NOVARTIS

Patient Safety & Pharmacovigilance

Brolucizumab

RTH258

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Brolucizumab
Product(s) concerned (brand name(s)):	Beovu®
Document status:	Final
Version number:	12.1
Data lock point for this RMP	21-Oct-2022
Date of final sign off	01-Oct-2024

Template version 6.4, Effective from 12-Dec-2023

Rationale for submitting an updated RMP: This RMP v12.1 is prepared in response to the type II variation assessment report (request for supplementary information) dated 30-May-2024 (procedure number EMEA/H/C/004913/II/0029), to align with the posology change for nAMD indication.

Summary of significant changes in this RMP: Key changes made compared to RMP v12.0 are:

- Product Overview section has been updated with proposed maintenance dosing options for the nAMD indication.
- Updated to reflect that Beovu is no longer subject to additional monitoring in the EU, as agreed as a part of the EU renewal procedure (procedure number EMEA/H/C/004913/R/0030).

The major changes made in RMP v12.1 are presented in the table below.

Part	Major changes compared to RMP v12.0
Part I	Information about maintenance dosing options for the nAMD indication was updated in line with SmPC. Changes were made to reflect that Beovu is no longer subject to additional monitoring in the EU.
Part II	No changes made
Part III	No changes made
Part IV	No changes made
Part V	No changes made
Part VI	No changes made
Part VII	Annex 8 was updated accordingly to reflect changes from previous version of RMP.

Other RMP versions under evaluation: CCI

Details of the currently approved RMP:

Version number: 11.0

Approved with procedure: EMEA/H/C/004913/II/0018 and EMEA/H/C/004913/II/0021

Date of approval (opinion date): 29-Jun-2023 (CHMP opinion date: 25-May-2023)

QPPV name: Dr. Justin Daniels, PhD

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

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List of abbreviations

ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AEs	Adverse events
AESI	Adverse events of special interest
AMD	Age-related macular degeneration
ATE	Arterial thromboembolic event
BCVA	Best Corrected Visual Acuity
CHF	Chronic heart failure
CI	Confidence interval
CSDME	Clinically significant diabetic macular edema
CVD	Cardiovascular disease
DME	Diabetic macular edema
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GVP	Good pharmacovigilance practices
HCP	Healthcare professional
IOI	Intraocular inflammation
IOP	Intraocular pressure
MedDRA	Medical Dictionary for Regulatory Affairs
nAMD	Neovascular age-related macular degeneration
NR	Not-reported
OCT	Optical coherence tomography
OR	Odds ratio
PFS	Pre-filled syringe
PL	Package leaflet
PSUR	Periodic Safety Update Report
PT	Preferred term
PTY	Patient Treatment year
QPPV	Qualified Person Responsible For Pharmacovigilance
RMP	Risk Management Plan
RO	Retinal vascular occlusion
RPE	Retinal pigment epithelium/epithelial
RR	Relative risk
RV	Retinal vasculitis
SAE	Serious adverse events
SCS	Summary of clinical safety
SD	Standard deviation
S-db	Safety database
SmPC	Summary of Product Characteristics
T1DM	Type 1 diabetes mellitus

T2DM	Type 2 diabetes mellitus
UK	United Kingdom
US	United States of America
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VTE	Venous thromboembolic event

1 Part I: Product(s) Overview

Table 1-1 Part I.1 - Product Overview

Active substance(s) (INN or common name)	Brolucizumab
Pharmacotherapeutic group(s) (ATC Code)	Ophthalmologicals, Anti-neovascularization agents (S01LA06)
Marketing Authorization Applicant	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Beovu®
Marketing authorization procedure	Centralized procedure
Brief description of the product	**Chemical class:** Humanized recombinant monoclonal antibody fragment
	Summary of mode of action: Increased levels of signalling through the vascular endothelial growth factor A (VEGF-A) pathway are associated with pathological ocular angiogenesis and retinal oedema. Brolucizumab binds with high affinity to 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. By inhibiting VEGF-A binding, brolucizumab suppresses endothelial cell proliferation, thereby reducing pathological neovascularisation and decreasing vascular permeability.
	Important information about its composition: 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 approved Summary of Product Characteristics (SmPC)] [Proposed SmPC]
Indication(s) in the EEA	**Current:** nAMD: Brolucizumab is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD). DME: Brolucizumab is indicated in adults for the treatment of visual impairment due to diabetic macular oedema (DME).

Dosage in the EEA	**Current:** nAMD: Treatment initiation – loading The recommended dose is 6 mg brolucizumab (0.05 ml solution), administered by intravitreal injection every 4 weeks (monthly) for the first 3 doses. A disease activity assessment is suggested 16 weeks (4 months) after treatment start. Alternatively, 6 mg brolucizumab (0.05 ml solution) may be administered every 6 weeks for the first 2 doses. A disease activity assessment is suggested 12 weeks (3 months) after treatment start. A third dose may be administered based on disease activity as assessed by visual acuity and/or anatomical parameters at week 12. Maintenance treatment After the last loading dose, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be considered. If visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment, Beovu should be discontinued. DME: The recommended dose is 6 mg brolucizumab (0.05 ml solution) administered by intravitreal injection every 6 weeks for the first 5 doses. Thereafter, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be considered. After 12 months of treatment, in patients without disease activity, treatment intervals up to 16 weeks (4 months) could be considered. If visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment, Beovu should be discontinued.
	Proposed: nAMD Treatment initiation – loading The recommended dose is 6 mg brolucizumab (0.05 ml solution), administered by intravitreal injection every 4 weeks (monthly) for the first 3 doses. A disease activity assessment is suggested 16 weeks (4 months) after treatment start. Alternatively, 6 mg brolucizumab (0.05 ml solution) may be administered every 6 weeks for the first 2 doses. A disease activity assessment is suggested 12 weeks (3 months) after treatment start. A third dose may be administered based on disease activity as assessed by visual acuity and/or anatomical parameters at week 12. Maintenance treatment After the last loading dose, the physician may individualise treatment intervals based on disease activity as assessed by visual acuity and/or anatomical parameters. In patients without disease activity, treatment every 12 weeks (3 months) should be considered. In patients with disease activity, treatment every 8 weeks (2 months) should be

	considered. If patients are being treated according to a treat-and-extend regimen and there are no signs of disease activity, the treatment intervals could be extended stepwise until signs of disease activity recur. The treatment interval should be extended or shortened by no more than 4 weeks (1 month) at a time. There are limited data on treatment intervals longer than 20 weeks (5 months). The treatment interval between two doses of Beovu should not be less than every 8 weeks (2 months) If visual and anatomical outcomes indicate that the patient is not benefiting from continued treatment, Beovu should be discontinued.
Pharmaceutical form(s) and strengths	**Current**: Solution for injection, 120 mg/mL Solution for injection in pre-filled syringe, 120 mg/mL
	Proposed: No change
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

2.1 Neovascular age-related macular degeneration

Incidence:

Annual incidence of treated neovascular age-related macular degeneration (nAMD) in the UK in 2008-2012 was stable at 120 eyes (95% confidence interval [CI] 110-138) or 100 persons (95% CI 89-115) per 100,000 population (Keenan et al 2013). nAMD is a disease of the elderly, and in an elderly population in France in 2006-2012, incidence of nAMD was 890 per 100,000 patient-years (95% CI 590-1360), and was higher in women (Saunier et al 2018). Further studies reporting cumulative (rather than annualized) incidence of nAMD and late AMD (defined as pure geographic atrophy, or exudative macular degeneration with or without geographic atrophy) 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, years	No. of patients	Baseline mean age, years ± SD	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
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, 1992-2010	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
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, Buch et al 2005a, Fisher et al 2016, Klein et al 2013, Joachim et al 2016, Cheung et al 2017, You et al 2012, Miyazaki et al 2005

Prevalence:

Prevalence: The prevalence of nAMD increases with age. In a pooled analysis of three population-based studies from three continents (Rotterdam Study, Beaver Dam Eye Study, and Blue Mountains Eye Study) 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). A recently published literature review found the reported prevalence of nAMD in China increased from 0.24% in the youngest included age group (45-49 years) to 2.79% in the oldest (85-89 years), and estimated that in 2015, 3.81 million (95% CI 2.57-5.51) persons in this country were affected with nAMD (Song et al 2017).

Further 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 N=57,173 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 N = 3.6 million	5.2	3.6*	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	5.7*	3.3 (2.8-3.8)	Jonasson et al 2011
Australia, 2015-2016	N=3,098 nonindigenous Australians aged 40-92 y Mean age 55.0±10 y, 41.1% men	0.96 (0.59-1.55)	0.24	Keel et al 2017
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	0.7 (0.5-0.9)	0.5 (0.4-0.8)	Cho et al 2014b

	Mean age 55.2±0.2 y, 47.9% men

* Calculated from the data provided in the article

Source: Owen et al 2012, Akuffo et al 2015, Lindekleiv and Erke 2013, Erke et al 2012, Jonasson et al 2011, Keel et al 2017, Cho et al 2014a, Cho et al 2014b.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors of the disease

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, with higher risk in men (e.g. Tomany et al 2004, Buch et al 2005a, Joachim et al 2016, Fisher et al 2016). Studies that evaluated risk of advanced AMD (late and nAMD) 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 and those of Hispanic ethnicity)

The main existing treatment options:

Anti-VEGF therapies delivered intravitreally are the main therapies used for treatment of nAMD and include ranibizumab (Lucentis, Novartis/Genentech) 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 its use in clinical practice is limited as is use of laser for extrafoveal lesions.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

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 is associated with increased 5-year mortality and even relatively mild visual impairment increases the risk of death more than 2-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 some studies have observed no association between nAMD and mortality after adjusting for other confounding factors (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 Blue Mountains Eye Study, nAMD was significantly associated with all-cause mortality only among persons younger than 75 years (Cugati et al 2007).

Important co-morbidities:

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 elderly general population	Anastasopoulos et al 2006, Cruess et al 2007, Soubrane et al 2007, Zlateva et al 2007, Ryskulova et al 2008
Glaucoma	6 – 10	Prevalence within the range reported in general population of similar ages	Anastasopoulos et al 2006, Soubrane et al 2007, Ryskulova et al 2008

Comorbidity	Prevalence, %	Comments	References
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 2007
Hyperlipidemia	18 – 46	Prevalence within the range reported in general population	Anastasopoulos et al 2006, Alexander et al 2007
Diabetes	8 – 33	Pooled meta-analysis estimates for risk of nAMD in diabetes: Cohort studies relative risk (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, Anastasopoulos et al 2006, Alexander et al 2007, Duan et al 2007, Sun et al 2007, Zlateva et al 2007, Chen et al 2014
Myocardial infarction	4 – 5	Pooled meta-analysis estimates for risk of cardiovascular disease 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, Ryskulova et al 2008, Klein et al 2007, Brody et al 2001, Tournier et al 2008, Augustin et al 2007, Chen et al 2014, Wu et al 2014, Fernandez et al 2015, Dawson et al 2014

2.2 Diabetic macular edema

Incidence

Recently published population-based studies that have provided incidence for DME 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 in diabetic populations worldwide

Country, study period	Follow-up, years	No. of patients	Baseline mean ±SD age, years	Cumulative incidence (%)	Reference
				DME	
T1DM					
Spain, 2007-2015	9	366	>12 (mean not reported)	8.46	Romero-Aroca et al 2017
T2DM					
Spain, 2007-2015	9	15,030	NR	6.36	Romero-Aroca et al 2017
Any diabetes					
Hong Kong, 2015-2016	At least 2 y (median 27.14 range 24.16-30.41 months)	129 (205 eyes from 129 patients)	62.92±9.88	8.76	Sun et al 2019
India, 2007-2011	4	853	55.35±9.45	2.64 (95% CI 1.48-3.40)	Raman et al 2017

Source: Sun et al 2019, Raman et al 2017, Romero-Aroca et al 2017

The reported cumulative incidence of DME depended on the length of follow-up of the patients in the different studies; highest estimates are provided in a T1DM population. The high cumulative incidence of DME in a population of T1DM and T2DM by Sun et al (2019) could be explained due to the use of optical coherence tomography (OCT), a new diagnostic tool noted by Kume et al (2020) to have an increased diagnostic accuracy and thus a significant increase in the incidence of DME detected.

Prevalence

A number of population-based studies have provided prevalence for DME and CSDME. Selected recent studies are summarized in the Table 2-5, stratified by diabetes subtype. CSDME is the most significant outcome of the early treatment diabetic retinopathy study (ETDRS) in that it established a method for classifying and diagnosing DME and determining when treatment is required. For the diagnosis of CSDME, one of the following characteristics must be present on clinical examination: Any retinal thickening within 500 microns of the center of the macula. Hard exudates within 500 microns of the center of the macula with adjacent retinal thickening. Retinal thickening at least 1 disc area in size, any part of which is within 1 disc diameter of the center of the macula. It is essential to realize that the determination of the presence of CSME is a clinical diagnosis based on a retinal biomicroscopic examination of the patient, and not based on fluorescein angiography (Ali F A 1997).

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

Data Source	No. of patients	Baseline mean age ±SD, y	Prevalence, %		Reference
			DME	CSDME	
T1DM					
Poland, 2012-2016	315	37.0±13.55	5.40	-	Stefanowicz-Rutkowska et al 2020
Slovenia, 2015	295	27.6±12.9	4.07 (95% CI 1.81-6.32) Males: 3.55 (95% CI 0.49-6.6) Females: 4.55 (95% CI 1.26-7.84)	-	Ondrejkova et al 2019
Brazil, 2010-2014	1,644	30.1±12.0	2.7	-	Melo et al 2018
Turkey, 2011-2012	27* (4+23)	≥18 y, mean age not stated	14.8	-	Acan et al 2018
T2DM					
Poland, 2012-2016	894	61.2±11.13	4.81	-	Stefanowicz-Rutkowska et al 2020
Slovenia, 2015	3,405	53.4±9.5	3.11 (95% CI 2.53-3.7) Males: 3.56 (95% CI 2.66-4.47) Females: 2.71 (95% CI 1.96-3.46)	-	Ondrejkova et al 2019
Turkey, 2011-2012	386* (59+327)	≥18, mean age not stated	15.3	-	Acan et al 2018
Any diabetes					
Croatia, 2016-2018	753	NR	33.70	-	Pidro et al 2019
Poland, 2012-2016	1,209	NR, adults	4.96	-	Stefanowicz-Rutkowska et al 2020
Nigeria, July 2015	80	61.2±11.1	31.3	-	Kizor-Akaraiwe et al 2016
Nepal, July-December 2014	658* (330+328)	55.43±11.86	5.5	-	Mishra et al 2016
Australia, 2009-2010	519	64.9±11.6	28.7	-	Rees et al 2016

Data Source	No. of patients	Baseline mean age ±SD, y	Prevalence, %		Reference
			DME	CSDME	
Singapore, NR	2,877	>40, mean age not stated	7.6 (95% CI 6.5-9.0)	6.39 (5.37-7.60)	Tan et al 2018
Turkey, 2011-2012	413	≥18, mean age not stated	15.3	-	Acan et al 2018

*own calculation/deduction using information provided in the article.

