(approx.)*:	**Stop date** *(dd/mm/yyyy)*:	**Outcome** *(recovered/ not recovered/ recovered with sequelae/ recovering/ fatal)*
◯OS ◯OD ◯OU				

If stop date is unknown, provide the approximate event duration (days):

If AE resolved/ is resolving, did the visual acuity (VA) recover to:
◯ same level before AE started
◯ VA is worse

Clinical presentation:

Treatment of adverse event

Treatment provided: ◯Yes ◯ No If yes, specify →	☐ **Antibiotics:**	☐ **Steroids** *(regimen details)*:	☐ **Surgery (vitrectomy):** **Date:** *(dd/mm/yyyy)*	☐ **Unknown**

◯ **Culture taken on:** **From:** ◯OS ◯OD ◯OU ◯Culture not taken /unknown	☐ **Positive for:** ◯OS ◯OD ◯OU	☐ **Negative for:** ◯OS ◯OD ◯OU

Reporter causality comment:

The event is considered:
◯ Related to Eylea
◯ Related to intravitreal injection procedure
◯ Not related to Eylea or intravitreal injection procedure

Alternative explanation (e.g. underlying disease/condition predisposing to the event):

Action taken with product

	Date from *(dd/mm/yyyy)*	**Date to** *(dd/mm/yyyy)*	
☐ Dose not changed	N/A	N/A	
☐ Stopped		N/A	
☐ Dose reduced			New dose:
☐ Interrupted			
☐ Unknown	N/A	N/A	

Did the event abate/stop after treatment stopped? ◯ YES ◯NO ◯ UNK	**Did the event reoccur upon resuming treatment:** ◯ Yes ◯No ◯UNK

Annex 4.1 QUESTIONNAIRE Endophthalmitis and intraocular inflammation (IOI) following the use of Bayer Eylea 40 mg/ml (0.4/2 mg dose) and Eylea 114.3 mg/ml (8 mg dose)

Aflibercept (Vials/PFS) Questionnaire - Intraocular Inflammation/Endophthalmitis

SECTION IV - RELEVANT CLINICAL SYMPTOMS *(to AE of Interest)* **Please indicate which eye was affected**

Signs or symptoms	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)

Additional Questions:
Did the patient experience the same event(s) in the past: ◯ Yes ◯ No
If yes, please provide relevant details:

SECTION V- RELEVANT (intravitreal) CONCOMITANT / HISTORICAL MEDICATION

Drug Name	From (dd/mm/yyyy)	To (dd/mm/yyyy)	Ongoing	Dose / number of injections	Indication	Similar event occurred? If yes, please specify
☐ Anti VEGF Please specify: ◯ OS ◯ OD ◯ OU			☐			
☐ Other Please specify: ◯ OS ◯ OD ◯ OU			☐			

SECTION VI- RELAVANT MEDICAL HISTORY / RISK FACTORS *(relevant to the reported event)*

Condition	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)	Ongoing
☐ Diabetes			☐
☐ Autoimmune disease, please specify:			☐
☐ Malignancy, specify:			☐
☐ Immunodeficiency, please specify:			☐
☐ Other, please specify:			☐

SECTION VII: ADDITIONAL INFORMATION /COMMENTS *(e.g. gender information if not male/female):*

Cause of death (If selected outcome was fatal)	Date of death (dd/mm/yyyy)	Autopsy done	Autopsy details (Continue with SECTION IV)
		☐	

This section can also be used to provide information on any of the sections above. Please note the relevant section number below.

Please sign electronically:	Signature:
If your signature is not yet configured on your computer, please follow the instruction when you click in the signature field	

Annex 4.2 QUESTIONNAIRE Intraocular pressure increase following the use of the Bayer Eylea 40 mg/ml (0.4/2 mg dose) pre-filled syringe

QUESTIONNAIRE Aflibercept-
Increase in Intraocular pressure (IOP) with Pre-filled syringes (PFS) of Aflibercept

