NOVARTIS

Chief Medical Office & Patient Safety

Ranibizumab

RFB002

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Ranibizumab
Product(s) concerned (brand name(s)):	Lucentis®
Document status:	Final
Version number:	Version 22.0
Data lock point for clinical trial data	30-Jun-2022
Data lock point for post-marketing data	05-Oct-2021
Date of final sign off	12-Oct-2022

Template version 6.3, Effective from 24-Feb-2021

Rationale for submitting an updated RMP:

This European Union (EU) Risk Management Plan (RMP) has been updated for the purpose of paediatric submission based on completion of the Study CRFB002H2301E1 (RAINBOW Extension study) with retinopathy of prematurity (ROP) as indication.

Summary of significant changes in this RMP:

Key changes for this RMP version 22.0 update compared to previously submitted RMP version 21.0 included:

- Updated the cumulative exposure data for the completed Study CRFB002H2301E1 (RAINBOW Extension study).
- Removal of the missing information topic 'Long term safety of ranibizumab in the condition ROP'.

The table below shows the major modifications/changes for Safety EU RMP version 22.0 from EU RMP version 21.0.

Part	Major changes compared to RMP v21.0
Part I	None
Part II	Module SIII: Updated the estimated cumulative subject exposure data by age, gender and race. Module SIV.2: Updated the data for the pivotal study CRFB002H2301 and open-label extension study CRFB002H2301E1. Module SV.1.2: Updated the cumulative post-marketing exposure data. Module SVII.2: Updated to reflect the removal of missing information topic 'Long term safety of ranibizumab in the condition ROP'. Module SVII.3.1: Updated the clinical trial data of Important identified risk 'Retinal detachment and retinal tear' and Important potential risk 'Neurodevelopment impaiment (ROP)'. Module SVII.3.2 and Module SVIII: Updated to reflect the removal of missing information topic 'Long term safety of ranibizumab in the condition ROP'.
Part III	No change
Part IV	Removed the Study CRFB002H2301E1 (RAINBOW Extension study) based on completion of the study.
Part V	Updated to reflect the removal of missing information topic 'Long term safety of ranibizumab in the condition ROP'.
Part VI	Updated to reflect the removal of missing information topic 'Long term safety of ranibizumab in the condition ROP' and removal of Study CRFB002H2301E1 (RAINBOW Extension study) based on completion of the study.
Part VII	Annex 2: Updated with information regarding completed Study CRFB002H2301E1 (RAINBOW Extension study). Annex 5: Updated with the removal of protocol of Study CRFB002H2301E1 (RAINBOW Extension study). Annex 7: Novartis internal reference updated. Annex 8: Updated to reflect the summary of changes made in this RMP update for Study CRFB002H2301E1 (RAINBOW Extension study) and removal of one missing information topic.

Other RMP versions under evaluation

No other RMP is under evaluation.

Details of the currently approved RMP:

Version number: Version 21.0

Approved with procedure: EMEA/H/C/000715/IB/0095/G

Date of approval (opinion date): 30-Nov-2021

QPPV name: Dr. David Lewis

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of abbreviations

ADR	Adverse drug reaction
AEs	Adverse events
AMD	Age-related macular degeneration
ATE	Arterial thromboembolic event
BCVA	Best corrected visual acuity
BDES	Beaver Dam Eye Study
BMI	Body mass index
BRVO	Branch Retinal Vein Occlusion
CI	Confidence interval
CNV	Choroidal neovascularization
CRAO	Central retinal artery occlusion
CRVO	Central Retinal Vein Occlusion
CSDME	Clinically significant diabetic macular edema
CSME	Clinically significant macular edema
CSR	Clinical study report
DM	Diabetes mellitus
DME	Diabetic macular edema
DR	Diabetic retinopathy
EEA	European Economic Area
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
GA	Gestational Age
HR	Hazard ratio
IA	Interim analysis
IBD	International birth date
IOP	Intraocular pressure
IVT	Intravitreal
LPLV	Last patient last visit
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Affairs
MOW	Most of the world
NA	Not applicable
nAMD	Neovascular age-related macular degeneration
OCT	Optical coherence tomography
OR	Odds ratio
PAES	Post-authorisation efficacy study
PDR	Proliferative Diabetic retinopathy
PDT	Photodynamic therapy
PFS	Pre-filled syringe
PL	Package leaflet
PM	Pathologic myopia
PRAC	Pharmacovigilance Risk Assessment Committee
PRN	Pro re nata: as needed (Latin abbreviation)
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance

RMP	Risk Management Plan
ROP	Retinopathy of prematurity
RPE	Retinal pigment epithelium/epithelial
RR	Relative risk
RVO	Retinal vein occlusion
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
TE	Treat and extend
T1DM	Type I diabetes mellitus
T2 DM	Type II diabetes mellitus
UK	United Kingdom
US	United States
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VLBW	Very low birth weight
vPDT	verteporfin-PDT

1 Part I: Product(s) Overview

Ranibizumab is a humanized recombinant monoclonal antibody fragment targeted against vascular endothelial growth factor A (VEGF-A). It is available as a 10 mg/mL solution for intravitreal (IVT) injection in a vial and a pre-filled syringe (PFS). Ranibizumab is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD; in this document also referred to as nAMD), the treatment of visual impairment due to choroidal neovascularization (CNV), the treatment of visual impairment due to diabetic macular edema (DME), the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) and the treatment of proliferative diabetic retinopathy (PDR). Ranibizumab 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 3+) or AP-ROP (aggressive posterior ROP) disease.

Table 1-1 Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Ranibizumab
Pharmacotherapeutic group(s) (ATC Code)	S01LA04
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Lucentis®
Marketing authorization procedure	Centralized Procedure
Brief description of the product	**Chemical class:** Humanized recombinant monoclonal antibody fragment
	Summary of mode of action: Lucentis® (ranibizumab) is targeted against vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (e.g., $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{165}$), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularization, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, pathologic myopia and CNV or to visual impairment caused by either diabetic macular oedema or macular oedema secondary to RVO in adults and retinopathy of prematurity in preterm infants.
	Important information about its composition: ranibizumab solution for injection complies with the EMA guideline (EMEA/410/01/rev.3 2004) "Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products". None of the excipients used are of human or animal origin. In addition, the primary container closure system does not pose a risk of transmitting spongiform animal encephalopathy agents.
Hyperlink to the Product Information	Current: [Current approved SmPC] Proposed SmPC: [Proposed SmPC]
Indication(s) in the EEA	**Current:** Lucentis is indicated in adults for:

	• The treatment of neovascular (wet) age-related macular degeneration (AMD) • The treatment of visual impairment due to choroidal neovascularisation (CNV) • The treatment of visual impairment due to diabetic macular oedema (DME) • The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) • The treatment of proliferative diabetic retinopathy (PDR) Lucentis 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 3+) or AP-ROP (aggressive posterior ROP) disease.
	Proposed (in addition to current indications): None
Dosage in the EEA	**Current:** Lucentis must be administered by a qualified ophthalmologist experienced in intravitreal injections. *Adults* The recommended dose for Lucentis is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05 mL. The interval between two doses injected into the same eye should be at least four weeks. Treatment is initiated with one injection per month until maximum visual acuity (VA) is achieved and/or there are no signs of disease activity e.g. no change in visual acuity and other signs and symptoms of the disease under continued treatment. In patients with nAMD, DME, PDR and RVO, initially, three or more consecutive, monthly injections may be needed. The treatment of visual impairment due to CNV should be determined individually per patient based on disease activity. Some patients may only need one injection during the first 12 months; others may need more frequent treatment, including a monthly injection. For CNV secondary to PM, many patients may only need one or two injections during the first year. Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters. If, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, Lucentis should be discontinued. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography [OCT] or fluorescein angiography). If patients are being treated according to a treat-and-extend regimen, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by no more than two weeks at a time for nAMD and may be extended by up to one month at a time for DME. For PDR and RVO, treatment intervals may also be gradually extended, however there are insufficient data to conclude on the length of these intervals. If disease activity recurs, the treatment interval should be shortened accordingly. *Lucentis and laser photocoagulation in DME and in macular edema secondary to BRVO* There is some experience of Lucentis administered concomitantly with laser photocoagulation. When given on the same day, Lucentis should be administered at least 30 minutes after laser photocoagulation. Lucentis can

	be administered in patients who have received previous laser photocoagulation. *Lucentis and Visudyne photodynamic therapy in CNV secondary to PM* There is no experience of concomitant administration of Lucentis and Visudyne. *Preterm infants* The recommended dose for Lucentis in preterm infants is 0.2 mg given as an intravitreal injection. This corresponds to an injection volume of 0.02 mL. In preterm infants, treatment of ROP is initiated with a single injection per eye and may be given bilaterally on the same day. In total, up to three injections per eye may be administered within six months of treatment initiation if there are signs of disease activity. Most patients (78%) in the conducted clinical study received one injection per eye. The administration of more than three injections per eye has not been studied. The interval between two doses injected into the same eye should be at least four weeks.
	Proposed: None
Pharmaceutical form(s) and strengths	Solution for injection. One mL contains 10 mg ranibizumab. Each single-dose vial contains 2.3 mg of ranibizumab in 0.23 mL solution. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab to adult patients and a single dose of 0.02 ml containing 0.2 mg ranibizumab to preterm infants.
Is the product subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

Ranibizumab is indicated in adults for:

- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of proliferative diabetic retinopathy (PDR)

Ranibizumab 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 3+), or aggressive posterior ROP (AP-ROP) disease

2.1 Neovascular age-related macular degeneration

2.1.1 Incidence (nAMD)

Incidence of nAMD and late nAMD in Europe, the US and Asia are reported in Table 2-1 below.

Table 2-1 Reported incidence of late AMD and nAMD worldwide

Country, study period	Follow-up, y	No. of patients	Baseline mean age, y	Cumulative incidence, %		Reference
				Late AMD	nAMD	
Iceland, 2002-2011	5	2,196	75±5	Overall 0.7 Men 0.6 Women 0.8	NR	Jonasson et al 2014
Netherlands, US, Australia, 1988-1999	5.5	9,523	63	Overall 1.1	NR	Tomany et al 2004
Denmark, 1986-2002	14	359	68	Overall 14.8 Men 11.2 Women 16.8	Overall 9.8	Buch et al 2005a
US, 2000-2012	8	3,802	61±9	Overall 2.3 Men 2.8 Women 2.1	NR	Fisher et al 2016
US, 1998-2010	10	1,700	67±9	Overall 4.0	Overall 2.6	Klein et al 2013
Australia, 1992-1999	5	2,335	64.5	Overall 1.1 Men 0.7 Women 1.4	Overall 1.0 Men 0.6 Women 1.2	Mitchell et al 2002
Australia, 1992-2010	15	1,149	64	Overall 6.8 Men 6.0 Women 7.5	Overall 4.4 Men 3.3 Women 5.2	Joachim et al 2016
Singapore, 2006-2013	6	1,809	56±10	Overall 0.8 Men 1.2 Women 0.5	NR	Cheung et al 2017

Country, study period	Follow-up, y	No. of patients	Baseline mean age, y	Cumulative incidence, %		Reference
				Late AMD	nAMD	
China, 2001-2006	5	3,251	55±10	Overall 0.1 Men 0.2 Women 0	Overall 0.1 Men 0.2 Women 0	You et al 2012
Japan, 1998-2003	5	948	64±8	Overall 0.8 Men 1.9 Women 0.2	Overall 0.5 Men 1.1 Women 0.2	Miyazaki et al 2005

NR = Not reported.

Source: Jonasson et al 2014, Tomany et al 2004, Buch et al 2005a, Fisher et al 2016, Klein et al 2013, Mitchell et al 2002, Joachim et al 2016, Cheung et al 2017, You et al 2012, Miyazaki et al 2005

2.1.2 Prevalence (nAMD)

Prevalence: The prevalence of nAMD increases with age. In a pooled analysis of three population-based studies from three continents (RS, Beaver Dam Eye Study [BDES], and BMES) the prevalence of nAMD increased from 0.17% among subjects aged 55 to 64 years to 5.8% for those older than 85 years (Smith et al 2001).

Another analysis on six studies in the US, Australia and Europe estimated a pooled prevalence of nAMD of 1.05% (95% CI: 0.57-1.52) for subjects aged 65-79 years (Owen et al 2003). The overall prevalence of nAMD in the US population 40 years and older in a pooled analysis of three studies was estimated to be 1.02% (95% CI: 0.93-1.11). In the US it is estimated that nAMD affects more than 1.75 million individuals and this number is projected to increase to almost three million by 2020 (Friedman et al 2004).

Further recently published studies are summarized in Table 2-2 below. Only overall estimates are presented; studies that report age-specific prevalence confirm the previous findings that prevalence of nAMD increases steeply with age, from approximately 0.1-0.2% in those aged under 65, to over 5% in those aged 75 and older.

Table 2-2 Reported prevalence of late AMD and nAMD worldwide, 2011-2015

Country, study period	Population characteristics	Prevalence % (95% CI)		Reference
		Late AMD	nAMD	
UK, 2007-2009	Meta-analysis of published data Subjects aged > 50y	2.4 (1.7–3.3)	1.2 (0.9–1.7)	Owen et al 2012
Republic of Ireland, 2009-2011	N=4,751 aged ≥50 y Mean age 61.6±8.1 y, 45.7% men	0.6 (0.4–0.8)	0.3 (0.1–0.5)	Akuffo et al 2015
Denmark; Norway; Sweden, 2012	Scandinavian general population age≥ 65 years	5.2	3.61	Lindekleiv and Erke 2013
Norway, 2007-2008	N=2,631 aged 65-87 y Mean age 72.3 y, 42.5% men	3.5 (2.8–4.2)	2.5 (1.9–3.1)	Erke et al 2012
Iceland, 2002-2006	N=5,272 aged ≥66 y Mean age 76±6 y, 42% men	5.3	3.3 (2.8–3.8)	Jonasson et al 2011
South Korea, 2010-2012	N=4,377 postmenopausal women Mean age 63.1±0.2 y	0.8 (0.5–1.2)	0.6 (0.4–1.0)	Cho et al 2014a
South Korea, 2010-2011	N=8,714 aged ≥40 y Mean age 55.2±0.2 y, 47.9% men	0.7 (0.5–0.9)	0.5 (0.4–0.8)	Cho et al 2014b

Source: Owen et al 2012, Akuffo et al 2015, Lindekleiv and Erke 2013, Erke et al 2012, Jonasson et al 2011, Cho et al 2014a, Cho et al 2014b.

2.1.3 Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors of the disease (nAMD)

Risk of nAMD steeply increases with age and appears to be higher in women, although studies in Asian population tend to demonstrate a reversed trend (e.g. Tomany et al 2014, Buch et al 2005a, Joachim et al 2016, Fisher et al 2016). Studies that evaluated risk of advanced AMD in various ethnicities reported that it may be significantly more common in White rather than Black patients or those of Hispanic ethnicities (Fisher et al 2016); data from Asian populations indicate that the age-specific prevalence of late AMD in Asians is largely similar to that in White people (Lim et al 2012).

A number of further risk factors have been linked to a higher risk of nAMD (Lim et al 2012):

- Environmental and behavioral factors
  - Cigarette smoking
  - Obesity
  - Low dietary intake of vitamins A, C, and E, and zinc
  - Low dietary intake of lutein and omega-3 fatty acids
  - Unhealthy lifestyle related to cardiovascular risk factors
- Ocular risk factors:
  - Darker iris pigmentation
  - Previous cataract surgery
  - Hyperopic refraction
- Main genetic loci identified:
  - CFH (complement factor H; chromosome [chr 1])
  - Age-related maculopathy (ARMS2)/HTRA1 (HtrA-serinepeptidase1; chr 10)
  - CFB (complement factor B [properdin]; chr 6)
  - C2 (complement component 2; chr 6)
  - CF1 (complement factor 1; chr 4)
- Other
  - Age (main risk factor)
  - Family history
  - Race (more common in Asian or White patients compared to Blacks)

2.1.4 Main existing treatment options (nAMD)

Anti-VEGF therapies delivered intravitreally are the main therapies used for treatment of neovascular AMD and include ranibizumab and aflibercept (Eylea, Bayer/Regeneron). Additionally, bevacizumab (Avastin, Genentech/ Roche) is unlicensed for ocular use yet broadly used in clinical practice worldwide.

Photodynamic therapy with verteporfin is also licensed in this indication although use in clinical practice is limited as is use of laser for extrafoveal lesions.

2.1.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity (nAMD)

Untreated nAMD is associated with a risk of impaired vision, including blindness. A study in the US Medicare database followed a cohort of patients newly diagnosed with any AMD between 1994 and 2004 (before anti-VEGF treatments became available). The 10-year cumulative incidences of blindness, severe vision loss and moderate vision loss in this cohort were 3.2%, 5.4% and 6.0%, respectively; there was a statistically significant 2.3-fold increase in blindness and 3.7-fold increase in severe vision loss when compared to the control population without AMD (Wysong et al 2009). Neovascular-AMD and the associated visual impairment have an impact on functional independence and quality of life (Ramrattan et al 2001, Cruess et al 2007, Soubrane et al 2007).

Mortality: Decreased visual acuity (VA) is associated with increased five-year mortality and even relatively mild visual impairment increases the risk of death more than two-fold (McCarty et al 2001). Findings from long-term follow-up studies regarding a possible association of nAMD with increased mortality risk have been inconsistent. Whereas results from some studies have observed no association between nAMD and mortality (Borger et al 2003, Thiagarajan et al 2005, Knudtson et al 2006, Pedula et al 2015), nAMD was reported as a significant risk factor for all-cause mortality in women in a population-based 14-year cohort study in people aged 60-80 years in Denmark (Buch et al 2005b) and in men only in a 15-year cohort study in Australia (Gopinath et al 2016). In a cohort study in Iceland, nAMD was associated with all-cause mortality only in the subgroup aged 83 years or older (Fisher et al 2015), while in the BMES, nAMD was significantly associated with all-cause mortality only among persons younger than 75 years (Cugati et al 2007b).

2.1.6 Important co-morbidities (nAMD)

The key comorbidities in the nAMD population are listed in the following Table 2-3.

Table 2-3 Important comorbidities in nAMD population

Comorbidity	Prevalence, %	Comments	References
Cataract	15 – 58	Prevalence in the range of the estimates in general population	Anastasopoulaos et al 2006, Cruess et al 2007, Soubrane et al 2007, Zlateva et al 2007, Ryskulova et al 2008
Glaucoma	8 – 9	Prevalence within the range reported in general population of similar ages	Anastasopoulos et al 2006, Soubrane et al 2007, Ryskulova et al 2008
Hypertension	38 – 82	Prevalence within the range reported in general population	Borger et al 2003, Thiagarajan et al 2005, Anastasopoulos et al 2006, Alexander et al 2007, Duan et al 2007, Sun et al 2007, Zlateva et al 2007, Klein et al 2007b
Hyperlipidemia	18 – 47	Prevalence within the range reported in general population	Anastasopoulos et al 2006, Alexander et al 2007

Comorbidity	Prevalence, %	Comments	References
Diabetes	8 – 33	Pooled meta-analysis estimates for risk of nAMD in diabetes: Cohort studies RR=1.10 (95%CI 0.96–1.26) Cross-sectional OR=1.48 (95%CI 1.44–1.51) Case-control OR=1.15 (95%CI 1.11–1.21)	Borger et al 2003, Thiagarajan et al 2005, Anastasopoulas et al 2006, Alexander et al 2007, Duan et al 2007, Sun et al 2007, Zlateva et al 2007, Chen et al 2014a
Myocardial infarction	4 – 5	Pooled meta-analysis estimates for risk of CVD in late AMD: RR=1.66 (95%CI 1.31–2.10)	Alexander et al 2007, Duan et al 2007, Wu et al 2014
Stroke	3 – 29	Pooled meta-analysis estimates for risk of stroke in any AMD: OR=1.08 (95%CI 0.81–1.44)	Zlateva et al 2007, Soubrane et al 2007, Sun et al 2007, Fernandez et al 2015
Depression	3 – 44	People with AMD more likely to experience symptoms of depression compared with those without AMD	Brody et al 2001, Alexander et al 2007, Sun et al 2007, Tournier et al 2008, Dawson et al 2014
Anxiety	4 – 30	People with AMD not more likely to experience symptoms of anxiety than those without	Soubrane et al 2007, Augustin et al 2007, Dawson et al 2014

Source: Borger et al 2003, Thiagarajan et al 2005, Anastasopoulas et al 2006, Cruess et al 2007, Alexander et al 2007, Duan et al 2007, Sun et al 2007, Zlateva et al 2007, Soubrane et al 2007, Wong et al 2007, Ryskulova et al 2008, Klein et al 2007b, Brody et al 2001, Tournier et al 2008, Augustin et al 2007, Chen et al 2014a, Wu et al 2014, Fernandez et al 2015, Dawson et al 2014

2.2 Diabetic macular edema

2.2.1 Incidence (DME)

Incidence: Recently published population-based studies that have provided incidence figures for DME and clinically significant diabetic macular edema (CSDME) are listed in Table 2-4. The results are grouped by diabetes subtype: Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM) or any diabetes.

Table 2-4 Incidence of DME and CSDME in diabetic populations worldwide

Country, study period	Follow-up, years	No. of patients	Baseline mean age, years	Cumulative incidence (CI) (%) or incidence rate (IR) per 100 PY		Reference
				DME	CSDME	
T1DM						
Finland, 1997-2009	24 (actual) 30 (model)	1,354	38.7±11.6	-	CI 0-4 y: 17 (95%CI 11–26) 5-15 y: 27 (23-32) 15-40 y: 34 (27-41)	Hietala et al 2013
Spain, 2000-2009	10	334	25.17±11.74	CI: 11.07	-	Romero-Aroca et al 2011
Sweden, 1990-1993	2.9	294	34.1	-	IR: 2.4 (95%CI 1.6–3.5)	Henricsson et al 1999

Country, study period	Follow-up, years	No. of patients	Baseline mean age, years	Cumulative incidence (CI) (%) or incidence rate (IR) per 100 PY		Reference
				DME	CSDME	
US, 1980-1996	14	634	26.8±11.2	CI: 26.1	CI: 17.0	Klein et al 1998
T2DM						
Sweden, 1990-1993	2.9	1,291	60.9	-	IR on insulin: 4.5 (95%CI 3.4-6.0) no insulin: 1.4 (1.0-1.9)	Henricsson et al 1999
Any diabetes						
UK THIN, 2000-2007	8	64,983 (T1DM 1,757)	T1DM 34.0; T2DM 62.8	IR: 18.0 (95%CI 16.4-19.8)	-	Martín-Merino et al 2014
US, 2000-2008	4	775	≥40 (mean not reported)	CI either eye: 5.4 1st eye 5.0 2nd eye 11.5	-	Varma et al 2010
Australia,1992-1999	5	121	61.9±9.3	CI: 8.0 (95%CI 2.7–13.3)	-	McCarty et al 2003

Source: Hietala et al 2013, Romero-Aroca et al 2011, Henricsson et al 1999, Klein et al 1998, Martín-Merino et al 2014, Varma et al 2010, McCarty et al 2003

The reported cumulative incidence of DME depended mainly on the length of follow-up of the patients in the different studies; highest estimates are provided by the studies in T1DM populations with very long follow-up times (e.g. 26% in a study with 14-year follow-up).

2.2.2 Prevalence (DME)

Prevalence: A number of population-based studies have provided prevalence figures for DME and CSDME. Selected recent studies are summarized in the Table 2-5, stratified by diabetes subtype.

Table 2-5 Prevalence of DME and CSDME in diabetic populations worldwide

Data source	No. of patients	Baseline mean age, y	Prevalence, % (95% CI)		Reference
			DME	CSDME	
T1DM					
Finland, 1997-2009	1,354	38.7±11.6	-	18	Hietala et al 2013
Sweden, 1990-1993	404	33.2±14.8	17	-	Henricsson et al 1999
T2DM					
Spain, 2008-2012	108,723	66.9±11.0	0.18	-	Rodriguez-Poncelas et al 2015
Germany, Austria, 2000-2013	64,784	68.7	0.8	-	Hammes et al 2015
Denmark, 2000	378	65±12	-	5.3	Hove et al 2004

Data source	No. of patients	Baseline mean age, y	Prevalence, % (95% CI) DME	Prevalence, % (95% CI) CSDME	Reference
Any diabetes					
UK, 2007-2010	48,450	not stated	-	13.9 Centre-involving: 7.4	Keenan et al 2013
UK, 2004-2005	27,178	not stated	7.05 (6.75–7.37) Bilateral: 2.33 (2.15–2.52)	resulting in sight loss: 2.75 (2.56–2.95)	Minassian et al 2012
Norway, 2007-2008	514 (T1DM = 18)	46-87 y, mean age not stated	3.9		Bertelsen et al 2013
US NHANES, 2005-2008	1,038	≥40 y, mean age not stated	3.8 (2.7–4.9) Black: 8.4 White: 2.6 Hispanic: 5.1	-	Varma et al 2014
Singapore, not stated	757	62.5±9.42	5.7 (3.2–9.9)	-	Wong et al 2008

Source: Hietala et al 2013, Henricsson et al 1999, Rodriguez-Poncelas et al 2015, Hove et al 2004, Varma et al 2014, Keenan et al 2013, Bertelsen et al 2013, Minassian et al 2012, Wong et al 2008, Hammes et al 2015

The described prevalence of DME and CSDME in T1DM is higher than in T2DM or mixed studies, probably because the studies include patients with longer disease duration. The prevalence of DME (any level or definition) in studies assessing information directly from fundus photographs in T2DM or any diabetes ranges between 1.6 and 8% in recent studies, with differences possibly due to different underlying populations in terms of disease duration or ethnic makeup. Studies that assess DME in various ethnicities consistently report highest prevalence in Black diabetes patients, followed by patients of Hispanic ethnicity. Prevalence estimates provided by electronic records or database studies are highly variable, reflecting potentially inconsistent/incomplete recording of DME diagnosis.

2.2.3 Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors of the disease (DME)

The key factor in the development of DME is diabetes duration, with as many as 70% of DME patients reporting duration of diabetes of 10 years or more (Varma et al 2014). The average age of patients depends on the diabetes type, with a mean age of T2DM patients with DME of about 60-70 years (e.g. Rodriguez-Poncelas et al 2015, Varma et al 2014), and a mean age of T1DM patients with DME of about 38-50 years (Hietala et al 2013, Romero-Aroca et al 2011).

Studies that assess DME in various ethnicities consistently report a higher prevalence in Black diabetes patients. Non-Hispanic White diabetes patients seem to be at the lowest risk of DME development, compared to Blacks and those of Hispanic ethnicity (Klein et al 2002, Varma et al 2014).

Risk factors: In a study assessing risk factors for clinically significant macular edema (CSME) in subjects with non-proliferative DR, the most relevant risk factors were HbA1c and total cholesterol levels (Jew et al 2012).

A recent literature review published studies that assess risk factors for DME in type 1 and type 2 diabetes came to the conclusion that key risk factors for DME are glycemic control, hypertension, and dyslipidemia. In addition, nephropathy, anemia, sleep apnea, glitazone usage, and pregnancy are also important modifiable risk factors (Diep and Tsui 2013).

In the US studies of patients with diabetes, non-Hispanic White patients seem to be at the lowest risk of DME development, compared to Blacks and those of Hispanic ethnicity (Klein et al 2002, Varma et al 2014).

2.2.4 Main existing treatment options (DME)

Currently, ranibizumab and aflibercept, anti-VEGF therapies, are approved for the treatment of visual impairment due to DME. Other treatments used include laser retinal photocoagulation, the intravitreal (IVT) administration of steroids or the use of IVT steroid-releasing implants.

2.2.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity (DME)

DME is a frequent manifestation of DR, and is a leading cause of legal blindness in diabetics (Ciulla et al 2003). Presence of DME has been associated with a doubling of the visual angle and loss of vision (Girach and Lund-Andersen 2007). A review of the published literature showed that DME was associated with a reduction in the quality of life of the affected patients (Sharma et al 2005). In the UK DR Screening Service for Wales dataset (2004-2005), CSDME resulting in sight loss (blindness and impaired vision) was present in 2.75% (95% CI: 2.56-2.95) of 27,178 diabetes patients; 2.64% (95% CI: 2.45-2.84) CSDME resulting in impaired vision and 0.11% (95% CI: 0.07−0.157) blindness attributable to diabetic macular edema (Minassian et al 2012).