Source: Stefanowicz-Rutkowska et al 2020, Ondrejkova et al 2019, Pidro et al 2019, Acan et al 2018, Melo et al 2018, Tan et al 2018, Kizor-Akaraiwe et al 2016, Mishra et al 2016, Rees et al 2016

The reported range in prevalence estimates of DME in T1DM and T2DM patients were similar (T1DM: 2.7-14.8%, T2DM: 3.11-15.3%). There was a large range in the prevalence estimates reported in the recent literature, which is most likely due to the various methods used to diagnose DME – notably the high prevalence of DME in both the T1DM and T2DM populations by Acan et al (2018) is likely due to the use of optical coherence tomography (OCT), a new diagnostic tool noted by Kume et al (2020) to have increased diagnostic accuracy and thus a significant increase in the prevalence of DME detected. Besides, prevalence estimated provided by electronic records or databases are highly variable, which reflects the inconsistency in reporting DME diagnosis.

Demographics of the DME population– age, gender, racial and/or ethnic origin and risk factors of the disease

A key factor associated with the development of DME is the duration of diabetes, with a rise in DME prevalence reported with increasing DM duration, irrespective of diabetic type (Ondreikova et al 2019). The mean age at diagnosis of DME was reported to range from 61 years in T1DM and T2DM patients (Eldem et al 2017), to 64 years in T2DM patients (Martín-Merino et al 2017). There was a slight preponderance reported in the literature, with males representing 55.2-59% of DME cases (Eldem et al 2017, Martín-Merino et al 2017), with Acan et al (2018) reporting a significantly higher prevalence of DME in males. One study assessed the prevalence of DME between three major ethnic groups in Singapore, with Indian Singaporeans found to have a higher prevalence compared to Chinese and Malays (Tan et al 2018).

Risk factors:

A recent literature review assessed the non-modifiable and modifiable risk factors for DME (Lee et al 2015) and concluded that hyperglycemia, hypertension, and dyslipidemia are key modifiable risk factors for DME. Pregnancy was identified as key non-modifiable risk factor, where DME can progress rapidly, especially in T1DM. In addition, the duration of diabetes and anemia were also important risk factors (Tan et al 2018, Raman et al 2017). HbA1c levels were also found to be a significant risk factor for the development of DME (Tan et al 2018), with an HbA1c level of >7% associated with increased risk of DME in T2DM patients (Martín-Merino et al 2017).

Main Existing treatment options

The current treatment options for patients with DME are: laser photocoagulation, and intravitreal injections (IVT) or intravitreal implants of corticosteroids and anti-VEGF. Due to the efficacy and safety profile of anti-VEGF therapy, it has become the first-line treatment. Corticosteroids are used as a second line treatment and focal / grid laser photocoagulation remains a therapeutic option, but with a lower expected benefit compared with steroid and anti-VEGF therapy.

Natural history of DME in the untreated population, including mortality and morbidity

No recent studies were identified to report the mortality or morbidity of DME.

Important co-morbidities

The key comorbidities in the population with DME are listed in the following Table 2-6.

Table 2-6 Important comorbidities in DME population

Comorbidity	Prevalence, %	Comments	References
Cardiovascular disease (CVD)	Prevalence: 4.5	During both the 6-month pre-index and 12-month post-index periods, DME patients had significantly higher rates of CVD, than matched non-DME diabetic patients.	Kiss et al (2016)
Cataract	IR: 59.0 (95% CI: 49.4-68.6) Prevalence: 17.1 Prevalence in T2DM patients: 27.5	The incidence rate and prevalence of cataracts were reported to be significantly higher in DME patients than in the general diabetic population. History of cataracts in T2DM patients was associated with a four-fold increased risk of DME.	Becker et al (2018), Martín-Merino et al (2017), Kiss et al (2016)
Chronic heart failure (CHF)	Prevalence: 5.3	During both the pre-index 6-month and post-index 12-month periods, DME patients had significantly higher rates of CHF, than matched non-DME diabetic patients.	Kiss et al (2016)
Hypercholesterolemia	T2DM Prevalence: 78.9	T2DM patients with DME had significantly higher prevalence of hypercholesterolemia than T2DM patients without DME.	Vié et al (2019)
Hypertension	T2DM prevalence: 63.5-89.5		Vié et al (2019), Martín-Merino et al (2017)
Renal disease	Prevalence: 13.1	During both the 6-month pre-index period and 12-month post-index periods, DME patients had significantly higher rates of renal disease, than matched non-DME diabetic patients did.	Kiss et al (2016)

Comorbidity	Prevalence, %	Comments	References
Sleep apnea	97.3	Apnea-hypopnea index was significantly higher in DME patients with T2DM compared to T2DM patients without DME.	Vié et al (2019)

Source: Kiss et al (2016), Becker et al (2018), Martín-Merino et al (2017), Vié et al (2019)

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 No safety findings have been observed in any nonclinical study. Three- and six-month Good Laboratory Practice (GLP) studies were conducted in cynomolgus monkeys, with intravitreal injections of brolucizumab administered up to 6 mg/eye every 3 to 4 weeks. Evaluations included daily observations for morbidity and mortality, clinical observations (including abnormal respiration and behavior), body weight determinations, biomicroscopic and indirect ophthalmoscopic examinations, intraocular pressure (IOP) measurements, electroretinogram analysis, clinical pathology, toxicokinetic analysis of the serum and vitreous, anti-drug antibody (ADA) analysis of the serum and vitreous, and macroscopic and microscopic tissue examinations. No ocular or systemic toxicity /effects were noted in any study. Pre-existing ADA were measured before dosing on Day 1 and although there appeared to be an increase in ADA incidence and titer over time, there was no dose-response relationship and no correlation between ADA titers and systemic exposure or adverse effects in any study.	No ocular or systemic toxicities were noted in non-clinical studies conducted using the clinical dose and clinical route of exposure.
Other toxicity-related information or data: • A study in pregnant cynomolgus monkeys did not indicate any harmful effects with respect to pre- or postnatal development at approximately 6-times the human exposure based on serum Cmax. • In the reproductive toxicity study, brolucizumab was not detected in the maternal milk or infant serum of cynomolgus monkeys.	There are no adequate and well-controlled studies of brolucizumab treatment in pregnant women. Based on the mechanism of action of VEGF inhibitors, there is a potential risk to female reproduction and to embryo-fetal development.

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 patients with nAMD and DME, this section provides an overview on the drug exposure related to the 3 mg and 6 mg treatment groups from various studies analyzed in this RMP.

Calculation of clinical trial exposure was done using the long-term safety database (S-db) of 96 weeks in nAMD and the 100 Week S-db in DME.

96-week Long-term S-db (nAMD):

This pool consisted of nAMD studies with a duration of at least 96 weeks and with a brolucizumab 6 mg/50 µL dose administered at 4-week intervals followed by q12w/q8w. Two Phase 3 pivotal double-masked parallel group studies (Study RTH258-C001 and Study RTH258-C002) were included in this pool. Only Study RTH258-C001 included a brolucizumab 3 mg group. Data from Screening up to Week 96 was included.

Exposure to brolucizumab in the long-term S-db is presented by injection frequency category in Table 4-1.

Table 4-1 SIII.1: Exposure to study treatment from baseline to week 96 (long term S-db, nAMD)

Number of injections	Bro 3mg N=358 n (%)	Bro 6mg N=730 n (%)
At least 1 injection	358 (100.0)	730 (100.0)
At least 2 injections	358 (100.0)	726 (99.5)
At least 3 injections	355 (99.2)	720 (98.6)
At least 4 injections	347 (96.9)	700 (95.9)
At least 5 injections	341 (95.3)	690 (94.5)
At least 6 injections	330 (92.2)	677 (92.7)
At least 7 injections	324 (90.5)	664 (91.0)
At least 8 injections	319 (89.1)	652 (89.3)
At least 9 injections	310 (86.6)	640 (87.7)
At least 10 injections	298 (83.2)	616 (84.4)
At least 11 injections	176 (49.2)	348 (47.7)
At least 12 injections	149 (41.6)	294 (40.3)
At least 13 injections	107 (29.9)	214 (29.3)
At least 14 injections	0 (0.0)	0 (0.0)

Source: [EU RMP version 2.0 Annex 7 Table 1-1RTHP2_RMP]

Additionally, the TALON study (RTH258A2303) was conducted in the nAMD patients comparing brolucizumab 6 mg with aflibercept 2 mg. The subjects were randomized in a ratio of 1:1 to be treated with brolucizumab 6 mg (n=368) or with aflibercept 2 mg (n=369). During the study up to 64 weeks, the subjects in the brolucizumab arm received a mean of 7.2

(median=7.0) active IVT injections, while the subjects in the aflibercept arm received a mean of 7.8 (median=7.5) active IVT injections [RTH258A2303 CSR].

100 Week S-db (DME)

This pool consisted of 100-week data from the two 2-year pivotal Phase III clinical studies in the DME indication: RTH258B2301 (KESTREL) and RTH258B2302 (KITE). Both studies included a brolucizumab 6 mg injection every 6 weeks for the first 5 doses (loading phase), then q12w/q8w during maintenance phase. In the RTH258B2302 study, the dosing interval could be extended up to q16w from Week 72 onwards when disease stability (no disease activity at Week 60 and Week 72) was observed. Study RTH258B2301 included a brolucizumab 3 mg treatment group in addition to the brolucizumab 6 mg and aflibercept 2 mg treatment groups.

Exposure to brolucizumab in the 100 Week S-db is presented by injection frequency category in Table 4-2.

Table 4-2 SIII.2: Exposure to study treatment 100 Week S-db (DME)

Number of injections	Bro 3mg N=190 n (%)	Bro 6mg N=368 n (%)
At least 1 injection	190 (100)	368 (100)
At least 2 injections	186 (97.9)	365 (99.2)
At least 3 injections	182 (95.8)	360 (97.8)
At least 4 injections	179 (94.2)	356 (96.7)
At least 5 injections	174 (91.6)	348 (94.6)
At least 6 injections	168 (88.4)	332 (90.2)
At least 7 injections	166 (87.4)	323 (87.8)
At least 8 injections	162 (85.3)	315 (85.6)
At least 9 injections	160 (84.2)	298 (81.0)
At least 10 injections	155 (81.6)	279 (75.8)
At least 11 injections	137 (72.1)	224 (60.9)
At least 12 injections	84 (44.2)	141 (38.3)
At least 13 injections	57 (30.0)	94 (25.5)
At least 14 injections	19 (10.0)	31 (8.4)

- n = Number of subjects satisfying the condition
Source: [EU RMP version 10.0 Annex 7 Table 1-1P1p_RMPB_Y2]

Exposure by age, gender and race

Exposure to brolucizumab in nAMD studies in the long-term S-db is presented by age and gender in Table 4-3, and by race in Table 4-5 respectively. Exposure to brolucizumab in DME studies in Week 100 S-db is presented by age and gender in Table 4-4, and by race in Table 4-6 respectively.

Table 4-3 SIII.3: Exposure to study treatment from baseline to week 96 by age group and gender (Long-term S-db (AMD)

		Bro 3mg		Bro 6mg	
Age Group	**Gender**	**Patients n (%)**	**No. of injections total (%)**	**Patients n (%)**	**No. of injections total (%)**
Total	Total	358 (100)	3772 (100)	730 (100)	7671 (100)
	Male	148 (41.3)	1552 (41.1)	315 (43.2)	3365 (43.9)
	Female	210 (58.7)	2220 (58.9)	415 (56.8)	4306 (56.1)
< 50 years	Total	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Male	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Female	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
50-64 years	Total	31 (100)	339 (100)	79 (100)	862 (100)
	Male	16 (51.6)	164 (48.4)	42 (53.2)	483 (56.0)
	Female	15 (48.4)	175 (51.6)	37 (46.8)	379 (44.0)
65-74 years	Total	103 (100)	1114 (100)	227 (100)	2439 (100)
	Male	46 (44.7)	475 (42.6)	115 (50.7)	1231 (50.5)
	Female	57 (55.3)	639 (57.4)	112 (49.3)	1208 (49.5)
75-84 years	Total	162 (100)	1685 (100)	305 (100)	3162 (100)
	Male	65 (40.1)	690 (40.9)	124 (40.7)	1309 (41.4)
	Female	97 (59.9)	995 (59.1)	181 (59.3)	1853 (58.6)
>=85 years	Total	62 (100)	634 (100)	119 (100)	1208 (100)
	Male	21 (33.9)	223 (35.2)	34 (28.6)	342 (28.3)
	Female	41 (66.1)	411 (64.8)	85 (71.4)	866 (71.7)

Source: [EU RMP version 2.0 Annex 7 Table 1-2RTHP2_RMP]

Table 4-4 SIII.4: Exposure to study treatment by age group and gender 100 Week S-db (DME)

		Bro 3mg		Bro 6mg	
Age Group	Gender	Patients n (%)	No. of injections total (%)	Patients n (%)	No. of injections total (%)
Total	Total	190 (100)	2019 (100)	368 (100)	3834 (100)
	Male	119 (62.6)	1267 (62.8)	230 (62.5)	2398 (62.5)
	Female	71 (37.4)	752 (37.2)	138 (37.5)	1436 (37.5)
< 50 years	Total	12 (100)	137 (100)	39 (100)	426 (100)
	Male	10 (83.3)	118 (86.1)	29 (74.4)	312 (73.2)
	Female	2 (16.7)	19 (13.9)	10 (25.6)	114 (26.8)
50-64 years	Total	85 (100)	933 (100)	165 (100)	1686 (100)
	Male	50 (58.8)	549 (58.8)	106 (64.2)	1094 (64.9)
	Female	35 (41.2)	384 (41.2)	59 (35.8)	592 (35.1)
65-74 years	Total	65 (100)	681 (100)	127 (100)	1352 (100)
	Male	35 (53.8)	376 (55.2)	76 (59.8)	814 (60.2)
	Female	30 (46.2)	305 (44.8)	51 (40.2)	538 (39.8)
75-84 years	Total	24 (100)	224 (100)	36 (100)	361 (100)
	Male	21 (87.5)	191 (85.3)	18 (50.0)	169 (46.8)
	Female	3 (12.5)	33 (14.7)	18 (50.0)	192 (53.2)
>=85 years	Total	4 (100)	44 (100)	1 (100)	9 (100)
	Male	3 (75.0)	33 (75.0)	1 (100)	9 (100)
	Female	1 (25.0)	11 (25.0)	0	0

- n = Number of subjects with at least one injection.
- Percentages (%) are calculated using the Total for the age group.

