

EU RISK MANAGEMENT PLAN FOR SUSVIMO®/ PORT DELIVERY SYSTEM WITH RANIBIZUMAB 100 MG/ML

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 21 January 2026

Date of final sign off: See electronic signature on the last page of this document

TABLE OF CONTENTS

Susvimo EU RMP v1.0	1
EU RMP Core Report	8
PART I: PRODUCT OVERVIEW	11
PART II: SAFETY SPECIFICATION	15
PART II: MODULE SI (EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)	15
SI.1 NEOVASCULAR AGE-RELATED MACULAR DEGENERATION....	15
PART II: MODULE SII(NONCLINICAL PART OF THE SAFETY SPECIFICATION	26
PART II: MODULE SIII(CLINICAL TRIAL EXPOSURE	31
PART II: MODULE SIV(POPULATIONS NOT STUDIED IN CLINICAL TRIALS	46
SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM.....	46
SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS	53
SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS	54
PART II: MODULE SV(POST-AUTHORIZATION EXPERIENCE	56
SV.1 POST-AUTHORIZATION EXPOSURE	56
SV.1.1 Method Used to Calculate Exposure.....	56
SV.1.2 Exposure	56
PART II: MODULE SVI(ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION	57
PART II: MODULE SVII(IDENTIFIED AND POTENTIAL RISKS	57
SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION.....	57
SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP.....	57
SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP.....	59

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP	62
SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION	63
SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks.....	63
SVII.3.2. Presentation of the Missing Information	86
PART II: MODULE SVIII(SUMMARY OF THE SAFETY CONCERNS.....	89
PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES).....	90
III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES	90
III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES	90
III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES.....	94
PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES ..	96
PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)	96
V.1 ROUTINE RISK MINIMIZATION MEASURES	96
V.2. ADDITIONAL RISK MINIMIZATION MEASURES	99
V.3 SUMMARY OF RISK MINIMIZATION MEASURES	102
PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN	108
I. THE MEDICINE AND WHAT IT IS USED FOR	108
II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS.....	108
II.A List of Important Risks and Missing Information.....	109
II.B Summary of Important Risks	110
II.C Post-Authorization Development Plan.....	119
II.C.1 Studies That Are Conditions of the Marketing Authorization	119
II.C.2 Other Studies in Post-Authorization Development Plan	119
REFERENCES.....	120

LIST OF TABLES

Susvimo EU RMP v1.0	1
EU RMP Core Report	8
Table 1 Product Overview	11
Table 2 Reported Incidence of nAMD Worldwide	16
Table 3 Reported Prevalence of nAMD Worldwide.....	19
Table 4 Important Comorbidities in nAMD Population	25
Table 5 Summary of the Clinical Studies with PDS Included in this RMP	31
Table 6 Overall Extent of PDS Exposure in Study Eye as of 02 September 2025 (CCOD), for All PDS Population.....	32
Table 7 Overall Extent of PDS Exposure in Study Eye as of 02 September 2025 (CCOD) by Age, for All PDS Population.....	34
Table 8 Overall Extent of PDS Exposure in Study Eye as of 02 September 2025 (CCOD) by Gender, for All PDS Population	38
Table 9 Overall Extent of PDS Exposure in Study Eye as of 02 September 2025 (CCOD) by Race, for All PDS Population	40
Table 10 Overall Extent of PDS Exposure in Study Eye as of 02 September 2025 (CCOD) by Ethnicity, for All PDS	43
Table 11 Important Exclusion Criteria in Pivotal Studies in the Development Program	46
Table 12 Exposure of Special Populations Included or Not in Clinical Trial Development Program.....	54
Table 13 Potential Mechanisms for the PDS Implant and PDS Procedures Complications	63
Table 14 PDS Implant and PDS Procedures Complications: Overall Frequency, Severity, Seriousness, and Outcomes in the All PDS Population.....	66
Table 15 Frequency of Occurrence of PDS Implant and PDS Procedures Complications in the All PDS 100 mg/mL Population compared to nAMD Patients Treated with Intravitreal Injections or other Similar Devices	67
Table 16 Impact on Patients' Quality of Life, Management Strategies, and Long-Term Outcomes for the PDS Implant and PDS Procedures Complications.....	69
Table 17 Risk Factors and Risk Groups for the PDS Implant and PDS Procedures Complications	73
Table 18 Septum Dislodgement: Overall Frequency with 95% CI, Severity, Seriousness, and Outcomes for All PDS Population	78

Table 19 Intraocular Inflammation (IOI): Overall Frequency with 95% CI, Severity, Seriousness, and Outcomes for All PDS Population.....	82
Table 20 Summary of Safety Concerns	89
Table 21 Study GR40549 (Portal)	91
Table 22 Re-implantation substudy in association with Study GR40549 (Portal)	92
Table 23 Study GR46011 (SightARC).....	93
Table 24 Ongoing and Planned Additional Pharmacovigilance Activities	94
Table 25 Description of Routine Risk Minimization Measures by Safety Concern	96
Table 26 Additional Risk Minimization Measures: Physician Guide	99
Table 27 Additional Risk Minimization Measure: Patient Educational Materials.....	101
Table 28 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern	102

LIST OF FIGURES

Susvimo EU RMP v1.0	1
EU RMP Core Report	8
Figure 1 Schematic of Septum Dislodged into Implant Reservoir	77
Figure 2 Component-Level Changes and Manufacturing Process Improvements Implemented to Strengthen the Septum–Overmold Bond	80

LIST OF ANNEXES

Susvimo EU RMP v1.0	1
Annex 1: EudraVigilance Interface	132
Annex 1 Title Page	132
Annex 2: Summary of Pharmacovigilance Study Programme	134
Annex 2 Title Page	134
Annex 3: Protocols for Studies in the Pharmacovigilance Plan	137
Annex 3 Title Page	137
Annex 4: Specific Adverse Drug Reaction Follow-up Forms	400
Annex 4 Title Page	400
Annex 5: Protocols for Studies in RMP Part IV	408
Annex 5 Title Page	408
Annex 6: Details of Proposed Additional Risk Minimization Activities ..	410
Annex 6 Title Page	410
Annex 7: Other Supporting Data.....	415
Annex 7 Title Page	415
Annex 8: Summary of Changes to the Risk Management Plan.....	802
Annex 8 Title Page	802

Rationale for Submitting an Updated Risk Management Plan (RMP)

This updated European Union (EU) Risk Management Plan (RMP) was updated as CHMP and Pharmacovigilance Risk Assessment Committee (PRAC) have agreed on the previous version 0.5. In order to have version 1.0 reflected as the final agreed EU RMP in the CHMP assessment report, the version was updated to version 1.0.

Summary of Significant Changes in This RMP

Annex 4 was updated to add back the subsections of traumatic cataracts and implant damage that were erroneously not included in the prior version of the guided questionnaire.

Annex 8 was updated to reflect changes in the EU RMP v1.0.

Other RMP Versions under Evaluation

RMP Version Number: Not applicable

Submitted on: Not applicable

Procedure Number: Not applicable

Details of Currently Approved RMP

RMP Version Number: Not applicable

Approved with Procedure Number: Not applicable

Date of Approval (Opinion Date): Not applicable

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Date

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Date

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active Substance(s) (INN or common name)	Ranibizumab
Pharmacotherapeutic group(s) (ATC Code)	Ophthalmological, antineovascularisation agents (S01LA04)
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Susvimo
Marketing authorization procedure	Centralized
Brief description of the product including:	<u>Description of the product:</u> The PDS is a drug-device combination product, composed of an ocular implant (hereafter referred to as the implant), a customized formulation of ranibizumab (Susvimo), and four ancillary devices (insertion tool assembly, initial fill needle, refill needle, and explant tool)*.
	<u>Chemical class:</u> Ranibizumab is a humanized recombinant monoclonal antibody fragment.
	<u>Summary of mode of action:</u> Ranibizumab is targeted against human VEGF-A. It binds with high affinity to all biologically active VEGF-A isoforms thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. The PDS is a drug delivery technology that enables a continuous drug delivery profile. The implant is an ocular refillable device that is surgically implanted through the pars plana to allow for a continuous delivery of ranibizumab into the vitreous. The implant is used in conjunction with a customized formulation of ranibizumab (100 mg/mL) to precisely control the rate and duration of drug delivery and is refillable through the implant septum in situ.
	<u>Important information about its composition:</u> Ranibizumab is produced by standard recombinant technology methods in an <i>Escherichia coli</i> expression vector and bacterial fermentation.

Active Substance(s) (INN or common name)	Ranibizumab
Hyperlink to the Product Information	See Module 1.3.1
Indication(s) in the EEA	<u>Current:</u> Not applicable
	<u>Proposed:</u> Susvimo is indicated in adult patients for the treatment of neovascular (wet) age-related macular degeneration (AMD) who have achieved stable disease after previously responding to intravitreal treatment with a vascular endothelial growth factor (VEGF) inhibitor medicinal product.
Dosage in the EEA	<u>Current:</u> Not applicable
	<u>Proposed:</u> The recommended dose of Susvimo is 2 mg (0.02 mL of solution) delivered via the implant with refills administered every 24 weeks (approximately 6 months).
Pharmaceutical form(s) and strengths	<u>Current:</u> Not applicable
	<u>Proposed:</u> Solution for injection supplied in a single-dose vial, containing 39.5 mg of ranibizumab in 0.395 mL of solution. The implant is designed to contain approximately 0.02 mL (2 mg) of ranibizumab solution when filled.
Is or will the product be subject to additional monitoring in the European Union?	Yes

AMD = age-related macular degeneration; ATC = Anatomical Therapeutic Chemical; EEA = European Economic Area; INN= International Non-proprietary Name; PDS = Port Delivery System with ranibizumab; RMP = Risk Management Plan; VEGF-A = vascular endothelial growth factor A; VEGFR = vascular endothelial growth factor receptor.