Reset form

Reporter Information	Name: _____ Email:	☐ Physician ☐ Nurse ☐ Other:
Institution Name and address		Telephone: Fax:
Patient Information	Initials *(leave empty for study participants)*:	☐ ♂ Male ☐ ♀ Female Age group *(at onset of event)*
Product Information	Number of Eylea doses before the event _____	Dose information: OS: ☐ 2.0 mg ☐ 0.4 mg OD: ☐ 2.0 mg ☐ 0.4 mg
		PFS batch number(s): OS: _____ Expiry date: _____ OD: _____ Expiry date: _____
		PDD Batch number(s): OS: _____ Expiry date: _____ OD: _____ Expiry date: _____
	Indication:	
Adverse Event (AE) Information	Intraocular Pressure (IOP) Increase onset date	Last Injection date before event onset:

Was the **IOP value** measured **pre-injection**? ☐ No ☐ Yes, if yes, please provide • IOP value(s) (mmHg) • Time/minutes pre-injection and date • Method	
Was the **IOP value** measured **post-injection**? ☐ No ☐ Yes, if yes, please provide • IOP value(s) (mmHg) • Timing(s)/minutes post-injection and dates • Method	
How long did the increased IOP last after the injection?	
Outcome of IOP increase event	☐ recovering/resolving ☐ recovered/resolved without sequelae ☐ recovered/resolved with sequelae, please detail sequelae: _____ ☐ not recovered/not resolved ☐ unknown
Did the patient experience any other clinical sign or symptom in the context of post-injection IOP increase? ☐ No ☐ Yes, if yes, which other medical conditions/symptoms were experienced and what is the outcome of the events? Please indicate outcome in box to the right.	Outcome of events (please indicate event in parenthesis): ☐ recovering/resolving (event(s): _____) ☐ recovered/resolved (event(s): _____) ☐ recovered/resolved with sequelae, (event(s): - _____) ☐ not recovered/not resolved (event(s): _____) ☐ unknown (event(s): _____) ☐ not applicable

Annex 4.2 QUESTIONNAIRE Intraocular pressure increase following the use of the Bayer Eylea 40 mg/ml (0.4/2 mg dose) pre-filled syringe

QUESTIONNAIRE Aflibercept-
Increase in Intraocular pressure (IOP) with Pre-filled syringes (PFS) of Aflibercept

Was post injection fundoscopy performed? ☐ No ☐ Yes, if yes, please provide results and post-injection timing	
Was there any intervention done to treat increased IOP? ☐ No ☐ Yes, if yes, please specify the measures taken including date and time	
Does the patient have a history of glaucoma, ocular hypertension or glaucoma surgery or take anti-glaucoma medication in the injected or the fellow eye? ☐ No ☐ Yes, if Yes, please provide details	☐ OS ☐ OD ☐ OU Details:
Has the patient's anterior chamber angle been assessed in the eye(s) with IOP increase? ☐ No ☐ Yes, if Yes, please detail result, date: timing (pre- or post-injection):	By which method? Is the angle open, narrow, or closed? ☐ OS ☐ OD Details:
Did the patient use corticosteroids or any other medication, that could potentially increase IOP? ☐ No ☐ Yes, if yes, please specify the drug names and indications	
Does the patient have any of the following co-morbid conditions (please check all that apply)? ☐ diabetes ☐ high blood pressure ☐ low blood pressure ☐ retinal ischemia ☐ CRAO ☐ BRAO ☐ eye trauma ☐ eye surgeries ☐ myopia ☐ pseudo exfoliation syndrome ☐ pigment dispersion syndrome ☐ corneal arcus present, details	
PFS details	
Who prepared the Aflibercept PFS injection (e.g., physician, nurse, other)? Was the individual specifically trained on the Aflibercept PFS? ☐ No ☐ Yes For ROP only: Was the individual specifically trained on the use of Aflibercept PFS in combination with Picleo pediatric dosing device (PDD)? ☐ No ☐ Yes	
Who conducted the Eylea injection with the PFS (e.g., physician, nurse)? Was the individual specifically trained on the Aflibercept PFS? ☐ No ☐ Yes For ROP only: Was the individual specifically trained on the use of Aflibercept PFS in combination with Picleo pediatric dosing device (PDD)? ☐ No ☐ Yes	
For ROP only: Was a Picleo pediatric dosing device (PDD) used for injection? ☐ Yes ☐ No; If no, please explain reason for not using a PDD?	
Was the 30G needle used for injections? ☐ Yes ☐ No If No, which needle size was used?Brand of injection needle, if known: For ROP only: Was a 30G low dead space needle used for injection? ☐ Yes ☐ No If No, which needle size was used? Brand of injection needle, if known:	