Source: [EU RMP version 10.0 Annex 7 Table 1-2P1_RMPB_Y2]

Table 4-5 SIII.5: Exposure to study treatment from baseline to week 96 by race (Long-term S-db, nAMD)

	Bro 3mg		Bro 6mg	
Race	Patients n (%)	No. of injections total (%)	Patients n (%)	No. of injections total (%)
Total	358 (100)	3772 (100)	730 (100)	7671 (100)
White	302 (84.4)	3188 (84.5)	625 (85.6)	6596 (86.0)
Black or African American	1 (0.3)	10 (0.3)	2 (0.3)	19 (0.2)
American Indian or Alaska native	1 (0.3)	9 (0.2)	1 (0.1)	2 (0.0)
Asian	44 (12.3)	455 (12.1)	83 (11.4)	853 (11.1)
Native Hawaiian Or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	9 (2.5)	100 (2.7)	14 (1.9)	146 (1.9)
Multiple	1 (0.3)	10 (0.3)	5 (0.7)	55 (0.7)

Source: [EU RMP version 2.0 Annex 7 Table 1-3RTHP2_RMP]

Table 4-6 SIII.6: Exposure to study treatment to week 100 by race S-db (DME)

	Bro 3mg		Bro 6mg	
Race	**Patients n (%)**	**No. of injections total (%)**	**Patients n (%)**	**No. of injections total (%)**
Total	190 (100)	2019 (100)	368 (100)	3834 (100)
White	151 (79.5)	1616 (80.0)	291 (79.1)	3069 (80.0)
Black or African American	13 (6.8)	127 (6.3)	7 (1.9)	61 (1.6)
Asian	25 (13.2)	269 (13.3)	68 (18.5)	678 (17.7)
Native Hawaiian Or Other Pacific Islander	0	0	2 (0.5)	26 (0.7)
American Indian or Alaska native	1 (0.5)	7 (0.3)	0	0
Unknown	0	0	0	0
Multiple	0	0	0	0

- n = Number of subjects with at least one injection.

Source: [EU RMP version 10.0 Annex 7 Table 1-3P1_RMPB_Y2]

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
Active intraocular or periocular infection.	Risk of worsening of an ongoing intraocular infection into a more severe stage and potential loss of vision. An active periocular infection might increase the risk of endophthalmitis.	No	Exclude patients to prevent worsening of intraocular infection and potential vision loss. Active or suspected ocular or periocular infections is a contraindication.
Active intraocular inflammation.	Risk of worsening of an ongoing intraocular inflammatory process, or inflammation due to another cause.	No	Exclude patients to prevent worsening of an inflammation. Active intraocular inflammation is a contraindication
Concurrent confounding ocular conditions (e.g., vitreous hemorrhage, retinal pigment epithelium rip/tear, aphakia and/or absence of the posterior capsule) 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, may confound study results and may require surgical intervention.	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.
Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP) >25 mmHg on medication	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 IOP >25 mmHg on medication or uncontrolled glaucoma should generally be avoided to avoid consequences of additional raised IOP, including a temporary increase associated with the intravitreal injection procedure.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
History of hypersensitivity to any component of the test article, control article, or clinically relevant sensitivity to fluorescein dye (or indocyanine green for subjects in Japan), as assessed by the Investigator	Due to the low systemic exposure of brolucizumab the chance for a systemic hypersensitivity reaction is low, but can however not be excluded. There are a number of concurrently administered agents during the intravitreal injection procedure which could also be the cause of a hypersensitivity reaction (e.g. fluorescein, indocyanine green)	No	To exclude subjects with known Hypersensitivity to any component of the test article, control article or other agents used as fluorescein, indocyanine green.
Stroke or myocardial infarction in the 90 day period prior to Baseline	Precautionary measure based on severity of a stroke or myocardial infarction.	No	Precautionary measure in clinical trial setting for patients with a recent event of stroke or myocardial infarction
Presence of amblyopia, amaurosis or ocular disorders with vision <20/200 (35 letters) in the fellow eye at screening or baseline	Vision of <20/200 (35 letters) is the cut-off for legal blindness. Brolucizumab is an investigational drug and this criteria is a precautionary measure to prevent severe disability in case of potential vision loss in the study eye.	No	Precautionary measure to prevent severe disability in case of potential vision loss in the study eye. Safety profile not expected to be different in this population.

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

The clinical development program is unlikely to detect certain types of adverse reactions such as “rare adverse reactions”, “adverse reactions with a long latency”, or those caused by “prolonged” or “cumulative exposure”.

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

Table 5-2 SIV.2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women and breastfeeding women	Not included in the clinical development program

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients	The systemic exposure of brolucizumab is low. Studying patients with these comorbidities is not relevant due to the pharmacokinetics of brolucizumab.
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 Table 4-5 and Table 4-6.
Subpopulations carrying relevant genetic polymorphisms	Not applicable

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

An estimate of patient exposure is calculated based on worldwide sales volume in Patient Treatment years (PTY) based on the number of brolucizumab vials and PFS sold worldwide, including drug samples distributed across the world. Vials and PFS are designed for single use and hence it is assumed that each vial/PFS represents one injection to one patient. Based on market research into prescribers' dosing behavior (Kim et al 2016) of the intravitreal VEGF inhibitors, the average number of vials/PFS used per patient per year is 5.4, and this will be used as basis for the estimate of the PTY exposure to brolucizumab. The number of vials/PFS used to calculate one PTY will be adapted if further information becomes available on the use of Beovu in the post-marketing setting.

6.1.2 Part II Module SV.1.2. Exposure

Brolucizumab received its first marketing authorization in the US on 07-Oct-2019. Up to 06-Oct-2022, based on overall use of CCI vials/ PFS (Table 6-1) and considering that the average number of vials/PFS used per patient per year is 5.4, it is estimated that overall post-marketing exposure of brolucizumab is 128,645 PTYs.

Table 6-1 Cumulative exposure from post-marketing experience based on use of number of vials/ PFS

Country	Patient Exposure (PTY)
EU/EEA	38,963
US	CCI
Japan	CCI
Other countries	34,977
Overall worldwide	128,645

This table includes cumulative data obtained from International birth date (IBD; 07-Oct-2019) through 06-Oct-2022

Source: Brolucizumab [PSUR 07-Apr-2022 to 06-Oct-2022]

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

Country	Number of units (vials/PFS)	Patient Exposure (PTY)
Austria	CCI	CCI
Belgium	CCI	CCI
Bulgaria	CCI	CCI
Croatia	CCI	CCI
Cyprus	CCI	CCI

Country	Number of units (vials/PFS)	Patient Exposure (PTY)
Czech Republic	CCI	CCI
Denmark	CCI	CCI
Estonia	CCI	CCI
Finland	CCI	CCI
France	CCI	CCI
Germany	CCI	CCI
Greece	CCI	CCI
Hungary	CCI	CCI
Iceland	CCI	CCI
Ireland	CCI	CCI
Italy	CCI	CCI
Lithuania	CCI	CCI
Luxembourg	CCI	CCI
Malta	CCI	CCI
Netherlands	CCI	CCI
Norway	CCI	CCI
Poland	CCI	CCI
Portugal	CCI	CCI
Romania	CCI	CCI
Slovakia	CCI	CCI
Slovenia	CCI	CCI
Spain	CCI	CCI
Sweden	CCI	CCI

This table includes cumulative data obtained from International birth date (IBD; 07-Oct-2019) through 30Sep2022.

Source: Novartis internal sales data

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 brolucizumab, 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

8.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

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

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

None

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

None

Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

Retinal pigment epithelial tear

Retinal pigment epithelial (RPE) tears are known to occur because of progression of underlying nAMD, and eyes with serous RPE detachments appear to be most vulnerable to developing RPE tears. Increased height and shorter duration of the RPE detachment are important risk factors for the development of subsequent RPE tears in patients receiving treatment with VEGF-inhibitors (Doguizi, Ozdek 2014, Guber et al 2014, Clemens, Eter 2016).

The reported incidence of RPE tear after treatment with VEGF-inhibitors varies widely and depends on the selected patients, the treatment regimens of the VEGF-inhibitors, and the nomenclature of the lesion morphology used (Clemens, Eter 2016, Ersoz et al 2017). In the brolucizumab pivotal studies the number of patients with a retinal pigment epithelial tear was low (target posology long term S-db: brolucizumab 3 mg 1.4%; brolucizumab 6 mg 2.7%; a higher incidence of RPE tear was reported for patients on brolucizumab 6 mg in Study RTH258-C001 (3.3%) compared to Study RTH258-C002 (2.2%)). The risk difference between brolucizumab 6 mg and aflibercept 2 mg was 1.6% [95% CI 0.13, 3.42] in the target posology long term S-db.

Retinal pigment epithelial tear is listed as a common ADR in the SmPC and is part of the Package Insert. There are no pharmacovigilance activities that will minimize the risk. Therefore,

retinal pigment epithelial tear is not considered an important identified risk for the RMP. Routine pharmacovigilance is considered sufficient.

Further details on Retinal pigment epithelial tear can be found in the Clinical Study Reports (Study RTH258-C001 and Study RTH258-C002).

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

Sustained intraocular pressure increase and Glaucoma

In the two pivotal trials for brolucizumab, sustained increases in IOP have not been observed (Study RTH258-C001 and Study RTH258-C002). The pre-injection values of IOP were similar to the baseline values with a low 95%CI, indicating that patients are not at risk for developing glaucoma due to a sustained increase in IOP. This finding is consistent with experience with the already marketed intravitreally administered VEGF-inhibitors. There are no pharmacovigilance activities that will minimize the risk for the patient and further characterization is not considered required. Sustained IOP increase and glaucoma are therefore not considered to meet the criteria for an important identified risk for an RMP. Routine pharmacovigilance is considered sufficient for this risk.

Further details on Sustained intraocular pressure increase and Glaucoma can be found in the Clinical Study Reports (Study RTH258-C001 and Study RTH258-C002).

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 8-1 Important identified risks

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
Intraocular inflammation	For treatment emergent ocular adverse events (AEs) in the study eye, the most pronounced numerical difference between brolucizumab and aflibercept was observed for intraocular inflammation and this was more pronounced in the Study RTH258-C001. Most intraocular inflammation cases were reported during the first 6 months of treatment. In the target posology long term S-db the incidence for Intraocular inflammation in the brolucizumab 6 mg group was 4.4%. Most Intraocular inflammation cases were mild to moderate (93.8% and 95.2% for 3 mg and 6 mg respectively in Study RTH258-C001, 81.8% for 6 mg in Study RTH258-C002), and most resolved with no sequelae. New Intraocular inflammation events in Year 2 were balanced across treatment arms. Intraocular inflammation most accurately represents the grouping of different PTs and was selected as an important identified risk in the RMP. All important identified risks should be considered adverse drug reactions (The Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev 4)). However, the SmPC guideline (revision 2, 2009) states that “Adverse reactions descriptions should be based on the most suitable representation within the Medical Dictionary for Regulatory Affairs (MedDRA) terminology." Intraocular inflammation is an umbrella term and is not available as PT, nor is it available at the Lowest Term Level or High Level Terms. Therefore, individual PTs

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
	representing the umbrella term Intraocular inflammation were proposed as ADRs. Intraocular inflammation is categorized as an important identified risk.
Endophthalmitis	Endophthalmitis is a well-known and well-characterized risk associated with the intravitreal injection procedure. The number of patients with an endophthalmitis in the brolucizumab pivotal studies was low (target posology long term S-db: brolucizumab 3 mg 1.1%; brolucizumab 6 mg 0.7%). The Risk difference between brolucizumab 6 mg and aflibercept 2 mg was less than 1.0% [0.5% (95% CI: −0.27, 1.67)] in the target posology long term S-db. The time to onset since the last active injection (all but two events started within 8 days) and the investigator assessment suggests that it is very likely that the reported endophthalmitis events are in most, if not all cases, caused by the intravitreal injection procedure and not by brolucizumab (Study RTH258-C001 and Study RTH258-C002). Endophthalmitis is listed as an ADR in the SmPC and is part of the Package Leaflet too. At the request of the EMA Endophthalmitis is categorized as an important identified risk.
Transient intraocular pressure increased	A transient increase in IOP is expected when an intravitreal injection of brolucizumab (volume of 0.05 mL) is administered. In the two pivotal trials for brolucizumab (Study RTH258-C001 and Study RTH258-C002), transient increases were observed immediately after the intravitreal injections were administered. This finding is consistent with experience with the already marketed intravitreally administered VEGF-inhibitors. Intraocular pressure increase is listed as a common ADR in the SmPC. As indicated in Section 4.4 of the SmPC 'Special warnings and precautions for use', transient increases in intraocular pressure (IOP) have been seen within 30 minutes of injection of brolucizumab (volume of 0.05 mL). Additionally, in the SmPC, advice is given to the administering health care provider that both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately (Section 4.4 SmPC). The monitoring of IOP increase is fully integrated into standard clinical practice to minimize the risk. In addition, these post-injection increases are short-lived or can be treated with standard of care. Therefore, Novartis considers the information provided in the SmPC for this well-known and well-characterized risk sufficient and there are no pharmacovigilance activities that will further minimize the risk for the patient. At the request of the EMA Transient intraocular pressure increased is categorized as an important identified risk.
Retinal detachment / tear	Retinal detachment and tear are mainly associated with the underlying disease and aging of the eye; rarely these are associated with the intravitreal injection. The number of patients with Retinal detachment and tear was low (target posology long term S-db: brolucizumab 3 mg 0.6%; brolucizumab 6 mg 1.6%). The Risk difference between brolucizumab 6 mg and aflibercept 2 mg was less than 1.0% in the target posology long term S-db. Overall, the reported incidences are similar to ranibizumab clinical studies (Lucentis EU RMP version 16.2 and Lucentis PSUR 12).

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
	Retinal detachment and tear is a well-known and well-characterized risk associated with the underlying disease and the aging of the eye. In line with VEGF-inhibitors approved for nAMD, retinal detachment and retinal tear are both listed as an ADR in the SmPC (as uncommon and common respectively) and are part of the Package Leaflet. At the request of the EMA, retinal detachment / tear is categorized as an important identified risk.
Source: Summary of Clinical Safety, Study RTH258-C001 and Study RTH258-C002	

Table 8-2 Important potential risks

Risk	Risk-benefit impact (Reasons for classification as important potential risk)
Non-ocular events (ATE, VTE, non-ocular haemorrhage, and hypertension)	No consistent increased incidences of ATEs and hypertension compared to sham/control have been reported for the intravitreally administered VEGF-inhibitors ranibizumab and aflibercept in patients with nAMD (Zarbin et al 2018, Kitchens et al 2016). The reported incidence for brolucizumab is consistent with those observed for Lucentis and sham treatment. The number of patients with an ATE, VTEs, non-ocular haemorrhage and hypertension in the ranibizumab nAMD studies varied between 4.3-8.1% for ATEs, 0.4-1.8% for VTEs, 2.1-15.0 for non-ocular haemorrhage, and 10.3-20.2% for hypertension after two years of treatment (total number of patients in the studies ranged from 440 to 549), and these incidences were similar to sham treatment (Lucentis EU RMP v16.2). Reported incidences for Study RFB002A2401 (n=755) were in general an exception with an incidence of 1.5% for ATEs, 0.5% for VTEs, 0.4% for non-ocular haemorrhage, and 2.5% for hypertension. However, at the request of the EMA non-ocular events have been categorized as an important potential risk.

Table 8-3 Missing information

Missing information	Risk-benefit impact (Reasons for classification as missing information)
Safety beyond two years of treatment	Study RTH258-C001 and Study RTH258-C002 had a duration of 96 weeks; the RTH258-C001 extension study provided safety data for 150 patients with a total treatment duration between 120 and 132 weeks.
Non-ocular safety after bilateral treatment	The safety of brolucizumab administered in both eyes concurrently has not been studied.

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

There was no change in safety concerns since the last update.