* The trade names of the PDS devices, that include the implant and the four ancillary devices, is Contivue.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AMD	age-related macular degeneration
AUC	area under the concentration-time curve
C2/CFB	complement component 2/complement factor B
CCOD	clinical cutoff date
CFH	complement factor H
CHMP	Committee for Medicinal Products for Human Use
Chr	Chromosome
CI	confidence interval
C _{max}	maximum concentration in the vitreous humor
CSR	clinical study report
eCRF	electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
GLP	Good Laboratory Practice
HR	hazard ratio
IBD	international birth date
ICH	International Conference on Harmonisation
IFU	Instructions for Use
IOI	intraocular inflammation
IOP	intraocular pressure
MAA	Marketing Authorization Application
nAMD	neovascular age-related macular degeneration
PBRER	Periodic Benefit-Risk Evaluation Report
PDS	Port Delivery System with ranibizumab
PL	Patient Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PRN	pro-re nata (as needed)
PSUR	Periodic Safety Update Report
PT	preferred term
Q24W	every 24 weeks
RMP	Risk Management Plan
SD	standard deviation
SmPC	summary of product characteristics

SUN	Standardization of Uveitis Nomenclature
UK	United Kingdom
US	United States
VEGF	vascular endothelial growth factor

PART II: SAFETY SPECIFICATION

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

SI.1 NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

- **Incidence**

The global cumulative incidence of neovascular age-related macular degeneration (nAMD; also known as wet AMD) ranged from 0.1% (over a 5-year follow-up period) to 9.8% (over a 14-year follow-up period) ([Loukovaara et al. 2022](#), [Farinha et al. 2019](#), [Buch et al. 2005a](#), [Kido et al. 2022](#), [Rim et al. 2019](#), [Foo et al. 2018](#), [Joachim et al. 2015](#), [You et al. 2012](#), [Klein et al. 2013](#)).

In Europe, three studies reported cumulative incidence ranging from 0.4% (Portugal) to 9.8% (Denmark) ([Loukovaara et al. 2022](#), [Farinha et al. 2019](#), [Buch et al. 2005a](#)), while three other studies found annual incidence between 0.1% in Germany and 4% in the United Kingdom (UK, [Schuster et al. 2024](#), [Korva-Gurung et al 2023](#), [Owen et al. 2012](#)).

The incidence of nAMD in Europe, the United States (US), Asia and Australia are reported in [Table 2](#) below.

Table 2 Reported Incidence of nAMD Worldwide

Country, Period, Study	Study Type Follow-up	Sample Size (Den)	No. of Cases (Num)	Baseline Mean Age (Years)	Cumulative Incidence (%)	Incidence Rate (in 100,000 Person years)
Europe						
Germany, 2012–2021, Schuster et al. 2024	Retrospective observational cohort study	NR	86,785	Age groups: < 65 65–74 75–84 ≥ 85	Annual incidence (2021): 0.10%	NR
Finland, 2001–2017, Loukovaara et al. 2022	Retrospective population-based study FU: 9.84 years	259,562 In PY: 2,554,290	2,947	Mean age: 63.2 ± 11.6	1.13%; 95% CI (1.09–1.17)	115; 95% CI (111–112)
Finland, 2006–2020, Korva-Gurung et al. 2023	Retrospective population-based study FU: 3 years	410,000	2,121	44–96	NR	In year 2020: 102; 95% CI (88–118)
France, 2008–2018, Creuzot-Garcher et al. 2022	Retrospective population-based study FU: 10 years	NR	38,852 (in 2018)	≥ 50	Annual incidence (in 2018): 0.15% (As reported)	NR
Portugal, 2009–2011, Farinha et al. 2019	Population-based cohort study FU: 6.5 years	1,616	7	≥ 55	0.4%	NR
UK, 2007–2009, Owen et al. 2012	Meta-analysis of published data FU: approx. 10 years	NR	NR	≥ 50	Mean annual incidence: Overall: 4.0 Male: 1.3 Female: 2.6	NR
Denmark, 1986–2002, Buch et al. 2005a	Population-based cohort study FU: 14 years	297	29	60–80	9.8 %	NR

Country, Period, Study	Study Type Follow-up	Sample Size (Den)	No. of Cases (Num)	Baseline Mean Age (Years)	Cumulative Incidence (%)	Incidence Rate (in 100,000 Person years)
Rest of the World						
Japan, 2011–2018, Kido et al. 2022	Retrospective population-based cohort study Study period: 8 years	NR	246,064	≥ 40	NR	Cumulative: 40.7; 95% CI (40.49–40.82) In men: 53.22; 95% CI (52.95–53.49) In women: 29.78; 95% CI (29.60–29.98)
South Korea, 2010–2015 Rim et al. 2019	Retrospective population-based cohort study FU: 6 years	519,661	912	≥ 40	0.17% (912/519,661); 95% CI (0.16–0.19)	Cumulative: 29; 95% CI (2.8–3.0) In men: 3.6; 95% CI (3.3–3.9) In women: 2.3; 95% CI (2.1–3.6)
Singapore, 2007–2015, Foo et al. 2018	Population-based cohort study FU: 6 years	2,105	2	56.2 ± 9.1 y	0.40	NR
Australia, 1992–2010, Joachim et al. 2015	Population-based cohort study FU: 15 years	1,149	NR	64.5	Overall: 4.4 Men: 3.3 Women: 5.2	NR

Country, Period, Study	Study Type Follow-up	Sample Size (Den)	No. of Cases (Num)	Baseline Mean Age (Years)	Cumulative Incidence (%)	Incidence Rate (in 100,000 Person years)
China, 2001–2006, You et al. 2012	Population-based cohort study FU: 5 years	3,251	NR	55±10	Overall: 0.1 Men: 0.2 Women: 0	NR
US, 1998–2010, Klein et al. 2013	Cohort study FU: 10 years	1,700	44	67±9	Overall: 2.6	NR

approx. = approximately; CI= confidence interval; Den = denominator; FU = follow-up; No = number; NR = not reported; Num = numerator; UK = The United Kingdom; US = The United States of America; PY = person years

- **Prevalence**

In Europe prevalence ranges were between 0.3% (Ireland) and 3.6% (Denmark), whereas in Asia, Australia and in the US, prevalence ranges were between 0.1% (South Korea) and 1.02% (US). The prevalence of nAMD in Europe, the US, Asia and Australia is reported in [Table 3](#) below.

Table 3 Reported Prevalence of nAMD Worldwide

Country, Period, Study	Study Type, Population Characteristics	Prevalence % (95% CI)
Europe		
Germany, 2012–2021 Schuster et al 2024	Retrospective cohort study on German population Age groups (years): < 65, 65–74, 75–84, ≥ 85	In 2021: 0.44%
Finland, 2006–2020, Korva-Gurung et al 2023	Retrospective population-based study N=410,000; Age = 44–96 years	In 2020: 0.9%; (0.8–0.96)
France, 2008–2018, Creuzot-Garcher et al 2022	Retrospective population-based study (French Population) N = 25,996,150; Age ≥ 50 years; 36% men	1.1%
Denmark, Norway, Sweden, 2012, Buch et al 2005a	Scandinavian general population Age ≥ 65 years	3.61%
Iceland, 2002–2006, Jonasson et al 2011	N = 5,272; Age ≥ 66 years; Mean age 76±6 years; 42% men	3.3% (2.8 – 3.8)
The Republic of Ireland, 2009–2011, Akuffo et al 2015	N = 4,751; Age ≥ 50 years Mean age 61.6±8.1 years; 45.7% men	0.3% (0.1 – 0.5)
Norway, 2007–2008, Erke et al. 2012	N = 2,631; Age = 65–87 years; Mean age 72.3 years; 42.5% men	2.5% (1.9 – 3.1)
Slovakia, March–May 2013, Krasnik et al 2018	Cross-sectional, population-based survey; N=2,924; Age ≥ 55 years; Mean age 66.6 years (SD = 8.7)	1.01% (0.65 – 1.38)
UK, 2002–2006, Wilde et al. 2017	Cross-sectional study; Age ≥ 65 years	1.8%
UK, 2007–2009, Owen et al. 2012	Meta-analysis of published data Age > 50 years	1.2% (0.9 – 1.7)
Rest of the World		
South Korea, 2010–2015, Rim et al. 2019	Retrospective population-based cohort study; (N = 519,961), age: ≥ 40 years	Overall: 0.11% Men: 0.12 Women: 0.1

Country, Period, Study	Study Type, Population Characteristics	Prevalence % (95% CI)
Australia, 2015-2016, Keel et al. 2017	Cross-sectional population-based survey (N=4,836, age 40–98 years) 45% males	0.24% (0.13 – 0.47)
Asian Countries, Rim et al. 2020	Cross-sectional meta-analyses (N=97,213) Mean age 60.8±10.8 years 43% males	0.5% (0.39 – 0.64)
China, (publications 1990–2016), Song et al. 2017	Systematic review and meta-analysis of nine published Chinese studies with high heterogeneity	0.69% (0.43 – 1.09)
South Korea, 2010–2011, Cho et al. 2014	N8,714, aged ≥40 years Mean age 55.2±0.2 years 47.9% men	0.5% (0.4 – 0.8)
US, (based on 2000 US Census), Friedman et al. 2004	Pooled data from population-based studies from US	1.02 % (0.93 – 1.11)

CI = confidence interval; N = number; nAMD = neovascular age-related macular degeneration; SD = standard deviation.

- **Demographics**

Age: nAMD primarily affects the elderly, becoming more prevalent in patients ≥ 75 years old ([Creuzot-Garcher et al. 2022](#), [Korva-Gurung et al. 2023](#), [Almony et al 2021](#), [Hu et al 2017](#), [Kim et al 2016](#)). As reported in a French study ([Creuzot-Garcher et al 2022](#)), the incidence of nAMD increases with age: 0.22% in individuals ≥60 years old, 0.38% in those ≥70 years old, and 0.60% in those ≥80 years old. A study conducted in Finland from 2006 to 2020 reported that nAMD prevalence significantly rose across age groups, being more pronounced in older individuals ([Korva-Gurung et al 2023](#)). In the US, a study showed a six-fold increase in nAMD prevalence from early 50s to those ≥ 75 years old ([Almony et al 2021](#)). Another US study involving 79,885 nAMD patients, confirmed the age-related trend noted in prior studies. The frequency of nAMD cases among patients of ≥90 years was found to be 2.6-fold higher compared to patients < 70 years ([Khanani et al 2020](#)).

Gender: In Asian population, the incidence of nAMD was reported as higher in males. Studies from China and South Korea report that males make up 59.6% and 56.6% of cases, respectively ([Hu et al 2017](#), [Rim et al. 2019](#), [Kido et al. 2022](#)). In Japan, the male-to-female incidence rate is 53.2 vs. 29.8 per 100,000 person years ([Kido et al. 2022](#)). In non-Asian countries, nAMD prevalence was reported as higher among females, with studies reporting 63.3%, 55.1%, and 62% female cases ([Korva-Gurung et al. 2023](#), [Almony et al. 2021](#), [Kim et al 2016](#)). Research from Finland and the US found that 62%

and 55.1% of nAMD cases respectively, were in female patients ([Korva-Gurung et al. 2023](#), [Almony et al. 2021](#)).