Mortality: Decreased VA is associated with increased five-year mortality and even relatively mild visual impairment increases the risk of death more than two-fold (McCarty et al 2001).

The relationship between DME and long-term survival has been studied in the Wisconsin Epidemiologic Study of DR. In its most recent report on mortality (Hirai et al 2008), all cause, ischemic heart disease, and stroke hazard ratios for death are reported for those with CSME and T1DM or T2DM. Results were adjusted for age, gender, diabetes mellitus duration, basal metabolic index (BMI), HbA1c, history of cardiovascular disease, nephropathy, hypertension, and smoking status. In the fully adjusted models when comparing to those without CSME, mortality appeared to be increased for T2DM patients with CSME, especially among those treated with insulin. In contrast, T1DM patients with CSME did not appear to be at an increased risk of death compared to T1DM without CSME.

Table 2-6 Risk of cause-specific mortality in diabetes patients with CSDME compared to those without CSDME

	HR (95% CI)			
	T1DM	All T2DM	T2DM w/o insulin	T2DM w insulin
All cause	0.67 (0.42-1.06)	1.27 (1.01-1.61)	1.18 (0.76-1.84)	1.29 (0.97-1.71)
Ischemic heart disease	0.66 (0.32-1.34)	1.28 (0.91-1.80)	0.81 (0.37-1.75)	1.58 (1.07-2.35)
Stroke	0.92 (0.19-4.47)	1.21 (0.69-2.13)	0.81 (0.29-2.24)	1.46 (0.72-2.99)

	HR (95% CI)			
	T1DM	All T2DM	T2DM w/o insulin	T2DM w insulin

Source: Hirai et al 2008

2.2.6 Important co-morbidities (DME)

The key comorbidities in the population with DME (or diabetes, when DME-specific estimates were not available) are listed in the following Table 2-7.

Table 2-7 Important comorbidities in DME population

Comorbidity	Prevalence, %	Comments	References
Cataract	In diabetes patients: 18 – 22 overall 40 – 68 in those aged ≥75 y	Increasing glycemic index associated with increased incidence of cortical cataract (Tan et al 2007a)	Orcutt et al 2004, Tan et al 2007a, Esteves et al 2008, Chen et al 2008, Zghal-Mokni et al 2008, Saaddine et al 2008
Glaucoma	In diabetes patients: 6 – 11 overall Higher in Blacks, Hispanics	Diabetes mellitus is a risk factor for both primary open-angle glaucoma and neovascular glaucoma (Jeganathan et al 2008)	Jeganathan et al 2008, Orcutt et al 2004, Zghal-Mokni et al 2008, Saaddine et al 2008
Hypertension	T1DM: 19 – 33 T2DM: 73 – 92 Treated for hypertension: 36 – 49	Prevalence of hypertension is higher in diabetic patients with CSME than those without (Hirai et al 2008)	Hirai et al 2008, Shea et al 2008, Bailey and Sparrow et al 2001, Rubino et al 2007, Lövestam-Adrian et al 2007, Zghal-Mokni et al 2008, Hietala et al 2013, Varma et al 2014
Hyperlipidemia	18 – 58	Recent meta-analysis: blood lipid levels significantly higher in patients with DME compared to those without DME	Higgins et al 2007, Imperatore et al 2004, Zghal-Mokni et al 2008, Das et al 2015
Nephropathy / proteinuria	21 – 49	Nephropathy and proteinuria appear to be associated with diffuse DME and increased retinal thickness	Romero Aroca et al 2004, Knudsen et al 2002, Hirai et al 2008, Zghal-Mokni et al 2008, Hietala et al 2013, Hammes et al 2015
Myocardial infarction	7.5 – 18	T2DM is a risk factor for myocardial infarction and CV death	Huxley et al 2006, Bailey and Sparrow et al 2001, Petrella et al 2012a
Stroke	6 – 7	Diabetic retinopathy associated with increased risk of stroke	Cheung et al 2007, Klein et al 2004, Fuller et al 2001, Bailey and Sparrow et al 2001, Petrella et al 2012a

Source: Orcutt et al 2004, Tan et al 2007a, Esteves et al 2008, Chen et al 2008, Zghal-Mokni et al 2008, Saaddine et al 2008, Jeganathan et al 2008, Hirai et al 2008, Shea et al 2008, Bailey and Sparrow et al 2001, Rubino et al 2007, Lövestam-Adrian et al 2007, Varma et al 2014, Higgins et al 2007, Imperatore et al 2004, Romero Aroca et al 2004, Knudsen et al 2002, Hietala et al 2013, Huxley et al 2006, Cheung et al 2007, Klein et al 2004, Fuller et al 2001, Hammes et al 2015, Das et al 2015, Petrella et al 2012a

2.3 Retinal vein occlusion

2.3.1 Incidence (RVO)

Incidence: A number of population-based studies have provided incidence figures for RVO, including branch RVO (BRVO) and central RVO (CRVO). Studies reporting cumulative

incidence over time are summarized in the Table 2-8. In addition, one study using a nationwide health insurance database in Korea (2008-2011; N=47,990,761) found that the overall incidence rate of RVO was 4.83 per 10,000 person-years (95% CI: 4.80-4.86); in males, the incidence was 4.24 (4.19-4.28) and in females, 5.41 (5.36-5.46) per 10,000 PY (Park et al 2014).

Table 2-8 Reported incidence of RVO, BRVO and CRVO worldwide

Country	Follow-up	No. of patients	Baseline age characteristics	Cumulative incidence, %			Reference
				RVO	BRVO	CRVO	
Sweden	6 years	708,587	Mean 72.6 y	-	-	0.02	Epstein et al 2015
US	8 years	492,488	Mean 69.2±8.5 y	-	0.5	-	Newman-Casey et al 2014
US	9 years	494,165	Mean age: Non CRVO: 65.7±8.1 y CRVO: 69.9±8.4 y	-	-	0.26	Stem et al 2013
US	10 years	1,636	Mean 65.1 y	2.1	-	-	Barnett et al 2010
US	15 years	4,068	Not provided	-	1.8	0.5	Klein et al 2008
China	10 years	2,695	Mean 54.6 y	1.9	1.6	0.3	Zhou et al 2013
Japan	9 years	1,775	Mean 63 y	3	2.7	0.3	Arakawa et al 2011

Source: Epstein et al 2015, Newman-Casey et al 2014, Stem et al 2013, Barnett et al 2010, Klein et al 2008, Zhou et al 2013, Arakawa et al 2011.

The cumulative incidence of RVO ranged between 0.8% and 3.0% in different populations, depending on the years of follow-up and the average age of the studied population. The incidence of BRVO appeared to be consistently higher than of CRVO.

2.3.2 Prevalence (RVO)

Prevalence: A number of recently published population-based studies have provided prevalence figures for RVO, CRVO and BRVO. A list of these studies is summarized in Table 2-9.

Table 2-9 Reported prevalence of RVO, BRVO and CRVO worldwide

Reference	Country, study period	No. patients	Cohort age characteristics	Prevalence, % (95% CI)		
				RVO	BRVO	CRVO
Rogers et al 2010	Multinational, 1950-2008	68,751	Not provided	0.44 (0.37-0.51)	0.38 (0.31-0.45)	0.06 (0.05-0.08)
Ponto et al 2015	Germany, not reported	12,954	Mean 55.0 y	Weighted 0.40	Weighted 0.32	Weighted 0.08
Cugati et al 2007a	US, 1988-1990, 1992-1994	8,384	Mean 61.8 y	1.14	-	-
Wong et al 2005	US, 1987-1995	15,466	Mean 63 y	0.3	0.25	0.05
Jonas et al 2013	India, not reported	4,711	Mean 48.8±13.0y	0.76 (0.50-1.01)	0.66 (0.42–0.90)	0.11 (0.01-0.21)
Yasuda et al 2010	Japan, 1988	1,775	Mean 67 y (RVO patients)	2.1	1.9	0.2

Reference	Country, study period	No. patients	Cohort age characteristics	Prevalence, % (95% CI)		
				RVO	BRVO	CRVO
Lim et al 2008	Singapore, 2004	3,280	Range 40-80 y	0.7	0.6	0.2
Mitchell et al 1996	Australia, 1992-1994	3,654	Lower limit ≥ 49 y	1.6	1.1	0.4

Source: Rogers et al 2010, Ponto et al 2015, Cugati et al 2007a, Wong et al 2005, Jonas et al 2013, Yasuda et al 2010, Lim et al 2008, Mitchell et al 1996.

To summarize, the overall prevalence of RVO in various populations usually is reported between 0.3% and 2%, with a BRVO to CRVO ratio between 3:1 and 8:1; a recent review article estimated that BRVO is 4 to 6 times more prevalent than CRVO (Kolar 2014).

Rogers et al (2010) conducted a pooled analysis that included the original data from published studies reporting RVO prevalence and unpublished data. In total 15 studies were included, with 68,751 subjects and 555 RVO cases. In this pooled analysis, the prevalence of RVO was estimated at 0.44%, with the prevalence of CRVO lower at 0.06%. In the individual studies, the prevalence of RVO was between 0.3% and 1.6%, and that of BRVO and CRVO were between 0.25%-1.1% and 0.05%-0.4%, respectively. A total of 5% to 11% of patients had bilateral involvement.

2.3.3 Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors of the disease (RVO)

The mean age of RVO patients ranged from 49 to 67 years in epidemiological studies assessing its prevalence (Wong et al 2005, Cugati et al 2007a, Yasuda et al 2010, Jonas et al 2013).

In the BDES, 42% of the subjects affected by RVO were males, and in the BMES, 38% of the affected subjects were men (Cugati et al 2007a).

The ethnicity of patients with RVO was assessed in a pooled analysis that showed the following prevalence of RVO according to race (Rogers et al 2010):

- Whites: 0.37% (0.28%-0.46%)
- Blacks: 0.39% (0.18%-0.60%)
- Asians: 0.57% (0.45%-0.68%)
- Hispanics: 0.69% (0.57%-0.83%)

Risk factors: A meta-analysis of published clinical data on the risk of RVO arrived at the following key conclusions (Kolar 2014):

- Basic risk factor for RVO is advancing age.
- Further risk factors include systemic conditions like hypertension, arteriosclerosis, diabetes mellitus, hyperlipidemia, vascular cerebral stroke, blood hyperviscosity, and thrombophilia.
- A strong risk factor for RVO is the metabolic syndrome (hypertension, diabetes mellitus, and hyperlipidemia). Individuals with end-organ damage caused by diabetes mellitus and hypertension have greatly increased risk for RVO.
- Socioeconomic status seems to be a risk factor too

- American Blacks are more often diagnosed with RVO than non-Hispanic Whites.
- Females are, according to some studies, at lower risk than men.
- The role of thrombophilic risk factors in RVO is still controversial.
- Congenital thrombophilic diseases like factor V Leiden mutation, hyperhomocysteinemia and anticardiolipin antibodies increase the risk of RVO.
- Cigarette smoking also increases the risk of RVO as do systemic inflammatory conditions like vasculitis and Behcet disease.
- Ophthalmic risk factors for RVO are ocular hypertension and glaucoma, higher ocular perfusion pressure, and changes in the retinal arteries.

2.3.4 Main existing treatment options (RVO)

Current treatments available for the management of retinal vein occlusion include: laser photocoagulation, intravitreal steroids such as triamcinolone acetonide, intravitreal steroid releasing implants such as fluocinolone (Iluvien®) and dexamethasone (Ozurdex®) (Kiire and Chong 2012). Ranibizumab and aflibercept, anti-VEGF therapies, are approved for the treatment of visual impairment due to macular edema associated with a retinal vein occlusion.

2.3.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity (RVO)

RVO is a frequent cause of eye disease in the middle aged and elderly. It may lead to severe vision loss from macular edema, macular ischemia, and vitreous hemorrhage. One paper evaluating the vision-related quality of life in patients with CRVO showed that this condition was associated with a decreased quality of life related to the degree of visual loss in the better-seeing eye and the overall systemic health of the patient (Deramo et al 2003). One recent study showed that BRVO is associated with a decreased vision-related quality of life that correlated with the involved eye VA, even when the uninvolved eye maintained good VA (Awdeh et al 2010).

Mortality: Several studies have assessed the mortality of patients with RVO; please refer to Table 2-10 and Table 2-11.

Table 2-10 All-cause, cardiovascular mortality in patients with RVO

Reference	Country, study period	Cohort characteristics	Follow-up, y	Mortality, %	
				All-cause	Cardiovascular
Siantar et al 2015	Singapore, 2004-2006	N=3,280 aged 40-80 **RVO** cases N=23	7.24	30.4	26.9
Bertelsen et al 2014	Denmark, 1976-2010	**CRVO** N=439; 73.9% > 60 y	5.1	5.9	-
Kuo et al 2010	China, 2000-2007	**CRVO** N=22, mean age 28.5 (people aged <40 y at diagnosis)	3	9.1	-
Christoffersen et al 2007	Denmark, 1973-1998	**BRVO** N=329, mean age 65.6	13	43.8 SMR=0.99 (0.84-1.16)	-

Reference	Country, study period	Cohort characteristics	Follow-up, y	Mortality, %	
				All-cause	Cardiovascular
Cugati et al 2007a	Australia, 1988-1990 US, 1992-1994 Follow-up until 2003	N=8,384; aged 43-97 y **RVO** cases n=97 Mean age in RVO 71 y	10 to 12	-	Age-adjusted: Cardiovascular: 26 Stroke: 5.3

Source: Siantar et al 2015, Bertelsen et al 2014, Kuo et al 2010, Christoffersen et al 2007, Cugati et al 2007a

A number of studies evaluated the potential association between RVO and all-cause and vascular mortality, summarized in Table 2-11. Results vary across studies, with some studies finding a statistically significant increase in mortality in patients with RVO, and others either failing to find association or finding that it attenuates after adjustment for concomitant cardiovascular disease and other risk factors.

Table 2-11 Association between RVO and all-cause and vascular mortality

Reference	Country, study period	Cohort characteristics	Risk estimate (95% CI)		Adjustment factors
			All-cause	Vascular	
Siantar et al 2015	Singapore, 2004-2006	**RVO** vs non-RVO N=3,280 aged 40-80 **RVO** cases N=23	Model 1: HR=2.33 (1.10-4.92) Model 2: HR=2.02 (0.91-4.63)	Model 1: HR=4.72 (2.08-10.7) Model 2: HR=3.14 (1.26-7.73)	Model 1: age and gender Model 2: age, gender, socio-economic status, hypertension, smoking, BMI, cardiovascular disease
Bertelsen et al 2014	Denmark, 1976-2010	**CRVO** vs general population Cases (n=439): mean follow-up 5.1 y Controls (n=2195): mean follow-up 5.7 y	Model 1: HR=1.45 (1.19-1.76) Model 2: HR=1.19 (0.96-1.46)	-	Model 1: age, gender, and time of diagnosis Model 2: Model 1 + comorbidity (myocardial infarction, IHD, CHF, cerebro-vascular disease, peripheral vascular disease, hypertension, diabetes)
Cugati et al 2007a	Australia, 1988-1990 US, 1992-1994 Follow-up until 2003	**RVO** vs non-RVO N=8,384; aged 43-97 Follow-up 10 to 12 y		Cerebrovascular HR=0.9 Cardiovascular: All ages: HR=1.2 Aged <70: HR=2.5 (1.2-5.2)	age, gender, body mass index (BMI), hypertension, diabetes, smoking, glaucoma, and study site
Klein et al 2000	US,1988-1995	**BRVO** vs non-RVO N=4,926, aged >43 Mean follow-up 5 y	-	IHD mortality: HR=1.18 (0.38-3.68)	Age, gender

Source: Siantar et al 2015, Bertelsen et al 2014, Cugati et al 2007a, Klein et al 2000

2.3.6 Important co-morbidities (RVO)

The key comorbidities in the RVO population are listed in the following Table 2-12.

Table 2-12 Important comorbidities in RVO population

Comorbidity	Prevalence, %	Comments	References
Cataract	3 – 18	No associations between cataract and RVO found in the literature	Scott et al 2009, Oh et al 2007, Ageno et al 2010, Klein et al 2000
Glaucoma	3 – 39 Neovascular glaucoma: 8% all CRVO, up to 82% of ischemic CRVO (MacDonald 2014)	Positive associations between glaucoma and incident or prevalent RVO reported in literature, with ORs ranging from 1.6 to >6	Hayreh et al 2004, Malayan et al 1999, McAllister et al 2010, Ageno et al 2010, MacDonald 2014, Klein et al 2000, Koizumi et al 2007, Shahsuvaryan and Melkonyan 2003, Ponto et al 2015, Kolar 2014
Hypertension	45 – 90	Hypertension is a recognized risk factor for RVO. Meta-analysis pooled estimates for any RVO: OR=3.5 (95%CI 2.5-5.1)	Farahvash et al 2008, Ho et al 2009, Scott et al 2009, McAllister et al 2010, Petrella et al 2012b, Stem et al 2013, O'Mahoney et al 2008, Kolar 2014
Hyperlipidemia	10 – 84	Hypertension is a recognized risk factor for RVO. Meta-analysis pooled estimates for any RVO: OR=2.5 (95%CI 1.7-3.7)	Tsaloumas et al 2000, Farahvash et al 2008, Ho et al 2009, Petrella et al 2012b, Stem et al 2013, O'Mahoney et al 2008, Kolar 2014
Diabetes	8 – 43	Positive associations between diabetes and RVO reported in literature; Meta-analysis pooled estimates for any RVO: OR=1.5 (95%CI 1.1-2.0)	Farahvash et al 2008, Ho et al 2009, Scott et al 2009, McAllister et al 2010, Stem et al 2013, O'Mahoney et al 2008, Kolar 2014
Myocardial infarction (MI)	10 – 18	Positive associations between atherosclerotic associated diseases and RVO reported in literature RVO is associated with increased risk of future MI; meta-analysis pooled estimates for any RVO: RR=1.3 (95%CI 1.2-1.4)	Farahvash et al 2008, Scott et al 2009, Petrella et al 2012b, Stem et al 2013, Kolar 2014, Zhong et al 2016
Stroke	3 – 6	RVO is associated with increased risk of future stroke; meta-analysis pooled estimates for any RVO: RR=1.5 (95%CI 1.2-1.9)	Tsaloumas et al 2000, Cugati et al 2007a, Petrella et al 2012b, Li et al 2016
Coagulopathies	Factor V Leiden deficiency: 2 – 8 Genetic thrombophilia and other deficiencies: 9 – 27	Role of thrombophilic risk factors in RVO remains controversial, but congenital thrombophilic diseases like factor V Leiden mutation etc. appear to increase the risk of RVO	Demirci et al 1999, Kalayci et al 1999, Johnson et al 2001, Greiner et al 1999, Larsson et al 1999, Kuhli et al 2002, Kuhli et al 2004, Kolar 2014

Source: Scott et al 2009, Oh et al 2007, Ageno et al 2010, Klein et al 2000, Hayreh et al 2004, Malayan et al 1999, McAllister et al 2010, MacDonald 2014, Koizumi et al 2007, Shahsuvaryan and Melkonyan 2003, Ponto et al 2015, Kolar 2014, Farahvash et al 2008, Ho et al 2009, O'Mahoney et al 2008, Klein et al 2000, Tsaloumas et al 2000, Stem et al 2013, Cugati et al 2007a, Petrella et al 2012b, Zhong et al 2016, Li et al 2016, Demirci et al 1999, Kalayci et al 1999, Johnson et al 2001, Greiner et al 1999, Larsson et al 1999, Kuhli et al 2002, Kuhli et al 2004.

2.4 Choroidal neovascularization (CNV)

2.4.1 Incidence and Prevalence (CNV)

The distribution of the underlying causes for the CNV (including nAMD) in different populations is displayed in Table 2-13.

Table 2-13 Distribution of CNV causes in different populations

Country, time period	France, 1990-1992	US 1986-2004	US prior to 1992	India 1978-2008
N	363	96	25	27
Age range, years	<50 years	24-96	8-20	7-17
Mean age, years	38	Not reported	15	13
Women, %	58	Not reported	72	37
Patients with bilateral CNV, %	14	20	8	33
Underlying conditions, % patients				
nAMD	-	47	-	-
Pathological myopia	62	-	4	7
Idiopathic	17	39	12	11
Angioid streaks	5	2	-	-
(Presumed) ocular histoplasmosis	12	1	16	4
Ocular toxoplasmosis	1	-	4	7
Ocular toxocariasis	-	-	8	-
Viral retinitis	-	-	8	4
Vogt-Koyanagi-Harada disease	-	-	-	4
Multifocal choroiditis	-	4	-	-
Serpiginous choroiditis	-	-	4	7
Unclassified choroiditis	-	-	-	18.5
Best disease	<1	-	4	18.5
Stargardt's disease	-	-	-	7
Pattern dystrophy	-	2	-	-
Optic nerve head drusen	-	1	16	7
Choroidal osteoma	-	2	4	-
Traumatic rupture	2	-	16	4
Other*	<1	2	4	-
Reference	(Cohen et al 1996)	(Browning and Fraser 2005)	(Goshorn et al 1995)	(Rishi et al 2013)

Source: Cohen et al 1996, Browning and Fraser 2005, Goshorn et al 1995, Rishi et al 2013

Notes: all studies were based on retrospective review of patient charts in single tertiary care centers.

Proportions of underlying conditions are reported as % of the total patient number. If the original papers did not report these proportions, they were calculated based on the information provided. Sums may not add up to 100 due to rounding.

* reported conditions in this category include peripapillary pseudopodal pigment epithelial and choroidal atrophy, dominant drusen, radiotherapy retinopathy, congenital disc anomaly and indeterminate choroidal scar

Epidemiology of CNV due to causes other than nAMD is challenging to describe, as in many conditions CNV has only been reported in individual case reports, with no data on the frequency of their occurrence. Some conditions, which may be complicated by CNV, are by themselves

very rare, so the incidence and prevalence estimates are not always available. Finally, the frequency and characteristics of the underlying conditions often vary across ethnicities and geographical areas. Therefore, the following section provides the incidence and prevalence of specific underlying conditions, and a proportion of patients that have been reported to eventually progress to CNV. No attempt is made to provide an exhaustive list of all conditions that have been associated with CNV; instead, the focus is on the main subtypes described in the literature:

- CNV secondary to pathological myopia (PM)
- Idiopathic CNV
- CNV secondary to angioid streaks
- CNV secondary to intraocular inflammation
  - Intraocular infections
  - Inflammatory chorioretinopathies in the "white dot syndrome" spectrum
  - Inflammation due to other causes
- CNV secondary to central serous chorioretinopathy (CSC)
- CNV secondary to other causes
  - Choroidal nevi, other ocular tumors
  - Choroidal trauma
  - Inherited retinal dystrophies

CNV secondary to pathologic myopia (PM)

Incidence: A study using nationwide health insurance records in Taiwan found that incidence of new CNV secondary to PM was 11.9 per 100,000 (95%CI 11.4-12.4) in 2010 and 12.5 per 100,000 (95% CI 12.0-13.0) in 2011 (Yang et al 2017).

Prevalence: The prevalence of myopic CNV among adults in the United States was estimated at 0.017% (Willis et al 2016). A study in Taiwan (2009-2011) provided the same prevalence estimate of 0.017% (Yang et al 2017).

The prevalence of myopic retinopathy, a clinical manifestation of pathological myopia, in the Blue Mountains Eye Study (population-based survey of common eye diseases in an urban population aged 49 years or older, residing in the Blue Mountains region, Australia) was 1.2% (1% in men and 1.4% in women) (Vongphanit et al 2002). The Hisayama Cohort Study in Japan recruited 1,892 participants aged ≥40 years that had an ophthalmic examination in 2005; the prevalence of pathological myopia was found to be 1.7% (Asakuma et al 2012). In the United States, a population-based study showed that the prevalence of progressive high myopia, a surrogate clinical diagnosis of pathological myopia, among adults, was estimated at 0.33% (Willis et al 2016).

Idiopathic CNV

A proportion of CNV cases either cannot be attributed to a known etiology or the associated etiology has not yet been identified. This proportion in most studies was between 11 and 17% (Cohen et al 1996, Goshorn et al 1995, Rishi et al 2013). In one US study (Browning and Fraser 2005) 39% of peripapillary subretinal neovascular membranes were reported as idiopathic.

There are no reports of the incidence and prevalence of idiopathic CNV. The initial diagnosis may be reclassified upon application of further diagnostic tools or as the underlying disease manifests with time. For instance, one study reported that 7% (4/58) of patients initially diagnosed with idiopathic CNV eventually were discovered to have various inflammatory chorioretinal diseases of the white dot syndrome spectrum (Machida et al 2008); in another study, 43% of all patients with punctate inner choroidopathy referred to a tertiary ophthalmic center had "idiopathic CNV" as the initial diagnosis (Zhang et al 2011).

CNV secondary to angioid streaks

Angioid streaks are most often associated with pseudoxanthoma elasticum (PXE). Most studies of CNV secondary to angioid streaks report prevalence of PXE of 40%-80%; remaining cases usually cannot be attributed to a known cause (Browning et al 2005, Mimoun et al 2010, Nakagawa et al 2013). Other underlying systemic diseases associated with angioid streaks such as sickle cell disease are reported rarely, mainly in areas of increased risk (Ladas et al 2010, Shaikh et al 2003).

Pseudoxanthoma elasticum (PXE): Virtually all patients with PXE will develop angioid streaks at some point in their lifetime (Georgalas et al 2011). Incidence estimates were not found. PXE prevalence may lie in the range between 1 and 4 per 100,000 population (Chassaing et al 2005).

Paget's disease of bone and juvenile Paget disease: Paget's disease of bone: a survey of 8 towns in Austria, Sweden, Denmark, Spain, Greece and Hungary (2000-2001) reported an age- and gender-adjusted prevalence of 0.3%, or 300 per 100,000 population (Poor et al 2006). In Minnesota Olmsted county (US, 1950-1994) age-adjusted incidence was 12.7 per 100,000 patient-years in men and 7.0 in women (Tiegs et al 2000). Angioid streaks are a rare complication of Paget disease of bone, the estimated frequency is about 1% (Dabbs and Skjodt 1990). Juvenile Paget disease is extremely rare: only about 50 cases were reported worldwide in 1956-2007. However, angioid streaks seem to be common in this population: angioid streaks were found in 5/7 (71%) juvenile Paget disease patients aged 13-31, the oldest of whom has also developed CNV (Kerr et al 2010).

Sickle cell disease, other hemoglobinopathies: Incidence and prevalence vary depending on ethnicity. In England (1990-1994) the annual incidence rates of sickle cell disease and β-thalassemia were 22-28 and 2-4 per 100,000, respectively (Hickman et al 1999). Newborn screening in California, US (1990-1995) identified sickle cell disease/sickle thalassemia in 13 per 100,000 live births; 143 in Blacks, 2.2 in Hispanics and 0.6 in non-Hispanic Whites. The prevalence of S/β+ sickle thalassemia was 2 per 100,000 overall and 25 in Blacks. The prevalence of β-thalassemia major was 0.9 per 100,000 live births; 10 in Southeast Asians and 25 in Asian Indians (Lorey et al 1996). The prevalence in adults is markedly lower than in newborns due to high mortality rate (Elagouz et al 2010).

Angioid streaks are usually observed in homozygous sickle cell disease and beta-thalassemia: ~2% adolescents and over 20% of patients older than 40-50 years (Elagouz et al 2010). A study in Greece reported angioid streaks in 6/58 (10%) adult sickle thalassemia patients (Aessopos et al 1994).

Risk of CNV development in angioid streaks: The proportion of patients with angioid streaks that will eventually develop CNV is 72-86% in different studies. Neovascularization commonly involves both eyes, but does not occur simultaneously (Georgalas et al 2009). In France, evaluation of 40 newly diagnosed PXE patients revealed active subfoveal neovascularization and/or a choroidal scar in 28 eyes (35%) (Orssaud et al 2015). In Germany, screening of PXE patients revealed CNV in 64 of 92 eyes (70%) (Finger et al 2009). In a prospective study in Italy, CNV was found in 80/112 eyes with angioid streaks (71%) (Pece et al 1997). A study in Kyoto, Japan (2004-2010) found CNV at the first presentation in 55/88 eyes (62.5%); of the remaining eyes, 9 developed CNV during a 3-year follow-up, bringing total proportion to 73% (Nakagawa et al 2013). It is not clear whether the risk of CNV is the same in angioid streaks with different underlying etiologies; a study in Italy found CNV in only 15% of eyes with angioid streaks in beta-thalassemia, but this population was relatively young (Barteselli et al 2014).