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

The risk tables include side by side pooled data presenting brolucizumab 6 mg, the approved dose and aflibercept 2 mg in nAMD and DME indications respectively. Annex 7 includes - detailed data presenting side by side pivotal trials in nAMD and DME indications. These detailed tables also include data on brolucizumab 3 mg. For the purpose of presentation of clinical trial data, data for only brolucizumab 6 mg is provided. However, 3 mg data is discussed where relevant.

In both nAMD and DME studies, comparison of event frequency between the brolucizumab 3 mg group and the brolucizumab 6 mg group has to be interpreted with caution since the brolucizumab 3 mg group was only included in some pivotal trials, while the brolucizumab 6 mg and 2 mg aflibercept results are obtained from the pooled pivotal trials.

8.3.1.1 Important identified risk: Intraocular inflammation

Table 8-4 Clinical trial data of Intraocular inflammation

	Pooled nAMD (Ocular, 96 Week long term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Number of patients with at least one event	32 (4.4) (2.30, 7.08)	6 (0.8) (0.14, 1.63)	12 (3.3) (1.40,5.82)	5 (1.4) (0.27,2.72)
Bro 6mg vs. Afl 2mg Risk Difference 95% CI	3.6 (1.08, 6.53)		1.9 (-0.54,5.02)	
Maximum severity				
Mild	16 (2.2)	1 (0.1)	7 (1.9)	2 (0.5)
Moderate	13 (1.8)	5 (0.7)	3 (0.8)	3 (0.8)
Severe	3 (0.4)	0 (0.0)	2 (0.5)	0 (0.0)
SAEs	7 (1.0)	0 (0.0)	1 (0.3)	1 (0.3)
AE outcome				
Recovered/resolved	26 (3.6)	5 (0.7)	9 (2.4)	5 (1.4)
Recovered/resolved with sequelae	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Not recovered/not resolved	3 (0.4)	1 (0.1)	2 (0.5)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	Pooled nAMD (Ocular, 96 Week long term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
- AEs with a start date on or after the date of first study treatment administration are included. AEs with a start date on or after the subject discontinued study treatment and started alternative DME treatment in the study eye are not included unless the AE led to permanent discontinuation of study treatment. - A subject with multiple occurrences of an AE for a risk is counted only once for that risk. - Severity: A subject with multiple occurrences of an AE for a risk is counted only once for that risk with the maximum severity. - Outcome: A subject with multiple occurrences of an AE for a risk is counted only once for that risk under the most 'severe' outcome. - The methodology used to calculate CIs depends on the number of subjects with the event. - MedDRA Version 25.0 has been used for reporting. Source: [EU RMP version 2.0 Annex 7 Table 2-3RTHP2_RMP], [EU RMP version 10.0 Annex 7 - Table 2-3P1p_RMPB_Y2]				

Table 8-5 Important identified risk Intraocular inflammation: Other details

Intraocular inflammation	Details
Potential mechanisms	The mechanism that might cause intraocular inflammation is currently not fully defined. Potential mechanisms include the quality of the test article, the pharmacology of the protein (e.g., binding of specific complement factors), Anti-Drug Antibodies (ADA) as with all therapeutic proteins, or the amount or molar dose of protein injected into the eye. No relationship has been found between batch numbers and the intraocular inflammation events. Data from a number of sources do also not support the hypothesis that the molar dose of protein injected into the eye correlates with the development of intraocular inflammation. Examples of other agents that contain greater molar doses of protein than that in a 6 mg dose of brolucizumab have not been associated with the development of intraocular inflammation. In two Phase 3 studies with lampalizumab (Spectri and Chroma), an anti-Factor D Fab with a molecular weight twice the molecular weight of brolucizumab, doses of 10 mg have been administered intravitreally every 4 weeks for 48 weeks without any reported notable tolerability issues. Additionally, in Novartis early development programs in non-human primates, intravitreal doses of 10 mg of Fab have been administered once every two weeks for 26 weeks, doses of 19 mg of a Fab-Fab bispecific construct have been administered once every two weeks for 3 doses and 12 mg of an single-chain variable fragments (scFv) have been administered once every two weeks for 2 doses, all without side effects or dose limiting toxicities (Novartis data on file). Also, in the Study RTH258-C001 and Study RTH258-C002, there was no increase in the incidence of patients with intraocular inflammation events in the second year of treatment, which would have been expected in case of a relationship between the exposure to the drug and/or the molar dose and

Intraocular inflammation	Details
	the development of intraocular inflammation. Hence, although a brolucizumab 6 mg dose represents the highest amount and highest molar dose of an anti-VEGF administered intravitreally, a relationship between the amount of protein and/or molar dose and the development of intraocular inflammation is highly unlikely. The immunogenicity of brolucizumab was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to brolucizumab in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. Pre-treatment antibodies have been detected in drug-naïve subjects for a variety of biotechnology-derived therapeutic proteins including single-chain antibodies. The pre-treatment incidence of anti-brolucizumab antibodies was 35-52%. After dosing with brolucizumab for 88 weeks, treatment-emergent anti-brolucizumab antibodies were detected in 23-25% of patients. Anti-brolucizumab antibodies were not associated with an impact on clinical efficacy. Among patients with treatment-emergent antibodies, a higher number of intraocular inflammation events were observed. All these events were treated with standard of care.
Evidence source(s) and strength of evidence	The evidence comes from 4 pivotal trials in nAMD and DME indications and overall there is an imbalance between the brolucizumab and aflibercept arms.
Characterization of the risk	The number of patients with an intraocular inflammation event for brolucizumab 6 mg was 4.4% in the long-term S-db (nAMD) and 3.3% in the 100 week S-db (DME). Most events of intraocular inflammation in the 100 week S-db (DME) were mild or moderate in severity. In nAMD, most patients with an intraocular inflammation event had an event occurring during the first 6 months of treatment and intraocular inflammation AEs newly occurring in Year 2 were balanced between the brolucizumab and aflibercept treatment arms. Most intraocular inflammation cases were mild to moderate, and most resolved without sequelae. In a Phase IIIa clinical trial (MERLIN), in patients with nAMD who received brolucizumab every 4 weeks (q4w) maintenance dosing, intraocular inflammation (including retinal vasculitis) and retinal occlusion were reported with a higher frequency in the brolucizumab 6 mg arm with continuous q4w (not approved regimen) compared to aflibercept 2 mg arm with continuous q4w regimen (IOI: 9.3% vs 4.5% of which RV: 0.8% vs 0.0%; RO: 2.0% vs 0.0%). In a Phase IIIb clinical trial (TALON), in patients with nAMD, the incidence of intraocular inflammation in brolucizumab 6 mg compared to aflibercept 2 mg treatment arms was 4.4% vs 1.4%.
Risk factors and risk groups	In nAMD clinical trials, a higher intraocular inflammation incidence was observed in Japanese patients treated with brolucizumab compared to non-Japanese patients. In Study RTH258-C001 the number of patients with an intraocular inflammation event was 7/60 (11.7%) in Japanese patients and 14/300 (4.7%) in non-Japanese patients. There is also a higher incidence of intraocular inflammation in females compared to males (long-term S-db): brolucizumab 6 mg 5.3% in females vs. 3.2% in males.

Intraocular inflammation	Details
	In DME clinical trials, the above observations were not possible to make due to the smaller size of the Japanese cohort (approximately 20 per treatment arm). In overall population included in the DME trials KESTREL and KITE, there is also a higher incidence of intraocular inflammation in females compared to males (100 Week S-db in DME): pooled brolucizumab 6 mg 5.1% in females (7/138) vs. 2.2% in males (5/230). In the nAMD clinical trials, a higher proportion of patients who developed intraocular inflammation had a positive status for treatment emergent (boosted or induced) ADAs, as compared to those with a negative post-treatment ADA status In the DME clinical trials, a higher proportion of patients who developed AESIs had a positive status for treatment emergent (boosted or induced) ADAs, as compared to those with a negative post-treatment ADA status.
Preventability	Given that there is no apparent mechanism leading to the reported incidence of intraocular inflammation events associated with brolucizumab, there are no additional steps to prevent intraocular inflammation specific to brolucizumab.
Impact on the benefit-risk balance of the product	Most intraocular inflammation cases were mild to moderate and most resolved with appropriate standard of care treatment and with no sequelae. Therefore, the impact on the benefit-risk balance of the product is considered to be low.
Public health impact	There is no public health impact.
Source: [EU RMP version 2.0 Annex 7 Table 2-1RTHP2_RMP], [EU RMP version 2.0 Annex 7 Table 2-1aRTHP2_RMP], [Summary of Clinical Safety], [Study RTH258-C001], [Study RTH258-C002], [EU RMP version 10.0 Annex 7 -Table 2-3P1p_RMPB_Y2], [EU RMP version 10.0 Annex 7 - Table 2-1aP1p_RMPB_Y2], [SCS DME Wk100], and [EU RMP version 12.0 Annex 7 Table RMP1]	

8.3.1.2 Important identified risk: Retinal vasculitis and/or retinal vascular occlusion

Table 8-6 Clinical trial data of Retinal vasculitis and/or retinal vascular occlusion

	Pooled nAMD (Ocular, 96 Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Number of patients with at least one event	6 (0.8) (0.27,1.78)	1 (0.1) (0.00,0.54)	4 (1.1) (0.00, 2.65)	2 (0.5) (0.00, 1.36)
Bro 6mg vs. Afl 2mg Risk Difference 95% CI	0.7 (-0.14,1.67)		0.5 (-0.82, 2.17)	
Maximum severity				
Mild	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)
Moderate	2 (0.3)	1 (0.1)	1 (0.3)	1 (0.3)

	Pooled nAMD (Ocular, 96 Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Severe	3 (0.4)	0 (0.0)	2 (0.5)	1 (0.3)
SAEs	3 (0.4)	1 (0.1)	2 (0.5)	0 (0.0)
AE outcome				
Recovered/resolved	1 (0.1)	1 (0.1)	1 (0.3)	1 (0.3)
Recovered/resolved with sequelae	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Not recovered/not resolved	4 (0.5)	0 (0.0)	3 (0.8)	1 (0.3)
Unknown	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- AEs with a start date on or after the date of first study treatment administration are included. AEs with a start date on or after the subject discontinued study treatment and started alternative DME treatment in the study eye are not included unless the AE led to permanent discontinuation of study treatment.
- A subject with multiple occurrences of an AE for a risk is counted only once for that risk.
- Severity: A subject with multiple occurrences of an AE for a risk is counted only once for that risk with the maximum severity.
- Outcome: A subject with multiple occurrences of an AE for a risk is counted only once for that risk under the most 'severe' outcome.
- The methodology used to calculate CIs depends on the number of subjects with the event.
- MedDRA Version 25.0 has been used for reporting

Source: [EU RMP version 4.0 Annex 7 Table 2-7RTHP2_RMPA] [EU RMP version 10.0 Annex 7 Table 2-3P1p_RMPB_Y2]

Table 8-7 Important identified risk retinal vasculitis and/or retinal vascular occlusion: Other details

Retinal vasculitis and/or retinal vascular occlusion	**Details**
Potential mechanisms	Typically, retinal vasculitis and/or retinal vascular occlusion events are seen in the presence of intraocular inflammation. The results from the BASICHR0049 mechanistic study represent an additional characterization of the risk and indicate that the underlying mechanism is immune mediated. These results suggest a mature, high affinity and diverse IgG-driven ADA response with ADAs recognizing multiple different B cell epitopes on the brolucizumab molecule. The presence of a polyclonal and diverse immune response against multiple epitopes to brolucizumab, along with a possible increased potential for platelet aggregation, could be consistent with an increased risk of the formation of immune complexes resulting in intraocular inflammation and vascular occlusion. In addition, the in vitro activation by brolucizumab of T-cell from case subjects is evidence that these master regulators of the immune response carried a memory of previous activation to

Retinal vasculitis and/or retinal vascular occlusion	**Details**
	brolucizumab. This provides evidence that subjects with brolucizumab-associated retinal vasculitis and/or retinal vascular occlusion had a coordinated and specific immunity to brolucizumab. In Study RTH258-C001 and Study RTH258-C002, the pre-treatment incidence of anti-brolucizumab antibodies was 35 – 52%. After dosing with brolucizumab for 88 weeks, treatment-emergent anti-brolucizumab antibodies were detected in 23 to 25% of patients. Among patients with treatment-emergent antibodies, a higher number of intraocular inflammation events were observed. The totality of the available evidence indicates that the treatment-emergent immune response against brolucizumab drives the immune-mediated adverse reactions. The presence of pre-existing ADA does not influence the likelihood that a patient would develop a treatment-emergent immune response against brolucizumab or influence the likelihood of developing IOI including RV, and/or RO.
Evidence source(s) and strength of evidence	Current evidence is based on the 4 pivotal trials in nAMD and DME indications and on post-marketing data for nAMD indication.
Characterization of the risk:	Retinal vasculitis was defined in the pivotal AMD Phase III studies as part of intraocular inflammation and no cases of retinal vasculitis were reported for brolucizumab 6 mg. One event was reported in a patient receiving brolucizumab 3 mg. Intraocular inflammation is characterized in the relevant section. In a Phase IIIa clinical trial (MERLIN), in patients with nAMD who received brolucizumab every 4 week maintenance dosing, intraocular inflammation (including retinal vasculitis) and retinal occlusion were reported with a higher frequency in the brolucizumab 6 mg every four weeks arm when compared to aflibercept 2 mg every four weeks (IOI: 9.3% vs 4.5% of which RV: 0.8% vs 0.0%; RO: 2.0% vs 0.0%.). DME studies The data from the patients experiencing RV and/or RO from DME studies is presented in table below.

Retinal vasculitis and/or retinal vascular occlusion	**Details**

Dose	Adverse event	Action taken with study drug	BCVA BL	BCVA Week 100 (vs BL)	Outcome
Patients treated with brolucizumab 6 mg					
Patient 1 Bro 6mg	Retinal vasculitis	None	72	84 (+12L)	Resolved
	Retinal artery occlusion	None			Resolved
Patient 2* Bro 6mg	(Central) Retinal artery occlusion	Drug withdrawn	75	Not applicable*	AE ongoing
Patient 3 Bro 6mg	Retinal artery stenosis	None	34	70	AE ongoing
Patient 4 Bro 6mg	Retinal vein occlusion Retinal artery occlusion	Drug withdrawn due to other event (Cerebrovascular accident)	78	Hand motion	AE ongoing
Patients treated with brolucizumab 3 mg					
Patient 5# Bro 3mg	Retinal vasculitis (also experienced iritis)	Drug withdrawn	75	Not applicable	AE ongoing
Patient 6 Bro 3mg	Retinal vasculitis (also experienced uveitis)	Drug interrupted	78	67 (-11L)	Resolved
Patient 7 Bro 3mg	Retinal vein thrombosis (also experienced 3 events of iridocyclitis)	None	72	9(-63)	AE ongoing
Patient 8 Bro 3mg	Retinal vasculitis (also experienced uveitis and vitritis)	None	51	54 (+3L)	Resolved
	Retinal artery occlusion	Drug withdrawn			AE ongoing
Patient 9 Bro 3mg	Retinal artery occlusion	Drug interrupted	69	Finger count	AE ongoing

BCVA: Best Corrected Visual Acuity; BL: Baseline; L: Letters

* Patient 2: BCVA reported as hand motion at the onset of AE. This patient was terminated early from the study, so Week 100 BCVA is not applicable.