Ethnicity: AMD is more prevalent among individuals of European descent compared to those of Asian, African, or Hispanic ancestry ([Zhou et al 2021](#); [Wong et al 2014](#)). A systematic review of 24 studies found that early AMD was most common in White populations (2.36%), followed by Black (1.73%), Asian (0.93%), and Hispanic (0.50%) populations. The annual incidence of late AMD was also highest in Whites (0.33%), with Asians (0.10%), Blacks (0.08%), and Hispanics (0.05%) having lower rates. Consistently, White populations show the highest incidence for both early and late AMD, while Hispanic populations have the lowest incidence across both stages ([Zhou et al 2021](#)).

- **Risk factors for the disease**

- Risk factors with a strong and consistent association with AMD include advanced age, cigarette smoking, prior cataract surgery, and family history of AMD. Moderate and consistent risk factors include higher body mass index, history of cardiovascular disease, hypertension, and higher plasma fibrinogen. Weak and inconsistent risk factors include gender, ethnicity, diabetes, dark iris color, history of cerebrovascular disease, serum total cholesterol, high-density lipoprotein cholesterol and triglyceride levels ([Chakravarthy et al. 2010](#), [Pugazhendhi et al 2021](#)).

The risk factors for AMD are presented below:

- Environmental and behavioral factors
 - Cigarette smoking ([Joo et al 2021](#), [Pugazhendhi et al 2021](#), [Wang et al 2022](#), [Detaram et al 2019](#), [Rim et al 2017](#), [Mitchell et al 2018](#))
 - Obesity ([Lim et al 2012](#), [Nice guideline 2018](#))
 - Low dietary intake of vitamins A, C, and E, zinc ([Ng et al 2019](#)), lutein and omega-3 fatty acids ([Pugazhendhi et al 2021](#), [Mitchell et al 2018](#))
 - Unhealthy lifestyle related to cardiovascular risk factors ([Lim et al 2012](#), [Colijn et al 2019](#), [Jungmin et al 2021](#), [Rim et al 2022](#), [Nice guideline 2018](#))
 - Low levels of physical activity ([Rim et al 2022](#), [Mauschitz et al 2022](#), [Nice guideline 2018](#))
- Ocular risk factors:
 - Darker iris pigmentation ([Lim et al 2012](#), [Nice guideline 2018](#))
 - Previous cataract surgery ([Lim et al 2012](#), [Yang et al 2022](#), [Nice guideline 2018](#))
 - Hyperopic refraction ([Cheung et al 2017](#), [Nice guideline 2018](#))
- Main genetic loci identified:
 - Complement factor H (CFH; chromosome [chr] 1; [Fritsche et al 2013](#), [Gorin 2012](#), [Matuskova et al 2020](#))
 - Age-related maculopathy susceptibility 2/HtrA-serine peptidase 1 (ARMS2/HTRA1; chr 10; [Matuskova et al 2020](#))
 - Complement component 2/complement factor B (C2/CFB; chr 6; [Su et al. 2020](#))

- Other:
 - Advanced age (main risk factor; [Lim et al. 2012](#), [Li et al. 2020](#), [Creuzot-Garcher et al. 2022](#), [Korva-Gurung et al. 2023](#), [Almony et al. 2021](#), [Kim et al 2016](#))
 - Family history ([Rim et al. 2022](#), [Nice guideline 2018](#))
 - Presence of AMD in the other eye ([Nice guideline 2018](#))
 - Race (more common in White patients compared to Asian, Black, or Hispanic patients, [Zhou et al. 2021](#))
 - Sleep deprivation (<6 hours; [Perez-Canales et al 2016](#))

- **The main existing treatment options**

The introduction of anti-VEGF agents in the mid-2000s marked a significant advancement in the management of exudative AMD and currently recognized as the gold standard in the treatment of exudative AMD ([Misiuk-Hojło et al 2021](#)). The American Academy of Ophthalmology's recommends intravitreal anti-VEGF injections as the primary treatment for nAMD ([Flaxel et al. 2020](#)).

Prior to this therapy, management options were limited to photodynamic therapy and focal argon laser ([Misiuk-Hojło et al 2021](#), [Brown et al 2009](#), [Brown et al 2006](#), [Rosenfeld et al. 2006](#), [Heier et al. 2012](#), [Nice guideline 2018](#)). Several anti-VEGF agents are currently approved as intravitreal injections for nAMD such as ranibizumab (e.g., Lucentis®, Accentrix®), aflibercept (e.g. Eylea®) or brolucizumab (Beovu®). In addition, faricimab (Vabysmo™), a bispecific antibody that selectively binds to and neutralizes both angiopoietin-2 and VEGF-A, is currently approved for the treatment of nAMD.

The efficacy of anti-VEGF agents in nAMD has been well established and intravitreal anti-VEGF injection therapy is the globally recognized standard of care treatment for nAMD ([Misiuk-Hojło et al 2021](#), [FDA 2023](#)). These agents block the pathophysiological functioning of nAMD by preventing abnormal angiogenesis and limiting fluid build-up in the retina, thereby preserving vision ([Rosenfeld et al 2006](#), [Jung et al 2024](#)).

Patients can be treated with intravitreal anti-VEGF injections as often as monthly for nAMD control. Newly approved nAMD therapies have shown efficacy in maintaining visual outcomes with extended intervals between injections, typically ranging from 8 to 16 weeks in clinical trials ([Khanani et al. 2024](#), [Lanzetta et al. 2024](#)). However, the gradual extension to these more infrequent dosing regimens takes time, and not all patients are able to extend beyond 8 weeks, with many patients requiring frequent treatment to adequately control disease activity and prevent vision loss ([Khanani et al. 2024](#); [Lanzetta et al. 2024](#), [Spitzer et al. 2025](#)). For example, after switching from monthly to quarterly dosing with intravitreal injections, the initial visual gain with ranibizumab is not maintained ([Regillo et al 2008](#)). Even with treat-and-extend regimens, relatively frequent injections are needed to achieve a good visual outcome ([Ehlken et al. 2020](#), [Skelly et al. 2019](#), [DeCroos et al. 2017](#), [Kertes et al. 2020](#)). Regardless of the frequency of injections, patients still require frequent eye examinations and office visits to achieve the patient's best visual outcomes, representing a burden for patients and

treatment centers ([Ehlken et al. 2020](#)). High treatment burden and frequent office visits, fear, and anxiety related to intravitreal injections, disappointed patient expectations, and lack of motivation to continue treatment have been reported as reasons for non-persistence with intravitreal anti-VEGF regimens ([Ehlken et al. 2020](#)). As a result, real-world data suggest that many patients are not able to achieve or maintain visual outcomes comparable with those observed in controlled clinical trials ([Cohen et al. 2013](#); [Finger et al. 2013](#); [Holz et al. 2020](#); [Holz et al. 2015](#)).

- **Natural history of the indicated condition in the (untreated) population**

Untreated nAMD is associated with a risk of impaired vision, including blindness. Neovascular AMD is the most debilitating form of AMD causing significant visual impairment ([Ghoshal et al 2018](#), [Jung et al 2024](#)). Patients with nAMD treated with sham injections in a Phase III clinical trial showed progressive visual acuity decline, with a mean loss in Early Treatment Diabetic Retinopathy Study (ETDRS) letter of 10.4 over 1 year ([Rosenfeld et al. 2006](#)). The development of nAMD typically manifests in one eye first. However, the presence of nAMD in one eye is a major risk factor for the development of nAMD in the fellow eye ([Wong et al 2020](#), [Lövestam et al 2022](#)).

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](#)). This includes the inability to drive, read, watch television, recognize faces, and engage in other valued daily activities. Visual impairment has many serious psychological and physical consequences; it often leads to a negative future outlook, a reduction in cognitive ability, anxiety, and depression, limited physical activity, an increased risk of falls and fractures, and a need for greater assistance to perform activities of daily life ([Brody et al 2001](#), [Tasman and Rovner 2004](#), [Berman and Brodaty 2006](#), [Ehlken et al. 2020](#)).

Decreased visual acuity is associated with increased five-year mortality, and even relatively mild visual impairment increases the risk of death more than two-fold ([McCarty et al 2001](#)). Findings from long-term follow-up studies regarding a possible association of nAMD with increased mortality risk have been inconsistent. Results from some studies have observed no association between nAMD and mortality ([Borger et al 2003](#), [Pedula et al 2015](#)); however, nAMD was reported as a significant risk factor for all-cause mortality in women in a population-based 14-year cohort study in people aged 60–80 years in Denmark ([Buch et al 2005b](#)), and in men in a 15-year cohort study in Australia ([Gopinath et al 2016](#)). In a cohort study in Iceland, nAMD was associated with all-cause mortality only in the subgroup aged 83 years or older ([Fisher et al 2015](#)). In a cohort study in Australia, nAMD was significantly associated with all-cause mortality only among persons younger than 75 years ([Cugati et al 2007](#)). A randomized, double-masked, controlled trial reported that participants with nAMD in one eye at baseline had a statistically significant increased risk for mortality compared with participants with no or few drusen ([Papudesu et al 2018](#)). Visual impairment could be associated with

depression, which has been linked with a poor quality of life and decreased life span ([Papudesu et al 2018](#)).

A systematic review and meta-analysis reported that late AMD was associated with a 20% increased rate of all-cause mortality (hazard ratio [HR] 1.20, 95% confidence interval [CI] 1.02–1.41), whereas no association was found for early AMD (HR 1.06, 95% CI 0.98–1.14) ([McGuinness et al 2017](#)). Individuals with late AMD had a hazard ratio of 2.01 (95% CI: 1.00-4.03) for all-cause mortality and 3.42 (95% CI: 1.38-8.49) for mortality from causes other than cardiovascular disease and cancer, indicating a substantial association between late AMD and reduced life expectancy ([Zhu et al 2019](#)).

- **Important comorbidities**

The key comorbidities in the nAMD population are listed in [Table 4](#) below.