CNV secondary to intraocular inflammation

In the studies conducted in Europe and North America, the incidence of uveitis at any anatomical location was between 25 and 52 per 100,000 persons per year, and the prevalence was between 70 and 145 per 100,000 persons (Llorenc et al 2015, Paivonsalo-Hietanen et al 1997, Acharya et al 2013, Suhler et al 2008, Gritz and Wong 2004). Two studies in Asia reported higher estimates: in Taiwan, the incidence of uveitis was 111 per 100,000 persons/year and the prevalence increased from 319 per 100,000 in 2003 to 623 in 2008 (Hwang et al 2012). In a study in India, the prevalence of active uveitis was 370 per 100,000 (Dandona et al 2000).

CNV is mainly associated with posterior uveitis or panuveitis, where its prevalence can be about 2.0% at presentation (Baxter et al 2013). The proportion of posterior uveitis/panuveitis in the studies above usually ranged between 10%-35%. In Europe, the maximum proportion of 39% was reported in Spain (Llorenc et al 2015); in one study in Japan, panuveitis alone accounted for over 49% of all uveitis cases (Keino et al 2009).

Ocular inflammation is a rare cause of CNV and there are a number of different ocular conditions which are thought be driven or associated primarily by inflammation as shown in Table 2-14.

Table 2-14 Distribution of causes of CNV secondary to intraocular inflammation in different populations

Country, time period	Multiple, prior to 2009	Switzerland 1995-2002	US, prior to 2008	US 1978-2007	China 2002-2013
Inclusion criteria	Inflammatory CNV treated with IVT bevacizumab	Subretinal neovascular membranes in uveitis	Inflammatory CNV treated with IVT bevacizumab	Patients with posterior uveitis/ panuveitis	Any inflammatory CNV
N patients	96	12	19	2307	125

Country, time period	Multiple, prior to 2009	Switzerland 1995-2002	US, prior to 2008	US 1978-2007	China 2002-2013
N affected eyes	99	Not reported	21	81	150
Age range, years	Not reported	14-78	7-83	Not reported	17-79
Mean age, years	39	Not reported	Median 52	38	36
Women, %	66	83	53	64	64
Underlying conditions, %	**% affected eyes**	**% total patients**	**% total patients**	**% affected eyes**	**% total patients**
(Presumed) ocular histoplasmosis	13	-	5	*see "other"*	-
Ocular toxoplasmosis	5	8	5	*see "other"*	-
Ocular toxocariasis	-	-	5	*see "other"*	-
Tuberculosis	2	17	-	*see "other"*	-
Cytomegalovirus retinitis	-	-	5	*see "other"*	-
Syphilitic chorioretinitis	-	-	-	-	1
Sarcoidosis	2	42	5	*see "other"*	-
Reactive arthritis	-	-	5	-	-
Vogt-Koyanagi-Harada disease	6	-	5	1	8
Behcet disease	-	-	-	-	2
Eales disease	4	-	-	*see "other"*	-
Multifocal choroiditis	19	17	11	35	22
Punctate inner choroidopathy	23	-	11	2	50
Birdshot retinochoroiditis	1	8	-	5	-
Serpiginous choroiditis	9	-	11	9	1
Multiple evanescent white dot syndrome	-	-	-	4	2
Acute placoid pigment epitheliopathy	1	-	-	*see "other"*	1
Sympathetic ophthalmia	2	8	5	*see "other"*	-
Inflammatory papillitis	-	-	5	-	-
Unclassified/idiopathic	12	-	21	14	13
Other*	N/A	N/A	N/A	23	N/A
Reference	(Mansour et al 2009)	(Perentes et al 2005)	(Lott et al 2009)	(Baxter et al 2013)	(Wu et al 2015)

Source: Mansour et al 2009, Perentes et al 2005, Lott et al 2009, Baxter et al 2013, Wu et al 2015.

Notes: if the original papers did not report % of underlying conditions, they were calculated based on the information provided. Sums may not add up to 100 due to rounding.

* Includes the following conditions not reported individually: sympathetic ophthalmia, acute posterior multifocal placoid pigment epitheliopathy, neuroretinitis, diffuse retinochoroiditis, focal retinochoroiditis, acute retinal necrosis syndrome, Eales disease, unspecified inflammatory chorioretinal scars, sarcoidosis, and necrotizing retinitis.

Theoretically, CNV can present as complicating factor in inflammation/uveitis associated with any etiology (Neri et al 2009). A retrospective chart review in the US (1978-2007) found that 11/1159 (1%) eyes with undifferentiated panuveitis had active CNV or sequelae of past CNV at presentation (Baxter et al 2013). However, certain inflammatory conditions are associated with a significantly higher risk of CNV; these are described below in more detail.

White dot syndromes

"White dot syndrome" is a term assigned to a group of inflammatory chorioretinopathies of unknown etiology, characterized by a unique appearance of yellow-white lesions affecting multiple layers of the retina, retinal pigment epithelium, choriocapillaris, and the choroid (Crawford and Igboeli 2013). These include the following conditions:

- Acute retinal pigment epitheliitis (ARPE)
- Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)
- Multiple evanescent white dot syndrome (MEWDS)
- Birdshot retinochoroidopathy
- Multifocal choroiditis and panuveitis syndrome (MCP)
- Punctate inner choroidopathy (PIC)
- Serpiginous choroidopathy (SC)
- Acute zonal occult outer retinopathy (AZOOR)

One study using linked medical records in Olmsted county, Minnesota, US (1988-2008) reported the overall incidence of white dot syndrome of 0.45 per 100,000 per year (Abu-Yaghi et al 2011); however, not all associated conditions were found in that population. Individual conditions in the white dot syndrome spectrum are therefore very rare. CNV-related complications have not been described or described very rarely in ARPE, APMPPE and AZOOR (Crawford and Igboeli 2013); the reported incidence and prevalence of the conditions associated with a high risk of developing CNV are listed in the Table 2-15.

Table 2-15 Reported incidence and prevalence of white dot syndromes and progression to CNV

White dot syndrome	Incidence rate, per 100,000 persons per year		Prevalence, per 100,000 persons		Proportion developing CNV		
	Estimate	Source (Open reference)	Estimate	Source (Open reference)	%	n/N	Source (Open reference)
MEWDS	0.22	US (1)	0.3	Spain (2)	14	3/21 eyes	US (5)
					0	0/34	US (6)
Birdshot	Not found	Not applicable	5	Spain (2)	2.5	2/80	France (7)
			0.14	US (3)	2.5	1/40	US (8)
					1.0	4/397 eyes	US (5)
MCP	0.03	US (1)	0.6	Spain (2)	15	3/20	UK (9)
					5	28/615 eyes	US (5)
					22	27/122 eyes	US (10)
					64	23/36	US (11)
					16	6/37 eyes	Canada (12)
					22	8/37 eyes	China (13)
PIC	0.04	US (1)	2	Spain (2)	75	85/113	UK (14)
					64	14/22 eyes	US (10)
					56	10/18 eyes	China (13)
					76	57/75	China (15)
SC	Not found	Not applicable	0.7	Spain (2)	20	9/45 eyes	Spain (16)
			0.07		29	10/34 eyes	

White dot syndrome	Incidence rate, per 100,000 persons per year	Prevalence, per 100,000 persons		Proportion developing CNV		
			Australia, New Zealand (4)	26	7/27	US (17) Australia, NZ (4)

Sources: (1) Abu-Yaghi et al 2011, (2) Llorenc et al 2015, (3) Levinson 2007, (4) Toniolo et al 2014, (5) Baxter et al 2013, (6) Marsiglia et al 2015, (7) Monnet et al 2007, (8) Thorne et al 2005, (9) MacLaren and Lightman 2006, (10) Kedhar et al 2007, (11) Haen and Spaide 2008, (12) Vianna et al 2004, (13) Shen et al 2011, (14) Essex et al 2010, (15) Zhang et al 2011, (16) Carreno et al 2012, (17) Christmas et al 2002

Other causes of uveitis

Vogt-Koyanagi-Harada (VKH) disease: VKH is relatively common in Asian, Native American, Hispanic and Middle Eastern populations, and uncommon in White populations and Black people of sub-Saharan African descent (Fang and Yang 2008). A nationwide survey in Japan estimated that the annual prevalence of VKH in 1985-1987 was 1.55 per 100,000 and the incidence 0.65 per 100,000 (Murakami et al 1994). In Barcelona, Spain (2009-2012) VKH accounted for 19/1022 uveitis cases in a tertiary center; the approximate prevalence could be calculated as 2.7 per 100,000. About half of VKH patients originated from South America (Llorenc et al 2015). Incidence and prevalence in countries with predominantly non-Hispanic White population may be significantly lower.

A study conducted across 10 uveitis centers in the US, Mediterranean region, Japan and Southeast Asia found subretinal neovascularization in 4/177 VKH patients (2%) at the time of diagnosis (Rao et al 2010). A study in Singapore (1994-2001) found CNV in 0/40 eyes with acute resolved VKH; 1/40 eyes (2.5%) with chronic and 6/66 eyes (9%) with chronic recurrent course (Chee et al 2007). Two US studies followed patients over time. In Maryland (1978-1996) CNV developed in 11/75 patients (14.7%) (Lertsumitkul et al 1999), and in California (1983-1997) in 15/101 patients (15%), or 22/202 eyes (11%) (Read et al 2001).

Infectious uveitis: the main contributors to CNV in uveitis of infectious etiology are presumed ocular histoplasmosis syndrome (POHS) and intraocular infection with Toxoplasma gondii. CNV has also been rarely reported in uveitis caused by tuberculosis, Toxocara canis infections and in some other viral and fungal infections (Neri et al 2009).

Clinical histoplasmosis is common in the US, where the overall incidence rate in 1999-2008 was 3.4 (95% CI: 3.0-4.1) per 100,000 person-years in those aged ≥65; in Indiana and Arkansas the rate was 13.0 and 12.0 per 100,000, respectively (Baddley 2011). A review of 7791 literature histoplasmosis cases found ocular manifestations in 1.6%; macular degeneration and CNV in 17 cases (0.9%) (Gta et al 2010).

The incidence rate of ocular toxoplasmosis in England (1994-1995) was 0.8 (95% CI: 0.6-1.0) per 100,000 population per year: 0.4 (95% CI: 0.3-0.6) per 100,000 for those born in Britain, yet 29.3 (95% CI: 18.8-43.6) for those born in West Africa (Gilbert et al 1999). In the US, the annual number of symptomatic ocular toxoplasmosis cases was estimated at 4,839 (range: 2,150–7,527), or 1.6 per 100,000 (Jones and Holland 2010). CNV development is relatively uncommon: a US study (1977-2000) found subretinal neovascularization in 3/53 eyes with inactive lesions (5.7%), but none in 107 eyes with active lesions (London et al 2011).

Other systemic causes of uveitis: systemic diseases such as sarcoidosis and Behçet disease are common causes of posterior/ panuveitis, but CNV in these conditions has been reported at the

frequency of less than 1% or in individual case reports only, e.g. (Bodaghi et al 2012, Kacmaz et al 2008). Incidence and prevalence vary across different countries and ethnicities, as shown in the Table 2-16.

Table 2-16 Incidence and prevalence of other common causes of uveitis rarely associated with CNV

	Incidence rate, per 100,000 persons per year		Prevalence, per 100,000 persons		% ocular involvement
	Estimate	Source	Estimate	Source	
Sarcoidosis	11.4	Finland, 1984 (1)	28.2	Finland, 1984 (1)	25-60%
	1	Japan, 1984, 2004 (1,2)	3.7	Japan, 1984 (1)	Of those, 30-70% uveitis (4,5)
	White: 10.9 Black: 35.5	US, 1990-1994 (3)			
Behçet disease	0.66	Spain, 1997-1998 (6)	15.9	Southern Italy, 2010 (9)	50-85% with posterior uveitis (7,8,9,12)
	0.2	Sweden, 1997-2010 (7)	3.8	Northern Italy, 2005 (10)	
	0.38	US, 2000 (8)	4.9	Sweden, 2011 (7)	
			5.2	US, 2000 (8)	
			170	Turkey (11)	

Sources: (1) Pietinalho et al 1995, (2) Morimoto et al 2008, (3) Rybicki et al 1997, (4) Rothova 2000, (5) Bodaghi et al 2012, (6) Gonzalez-Gay et al 2000, (7) Mohammad et al 2013, (8) Calamia et al 2009, (9) Olivieri et al 2013, (10) Salvarani et al 2007, (11) Colgecen et al 2015, (12) Kacmaz et al 2008

CNV secondary to central serous chorioretinopathy (CSC)

Incidence (underlying condition): A study using linked medical records in Olmsted county, Minnesota, US (1980-2002) reported mean age-adjusted annual incidence of CSC of 9.9 (95% CI: 7.4-12.4) per 100,000 in men and 1.7 (95% CI: 0.74-2.7) in women (Kitzmann et al 2008). A study in the Taiwan National Health Insurance database (2001-2006) reported a mean annual incidence of 27 per 100,000 in men and 15 per 100,000 in women (Tsai et al 2013).

Prevalence (underlying condition): estimates not found.

Proportion developing CNV: Retrospective medical records review from a tertiary center in Italy (2008-2013) found CNV in 41/272 (15%) eyes of 136 patients, followed for a mean 14±12 months (Peiretti et al 2015). However, a retrospective case series in Miami, US (1970-1997) found CNV in only 2/101 eyes (2%) followed for a mean of 10 years (Loo et al 2002).

CNV secondary to other causes – choroidal nevi

Incidence (underlying condition): estimates not found.

Prevalence (underlying condition): In the US NHANES 2005-2008, the prevalence of choroidal nevus among 5575 participants aged ≥40 years was 4.7%. The highest prevalence was noted in White participants (5.6%) and the lowest in Blacks (0.2%) (Qiu and Shields 2015). In the US Multi-Ethnic Study of Atherosclerosis (2002-2004, 6176 persons) prevalence of choroidal nevi was 2.1%, with the highest risk in Whites (4.1%) and the lowest risk in Chinese (0.4%) (Greenstein et al 2011). In the Australian Blue Mountains Eye Study (1992-1994) prevalence was 6.5% (Sumich et al 1998). In the Beijing Eye Study (2001) prevalence of

choroidal nevi in 4277 participants was 2.9%±0.3% per subject or 1.5%±0.1% per eye (Jonas et al 2008).

Proportion developing CNV: A retrospective clinic-based study in the US (1974-2006) found evidence of CNV in 20/3422 eyes with choroidal nevus (0.6%) (Shields et al 2008a); a subset of 322 giant nevi was reviewed in the same center at a later timepoint and found CNV in 3 eyes (0.9%) (Li et al 2010).

CNV secondary to other causes – other ocular tumors

Various benign and malignant ocular tumors have been associated with CNV in the literature.

Table 2-17 Proportion of patients with various ocular tumors developing CNV

Tumor type	%	n/N	Country, year	Reference
Circumscribed choroidal hemangioma	1.5	3/200	US, 1974-2000	(Shields et al 2001)
Combined hamartoma of the retina and retinal pigment epithelium	4	3/79 eyes	US, prior to 2008	(Shields et al 2008b)
Malignant melanoma of the choroid	6	14/229 eyes	UK, 2001-2004	(Guerin et al 2006)
Choroidal osteoma – at first visit	19	14/74 eyes	US, 1977-2003	(Shields et al 2005)
	18	2/11 eyes	US, 1986-2002	
	17	6/36	US, prior to 1998	
Choroidal osteoma – 10-year follow-up	56	20/36	US, prior to 1998	(Browning 2003)

Source: Shields et al 2001, Shields et al 2008b, Guerin et al 2006, Shields et al 2005, Browning 2003.

The age-adjusted incidence of all malignant ocular tumors in the US and England (UK) in 2003-2007 did not exceed 1 per 100,000 persons per year (Kosary et al 2014, Rashbass et al 2014). Individual estimates of the incidence and prevalence of benign ocular tumors other than choroidal nevi were not found.

CNV secondary to other causes – choroidal trauma

Incidence (underlying condition): In Scotland (1991-1992), the annual cumulative incidence of ocular trauma hospital admission was 8.1 per 100,000 population (95% CI: 7.4-9.0) (Desai et al 1996); a follow-up study in 2008-2009 reported a lower incidence of about 2 per 100,000 (Morris et al 2014). A study in Sicily, Italy (2001-2005) found that the incidence of eye injuries leading to hospitalization was 4.9 per 100,000 (Cillino et al 2008). In Sardinia, Italy (1993-2004) the annual incidence of hospitalizations due to ocular trauma was 3.2 per 100,000 (Pinna et al 2007).

Only a small proportion of all eye injuries results in choroidal trauma. Out of 3620 eyes with severe ocular trauma in the United States Eye Injury Registry (1988-2003) only 224 (6%) were associated with choroidal rupture (Kuhn et al 2006).

Prevalence (underlying condition): Prevalence estimates for choroidal rupture were not found. Some studies report lifetime prevalence of any ocular injuries to be as high as 10-20%, e.g. (Krishnaiah et al 2006, McCarty et al 1999, Wong et al 2000); however, only a very small proportion of those would result in choroidal rupture.

Proportion developing CNV: a retrospective clinic-based study in the US (1993-2001) recorded CNV as a late complication in 12/111 eyes with traumatic choroidal rupture (11%)

(Ament et al 2006). A chart review in the US in 1988-1998 found evidence of CNV in 2 of 32 eyes with choroidal rupture (6%) (Raman et al 2004). However, a study in Canada (1984-2004) reported CNV developing in 7/26 eyes (27%) (Harissi-Dagher et al 2005).

CNV secondary to other causes – inherited retinal dystrophies

The reported incidence and prevalence of the few selected conditions that have been associated with the development of CNV are listed in Table 2-18.

Table 2-18 Reported incidence and prevalence of the inherited retinal dystrophies associated with CNV

	Incidence rate, per 100,000 persons per year		Prevalence, per 100,000 persons		Risk of developing CNV
	Estimate	Source	Estimate	Source	
Stargardt disease	0.11	UK (1)	10-12.5	Unspecified (2)	Very rare (5)
Best disease	0.035	UK (1)	1.5	Denmark (3)	2-9% (5)
Pattern dystrophies	Unknown	-	May be similar to Best disease	France (4)	Develops in advanced disease (5)
Doyne honeycomb dystrophy	Unknown, rare	-	Unknown, rare	-	6-24% patients aged >45 (5)
North Carolina macular dystrophy	Unknown, very rare	-	Unknown, very rare	-	Rare (5)
Sorsby's macular dystrophy	Unknown, very rare	-	Unknown, very rare	-	100% (2,5)

Sources: (1) Hamblion et al 2012, (2) Gelman and Tsang 2011, (3) Bitner et al 2012, (4) Bocquet et al 2013, (5) Saksens et al 2014

2.4.2 Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors of the disease (CNV)

Demographic characteristics of selected populations with CNV secondary to conditions other than nAMD are presented in the Table 2-19. Data are mainly drawn from convenience samples selected for CNV treatment in an observational or interventional setting, which may not be fully representative of the entire CNV population due to small sample size, application of exclusion criteria or other selection criteria. Population characteristics may also vary depending on geographical location, genetic makeup, access to care and other factors. However, certain differences in age and gender distribution are apparent even from the small samples, e.g. patients in idiopathic CNV and inflammatory CNV categories are characterized by relatively young age and female preponderance; CNV secondary to CSC is most common in men, reflecting the gender distribution of the underlying population, etc.

Table 2-19 Demographic characteristics of selected populations with CNV secondary to conditions other than PM

	Characteristics of specific CNV populations					
Underlying condition	**Region, Study time period**	**N**	**Mean age, y (range)**	**% female**	**Race/ ethnicity**	**Reference**
Pathologic myopia	Germany, 1995-2000	1,519	64.8	66	Not reported	(Neuhann et al 2008)
	Taiwan, 2009-2011	9,068	52	61	Not reported	(Yang et al 2017)
	Japan, 2008-2009	82	55.4	62	100% Japanese	(Shoji et al 2011)
	Tokyo, Japan, 1988-2003	324	57.7	44	100% Japanese	(Shimada et al 2006)
Idiopathic	Texas, US 2009-2014	34	38.7	56	Not reported	(Rush and Rush 2015)
	Zhengzhou, China 2009-2012	60	30.8 (18-40)	60	Not reported	(Zhou et al 2015)
	Kolkata, India 2008-2013	37	36.1 (13-49)	42	Not reported	(Saurabh et al 2015)
	Osaka, Japan 1990-2004	46	33.9 (18-49)	63	100% Japanese	(Machida et al 2006)
Angioid streaks						
Any angioid streaks	Paris, France 2007-2010	27	63.7 (30-86)	59	Not reported	(Mimoun et al 2010)
	Multicenter, UK 2000-2003	22	Men: 49 (40-72) Women: 58 (46-76)	18	Not reported	(Browning et al 2005)
Due to PXE only	Bonn, Germany 2003-2007	15	53 (24-72)	40	Not reported	(Finger et al 2008)
	Kyoto, Japan 2008-2010	24	66.8 (50-89)	33	100% Japanese	(Ellabban et al 2012)
Inflammatory						
Multifocal choroiditis	Milan, Italy 2005-2009	27	39 (22-57)	67	Not reported	(Parodi et al 2010b)
	Europe, North / South America, Middle East, Asia 2007-2010	12	37.8	75	91.7% White	(Mansour et al 2012)
Punctate inner choroidopathy	Europe, North / South America, Middle East, Asia 2007-2010	24	41.5	79	29.2% White	(Mansour et al 2012)
	Oxford, UK not reported	10	40.7 (25-58)	80	Not reported	(Menezo et al 2010)
	China, 2008-2010	12	32.9 (20-45)	92	100% Chinese	(Zhang et al 2012)
Serpiginous choroiditis	Europe, North / South America, Middle East, Asia 2007-2010	10	51.7	70	60% White	(Mansour et al 2012)
	Italy not reported	7	46 (35-67)	86	Not reported	(Parodi et al 2014)
Vogt-Koyanagi-Harada syndrome	Europe, North / South America, Middle East, Asia 2007-2010	4	34.3	50	50% White	(Mansour et al 2012)

	Characteristics of specific CNV populations					
Underlying condition	**Region, Study time period**	**N**	**Mean age, y (range)**	**% female**	**Race/ ethnicity**	**Reference**
	Saudi Arabia, 2000-2003	6	22 (17-27)	83	Not reported	(Nowilaty et al 2006)
Presumed ocular histoplasmosis	Europe, North / South America, Middle East, Asia 2007-2010	19	50.7	47	89.5% White	(Mansour et al 2012)
Ocular toxoplasmosis	Europe, North / South America, Middle East, Asia 2007-2010	5	29.4	60	100% White	(Mansour et al 2012)
Central serous chorioretinopathy	Europe, North / South America, Middle East, Asia, Oceania; 2009-2014	43	57.6 (29-79)	30	Not reported	(Chhablani et al 2015)
Other causes						
Choroidal nevi	London, UK 2009-2012	17	68 (53-85)	Not reported	Not reported	(Papastefanou et al 2013)
	Florida, US 2008-2012	27	66.6 (40-86)	63	Not reported	(Cavalcante et al 2014)
	Philadelphia, US 2006-2009	10	64 (44-74)	60	100% White	(Chiang et al 2012)
Choroidal osteoma	Europe, North America, Middle East, Asia not reported	25	29 (8-57)	64	72% White 16% Indian 12% Asian	(Mansour et al 2014)
Choroidal trauma	Massachusetts, US 1993-2001	12	37 (18-62)	25	Not reported	(Ament et al 2006)
Adult-onset foveomacular vitelliform dystrophy	Creteil, France 2007-2010	20	76.6 (60-89)	60	Not reported	(Mimoun et al 2013)
	Jerusalem, Israel 2006-2011	11	79.6 (59-90)	64	Not reported	(Tiosano et al 2014)
Pattern dystrophy (any)	Italy, 2006-not reported	12	54.5 (46-63)	50	Not reported	(Parodi et al 2010a)

Source: Neuhann et al 2008, Yang et al 2017, Shoji et al 2011, Shimada et al 2006, Rush and Rush 2015, Zhou et al 2015, Saurabh et al 2015, Machida et al 2006, Mimoun et al 2010, Browning et al 2005, Finger et al 2008, Ellabban et al 2012, Mansour et al 2012, Parodi et al 2010b, Menezo et al 2010, Zhang et al 2012, Parodi et al 2014, Nowilaty et al 2006, Chhablani et al 2015, Papastefanou et al 2013, Cavalcante et al 2014, Chiang et al 2012, Mansour et al 2014, Ament et al 2006, Mimoun et al 2013, Tiosano et al 2014, Parodi et al 2010a

Risk factors for the disease: The information on the risk factors of developing CNV secondary to etiologies other than nAMD is relatively scarce.

Pathologic myopia: Although there are risk factors known for the development of PM, there is still little information on the cause of the condition (Soubrane 2008, Silva 2012).

Main risk factors identified:

- High Myopia
- Female gender
- Ethnicity: higher risk among Asians and lower among Africans and Pacific Islanders

Strong genetic basis as shown by twin studies. Several association studies have identified some candidate genes but most of the genetic association remains to be elucidated.

Idiopathic: Apart from female gender, which was identified as a risk factor in a number of studies (Lee and Ferrucci 2011), there exists no definite information on specific risk factors for the development of idiopathic CNV. One study in Japan noted that patients with idiopathic CNV were significantly more likely to have high myopia (in absence of myopic retinopathy) than community-sampled controls without CNV (Machida et al 2006).

Angioid streaks: Patient age has been reported as the main risk factor for CNV development. Width, length and location of the angioid streaks seem to also play a role: the wider and longer are the angioid streaks the higher the risk for CNV, especially if the lesions are located in a distance less than one optic disc diameter from the foveola. In addition, even mild head injuries are a risk factor for the breaks in the Bruch's membrane (Georgalas et al 2009).

Inflammation: A large study looking at 15,137 uveitic eyes (8868 patients) found that CNV was rare in the cases of anterior or intermediate uveitis. Risk factors for CNV at presentation included posterior uveitis in general and specific uveitis syndromes affecting the outer retina–retinal pigment epithelium–choroid interface. Risk factors for incident CNV included currently active inflammation (adjusted HR, 2.13; 95% CI: 1.26-3.60), preretinal neovascularization, HR=3.19 (95% CI: 1.30-7.80), and prior diagnosis of CNV in the contralateral eye, HR=5.79 (95% CI: 2.77-12.09). Among specific syndromes, the incidence was greater in Vogt-Koyanagi-Harada syndrome, HR=3.37 (95% CI: 1.52-7.46) and punctate inner choroiditis, HR=8.67 (95% CI: 2.83-26.54) (Baxter et al 2013). Smoking has also been reported as a risk factor for CNV development in ocular histoplasmosis (Chheda et al 2012).

Central serous chorioretinopathy: No information has been identified on the risk factors predisposing to CNV development in CSC. The main risk factors for CSC include systemic corticosteroid use, male gender, type A personality, pregnancy, endogenous Cushing's syndrome, and acute stress (Liew et al 2013).

Other causes: A retrospective review of 17 patients with CNV secondary to choroidal nevi and literature case review concluded that CNV is not associated with the nevus size, may be of variable type and location, and is not associated with malignant transformation, but on the contrary, may be associated with a benign nature of a melanocytic lesion (Papastefanou et al 2013). The main risk factor for choroidal nevi in general is White race, which confers 10-fold higher risk than in Blacks and 2-fold higher than in Hispanics (Qiu and Shields 2015).

A study in 74 eyes of 61 patients with choroidal osteoma found that the following factors were associated with development of CNV in a univariate analysis: presence of symptoms, irregular surface of tumor (vs. smooth), VA ≥20/40 at initial examination, hemorrhage on tumor, yellow color of tumor (vs. orange) and presence of subretinal fluid. In a multivariate analysis, only irregular surface of tumor, RR=10.6 (95% CI 1.1-98.6) and hemorrhage on tumor, RR=15.1 (2.4-93.2) remained significant factors (Shields et al 2005).

A study in the US evaluating 111 patients with traumatic choroidal ruptures found that older age and location of rupture within the arcades were positively associated with CNV formation (Ament et al 2006).