Retinal vasculitis and/or retinal vascular occlusion	**Details**
	#Patient 5: BCVA reported after onset of the AE was 69 (loss of 6L compared to BL) which then recovered to 73L Source: [Brolucizumab summary of clinical safety-DME] Events of "retinal vasculitis" and/or "retinal vascular occlusion" reported in the post-marketing setting have occurred in the presence of intraocular inflammation. Some of these events have been reported with severe vision loss. In a Phase IIIb clinical trial (TALON), in patients with nAMD, the incidence of retinal vasculitis and/or retinal vascular occlusion in brolucizumab 6 mg compared to aflibercept 2 mg treatment arms was 1.4% vs 0.3%. Source: [EU RMP version 12.0 Annex 7 Table RMP1]
Risk factors and risk groups	Patients who are at risk for intraocular inflammation or with active intraocular inflammation at the time of brolucizumab administration are considered as a risk groups for retinal vasculitis and retinal vascular occlusion. Based on a retrospective real world evidence analysis, patients with a medical history of intraocular inflammation and/or retinal vascular occlusion in the year prior to treatment with brolucizumab were more likely to present with similar events after brolucizumab injection, as compared to nAMD patients with no history of these events.
Preventability	Retinal vasculitis and retinal vascular occlusion are typically seen in the presence of intraocular inflammation. A careful eye examination before each intravitreal injection should be performed to exclude an intraocular inflammation. Intraocular inflammation is a contraindication in anti-VEGF drugs for intravitreal use. Furthermore, patient awareness of signs of inflammation and prompt reporting of these to the healthcare provider could allow for timely and corrective therapeutic measures. Discontinuation of the treatment with brolucizumab in patients developing retinal vasculitis and/or retinal vascular occlusion events, managing the symptoms and discontinuation of treatment in the patients experiencing intraocular inflammation is advised as these patients may be at risk of developing retinal vasculitis and/or retinal vascular occlusion. Patients treated with brolucizumab with a medical history of intraocular inflammation and/or retinal vascular occlusion (within 12 months prior to the first brolucizumab injection) should be closely monitored, since they are at increased risk of developing retinal vasculitis and/or retinal vascular occlusion.
Impact on the benefit-risk balance of the product	Retinal vasculitis was observed to occur with uncommon frequency and the frequency of retinal vascular occlusion was changed from 'uncommon' to 'common' in the pooled DME studies through Week 100. The impact of retinal vasculitis and/or retinal vascular occlusion on the benefit-risk balance of the product is considered to be low.
Public health impact	The impact on public health is considered to be low.

8.3.1.3 Important identified risk: Endophthalmitis

Table 8-8 Clinical trial data of Endophthalmitis

	Pooled nAMD (Ocular, 96 Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Number of patients with at least one event	5 (0.7) (0.00, 1.67)	1 (0.1) (0.00, 0.54)	2 (0.5) (0.07, 1.95)	2 (0.5) (0.07, 1.95)
Bro 6mg vs. Afl 2mg Risk Difference 95% CI	0.5 (-0.27, 1.67)		0.0 (-7.35, 7.35)	
Maximum severity				
Mild	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Moderate	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Severe	3 (0.4)	1 (0.1)	2 (0.5)	1 (0.3)
SAEs	4 (0.5)	1 (0.1)	2 (0.5)	2 (0.5)
AE outcome				
Recovered/resolved	2 (0.3)	0 (0.0)	2 (0.5)	1 (0.3)
Recovered/resolved with sequelae	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Not recovered/not resolved	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- AEs with a start date on or after the date of first study treatment administration are included. AEs with a start date on or after the subject discontinued study treatment and started alternative DME treatment in the study eye are not included unless the AE led to permanent discontinuation of study treatment.
- A subject with multiple occurrences of an AE for a risk is counted only once for that risk.
- Severity: A subject with multiple occurrences of an AE for a risk is counted only once for that risk with the maximum severity.
- Outcome: A subject with multiple occurrences of an AE for a risk is counted only once for that risk under the most 'severe' outcome.
- The methodology used to calculate CIs depends on the number of subjects with the event.
- MedDRA Version 25.0 has been used for reporting.

Source: [EU RMP version 2.0 Annex 7 Table 2-3RTHP2_RMP] [EU RMP version 10.0 Annex 7 Table 2-3P1p_RMPB_Y2]

Table 8-9 Important identified risk- Endophthalmitis: Other details

Endophthalmitis	Details
Potential mechanisms	Intravitreal injection procedures, including those with brolucizumab, have been associated with endophthalmitis.

Endophthalmitis	Details
Evidence source(s) and strength of evidence	The incidence of endophthalmitis after an intravitreal injection is low. Current evidence is based on the 4 pivotal trials in nAMD and DME indications.
Characterization of the risk	Endophthalmitis is a well-known and well-characterized risk associated with the intravitreal injection procedure. The number of patients with an endophthalmitis in the brolucizumab pivotal studies was low (long-term S-db: brolucizumab 3 mg 1.1%; brolucizumab 6 mg 0.7%). The risk difference between brolucizumab 6 mg and aflibercept 2 mg in nAMD was less than 1.0% [0.5% (95% CI: −0.27%, 1.67%)] in the long-term S-db. The number of patients with an endophthalmitis is similar to incidences reported in ranibizumab clinical studies. In DME, very few patients (0.5%) experienced endophthalmitis and the risk difference is thus difficult to interpret. In a Phase IIIb clinical trial (TALON), in patients with nAMD, the incidence of endophthalmitis in brolucizumab 6 mg compared to aflibercept 2 mg treatment arms was 0.3% vs 0%.
Risk factors and risk groups	There is an increased risk of endophthalmitis if the intravitreal injection procedure is not carried out under aseptic conditions.
Preventability	The SmPC specifically mentions that the intravitreal injection procedure should be carried out under aseptic conditions, which include the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.
Impact on the benefit-risk balance of the product	The incidence of endophthalmitis in the brolucizumab pivotal studies was low. The impact of endophthalmitis on the benefit-risk balance of the brolucizumab is considered to be low since 'how to administer an intravitreal injection' and 'how to communicate to the patients when to seek urgent medical attention' are standard clinical practice to minimize the risk of infections with the use of intravitreal injections.
Public health impact	The impact on public health is considered to be low. Events are generally manageable with appropriate treatment.
Source: [EU RMP version 2.0 Annex 7 Table 2-1RTHP2_RMP], [EU RMP version 2.0 Annex 7 Table 2-1aRTHP2_RMP], [Summary of Clinical Safety], [Study RTH258-C001], [Study RTH258-C002], [EU RMP version 10.0 Annex 7 -Table 2-3P1p_RMPB_Y2], [SCS DME Wk100], and [EU RMP version 12.0 Annex 7 Table RMP1]	

8.3.1.4 Important identified risk: Transient intraocular pressure increased

Table 8-10 Clinical trial data of Transient intraocular pressure increased

	Pooled nAMD (Ocular, 96 Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Number of patients with at least one event	26 (3.6) (2.08, 4.93)	30 (4.1) (2.64, 5.56)	17 (4.6) (2.23, 7.67)	7 (1.9) (0.53, 3.31)

	Pooled nAMD (Ocular, 96 Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Bro 6mg vs. Afl 2mg Risk Difference 95% CI	-0.6 (-2.64, 1.48)		2.7 (-0.25, 6.34)	
Maximum severity				
Mild	15 (2.1)	23 (3.2)	9 (2.4)	6 (1.6)
Moderate	11 (1.5)	6 (0.8)	7 (1.9)	1 (0.3)
Severe	0 (0.0)	1 (0.1)	1 (0.3)	0 (0.0)
SAEs	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
AE outcome				
Recovered/resolved	18 (2.5)	25 (3.4)	16 (4.3)	7 (1.9)
Recovered/resolved with sequelae	0 (0.0)	1 (0.1)	1 (0.3)	0 (0.0)
Not recovered/not resolved	7 (1.0)	4 (0.5)	0 (0.0)	0 (0.0)
Unknown	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- AEs with a start date on or after the date of first study treatment administration are included. AEs with a start date on or after the subject discontinued study treatment and started alternative DME treatment in the study eye are not included unless the AE led to permanent discontinuation of study treatment.
- A subject with multiple occurrences of an AE for a risk is counted only once for that risk.
- Severity: A subject with multiple occurrences of an AE for a risk is counted only once for that risk with the maximum severity.
- Outcome: A subject with multiple occurrences of an AE for a risk is counted only once for that risk under the most 'severe' outcome.
- The methodology used to calculate CIs depends on the number of subjects with the event.
- MedDRA Version 25.0 has been used for reporting.

Source: [EU RMP version 2.0 Annex 7 Table 2-3RTHP2_RMP] [EU RMP version 10.0 Annex 7 Table 2-3P1p_RMPB_Y2]

Table 8-11 Important identified risk- Transient intraocular pressure increased: other details

Transient intraocular pressure increased	Details
Potential mechanisms	Transient intraocular pressure increased is a well-known and well-characterized risk associated with an intravitreal injection volume of 0.05 mL. Brolucizumab is also administered with a volume 0.05 mL and therefore a transient intraocular pressure increase due to increased intraocular volume may be anticipated.

Transient intraocular pressure increased	Details
Evidence source(s) and strength of evidence	Current evidence is based on the 4 pivotal trials in nAMD and DME indications. In the two pivotal nAMD trials for brolucizumab (Study RTH258-C001 and Study RTH258-C002), transient increases in intraocular pressure have been seen within 30 minutes of injection, similar to those observed with intravitreal administration of other VEGF inhibitors. These post-injection increases are self-limiting or can be treated with standard of care.
Characterization of the risk	Transient intraocular pressure increased is a well-known and well-characterized risk associated with the intravitreal injection of 0.05 mL brolucizumab solution. The number of patients with an intraocular pressure increased in the brolucizumab pivotal studies was low. The risk difference between brolucizumab 6 mg and aflibercept 2 mg was comparable in nAMD, while it was slightly higher in DME. In a Phase IIIb clinical trial (TALON), in patients with nAMD, the incidence of transient intraocular pressure increased in brolucizumab 6 mg compared to aflibercept 2 mg treatment arms was 1.4% vs 3.0%.
Risk factors and risk groups	Patients with intraocular pressure increased or glaucoma prior to the intravitreal injection.
Preventability	As per SmPC both intraocular pressure and perfusion of the optic nerve head must be monitored and managed appropriately. If needed, an intraocular pressure increased can be treated with standard of care.
Impact on the benefit-risk balance of the product	The impact of transient intraocular pressure increased on the benefit-risk balance of the product is considered to be low.
Public health impact	The impact on public health is considered to be low. Events are generally manageable with standard of care.
Source: [EU RMP version 2.0 Annex 7 Table 2-1RTHP2_RMP], [EU RMP version 2.0 Annex 7 Table 2-1aRTHP2_RMP], [Summary of Clinical Safety], [Study RTH258-C001], [Study RTH258-C002], [EU RMP version 10.0 Annex 7 -Table 2-3P1p_RMPB_Y2], [SCS DME Wk100], and [EU RMP version 12.0 Annex 7 Table RMP1]	

8.3.1.5 Important identified risk: Retinal detachment / tear

Table 8-12 Clinical trial data of Retinal detachment / tear

	Pooled nAMD (Ocular, 96 Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Number of patients with at least one event	12 (1.6) (0.68, 3.06)	7 (1.0) (0.28, 1.81)	1 (0.3) (0.01, 1.50)	3 (0.8) (0.17, 2.36)
Bro 6mg vs. Afl 2mg Risk Difference 95% CI	0.7 (-0.54, 2.08)		-0.5 (-7.89, 6.81)	

	Pooled nAMD (Ocular, 96 Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Maximum severity				
Mild	7 (1.0)	5 (0.7)	1 (0. 3)	0 (0.0)
Moderate	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Severe	3 (0.4)	2 (0.3)	0 (0.0)	2 (0.5)
SAEs	3 (0.4)	3 (0.4)	0 (0.0)	2 (0.5)
AE outcome				
Recovered/resolved	7 (1.0)	3 (0.4)	0 (0.0)	2 (0.5)
Recovered/resolved with sequelae	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)
Not recovered/not resolved	3 (0.4)	4 (0.5)	1 (0.3)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- AEs with a start date on or after the date of first study treatment administration are included. AEs with a start date on or after the subject discontinued study treatment and started alternative DME treatment in the study eye are not included unless the AE led to permanent discontinuation of study treatment.
- A subject with multiple occurrences of an AE for a risk is counted only once for that risk.
- Severity: A subject with multiple occurrences of an AE for a risk is counted only once for that risk with the maximum severity.
- Outcome: A subject with multiple occurrences of an AE for a risk is counted only once for that risk under the most 'severe' outcome.
- The methodology used to calculate CIs depends on the number of subjects with the event.
- MedDRA Version 25.0 has been used for reporting.

Source: [EU RMP version 2.0 Annex 7 Table 2-3RTHP2_RMP] [EU RMP version 10.0 Annex 7 Table 2-3P1p_RMPB_Y2]

Table 8-13 Important identified risk- Retinal detachment / tear: Other details

Retinal detachment / tear	Details
Potential mechanisms	Retinal detachment and tear are mainly associated with the underlying disease and aging; rarely these are associated with the intravitreal injection or with intravitreally administered VEGF-inhibitors.
Evidence source(s) and strength of evidence	Retinal detachment and tear is a well-known and well-characterized risk associated with the underlying disease and the aging of the eye.
Characterization of the risk	The number of patients with retinal detachment and tear was low (brolucizumab 6 mg nAMD 1.6% and DME 0.3%). The risk difference between brolucizumab 6 mg and aflibercept 2 mg was less than 1.0% in both indication pivotal studies. Overall, the reported incidences are similar

Retinal detachment / tear	Details
	to ranibizumab clinical studies (Lucentis EU RMP version 17.2 and Lucentis PSUR 12). In a Phase IIIb clinical trial (TALON), in patients with nAMD, the incidence of retinal detachment / tear in brolucizumab 6 mg compared to aflibercept 2 mg treatment arms was 0.3% vs 0.3%.
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, or severe high blood pressure.
Preventability	Caution should be used in patients having risk factors for retinal detachment.
Impact on the benefit-risk balance of the product	The impact of retinal detachment/ tear on the benefit-risk balance of the product is considered to be low.
Public health impact	The impact on public health is considered to be low.
Source: [EU RMP version 2.0 Annex 7 Table 2-1RTHP2_RMP], [EU RMP version 2.0 Annex 7 Table 2-1aRTHP2_RMP], [Summary of Clinical Safety], [Study RTH258-C001], [Study RTH258-C002], [EU RMP version 10.0 Annex 7 -Table 2-3P1p_RMPB_Y2], [SCS DME Wk100], and [EU RMP version 12.0 Annex 7 Table RMP1]	

8.3.1.6 Important potential risk: Non-ocular events (ATE, VTE, non-ocular haemorrhage, and hypertension)

Table 8-14 Clinical trial data of Non-ocular events (ATE)

	Pooled nAMD (Ocular, 96 Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Number of patients with at least one event	22 (3.0) (1.67, 4.25)	30 (4.1) (2.64, 5.69)	21 (5.7) (3.35, 8.15)	26 (7.1) (4.62, 9.89)
Bro 6mg vs. Afl 2mg Risk Difference 95% CI	-1.1 (-3.19, 0.82)		-1.4 (-5.38, 2.17)	
Maximum severity				
Mild	4 (0.5)	5 (0.7)	5 (1.4)	4 (1.1)
Moderate	5 (0.7)	13 (1.8)	4 (1.1)	5 (1.4)
Severe	13 (1.8)	12 (1.6)	12 (3.3)	17 (4.6)
SAEs	17 (2.3)	21 (2.9)	13 (3.5)	22 (6.0)
AE outcome				
Recovered/resolved	10 (1.4)	14 (1.9)	11 (3.0)	14 (3.8)
Recovered/resolved with sequelae	5 (0.7)	5 (0.7)	1 (0.3)	5 (1.4)

	Pooled nAMD (Ocular, 96 Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Not recovered/not resolved	4 (0.5)	9 (1.2)	6 (1.6)	3 (0.8)
Unknown	0 (0.0)	1 (0.1)	1 (0.3)	2 (0.5)
Fatal	3 (0.4)	1 (0.1)	2 (0.5)	2 (0.5)

- AEs with a start date on or after the date of first study treatment administration are included. AEs with a start date on or after the subject discontinued study treatment and started alternative DME treatment in the study eye are not included unless the AE led to permanent discontinuation of study treatment.
- A subject with multiple occurrences of an AE for a risk is counted only once for that risk.
- Severity: A subject with multiple occurrences of an AE for a risk is counted only once for that risk with the maximum severity.
- Outcome: A subject with multiple occurrences of an AE for a risk is counted only once for that risk under the most 'severe' outcome.
- The methodology used to calculate CIs depends on the number of subjects with the event.
- MedDRA Version 25.0 has been used for reporting.