Table 4 Important Comorbidities in nAMD Population

Comorbidity	Prevalence % (Reference)
Ocular	
Cataract	14.9% (Cruess 2007), 22.9% (Soubrane 2007), 28% (Anastasopoulos 2006), 30.3% (Ruiz-Moreno 2008), 47.6% (Creuzot-Garcher et al 2022)
Glaucoma	8% (Soubrane 2007), 9% (Anastasopoulos 2006), 7.7% (Almony et al 2021), 2.9% (Loukovaara et al 2022)
Diabetic retinopathy	5.1% (Almony et al 2021)
Ocular hypertension	17.3% (Creuzot-Garcher et al 2022)
Non-ocular	
Anxiety	1.5% (Cruess 2007), 3.4% (Ruiz-Moreno 2008), 3.7% (Soubrane 2007)
Arrhythmia	8.3% (Lee 2017), 13.7% (Almony et al 2021), 1.9% (Loukovaara et al 2022)
Cerebrovascular disease	2.0% (Rim et al 2017), 8.1% (Loukovaara et al 2022)
Coronary heart disease	4.9% (Mao 2019), 8.1% (Loukovaara et al 2022)
Depression	18.0% (Ruiz-Moreno 2008)
Diabetes	1.6% (Mao 2019), 25.1% (Lee 2017), 46% (Hu 2017), 22.3% (Almony et al 2021), 12.8% (Creuzot-Garcher et al 2022)
Heart failure	4.1% (Lee 2017), 10.4% (Creuzot-Garcher et al 2022)
Hyperlipidemia	4.5% (Farinha 2019), 18.0% (Lee 2017), 58.3% (Hu 2017), 41.7% (Almony et al 2021)
Hypertension	19% (Rim 2017), 41.1% (Lee 2017), 50.3% (Almony et al 2021), 69.5% (Creuzot-Garcher et al 2022), 18.4% (Loukovaara et al 2022)
Liver disease	6.1% (Rim 2017), 9.3% (Lee 2017)
Renal disease	9.6% (Lee 2017), 7.1% (Creuzot-Garcher et al 2022)
Stroke	2.2% (Mao 2019), 7.95% (Lee 2017), 11.4% (Creuzot-Garcher et al 2022)
Osteoarthritis	29.7% (Almony et al 2021)
Non-metastatic cancer	20.4% (Creuzot-Garcher et al 2022), 3.2% (Loukovaara et al 2022)
Sleep disorders	11.1% (Almony et al 2021), 3.9% (Creuzot-Garcher et al 2022)
Thyroid disorders	13.8% (Almony et al 2021), 2.5% (Creuzot-Garcher et al 2022)

nAMD = neovascular age-related macular degeneration.

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

To support the Port Delivery System with ranibizumab (PDS) clinical development program and registration, toxicology and investigative studies have been performed as well as a battery of biocompatibility studies ([Bantseev et al. 2021](#)). Toxicology studies with the PDS include a 6-month chronic toxicity study in minipigs (Study 14-2350) and two tolerability studies in rabbits using PDS surrogate implants (Studies 13-1963 and 14-0137). An investigative surgery study was performed to qualitatively evaluate various surgical techniques for decreasing the post-operative vitreous hemorrhage rate observed in Yucatan minipigs (Study 16-0261).

To support the initial development of ranibizumab administered via intravitreal injection, the safety of ranibizumab was characterized in nonclinical studies including single-dose toxicity studies in New Zealand White rabbits, repeat-dose toxicity studies in cynomolgus monkeys (representative studies include Studies 98-358-1757, 98-361-1757, and 01-463-1757), and an embryo-fetal development study in pregnant cynomolgus monkeys (Study 08-0590).

Repeat-dose toxicity

A Good Laboratory Practice (GLP) chronic 6-month toxicology and toxicokinetics PDS study in Yucatan minipigs (Study 14-2350) did not show any safety concerns relative to the implant or the combination of implant and ranibizumab. The implant was overall well tolerated in 9 of 10 animals. Ranibizumab-related ophthalmologic and histological findings were observed after administration of single or multiple doses via the implant, and were limited to dose-dependent ocular inflammation, which necessitated unscheduled euthanasia of 1 animal. All of the ranibizumab-related findings were considered related to an immune-mediated response to a foreign protein, which was supported by the presence of systemic anti-drug antibodies in all animals administered ranibizumab. Immunogenicity of human recombinant therapeutics in nonclinical species is generally not predictive of immunogenicity in humans ([van Meer et al. 2013](#)).

The procedure for implant insertion with or without ranibizumab was associated with transient mild conjunctival hyperemia localized over the implant, vitreous hemorrhage that sometimes prohibited fundus visualization, and movement (protrusion/extrusion) of the implant (sutured in place due to the scleral thickness differences between porcine and human eye) leading to traumatic cataracts or retinal pigment epithelium mottling. No systemic toxicity was observed.

A GLP 6-month toxicity study in rabbits with the surrogate implant (scaled one-third size, non-functional; Study 14-0137) showed the implant was well tolerated. Procedure-related ocular findings were comparable between implanted right eyes and sham surgery left eyes and persisted generally up to 1 month after surgery, resolving

with dissolution of absorbable sutures in the conjunctiva. The implant remained in place in 23 of 24 eyes. The implant movement/extrusion observed in the rabbit eye can be explained by the anatomical differences between the rabbit and human eye. Microscopic findings at the implantation sites were similar to sham surgery sites.

Relevance to human usage:

Immune-mediated ocular inflammation due to administration of ranibizumab (a humanized biologic) in nonclinical species is very unlikely to translate to humans. Immunogenicity of human recombinant therapeutics in nonclinical species is generally not predictive of immunogenicity in humans ([van Meer et al. 2013](#)). In patients treated with PDS in Study GR40548, no meaningful difference in the rate of intraocular inflammation was observed between patients with anti-ranibizumab antibodies in serum and those without. However, intraocular inflammation is expected in the context of ocular implants and/or intravitreal injections, and so is considered an important identified risk associated with PDS (see [Part II Module SVII 3.1](#)).

Vitreous hemorrhage was observed in the clinical development program and is a PDS implant and PDS procedures complication, which is considered an important identified risk associated with PDS (see [Part II Module SVII 3.1](#)).

The events of traumatic cataract or device (implant) dislocation which were observed in the nonclinical toxicology studies were due to anatomical differences between porcine or rabbit and human eye ([Bantseev et al. 2020](#)). These events do not directly translate to patients because the PDS implant or surrogate implant were not optimized for use in the minipig or rabbit eye, respectively. However, traumatic cataract is considered an important identified risk for ocular implant and intravitreal injection in the RMP (see [Part II Module SVII 3.1](#)). Septum dislodgement was observed in the clinical development program and is considered an important identified risk associated with PDS (see [Part II Module SVII 3.1](#)).

Reproductive/developmental toxicity

In accordance with [ISO 10993-1](#) Biological Evaluation of Medical Devices, no reproductive and developmental toxicity studies with the implant were conducted. No macroscopic or microscopic findings were observed in the reproductive organs of sexually mature animals in the GLP 6-month PDS toxicology study in minipigs (Study 14-2350) or in the ocular implantation toxicology study in rabbits (Study 14-0137).

The effect of ranibizumab on fertility has not been investigated extensively. Although no effects on reproductive tissues were noted in legacy repeat-dose intravitreal monkey studies (Studies 98-358-1757; 98-361-1757; 01-463-1757), inhibition of VEGF in human female reproductive tissues could potentially impair fertility. An embryofetal developmental toxicity study was performed with intravitreal injection ranibizumab in

pregnant cynomolgus monkeys (Study 08-0590). Pregnant animals received bilateral intravitreal injections of ranibizumab every 14 days starting on Day 20 through Day 62 of gestation at a dose of 0, 0.125, and 1.0 mg/eye.

The observed maternal trough serum ranibizumab concentrations following ranibizumab administration via intravitreal injection at 1.0 mg/eye were up to 18-fold higher than maximum concentration (C_{max}) levels observed with single eye treatment with PDS 100 mg/mL in humans. Skeletal abnormalities including incomplete ossification of the petrosal bone of the skull and shortened supernumerary vertebra were seen at a low incidence in fetuses from dams given 1.0 mg/eye of ranibizumab; no skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose that resulted in trough exposures equivalent to single eye treatment with PDS 100 mg/mL every 24 weeks (Q24W) in humans. No effect on the weight or structure of the placenta, maternal toxicity, embryotoxicity, or teratogenicity was observed.

Relevance to human usage:

VEGF is a major angiogenic factor involved in the formation of new blood vessels during embryonic and fetal development and placentation, and ranibizumab can reach the systemic circulation and inhibit VEGF systemically. The systemic exposure to ranibizumab via the PDS is relatively low; however, because of its mechanism of action, it is considered as potentially teratogenic and embryo-/fetotoxic and is not recommended during pregnancy unless the expected benefit outweighs the potential risk to the fetus.

Genotoxicity

In accordance with the International Conference on Harmonisation (ICH) S6(R1) Guidance on the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals ([ICH S6\(R1\) 2011](#)), no genotoxicity studies were conducted with ranibizumab. The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed.

Extracts from the implant were non-mutagenic in a bacterial reverse mutation assay in vitro (Study 14-0447) and in mouse lymphoma genotoxicity assay in vitro (Study 14-0448).

Relevance to human usage:

It is not expected that ranibizumab would interact directly with DNA or other chromosomal material. Considering this in conjunction with the negative findings for the implant genotoxicity studies, a direct genotoxic effect of PDS when administered in patients is unlikely.

- **Carcinogenicity**

In accordance with the ICH Guideline S6(R1) ([ICH S6\(R1\) 2011](#)), no carcinogenicity studies were conducted with ranibizumab. Based on negative in vitro genotoxicity results, the lack of potentially genotoxic extractables, and consistent with [ISO 10993-1](#), no carcinogenicity studies with the implant were conducted.

Relevance to human usage:

Based on ranibizumab being a biotechnology-derived pharmaceutical, the mechanism of action of ranibizumab, and the negative in vitro genotoxicity results, a carcinogenic effect of PDS when administered in patients is unlikely.

General safety pharmacology

While no stand-alone safety pharmacology studies were conducted with intravitreal injection ranibizumab, several safety pharmacology endpoints were incorporated into the legacy repeat-dose toxicology intravitreal injection studies in cynomolgus monkeys (Studies 98-358-1757; 98-361-1757; 01-463-1757). No treatment-related effects on physical examination parameters, including respiration rate, heart rate, and body temperature, were observed in cynomolgus monkeys given up to 2.0 mg/eye of ranibizumab administered via intravitreal injection as often as every 2 weeks for up to 26 weeks. Because the ocular and systemic ranibizumab concentrations following treatment with PDS 100 mg/mL are within the range experienced with monthly intravitreal ranibizumab 0.5 mg and lower than those achieved in studies in monkeys with intravitreal ranibizumab injections every other week, no safety pharmacology studies have been conducted for the PDS.

Relevance to human usage:

The repeat-dose toxicity studies in cynomolgus monkeys conducted with intravitreal injection ranibizumab showed no treatment-related effects. In humans, the systemic exposure to ranibizumab via the PDS is low relative to ocular exposures. The pharmacokinetic profile following treatment with PDS results in serum maximum ranibizumab concentrations and total exposure (area under the curve [AUC]) less than that following monthly intravitreal ranibizumab 0.5 mg. In the Phase III Study GR40548, the rate of non-ocular adverse events (AEs) was comparable between the PDS and intravitreal ranibizumab arms. In both the All 100 mg/mL Population and the All PDS Population, the PDS was generally well tolerated by patients, with no systemic safety signals, as expected.