2.4.3 Main existing treatment options (CNV)

There exist no specific guidelines for the treatment of CNV secondary to causes other than nAMD. Recent review articles identified the following approaches that have been used for the treatment of CNV of various etiologies:

- Submacular surgery: before the introduction of anti-VEGF agents, surgical excision of neovascular membranes has been attempted in cases where laser or photodynamic treatment has been contraindicated, with variable levels of success. This method is burdened with a risk of surgery-related complications and high recurrence rate (Lee and Ferrucci 2011, Parodi et al 2010c). Retinal surgery (macular 360° rotation or limited translocation with scleral shortening) is also used for treatment of PM (Soubrane 2008, Silva 2012).
- Laser photocoagulation: it was a common treatment modality before the advent of photodynamic and anti-angiogenic therapy; however, is only recommended for the treatment of extrafoveal lesions and juxtafoveal CNV and cannot be used for large lesions (Jian et al 2013, Lee and Ferrucci 2011). In a series of studies of peripapillary choroidal neovascular membranes of various etiologies laser treatment was associated with a recurrence rate of 19% to 50% (Lee and Ferrucci 2011).
- Photodynamic therapy: has shown good success rates in various CNV subtypes: a review of published case series concluded there was an overall 78.4% success rate in inflammatory CNV (D'Ambrosio et al 2014). The same paper recommended it as first-line treatment for patients with early extrafoveal lesions not causing a decrease in the VA as a less invasive option compared to anti-VEGF treatment.
- Corticosteroids or other immunosuppressants: systemic or topical immunosuppressants are commonly used in CNV secondary to uveitis to control active inflammation (D'Ambrosio et al 2014, Parodi et al 2010c). Use of intravitreal triamcinolone acetonide has also been reported in CNV, usually as adjunct to photodynamic therapy (Jian et al 2013, Lee and Ferrucci 2011).
- Anti-VEGF agents: although there is a dearth of randomized clinical trials, a number of case reports and nonrandomized case series reported successful treatment of CNV of various etiologies with intravitreal VEGF inhibitors, mainly ranibizumab and bevacizumab (not approved for intravitreal use). A review of published case series concluded that the overall treatment success rate in inflammatory CNV was about 87% for off-label bevacizumab and about 90% for ranibizumab (D'Ambrosio et al 2014). Other recent review papers also highlighted VEGF inhibitors as promising treatment or recommended it for the treatment CNV of various etiologies (Georgalas et al 2011, Jian et al 2013, Lee and Ferrucci 2011, Parodi et al 2010c). Ranibizumab and aflibercept, anti-VEGF therapy, are approved for the treatment of CNV due to PM.

2.4.4 Natural history of the indicated condition in the untreated population, including mortality and morbidity (CNV)

Morbidity associated with CNV with the underlying etiologies other than nAMD varies depending on the condition.

Pathologic myopia remains a common cause of blindness and visual impairment in various countries. In a study in Italy, degenerative myopia was the cause of 10.5% of all binocular blindness and 3.2% of all monocular blindness, although results were based on small numbers (Nucci et al 2005). A study in Spain found that the prevalence of PM in elderly blind patients and visually impaired patients was 23.3% (95% CI: 11.75-38.63) and 12% (95% CI: 6.12-20.38), respectively (Sainz-Gómez et al 2010). In a study in Netherlands, myopic degeneration was the underlying cause of visual impairment in 6% of the elderly blind population and 6% of visually impaired population (Klaver et al 1998). In a study in China, high myopia macular degeneration caused 31 (10.5%) of 295 cases of blindness and 41 (9.4%) of 437 cases of low vision (Yao et al 2013).

A number of studies that observed untreated idiopathic CNV cases concluded that the visual prognosis in such patients is better than may be expected in nAMD, with a majority of patients retaining useful vision after a few years of follow up (Lindblom and Andersson 1998). However, observational studies of treatment with VEGF inhibitors in this patient population report a significant and sustained improvement in visual acuity (Zhou et al 2015).

CNV secondary to angioid streaks is a vision-threatening complication; earlier studies reported that as many as 50% of patients may progress to legal blindness (VA <1/20) if left untreated (Georgalas et al 2009). CNV is one of the most severe complications in uveitis of different etiologies, and when untreated often leads to permanent and severe visual impairment (Neri et al 2009). Acute CSC resolves spontaneously in most cases, however, CNV may occur at any time after the initial diagnosis and is associated with poor visual outcome (Liew et al 2013). Development of CNV is a major cause of visual loss in choroidal osteoma (Aylward et al 1998) and a risk factor for decreased vision in patients with choroidal nevi (Li et al 2010).

Mortality: No specific data on the mortality in patients with CNV of etiologies other than nAMD has been found in literature. However, on a general note, decreased visual acuity has been associated with increased five-year mortality and even relatively mild visual impairment increases the risk of death more than two-fold (McCarty et al 2001).

Some systemic conditions associated with CNV may confer increased mortality; e.g. patients with sickle-cell anemias are at increased risk of death from infections, stroke, acute chest syndrome, heart disease and other complications (Rees et al 2010). Systemic inflammatory conditions may be also associated with increased mortality, e.g. patients with sarcoidosis have increased risk of death due to cardiomyopathy or other complications (Judson 2007). Patients with Behçet disease and cardiac involvement (between 7% and 46%) have poorer survival than those without (Demirelli et al 2015); in a retrospective study in China (1995-2010) 102 of 796 patients with Behçet disease (mean age 34 years) demonstrated vascular lesions; of those, 4 died during follow-up from arterial aneurysms rupture (Fei et al 2013).

2.4.5 Important co-morbidities (CNV)

Common comorbidities in the populations with CNV secondary to conditions other than nAMD vary across the underlying etiologies. Ocular complications are common in inflammatory ocular diseases, while systemic diseases may be more frequently associated with systemic cardiovascular and renal complications. In rare conditions the exact prevalence of specific

comorbidities or the extent of the increase in risk is often unknown. Below the available information is summarized, grouped by the comorbidity type.

Cataract: Cataract is a common comorbidity in many underlying CNV etiologies, especially those associated with uveitis. In ocular sarcoidosis and Vogt-Koyanagi-Harada disease, cataract is reported in approximately one third of all patients (Bodaghi et al 2012, Fang and Yang 2008). Cataract was reported in 5-13% of patients with ocular toxoplasmosis (Butler et al 2013). In a US study of 24 patients with ocular toxocariasis, 3 (12%) had cataract (Stewart et al 2005). Conditions of the white dot syndrome spectrum present with varying risk: e.g. cataract was reported in 32% patients with MCP, but none with PIC (Kedhar et al 2007).

Two observational studies also found an increased risk (above 3-fold) of nuclear cataract ion patients with high myopia, compared to controls without myopia (Younan et al 2002, Praveen et al 2008).

In a US study of 111 patients with traumatic choroidal ruptures, 15 patients (14%) developed traumatic cataract (Ament et al 2006).

Glaucoma: Glaucoma is a common comorbidity in many conditions associated with CNV, especially intraocular inflammation. In ocular sarcoidosis, secondary glaucoma occurs in approximately one third of all patients (Bodaghi et al 2012, Rothova 2000); same proportion is reported in Vogt-Koyanagi-Harada disease (Fang and Yang 2008). Increased intraocular pressure was reported in 30-38% of patients with ocular toxoplasmosis (Butler et al 2013).

In a meta-analysis of 11 cross-sectional studies the odds ratio (OR) of the association between high myopia (≤ -3D) and glaucoma was 2.46 (95% CI: 1.93-3.15) (Marcus et al 2011). A prospective study in Italy reported a RR of incident primary open angle glaucoma in high myopia in patients of 7.2 (95% CI: 1.3-39.9) (Cedrone et al 2012).

In a US study of 111 patients with traumatic choroidal ruptures, 7 patients (6%) developed traumatic glaucoma (Ament et al 2006).

A case-control study in Japan found glaucoma in 10/287 (3.4%) patients with CSC and in 20/235 (8.5%) gender- and age-matched control subjects; OR=0.39 (95% CI: 0.16-0.89). The number of patients diagnosed with ocular hypertension (0.3% versus 3.4%) and the number of patients using pressure-lowering eye drops (3.8% versus 13.2%) were significantly less in the CSC group. The authors concluded that glaucoma and related conditions are less frequent in CSC (Imamura et al 2010).

Macular edema: Macular edema is a common finding in uveitis. In ocular sarcoidosis, 76% of patients with posterior involvement may present with macular edema (Rothova 2000). ME was reported in 12% of patients with ocular toxoplasmosis (Butler et al 2013), in 6% of patients with Behçet disease and anterior uveitis, and 14% with Behçet disease and posterior uveitis (Kacmaz et al 2008). In a US study of 24 patients with ocular toxocariasis, 9 (37.5%) had cystoid ME and further 2 macular edema outside fovea (Stewart et al 2005).

Conditions of the white dot syndrome spectrum present with varying risk: e.g. cystoid ME was reported in 14% patients with MCP, but none with PIC (Kedhar et al 2007).

Hypertension: Pulmonary hypertension is a serious and common complication in patients with sickle cell disease (Rees et al 2010).

A retrospective study in the US examined records of 230 CSC patients (mean age 51 years) and found that prevalence of hypertension in CSC patients (27%) was almost two-fold higher than in gender- and age-matched controls (OR=2.25; 95% CI: 1.39-3.63) (Tittl et al 1999).

The US NHANES study (2005-2008) found possible association between choroidal nevi and self-reported hypertension, OR=1.40 (95% CI: 0.99-1.98) (Qiu and Shields 2015).

Coronary heart disease, myocardial infarction: Myocardial infarction has been reported in teenagers and young individuals with PXE (Chassaing et al 2005). Behçet disease often presents with cardiovascular manifestations, and arterial involvement is estimated to range between 8 and 18%; one study reported that as many as 6% Behçet disease patients aged 30 on average had heart pathologies, of which 17% were myocardial infarctions (Demirelli et al 2015).

A population-based cohort study in Taiwan's national health insurance research database (2000-2009) followed 835 CSC patients and 4,175 controls matched by age and gender. The 5-year cumulative incidence of CHD in CSC patients was nearly two-fold that of the controls (6.12% vs 3.29%). After adjusting for urbanization level, income and comorbidities, CSC patients remained at a higher risk of CHD versus controls; HR = 1.61 (95% CI: 1.12-2.30) (Chen et al 2014b). A retrospective study in the US examined records of patients with CSC (mean age 51 years) and 1:1 gender- and age-matched controls; 7/230 (3%) CSC patients had MI vs. 3/230 controls, although the increase in risk was not significant (OR=2.38; 95% CI: 0.53-14.40) (Tittl et al 1999).

The US NHANES study (2005-2008) found no association between choroidal nevi and self-reported history of heart attack, OR=1.46 (95% CI: 0.48-4.47) (Qiu and Shields 2015).

Stroke: Ischemic stroke is uncommon in PXE patients but more prevalent than in the general population (Chassaing et al 2005). Stroke is a common complication of sickle cell disease: a recent review paper reported that as many as 11% patients may have a stroke by the age of 20 years (Rees et al 2010).

A population-based cohort study in Taiwan's national health insurance research database (2000-2007) followed 1814 patients with newly diagnosed CSC and 9648 controls matched by age, sex, income, location and calendar time. After adjusting for age, sex and chronic comorbidities, CSC patients were found to have a 1.56-fold (95% CI: 1.11-2.18) greater risk of a subsequent ischaemic stroke than controls (Tsai et al 2012).

The US NHANES study (2005-2008) found no association between choroidal nevi and self-reported history of stroke, OR=0.83 (95% CI: 0.39-1.75) (Qiu and Shields 2015).

Renal disease: Microalbuminuria is common in children with sickle-cell disease and up to 20% of adults develop nephrotic-range protein loss; 30% of adults with sickle-cell disease develop chronic renal failure, and other renal complications are common (Rees et al 2010).

A review of 7,791 histoplasmosis cases published in the literature found that frequency of acute renal failure was 2.8% (Gta et al 2010). Extrapulmonary sarcoidosis may also be complicated by renal insufficiency or acute renal failure (Judson 2007).

2.5 Retinopathy of prematurity (ROP)

ROP is a neovascular retinal disorder that occurs in the incompletely vascularized, developing retina of very low birth-weight (VLBW) or very preterm infants. The disruption of angiogenesis in preterm infants with ROP typically occurs in 2 postnatal phases. In Phase 1 (~22 to 30 weeks postmenstrual age), high oxygen saturation in the immature retina (relative hyperoxia), coupled with low concentrations of growth factors and nutrients normally present in utero during the third trimester of pregnancy, lead to suppression of new vessel growth. As a result, the metabolically active but poorly vascularized retina becomes hypoxic. In Phase 2 (~31 to 44 weeks postmenstrual age), the hypoxic environment in the retina stimulates release of various angiogenic factors, such as vascular endothelial growth factor (VEGF), that lead to proliferation of new blood vessels. In preterm infants with disrupted angiogenesis, the abnormal neovascularization and the leaky new blood vessels formed in this environment result in intraocular fibrosis, leading to retinal distortion, detachment, and visual disability.

Left untreated, vascular changes of ROP may be mild and regress completely with time and without major long-term sequelae, or they may increase in severity and lead to macular dragging, total retinal detachment, severe visual impairment, and lifelong blindness (Hardy et al 2004).

2.5.1 Incidence (ROP)

In the EU, ROP is seen predominantly in infants with VLBW (≤1500 g) and/or low gestational age (GA; ≤32 weeks), with a reported incidence of ROP in these infants ranging from 20% to 60% (Hoogerwerf et al 2010; Borroni et al 2014; van Sorge et al 2014).

Recently published population-based studies that have provided information on the cumulative incidence of ROP in developed countries worldwide are listed in Table 2-20. Incidence figures presented in this table were recalculated, if needed, to standardize the presentation to a denominator per 10,000 live births.

The cumulative incidence of any ROP ranged between 12 and 20 per 10,000 live births (Table 2-20). The incidence of treated ROP reported in the observational studies in the EU and the US ranged from 1.4 to 5.9 per 10,000 live births (Painter et al 2015, Dhaliwal et al 2008, Chamney et al 2015, Lad et al 2009).

Table 2-20 Cumulative incidence of ROP reported in population-based studies

Country, study period	Population characteristics	Denominator (live births)	Cumulative incidence of ROP, per 10,000 live births	Reference
UK (England), 2011	English national Hospital Episode Statistics	688,120*	14.6*	Painter et al (2015)
UK (Scotland), 2000-2004	All infants born in Lothian, southeast Scotland	40,833	19.8*	Dhaliwal et al (2008)
Sweden, 2004-2007	All infants born in Sweden who survived to ROP screening beginning at postnatal week 5	305,318	12.1*	Austeng et al (2014) Austeng et al (2009)
USA, 1997-2005	All infants in the National Inpatient Sample	34 million	17	Lad et al (2009)

Country, study period	Population characteristics	Denominator (live births)	Cumulative incidence of ROP, per 10,000 live births	Reference
New Zealand, 1998-1999	All VLBW infants in the Australian and New Zealand Neonatal Network	52,824	12.3*	Darlow et al (2003)

Source: Painter et al 2015, Dhaliwal et al 2008, Austeng et al 2014; Austeng et al 2009, Lad et al 2009, Darlow et al 2003

*denotes own calculation based on the information provided in the article

A trend of increasing incidence of ROP in the recent years was noted by many researchers (Darlow 2015, Painter et al 2015). Among frequently cited reasons for this increase are the increased neonatal survival of VLBW and very preterm infants, improved awareness of ROP and dissemination of guidance on ROP screening and treatment of ROP.

2.5.2 Prevalence (ROP)

ROP primarily affects preterm infants shortly after birth and may resolve spontaneously, therefore prevalence is not a useful epidemiological measure to describe this condition. For the estimates of prevalence of long-term sequelae of ROP such as blindness, please refer to Section 2.5.5.

2.5.3 Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors of ROP

The incidence and severity of ROP increase with the degree of prematurity at birth, with low gestational age at birth and low birth weight being the main risk factors (Hartnett and Penn 2012, Fierson et al 2013, Kim et al 2018). ROP does not occur in full-term neonates and older infants, as their retina and retinal vasculature are fully developed.

Gestational age

GA at birth and birth weight are the two strongest known risk factors for development of ROP. An older multicenter study of cryotherapy for ROP followed 4,099 infants with BW < 1,251g and found that lower BW and younger GA were strongly associated with developing ROP. In this cohort, each week increase in GA at birth decreased the odds of stage 3+ ROP by 19% (Kim et al 2018). Ying et al (2016) showed that every week decrease in GA at birth (continuous variable) was associated with an almost doubling of odds of developing ROP for infants born in the USA between 2011-2013; a similar finding was reported by a meta-analysis of 18 studies on ROP in Iran (Azami et al 2018).

In the recent observational studies in EU, USA and Canada, the mean GA at birth in weeks (± SD) for preterm infants with severe or treatment requiring ROP ranged from 24.5 ± 1.2 to 26.7 ± 1.5 (Giannantonio et al 2012, Isaza et al 2013, Hartnett et al 2014).

In areas with insufficient access to neonatal medical care, ROP is occurring in larger, more mature babies compared to areas with access to intensive neonatal care (Gilbert et al 1997, Gilbert 2008, Mintz-Hittner et al 2011). Except for the broader span of gestational ages and body weights of neonates with ROP in these regions, no differences in disease characteristics and pathophysiology were reported.

Birth weight

Together with GA, birth weight is the strongest risk factor for development of ROP. In the large ROP cohort, each 100 g increase in birth weight decreased the odds of reaching stage 3+ ROP by 27%, and these findings have been since replicated by multiple observational studies (Kim et al 2018).

Gender

The research has been conflicting, with some studies reporting a slight preponderance of female infants in the ROP population (Ludwig et al 2017), and other suggesting male gender as a risk factor or no difference (Kim et al 2018, Azami et al 2018).

Race / ethnic origin

Multiple North American studies found that black infants had a lower incidence of ROP than white infants. However, black infants in the UK were reported to have a higher risk of severe ROP than white infants. Asians and Alaskan natives in the US also appear to have a greater risk of ROP than white infants (Kim et al 2018).

A recent study using the California statewide database with 3,160,268 live births from the period 2007-2012, reported similar racial disparity trends for ROP requiring surgery in extremely preterm infants. Asian infants born at 22–25 weeks were more likely than white infants to develop ROP requiring surgery (OR 1.39; 95% CI 1.02–1.90). In contrast, black infants were less likely to develop ROP requiring surgery than their white counterparts: OR 0.46; 95% CI 0.37–0.63 for infants born at 22-25 weeks and OR 0.47; 95% CI 0.28–0.80 for infants born at 26-28 weeks (Anderson et al 2018).

Other risks factors

The use of supplemental oxygen, oxygen concentration, duration, and prolonged mechanical ventilation are among the most frequently identified risk factors for severe and treatment-requiring ROP. Multiple interventional and observational studies found significant risk factors for severe ROP such as the exposure to >50% oxygen, duration of oxygen therapy and prolonged mechanical ventilation (Kim et al 2018, Azami et al 2018).

Other risk factors frequently cited in literature include maternal factors (diabetes, preeclampsia, mother's smoking, maternal age), assisted conception, chorioamnionitis, neonatal infection and sepsis, blood transfusion, apnea, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, vitamin E deficiency, heart disease, increased blood carbon dioxide, decreased PH, bradycardia etc (Kim et al 2018, Azami et al 2018).

2.5.4 Main existing treatment options (ROP)

Ablation of the peripheral avascular retina with cryotherapy to induce the regression of neovascularization was the first standard treatment for ROP (Cryotherapy for Retinopathy of Prematurity Cooperative Group 1988). In the 1990s, the use of laser photocoagulation to ablate the peripheral avascular retina gained widespread acceptance, and this modality has now almost completely replaced cryotherapy to become the current standard of care (Good 2004, International Committee for the Classification of Retinopathy of Prematurity 2005, Royal

College of Paediatrics and Child Health 2008, Fierson et al 2013). Compared to cryotherapy, laser ablation therapy (hereafter referred to as laser therapy) is associated with better long-term structural, visual and refractive outcomes (Houston et al 2013).

Laser therapy does not fully address the underlying cause of ROP, which is the abnormal neovascularization mediated in part by high levels of VEGF. While both cryotherapy and laser therapy destroy the majority of retinal cells that produce VEGF (Smith 2008), these therapies do not reduce the elevated levels of VEGF already present.

Peripheral retinal ablation with laser therapy helps to prevent blindness, particularly when the risk of retinal detachment is substantial, but this therapy is associated with complications and irreversible damage to the retina. Laser therapy destroys the peripheral retina, causing permanent loss of peripheral vision, and often induces clinically significant myopia (ETROP Group 2003, Mintz-Hittner et al 2011). Vitrectomy is the last resort for those patients who fail to respond to multiple applications of laser therapy.

Additionally, it may not be possible to perform laser therapy for certain patients. Conventional laser therapy is laborious, usually requiring general anesthesia and adequate visualization of the retina, which may be problematic in preterm infants with associated comorbidities.

Therefore, there is a high unmet need for effective, simpler and less destructive therapeutic options for ROP. Given the key role of VEGF in the pathophysiology of ROP, there is a strong scientific rationale for targeting VEGF in the treatment of ROP in infants born prematurely. Availability of anti-VEGF agents administered via intravitreal injection allows for suppression of excessive levels of VEGF present within the retina and vitreous that are responsible for the abnormal vascularization observed in ROP. Treatment modalities targeted toward reducing VEGF levels have the potential to halt and reverse the hypoxic neovascular response (Smith 2008). Several publications have reported the successful treatment of infants with ROP with anti-VEGF agents (Mintz-Hittner et al 2011, Stahl et al 2018). Therefore, there is a strong scientific rationale and existing clinical evidence for targeting VEGF in the treatment of ROP.

2.5.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity (ROP)

Infants born prematurely have an immature retina with a peripheral avascular zone. ROP develops if there is a disruption in the new vessel formation (angiogenesis) in this zone. The vascular changes of ROP may be mild and regress completely with time and without major long-term sequelae, or they may increase in severity and lead to macular dragging, total retinal detachment, severe visual impairment, and lifelong blindness (Hardy et al 2004).

ROP is a leading cause of childhood blindness, with an estimated prevalence of 50,000 children blind from ROP worldwide in 2008 (Gilbert 2008). According to the Global Burden of Disease (GBD) study, in 2015 there were about 50,000 children aged 5-14 and about 42,000 children aged <5 years that were blind due to ROP worldwide. In Western Europe, GBD estimated that the total number of children aged up to 14 years blind due to ROP was approximately 1750 in 2015 (Table 2-21).

Prevalence of blindness due to ROP worldwide was estimated at 6.6 per 100,000 in children aged <5 and 4.0 per 100,000 in those aged 5-14; in Western Europe, these rates were 2.4 and 2.7, respectively (Table 2-22). Prevalence of blindness due to ROP in Western Europe

decreased slowly over the last 15 years; global prevalence was decreasing from 1990-2011 but remained relatively stable since (GBD 2016a).

Further information on the prevalence and burden of severe and moderate vision impairment due to ROP is provided in Table 2-21 and Table 2-22.

Table 2-21 Total number of children aged <5 and 5-14 years affected by blindness, moderate or severe vision impairment due to ROP in 2015

	<5 years		5-14 years	
	N	95%CI	N	95%CI
Worldwide				
Blindness	41,996	(15,662 - 82,485)	50,328	(21,100 - 106,739)
Severe vision impairment	208,140	(151,461 - 288,970)	403,434	(292,835 - 563,269)
Moderate vision impairment	337,289	(201,790 - 482,230)	654,551	(391,570 - 935,434)
Western Europe				
Blindness	532	(204 - 1075)	1220	(468 - 2389)
Severe vision impairment	5151	(2950 - 7562)	10,541	(5998 - 15,463)
Moderate vision impairment	9667	(5889 - 13707)	19,754	(12,054 - 28,025)

Source: GBD 2016a, GBD 2016b

Western Europe data was provided as data on European Union was not available

Table 2-22 Prevalence of blindness and moderate or severe vision impairment due to ROP among children aged <5 and 5-14 years in 2015

	<5 years		5-14 years	
	Rate per 100,000	95%CI	Rate per 100,000	95%CI
Worldwide				
Blindness	6.6	(2.5 - 13.0)	4.0	(1.7 - 8.6)
Severe vision impairment	32.8	(23.8 - 45.5)	32.5	(23.6 - 45.3)
Moderate vision impairment	53.1	(31.8 - 75.9)	52.6	(31.5 - 75.2)
Western Europe				
Blindness	2.4	(0.9 - 4.9)	2.7	(1.0 - 5.3)
Severe vision impairment	23.4	(13.4 - 34.3)	23.3	(13.3 - 34.2)
Moderate vision impairment	43.8	(26.7 - 62.1)	43.7	(26.6 - 61.9)

Source: GBD 2016a, GBD 2016b

Western Europe data was provided as data on European Union was not available

2.5.6 Important co-morbidities and long-term sequelae

The underlying prematurity is associated with high mortality and morbidity, therefore ROP is associated with a high prevalence of other neonatal conditions related to prematurity. The key comorbidities reported in the ROP populations are listed in Table 2-23.

Table 2-23 Reported prevalence of key co-morbidities associated with ROP

Comorbidity	ROP type	Prevalence range, %	Reported associations between ROP and comorbidity
Bronchopulmonary dysplasia	Mild/any ROP	16.7-100.0	Positive, with unadjusted odds ranging from 1.9 to 15.9 and adjusted OR of 5.1 (95% CI 2.3-11.3).

Comorbidity	ROP type	Prevalence range, %	Reported associations between ROP and comorbidity
Brain hemorrhage or intraventricular hemorrhage	Mild/any ROP	5.2-71.0	Positive, with adjusted ORs ranging from 2.1 to 2.4 for mild/any ROP and 5.4 (95% CI 1.1-26.3) for severe ROP
Necrotizing enterocolitis	Treatment requiring ROP	3.6-89.0	Positive, with adjusted OR of 9.0 (95% CI 2.1-43.5) and adjusted hazard ratio of 1.5 (95% CI 1.1–2.2). Necrotizing enterocolitis as independent risk factor not confirmed in all multivariate analyses.
	Mild/any ROP	0.0-36.4	
Patent ductus arteriosis	Treatment requiring ROP	23.0-71.4	Positive in 4 out of 8 studies, with adjusted ORs ranging from 1.7 to 3.2 and adjusted HR of 1.6 (95% CI 1.1–2.3).
	Mild/any ROP	3.0-66.0	
Respiratory distress syndrome	Treatment requiring ROP	36.1-83.9	Positive in 3 out of 7 studies, with adjusted odds ranging between 2.2 and 8.1.
	Mild/any ROP	26.5-100	

CI = confidence interval; HR = hazard ratio; OR = odds ratio; ROP = Retinopathy of prematurity

References: Adio et al 2014, Araz-Ersan et al 2013, Borroni et al 2013, Celebi et al 2014, Chaudhari et al 2009, Chen et al 2011, Chen et al 2013, Chen et al 2015, Ebrahim et al 2010, Fajolu et al 2015, Fortes Filho et al 2009, Ghaseminejad et al 2011, Giannantonio et al 2012, Goncalves et al 2014, Hakeem et al 2012, Hartnett et al 2014, Hungi et al 2012, Isaza et al 2013, Karkhaneh et al 2008, Kavurt et al 2014, Kucukevcilioglu et al 2013, Kumar et al 2011, Lad et al 2009, Ludwig et al 2017, Lundgren et al 2017, Maini et al 2014, Mehmet et 2011, Rao et al 2013, Shah et al 2005, Taqui et al 2008, Walz et al 2016, Wang et al 2015, Wu et al 2018, Yau et al 2015

Further complications of very preterm birth that have a long-term impact on disability include chronic lung disease, cardiovascular disease, hearing impairment and neurodevelopmental impairments, which include motor impairment, cognitive impairment, behavioural, social and emotional development delays (Johnson & Marlow 2017, Saigal & Doyle 2008).

Cognitive impairment is an important long-term disability in extremely and very preterm populations. Meta-analyses have identified weighted mean differences of 11–12 IQ points in preterm versus term-born children, equating to 0.7 SD to 0.8 SD deficits relative to controls. IQ is significantly associated with gestational age at birth, with a 14-point weighted mean difference (~1 SD) reported for cohorts with mean gestational age <28 weeks (Johnson & Marlow 2017).