Annex 4.2 QUESTIONNAIRE Intraocular pressure increase following the use of the Bayer Eylea 40 mg/ml (0.4/2 mg dose) pre-filled syringe

QUESTIONNAIRE Aflibercept-
Increase in Intraocular pressure (IOP) with Pre-filled syringes (PFS) of Aflibercept

For adult patients only: Were all the bubbles eliminated/expelled, excess drug expelled, and the plunger correctly adjusted to the dose line before injection (moving the base of plunger dome (not the tip) to dosing line)? ☐Yes ☐No If No, please provide details: For ROP only: Were all the air bubbles eliminated/expelled and was the system (Aflibercept PFS/Picleo pediatric dosing device) primed correctly before injection ? ☐Yes ☐No, if No please provide details:
Was there any difficulty in preparing the PFS/PFS in combination with Picleo pediatric dosing device according to the instructions prior to the injection? ☐ No ☐ Yes If yes, please explain:
Was there any physical or handling abnormality observed with the syringe/ PFS in combination with Picleo pediatric dosing device? ☐No ☐Yes If yes, please specify:
For this event, did you see any foreign particles, discoloration or change in physical appearance of the Aflibercept solution? ☐ No ☐ Yes If Yes provide details:
For this event, have you injected, or attempted to inject, the residual volume which remained in the syringe after completion of injection? ☐No ☐Yes, if yes please provide details:

Other anti VEGF treatment:		
Did the patient have previous intravitreal injections? ☐No ☐yes If, yes please fill adjacent columns to the right	Aflibercept: ☐Vial ☐PFS Other intravitreal injections ☐	Was IOP increase also observed after previous intraocular injections? ☐No ☐Yes, please detail:
Further notes *(free text)*:		

Please sign here: If your electronic signature is not yet configured on your device, please follow the instructions which appear when you click in the Signature field	**Signature:**

Annex 6 – Details of proposed additional risk minimisation activities

The following material is provided in this annex:

Eylea (Aflibercept) EU Educational Material Eylea 40 mg/mL (vial and pre-filled syringe) and Eylea 114.3 mg/ml (vial and pre-filled syringe) – KEY MESSAGES

The MAH has agreed to provide EU Educational Material for Eylea. Prior to launch and during the product's lifecycle in each Member State the Marketing Authorisation Holder (MAH) will agree the final Educational Material with the National Competent Authority. The MAH ensures that, following discussions and agreement with the National Competent Authorities in each Member State where Eylea is marketed, ophthalmological clinics where Eylea is expected to be used are provided with an updated physician information pack containing the following elements:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information packs (for adult population only)

The physician information in the educational material contains the following key elements:

- Techniques for the intravitreal injection including use of a 30 G needle, and angle of injection
- The vial and the pre-filled syringe are for single use only
- The need to expel excess volume of the syringe before injecting Eylea to avoid overdose (in adult population only)
- Patient monitoring after intravitreal injection including monitoring for visual acuity and increase of intraocular pressure post-injection
- Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, intraocular inflammation, increased intraocular pressure, retinal pigment epithelial tear and cataract
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eylea (in adult population only)

The following key elements are specific to the ROP (retinopathy of prematurity) indication:

- Use of the paediatric dosing device is mandatory
- The need to properly prime the paediatric dosing device before injection
- The paediatric dosing device is for single use only

The patient information pack of the educational material for the adult population includes a patient information guide and its audio version. The patient information guide contains following key elements:

- Patient information leaflet
- Who should be treated with Eylea
- How to prepare for Eylea treatment

EYLEA®
(Aflibercept)
EU Risk Management Plan
Annex 6 – Details of proposed additional risk minimisation activities

- What are the steps following treatment with Eylea
- Key signs and symptoms of serious adverse events including endophthalmitis, intraocular inflammation, intraocular pressure increased, retinal pigment epithelial tear and cataract
- When to seek urgent attention from their health care provider
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eylea

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Approval Task	Jutta Pospisil jutta.pospisil@bayer.com Qualified Person for Pharmacovigilance 23-Apr-2024 13:19:19 GMT+0000

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