Other toxicity-related information or data

Vitreous hemorrhage

A Yucatan minipig animal model of vitreous hemorrhage was developed to explore the impact of surgical parameters on vitreous hemorrhage associated with PDS implant surgery. In this model, pars plana laser ablation following scleral dissection was determined to be the most appropriate and effective way to mitigate the risk of post-operative vitreous hemorrhage ([Bantseev et al. 2020](#)).

Relevance to human usage:

During the conduct of the Phase II Study GX28228, an unexpectedly high rate of vitreous hemorrhage was initially reported during the post-operative period after implant insertion. The study was paused, and a root cause analysis was performed, including a surgical study using a nonclinical Yucatan minipig model for vitreous hemorrhage. The evidence generated in the nonclinical surgical study led to the development of an optimized PDS implant insertion surgery. The Phase II study was restarted with implementation of the optimized surgical technique for implant insertion (including scleral dissection followed by pars plana laser ablation and pars plana incision), as supported by the results of the Yucatan minipig study. The rate of vitreous hemorrhage (non-serious or serious) occurring during the post-operative period decreased from 11/22 patients (50.0%) prior to optimization to 6/157 patients (3.8%) after optimization. PDS implant and PDS procedures complications, including vitreous hemorrhage, remain an important identified risk associated with PDS (see [Part II Module SVII 3.1](#)).

PART II: MODULE SIII— CLINICAL TRIAL EXPOSURE

The PDS exposure and safety data included in this RMP are derived from three clinical studies in the PDS clinical development program: GX28228 (Ladder), GR40548 (Archway), and GR40549 (Portal). A brief description of these studies is presented in [Table 5](#) below.

Table 5 Summary of the Clinical Studies with PDS Included in this RMP

Study, Phase, Status	Study Design	Population	Dose, Route, and Regimen
Study GX28228 (Ladder) Phase II ^a Completed	Multicenter, dose-ranging, randomized, active treatment-controlled study	nAMD treated with prior anti-VEGF intravitreal injections	<u>PDS arms:</u> 100 mg/mL, 40 mg/mL, or 10 mg/mL refill-exchanged PRN <u>Control arm:</u> intravitreal ranibizumab 0.5 mg monthly
	Non-randomized, uncontrolled, open-label substudy (patients who require ongoing oral antithrombotic therapy)	nAMD treated with prior anti-VEGF intravitreal injections, who require ongoing oral antithrombotic therapy	PDS 100 mg/mL refill-exchanged PRN, up to Q6M
Study GR40548 (Archway) Phase III Completed	Randomized, multicenter, open-label (VA-masked), active-comparator study	nAMD treated with prior anti-VEGF intravitreal injections	<u>PDS arm:</u> 100 mg/mL refill-exchanged Q24W <u>Control arm:</u> intravitreal ranibizumab 0.5 mg Q4W
Study GR40549 (Portal) Phase III Ongoing ^b	Multicenter, open-label (VA-masked), multiple-cohort extension study	Patients with nAMD who completed Studies GX28228, GR40548	PDS 100 mg/mL refill-exchanged Q24W

nAMD = neovascular age-related macular degeneration; PDS = Port Delivery System with ranibizumab; PRN = pro-re nata (as needed); Q24W = every 24 weeks; Q4W = every 4 weeks; Q6M = every 6 months; RMP = Risk Management Plan; VA = visual assessor; VEGF = vascular endothelial growth factor.

^a Patients implanted with PDS prior to implementation of the optimized surgical technique for implant insertion (May 2016 Instructions for Use) were not considered for the pooled exposure to PDS, due to significant differences in the safety of the surgical technique and the expected outcomes.

^b Data from the WR42221 (Velodrome) patients who already enrolled in Study GR40549 are not included in this RMP.

The overall extent of exposure in the clinical development program as of 02 September 2025 is presented by duration of exposure in [Table 6](#) for the All PDS Population. The All PDS Population is defined as all patients who received an implant in either parent study GR40548 or GX28228 or in the extension study GR40549 except for patients who received a PDS implant using Instructions for Use (IFU) versions published

prior to May 2016 or who were at a non-compliant GX28228 site. Summaries of the All PDS Population includes data from all three studies starting from the date of the PDS implant (10/40/100 mg/mL pro-re nata [PRN] or 100 mg/mL Q24W) and thereafter.

A total of 577 patients in All PDS Population received PDS, accounting for a mean (standard deviation; SD) duration of exposure of 252.37 weeks (87.09), and a maximum duration of exposure of more than 7 years. Overall, 84.9% of patients (490/577) had >3 years of follow-up, 75.2% (434/577) had >4 years of follow-up, and 48.0% (277/577) had >5 years of follow-up ([Table 6](#)). Exposure by age and gender, race, and ethnicity is presented for the All PDS Population in [Table 7](#), [Table 8](#), [Table 9](#), and [Table 10](#) respectively.

Table 6 Overall Extent of PDS Exposure in Study Eye as of 02 September 2025 (CCOD), for All PDS Population

Protocol: GX28228, GR40548, GR40549

		All PDS (N=577)
Duration of Study Treatment (Weeks)		
N		577
Mean (SD)		252.37 (87.09)
Median		244.43
Min - Max		1.1 - 384.9
Any Exposure		577 (100%)
>37 days		575 (99.7%)
>6 months		570 (98.8%)
>1 year		558 (96.7%)
>1.5 years		547 (94.8%)
>2 years		526 (91.2%)
>3 years		490 (84.9%)
>4 years		434 (75.2%)
>5 years		277 (48.0%)
>6 years		219 (38.0%)
>7 years		4 (0.7%)
Number of Study Treatments per Patient(PDS initial fill +refill-exchanges +PDS re-implant fill)		
N		577
Mean (SD)		10.2 (3.5)
Median		10.0
Min - Max		1 - 21
1		11 (1.9%)
2		6 (1.0%)
3		13 (2.3%)
4		19 (3.3%)
5		22 (3.8%)
6		12 (2.1%)
7		37 (6.4%)
8		34 (5.9%)
9		30 (5.2%)
10		122 (21.1%)
11		53 (9.2%)
12		57 (9.9%)
13		29 (5.0%)
14		105 (18.2%)
15		16 (2.8%)
16		3 (0.5%)
17		3 (0.5%)
18		1 (0.2%)
19		2 (0.3%)
21		2 (0.3%)

Table continued from previous page

	All PDS (N=577)
Number of Supplemental Treatments per Patient	
N	577
Mean (SD)	0.5 (1.3)
Median	0.0
Min - Max	0 - 11
0	454 (78.7%)
1	60 (10.4%)
2	28 (4.9%)
3	13 (2.3%)
4	8 (1.4%)
5	5 (0.9%)
6	2 (0.3%)
7	2 (0.3%)
8	2 (0.3%)
9	1 (0.2%)
11	2 (0.3%)
Number of ranibizumab Treatments per Patient (initial fill, refill-exchanges, PDS re-implant fill, and supplemental treatments)	
N	577
Mean (SD)	10.7 (4.0)
Median	11.0
Min - Max	1 - 32
1	11 (1.9%)
2	5 (0.9%)
3	12 (2.1%)
4	18 (3.1%)
5	18 (3.1%)
6	12 (2.1%)
7	34 (5.9%)
8	37 (6.4%)
9	23 (4.0%)
10	113 (19.6%)
11	54 (9.4%)
12	56 (9.7%)
13	26 (4.5%)
14	92 (15.9%)
15	23 (4.0%)
16	17 (2.9%)
17	9 (1.6%)
18	5 (0.9%)
19	3 (0.5%)
20	2 (0.3%)
21	2 (0.3%)
22	2 (0.3%)
23	1 (0.2%)
25	1 (0.2%)
32	1 (0.2%)

Ranibizumab treatment is based on the actual treatment that patients have received. The summary only includes Genentech-supplied and commercially available ranibizumab administered to Study Eye, per the protocol following PDS implantation (PDS implantation, PDS refill-exchanges and supplemental intravitreal ranibizumab injection). Duration of treatment is defined as the time from first study treatment to treatment end date (as recorded in eCRF). For patients in the GX28228 / GR40548 Intravitreal to GR40549 group, only exposure data collected as part of GR40549 is included.

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Table 7 Overall Extent of PDS Exposure in Study Eye as of 02 September 2025 (CCOD) by Age, for All PDS Population

Protocol: GX28228, GR40548, GR40549

Age Group (years)	All PDS (N=577)				
	<65 (N=65)	65 -< 75 (N=180)	75 -< 85 (N=267)	>=85 (N=65)	Total (N=577)
Duration of Study Treatment (Weeks)					
N	65	180	267	65	577
Mean (SD)	277.68 (78.02)	253.80 (88.66)	251.24 (87.03)	227.75 (86.19)	252.37 (87.09)
Median	310.86	247.71	242.29	239.57	244.43
Min - Max	50.3 - 368.7	8.1 - 384.9	1.1 - 368.1	31.7 - 360.1	1.1 - 384.9
Any Exposure	65 (100%)	180 (100%)	267 (100%)	65 (100%)	577 (100%)
>37 days	65 (100%)	180 (100%)	265 (99.3%)	65 (100%)	575 (99.7%)
>6 months	65 (100%)	177 (98.3%)	263 (98.5%)	65 (100%)	570 (98.8%)
>1 year	64 (98.5%)	172 (95.6%)	258 (96.6%)	64 (98.5%)	558 (96.7%)
>1.5 years	62 (95.4%)	169 (93.9%)	253 (94.8%)	63 (96.9%)	547 (94.8%)
>2 years	60 (92.3%)	165 (91.7%)	244 (91.4%)	57 (87.7%)	526 (91.2%)
>3 years	59 (90.8%)	152 (84.4%)	230 (86.1%)	49 (75.4%)	490 (84.9%)
>4 years	58 (89.2%)	141 (78.3%)	194 (72.7%)	41 (63.1%)	434 (75.2%)
>5 years	40 (61.5%)	88 (48.9%)	126 (47.2%)	23 (35.4%)	277 (48.0%)
>6 years	31 (47.7%)	72 (40.0%)	99 (37.1%)	17 (26.2%)	219 (38.0%)
>7 years	1 (1.5%)	1 (0.6%)	2 (0.7%)	0	4 (0.7%)
Number of Study Treatments per Patient (PDS initial fill + refill-exchanges + PDS re-implant fill)					
N	65	180	267	65	577
Mean (SD)	11.2 (3.5)	10.4 (3.6)	10.1 (3.5)	9.2 (3.2)	10.2 (3.5)
Median	12.0	10.0	10.0	10.0	10.0
Min - Max	1 - 21	1 - 19	1 - 21	2 - 15	1 - 21