Source: [EU RMP version 2.0 Annex 7 Table 2-4RTHP2_RMP] [EU RMP version 10.0 Annex 7 Table 2-4P1p_RMPB_Y2]

Table 8-15 Clinical trial data of Non-ocular events (VTE)

	Pooled nAMD (Ocular, 96 Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Number of patients with at least one event	5 (0.7) (0.14, 1.39)	9 (1.2) (0.42, 2.06)	5 (1.4) (0.27, 3.26)	3 (0.8) (0.00, 1.93)
Bro 6mg vs. Afl 2mg Risk Difference 95% CI	-0.5 (-1.63, 0.56)		0.5 (-0.83, 2.45)	
Maximum severity				
Mild	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.5)
Moderate	4 (0.5)	6 (0.8)	0 (0.0)	0 (0.0)
Severe	1 (0.1)	2 (0.3)	5 (1.4)	1 (0.3)
SAEs	2 (0.3)	4 (0.5)	4 (1.1)	2 (0.5)
AE outcome				
Recovered/resolved	3 (0.4)	7 (1.0)	4 (1.1)	0 (0.0)
Recovered/resolved with sequelae	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not recovered/not resolved	2 (0.3)	2 (0.3)	1 (0.3)	3 (0.8)

	Pooled nAMD (Ocular, 96 Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- AEs with a start date on or after the date of first study treatment administration are included. AEs with a start date on or after the subject discontinued study treatment and started alternative DME treatment in the study eye are not included unless the AE led to permanent discontinuation of study treatment.
- A subject with multiple occurrences of an AE for a risk is counted only once for that risk.
- Severity: A subject with multiple occurrences of an AE for a risk is counted only once for that risk with the maximum severity.
- Outcome: A subject with multiple occurrences of an AE for a risk is counted only once for that risk under the most 'severe' outcome.
- The methodology used to calculate CIs depends on the number of subjects with the event.
- MedDRA Version 25.0 has been used for reporting.

Source: [EU RMP version 2.0 Annex 7 Table 2-4RTHP2_RMP] [EU RMP version 10.0 Annex 7 Table 2-4P1p_RMPB_Y2]

Table 8-16 Clinical trial data of Non-ocular events (non-ocular haemorrhage)

	Pooled nAMD (Ocular, 96Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Number of patients with at least one event	52 (7.1) (5.21, 9.32)	57 (7.8) (4.34, 12.22)	15 (4.1) (2.12, 6.15)	16 (4.3) (2.45, 6.79)
Bro 6mg vs. Afl 2mg Risk Difference 95% CI	-0.7 (-5.00, 2.69)		-0.3 (-3.53, 2.72)	
Maximum severity				
Mild	28 (3.8)	31 (4.3)	5 (1.4)	11 (3.0)
Moderate	17 (2.3)	19 (2.6)	4 (1.1)	4 (1.1)
Severe	7 (1.0)	7 (1.0)	6 (1.6)	1 (0.3)
SAEs	13 (1.8)	13 (1.8)	9 (2.4)	3 (0.8)
AE outcome				
Recovered/resolved	38 (5.2)	41 (5.6)	8 (2.2)	9 (2.4)
Recovered/resolved with sequelae	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Not recovered/not resolved	10 (1.4)	14 (1.9)	3 (0.8)	5 (1.4)
Unknown	1 (0.1)	2 (0.3)	3 (0.8)	1 (0.3)

	Pooled nAMD (Ocular, 96Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Fatal	1 (0.1)	0 (0.0)	1 (0.3)	1 (0.3)

- AEs with a start date on or after the date of first study treatment administration are included. AEs with a start date on or after the subject discontinued study treatment and started alternative DME treatment in the study eye are not included unless the AE led to permanent discontinuation of study treatment.
- A subject with multiple occurrences of an AE for a risk is counted only once for that risk.
- Severity: A subject with multiple occurrences of an AE for a risk is counted only once for that risk with the maximum severity.
- Outcome: A subject with multiple occurrences of an AE for a risk is counted only once for that risk under the most 'severe' outcome.
- The methodology used to calculate CIs depends on the number of subjects with the event.
- MedDRA Version 25.0 has been used for reporting.

Source: [EU RMP version 2.0 Annex 7 Table 2-3RTHP2_RMP] [EU RMP version 10.0 Annex 7 Table 2-4P1p_RMPB_Y2]

Table 8-17 Clinical trial data of Non-ocular events (Hypertension)

	Pooled nAMD (Ocular, 96 Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
Number of patients with at least one event	66 (9.0) (6.99, 11.25)	72 (9.9) (7.41, 12.07)	48 (13.0) (9.51,17.20)	50 (13.6) (9.94,17.93)
Bro 6mg vs. Afl 2mg Risk Difference 95% CI	-0.8 (-3.99, 2.78)		-0.5 (-5.50, 4.35)	
Maximum severity				
Mild	45 (6.2)	50 (6.9)	30 (8.2)	29 (7.9)
Moderate	20 (2.7	20 (2.7.3)	13 (3.5)	17 (4.6)
Severe	1 (0.1)	2 (0.3)	5 (1.4)	4 (1.1)
SAEs			5 (1.4)	3 (0.8)
AE outcome				
Recovered/resolved	28 (3.8)	42 (5.8)	27 (7.3)	22 (6.0)
Recovered/resolved with sequelae	0 (0.0)	1 (0.1)	2 (0.5)	4 (1.1)
Not recovered/not resolved	35 (4.8)	28 (3.8)	17 (4.6)	23 (6.3)
Unknown	3 (0.4)	1 (0.1)	2 (0.5)	1 (0.3)
Fatal			0 (0.0)	0 (0.0)

	Pooled nAMD (Ocular, 96 Week Long-term S-db)		Pooled DME (100 Week S-db)	
	Bro 6mg N=730 n (%) 95% Bootstrap CI	Afl 2mg N=729 n (%) 95% Bootstrap CI	Bro 6mg N=368 n (%) (95% CI)	Afl 2mg N=368 n (%) (95% CI)
- AEs with a start date on or after the date of first study treatment administration are included. AEs with a start date on or after the subject discontinued study treatment and started alternative DME treatment in the study eye are not included unless the AE led to permanent discontinuation of study treatment. - A subject with multiple occurrences of an AE for a risk is counted only once for that risk. - Severity: A subject with multiple occurrences of an AE for a risk is counted only once for that risk with the maximum severity. - Outcome: A subject with multiple occurrences of an AE for a risk is counted only once for that risk under the most 'severe' outcome. - The methodology used to calculate CIs depends on the number of subjects with the event. - MedDRA Version 25.0 has been used for reporting. Source: [EU RMP version 2.0 Annex 7 Table 2-4RTHP2_RMP] [EU RMP version 10.0 Annex 7 Table 2-4P1p_RMPB_Y2]				

Table 8-18 Important potential risk- Non-ocular events (ATE, VTE, non-ocular haemorrhage and hypertension): Other details

Non-ocular events (ATE, VTE, non-ocular haemorrhage and hypertension)	Details
Potential mechanisms	Systemically administered VEGF-inhibitors in patients with cancer have been associated with an increased risk of ATEs, VTEs, non-ocular haemorrhage and hypertension (see e.g. SmPCs of Zaltrep, Avastin, Votrient) due to its effect on the microvasculature.
Evidence source(s) and strength of evidence	Although there is an increased risk of ATEs, VTEs, non-ocular haemorrhage and hypertension after intravenously administered high doses of VEGF-inhibitors for the treatment of cancer, there is currently no evidence of increased incidences of ATEs, VTEs, non-ocular haemorrhage and hypertension for the much lower intravitreally administered doses of VEGF-inhibitors in patients with nAMD (Zarbin et al 2018, Kitchens et al 2016, Lucentis RMP version 16.2). After intravitreal administration in cynomolgus monkeys, the systemic maximal concentration of brolucizumab is approximately 1000-fold less than the trough concentration of a therapeutic dose of intravenously administered anti-VEGFs.
Characterization of the risk	The number of patients with ATEs in the brolucizumab pivotal studies was low (brolucizumab 6 mg: 3.0% in the long-term S-db in nAMD and 5.7% in the 100 week S-db in DME). The risk difference between brolucizumab 6 mg and aflibercept 2 mg was less than 1.0% in both indications.

Non-ocular events (ATE, VTE, non-ocular haemorrhage and hypertension)	Details
	The number of patients with VTEs in the brolucizumab pivotal studies was low (brolucizumab 6 mg: 0.7% in the long-term S-db in nAMD and 1.4% in the 100 week S-db in DME). The Risk difference between brolucizumab 6 mg and aflibercept 2 mg was balanced overall. The number of patients with a non-ocular haemorrhage in the brolucizumab pivotal studies was low (brolucizumab 6 mg: 7.1% in the long-term S-db in nAMD and 4.1% in the 100 week S-db in DME). The risk difference between brolucizumab 6 mg and aflibercept 2 mg was less than < 1.0% in both indications. The number of patients with a hypertension in the brolucizumab pivotal studies was low (brolucizumab 6 mg: 9.0% in the long-term S-db in nAMD and 13.0% in the 100 week S-db in DME). The risk difference between brolucizumab 6 mg and aflibercept 2 mg was less than < 1.0% in both indications. A reduction in systolic and diastolic blood pressure from baseline was observed in the two pivotal studies RTH258-C001 and RTH258-C002 over a period of 96 weeks. The observed reduction is considered not clinically relevant. In a Phase IIIb clinical trial (TALON), in patients with nAMD, the incidence of non-ocular events in brolucizumab 6 mg compared to aflibercept 2 mg treatment arms was 1.6% vs 2.2% (ATE), 0.3% vs 0.5% (VTE), 3.6% vs 2.4% (non-ocular haemorrhage), and 6.6% vs 5.7% (hypertension).
Risk factors and risk groups	Patients with cardiovascular risk factors or clotting disorders have a higher risk for ATEs, VTEs, non-ocular haemorrhage, and hypertension. In DME patients, underlying disease (diabetes) is a risk factor (Lee et al 2015).
Preventability	Patients with cardiovascular risk factors or clotting disorders have a higher risk for ATEs, VTEs, non-ocular haemorrhage and hypertension should be treated with standard of care.
Impact on the benefit-risk balance of the product	The impact of non-ocular events on the benefit-risk balance of the product is considered to be very low.
Public health impact	The impact on public health is considered to be very low due to the low incidence of these events.
Source: [EU RMP version 2.0 Annex 7 Table 2-1RTHP2_RMP], [EU RMP version 2.0 Annex 7 Table 2-1aRTHP2_RMP], [Summary of Clinical Safety], [Study RTH258-C001], [Study RTH258-C002], [EU RMP version 10.0 Annex 7 -Table 2-4P1p_RMPB_Y2], [SCS DME Wk100], and [EU RMP version 12.0 Annex 7 Table RMP2]	

Although this section on potential risks is primarily intended for non-ocular events, Table 8-19 provides the incidence rates for ocular adverse events in the 100 week S-db in DME which fall under each of the potential risk categories. The ocular AEs were retrieved in the pre-defined

search for the potential risks either based on the broad nature of the MedDRA search or due to the use of non-specific MedDRA coding.

Table 8-19 Clinical trial data of ocular events in the Non-ocular risk group

	Pooled DME (100 week S-db)		
Non-ocular Risk Category Ocular AE (PT)	**Bro 6mg N=368 n (%) (95% CI)**	**Afl 2mg N=368 n (%) (95% CI)**	**Bro 6mg vs Afl 2mg Risk Difference (95% CI)**
Arterial Thromboembolic Events	4 (1.1) (0.26,2.17)	1 (0.3) (0.00,1.09)	0.8 (-0.27,2.12)
Retinal artery occlusion	3 (0.8)	1 (0.3)	
Amaurosis	1 (0.3)	0	
Hypertension	1 (0.3) (0.01,1.50)	0 (0.0) (0.00,1.00)	0.3 (-7.08,7.62)
Retinopathy hypertensive	1 (0.3)	0	
Non-ocular hemorrhage	1 (0.3) (0.01,1.50)	0 (0.0) (0.00,1.00)	0.3 (-7.08,7.62)
Injection site hematoma	1 (0.3)	0	
Venous thromboembolic events	1 (0.3) (0.01,1.50)	0 (0.0) (0.00,1.00)	0.3 (-7.08,7.62)
Retinal vein occlusion	1 (0.3)	0	

- AEs with a start date on or after the date of first study treatment administration are included. AEs with a start date on or after the subject discontinued study treatment and started alternative DME treatment in the study eye are not included unless the AE led to permanent discontinuation of study treatment.
- A subject with multiple occurrences of an AE for a risk is counted only once for that risk.
- Risks are presented alphabetically.
- The methodology used to calculate CIs depends on the number of subjects with the event.
- MedDRA Version 25.0 has been used for reporting.

Source: [EU RMP version 10.0 Annex 7 -Table 2-1P1p_RMPB_Y2]

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

Table 8-20 Safety beyond two years of treatment

Safety beyond two years of treatment	Details
Evidence source	The safety of brolucizumab has been studied up to 96 weeks in the Study RTH258-C001 and Study RTH258-C002 and up to 100 weeks in DME studies (RTH258B2301 and RTH258B2302). The RTH258-C001 extension study provided safety data for 150 patients with a total treatment duration between 120 and 132 weeks. Population in need of further characterization:

Safety beyond two years of treatment	Details
	nAMD and DME are progressive diseases, and long term treatment is often required to control the disease. It is therefore likely that nAMD and DME patients will be treated with brolucizumab beyond two years of treatment. Anticipated risk/consequence of the missing information: The safety profile of brolucizumab beyond two years of treatment has not been studied in controlled clinical trials. Study RTH258A2301E1 enrolled 150 subjects who were treated up to 2.5 years.
Anticipated risk/ consequence of the missing information:	The safety profile of brolucizumab beyond two years of treatment is not known.
Source: [Study RTH258-C001], [Study RTH258-C002] [SCS DME Wk100]	

Table 8-21 Non-ocular safety after bilateral treatment

Non-ocular safety after bilateral treatment	Details
Evidence source	Population in need of further characterization: The safety of brolucizumab administered in both eyes concurrently has not been studied. Anticipated risk/consequence of the missing information: The safety of brolucizumab after bilateral treatment is not known.
Anticipated risk/ consequence of the missing information:	The safety of brolucizumab administered in both eyes concurrently has not been studied.