Rates of hearing impairment in very premature and VLBW infants were reported between 3% and 7% in most observational studies (Johnson & Marlow 2017, Saigal & Doyle 2008).

The estimated prevalence of moderate and severe motor impairment and epilepsy among children born extremely and very prematurely in Western Europe and worldwide is presented in the following table. In addition, prevalence of moderate or severe motor impairment with cognitive impairment and epilepsy due to extremely or very preterm birth among children aged 5-14 years was estimated between 1.0 and 2.8 per 100,000 in Western Europe and between 9 and 29 per 100,000 in different GA subgroups worldwide in 2015 (GBD 2016c).

Table 2-24 Prevalence of sequelae due to complications of extremely and very preterm birth among children aged <5 and 5-14 years in 2015

	<5 years		5-14 years	
	Rate per 100,000	95%CI	Rate per 100,000	95%CI
Worldwide, GA <28 weeks				
Moderate motor impairment	63.8	(28.7 - 127.1)	32.6	(15.0 - 66.3)
Moderate motor impairment with epilepsy	12.7	(6.3 - 24.9)	10.3	(4.9 - 19.7)
Severe motor impairment	68.7	(30.0 - 138.1)	42.3	(18.8 - 89.2)
Severe motor impairment with epilepsy	4.2	(2.1 - 8.1)	3.4	(1.6 - 6.3)
Worldwide, GA 28-32 weeks				
Moderate motor impairment	93.3	(62.6 - 129.3)	50.7	(32.5 - 71.8)
Moderate motor impairment with epilepsy	17.4	(11.2 - 24.9)	14.8	(9.4 - 20.9)
Severe motor impairment	101.0	(70.8 - 135.5)	66.7	(44.4 - 96.8)
Severe motor impairment with epilepsy	5.8	(4.0 - 7.8)	4.9	(3.3 - 6.7)
Western Europe, GA <28 weeks				
Moderate motor impairment	38.5	(21.3 - 62.6)	33.4	(19.1 - 52.9)
Moderate motor impairment with epilepsy	9.0	(5.0 - 14.2)	8.8	(4.9 - 13.8)
Severe motor impairment	39.7	(21.8 - 63.6)	36.5	(20.4 - 59.3)
Severe motor impairment with epilepsy	3.0	(1.7 - 4.6)	2.9	(1.6 - 4.4)
Western Europe, GA 28-32 weeks				
Moderate motor impairment	41.9	(23.8 - 67.5)	36.5	(20.2 - 61.7)
Moderate motor impairment with epilepsy	9.8	(5.6 - 15.8)	9.6	(5.5 - 15.6)
Severe motor impairment	43.3	(24.8 - 70.6)	40.1	(23.6 - 66.0)
Severe motor impairment with epilepsy	3.3	(1.9 - 5.3)	3.2	(1.8 - 5.3)

Source: GBD 2016c

Western Europe region was provided as data on European Union was not available.

2.6 Diabetic retinopathy

2.6.1 Incidence (DR)

Recently published studies that reported incidence rate of DR are listed in Table 2-25. The results are grouped by diabetes subtype: Type 1 diabetes mellitus (T1DM), Type 2 diabetes mellitus (T2DM) or any diabetes; results were rounded as needed or recalculated per 100 persons if provided in a different format.

Reported annual incidence of DR ranged between 1.8 and 12.5 per 100 persons, with higher incidence reported in T1DM, older populations with T2DM and those of Hispanic ethnicity, and lower incidence in younger populations with T2DM and Asian populations (Table 2-25).

Table 2-25 Incidence of DR in diabetic populations worldwide

Country, study period	Maximum follow-up, years	No. of patients	Baseline mean age, years	Annual incidence rate, per 100 (95%CI)	Reference
T1DM					
Spain, 2000-2009	10	334	25.2	3.6	(Romero-Aroca et al 2011)

Country, study period	Maximum follow-up, years	No. of patients	Baseline mean age, years	Annual incidence rate, per 100 (95%CI)	Reference
US, 2001-2014	13	2,240	12	5.2	(Wang et al 2017)
Taiwan, 1999-2013	15	4,007	Early-onset: 7.7 Late-onset: 26.5	9.8 (9.3-10.3)	(Ou et al 2017)
T2DM					
UK, Wales, 2005-2009	4	49,763	64.4	1st year: 12.5 4th year: 6.7	(Thomas et al 2012)
Spain, 2007-2011	4	2,405	67.5	2.4 (2.1-2.8)	(Salinero-Fort et al 2013)
Portugal, 2009-2014	5	30,641	70 (only median reported)	1st year: 4.6 (4.0-4.8) 5th year: 3.9 (2.6-5.8)	(Dutra Medeiros et al 2015)
US, 2001-2014	12.7	1,768	18 (only median reported)	2.0	(Wang et al 2017)
Japan, 1996-2003	8	1,221	58.2	3.8	(Kawasaki et al 2011)
China, 2010-2014	5	622	69	1.8 (1.2-2.4)	(Liu et al 2015)
Any diabetes (mixed)					
UK THIN, 2006-2007	2	19,569	59.4	4.8 (4.5-5.1)	(Martín-Merino et al 2014)
US, Los Angeles, 2000-2008	4	775	58	7.1 (4.6-9.6)	(Varma et al 2010)

Source: Romero-Aroca et al 2011, Wang et al 2017, Ou et al 2017, Thomas et al 2012, Salinero-Fort et al 2013, Dutra Medeiros et al 2015, Kawasaki et al 2011, Liu et al 2015, Lin et al 2014, Martín-Merino et al 2014, Varma et al 2010

A recently published systematic review provided a similar range of reported incidence ranges and noted a decrease in DR incidence reported by studies published after 2000 compared to those published before 2000 (Sabanayagam et al 2018).

2.6.2 Prevalence (DR)

A recent meta-analysis collated data from 22,896 individuals with diabetes from 35 studies in the US, Australia, Europe, and Asia. Age-standardized prevalence of any DR in individuals with DM aged 20-79 was 35.4% (95% CI: 35.2–35.6), and prevalence of vision threatening DR was 11.7% (95% CI: 11.6–11.8) when analysis was limited to studies with similar methodologies and rigorous outcome definitions (Yau et al 2012).

Prevalence was higher in individuals with T1DM, compared to T2DM, and increased with diabetes duration. Age-standardized prevalence in T1DM was 77.3% (95% CI: 76.3–78.3) for DR and 38.5% (95% CI: 37.8–39.2) for vision-threatening DR; in T2DM, it was 25.2% (95% CI: 25.0–25.4) for DR and only 6.9% (95% CI: 6.8–7.0) for vision-threatening DR. Prevalence of DR in long-standing diabetes (20+ years) was as high as 86.2% (95% CI: 85.1–87.4) in T1DM and 52.2% (95% CI: 51.1–53.2) in T2DM (Yau et al 2012).

2.6.3 Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors of the disease (DR)

In a recent meta-analysis that summarized data from US, Australia, Europe, and Asia, prevalence of DR across both diabetes types was slightly higher in men, compared to women: 36.3% (95% CI: 36.0–36.6) in men and 34.5 (95% CI: 34.2–34.7) in women (Yau et al 2012). The risk of DR was the greatest in Black (African American) diabetes patients with prevalence of 49.6% (95%CI 48.6–50.5), followed by Caucasian and Hispanic patients: 45.8% (95%CI 45.4–46.1) and 34.6% (95%CI 33.2–35.9), respectively. In contrast, prevalence of DR in Chinese patients was 25.1% (95%CI 24.3–25.9) and in South Asian patients it was as low as 19.1% (95%CI 18.9–19.4). Similar trend was observed for STDR (Yau et al 2012).

Other reviews confirmed the apparent geographic and ethnic variability in the rate of retinopathy in both T1DM and T2DM that cannot be explained by the variations in study methodologies alone. It remains uncertain at present whether these apparent ethnic variations represent subpopulation differences associated with access to and the level of medical care, differential susceptibility to risk factors, variability in genetic predisposition to microvascular damage, or environmental risk factors such as urbanization or dietary exposures (Ding and Wong 2012, Sivaprasad et al 2012, Wat et al 2016).

DR is positively associated with other microvascular complications of diabetes, such as peripheral and autonomous neuropathy and nephropathy (Ding and Wong 2012, Kramer et al 2011). A recent study concluded that presence of diabetic polyneuropathy increases risk of DR more than 5-fold (HR=5.41; 95%CI 4.92–5.94) even after adjustment for age, sex, diabetes duration, nephropathy and other comorbidities (Lin et al 2015).

Two recent review articles evaluated other systemic risk factors for DR, which are summarized in the following table.

Table 2-26 Summary of systemic risk factors for DR

Risk factor	Association	Additional comments
Glycemic control	Positive	HbA1c level of 7% or less is ideal in reducing progression and new development of DR HbA1c decrease in every 1% = reduction in 40% of retinopathy, 25% less need for retinal laser and 15% reduction of blindness
Diabetes duration	Positive	Prolonged duration of diabetes is a risk factor for DR
Diabetic drug use	Positive	Patients with DR are more likely to require insulin for glycemic control
Obesity	Positive for waist-to-hip ratio; indeterminate for BMI	Greater waist-hip ratio and waist circumference are positively associated with DR Some studies indicate BMI in the obesity range as a risk factor, while others have shown no increased risk or an inverse relationship between BMI and DR
Hypertension	Positive	Hypertension has a positive association with the development of DR Every 10mmHg decrease in systolic BP = 35% reduction of DR and 50% reduction of blindness
Hyperlipidemia	Indeterminate	Some studies demonstrated a positive relationship, while others showed no association between DR and hyperlipidemia
Chronic kidney disease	Positive	DR is positively associated with chronic kidney disease and high urine albumin-to-creatinine ratio

Risk factor	Association	Additional comments
Sex	Indeterminate	While some studies have demonstrated male sex as an independent risk factor for DR, other studies failed to replicate this relationship
Smoking	Indeterminate	Several studies have shown a non-significant positive trend between DR and smoking, but one large study (United Kingdom Prospective Diabetes Study) indicated a protective effect of smoking
Myopia	Negative	Two meta-analyses confirmed that myopia and longer axial length are associated with low prevalence of DR, although mechanism of this association remains unclear. Patients with myopia have up to 30% lower risk of DR, compared to those with emmetropic eyes.
Pregnancy	Positive	Pregnant women with retinopathy are at much higher risk of DR progression

Source: Ting et al 2016, Wat et al 2016

2.6.4 Main existing treatment options (DR)

In the EU, anti-VEGF therapy is currently approved for the treatment of patients with visual impairment due to DME, which is a complication of DR.

Treatment of mild NPDR is not warranted; however, once progression to more severe NPDR or PDR occurs, or if DME occurs, it is recommended that ocular therapy is initiated (Royal College of Ophthalmologists 2012, American Academy of Ophthalmology Retinal [AAO] 2017). In the EU, the standard of care for severe NPDR and PDR is panretinal photocoagulation (PRP) (Royal College of Ophthalmologists 2012). PRP is a laser treatment involving tiny burns that seal the retina and stop blood vessels from growing and leaking. The goal of PRP treatment is not to regain lost vision, but to stop progression or worsening of vision loss. Typically, the PRP procedure involves the application of 1200-1600 laser burns, approximately 500 µm in size, applied throughout the retinal tissue but away from the macula, destroying viable areas of the retina. The destructive nature of this treatment is associated with significant ocular side effects (ETDRS Research Group 1991a, Fong et al 2004, Fong et al 2007, Heng et al 2013). Consequences of PRP include irreversible destruction of peripheral retinal tissue, including potentially severe and permanent peripheral visual field loss, night blindness, loss of color vision, reduced contrast sensitivity, recurrent vitreous hemorrhages, and PRP-induced DME exacerbation with central vision loss (Fong et al 2007, Ip et al 2012). Patients who undergo PRP may experience spatial orientation deficits related to peripheral vision loss contributing to difficulties with executing activities of daily living.

Vitreous surgery may be considered in patients with high-risk PDR. The well-known risks of invasive surgical intervention include infection, iatrogenic cataract, and hemorrhage (Stefánsson 2001, American Academy of Ophthalmology Retinal [AAO] 2017).

There remains an unmet medical need for additional treatment options for DR, specifically for advanced NPDR to prevent developing PDR, and to prevent complications associated with vision loss or to induce regression of the disease severity.

The role of VEGF throughout the spectrum of DR provides a strong rationale to expect a therapeutic benefit of VEGF inhibitors in the treatment of DR (NPDR and PDR) in the absence of DME. Several studies have reported on changes in DR following anti-VEGF treatment in a broad patient population, including patients with NPDR and PDR with or without DME (Sivaprasad et al 2017, Gross et al 2015, Ip et al 2012). In comparison to the respective control

treatments, these papers collectively point to a larger proportion of anti-VEGF-treated patients experiencing a relevant improvement (≥2 steps in diabetic retinopathy severity score (DRSS)) in DR and also to a lower proportion of anti-VEGF-treated patients experiencing worsening of DR, new onset of DME or PDR, need for vitrectomy, or PRP. When stratified by baseline DRSS, greater proportions of patients with moderately severe to severe NPDR and with PDR than with mild NPDR had ≥2 step improvement in DRSS from baseline following anti-VEGF treatment (Wykoff et al 2018).

By halting and/or reversing DR progression, anti-VEGF agents have the potential to prevent onset and recurrence of vision threatening complications of DR. As a result, anti-VEGF treatment would reduce the consequences of advanced DR, like DME or proliferating vessels, and hence the need for PRP or vitreous surgery. Therefore, anti-VEGF treatment, with the goal to improve DR severity (regardless of presence of DME), appears to be beneficial considering the inevitable course of DR.

2.6.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity (DR)

A systematic review and meta-analysis of published and unpublished population-based data for the causes of vision impairment and blindness from 1980 to 2014 had included 3,983,541 participants from 98 countries. It concluded that among the global population with moderate or severe vision impairment in 2015 (estimated as 216.6 million with 80% uncertainty interval 98.5 to 359.1 million), DR was the fifth leading cause after uncorrected refractive error, cataract, age-related macular degeneration and glaucoma. It was estimated to cause 2.6 million cases of vision impairment and blindness globally in 2015 (80% uncertainty interval 0.2 to 9.9 million). By 2020, among the global population with moderate or severe vision impairment, the number of people affected by DR is anticipated to rise to 3.2 million (0.2 to 12.9 million) (Flaxman et al 2017).

Mortality: Multiple studies have evaluated association between DR and all cause and cardiovascular mortality. A meta-analysis that included 20 studies providing data from 19,234 diabetes patients concluded that in patients with type 2 diabetes (n = 14,896), the presence of any degree of DR increased the chance for all-cause mortality and/or CV events by 2.34 (95%CI 1.96–2.80) compared with patients without DR. In patients with type 1 diabetes (n = 4,438), the corresponding odds ratio was 4.10 (95% CI: 1.50–11.18). These associations remained after adjusting for traditional CV risk factors. DR was also predictive of all-cause mortality in type 2 diabetes (OR=2.41; 95%CI 1.87–3.10) and type 1 diabetes (OR=3.65; 1.05–12.66) (Kramer et al 2011).

Another meta-analysis concluded that DR was associated with higher risk of all-cause mortality in patients with both T2DM (RR=2.25, 95% CI 1.91–2.65) and T1DM (RR=2.68, 95% CI 1.34–5.36). Risk of all-cause mortality varied according to different grades of DR in patients with T2DM; the risk increase in patients with NPDR was 1.38 (95%CI 1.11–1.70), while the risk in PDR was 2.32 (1.75–3.06) (Zhu et al 2017).

2.6.6 Important co-morbidities

The key comorbidities in the population with DR, stratified by DR severity (or diabetes, when DR-specific estimates were not available) are listed in the following table.

Table 2-27 Important comorbidities in DR population

Comorbidity	Prevalence, %	Comments	References
Cataract	Any diabetes: 18 – 22 overall 40 – 68 in those aged ≥75 y	Increasing glycemic index associated with increased incidence of cortical cataract (Tan et al 2007a)	Orcutt et al 2004, Tan et al 2007a, Esteves et al 2008, Chen et al 2008, Zghal-Mokni et al 2008, Saaddine et al 2008
Glaucoma	Any diabetes: 6 – 11 overall Higher in Blacks, Hispanics	Diabetes mellitus is a risk factor for both primary open-angle glaucoma and neovascular glaucoma (Jeganathan et al 2008)	Jeganathan et al 2008, Orcutt et al 2004, Zghal-Mokni et al 2008, Saaddine et al 2008
Hypertension	Any DR: 60 – 73 NPDR: 56 – 88 PDR: 65 – 91	Multiple studies demonstrated that prevalence of hypertension is higher in diabetic patients with DR compared to those without and increases with DR severity	Rubino et al 2007, Targher et al 2008, Salinero-Fort et al 2013, Lamparter et al 2014, Venkatesh et al 2014, Rodriguez-Poncelas et al 2015, Park et al 2017, Shah et al 2018
Hyperlipidemia	Any DR: 35 – 63 NPDR: 33 – 52 PDR: 41 – 52	Association between DR and blood lipid levels remains uncertain	Rubino et al 2007, Lamparter et al 2014, Venkatesh et al 2014, Shah et al 2018
Peripheral neuropathy	Any DR: 34 – 52 NPDR: 44 – 50 PDR: 36 – 49	Retinopathy is a recognized comorbidity of neuropathy (Papanas and Ziegler 2015)	Bailey and Sparrow 2001, Rubino et al 2007, Venkatesh et al 2014, Park et al 2017
Proteinuria	Any DR: 24 – 68 NPDR: 22 – 64 PDR: 30 – 74	Nephropathy and proteinuria are associated with increased risk of DR in diabetes patients; prevalence increases with DR severity	Rubino et al 2007, Targher et al 2008, Romero-Aroca et al 2011, Salinero-Fort et al 2013, Park et al 2017, Shah et al 2018
Chronic kidney disease	Any DR: 9 – 32 NPDR: 13 – 30 PDR: 14 – 41	DR is positively associated with chronic kidney disease and high urine albumin-to-creatinine ratio	Bailey and Sparrow 2001, Venkatesh et al 2014, Rodriguez-Poncelas et al 2015, Park et al 2017, Shah et al 2018
Myocardial infarction	Any DR: 5 – 10 PDR: 0 – 11	Meta-analysis: persons with PDR or DME are more likely to have incident CVD (IRR=1.39; 95%CI 1.16-1.67) and fatal CVD (IRR=2.33; 95%CI 1.49-3.67) compared with those without PDR or DME (Xie et al 2017) In 3,433 T2DM patients, risk of incident MI increased by 40% (HR=1.40, 95%CI 1.08–1.80) for every change in DR category severity (Gerstein et al 2013)	Bailey and Sparrow 2001, Salinero-Fort et al 2013, Lamparter et al 2014, Park et al 2017
Stroke or transient ischemic attack	Any DR: 4 – 9 NPDR: 4 – 14 PDR: 8 – 15	DR is associated with increased risk of stroke in both T2DM (Cheung et al 2007) and T1DM patients (Hagg et al 2013). Meta-analysis: patients with DR are at increased risk of stroke (HR=1.74; 95%CI 1.35–2.24) compared to diabetes patients without DR (Zhu et al 2017).	Bailey and Sparrow 2001, Salinero-Fort et al 2013, Lamparter et al 2014, Venkatesh et al 2014, Park et al 2017

Comorbidity	Prevalence, %	Comments	References
Source: Orcutt et al 2004, Tan et al 2007a, Esteves et al 2008, Chen et al 2008, Zghal-Mokni et al 2008, Saaddine et al 2008, Jeganathan et al 2008, Bailey and Sparrow 2001, Rubino et al 2007, Romero-Aroca et al 2011, Cheung et al 2007, Hagg et al 2013, Xie et al 2017, Lamparter et al 2014, Rodriguez-Poncelas et al 2015, Salinero-Fort et al 2013, Targher et al 2008, Gerstein et al 2013, Papanas and Ziegler 2015, Park et al 2017, Shah et al 2018, Venkatesh et al 2014, Zhu et al 2017			

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key Safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity: • Key issues identified from acute or repeat-dose toxicity studies Bilateral IVT administration of ranibizumab to cynomolgus monkeys at doses between 0.25 mg/eye and 2.0 mg/eye once every two weeks for up to 26 weeks resulted in dose-dependent ocular effects. Intraocularly, there were dose-dependent increases in anterior chamber flare and cells with a peak two days after injection. The severity of the inflammatory response generally diminished with subsequent injections or during recovery. In the posterior segment, there were vitreal cell infiltration and floaters, which also tended to be dose-dependent and generally persisted to the end of the treatment period. In the 26-week study, the severity of the vitreous inflammation increased with the number of injections. However, evidence of reversibility was observed after recovery. The nature and timing of the posterior segment inflammation is suggestive of an immune-mediated antibody response to a humanized protein, which may be clinically irrelevant. Cataract formation was observed in some animals after a relatively long period of intense inflammation, suggesting that the lens changes were secondary to severe inflammation. A transient increase in post-dose intraocular pressure was observed following intravitreal injections, irrespective of dose. Microscopic ocular changes were related to inflammation and did not indicate degenerative processes. Granulomatous inflammatory changes were noted in the optic disc of some eyes. These posterior segment changes diminished, and in some instances resolved, during the recovery period. Following IVT administration, no signs of systemic toxicity were detected. Serum and vitreous antibodies to ranibizumab were found in a subset of treated animals.	Intraocular inflammation and transient increases in intraocular pressure are identified risks following IVT administration of ranibizumab. These events are followed in the RMP, the periodic safety update report (PSUR) and are also included in Section 4.4 'Special warnings and precautions for use' in the ranibizumab Summary of Product Characteristics (SmPC).
• Reproductive/developmental toxicity The potential of ranibizumab to affect embryo-fetal and/or placental development has been investigated in pregnant cynomolgus monkeys given bilateral IVT injections of ranibizumab every 14 days. Due to restrictions dictated by the IVT route of administration the doses used (up to 1.0 mg/eye) did not allow to reach maternal toxicity but only a multiple with respect to human systemic exposure. Under these conditions, ranibizumab treatment did not elicit developmental toxicity or teratogenicity, and had no effect on weight or structure of the placenta.	For ranibizumab no clinical data on exposed pregnancies are available. The systemic exposure to ranibizumab is low after ocular administration, but due to its mechanism of action, ranibizumab must be regarded as potentially teratogenic and embryo-/fetotoxic. Studies in cynomolgus monkeys do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/foetal development. As the embryo-fetal development investigations were performed in healthy pregnant animals and disease (such as e.g. diabetes) may modify the permeability of the placenta towards a Fab fragment, ranibizumab should be used with caution in women of childbearing potential in general, and during pregnancy, in particular. In the SmPC Section 4.6 'Fertility, pregnancy and

Key Safety findings (from non-clinical studies)	Relevance to human usage
	lactation' it is stated that women of childbearing potential should use effective contraception during treatment and that, for women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

For the assessment of safety concerns in adult patients with nAMD, visual impairment due to DME, macular edema secondary to RVO, visual impairment due to CNV secondary to PM, visual impairment due to CNV (other than secondary to PM), and PDR, this section provides an overview on the drug exposure related to the 0.5 mg treatment groups from various studies. In addition, to ensure completeness, an overview of the exposure related to ranibizumab 0.3 mg and 2.0 mg treatment groups is provided. The exposure data included all studies of the RMP and with all adult patients exposed to ranibizumab pooled within each indication, namely the wet AMD (nAMD), DME, RVO, PM, CNV, extended indications and PDR. More details regarding the pooling strategy are described in RMP version 17.0 Attachment to Annex 7 of the EU Safety Risk Management Plan.

For the pediatric ROP indication, this section provides drug exposure in patients who received ranibizumab 0.1 mg and 0.2 mg in the study H2301 (See RMP version 18.0 Attachment to Annex 7).

Estimated cumulative exposure to ranibizumab by indication is presented by age and gender in Table 4-1, and by race in Table 4-2.

Table 4-1 Estimated cumulative subject exposure to ranibizumab by age and gender (Safety population)

		Male		Female		Total	
Indication	**Age Group (years – except for ROP as gestation age in weeks)***	**Subjects n (%)**	**No of Injections (% total)**	**Subjects n (%)**	**No of Injections (% total)**	**Subjects n (%)**	**No of Injections (% total)**
nAMD	<50	1 (0.02%)	2 (0.005%)	3 (0.05%)	8 (0.01%)	4 (0.04%)	10 (0.01%)
	50 - <65	490 (11.2%)	5444 (12.7%)	461 (7.8%)	4698 (8.7%)	951 (9.3%)	10142 (10.5%)
	65 - <75	1266 (28.9%)	12767 (29.7%)	1332 (22.7%)	13369 (24.8%)	2598 (25.3%)	26136 (27.0%)
	75 - <85	2031 (46.4%)	19783 (46.0%)	2856 (48.6%)	25990 (48.2%)	4887 (47.7%)	45773 (47.2%)
	>=85	587 (13.4%)	4991 (11.6%)	1228 (20.9%)	9832 (18.2%)	1815 (17.7%)	14823 (15.3%)
	Mean Age (SD)	75.6 (8.45)	-	77.7 (8.37)	-	76.8 (8.46)	-
	Total	4375 (100%)	42987 (100%)	5880 (100%)	53897 (100%)	10255 (100%)	96884 (100%)
DME	<55	254 (22.3%)	4283 (21.1%)	152 (17.1%)	2653 (17.7%)	406 (20.0%)	6936 (19.7%)
	55 - <65	407 (35.7%)	7190 (35.5%)	384 (43.3%)	6266 (41.7%)	791 (39.0%)	13456 (38.2%)
	65 - <75	383 (33.6%)	6845 (33.8%)	266 (30.0%)	4887 (32.5%)	649 (32.0%)	11732 (33.3%)
	>=75	96 (8.4%)	1933 (9.5%)	85 (9.6%)	1213 (8.1%)	181 (8.9%)	3146 (8.9%)
	Mean Age (SD)	61.7 (9.90)	-	62.4 (9.48)	-	62.0 (9.72)	-
	Total	1140 (100%)	20251 (100%)	887 (100%)	15019 (100%)	2027 (100%)	35270 (100%)
RVO	<55	309 (24.6%)	2751 (21.7%)	184 (18.2%)	1503 (14.7%)	493 (21.7%)	4254 (18.5%)
	55 - <65	380 (30.2%)	3782 (29.8%)	275 (27.2%)	2666 (26.0%)	655 (28.9%)	6448 (28.1%)
	65 - <75	316 (25.1%)	3430 (27.0%)	304 (30.0%)	3326 (32.4%)	620 (27.3%)	6756 (29.5%)
	>=75	250 (19.9%)	2710 (21.4%)	249 (24.6%)	2756 (26.9%)	499 (22.0%)	5466 (23.8%)
	Unknown**	2 (0.2%)	14 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	14 (0.1%)
	Mean Age (SD)	62.8 (12.78)	-	65.8 (12.05)	-	64.1 (12.54)	-
	Total	1257 (100%)	12687 (100%)	1012 (100%)	10251 (100%)	2269 (100%)	22938 (100%)
PM	<45	74 (36.1%)	275 (36.8%)	99 (19.8%)	349 (16.9%)	173 (24.6%)	624 (22.2%)
	45 - <55	36 (17.6%)	136 (18.2%)	126 (25.3%)	488 (23.6%)	162 (23.0%)	624 (22.2%)
	55 - <65	64 (31.2%)	242 (32.4%)	167 (33.5%)	748 (36.2%)	231 (32.8%)	990 (35.2%)
	65 - <75	25 (12.2%)	71 (9.5%)	92 (18.4%)	425 (20.6%)	117 (16.6%)	496 (17.6%)
	>=75	6 (2.9%)	23 (3.1%)	15 (3.0%)	54 (2.6%)	21 (3.0%)	77 (2.7%)

		Male		Female		Total	
Indication	**Age Group (years – except for ROP as gestation age in weeks)***	**Subjects n (%)**	**No of Injections (% total)**	**Subjects n (%)**	**No of Injections (% total)**	**Subjects n (%)**	**No of Injections (% total)**
	Mean Age (SD)	50.4 (14.02)	-	54.3 (12.52)	-	53.1 (13.09)	-
	Total	205 (100%)	747 (100%)	499 (100%)	2064 (100%)	704 (100%)	2811 (100%)
CNV	<18	1 (1.1%)	2 (0.3%)	4 (4.5%)	17 (3.5%)	5 (2.8%)	19 (1.8%)
	18 - <45	24 (27.6%)	107 (18.4%)	26 (29.2%)	93 (19.4%)	50 (28.4%)	200 (18.9%)
	45 - <55	22 (25.3%)	154 (26.5%)	17 (19.1%)	97 (20.2%)	39 (22.2%)	251 (23.7%)
	55 - <65	15 (17.2%)	106 (18.2%)	14 (15.7%)	84 (17.5%)	29 (16.5%)	190 (17.9%)
	65 - <75	18 (20.7%)	150 (25.8%)	17 (19.1%)	117 (24.4%)	35 (19.9%)	267 (25.2%)
	>=75	7 (8.0%)	62 (10.7%)	11 (12.4%)	72 (15.0%)	18 (10.2%)	134 (12.6%)
	Mean Age (SD)	53.3 (15.05)	-	52.7 (18.55)	-	53.0 (16.87)	-
	Total	87 (100%)	581 (100%)	89 (100%)	480 (100%)	176 (100%)	1061 (100%)
Extended indications	<18	1 (0.9%)	12 (1.6%)	2 (2.9%)	22 (4.6%)	3 (1.7%)	34 (2.8%)
	18 - <45	16 (14.7%)	109 (14.8%)	4 (5.8%)	25 (5.2%)	20 (11.2%)	134 (11.0%)
	45 - <55	21 (19.3%)	152 (20.7%)	8 (11.6%)	41 (8.6%)	29 (16.3%)	193 (15.9%)
	55 - <65	22 (20.2%)	201 (27.3%)	18 (26.1%)	145 (30.4%)	40 (22.5%)	346 (28.5%)
	65 - <75	29 (26.6%)	152 (20.7%)	15 (21.7%)	110 (23.1%)	44 (24.7%)	262 (21.6%)
	>=75	20 (18.3%)	110 (14.9%)	22 (31.9%)	134 (28.1%)	42 (23.6%)	244 (20.1%)
	Mean Age (SD)	60.4 (15.55)	-	64.5 (15.82)	-	62.0 (15.74)	-
	Total	109 (100%)	736 (100%)	69 (100%)	477 (100%)	178 (100%)	1213 (100%)
ROP	≤24	32 (42.1%)	72 (38.9%)	31 (36.0%)	84 (39.6%)	63 (38.9%)	156 (39.3%)
	>24 - <27	20 (26.3%)	51 (27.6%)	21 (24.4%)	45 (21.2%)	41 (25.3%)	96 (24.2%)
	≥27	24 (31.6%)	62 (33.5%)	34 (39.5%)	83 (39.2%)	58 (35.8%)	145 (36.5%)
	Mean Age (SD)	25.6 (2.13)	-	26.3 (2.60)	-	26.0 (2.40)	-
	Total	76 (100%)	185 (100%)	86 (100%)	212 (100%)	162 (100%)	397 (100%)
PDR	<65	100 (92.6%)	1103 (92.8%)	73 (88.0%)	699 (88.0%)	173 (90.6%)	1802 (90.9%)
	≥65	8 (7.4%)	86 (7.2%)	10 (12.0%)	95 (12.0%)	18 (9.4%)	181 (9.1%)
	Mean Age (SD)	49.8 (10.79)	-	51.3 (12.34)	-	50.4 (11.48)	-
	Total	108 (100%)	1189 (100%)	83 (100%)	794 (100%)	191 (100%)	1983 (100%)

		Male		Female		Total	
Indication	**Age Group (years – except for ROP as gestation age in weeks)***	**Subjects n (%)**	**No of Injections (% total)**	**Subjects n (%)**	**No of Injections (% total)**	**Subjects n (%)**	**No of Injections (% total)**

* Age is presented in years for the all indications except ROP. For indication, ROP, age is presented as gestational age at birth in weeks. Age is unknown for 2 subjects from RVO Indication and these subjects received 14 injections.