Table continued from previous page

Age Group (years)	All PDS (N=577)				
	<65 (N=65)	65 -< 75 (N=180)	75 -< 85 (N=267)	>=85 (N=65)	Total (N=577)
1	1 (1.5%)	4 (2.2%)	6 (2.2%)	0	11 (1.9%)
2	1 (1.5%)	3 (1.7%)	1 (0.4%)	1 (1.5%)	6 (1.0%)
3	3 (4.6%)	4 (2.2%)	5 (1.9%)	1 (1.5%)	13 (2.3%)
4	0	3 (1.7%)	11 (4.1%)	5 (7.7%)	19 (3.3%)
5	0	8 (4.4%)	9 (3.4%)	5 (7.7%)	22 (3.8%)
6	0	3 (1.7%)	7 (2.6%)	2 (3.1%)	12 (2.1%)
7	3 (4.6%)	12 (6.7%)	18 (6.7%)	4 (6.2%)	37 (6.4%)
8	1 (1.5%)	11 (6.1%)	16 (6.0%)	6 (9.2%)	34 (5.9%)
9	4 (6.2%)	5 (2.8%)	15 (5.6%)	6 (9.2%)	30 (5.2%)
10	11 (16.9%)	38 (21.1%)	59 (22.1%)	14 (21.5%)	122 (21.1%)
11	6 (9.2%)	16 (8.9%)	27 (10.1%)	4 (6.2%)	53 (9.2%)
12	10 (15.4%)	14 (7.8%)	27 (10.1%)	6 (9.2%)	57 (9.9%)
13	8 (12.3%)	10 (5.6%)	8 (3.0%)	3 (4.6%)	29 (5.0%)
14	14 (21.5%)	37 (20.6%)	47 (17.6%)	7 (10.8%)	105 (18.2%)
15	1 (1.5%)	10 (5.6%)	4 (1.5%)	1 (1.5%)	16 (2.8%)
16	0	0	3 (1.1%)	0	3 (0.5%)
17	1 (1.5%)	1 (0.6%)	1 (0.4%)	0	3 (0.5%)
18	0	0	1 (0.4%)	0	1 (0.2%)
19	0	1 (0.6%)	1 (0.4%)	0	2 (0.3%)
21	1 (1.5%)	0	1 (0.4%)	0	2 (0.3%)

Table continued from previous page

		All PDS (N=577)				
Age Group (years)		<65 (N=65)	65 -< 75 (N=180)	75 -< 85 (N=267)	>=85 (N=65)	Total (N=577)
Number of Supplemental Treatments per Patient						
N		65	180	267	65	577
Mean (SD)		0.8 (1.9)	0.4 (1.1)	0.5 (1.4)	0.2 (0.5)	0.5 (1.3)
Median		0.0	0.0	0.0	0.0	0.0
Min - Max		0 - 11	0 - 8	0 - 11	0 - 2	0 - 11
0		45 (69.2%)	145 (80.6%)	209 (78.3%)	55 (84.6%)	454 (78.7%)
1		9 (13.8%)	17 (9.4%)	28 (10.5%)	6 (9.2%)	60 (10.4%)
2		6 (9.2%)	4 (2.2%)	14 (5.2%)	4 (6.2%)	28 (4.9%)
3		0	9 (5.0%)	4 (1.5%)	0	13 (2.3%)
4		1 (1.5%)	3 (1.7%)	4 (1.5%)	0	8 (1.4%)
5		1 (1.5%)	1 (0.6%)	3 (1.1%)	0	5 (0.9%)
6		1 (1.5%)	0	1 (0.4%)	0	2 (0.3%)
7		1 (1.5%)	0	1 (0.4%)	0	2 (0.3%)
8		0	1 (0.6%)	1 (0.4%)	0	2 (0.3%)
9		0	0	1 (0.4%)	0	1 (0.2%)
11		1 (1.5%)	0	1 (0.4%)	0	2 (0.3%)
Number of ranibizumab Treatments per Patient (initial fill, refill-exchanges, PDS re-implant fill, and supplemental treatments)						
N		65	180	267	65	577
Mean (SD)		12.0 (4.4)	10.8 (3.8)	10.6 (4.0)	9.4 (3.3)	10.7 (4.0)
Median		12.0	11.0	10.0	10.0	11.0
Min - Max		1 - 32	1 - 22	1 - 25	2 - 16	1 - 32

Table continued from previous page

Age Group (years)	All PDS (N=577)				
	<65 (N=65)	65 -< 75 (N=180)	75 -< 85 (N=267)	>=85 (N=65)	Total (N=577)
1	1 (1.5%)	4 (2.2%)	6 (2.2%)	0	11 (1.9%)
2	0	3 (1.7%)	1 (0.4%)	1 (1.5%)	5 (0.9%)
3	4 (6.2%)	4 (2.2%)	3 (1.1%)	1 (1.5%)	12 (2.1%)
4	0	2 (1.1%)	12 (4.5%)	4 (6.2%)	18 (3.1%)
5	0	6 (3.3%)	7 (2.6%)	5 (7.7%)	18 (3.1%)
6	0	1 (0.6%)	8 (3.0%)	3 (4.6%)	12 (2.1%)
7	2 (3.1%)	12 (6.7%)	18 (6.7%)	2 (3.1%)	34 (5.9%)
8	1 (1.5%)	14 (7.8%)	15 (5.6%)	7 (10.8%)	37 (6.4%)
9	5 (7.7%)	4 (2.2%)	9 (3.4%)	5 (7.7%)	23 (4.0%)
10	6 (9.2%)	36 (20.0%)	56 (21.0%)	15 (23.1%)	113 (19.6%)
11	6 (9.2%)	15 (8.3%)	28 (10.5%)	5 (7.7%)	54 (9.4%)
12	11 (16.9%)	13 (7.2%)	27 (10.1%)	5 (7.7%)	56 (9.7%)
13	6 (9.2%)	10 (5.6%)	7 (2.6%)	3 (4.6%)	26 (4.5%)
14	11 (16.9%)	35 (19.4%)	40 (15.0%)	6 (9.2%)	92 (15.9%)
15	5 (7.7%)	8 (4.4%)	9 (3.4%)	1 (1.5%)	23 (4.0%)
16	2 (3.1%)	5 (2.8%)	8 (3.0%)	2 (3.1%)	17 (2.9%)
17	2 (3.1%)	4 (2.2%)	3 (1.1%)	0	9 (1.6%)
18	1 (1.5%)	2 (1.1%)	2 (0.7%)	0	5 (0.9%)
19	1 (1.5%)	1 (0.6%)	1 (0.4%)	0	3 (0.5%)
20	0	0	2 (0.7%)	0	2 (0.3%)
21	0	0	2 (0.7%)	0	2 (0.3%)
22	0	1 (0.6%)	1 (0.4%)	0	2 (0.3%)
23	0	0	1 (0.4%)	0	1 (0.2%)
25	0	0	1 (0.4%)	0	1 (0.2%)
32	1 (1.5%)	0	0	0	1 (0.2%)

Ranibizumab treatment is based on the actual treatment that patients have received. The summary only includes Genentech-supplied and commercially available ranibizumab administered to Study Eye, per the protocol following PDS implantation (PDS implantation, PDS refill-exchanges and supplemental intravitreal ranibizumab injection). Duration of treatment is defined as the time from first study treatment to treatment end date (as recorded in eCRF). For patients in the GX28228 / GR40548 Intravitreal to GR40549 group, only exposure data collected as part of GR40549 is included.

Program: /builds/studies/clinicalreporting/CDT3728_OtherAct_pool_SUR6M_2790423/programs/tlg/t_ex_age.sas
Output: /ocean/harbour/CDT3728/OtherAct_pool_SUR6M/prod_SUR_CCOD_2SEP2025_snapshot_7NOV2025_v3/output/
t_ex_age_ALP_EMA_02SEP2025_3728.out
21JAN2026 12:53

Table 8 Overall Extent of PDS Exposure in Study Eye as of 02 September 2025 (CCOD) by Gender, for All PDS Population

Protocol: GX28228, GR40548, GR40549

Gender	All PDS (N=577)		
	Male (N=227)	Female (N=350)	Total (N=577)
Duration of Study Treatment (Weeks)			
N	227	350	577
Mean (SD)	247.69 (88.13)	255.41 (86.39)	252.37 (87.09)
Median	241.00	260.71	244.43
Min - Max	2.0 - 384.9	1.1 - 368.7	1.1 - 384.9
Any Exposure	227 (100%)	350 (100%)	577 (100%)
>37 days	226 (99.6%)	349 (99.7%)	575 (99.7%)
>6 months	223 (98.2%)	347 (99.1%)	570 (98.8%)
>1 year	218 (96.0%)	340 (97.1%)	558 (96.7%)
>1.5 years	215 (94.7%)	332 (94.9%)	547 (94.8%)
>2 years	206 (90.7%)	320 (91.4%)	526 (91.2%)
>3 years	191 (84.1%)	299 (85.4%)	490 (84.9%)
>4 years	166 (73.1%)	268 (76.6%)	434 (75.2%)
>5 years	102 (44.9%)	175 (50.0%)	277 (48.0%)
>6 years	76 (33.5%)	143 (40.9%)	219 (38.0%)
>7 years	1 (0.4%)	3 (0.9%)	4 (0.7%)
Number of Study Treatments per Patient (PDS initial fill + refill-exchanges + PDS re- implant fill)			
N	227	350	577
Mean (SD)	10.0 (3.5)	10.4 (3.5)	10.2 (3.5)
Median	10.0	10.0	10.0
Min - Max	1 - 18	1 - 21	1 - 21
1	7 (3.1%)	4 (1.1%)	11 (1.9%)
2	2 (0.9%)	4 (1.1%)	6 (1.0%)
3	6 (2.6%)	7 (2.0%)	13 (2.3%)
4	6 (2.6%)	13 (3.7%)	19 (3.3%)
5	7 (3.1%)	15 (4.3%)	22 (3.8%)
6	5 (2.2%)	7 (2.0%)	12 (2.1%)
7	15 (6.6%)	22 (6.3%)	37 (6.4%)
8	15 (6.6%)	19 (5.4%)	34 (5.9%)
9	17 (7.5%)	13 (3.7%)	30 (5.2%)
10	47 (20.7%)	75 (21.4%)	122 (21.1%)
11	22 (9.7%)	31 (8.9%)	53 (9.2%)
12	21 (9.3%)	36 (10.3%)	57 (9.9%)
13	7 (3.1%)	22 (6.3%)	29 (5.0%)
14	41 (18.1%)	64 (18.3%)	105 (18.2%)
15	6 (2.6%)	10 (2.9%)	16 (2.8%)
16	0	3 (0.9%)	3 (0.5%)
17	2 (0.9%)	1 (0.3%)	3 (0.5%)
18	1 (0.4%)	0	1 (0.2%)
19	0	2 (0.6%)	2 (0.3%)
21	0	2 (0.6%)	2 (0.3%)