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

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

Important identified risks	Intraocular inflammation
	Retinal vasculitis and/or retinal vascular occlusion
	Endophthalmitis
	Transient intraocular pressure increased
	Retinal detachment/ tear
Important potential risks	Non-ocular events (ATE, VTE, non-ocular haemorrhage, and hypertension)
Missing information	Safety beyond two years of treatment
	Non-ocular safety after bilateral treatment

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

Specific adverse reaction follow-up checklists:

Specific AE follow-up checklists will be used to collect further data to help further characterize and/or closely monitor the important identified risk "Intraocular inflammation" and "Retinal vasculitis and/or retinal vascular occlusion".

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

Other forms of routine pharmacovigilance activities:

A summary of the data collected using the follow-up checklist for the identified risk of "retinal vasculitis and/or retinal vascular occlusion" will be presented with the PSUR until the risk is characterized or information collected this way is not considered to be further contributory.

Follow up of case reports for biologics: The additional desired information besides the minimal case information for brolucizumab includes the brand name and batch number of the suspect product. Additional efforts are made to collect this information in accordance with GVP VI.

10.2 Part III.2. Additional pharmacovigilance activities

No additional pharmacovigilance studies (category 1-3) are planned or ongoing for brolucizumab as part of this RMP.

10.3 Part III.3. Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Not applicable				

11 Part IV: Plans for post-authorization efficacy studies

Not applicable.

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

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

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

Safety concern	Routine risk minimization activities
Intraocular inflammation	**Routine risk communication** SmPC Sections 4.2, 4.3, 4.4, 4.8. PL Sections 2, 4. Routine risk minimization activities recommending specific clinical measures to address the risk: Brolucizumab is contraindicated in patients with active intraocular inflammation. Physicians are advised to follow proper aseptic injection when administering Beovu. Patients should be advised to promptly report any symptoms suggestive of intraocular inflammation. Physicians are advised that the treatment interval between two doses should not be less than every 8 weeks (2 months) during the maintenance phase. SmPC section 4.4, where information is provided that treatment should be discontinued. Other routine risk minimization measures beyond the Product Information: Pack size: One vial or pre-filled syringe (PFS) for single use only Legal status: Restricted medical prescription
Retinal vasculitis and/or retinal vascular occlusion	SmPC Sections 4.4, 4.8. PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Physicians are advised to instruct the patients to report any symptoms without delay; in patients developing these events, treatment with brolucizumab should be discontinued and the events should be promptly managed. Physicians are advised that the treatment interval between two doses should not be less than every 8 weeks (2 months) during the maintenance phase. Physicians are advised to discontinue the treatment with brolucizumab in patients developing intraocular inflammation including retinal vasculitis and/or retinal vascular occlusion events and manage the symptoms promptly. Patients treated with brolucizumab with a medical history of intraocular inflammation and/or retinal vascular occlusion (within 12 months prior to the first brolucizumab injection) should be closely monitored, since they are at increased risk of developing retinal vasculitis and/or retinal vascular occlusion.

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: Pack size: One vial or pre-filled syringe (PFS) for single use only Legal status: Restricted medical prescription
Endophthalmitis	SmPC Sections 4.2, 4.4, 4.8. PL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Physicians are advised to follow proper aseptic injection when administering Beovu. Patients should be advised to promptly report any symptoms suggestive of endophthalmitis. Other routine risk minimization measures beyond the Product Information: Pack size: One vial or pre-filled syringe (PFS) for single use only Legal status: Restricted medical prescription
Transient intraocular pressure increased	SmPC Sections 4.2, 4.4, 4.8, 4.9. PL Sections 2, 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available. Instructions provided in SmPC to monitor and manage the transient intraocular pressure and perfusion of optic nerve head in patients with poorly controlled glaucoma. Brolucizumab should not be administered while the intraocular pressure is ≥30 mmHg Patients should be advised to inform their physician if they develop symptoms suggestive of transient intraocular pressure increase such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, or increased sensitivity to light. Other routine risk minimization measures beyond the Product Information: Pack size: One vial or pre-filled syringe (PFS) for single use only Legal status: Restricted medical prescription
Retinal detachment/ tear	SmPC Sections 4.4, 4.8. PL Sections 2, 4 Routine risk minimization activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimization activities
	Physicians are advised to follow proper aseptic injection when administering Beovu. Physician are instructed to discontinue the treatment in patients with rhegmatogenous retinal detachment. Other routine risk minimization measures beyond the Product Information: Pack size: One vial or pre-filled syringe (PFS) for single use only Legal status: Restricted medical prescription
Non-ocular events (ATE, VTE, non-ocular haemorrhage, and hypertension)	SmPC Sections 4.4, 4.8. PL Sections 2, 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Physicians are instructed to exercise caution when treating patients with non-ocular haemorrhages and ATE. Other routine risk minimization measures beyond the Product Information: Pack size: One vial or pre-filled syringe (PFS) for single use only Legal status: Restricted medical prescription
Safety beyond two years of treatment	No routine risk minimization activity are planned Other routine risk minimization measures beyond the Product Information: Pack size: One vial or pre-filled syringe (PFS) for single use only Legal status: Restricted medical prescription
Non-ocular safety after bilateral treatment	SmPC Section 4.4. PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Pack size: One vial or pre-filled syringe (PFS) for single use only Legal status: Restricted medical prescription

12.2 Part V.2. Additional Risk minimization measures

Educational materials for patients (Annex 6)

Educational materials for patients for the important identified risks intraocular inflammation, retinal vasculitis and/or retinal vascular occlusion, endophthalmitis, transient intraocular pressure increased, and retinal detachment/ tear are included.

Objectives:

To ensure that patients are adequately informed about the potential to develop intraocular inflammation, retinal vasculitis and/or retinal vascular occlusion, endophthalmitis, transient intraocular pressure increased or retinal detachment/ tear after an intravitreal injection of brolucizumab.

Rationale for the additional risk minimization activity:

Although intraocular inflammation, retinal vasculitis and/or retinal vascular occlusion, endophthalmitis, transient intraocular pressure increased, and retinal detachment/tear is mentioned in the Package Leaflet (PL) and clear instructions are provided in the PL when to seek immediate medical help, a patient guide has been developed.

Intraocular inflammation can lead to vision loss if not treated with standard of care. Retinal vasculitis and/or retinal vascular occlusion may lead to vision loss. Endophthalmitis is a serious intraocular condition that can lead to vision loss. In most, if not all cases, endophthalmitis is caused by the intravitreal injection procedure and not by brolucizumab. Retinal detachment/tear are mainly associated with the underlying disease and aging; rarely these are associated with the intravitreal injection procedure or brolucizumab.

The patient guide aims to provide adequate patient education on key signs and symptoms of a potential endophthalmitis, intraocular inflammation, retinal vasculitis and/or retinal vascular occlusion, transient intraocular pressure increased and retinal detachment/ tear and when to seek urgent attention from their physician, ensuring rapid identification and treatment.

Target audience and planned distribution path:

A patient guide is prepared nationally, in line with the key important risks defined in the RMP and with each EU member state's national regulations and legislations. The patient guide is distributed to all ophthalmology clinics where brolucizumab is expected to be used in patients. The treating physician is expected to provide the patient guide to the patients receiving treatment with brolucizumab.

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

Success of the proposed risk minimization measure will be assessed by the reported frequency in the PSUR of intraocular inflammation, retinal vasculitis and/or retinal vascular occlusion, endophthalmitis, transient intraocular pressure increased and retinal detachment/ tear over time.

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
Intraocular inflammation	Routine risk minimization: SmPC Sections 4.2, 4.3, 4.4, 4.8. PL Sections 2, 4. SmPC section 4.4, where information is provided that treatment should be discontinued. Additional Risk Minimization Measures: Patient educational materials	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up using targeted checklist. Additional pharmacovigilance activities: None
Retinal vasculitis and/or retinal vascular occlusion	Routine risk minimization: SmPC Sections 4.2, and 4.8. SmPC section 4.4, where information is provided that treatment should be discontinued and that these immune mediated adverse events may occur following the first intravitreal injection and at any time of treatment. They were observed more frequently at the beginning of the treatment. PL Sections 2 and 4. Additional Risk Minimization Measures: Patient educational materials	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up using targeted checklist. Data gathered in this way will be presented in the PSUR. Additional pharmacovigilance activities: None
Endophthalmitis	Routine risk minimization: SmPC Sections 4.2, 4.4, 4.8. PL Section 4. Additional Risk Minimization Measures: Patient educational materials	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Transient intraocular pressure increased	Routine risk minimization: SmPC Sections 4.2, 4.4, 4.8, 4.9. PL Sections 2, 4. Additional Risk Minimization Measures: Patient educational materials	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Retinal detachment/ tear	Routine risk minimization: SmPC Sections 4.4, 4.8. PL Sections 2, 4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimization measures	Pharmacovigilance activities
		None
	Additional Risk Minimization Measures: Patient educational materials	Additional pharmacovigilance activities: None
Non-ocular events (ATE, VTE, non-ocular haemorrhage, and hypertension)	Routine risk minimization: SmPC Sections 4.4, 4.8. PL Sections 2, 4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional Risk Minimization Measures: None	Additional pharmacovigilance activities: None
Safety beyond two years of treatment	Routine risk minimization: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional Risk Minimization Measures: None	Additional pharmacovigilance activities: None
Non-ocular safety after bilateral treatment	Routine risk minimization: SmPC Section 4.4. PL Section 2.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional Risk Minimization Measures: None	Additional pharmacovigilance activities: None

13 Part VI: Summary of the risk management plan for Beovu® (brolucizumab)

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

Beovu's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Beovu® should be used.

This summary of the RMP for Beovu® 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 Beovu's RMP.

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

Beovu® is authorized for the treatment of neovascular (wet) age-related macular degeneration (AMD) and visual impairment due to diabetic macular edema (DME) in adults (see SmPC for full indication).

It contains brolucizumab as the active substance and it is given by intravitreal injections.

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

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

Important risks of Beovu® together with measures to minimize such risks and the proposed studies for learning more about Beovu'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 HCP;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Beovu®, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Beovu® 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 Beovu® 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 Beovu®. 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	Intraocular inflammation
	Retinal vasculitis and/or retinal vascular occlusion
	Endophthalmitis
	Transient intraocular pressure increased
	Retinal detachment/tear
Important potential risks	Non-ocular events (ATE, VTE, non-ocular haemorrhage and hypertension)
Missing information	Safety beyond two years of treatment
	Non-ocular safety after bilateral treatment

13.2.2 Part VI - II B: Summary of important risks

Table 13-2 Important identified risk: Intraocular inflammation

Evidence for linking the risk to the medicine	The evidence comes from 4 pivotal trials in nAMD and DME indications and overall there is an imbalance between the brolucizumab and aflibercept arms.
Risk factors and risk groups	In nAMD clinical trials, a higher intraocular inflammation incidence was observed in Japanese patients treated with brolucizumab compared to non-Japanese patients. In Study RTH258-C001 the number of patients with an intraocular inflammation event was 7/60 (11.7%) in Japanese patients and 14/300 (4.7%) in non-Japanese patients. There is also a higher incidence of intraocular inflammation in females compared to males (long-term S-db): brolucizumab 6 mg 5.3% in females vs. 3.2% in males. In DME clinical trials, the above observations were not possible to make due to the smaller size of the Japanese cohort (approximately 20 per treatment arm).

	In overall population included in the DME trials, there is also a higher incidence of intraocular inflammation in females compared to males (100 Week S-db): 5.1% in females (7/138) vs. 2.2% in males (5/230) receiving brolucizumab 6 mg. In the nAMD clinical trials, a higher proportion of patients who developed intraocular-inflammation had a positive status for treatment emergent (boosted or induced) ADAs, as compared to those with a negative post-treatment ADA status. In the DME clinical trials, a higher proportion of patients who developed AESIs had a positive status for treatment-emergent (boosted and induced) ADAs as compared to those with a negative post-treatment ADA status.
Risk minimization measures	Routine risk minimization: SmPC Sections 4.2, 4.3, 4.4, 4.8. SmPC section 4.4, where information is provided that treatment should be discontinued. PL Sections 2, 4. Additional Risk Minimization Measures: Patient educational materials
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 13-3 Important identified risk: Retinal vasculitis and/or retinal vascular occlusion

Evidence for linking the risk to the medicine	Current evidence is based on the 4 pivotal trials in nAMD and DME indications and on post-marketing data for nAMD indication.
Risk factors and risk groups	Patients at risk for intraocular inflammation or with active intraocular inflammation at the time of brolucizumab administration. Based on a retrospective real world evidence analysis, patients with a medical history of intraocular inflammation and/or retinal vascular occlusion in the year prior to treatment with brolucizumab were more likely to present with similar events after brolucizumab injection, as compared to nAMD patients with no history of these events.
Risk minimization measures	Routine risk minimization: SmPC Sections 4.2, and 4.8 PL Sections 2 and 4 SmPC section 4.4, where information is provided that treatment should be discontinued and that these immune mediated adverse events may occur following the first intravitreal injection and at any time of treatment. They were observed more frequently at the beginning of the treatment. Additional Risk Minimization Measures: Patient educational materials
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 13-4 Important identified risk: Endophthalmitis

Evidence for linking the risk to the medicine	The incidence of endophthalmitis after an intravitreal injection is low. Current evidence is based on the 4 pivotal trials in nAMD and DME indications.
Risk factors and risk groups	There is an increased risk of endophthalmitis if the intravitreal injection procedure is not carried out under aseptic conditions.
Risk minimization measures	Routine risk minimization: SmPC Sections 4.2, 4.4, 4.8. PL Section 4. Additional Risk Minimization Measures: Patient educational materials
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 13-5 Important identified risk: Transient intraocular pressure increased

Evidence for linking the risk to the medicine	Current evidence is based on the 4 pivotal trials in nAMD and DME indications. In the two pivotal nAMD trials for brolucizumab (Study RTH258-C001 and Study RTH258-C002), transient increases in intraocular pressure have been seen within 30 minutes of injection, similar to those observed with intravitreal administration of other VEGF inhibitors. These post-injection increases are self-limiting or can be treated with standard of care.
Risk factors and risk groups	Patients with intraocular pressure increased or glaucoma prior to the intravitreal injection.
Risk minimization measures	Routine risk minimization: SmPC Sections 4.2, 4.4, 4.8, 4.9. PL Sections 2, 4. Additional Risk Minimization Measures: Patient educational materials
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 13-6 Important identified risk: Retinal detachment/ tear

Evidence for linking the risk to the medicine	Retinal detachment and tear is a well-known and well-characterized risk associated with the underlying disease and the aging of the eye.
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, or severe high blood pressure.
Risk minimization measures	Routine risk minimization: SmPC Sections 4.4, 4.8 PL Sections 2, 4.