Source: PSUR (review period 06-Oct-2020 to 05-Oct-2021), RMP version 17.0 Attachment to Annex 7 Table 6-2, RMP version 18.0 Attachment to Annex 7 Table 2-2, Table 2-3, RMP v 20.0 Attachment to Annex 7 Table 8-2-1

Table 4-2 Estimated cumulative subject exposure to ranibizumab by race (Safety population)

Indication	Race	Subjects n (%)	No of Injections (% total)
nAMD	Asian	790 (7.7%)	9688 (10.0%)
	Black	23 (0.2%)	191 (0.2%)
	Caucasian	9246 (90.2%)	85360 (88.1%)
	Other	187 (1.8%)	1497 (1.5%)
	Unknown	9 (0.1%)	148 (0.2%)
	Total	10255 (100%)	96884 (100%)
DME	Asian	613 (30.2%)	5254 (14.9%)
	Black	89 (4.4%)	2358 (6.7%)
	Caucasian	1280 (63.1%)	26658 (75.6%)
	Other	28 (1.4%)	475 (1.3%)
	Unknown	17 (0.8%)	525 (1.5%)
	Total	2027 (100%)	35270 (100%)
RVO	Asian	575 (25.3%)	4051 (17.7%)
	Black	96 (4.2%)	999 (4.4%)
	Caucasian	1525 (67.2%)	17090 (74.5%)
	Other	31 (1.4%)	346 (1.5%)
	Unknown	42 (1.9%)	452 (2.0%)
	Total	2269 (100%)	22938 (100%)
PM	Asian	550 (78.1%)	2170 (77.2%)
	Caucasian	153 (21.7%)	639 (22.7%)
	Other	1 (0.1%)	2 (0.1%)
	Total	704 (100%)	2811 (100%)
CNV	Asian	11 (6.3%)	27 (2.5%)
	Black	1 (0.6%)	5 (0.5%)
	Caucasian	157 (89.2%)	968 (91.2%)
	Other	7 (4.0%)	61 (5.7%)
	Total	176 (100%)	1061 (100%)
Extended indications	Asian	17 (9.6%)	99 (8.2%)
	Black	2 (1.1%)	11 (0.9%)
	Caucasian	157 (88.2%)	1088 (89.7%)
	Other	2 (1.1%)	15 (1.2%)
	Total	178 (100%)	1213 (100%)
Total (Adults)	Asian	2925 (18.2%)	23471 (14.4%)
	Black	216 (1.3%)	3576 (2.2%)
	Caucasian	12616 (78.4%)	132042 (81.2%)
	Other	266 (1.7%)	2418 (1.5%)
	Unknown	68 (0.4%)	1125 (0.7%)
	Total	16091 (100%)	162632 (100%)
ROP	Asian	49 (30.2%)	124 (31.2%)
	Black	5 (3.1%)	12 (3.0%)
	Caucasian	98 (60.5%)	239 (60.2%)
	Other	10 (6.2%)	22 (5.5%)

Indication	Race	Subjects n (%)	No of Injections (% total)
	Total	162 (100%)	397 (100%)
PDR	Asian	2 (1.0%)	21 (1.1%)
	Black	40 (20.9%)	402 (20.3%)
	Caucasian	135 (70.7%)	1397 (70.4%)
	Other	2 (1.0%)	27 (1.4%)
	Unknown	12 (6.3%)	136 (6.9%)
	Total	191 (100%)	1983 (100%)

Source: PSUR (review period 06-Oct-2020 to 05-Oct-2021), RMP version 17.0 Attachment to Annex 7 - Table 6-4, RMP version 18.0 Attachment to Annex 7 Table 2-5, RMP v 20.0 Attachment to Annex 7 Table 8-4-1

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
1 Active intraocular inflammation	There is a risk of worsening of an ongoing inflammatory process, or masking inflammation due to another cause. In addition, active intraocular inflammation may be associated with an increased intraocular pressure (IOP); administering an intraocular injection when there is ongoing inflammation is contraindicated.	No	Active severe intraocular or inflammation is a contraindication
2 Active or suspected ocular or periocular infections.	Procedure of intravitreal injection could potentially increase the chance of contamination of the intraocular structures and decrease visual outcome	No	Active or suspected ocular or periocular infections is a contraindication
3 Known hypersensitivity to ranibizumab or any component of the ranibizumab formulation.	Hypersensitivity to ranibizumab would potentially elicit a severe reaction. Although allergic reactions such as rash, urticaria, pruritus and erythema have been seen following treatment with ranibizumab, there are a number of concurrently administered agents during the injection procedure which could also be the cause of a hypersensitivity reaction (e.g. topical anesthetics or antibiotics, dilating drops such as phenylephrine, or rarely, povidone-iodine)	No	Hypersensitivity to ranibizumab or any component of the excipients listed in the prescribing information is a contraindication
4 Concurrent systemic conditions (e.g. active systemic infection)	A systemic infection could spread into the eye through hematogenous circulation, and confound study results. Also, the presence of systemic infection may put the patient at higher risk for	No	Precaution in a clinical trial setting

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	infection related to the intraocular injection.		
5 Concurrent ocular conditions (e.g. macular hole)	A patient's macular hole may cause a decline in VA, an important endpoint for safety and efficacy of an intervention for intraocular use. Therefore, the presence of a macular hole could confound efficacy outcomes.	No	Patients with stage 3 or 4 macular hole included in precautions and warnings for use
6 Received or had prior treatments (e.g. verteporfin photodynamic therapy (PDT), anti-angiogenic drugs, anticoagulants, corticosteroids)	Precautionary measure. Use of these agents could interfere with interpretation of the clinical outcomes.	No	Aim of studies to study ranibizumab in previously untreated eyes/patients
7 Lesion characteristics (e.g. subretinal hemorrhage in the study eye involving the fovea, with a size of either > 50% of the total lesion or > 1 disc area).	Large subretinal hemorrhage can confound the assessment of the extent and size of the neovascular lesion that needs treatment.	No	Not to include patient with disease features that would confound or make the results difficult to interpret
8 Atrophy of the retinal pigment epithelium (RPE), subretinal fibrosis, laser scar(s) or organized hard exudates plaques	These anatomic characteristics are representative of pre-existing pathology, which make interpretation of patient data obtained during a clinical trial difficult and may confound study results.	No	Exclude patient with preexisting pathology from late stage disease where ranibizumab is unlikely to have an effect
9 Neovascularization of the iris in the study eye, vitreous hemorrhage, traction retinal detachment or preretinal fibrosis involving the macula in the study eye	Precautionary measure. These anatomic characteristics are representative of pre-existing pathology, which make interpretation of patient data obtained during a clinical trial difficult and may confound study results.	No	In a study setting exclude patients with pre-existing pathology, which make interpretation of patient data obtained during a clinical trial difficult and may confound study results.
10 Poor glycemic control or systolic blood pressure > 150 mmHg or diastolic blood pressure > 90 mmHg	Systemic conditions such as uncontrolled diabetes or hypertension are serious risks impacting the patient's overall health. When the patient is undergoing treatment for serious systemic conditions, study participation and required follow up visits may be difficult to make. In addition, poor glycemic control is correlated with worsening	No	In a clinical trial setting exclude patients with poor control of common diseases/condition that may impact overall health and their ability to meet the requirements for study visits and assessments.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	DR and may confound the results.		
11 History of vitreoretinal surgery in the study eye	Vitreoretinal surgery is associated with the removal of the vitreous gel; thus, it may influence the pharmacodynamics of an intraocular pharmacological treatment. Precautionary measure due to limited data in patients with vitrectomized eyes.	No	To not introduce confounding factors for interpretation of study results
12 Presence of confirmed IOP > 25 mmHg for any reason in either eye at the time of enrollment or uncontrolled glaucoma (defined as intraocular pressure [IOP] ≥ 30 mmHg despite treatment with antiglaucoma medication) or previous filtration surgery in the study eye	Precautionary measure. Increased IOP and uncontrolled glaucoma is a general contraindication to any invasive intraocular procedure due to known possible associated complications.	No	Injection of additional volume to the vitreous in patients with increased IOP or uncontrolled glaucoma should generally be avoided to avoid consequences of additional raised IOP including a temporary increase associated with the procedure.
13 History of cerebral vascular accident or myocardial infarction within 3 months	Precautionary measure based on effects which have been identified following intravenous administration of VEGF inhibitors	No	Precautionary measure in clinical trial setting for patients with a recent event of cerebral vascular accident or myocardial infarction
14 Renal failure requiring dialysis or renal transplant	Precautionary measure due to limited pharmacokinetic data available	No	In a clinical trial setting, precautionary measure due to limited pharmacokinetic data available Information included in the prescribing information regarding special populations
15 Brisk afferent pupillary defect	The occurrence of this ocular sign indicates vision loss is due to causes other than macular edema or CNV, such as severe, extensive retina disease or optic nerve pathology.	No	In clinical trial setting exclude patients where vision loss is likely due to other causes that those condition under study
16 History of radial optic neurotomy or sheathotomy	Radial optic neurotomy is a surgical procedure that has been used for the treatment of CRVO. Similarly, sheathotomy is a procedure that has been used for the treatment of BRVO. Previous history of either BRVO or CRVO and residual anatomic	No	To not introduce confounding factors for interpretation of study results

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	or functional impact from the ocular disease or surgical complication would confound study results.		
17 History of malignancy of any organ system (other than localized basal or squamous cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.	Precautionary measure implemented in most non-oncology investigational studies	No	Standard exclusion in clinical trials

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

Table 5-2 Limitations of Adverse drug reaction (ADR) detection common to clinical trial development programs

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are very rare	Adult populations (nAMD, CNV, DME, RVO): Approximately 16,091 patients were exposed in interventional clinical trials up to 05-Oct-2021. Pediatric population (ROP): 162 patients, including those who were intiially randomized to laser therapy, were exposed to ranibizumab in the pivotal RAINBOW study (H2301)	Adult populations (nAMD, CNV, DME, RVO): In addition to the patients having been exposed in the clinical trial (CT) program up to 05-Oct-2021, more than 8.2 million patient years have been exposed to marketed ranibizumab (PSUR, review period 06-Oct-2020 to 05-Oct-2021), greatly increasing the probability that rare adverse reactions would have been detected in the years the product has been studied. Pediatric population (ROP): The overall ADR profile for the ROP population is considered to be consistent with the well-established ADR profile for adult indications. No new ADRs specific to the ROP population have been identified. Due to the number of patients treated in Study H2301, consistency of incidence rates of listed ADRs in the adult population and those observed in Study H2301 could not be conclusively evaluated. Hence, no ROP specific incidence rates based upon data from Study H2301 will be provided, and the same frequency categories are applicable for ADRs in pediatrics as in adults.

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Due to prolonged exposure	Adult populations (nAMD, CNV, DME, RVO): The duration of key pivotal studies in the approved indications generally did not exceed two years. However, a 3-year exposure has been completed for the RESTORE extension study and 5-year exposure for RISE and RIDE studies in DME. EXTEND I study for nAMD had a total of three years exposure reported. The data from these studies are included in this current RMP.	Adult populations (nAMD, CNV, DME, RVO): Data collected to date do not suggest an adverse effect of long-term exposure, and some patients have been exposed for more than five years to marketed ranibizumab. In addition, there are three-year and five-year safety data from RISE and RIDE studies in patients with DME, two-year data from the CRYSTAL and BRIGHTER studies in patients with RVO, and the LUMINOUS study included patients exposed for up to five years. These longer duration studies support the finding of no adverse effects with long-term exposure.
	Pediatric population (ROP): The clinical safety of ranibizumab in preterm infants with ROP has been assessed based on the 24-week data of the pivotal RAINBOW study (H2301)	Pediatric population (ROP): The long-term safety of ranibizumab for the treatment of infants born prematurely with ROP has been evaluated in the open-label extension study H2301E1 where safety and efficacy data were collected up to the age of five.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-3 presents an overview of special populations in the pre-authorization clinical development program.

Table 5-3 Exposure of special populations included or not in the clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Clinical trial exposure data on ethnicity is presented in to Table 4-4
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Pediatric population	Clinical trial exposure data in the pediatric population is presented in Table 4-5

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

The estimate of patient exposure was calculated in patient-years, based on the number of ranibizumab vials and PFS sold worldwide. Vials and PFS are designed for single use and hence it may be assumed that each vial represents one injection to one patient. Based on market research into prescribers' dosing behavior, the average number of vials/PFS used per patient per year is six. This may vary for different indications and regions (e.g. in the US, the regimen is monthly and outside the US, it is pro re nata (PRN)).

The number of vials of ranibizumab sold in the United States (US) was provided by Genentech-Roche and those sold in Europe and most of the world (MOW) was provided by Novartis.

6.1.2 Part II Module SV.1.2. Exposure

Table 6-1 Cumulative sales and exposure from marketing experience

		EEA*	USA	Canada	Japan	MOW	Total
Lucentis vials	**# of vials**	7,132,731	8,763,717	1,697,788	698,227	8,961,278	**27,253,740**
	PTY	1,188,788	1,460,620	282,965	116,371	1,493,546	**4,542,290**
Accentrix/Patizra vials**	**# of vials**	-	-	-	-	497,429	**497,429**
	PTY	-	-	-	-	82,905	**82,905**
Lucentis PFS	**# of PFS**	9,962,779	5,034,296	1,036,401	1,028,238	4,382,190	**21,443,904**
	PTY	1,660,463	839,049	172,734	171,373	730,365	**3,573,984**
Total ranibizumab	**# of units**	17,095,510	13,798,013	2,734,189	1,726,465	13,840,898	**49,195,074**
	PTY	2,849,252	2,299,669	455,698	287,744	2,306,816	**8,199,179**

This table includes cumulative data obtained from International birth date (IBD; 30-Jun-2006) through 30-Sep-2021.

*EEA consists of 27 EU member states, Iceland, Norway and Switzerland. The EEA exposure data no longer includes data from the UK.

**Brandnames for ranibizumab in emerging markets

Source of data: NPMR (Novartis Product Margin Reporting) P79

Table 6-2 Cumulative exposure from marketing experience in the European Economic Area

	Ranibizumab Vials	PTY	Ranibizumab PFS	PTY	Ranibizumab Total	Total PTY
Austria	75,486	12,581	206	34	75,692	**12,615**
Belgium	222,191	37,032	542,408	904,01	764,599	**127,433**
Bulgaria	121	20	-	-	121	**20**
Croatia	1,844	307	3,621	604	5,465	**911**
Cyprus	2,099	350	944	157	3,043	**507**
CzechRepublic	46,573	7,762	118,824	19,804	165,397	**27,566**
Denmark	192,522	32,087	48,881	8,147	241,403	**40,234**

	Ranibizumab Vials	PTY	Ranibizumab PFS	PTY	Ranibizumab Total	Total PTY
Estonia	3,089	515	-	-	3,089	**515**
Finland	13,135	2,189	2,977	496	16,112	**2,685**
France	2,248,380	374,730	3,879,424	646,571	612,7804	**1,021,301**
Germany	1,876,315	312,719	2,482,268	413,711	4,358,583	**726,431**
Greece	209,652	34,942	124,027	20,671	333,679	**55,613**
Hungary	37,480	6,247	-	-	37,480	**6,247**
Iceland	995	166	17	3	1,012	**169**
Ireland	49,288	8,215	118,693	19,782	167,981	**27,997**
Italy	497,456	82,909	778,879	129,813	1,276,335	**212,723**
Latvia	2,437	406	-	-	2,437	**406**
Liechtenstein**	NA	NA	NA	-	-	**-**
Lithuania	27,753	4,626	-	-	27,753	**4,626**
Luxembourg	18,008	3,001	33,661	5,610	51,669	**8,611**
Malta	130	22	284	47	414	**69**
Netherlands	176,455	29,409	148,836	24,806	325,291	**54,215**
Norway	51,450	8,575	630	105	52,080	**8,680**
Poland	137,390	22,898	557	93	137,947	**22,991**
Portugal	89,147	14,858	59,862	9,977	149,009	**24,835**
Romania	-	-	-	-	-	**-**
Slovakia	82,732	13,789	111,643	18,607	194,375	**32,396**
Slovenia	14,981	2,497	89,471	14,912	104,452	**17,409**
Spain	543,503	90,584	781,347	130,225	1,324,850	**220,808**
Sweden	151,106	25,184	142,212	23,702	293,318	**48,886**
Switzerland	361,011	60,169	493,107	82,185	854,118	**142,353**

*EEA consists of 27 EU member states, Iceland, Norway and Switzerland. The EEA exposure data no longer includes data from the UK.

**Liechtenstein sales data are included in Swiss sales data and are presented within MOW (Most of the World).

This table includes cumulative data obtained from IBD (30-Jun-2006) through 30-Sep-2021.

Source of data: NPMR (Novartis Product Margin Reporting) P79

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

Based on the mechanism of action of ranibizumab, there is no indication to suggest a potential for abuse or dependence.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

This section is not applicable, the RMP was already approved.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

The description of changes since the last updated RMP v21.0 are presented in Table 8-1.

Table 8-1 Description of changes done in the list of safety concerns since the RMP version 21.0

Safety concerns	Previous Classification	Reclassification or Removed	Rationale
Long term safety of ranibizumab in the condition ROP	Missing information	Removed from the RMP	The long-term safety of ranibizumab for the treatment of infants born prematurely with ROP has been evaluated in the open-label extension study H2301E1 where safety and efficacy data were collected up to the age of five. Based on the final analysis for study H2301E1, ranibizumab 0.2 mg was noted to be safe and well-tolerated in patients with ROP up to 5 years of post-treatment observation. The long-term safety profile of ranibizumab 0.2 mg was in line with safety data from the core study H2301, with no new safety signals observed. Results from the extension study demonstrate that the long-term efficacy and safety of ranibizumab 0.2 mg are comparable with the favorable benefit-risk profile that was established in the core study.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risks and important potential risks are presented separately for indications in adults (nAMD, CNV, DME, RVO and PDR) and pediatric patients (ROP indication). In ROP patients, retinal detachment is associated with advanced stages of the disease and can be prevented by treatment of ROP. Though considered medically unrelated to IVT treatment with ranibizumab, events of retinal detachment are presented in this section also for the ROP population. There are no potential risks and no non-ocular (systemic) risks for the adult indications.

Clinical trial data and other details of important identified risks and important potential risks are presented in Table 8-2 to Table 8-15. Of note, the events of infectious endophthalimitis, intraocular inflammation and intraocular pressure increased were not observed in the long-term follow-up RAINBOW Extension study in pre-term infants with ROP. The search strategy including MedDRA terms for each risk is presented in attachment to Annex 7 of EU RMP v

17.0 (nAMD, DME, RVO, CNV), Annex 7 of EU RMP v 18.0 (ROP), Annex 7 of EU RMP v 20.0 (PDR), and Annex 7 of EU RMP v 22.0 (ROP).

Table 8-2 Clinical trial data of Important Identified risk: Infectious endophthalmitis (for indications in adults)

Study(ies)	Patients treated for up to	Ranibizumab 0.5mg N	Ranibizumab 0.5mg n (%) (95% CI)	Control Type	Control N	Control n (%) (95% CI)	Relative Risk (95% CI)
Neovascular age-related macular degeneration (nAMD)							
Pooled studies Extend I (Part A+B) (CRFB002A1201), Extend II (CRFB002A2203), Extend III (CRFB002A2304), Mont-Blanc (CBPD952A2309), Denali (CBPD952A2308) and Excite (CRFB002A2302)	1 year	618	3 (0.5) (0.1,1.4)				
Study Extend I extension (Part A + B) (CRFB002A1201E1) combined with corresponding observations from Extend I (CRFB002A1201), Patients enrolled into extension phase	3 years	39	0 (0.0) (0.0,7.4)				
Study Everest (CBPD952A2209)	6 months	21	0 (0.0) (0.0,13.3)				
Study Denali (CBPD952A2308)	2 years	111	2 (1.8) (0.2,6.4)				
Study Epi-Cohort (CRFB002A2401)	2 years	755	1 (0.1) (0.0,0.7)				
Secure (CRFB002A2402)	2 years	234	2 (0.9) (0.1,3.1)				
Pooled studies Marina (FVF2598g), Anchor (FVF2587g) and Pier (FVF3192g)	1 year	440	4 (0.9) (0.2,2.3)	Sham/ PDT	441	0(0.0) (0.0,0.7)	nana
	2 years	440	7 (1.6) (0.6,3.3)	Sham/ PDT	441	0(0.0) (0.0,0.7)	nana
Visual impairment due to DME							
Pooled studies Resolve (Group A+B) (CRFB002D2201), Restore (CRFB002D2301), Reveal (CRB002D2303) and Refine (CRFB002D2305)	1 year	657	4 (0.6) (0.2,1.6)	Sham/ Laser	362	0(0.0) (0.0,0.8)	nana
Pooled studies RESTORE extension (CRFB002D2301E1) combined with 1-year core study for 2 years exposure + RETAIN (CRFB002D2304) PRN and TE treatment arms	2 years	327	0 (0.0) (0.0,0.9)				
Study Restore extension (CRFB002D2301E1)	3 years	83	0 (0.0) (0.0,3.5)				

Study(ies)	Patients treated for up to	Ranibizumab 0.5mg N	Ranibizumab 0.5mg n (%) (95% CI)	Control Type	Control N	Control n (%) (95% CI)	Relative Risk (95% CI)
combined with corresponding observations from Restore (CRFB002D2301) in patients enrolled into Restore extension							
Visual impairment due to macular edema secondary to RVO							
Study CRFB002E2301	3 months	31	0 (0.0) (0.0,9.2)				
Study Camellia (CRFB002E2302)	3 months	190	1 (0.5) (0.0,2.9)	Sham	61	0(0.0) (0.0,4.8)	nana
	1 year	190	1 (0.5) (0.0,2.9)				
Study Blossom (CRFB002E2303)	6 months	190	0 (0.0) (0.0,1.6)	Sham	92	0(0.0) (0.0,3.2)	nana
	1 year	190	0 (0.0) (0.0,1.6)				
Study Crystal (CRFB002E2401)	2 years	357	0 (0.0) (0.0,0.8)				
Study Brighter (CRFB002E2402)	6 months	180	0 (0.0) (0.0,1.7)	Laser	88	0(0.0) (0.0,3.3)	nana
	2 years	180	0 (0.0) (0.0,1.7)				
Pooled studies Bravo (FVF4165g) and Cruise (FVF4166g)	6 months	259	1 (0.4) (0.0,2.1)	Sham	260	0(0.0) (0.0,1.1)	nana
	1 year	259	1 (0.4) (0.0,2.1)				
Visual impairment due to CNV							
Pooled studies Radiance (CRFB002F2301) and Brilliance (CRFB002F2302)	3 months	591	0 (0.0) (0.0,0.5)	vPDT	142	0(0.0) (0.0,2.1)	nana
	1 year	591	0 (0.0) (0.0,0.5)				
Study Minerva (CRFB002G2301)	2 months	119	0 (0.0) (0.0,2.5)	Sham	59	0(0.0) (0.0,5.0)	nana
	6 months	119	0 (0.0) (0.0,2.5)				
	1 year	119	0 (0.0) (0.0,2.5)				
Study Prometheus (CRFB002G2302)	2 months	119	1 (0.8) (0.0,4.6)	Sham	58	0(0.0) (0.0,5.0)	nana
	6 months	119	1 (0.8) (0.0,4.6)				
	1 year	119	1 (0.8) (0.0,4.6)				
PDR							
Study Protocol S (ML27976)	2 year	191	1 (0.5) (0.0,2.9)	PRP*	203	0 (0.0) (0.0,1.5)	na na

Study(ies)	Patients treated for up to	Ranibizumab 0.5mg N	Ranibizumab 0.5mg n (%) (95% CI)	Control Type	Control N	Control n (%) (95% CI)	Relative Risk (95% CI)

* PRP- Panretinal photocoagulation

Multiple occurrences of the same event in a patient were counted only once.

AEs with onset date on/after switch date to ranibizumab for Control patients are excluded from the analysis.

95% CI - for rates: Clopper-Pearson exact method and for RR (relative risk): normal approximation.

Source: Attachment to Annex 7 of RMP v 17.0 Table 7-1., Attachment to Annex 7 of RMP v 20.0 Table 7-2-1

Table 8-3 Clinical trial data of Important Identified risk: Infectious endophthalmitis (for ROP indication in preterm infants)

Study(ies)	Patients treated for up to	Ranibizumab Dose (mg)	Ranibizumab N	Ranibizumab n (%) (95% CI)		Control Type	Control N	Control n (%) (95% CI)		Relative Risk (95% CI)
Retinopathy of Prematurity (ROP)										
Study Rainbow (CRFB002H2301)	24 weeks	0.2	73	0 (0.0)	(0.0,4.0)	Laser	69	0(0.0)	(0.0,4.2)	na na
		0.1	76	1 (1.3)	(0.0,7.1)	Laser	69	0(0.0)	(0.0,4.2)	na na

Multiple occurrences of the same event in a patient were counted only once.