Table continued from previous page

All PDS
(N=577)

Gender	Male (N=227)	Female (N=350)	Total (N=577)
Number of Supplemental Treatments per Patient			
N	227	350	577
Mean (SD)	0.5 (1.3)	0.5 (1.4)	0.5 (1.3)
Median	0.0	0.0	0.0
Min - Max	0 - 9	0 - 11	0 - 11
0	179 (78.9%)	275 (78.6%)	454 (78.7%)
1	23 (10.1%)	37 (10.6%)	60 (10.4%)
2	12 (5.3%)	16 (4.6%)	28 (4.9%)
3	3 (1.3%)	10 (2.9%)	13 (2.3%)
4	4 (1.8%)	4 (1.1%)	8 (1.4%)
5	3 (1.3%)	2 (0.6%)	5 (0.9%)
6	0	2 (0.6%)	2 (0.3%)
7	1 (0.4%)	1 (0.3%)	2 (0.3%)
8	1 (0.4%)	1 (0.3%)	2 (0.3%)
9	1 (0.4%)	0	1 (0.2%)
11	0	2 (0.6%)	2 (0.3%)
Number of ranibizumab Treatments per Patient (initial fill, refill-exchanges, PDS re-implant fill, and supplemental treatments)			
N	227	350	577
Mean (SD)	10.5 (3.9)	10.9 (4.0)	10.7 (4.0)
Median	10.0	11.0	11.0
Min - Max	1 - 23	1 - 32	1 - 32
1	7 (3.1%)	4 (1.1%)	11 (1.9%)
2	2 (0.9%)	3 (0.9%)	5 (0.9%)
3	5 (2.2%)	7 (2.0%)	12 (2.1%)
4	6 (2.6%)	12 (3.4%)	18 (3.1%)
5	7 (3.1%)	11 (3.1%)	18 (3.1%)
6	5 (2.2%)	7 (2.0%)	12 (2.1%)
7	14 (6.2%)	20 (5.7%)	34 (5.9%)
8	15 (6.6%)	22 (6.3%)	37 (6.4%)
9	12 (5.3%)	11 (3.1%)	23 (4.0%)
10	42 (18.5%)	71 (20.3%)	113 (19.6%)
11	22 (9.7%)	32 (9.1%)	54 (9.4%)
12	22 (9.7%)	34 (9.7%)	56 (9.7%)
13	7 (3.1%)	19 (5.4%)	26 (4.5%)
14	35 (15.4%)	57 (16.3%)	92 (15.9%)
15	8 (3.5%)	15 (4.3%)	23 (4.0%)
16	9 (4.0%)	8 (2.3%)	17 (2.9%)
17	5 (2.2%)	4 (1.1%)	9 (1.6%)
18	1 (0.4%)	4 (1.1%)	5 (0.9%)
19	1 (0.4%)	2 (0.6%)	3 (0.5%)
20	0	2 (0.6%)	2 (0.3%)
21	1 (0.4%)	1 (0.3%)	2 (0.3%)
22	0	2 (0.6%)	2 (0.3%)
23	1 (0.4%)	0	1 (0.2%)
25	0	1 (0.3%)	1 (0.2%)
32	0	1 (0.3%)	1 (0.2%)

Ranibizumab treatment is based on the actual treatment that patients have received. The summary only includes Genentech-supplied and commercially available ranibizumab administered to Study Eye, per the protocol following PDS implantation (PDS implantation, PDS refill-exchanges and supplemental intravitreal ranibizumab injection). Duration of treatment is defined as the time from first study treatment to treatment end date (as recorded in eCRF). For patients in the GX28228 / GR40548 Intravitreal to GR40549 group, only exposure data collected as part of GR40549 is included.

Program:
/builds/studies/clinicalreporting/CDT3728_OtherAct_pool_SUR6M_2790423/programs/tlg/t_ex_s
ex.sas
Output:
/ocean/harbour/CDT3728/OtherAct_pool_SUR6M/prod_SUR_CCOD_2SEP2025_snapshot_7NOV2025_v3/ou
tput/t_ex_sex_ALP_EMA_02SEP2025_3728.out
21JAN2026 12:55

Table 9 Overall Extent of PDS Exposure in Study Eye as of 02 September 2025 (CCOD) by Race, for All PDS Population

Protocol: GX28228, GR40548, GR40549

Race	All PDS (N=577)						
	American Indian or Alaska Native (N=2)	Asian (N=3)	Black or African American (N=5)	White (N=560)	Multiple (N=1)	Unknown (N=6)	Total (N=577)
Duration of Study Treatment (Weeks)							
N	2	3	5	560	1	6	577
Mean (SD)	332.21 (2.32)	289.76 (66.83)	199.43 (145.67)	251.87 (86.80)	335.57 (NE)	284.38 (60.99)	252.37 (87.09)
Median	332.21	316.43	239.14	243.64	335.57	284.79	244.43
Min - Max	330.6 - 333.9	213.7 - 339.1	1.1 - 333.3	2.0 - 384.9	335.6 - 335.6	209.6 - 351.1	1.1 - 384.9
Any Exposure	2 (100%)	3 (100%)	5 (100%)	560 (100%)	1 (100%)	6 (100%)	577 (100%)
>37 days	2 (100%)	3 (100%)	4 (80.0%)	559 (99.8%)	1 (100%)	6 (100%)	575 (99.7%)
>6 months	2 (100%)	3 (100%)	4 (80.0%)	554 (98.9%)	1 (100%)	6 (100%)	570 (98.8%)
>1 year	2 (100%)	3 (100%)	4 (80.0%)	542 (96.8%)	1 (100%)	6 (100%)	558 (96.7%)
>1.5 years	2 (100%)	3 (100%)	4 (80.0%)	531 (94.8%)	1 (100%)	6 (100%)	547 (94.8%)
>2 years	2 (100%)	3 (100%)	3 (60.0%)	511 (91.3%)	1 (100%)	6 (100%)	526 (91.2%)
>3 years	2 (100%)	3 (100%)	3 (60.0%)	475 (84.8%)	1 (100%)	6 (100%)	490 (84.9%)
>4 years	2 (100%)	3 (100%)	3 (60.0%)	419 (74.8%)	1 (100%)	6 (100%)	434 (75.2%)
>5 years	2 (100%)	2 (66.7%)	2 (40.0%)	267 (47.7%)	1 (100%)	3 (50.0%)	277 (48.0%)
>6 years	2 (100%)	2 (66.7%)	2 (40.0%)	209 (37.3%)	1 (100%)	3 (50.0%)	219 (38.0%)
>7 years	0	0	0	4 (0.7%)	0	0	4 (0.7%)
Number of Study Treatments per Patient(PDS initial fill + refill-exchanges + PDS re-implant fill)							
N	2	3	5	560	1	6	577
Mean (SD)	12.0 (2.8)	11.0 (3.0)	8.4 (5.3)	10.2 (3.5)	14.0 (NE)	11.0 (1.8)	10.2 (3.5)
Median	12.0	11.0	10.0	10.0	14.0	10.5	10.0
Min - Max	10 - 14	8 - 14	1 - 14	1 - 21	14 - 14	9 - 14	1 - 21
1	0	0	1 (20.0%)	10 (1.8%)	0	0	11 (1.9%)
2	0	0	0	6 (1.1%)	0	0	6 (1.0%)
3	0	0	0	13 (2.3%)	0	0	13 (2.3%)
4	0	0	0	19 (3.4%)	0	0	19 (3.3%)
5	0	0	1 (20.0%)	21 (3.8%)	0	0	22 (3.8%)
6	0	0	0	12 (2.1%)	0	0	12 (2.1%)
7	0	0	0	37 (6.6%)	0	0	37 (6.4%)
8	0	1 (33.3%)	0	33 (5.9%)	0	0	34 (5.9%)
9	0	0	0	29 (5.2%)	0	1 (16.7%)	30 (5.2%)
10	1 (50.0%)	0	1 (20.0%)	118 (21.1%)	0	2 (33.3%)	122 (21.1%)
11	0	1 (33.3%)	0	51 (9.1%)	0	1 (16.7%)	53 (9.2%)
12	0	0	1 (20.0%)	55 (9.8%)	0	1 (16.7%)	57 (9.9%)
13	0	0	0	29 (5.2%)	0	0	29 (5.0%)
14	1 (50.0%)	1 (33.3%)	1 (20.0%)	100 (17.9%)	1 (100%)	1 (16.7%)	105 (18.2%)
15	0	0	0	16 (2.9%)	0	0	16 (2.8%)
16	0	0	0	3 (0.5%)	0	0	3 (0.5%)

Table continued from previous page

All PDS (N=577)							
Race	American Indian or Alaska Native (N=2)	Asian (N=3)	Black or African American (N=5)	White (N=560)	Multiple (N=1)	Unknown (N=6)	Total (N=577)
17	0	0	0	3 (0.5%)	0	0	3 (0.5%)
18	0	0	0	1 (0.2%)	0	0	1 (0.2%)
19	0	0	0	2 (0.4%)	0	0	2 (0.3%)
21	0	0	0	2 (0.4%)	0	0	2 (0.3%)
Number of Supplemental Treatments per Patient							
N	2	3	5	560	1	6	577
Mean (SD)	0.0 (0.0)	0.0 (0.0)	1.4 (2.2)	0.5 (1.3)	0.0 (NE)	1.0 (1.3)	0.5 (1.3)
Median	0.0	0.0	0.0	0.0	0.0	0.5	0.0
Min - Max	0 - 0	0 - 0	0 - 5	0 - 11	0 - 0	0 - 3	0 - 11
0	2 (100%)	3 (100%)	3 (60.0%)	442 (78.9%)	1 (100%)	3 (50.0%)	454 (78.7%)
1	0	0	0	59 (10.5%)	0	1 (16.7%)	60 (10.4%)
2	0	0	1 (20.0%)	26 (4.6%)	0	1 (16.7%)	28 (4.9%)
3	0	0	0	12 (2.1%)	0	1 (16.7%)	13 (2.3%)
4	0	0	0	8 (1.4%)	0	0	8 (1.4%)
5	0	0	1 (20.0%)	4 (0.7%)	0	0	5 (0.9%)
6	0	0	0	2 (0.4%)	0	0	2 (0.3%)
7	0	0	0	2 (0.4%)	0	0	2 (0.3%)
8	0	0	0	2 (0.4%)	0	0	2 (0.3%)
9	0	0	0	1 (0.2%)	0	0	1 (0.2%)
11	0	0	0	2 (0.4%)	0	0	2 (0.3%)
Number of ranibizumab Treatments per Patient (initial fill, refill-exchanges, PDS re-implant fill, and supplemental treatments)							
N	2	3	5	560	1	6	577
Mean (SD)	12.0 (2.8)	11.0 (3.0)	9.8 (6.5)	10.7 (4.0)	14.0 (NE)	12.0 (2.5)	10.7 (4.0)
Median	12.0	11.0	12.0	11.0	14.0	11.0	11.0
Min - Max	10 - 14	8 - 14	1 - 16	1 - 32	14 - 14	10 - 16	1 - 32
1	0	0	1 (20.0%)	10 (1.8%)	0	0	11 (1.9%)
2	0	0	0	5 (0.9%)	0	0	5 (0.9%)
3	0	0	0	12 (2.1%)	0	0	12 (2.1%)
4	0	0	0	18 (3.2%)	0	0	18 (3.1%)
5	0	0	1 (20.0%)	17 (3.0%)	0	0	18 (3.1%)
6	0	0	0	12 (2.1%)	0	0	12 (2.1%)
7	0	0	0	34 (6.1%)	0	0	34 (5.9%)
8	0	1 (33.3%)	0	36 (6.4%)	0	0	37 (6.4%)
9	0	0	0	23 (4.1%)	0	0	23 (4.0%)
10	1 (50.0%)	0	0	109 (19.5%)	0	3 (50.0%)	113 (19.6%)
11	0	1 (33.3%)	0	53 (9.5%)	0	0	54 (9.4%)
12	0	0	1 (20.0%)	54 (9.6%)	0	1 (16.7%)	56 (9.7%)
13	0	0	0	26 (4.6%)	0	0	26 (4.5%)
14	1 (50.0%)	1 (33.3%)	0	88 (15.7%)	1 (100%)	1 (16.7%)	92 (15.9%)
15	0	0	1 (20.0%)	22 (3.9%)	0	0	23 (4.0%)