	Additional Risk Minimization Measures: Patient educational materials
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 13-7 Important potential risk: Non-ocular events (ATE, VTE, non-ocular haemorrhage, and hypertension)

Evidence for linking the risk to the medicine	Although there is an increased risk of ATEs, VTEs, non-ocular haemorrhage and hypertension after intravenously administered high doses of VEGF-inhibitors for the treatment of cancer, there is currently no evidence of increased incidences of ATEs, VTEs, non-ocular haemorrhage and hypertension for the much lower intravitreally administered doses of VEGF-inhibitors in patients with nAMD. After intravitreal administration in cynomolgus monkeys, the systemic maximal concentration of brolucizumab is approximately 1000-fold less than the trough concentration of a therapeutic dose of intravenously administered anti-VEGFs.
Risk factors and risk groups	Patients with cardiovascular risk factors or clotting disorders have a higher risk for ATEs, VTEs, non-ocular haemorrhage and hypertension. In DME patients, underlying disease (diabetes) is a risk factor.
Risk minimization measures	Routine risk minimization: SmPC Sections 4.4, 4.8. PL Sections 2, 4 Additional Risk Minimization Measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table 13-8 Missing information: Safety beyond two years of treatment

Risk minimization measures	Routine risk minimization: None Additional Risk Minimization Measures: None

Table 13-9 Missing information: Non-ocular safety after bilateral treatment

Risk minimization measures	Routine risk minimization: SmPC Sections 4.4. PL Section 2. 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 of Beovu®.

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

There are no studies in post-authorization development plan for Beovu®.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

For the important identified risk "Intraocular inflammation" the targeted follow-up checklist below is used:

Targeted Follow-up Checklist: Beovu (brolucizumab) Intraocular inflammation without vasculitis (Version 3.0 /Mar-2023)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

For any case reporting retinal vasculitis and/or retinal vascular occlusion (including, retinal vasculitis, eye infarction, choroidal infarction, retinal artery embolism, retinal artery occlusion, retinal artery stenosis, retinal artery thrombosis, retinal infarction, retinal vascular occlusion, retinal vascular thrombosis, retinal vein occlusion, retinal vein thrombosis, macular ischemia, retinal ischemia and ocular ischemic syndrome), please use the new targetted follow up checklist 'Retinal vasculitis and/or retinal vascular occlusion' instead.

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

1.Follow up questions for Interventional Clinical Trials Only (skip for all other report types)

Event Description:

Is the intraocular inflammation:

- ☐ Acute: sudden onset and limited duration
- ☐ Chronic: repeated episodes separated by periods of inactivity without treatment, lasting >3 months
- ☐ Recurrent: persistent intraocular inflammation with relapse in <3 months after discontinuing treatment

Did the patient receive anti-VEGF intravitreal injections before starting study medication?

☐ Yes ☐ No ☐ Unknown

►If yes, what product and how many injections.

_____

_____

What were the presenting symptom(s)?

_____

Is the intraocular inflammation

☐ non-infectious ☐ infectious, please provide details of any cultures taken and microbiology findings

What was the outcome of the event?

☐ Ongoing ☐ Resolved (*dd/mmm/yyyy*): _____/_____/_____ ☐ Unknown

☐ Resolved with sequelae, please specify:_____

Medical history and underlying disorders

Did the patient have any of the following?
☐ Hypertension ☐ Myocardial infarction ☐ Stroke ☐ Cardiac arrhythmia ☐ Diabetes ☐ Smoking
☐ Auto-immune diseases, please specify:_____ ☐ Other ocular diseases, please specifify:_____
☐ Other, please specify:_____ ☐ None ☐ Unknown

Treatment of the intraocular inflammation event

Please specify any treatment given (drug, dose and route of administration), duration of treatment:

Drug	Dose	Route of administration	Dates (start-stop)

The section below is not for use in interventional clinical trial cases

2. Follow up questions for all report types except interventional clinical trial cases

Event Description:

Eye(s) affected by intraocular inflammation: ☐ Right eye ☐ Left eye ☐ Both eyes ☐ Unknown

Eye(s) treated with the suspect medication: ☐ Right eye ☐ Left eye ☐ Both eyes ☐ Unknown

Did the intraocular inflammation event occur in the eye(s) injected with the suspect medication?
☐ Yes ☐ No ☐ Unknown

Is the intraocular inflammation:
- ☐ Acute: sudden onset and limited duration
- ☐ Chronic: repeated episodes separated by periods of inactivity without treatment, lasting >3 months
- ☐ Recurrent: persistent intraocular inflammation with relapse in <3 months after discontinuing treatment

Number of days between the last injection of the suspect medication and the development of the intraocular inflammation event: ___

Please provide the **number** of suspect medication injections received prior to the onset of intraocular inflammation (including most recent injection): ____

Please enter calendar dates of the suspect medication injections (at least **for the last 3** injections) received prior to the onset of intraocular inflammation (including most recent injection) (*dd/mmm/yyyy*):
_____/_____/_____ _____/_____/_____ _____/_____/_____

Did the patient receive anti-VEGF intravitreal injections before starting the suspect medication?
☐ Yes ☐ No ☐ Unknown
►If yes, what product and how many injections.

Were any other medications administered via intravitreal injection **prior** to the event?
☐ Yes ☐ No ☐ Unknown
►If yes, please describe and provide the calendar dates of administration (*dd/mmm/yyyy*), including which eye(s) was treated.

What were the presenting symptom(s)?

Is the intraocular inflammation
☐ non-infectious ☐ infectious, please provide details of any cultures taken and microbiology findings

Was this the first presentation of intraocular inflammation since the suspect medication administration started?
☐ Yes ☐ No ☐ Unknown
►If no, please describe the earlier intraocular inflammation events (including prior injection dates and intraocular inflammation event dates)

What was the outcome of the event?
☐ Ongoing ☐ Resolved (*dd/mmm/yyyy*): _____/_____/_____ ☐ Unknown
☐ Resolved with sequelae, please specify:

Eye examinations performed

Please provide a description of the eye examination (e.g. slit-lamp, ophthalmoscopy, visual acuity) :

Please provide a description of the retinal image taken or a copy of the examination report

Medical history and underlying disorders

Did the patient have any of the following?
☐ Hypertension ☐ Myocardial infarction ☐ Stroke ☐ Cardiac arrhythmia ☐ Diabetes ☐ Smoking
☐ Auto-immune diseases, please specify: ☐ Other ocular diseases, please specifify:
☐ Other, please specify: ☐ None ☐ Unknown

Treatment of the intraocular inflammation event

Please specify any treatment given (drug, dose and route of administration), duration of treatment:

Drug	Dose	Route of administration	Dates (start-stop)

For the important identified risk "Retinal vasculitis and/or retinal vascular occlusion" the targeted follow-up checklist below is used:

Targeted Follow-up Checklist: Beovu (brolucizumab) – Retinal vasculitis and/or retinal vascular occlusion (Version 3.0/ Mar-2023)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.
For cases reporting retinal vasculitis and/or retinal vascular occlusion (including ocular vasculitis, retinal vasculitis, necrotising retinitis, choroidal infarction, eye infarction, macular ischemia, ocular ischemic syndrome, retinal artery embolism, retinal artery occlusion, retinal artery stenosis, retinal artery thrombosis, retinal infarction, retinal ischemia, retinal vascular occlusion, retinal vascular thrombosis, retinal vein occlusion, and retinal vein thrombosis), please ask the following questions:

1.Follow up questions for Interventional Clinical Trials Only (skip for all other report types)

Event Description:

What were the presenting symptom(s) and diagnosis? (Specify if it was an intraocular inflammation with or without retinal vasculitis/ retinal vascular occlusion)

Symptoms: _____ (*dd/mmm/yyyy*): _____/_____/_____

Diagnosis: _____ (*dd/mmm/yyyy*): _____/___

Date of last administration of study medication: _____

Is the intraocular inflammation

☐ non-infectious ☐ infectiousWhat tests were done?:

_____

Treatment of the event

Please specify any treatment given (drug, dose and route of administration), duration of treatment:

Drug	Dose	Route of administration / Duration of administration	Start date	Stop date

Outcome of the event

Event	Outcome					
	Ongoing	Resolved	Resolved with sequelae, please specify	Improved	Deteriorated	Unknown
1.						
2.						

Did the patient receive anti-VEGF intravitreal injections before starting study medication?
☐ Yes ☐ No ☐ Unknown
►If yes, what product and approximately how many injections.

_____
_____

Details for specific events: vascular occlusion *If vascular occlusion was not reported, move to next question*
Was the retinal vascular occlusion in an ☐ Artery or ☐ Vein
Was the retinal vascular occlusion ☐ Central ☐ Branch, or ☐ Peripheral
Please provide any other relevant details:

Medical history and underlying disorders

Did the patient have any of the following?
☐ Hypertension ☐ Myocardial infarction ☐ Stroke ☐ Cardiac arrhythmia ☐ Diabetes ☐ Smoking
☐ Auto-immune diseases, please specify:_____ ☐ Other ocular diseases, please specify:_____
☐ Other, please specify:_____ ☐ None ☐ Unknown

☐ Prior history of Intraocular inflammation (within 12 months before study medication treatment), please specify if known etiology, for example with other anti-VEGFs or treatments:_____

The section below is not for use in interventional clinical trial cases

2.Follow up questions for all report types except interventional clinical trial cases

Event Description:
What were the presenting symptom(s) and diagnosis? (Specify if it was an intraocular inflammation with or without retinal vasculitis/ retinal vascular occlusion)
Symptoms: _____ *(dd/mmm/yyyy)*: _____/_____/_____
Diagnosis: _____ *(dd/mmm/yyyy)*: _____/___
Date of last administration of the suspect medication: _____

Did the adverse event occur in the eye(s) injected with the suspect medication?
☐ Yes ☐ No ☐ Unknown

Eye(s) affected: ☐ Right eye ☐ Left eye ☐ Both eyes ☐ Unknown

Eye(s) treated with the suspect medication: ☐ Right eye ☐ Left eye ☐ Both eyes ☐ Unknown

Did the event cause significant vision loss/ decrease of visual acuity ? ☐ Yes ☐ No ☐ Unknown

► If yes, please provide:
VA before event _____/_____ Snellen / LogMAR (please select) (*dd/mmm/yyyy*): _____/_____/_____
VA at time of event _____/_____ Snellen / LogMAR (please select) (*dd/mmm/yyyy*): _____/_____/_____
VA after event (if available) _____/_____ Snellen / LogMAR (please select) (*dd/mmm/yyyy*): _____/___-__/_____

What were the clinical features?
Anterior segment: _____
Posterior segment: _____

Is the intraocular inflammation
☐ non-infectious ☐ infectiousWhat tests were done?:
_____

Treatment of the event

Please specify any treatment given (drug, dose and route of administration), duration of treatment:

Drug	Dose	Route of administration / Duration of administration	Start date	Stop date

Outcome of the event

Event	Outcome					
	Ongoing	Resolved	Resolved with sequelae, please specify	Improved	Deteriorated	Unknown
1.						
2.						

Please provide the **number** of the suspect medication injections received prior to the onset of the event (including most recent injection): ____

Please enter calendar dates of the suspect medication injections (at least **for the last 3** injections) received prior to the onset of the event (including most recent injection) (*dd/mmm/yyyy*):
_____/_____/_____ _____/_____/_____ _____/_____/_____

Did the patient receive anti-VEGF intravitreal injections before starting the suspect medication?
☐ Yes ☐ No ☐ Unknown
►If yes, what product and approximately how many injections.
_____
_____

Were any other medications administered via intravitreal injection **prior** to the event?
☐ Yes ☐ No ☐ Unknown
►If yes, please describe and provide the calendar dates of administration (*dd/mmm/yyyy*), including which eye(s) was treated
_____
_____

Please provide a description of findings on the retinal image taken. Please specify the image modality:
_____
_____
_____
_____

Details for specific events: vascular occlusion *If vascular occlusion was not reported, move to next question*
Was the retinal vascular occlusion in an ☐ Artery or ☐ Vein
Was the retinal vascular occlusion ☐ Central ☐ Branch, or ☐ Peripheral
Please provide any other relevant details:

Medical history and underlying disorders

Did the patient have any of the following?
☐ Hypertension ☐ Myocardial infarction ☐ Stroke ☐ Cardiac arrhythmia ☐ Diabetes ☐ Smoking
☐ Auto-immune diseases, please specify:_____ ☐ Other ocular diseases, please specifify:_____
☐ Other, please specify:_____ ☐ None ☐ Unknown

☐ Prior history of Intraocular inflammation (within 12 months before the suspect medication treatment), please specify if known etiology, for example with other anti-VEGFs or treatments:_____

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

The patient educational materials will be implemented in accordance to the addendum to GVP Module XVI and the national guidelines of each of the EU Member States.

Approved key messages of the additional risk minimization measures

The 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 patient guide will contain the following:

- What is neovascular (wet) age related macular degeneration and diabetic macular oedema (DME)
- What is Beovu, how does it work, how is it administered and what to expect from the treatment
- What are the steps following treatment with Beovu
- Description of the risks including increased intraocular pressure, intraocular inflammation, retinal vasculitis and/or retinal vascular occlusion, retinal detachment and retinal tear and endophthalmitis and their key signs and symptoms. Also, patients should be informed of the signs and symptoms of immunogenicity
- Patients should be alerted of the importance of reporting adverse reactions without delay
- Description of the best course of action if sign and symptoms of those risks present themselves (e.g. How to reach your doctors)
- Recommendations for monitoring and required examinations: Following intravitreal injection: measurement of increased intraocular pressure and perfusion of the optic nerve
- The patient guide will also be available in spoken form in audio format.

The following are the key safety messages to be communicated to allow early diagnosis and appropriate treatment of these events:

- Beovu belongs to a group of medicines called anti-neovascularization agents (“anti-VEGF”) that are given as an injection into your eye (intravitreal injection). An uncommon severe inflammation (endophthalmitis), usually associated with infection, inside the eye or a detachment of one of the layers in the back of the eye (retinal detachment/tear) sometimes develops after an injection into the eye. A transient increase in eye pressure (transient intraocular pressure increased) is common but is usually asymptomatic; the doctor needs to do measurements of the pressure inside the eye to detect this.
- Inflammation of the blood vessels in the retina (retinal vasculitis) and/or blockage of the blood vessels in the eye (retinal vascular occlusion), or a less severe inflammation in the eye (intraocular inflammation) may occur. Patients who are female or of Japanese ethnicity may be more at risk of developing similar events.

Patients who have had intraocular inflammation and/or retinal vascular occlusion in the last year are at increased risk of developing retinal vasculitis and/or retinal vascular occlusion.

An immune response (immunogenicity) is also possible.

- Seek immediate medical help if you experience any of the following:
  - a sudden decrease or change in vision, including an increased number of small particles in your vision (floaters)
  - pain, discomfort, redness in your eye
  - flashes of light
  - increased sensitivity to light (discomfort to bright lights)

Annex 7 - Other supporting data (including referenced material)

References List

External references (available upon request)

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