AEs with onset date on/after switch date to ranibizumab for Control patients are excluded from analysis.

95% CI - for rates: Clopper-Pearson exact method and for RR (relative risk): normal approximation.

Source: Attachment to Annex 7 of RMP v18.0, Table 1-1, Table 1-6

Table 8-4 Important Identified risk Infectious endophthalmitis: Other details

Name of the risk: Infectious endophthalmitis	Details
Potential mechanisms	Intravitreous injections, including those with ranibizumab, have been associated with endophthalmitis. Proper aseptic injection techniques must always be used when administering ranibizumab.
Evidence source(s) and strength of evidence	Infectious endophthalmitis can possibly lead to a loss of vision and in sometimes even to the loss of the eye itself.
Characterization of the risk:	Reference is made to the table above.
Risk factors and risk groups	Lucentis is contraindicated in patients with active or suspected ocular or periocular infections or in patients with active severe intraocular inflammation.
Preventability	Proper aseptic injection techniques must always be used when administering ranibizumab. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Adult patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.
Impact on the benefit-risk balance of the product	The reporting rate of infectious endophthalmitis following an intravitreal injection of ranibizumab is low and the benefit-risk balance remains positive for ranibizumab.
Public health impact	The reporting rate of infectious endophthalmitis following an intravitreal injection of ranibizumab for approved indications during post-marketing surveillance is low PSUR 13, review period 06-Oct-2015 to 05-Oct-2016.

Table 8-5 Clinical trial data for Important Identified Risk: Intraocular inflammation (for indications in adults)

		Ranibizumab 0.5mg		Control			
Study(ies)	Patients treated for up to	N	n (%) (95% CI)	Type	N	n (%) (95% CI)	Relative Risk (95% CI)
Neovascular age-related macular degeneration (nAMD)							
Pooled studies Extend I (Part A+B) (CRFB002A1201), Extend II (CRFB002A2203), Extend III (CRFB002A2304), Mont-Blanc (CBPD952A2309), Denali (CBPD952A2308) and Excite (CRFB002A2302)	1 year	618	36 (5.8) (4.1,8.0)				
Study Extend I extension (Part A + B) (CRFB002A1201E1) combined with corresponding observations from Extend I (CRFB002A1201), Patients enrolled into extension phase	3 years	39	0 (0.0) (0.0,7.4)				
Study Everest (CBPD952A2209)	6 months	21	0 (0.0) (0.0,13.3)				
Study Denali (CBPD952A2308)	2 years	111	8 (7.2) (3.2,13.7)				
Study Epi-Cohort (CRFB002A2401)	2 years	755	7 (0.9) (0.4,1.9)				
Secure (CRFB002A2402)	2 years	234	11 (4.7) (2.4,8.3)				
Pooled studies Marina (FVF2598g), Anchor (FVF2587g) and Pier (FVF3192g)	1 year	440	90 (20.5) (16.8,24.5)	Sham/PDT	441	70 (15.9) (12.6,19.6)	1.29 (0.97,1.71)
	2 years	440	111 (25.2) (21.2,29.6)	Sham/ PDT	441	91 (20.6) (17.0,24.7)	1.22 (0.96,1.56)
Visual impairment due to DME							
Pooled studies Resolve (Group A+B) (CRFB002D2201), Restore (CRFB002D2301), Reveal (CRB002D2303) and	1 year	657	10 (1.5) (0.7,2.8)	Sham/ Laser	362	10 (2.8) (1.3,5.0)	0.55 (0.23,1.31)

Study(ies)	Patients treated for up to	Ranibizumab 0.5mg N	Ranibizumab 0.5mg n (%) (95% CI)	Control Type	Control N	Control n (%) (95% CI)	Relative Risk (95% CI)
Refine (CRFB002D2305)							
Pooled studies RESTORE extension (CRFB002D2301E1) combined with 1-year core study for 2 years exposure + RETAIN (CRFB002D2304) PRN and TE treatment arms	2 years	327	9 (2.8) (1.3,5.2)				
Study Restore extension (CRFB002D2301E1) combined with corresponding observations from Restore (CRFB002D2301) in patients enrolled into Restore extension	3 years	83	4 (4.8) (1.3,11.9)				
Visual impairment due to macular edema secondary to RVO							
Study CRFB002E2301	3 months	31	0 (0.0) (0.0,9.2)				
Study Camellia (CRFB002E2302)	3 months	190	7 (3.7) (1.5,7.4)	Sham	61	5 (8.2) (2.7,18.1)	0.45 (0.15,1.36)
	1 year	190	9 (4.7) (2.2,8.8)				
Study Blossom (CRFB002E2303)	6 months	190	1 (0.5) (0.0,2.9)	Sham	92	0 (0.0) (0.0,3.2)	nana
	1 year	190	3 (1.6) (0.3,4.5)				
Study Crystal (CRFB002E2401)	2 years	357	31 (8.7) (6.0,12.1)				
Study Brighter (CRFB002E2402)	6 months	180	7 (3.9) (1.6,7.8)	Laser	88	1 (1.1) (0.0,6.2)	3.42 (0.43,27.39)
	2 years	180	14 (7.8) (4.3,12.7)				
Pooled studies Bravo (FVF4165g) and Cruise (FVF4166g)	6 months	259	19 (7.3) (4.5,11.2)	Sham	260	28 (10.8) (7.3,15.2)	0.68 (0.39,1.19)
	1 year	259	42 (16.2) (11.9,21.3)				

Study(ies)	Patients treated for up to	Ranibizumab 0.5mg N	Ranibizumab 0.5mg n (%) (95% CI)	Control Type	Control N	Control n (%) (95% CI)	Relative Risk (95% CI)
Visual impairment due to CNV							
Pooled studies Radiance (CRFB002F2301) and Brilliance (CRFB002F2302)	3 months	591	4 (0.7) (0.2,1.7)	vPDT	142	1 (0.7) (0.0,3.9)	0.96 (0.11,8.53)
	1 year	591	10 (1.7) (0.8,3.1)				
Study Minerva (CRFB002G2301)	2 months	119	2 (1.7) (0.2,5.9)	Sham	59	2 (3.4) (0.4,11.7)	0.50 (0.07,3.43)
	6 months	119	3 (2.5) (0.5,7.2)				
	1 year	119	3 (2.5) (0.5,7.2)				
Study Prometheus (CRFB002G2302)	2 months	119	8 (6.7) (2.9,12.8)	Sham	58	1 (1.7) (0.0,9.2)	3.90 (0.50,30.44)
	6 months	119	12 (10.1) (5.3,17.0)				
	1 year	119	15 (12.6) (7.2,19.9)				
PDR							
Study Protocol S (ML27976)	2 year	191	0 (0.0) (0.0,1.6)	PRP*	203	3 (1.5) (0.3,4.3)	na na

* PRP- Panretinal photocoagulation

Multiple occurrences of the same event in a patient were counted only once.

AEs with onset date on/after switch date to ranibizumab for Control patients are excluded from the analysis.

95% CI - for rates: Clopper-Pearson exact method and for RR (relative risk): normal approximation.

Source: Attachment to Annex 7 of RMP v 17.0 Table 7-2, Attachment to Annex 7 of RMP v 20.0 Table 7-2-1

Table 8-6 Clinical trial data of Important Identified risk: Intraocular inflammation (for ROP indication in preterm infants)

Study	Patients treated for up to	Ranibizumab Dose (mg)	Ranibizumab N	Ranibizumab n (%) (95% CI)	Control Type	Control N	Control n (%) (95% CI)	Relative Risk (95% CI)
Retinopathy of Prematurity (ROP)								
Study Rainbow (CRFB002H2301)	24 weeks	0.2	73	0 (0.0) (0.0,4.0)	Laser	69	0(0.0) (0.0,4.2)	na na
		0.1	76	1 (1.3) (0.0,7.1)	Laser	69	0(0.0) (0.0,4.2)	na na

Multiple occurrences of the same event in a patient were counted only once.

AEs with onset date on/after switch date to ranibizumab for Control patients are excluded from analysis.

95% CI - for rates: Clopper-Pearson exact method and for RR (relative risk): normal approximation.

Source: Attachment to Annex 7 of RMP v18.0, Table 1-2, Table 1-7

Table 8-7 Important identified risk Intraocular inflammation: Other details

Name of the risk: Intraocular inflammation	Details
Potential mechanisms	Intravitreous injections, including those with ranibizumab, have been associated with intraocular inflammation. Proper aseptic injection techniques must always be used when administering ranibizumab.
Evidence source(s) and strength of evidence	Intraocular inflammation can possibly lead to a loss of vision and in sometimes even to the loss of the eye itself.
Characterization of the risk:	Reference is made to the table above.
Risk factors and risk groups	Proper aseptic injection techniques must always be used when administering ranibizumab.
Preventability	Proper aseptic injection techniques must always be used when administering ranibizumab. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Adult patients should be instructed to report any symptoms suggestive of an intraocular inflammation without delay.
Impact on the benefit-risk balance of the product	The reporting rate of intraocular inflammation following an intravitreal injection of ranibizumab is low and the benefit-risk balance remains positive for ranibizumab.
Public health impact	The reporting rate of intraocular inflammation following an intravitreal injection of ranibizumab for approved indications during post-marketing surveillance is low (PSUR 13, 06-Oct-2015 to 05-Oct-2016).

Table 8-8 Clinical trial data of Important Identified Risk: Retinal Detachment and Retinal Tear (for indication in adults)

		Ranibizumab 0.5mg		Control			
Study(ies)	Patients treated for up to	N	n (%) (95% CI)	Type	N	n (%) (95% CI)	Relative Risk (95% CI)
Neovascular age-related macular degeneration (nAMD)							
Pooled studies Extend I (Part A+B) (CRFB002A1201), Extend II (CRFB002A2203), Extend III (CRFB002A2304), Mont-Blanc (CBPD952A2309), Denali (CBPD952A2308) and Excite (CRFB002A2302)	1 year	618	3 (0.5) (0.1,1.4)				

Study(ies)	Patients treated for up to	Ranibizumab 0.5mg N	Ranibizumab 0.5mg n (%) (95% CI)	Control Type	Control N	Control n (%) (95% CI)	Relative Risk (95% CI)
Study Extend I extension (Part A + B) (CRFB002A1201E1) combined with corresponding observations from Extend I (CRFB002A1201), Patients enrolled into extension phase	3 years	39	5 (12.8) (4.3,27.4)				
Study Everest (CBPD952A2209)	6 months	21	0 (0.0) (0.0,13.3)				
Study Denali (CBPD952A2308)	2 years	111	0 (0.0) (0.0,2.7)				
Study Epi-Cohort (CRFB002A2401)	2 years	755	2 (0.3) (0.0,1.0)				
Secure (CRFB002A2402)	2 years	234	1 (0.4) (0.0,2.4)				
Pooled studies Marina (FVF2598g), Anchor (FVF2587g) and Pier (FVF3192g)	1 year	440	128 (29.1) (24.9,33.6)	Sham/ PDT	441	207 (46.9) (42.2,51.7)	0.62 (0.52,0.74)
	2 years	440	149 (33.9) (29.4,38.5)	Sham/ PDT	441	254 (57.6) (52.8,62.3)	0.59 (0.50,0.69)
Visual impairment due to DME							
Pooled studies Resolve (Group A+B) (CRFB002D2201), Restore (CRFB002D2301), Reveal (CRB002D2303) and Refine (CRFB002D2305)	1 year	657	0 (0.0) (0.0,0.5)	Sham/ Laser	362	1 (0.3) (0.0,1.5)	0.00na
Pooled studies RESTORE extension (CRFB002D2301E1) combined with 1 year core study for 2 years exposure + RETAIN (CRFB002D2304) PRN and TE treatment arms	2 years	327	1 (0.3) (0.0,1.7)				

Study(ies)	Patients treated for up to	Ranibizumab 0.5mg N	Ranibizumab 0.5mg n (%) (95% CI)	Control Type	Control N	Control n (%) (95% CI)	Relative Risk (95% CI)
Study Restore extension (CRFB002D2301E1) combined with corresponding observations from Restore (CRFB002D2301) in patients enrolled into Restore extension	3 years	83	0 (0.0) (0.0,3.5)				
Visual impairment due to macular edema secondary to RVO							
Study CRFB002E2301	3 months	31	0 (0.0) (0.0,9.2)				
Study Camellia (CRFB002E2302)	3 months	190	0 (0.0) (0.0,1.6)	Sham	61	0 (0.0) (0.0,4.8)	nana
	1 year	190	0 (0.0) (0.0,1.6)				
Study Blossom (CRFB002E2303)	6 months	190	0 (0.0) (0.0,1.6)	Sham	92	0 (0.0) (0.0,3.2)	nana
	1 year	190	0 (0.0) (0.0,1.6)				
Study Crystal (CRFB002E2401)	2 years	357	1 (0.3) (0.0,1.6)				
Study Brighter (CRFB002E2402)	6 months	180	0 (0.0) (0.0,1.7)	Laser	88	0 (0.0) (0.0,3.3)	nana
	2 years	180	1 (0.6) (0.0,3.1)				
Pooled studies Bravo (FVF4165g) and Cruise (FVF4166g)	6 months	259	2 (0.8) (0.1,2.8)	Sham	260	2 (0.8) (0.1,2.8)	1.00 (0.14,7.07)
	1 year	259	3 (1.2) (0.2,3.3)				
Visual impairment due to CNV							
Pooled studies Radiance (CRFB002F2301) and Brilliance (CRFB002F2302)	3 months	591	3 (0.5) (0.1,1.5)	vPDT	142	0 (0.0) (0.0,2.1)	nana
	1 year	591	7 (1.2) (0.5,2.4)				
Study Minerva (CRFB002G2301)	2 months	119	0 (0.0) (0.0,2.5)	Sham	59	0 (0.0) (0.0,5.0)	nana
	6 months	119	0 (0.0) (0.0,2.5)				
	1 year	119	0 (0.0) (0.0,2.5)				

Study(ies)	Patients treated for up to	Ranibizumab 0.5mg N	Ranibizumab 0.5mg n (%) (95% CI)	Control Type	Control N	Control n (%) (95% CI)	Relative Risk (95% CI)
Study Prometheus (CRFB002G2302)	2 months	119	0 (0.0) (0.0,2.5)	Sham	58	0 (0.0) (0.0,5.0)	nana
	6 months	119	0 (0.0) (0.0,2.5)				
	1 year	119	0 (0.0) (0.0,2.5)				
PDR							
Study Protocol S (ML27976)	2 year	191	9 (4.7) (2.2, 8.8)	PRP*	203	17 (8.4) (5.0,13.1)	0.6(0.3, 1.2)

* PRP- Panretinal photocoagulation

Multiple occurrences of the same event in a patient were counted only once.

AEs with onset date on/after switch date to ranibizumab for Control patients are excluded from the analysis.

95% CI - for rates: Clopper-Pearson exact method and for RR (relative risk): normal approximation.

Source: Attachment to Annex 7 of RMP v 17.0 Table 7-3, Attachment to Annex 7 of RMP v 20.0 Table 7-2-1

Table 8-9 Clinical trial data of Important Identified risk: Retinal Detachment and Retinal Tear (for ROP indication in preterm infants)*

Study	Patients treated/ observed up to	Ranibizumab Dose (mg)	Ranibizumab N	Ranibizumab n (%) (95% CI)	Control Type	Control N	Control n (%) (95% CI)	Relative Risk (95% CI)
Retinopathy of Prematurity (ROP)								
Study Rainbow (CRFB002H2301)	24 weeks	0.2	73	1 (1.4) (0.0,7.4)	Laser	69	0(0.0) (0.0,4.2)	na na
		0.1	76	0 (0.0) (0.0,3.9)	Laser	69	0(0.0) (0.0,4.2)	na na
Study RAINBOW Extension (CRFB002H2301E1)	Up to the age of five	0.2	61	0 (0.0)	Laser	54	0 (0.0)	na
		0.1	65	2 (3.1)	Laser	54	0 (0.0)	na

Multiple occurrences of the same event in a patient were counted only once.

AEs with onset date on/after switch date to ranibizumab for Control patients are excluded from analysis.

95% CI - for rates: Clopper-Pearson exact method and for RR (relative risk): normal approximation.

Source: Attachment to Annex 7 of RMP v18.0, Table 1-3, Table 1-8; [EU RMP v 22.0 Annex 7, Table 14.3.1-9.1]

*Investigators were instructed to collect retinal detachment as study endpoint and not report these as adverse events. Nevertheless, a single AE of tractional retinal detachment was reported in the ranibizumab 0.2 mg group.

Table 8-10 Important identified risk Retinal Detachment and Retinal Tear: Other details

Name of the risk: Retinal Detachment and Retinal Tear	Details
Potential mechanisms	Rhegmatogenous retinal detachment occurs when the liquefied vitreous enters between the choroid and the pigmented epithelium detaching the retinal layer from the underlying choroid. Traction retinal detachment occurs when scar tissue or other abnormal tissue grows on the surface of the retina, pulling the retina away from the layer beneath it. This does not necessarily cause a specific tear or break in the retina. In patients with advanced stages of ROP, retinal detachment develops when neovascularization progresses and proliferous fibrous and vascular tissue lead to traction at the demarcation zone between vascular and avascular retina often thickened into an ophthalmoscopically visible ridge. Though considered medically unrelated to IVT treatment with ranibizumab, events of retinal detachment are presented in this section also for the ROP population. For the RAINBOW study, investigators were instructed to collect retinal detachment as study endpoint and not report these as adverse events. Nevertheless, a single AE of tractional retinal detachment was reported in the ranibizumab 0.2 mg group. Exudative retinal detachment occurs when blood or fluid from the choroid flows into the space under the retina and separates the retina from the layer beneath it. The detachment does not involve tears in the retina or traction from the vitreous. Exudative retinal detachment is most often a complication of other diseases including macular degeneration, eye tumors, inflammation in the choroid or the retina, or severe high blood pressure.
Evidence source(s) and strength of evidence	Retinal detachment leads to visual distortion, and untreated retinal detachment leads to retinal cell death and loss of vision.
Characterization of the risk	Reference is made to the table above.
Risk factors and risk groups	The following conditions might increase the risk for retinal detachment: previous retinal detachment or retinal tear, eye tumors, inflammation in the choroid or the retina, eye injury, high myopia or severe high blood pressure.
Preventability	In most cases a retinal detachment or retinal tear cannot be prevented. In ROP patients, retinal detachment is associated with advanced stages of the disease and can be prevented by treatment.
Impact on the benefit-risk balance of the product	The reporting rate of retinal detachment and retinal tear following an intravitreal injection of ranibizumab is low and the benefit-risk balance remains positive for ranibizumab.
Public health impact	The reporting rate of retinal detachment and retinal tear following an intravitreal injection of ranibizumab for approved indications in post-marketing surveillance is low (PSUR 13, 06-Oct-2015 to 05-Oct-2016)

Table 8-11 Clinical trial data for Important Identified Risk: Intraocular pressure increase (for indication in adults)

		Ranibizumab 0.5mg		Control			
Study(ies)	Patients treated for up to	N	n (%) (95% CI)	Type	N	n (%) (95% CI)	Relative Risk (95% CI)
Neovascular age-related macular degeneration (nAMD)							
Pooled studies Extend I (Part A+B) (CRFB002A1201), Extend II (CRFB002A2203), Extend III (CRFB002A2304),	1 year	618	49 (7.9) (5.9,10.3)				

Study(ies)	Patients treated for up to	Ranibizumab 0.5mg N	Ranibizumab 0.5mg n (%) (95% CI)	Control Type	Control N	Control n (%) (95% CI)	Relative Risk (95% CI)
Mont-Blanc (CBPD952A2309), Denali (CBPD952A2308) and Excite (CRFB002A2302)							
Study Extend I extension (Part A + B) (CRFB002A1201E1) combined with corresponding observations from Extend I (CRFB002A1201), Patients enrolled into extension phase	3 years	39	4 (10.3) (2.9,24.2)				
Study Everest (CBPD952A2209)	6 months	21	1 (4.8) (0.1,23.8)				
Study Denali (CBPD952A2308)	2 years	111	3 (2.7) (0.6,7.7)				
Study Epi-Cohort (CRFB002A2401)	2 years	755	28 (3.7) (2.5,5.3)				
Secure (CRFB002A2402)	2 years	234	15 (6.4) (3.6,10.4)				
Pooled studies Marina (FVF2598g), Anchor (FVF2587g) and Pier (FVF3192g)	1 year	440	77 (17.5) (14.1,21.4)	Sham/ PDT	441	20 (4.5) (2.8,6.9)	3.86 (2.40,6.20)
	2 years	440	112 (25.5) (21.4,29.8)	Sham/ PDT	441	28 (6.3) (4.3,9.0)	4.01 (2.71,5.94)
Visual impairment due to DME							
Pooled studies Resolve (Group A+B) (CRFB002D2201), Restore (CRFB002D2301), Reveal (CRB002D2303) and Refine (CRFB002D2305)	1 year	657	47 (7.2) (5.3,9.4)	Sham/ Laser	362	1 (0.3) (0.0,1.5)	25.90 (3.59,186.91)
Pooled studies RESTORE extension (CRFB002D2301E1) combined with 1-year core study for 2 years exposure + RETAIN (CRFB002D2304) PRN and TE treatment arms	2 years	327	22 (6.7) (4.3,10.0)				
Study Restore extension (CRFB002D2301E1) combined with corresponding observations from Restore (CRFB002D2301) in patients enrolled into Restore extension	3 years	83	6 (7.2) (2.7,15.1)				

Study(ies)	Patients treated for up to	Ranibizumab 0.5mg N	Ranibizumab 0.5mg n (%) (95% CI)	Control Type	Control N	Control n (%) (95% CI)	Relative Risk (95% CI)
Visual impairment due to macular edema secondary to RVO							
Study CRFB002E2301	3 months	31	3 (9.7) (2.0,25.8)				
Study Camellia (CRFB002E2302)	3 months	190	6 (3.2) (1.2,6.7)	Sham	61	3 (4.9) (1.0,13.7)	0.64 (0.17,2.49)
	1 year	190	10 (5.3) (2.6,9.5)				
Study Blossom (CRFB002E2303)	6 months	190	7 (3.7) (1.5,7.4)	Sham	92	0 (0.0) (0.0,3.2)	nana
	1 year	190	12 (6.3) (3.3,10.8)				
Study Crystal (CRFB002E2401)	2 years	357	61 (17.1) (13.3,21.4)				
Study Brighter (CRFB002E2402)	6 months	180	6 (3.3) (1.2,7.1)	Laser	88	1 (1.1) (0.0,6.2)	2.93 (0.36,23.99)
	2 years	180	20 (11.1) (6.9,16.6)				
Pooled studies Bravo (FVF4165g) and Cruise (FVF4166g)	6 months	259	18 (6.9) (4.2,10.8)	Sham	260	7 (2.7) (1.1,5.5)	2.58 (1.10,6.08)
	1 year	259	28 (10.8) (7.3,15.2)				
Visual impairment due to CNV							
Pooled studies Radiance (CRFB002F2301) and Brilliance (CRFB002F2302)	3 months	591	8 (1.4) (0.6,2.6)	vPDT	142	3 (2.1) (0.4,6.0)	0.64 (0.17,2.38)
	1 year	591	18 (3.0) (1.8,4.8)				
Study Minerva (CRFB002G2301)	2 months	119	2 (1.7) (0.2,5.9)	Sham	59	0 (0.0) (0.0,5.0)	nana
	6 months	119	3 (2.5) (0.5,7.2)				
	1 year	119	4 (3.4) (0.9,8.4)				
Study Prometheus (CRFB002G2302)	2 months	119	1 (0.8) (0.0,4.6)	Sham	58	0 (0.0) (0.0,5.0)	nana
	6 months	119	3 (2.5) (0.5,7.2)				
	1 year	119	6 (5.0) (1.9,10.7)				
PDR							
Study Protocol S (ML27976)	2 year	191	4 (2.1) (0.6, 5.3)	PRP*	203	9 (4.4) (2.0, 8.2)	0.5 (0.1, 1.5)

* PRP- Panretinal photocoagulation

Study(ies)	Patients treated for up to	Ranibizumab 0.5mg N	Ranibizumab 0.5mg n (%) (95% CI)	Control Type	Control N	Control n (%) (95% CI)	Relative Risk (95% CI)

Multiple occurrences of the same event in a patient were counted only once.
AEs with onset date on/after switch date to ranibizumab for Control patients are excluded from the analysis.
95% CI - for rates: Clopper-Pearson exact method and for RR (relative risk): normal approximation.
Source: Attachment to Annex 7 of RMP v 17.0 Table 7-4, Attachment to Annex 7 of RMP v 20.0 Table 7-2-1

Table 8-12 Clinical trial data of Important Identified risk: Intraocular pressure increase (for ROP indication in preterm infants)

Study(ies)	Patients treated for up to	Ranibizumab Dose (mg)	Ranibizumab N	Ranibizumab n (%) (95% CI)	Control Type	Control N	Control n (%) (95% CI)	Relative Risk (95% CI)
Retinopathy of Prematurity (ROP)								
Study Rainbow (CRFB002H2301)	24 weeks	0.2	73	0 (0.0) (0.0,4.0)	Laser	69	0(0.0) (0.0,4.2)	na na
		0.1	76	1 (1.3) (0.0,7.1)	Laser	69	0(0.0) (0.0,4.2)	na na

Multiple occurrences of the same event in a patient were counted only once.
AEs with onset date on/after switch date to ranibizumab for Control patients are excluded from analysis.
95% CI - for rates: Clopper-Pearson exact method and for RR (relative risk): normal approximation.
Source: Attachment to Annex 7 of RMP v18.0, Table 1-4, Table 1-9

Table 8-13 Important identified risk Intraocular pressure increase: Other details

Name of the risk: Intraocular pressure increase	Details
Potential mechanisms	Following an intravitreal injection of ranibizumab, a transient increase in IOP may be anticipated. IOP and perfusion of the optic nerve head should be monitored and managed appropriately.
Evidence source(s) and strength of evidence	The injected volume of ranibizumab may lead to an increase in IOP.
Characterization of the risk	Reference is made to the table above.
Risk factors and risk groups	Pre-existing high IOP; ranibizumab should not be administered in the event of an intraocular pressure of ≥30 mmHg.
Preventability	Adult patients are advised to call their ophthalmologist if they have eye pain or vision loss or other signs or symptoms that may indicate acute increase of IOP following an injection.
Impact on the benefit-risk balance of the product	The reporting rate of increased IOP following an intravitreal injection of ranibizumab has been consistent over the years and this risk is well-characterized. The benefit-risk balance remains positive for ranibizumab.
Public health impact	The reporting rate of IOP increase following an intravitreal injection of ranibizumab for approved indications in the post-marketing section is low (PSUR 13, review period 06-Oct-2015 to 05-Oct-2016).

Table 8-14 Clinical trial data for Important Potential Risk: Neurodevelopmental impairment (ROP)*

Study(ies)	Patients treated/ observed up to	Ranibizumab Dose (mg)	N	n (%) (95% CI)	Control Type	N	n (%) (95% CI)	Relative Risk (95% CI)
Retinopathy of Prematurity (ROP)								
Study Rainbow (CRFB002H2301)	24 weeks	0.2	73	5(6.8) (2.3,15.3)	Laser	69	0(0.0) (0.0,4.2)	na na
		0.1	76	2(2.6) (0.3,9.2)	Laser	69	0(0.0) (0.0,4.2)	na na
Study RAINBOW Extension (CRFB002H2301E1)	Up to the age of five	0.2	61	10 (16.4)	Laser	54	9 (16.7)	na
		0.1	65	6 (9.2)	Laser	54	9 (16.7)	na

Multiple occurrences of the same event in a patient were counted only once.

AEs with onset date on/after switch date to ranibizumab for Control patients are excluded from analysis.

95% CI - for rates: Clopper-Pearson exact method and for RR (relative risk): normal approximation.

Source: Attachment to Annex 7 of RMP v18.0, Table 1-5, Table 1-10; [EU RMP v 22.0 Annex 7, Table 14.3.1-9.2]

* The case retrieval strategy for events of Neurodevelopmental impairment (ROP) includes terms associated with impairments of motor function, cognitive function and language development. In addition, events related to impaired auditory function are included under the risk Neurodevelopmental impairment, as hearing impairments have a cumulative detrimental effect on the acquisition of language skills and learning at school (See RMP v18.0 Attachment to Annex 7). Details on events from Study H2301 that were retrieved for Neurodevelopmental impairment are provided in Table 8-15.

Table 8-15 Important potential risk Neurodevelopmental impairment (ROP): Other details

Name of the risk: Neurodevelopmental impairment (ROP)	Details
Potential mechanisms	Based on non-clinical studies, the VEGF pathway has been implicated in neurodevelopment and neurodegeneration; systemic suppression of VEGF may be a contributing factor affecting neurodevelopmental outcomes (Carmeliet & Ruiz de Almodovar 2013, Malik 2013).
Evidence source(s) and strength of evidence	Higher incidence of cognitive and psychomotor impairment was reported in ROP patients treated off-label with intravitreal anti-VEGF bevacizumab as compared to laser in three studies (Araz-Ersan 2015, Lien 2016, Morin 2016). In contrast to these 3 non-randomized studies, a 2-year follow-up study evaluating 16 infants treated with bevacizumab (n=7) or laser (n=9) from the randomized, controlled BEAT-ROP study reported no adverse effects on neurodevelopmental outcomes at 18-28 months of corrected age (Kennedy and Mintz-Hittner 2018). Another study reported lower, though not statistically significant, incidence of neurodevelopmental delays with intravitreal bevacizumab, compared to laser (Chen et al 2018). Small patient numbers reported in these studies limit the ability to draw conclusions (individual studies included ≤28 patients treated with IVT bevacizumab as monotherapy or in combination with laser). Further, channeling of anti-VEGF treatment to more frail / systemically sick ROP patients in clinical practice, as well as those with Zone 1 / AP-ROP is introducing a potential bias predisposing laser-treated patients towards better long-term outcomes. Neurodevelopmental impairment as a potential long term effect associated with use of ranibizumab has not been studied in preterm infants with ROP.

Name of the risk: Neurodevelopmental impairment (ROP)	Details
	The risk neurodevelopmental impairment includes events associated with impairments of motor function, cognitive function and language development. In addition, events related to impaired auditory function are included, as hearing impairments have a cumulative detrimental effect on the acquisition of language skills and learning at school (Saigal & Doyle 2008). For the Study H2301 (RAINBOW), 5/7 events retrieved for neurodevelopmental impairment were hearing disorders. Birth weight was 700 g or less for all affected patients, and in 4/5 cases patients were born at gestational age of 24 weeks or below. Three of 5 affected patients had CNS bleedings or lesions in their medical history, and an additional patient experienced CNS bleeding at the same day when hearing impairment was first reported. Events of hearing impairment were not suspected by the reporting investigator to be related to treatment with ranibizumab. Hearing impairment is a known complication of prematurity and incidences observed in Study H2301 were close to reported rates (see Section 2.5.6). No evidence for a causal relation to treatment with ranibizumab was derived from medical review, and cases of hearing impairment are not considered an ADR for the ROP indication. In the Study H2301E (RAINBOW Extension study), based on a medical review of all AEs of neuro-/developmental impairment, it was confirmed that these events were predominantly reported in patients born extremely premature, i.e., with an extremely low birth weight ≤1000g, and a history of CNS lesions prior to first treatment at core study baseline. The overall incidence of neurodevelopmental impairment-related terms based on the RMP-based search strategy was balanced between the ranibizumab 0.2 mg and laser treatment arms. A higher number of events of developmental delay and motor developmental delay was reported in the ranibizumab 0.2 mg arm as compared to laser, however, none of the neuro-/developmental impairment AEs were assessed as related to ranibizumab treatment by the investigator. Moreover, the mean gestational age at birth as well as birth weight for the pre-term infants randomized to ranibizumab 0.2 mg (25.8 weeks; 793.2 g) was lower as compared to that for the laser arm (26.4 weeks; 859.4 g).
Characterization of the risk	Reference has been made to above table
Risk factors and risk groups	Presence of other concurrent neurological conditions; neurodevelopmental impairment is an important long-term disability in extremely and very preterm populations. An association of severe ROP was observed for both cognitive and motor impairments in assessments performed at patient ages ranging from 18 months to 18 years (Beligere et al 2015, Glass et al 2017, Molloy et al 2016).
Preventability	Neurodevelopmental impairment associated with preterm birth cannot be prevented.
Impact on the benefit-risk balance of the product	Given the multi-morbidity (due to preterm nature of birth) of the target population, this safety concern has a moderate impact on the benefit-risk balance in this indication.
Public health impact	The impact on public health is expected to be low.

8.3.2 Part II Module SVII.3.2. Presentation of the missing information

Not applicable.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Part II SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Infectious endophthalmitis Intraocular inflammation Retinal detachment and retinal tear Intraocular pressure increase
Important potential risks	Neurodevelopmental impairment (ROP)
Missing information	None

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

10.1.1.1 Specific adverse reaction follow-up questionnaires

Specific AE follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concern specified below:

- Infectious endophthalmitis
- Use of Lucentis in pediatric patients including off-label use

The targeted follow-up checklists are provided in Annex 4.

10.1.1.2 Other forms of routine pharmacovigilance activities

Follow up of case reports: The minimum desired case information for ranibizumab includes the brand name and batch number of the suspect product. Additional efforts must be made to collect this information in accordance with GVP VI.

10.2 Part III.2 Additional pharmacovigilance activities

None

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Not applicable. No additional pharmacovigilance activities are proposed.

11 Part IV: Plans for post-authorization efficacy studies

Table 11-1 Planned and ongoing post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Infectious endophthalmitis	**Routine risk communication:** SmPC Sections 4.2, 4.3, 4.4, 4.8, 6.6. PL Sections 2, 3, 4 Routine risk minimization activities recommending specific clinical measures to minimize the potential to develop infectious endophthalmitis associated with an intravitreal injection in SmPC Section 6.6: To minimize the occurrence of endophthalmitis by providing guidance on how to administer an IVT injection and to inform and educate physicians and patients on prevention and management of this event. Other routine risk minimization measures beyond the Product Information: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR) (Annex 6) to ensure that patients are adequately informed on the key signs and symptoms of infectious endophthalmitis and when to seek urgent attention from the physician. Pack size: one vial or one PFS for single use only. Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.
Intraocular inflammation	**Routine risk communication:** SmPC Sections 4.3, 4.4 PL Section 2, 4 Routine risk minimization activities recommending specific clinical measures to address the risk: none Other routine risk minimization measures beyond the Product Information: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR) (Annex 6) to ensure that patients are adequately informed on the key signs and symptoms of intraocular inflammation and when to seek urgent attention from the physician. Pack size: one vial or one PFS for one injection Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.
Retinal detachment and retinal tear	**Routine risk communication:** SmPC Sections 4.4, 4.8. PL Section 2, 4 Routine risk minimization activities recommending specific clinical measures to address the risk: none Other routine risk minimization measures beyond the Product Information: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR) (Annex 6) to ensure that patients are adequately informed on the key signs and symptoms of retinal detachment and retinal tear and when to seek urgent attention from the physician. Pack size: one vial or one PFS for single use only. Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.

Safety concern	Routine risk minimization activities
Intraocular pressure increase	**Routine risk communication:** SmPC Sections 4.4, 4.8, 4.9. PL Sections 2, 4 Routine risk minimization activities recommending specific clinical measures to address the risk; SmPC Section 4.4: Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately. Other routine risk minimization measures beyond the Product Information: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR) (Annex 6) to ensure that patients are adequately informed on the key signs and symptoms of intraocular pressure increase and when to seek urgent attention from the physician. Pack size: one vial or one PFS for single use only. Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.
Important potential risks	
Neurodevelopmental impairment (ROP)	**Routine risk communication:** SmPC sections: This risk is not mentioned in SmPC PL Sections: This risk is not mentioned in PL Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: None Pack size: one vial Legal status: Prescription only medicine. Ranibizumab must be administered by a qualified ophthalmologist experienced in intravitreal injections.
Missing information	

12.2 Part V.2. Additional Risk minimization measures

Adult patients

Educational plan for adult patients in the indications of nAMD, CNV, DME, RVO and PDR (Annex 6)

Objectives:

To ensure that patients are adequately informed about the potential to develop intraocular pressure increase, intraocular inflammation, retinal detachment and retinal tear and infectious endophthalmitis after an intravitreal injection of ranibizumab, a patient information booklet (also available in spoken form in audio-CD format) was developed. The booklets are provided to the physician for distribution to the patient after ranibizumab is prescribed to them. Similarly, Patient information booklets covering the PDR indication will be provided.

Rationale for the additional risk minimization activity:

The patient information booklets aim to provide adequate patient education on key signs and symptoms of potential adverse reactions and when to seek urgent attention from their physician, ensuring rapid identification and treatment of these events.

Key signs and symptoms of the following identified risks are covered in the patient information booklet:

Infectious Endophthalmitis

- Infectious endophthalmitis is a serious ocular condition, often caused by an intraocular infection, and can potentially lead to blindness.
- Patients need to contact their clinic immediately if they develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision or increased sensitivity to light.

Intraocular Inflammation

- Intraocular inflammation can cause eye pain, worsening eye redness, blurred vision, an increased number of small particles in the patient's vision or increased sensitivity to light.

Retinal detachment and retinal tear

- Warning signs may include symptoms such as increased eye discomfort, light flashes and blurred or decreased vision.

Intraocular pressure increase

- Increases in intraocular pressure (IOP) within 60 minutes of injection of ranibizumab are very common. They may be asymptomatic, or could cause eye pain and decreased vision.

In addition, the booklet contains follow-up recommendations for adequate care after the injection, including recommendations to contact the physician in case of additional questions.

Target audience and planned distribution path:

Patient information packs are prepared nationally, in line with the key important risks defined in the RMP and with each member state's national regulations and legislations. The submission of the material to the respective member state national authorities should take place before the launch of ranibizumab in a new indication (according to the national legislation in the respective countries), and the distribution of the material to all ophthalmology clinics where ranibizumab is expected to be used in adult patients.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Success of the proposed risk minimization measures will be evaluated by the criterion of a consistent spontaneous reporting rate of infectious endophthalmitis, intraocular inflammation, retinal detachment and retinal tear and intraocular pressure increase in adult patients at the time of the PSUR. Educational materials for adult patients have been in place since the launch of ranibizumab, and further studies to assess continued effectiveness are not considered to be required.

Pediatric patients (ROP indication)

No additional risk minimization measures are proposed for the premature infants with ROP. Specifically, no educational materials are proposed to guardians of pediatric patients receiving ranibizumab for the treatment of ROP. Premature infants with ROP will be generally injected with ranibizumab in a clinical setting and relevant ocular risks will be monitored by the treating physician. While Lucentis may be given to a maximum of 3 injections per eye for up to six months from the initial ROP treatment, re-treatments are also expected to occur in a clinical setting and the infants are closely followed up by health care professionals as per clinical practice.

Guardians of premature infants with ROP are provided with all relevant information on the use of ranibizumab for the treatment of ROP in layman's terms in the proposed double-sided PL with one side fully dedicated to pediatric information (Information to guardians of babies born prematurely). The pediatric side of the PL covers the same aspects as provided in Educational Materials to adult patients defined in Annex 6 of the RMP. Briefly, the PL for use of Lucentis in premature infants with ROP educates guardians of ROP patients

- on the disease background of ROP, how Lucentis works and administration of the drug
- Contraindications for use of ranibizumab in premature infants
- Warnings and Precaution, possible side effects and monitoring procedures, and when to contact the treating physician

Specifically, guardians of premature infants with ROP are advised in the PL to inform the doctor immediately if their baby develops signs such as eye pain or worsening eye redness.

EMA GPV Module XVI Addendum I on Educational materials states that "the content of any educational material should be fully aligned with the currently authorized product information for the medicinal product, i.e. the summary product characteristics (SmPC), the package leaflet (PL) and the labelling, and should add rather than replicate SmPC and PL information.

The MAH considers the PL as the relevant document for guardians of premature infants with ROP to inform and educate about use of Lucentis in ROP patients. Provision of information already included in the PL as separate Educational materials would not add further value in communicating relevant safety related information to guardians. Consequently, RMP Educational material as additional risk-minimization activity is not considered necessary.

12.3 Part V.3. Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Infectious endophthalmitis	Routine risk minimization: SmPC Sections 4.2, 4.3, 4.4, 4.8, 6.6. SmPC Section with specific clinical measure: 6.6. PL Sections 2, 3, 4. Additional Risk Minimization Measures: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR) (Annex 6) to ensure that patients are adequately informed on the key signs and symptoms of infectious endophthalmitis and when to seek urgent attention from the physician.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up using targeted checklist. Additional pharmacovigilance activities: None
Intraocular inflammation	Routine risk minimization: SmPC Sections 4.3, 4.4. PL Sections 2, 4. Additional Risk Minimization Measures: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR) (Annex 6) to	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none. Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	ensure that patients are adequately informed on the key signs and symptoms of intraocular inflammation and when to seek urgent attention from the physician.	
Retinal detachment and retinal tear	Routine risk minimization: SmPC Sections 4.4, 4.8. PL Sections 2, 4. Additional Risk Minimization Measures: Educational plan for adult patients (for indications of AMD, CNV, DME, RVO and PDR) (Annex 6) to ensure that patients are adequately informed on the key signs and symptoms of retinal detachment and retinal tear and when to seek urgent attention from the physician.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none. Additional pharmacovigilance activities: None
Intraocular pressure increase	Routine risk minimization: SmPC Section 4.4, 4.8, 4.9. SmPC Section with specific clinical measure: 4.4 PL Sections 2, 4. Additional Risk Minimization Measures: Educational plan for adult patients (for indications of AMD, CNV, DME, RVO and PDR) (Annex 6) to ensure that patients are adequately informed on the key signs and symptoms of IOP increase and when to seek urgent attention from the physician.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none. Additional pharmacovigilance activities: None
Important potential risks		
Neurodevelopmental impairment (ROP)	Routine risk minimization: SmPC Section: This risk is not presented in SmPC. PL Sections: This risk is not presented in PL Additional Risk Minimization Measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

13 Part VI: Summary of the risk management plan of ranibizumab

This is a summary of the risk management plan (RMP) for ranibizumab. The RMP details important risks of ranibizumab (how these risks can be minimized), and how more information will be obtained where information is still insufficient (missing information).

The summary of product characteristics (SmPC) and package leaflet for ranibizumab give essential information to healthcare professionals and patients on how ranibizumab should be used.

This summary of the RMP for ranibizumab 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 ranibizumab RMP.

13.1 Part VI: I. The medicine and what it is used for

Ranibizumab is authorised in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to choroidal neovascularisation (CNV), visual impairment due to diabetic macular oedema (DME), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), and proliferative diabetic retinopathy (PDR). Ranibizumab 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 3+) or aggressive posterior ROP (AP-ROP) disease. Ranibizumab is a solution for injection and must be administered by a qualified ophthalmologist experienced in intravitreal injections.

Further information about the evaluation of ranibizumab's benefits can be found in ranibizumab EPAR, including in its plain-language summary, available on the EMA website, under the medicine's Webpage: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000715/human_med_000890.jsp&mid=WC0b01ac058001d124

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of ranibizumab together with measures to minimize such risks and the proposed studies for learning more about ranibizumab'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 packaging of the medicine;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The legal status of the medicine— 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 ranibizumab, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition, 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 ranibizumab is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI: II.A: List of important risks and missing information

Important risks of ranibizumab 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 ranibizumab. 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 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Infectious endophthalmitis Intraocular inflammation Retinal detachment and retinal tear Intraocular pressure increase
Important potential risks	Neurodevelopmental impairment (ROP)
Missing information	None

13.2.2 Part VI: II.B: Summary of important risks

Table 13-2 Important identified risk: Infectious endophthalmitis

Evidence for linking the risk to the medicine	Intravitreous injections, including those with ranibizumab, have been associated with endophthalmitis. Infectious endophthalmitis can possibly lead to a loss of vision and in sometimes even to the loss of the eye itself.
Risk factors and risk groups	To minimize the occurrence of endophthalmitis guidance is provided in SmPC on how to administer an IVT injection and to inform and educate physicians and patients on prevention and management of this event.
Risk minimization measures	Routine risk minimization: SmPC Sections 4.2, 4.3, 4.4, 4.8, 6.6. SmPC Section with specific clinical measure: 6.6 PL Sections 2, 3, 4 Additional Risk Minimization Measures (for indications of AMD, CNV, DME, RVO and PDR): Educational plan for adult patients

Table 13-3 Important identified risk: Intraocular inflammation

Evidence for linking the risk to the medicine	Intravitreous injections, including those with ranibizumab, have been associated with intraocular inflammation. Intraocular inflammation can possibly lead to a loss of vision and in sometimes even to the loss of the eye itself.
Risk factors and risk groups	Proper aseptic injection techniques must always be used when administering ranibizumab.
Risk minimization measures	Routine risk minimization: SmPC Sections 4.3, 4.4. PL Sections 2, 4 Additional routine risk minimization measures (for indications of AMD, CNV, DME, RVO and PDR): Educational plan for adult patients

Table 13-4 Important identified risk: Retinal detachment and retinal tear

Evidence for linking the risk to the medicine	Rhegmatogenous retinal detachment occurs when the liquefied vitreous enters between the choroid and the pigmented epithelium detaching the retinal layer from the underlying choroid. Traction retinal detachment occurs when scar tissue or other abnormal tissue grows on the surface of the retina, pulling the retina away from the layer beneath it. This does not necessarily cause a specific tear or break in the retina. In patients with advanced stages of ROP, retinal detachment develops when neovascularisation progresses and proliferous fibrous and vascular tissue lead to traction over the ridge. Exudative retinal detachment occurs when blood or fluid from the choroid flows into the space under the retina and separates the retina from the layer beneath it. The detachment does not involve tears in the retina or traction from the vitreous. Exudative retinal detachment is most often a complication of other diseases including macular degeneration, eye tumors, inflammation in the choroid or the retina, or severe high blood pressure. Retinal detachment leads to visual distortion, and untreated retinal detachment leads to retinal cell death and loss of vision.
Risk factors and risk groups	The following conditions might increase the risk for retinal detachment: previous retinal detachment or retinal tear, eye tumors, inflammation in the choroid or the retina, eye injury, high myopia or severe high blood pressure.
Risk minimization measures	Routine risk minimization: SmPC Section 4.4, 4.8 PL Sections 2, 4 Additional Risk Minimization Measures (for indications of AMD, CNV, DME, RVO and PDR): Educational plan for adult patients.

Table 13-5 Important identified risk: Intraocular pressure increase (IOP)

Evidence for linking the risk to the medicine	Following an intravitreal injection of ranibizumab, a transient increase in IOP may be anticipated.
Risk factors and risk groups	Pre-existing high IOP
Risk minimization measures	Routine risk minimization: Ranibizumab should not be administered in the event of an intraocular pressure of ≥30 mmHg. SmPC Sections 4.4, 4.8, 4.9. SmPC Section with specific clinical measure: SmPC Section 4.4 - Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately. PL Section 2, 4 Additional risk minimization measures (for indications of AMD, CNV, DME, RVO and PDR): Educational plan for adult patients

Table 13-6 Important potential risk: Neurodevelopmental impairment (ROP)

Evidence for linking the risk to the medicine	Based on non-clinical studies, the VEGF pathway has been implicated in neurodevelopment and neurodegeneration; systemic suppression of VEGF may be a contributing factor affecting neurodevelopmental outcomes. Higher incidence of mental and psychomotor impairment was reported in ROP patients treated off-label with intravitreal anti-VEGF bevacizumab as compared to laser. Neurodevelopmental impairment as a potential long term effect associated with use of ranibizumab has not been studied in preterm infants with ROP.
Risk factors and risk groups	Presence of other concurrent neurological conditions; neurodevelopmental impairment is an important long-term disability in extremely and very preterm populations, and association of severe ROP was observed for both cognitive and motor impairments in assessments performed at patient ages ranging from 18 months to 18 years.
Risk minimization measures	Routine risk minimization: SmPC Section: This risk is not mentioned in SmPC. PL Sections: This risk is not mentioned in PL Additional risk minimization measures: None

13.2.3 Part VI: II.C: Post-authorization development plan

13.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation for ranibizumab.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no other studies required for ranibizumab.

Annex 4 - Specific adverse drug reaction follow-up forms

Targeted Follow-up Checklist: Lucentis Endophthalmitis (Version 3/ May-2019)

In addition to collecting routine information for this AE, please ensure the following additional information is provided and/or confirmed.

Event Description:

- Date of last ranibizumab injection before event onset:
- Number of ranibizumab injections received before event onset:
- Eye(s) affected: ☐ Right eye ☐ Left eye ☐ Both eyes
- Was the event in the injected eye? ☐ Yes ☐ No ☐ Unknown
- Did the patient have eye pain as a presenting symptom?
  ☐ Yes ☐ No ☐ Unknown
- Did the patient have any other presenting symptom(s)?
  ☐ Yes ☐ No ☐ Unknown
  - If yes, please describe
- Did the patient receive prophylactic topical antibiotics prior to injection?
  ☐ Yes ☐ No ☐ Unknown
  - If yes, for how many days?
- Did patient receive post injection antibiotics? ☐ Yes ☐ No ☐ Unknown
  - If yes, for how many days?
- Was full aseptic technique used when injection was administered? (e.g. use of sterile gloves, drape, eye speculum, povidone iodine flush)
  ☐ Yes ☐ No ☐ Unknown
  - If no, please describe what was used
- Was a culture done?
  ☐ Yes ☐ No ☐ Unknown
  - If yes, what were the results?
- Any other relevant examination or laboratory data?
- Any other relevant information?

Relevant medical history (concurrent and pre-existing conditions):

- Did the patient receive prior laser therapy?
  ☐ Yes ☐ No ☐ Unknown
  - If yes, please provide date and which eye(s) was treated
- Any medications administered via intravitreal injection previous to AE?
  ☐ Yes ☐ No ☐ Unknown
  - If yes, please describe, including which eye(s) was treated
- Prior history of endophthalmitis?
  ☐ Yes ☐ No ☐ Unknown
  - If yes, please describe including date of occurrence and affected eye

Prior history of periocular infection? ☐ Yes ☐ No ☐ Unknown

►If yes, please describe including date of occurrence, affected eye, therapeutic management, and outcome (ongoing or resolved)

- Prior eye surgery or trauma to affected eye(s)?
  ☐ Yes ☐ No ☐ Unknown
  1. If yes, please describe including date of occurrence and affected eye
     - Is the patient immunocompromised?
       ☐ Yes ☐ No ☐ Unknown
     - If yes, please describe

Targeted Follow-up Checklist: Follow-up Questionnaire for use of Lucentis in pediatric patients including pediatric off-label use (Version 2/ May-2019)

Patient demography and indication

A. What was the age of the child when Lucentis was started? _____

B. What is the age group of the child at the time of reported event?

☐ Neonate (0 - ≤ 27 days) ☐ Infant (28 days to 23 months) ☐ Child (2 to 11 years)

☐ Adolescent (12 to 17 years)

C. What was the age of the child at the time of reported event? _____

D. What is the ocular condition being treated?

☐ Retinopathy of Prematurity (ROP)

- If ROP, please specify gestational age at birth _____ and birth weight of the child_____

☐ Choroidal neovascularization (CNV), please specify reason for CNV _____

☐ Macular edema

☐ Other, specify _____

E. Which eye(s) is affected? ☐ Right ☐ Left ☐ Both

Patient history

F. Did the patient receive intravitreal injections prior to event? ☐ Yes ☐ No ☐ Unknown

- If YES, please describe, including

A. Which eye(s) was treated? ☐ Right ☐ Left ☐ Both

B. Which anti-VEGF did the patient receive previously?

☐ Ranibizumab ☐ Aflibercept ☐ Bevacizumab ☐ Unknown

☐ Other, specify _____

- If ranibizumab injection was given:
  - What is the number of injections received before event onset? _____
  - What is the date of last injection before event onset? _____
  - What dose was used?
  - What regimen was used (e.g. PRN, monthly, duration)?

G. Did the patient receive laser therapy prior to the event? ☐ Yes ☐ No ☐ Unknown

- If YES, please provide:

- Which eye(s) was treated ☐ Right ☐ Left ☐ Both

Date of last treatment _____

Change in visual acuity in treated eye(s)

H. Did the patient have any improvement of visual acuity? ☐ Yes ☐ No ☐ Unknown

- If YES, please provide available information on visual acuity gain: _____
- If NO, was there vision loss: ☐ Yes ☐ No
- Please provide any other relevant information on visual acuity data:

_____

_____

Funduscopic examination findings in treated eye

I. Did the patient have any funduscopic exam? ☐ Yes ☐ No ☐ Unknown

- If YES, please describe results and/or any other relevant information:

_____

_____

Imaging data (e.g. OCT or fluorescein angiography) in treated eye

J. Did the patient have an OCT or fluorescein angiography exam? ☐ Yes ☐ No ☐ Unknown

- If YES, please describe result or any other relevant information on imaging data (i.e. change in central subfield thickness, intraretinal cyst, CNV lesion, etc):

_____

_____

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

The MAH shall ensure that, following discussions and agreements with the National Competent Authorities in each Member State where Lucentis is marketed, at launch and after launch all ophthalmological clinics where Lucentis is expected to be used for treatment of adult patients are provided with an up-to-date patient information pack.

No educational materials are provided to parents/guardians of pediatric patients receiving ranibizumab for the treatment of ROP. Infants with ROP will be generally injected with ranibizumab in a clinical setting and relevant ocular risks will be monitored by the treating physician. Parents/guardians can obtain relevant information on the use of ranibizumab for the treatment of ROP from the PL.

Key messages of the additional risk minimization measures for adult patients in the indications of nAMD, CNV, DME, RVO and PDR

The patient information pack

The patient educational material has been developed and distributed to the local representatives of the Marketing Authorization Holder, and from the local organization to the physician who can distribute it further to their patients, in order to support the safe use of ranibizumab. The patient information booklet provides information on the key signs and symptoms of potential adverse reactions, ensuring rapid identification and treatment of these events. Patient information booklets are provided to all ophthalmology clinics where ranibizumab is expected to be used for treatment of adult patients.

The patient information pack should be provided in both the form of patient information booklets and an audio-file that contain following key elements:

- Patient information leaflet
- How to prepare for Lucentis treatment
- What are the steps following treatment with Lucentis
- Key signs and symptoms of serious adverse events including increased intraocular pressure, intraocular inflammation, retinal detachment and retinal tear and infectious endophthalmitis
- When to seek urgent attention from the health care provider

Details of proposed educational program for adult patients

To ensure that patients are adequately informed about potential adverse events of ranibizumab, a patient information booklet (also available in spoken form in is available. The booklets are provided to the physician for distribution to the patient after ranibizumab is prescribed to them.

The booklets aim to provide adequate patient education on:

- What is nAMD, CNV (including secondary to PM), DR with or without DME, and RVO
- How does ranibizumab work, what to expect from ranibizumab treatment, and how is ranibizumab administered

- What are the key signs and symptoms of serious adverse events including increased intraocular pressure, intraocular inflammation, retinal detachment and retinal tear and infectious endophthalmitis
- When to seek urgent attention from the health care provider

Key safety messages are focused on facilitating the patient recognizing the key signs and symptoms of potential adverse reactions to ensure the patient informs their ophthalmologist of these potentially severe outcomes. The following are the key safety messages to be communicated to allow early diagnosis and appropriate treatment of these events:

- It is important that patients monitor any changes in the condition of their eye and their overall wellbeing in the week following injection with ranibizumab
- Patients need to contact their clinic immediately if they develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision, or increased sensitivity to light

In addition, the booklet contains follow-up recommendations for adequate care after the injection, including recommendations to contact the physician in case of additional questions.

Patient information packs are prepared nationally, in line with the key important risks defined in the RMP and with each member state's national regulations and legislations. Local MAHs are responsible to convey the key safety messages into the local versions of the educational materials. The submission of the material to the respective member state national authorities should take place before the launch of ranibizumab in a new indication (according to the national legislation in the respective countries), and the distribution of the material to all ophthalmology clinics where ranibizumab is expected to be used for treatment of adult patients.