Table continued from previous page

Race	All PDS (N=577)						Total (N=577)
	American Indian or Alaska Native (N=2)	Asian (N=3)	Black or African American (N=5)	White (N=560)	Multiple (N=1)	Unknown (N=6)	
16	0	0	1 (20.0%)	15 (2.7%)	0	1 (16.7%)	17 (2.9%)
17	0	0	0	9 (1.6%)	0	0	9 (1.6%)
18	0	0	0	5 (0.9%)	0	0	5 (0.9%)
19	0	0	0	3 (0.5%)	0	0	3 (0.5%)
20	0	0	0	2 (0.4%)	0	0	2 (0.3%)
21	0	0	0	2 (0.4%)	0	0	2 (0.3%)
22	0	0	0	2 (0.4%)	0	0	2 (0.3%)
23	0	0	0	1 (0.2%)	0	0	1 (0.2%)
25	0	0	0	1 (0.2%)	0	0	1 (0.2%)
32	0	0	0	1 (0.2%)	0	0	1 (0.2%)

Ranibizumab treatment is based on the actual treatment that patients have received. The summary only includes Genentech-supplied and commercially available ranibizumab administered to Study Eye, per the protocol following PDS implantation (PDS implantation, PDS refill-exchanges and supplemental intravitreal ranibizumab injection). Duration of treatment is defined as the time from first study treatment to treatment end date (as recorded in eCRF). For patients in the GX28228 / GR40548 Intravitreal to GR40549 group, only exposure data collected as part of GR40549 is included.

Program: /builds/studies/clinicalreporting/CDT3728_OtherAct_pool_SUR6M_2790423/programs/tlg/t_ex_race.sas
Output: /ocean/harbour/CDT3728/OtherAct_pool_SUR6M/prod_SUR_CCOD_2SEP2025_snapshot_7NOV2025_v3/output/t_ex_race_ALP_EMA_02SEP2025_3728.out
21JAN2026 12:58

Table 10 Overall Extent of PDS Exposure in Study Eye as of 02 September 2025 (CCOD) by Ethnicity, for All PDS

Protocol: GX28228, GR40548, GR40549

Ethnicity	All PDS (N=577)				
	Hispanic or Latino (N=22)	Not Hispanic or Latino (N=552)	Not Stated (N=1)	Unknown (N=2)	Total (N=577)
Duration of Study Treatment (Weeks)					
N	22	552	1	2	577
Mean (SD)	235.78 (92.12)	253.01 (87.00)	323.00 (NE)	221.93 (80.31)	252.37 (87.09)
Median	239.50	248.07	323.00	221.93	244.43
Min - Max	54.4 - 351.1	1.1 - 384.9	323.0 - 323.0	165.1 - 278.7	1.1 - 384.9
Any Exposure	22 (100%)	552 (100%)	1 (100%)	2 (100%)	577 (100%)
>37 days	22 (100%)	550 (99.6%)	1 (100%)	2 (100%)	575 (99.7%)
>6 months	22 (100%)	545 (98.7%)	1 (100%)	2 (100%)	570 (98.8%)
>1 year	22 (100%)	533 (96.6%)	1 (100%)	2 (100%)	558 (96.7%)
>1.5 years	21 (95.5%)	523 (94.7%)	1 (100%)	2 (100%)	547 (94.8%)
>2 years	18 (81.8%)	505 (91.5%)	1 (100%)	2 (100%)	526 (91.2%)
>3 years	17 (77.3%)	470 (85.1%)	1 (100%)	2 (100%)	490 (84.9%)
>4 years	16 (72.7%)	416 (75.4%)	1 (100%)	1 (50.0%)	434 (75.2%)
>5 years	9 (40.9%)	266 (48.2%)	1 (100%)	1 (50.0%)	277 (48.0%)
>6 years	6 (27.3%)	212 (38.4%)	1 (100%)	0	219 (38.0%)
>7 years	0	4 (0.7%)	0	0	4 (0.7%)
Number of Study Treatments per Patient(PDS initial fill + refill-exchanges + PDS re-implant fill)					
N	22	552	1	2	577
Mean (SD)	9.5 (3.4)	10.2 (3.5)	14.0 (NE)	8.0 (5.7)	10.2 (3.5)
Median	10.0	10.0	14.0	8.0	10.0
Min - Max	3 - 15	1 - 21	14 - 14	4 - 12	1 - 21
1	0	11 (2.0%)	0	0	11 (1.9%)
2	0	6 (1.1%)	0	0	6 (1.0%)
3	1 (4.5%)	12 (2.2%)	0	0	13 (2.3%)
4	2 (9.1%)	16 (2.9%)	0	1 (50.0%)	19 (3.3%)
5	0	22 (4.0%)	0	0	22 (3.8%)
6	1 (4.5%)	11 (2.0%)	0	0	12 (2.1%)
7	1 (4.5%)	36 (6.5%)	0	0	37 (6.4%)
8	3 (13.6%)	31 (5.6%)	0	0	34 (5.9%)
9	2 (9.1%)	28 (5.1%)	0	0	30 (5.2%)
10	4 (18.2%)	118 (21.4%)	0	0	122 (21.1%)
11	2 (9.1%)	51 (9.2%)	0	0	53 (9.2%)
12	2 (9.1%)	54 (9.8%)	0	1 (50.0%)	57 (9.9%)
13	0	29 (5.3%)	0	0	29 (5.0%)
14	3 (13.6%)	101 (18.3%)	1 (100%)	0	105 (18.2%)

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All PDS (N=577)					
Ethnicity	Hispanic or Latino (N=22)	Not Hispanic or Latino (N=552)	Not Stated (N=1)	Unknown (N=2)	Total (N=577)
15	1 (4.5%)	15 (2.7%)	0	0	16 (2.8%)
16	0	3 (0.5%)	0	0	3 (0.5%)
17	0	3 (0.5%)	0	0	3 (0.5%)
18	0	1 (0.2%)	0	0	1 (0.2%)
19	0	2 (0.4%)	0	0	2 (0.3%)
21	0	2 (0.4%)	0	0	2 (0.3%)
Number of Supplemental Treatments per Patient					
N	22	552	1	2	577
Mean (SD)	0.5 (0.7)	0.5 (1.4)	0.0 (NE)	0.0 (0.0)	0.5 (1.3)
Median	0.0	0.0	0.0	0.0	0.0
Min - Max	0 - 2	0 - 11	0 - 0	0 - 0	0 - 11
0	15 (68.2%)	436 (79.0%)	1 (100%)	2 (100%)	454 (78.7%)
1	4 (18.2%)	56 (10.1%)	0	0	60 (10.4%)
2	3 (13.6%)	25 (4.5%)	0	0	28 (4.9%)
3	0	13 (2.4%)	0	0	13 (2.3%)
4	0	8 (1.4%)	0	0	8 (1.4%)
5	0	5 (0.9%)	0	0	5 (0.9%)
6	0	2 (0.4%)	0	0	2 (0.3%)
7	0	2 (0.4%)	0	0	2 (0.3%)
8	0	2 (0.4%)	0	0	2 (0.3%)
9	0	1 (0.2%)	0	0	1 (0.2%)
11	0	2 (0.4%)	0	0	2 (0.3%)
Number of ranibizumab Treatments per Patient (initial fill, refill-exchanges, PDS re-implant fill, and supplemental treatments)					
N	22	552	1	2	577
Mean (SD)	10.0 (3.6)	10.7 (4.0)	14.0 (NE)	8.0 (5.7)	10.7 (4.0)
Median	10.0	11.0	14.0	8.0	11.0
Min - Max	3 - 16	1 - 32	14 - 14	4 - 12	1 - 32
1	0	11 (2.0%)	0	0	11 (1.9%)
2	0	5 (0.9%)	0	0	5 (0.9%)
3	1 (4.5%)	11 (2.0%)	0	0	12 (2.1%)
4	1 (4.5%)	16 (2.9%)	0	1 (50.0%)	18 (3.1%)
5	1 (4.5%)	17 (3.1%)	0	0	18 (3.1%)
6	1 (4.5%)	11 (2.0%)	0	0	12 (2.1%)
7	0	34 (6.2%)	0	0	34 (5.9%)
8	3 (13.6%)	34 (6.2%)	0	0	37 (6.4%)
9	2 (9.1%)	21 (3.8%)	0	0	23 (4.0%)
10	5 (22.7%)	108 (19.6%)	0	0	113 (19.6%)
11	1 (4.5%)	53 (9.6%)	0	0	54 (9.4%)
12	3 (13.6%)	52 (9.4%)	0	1 (50.0%)	56 (9.7%)
13	0	26 (4.7%)	0	0	26 (4.5%)
14	1 (4.5%)	90 (16.3%)	1 (100%)	0	92 (15.9%)

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Ethnicity	All PDS (N=577)				
	Hispanic or Latino (N=22)	Not Hispanic or Latino (N=552)	Not Stated (N=1)	Unknown (N=2)	Total (N=577)
15	0	23 (4.2%)	0	0	23 (4.0%)
16	3 (13.6%)	14 (2.5%)	0	0	17 (2.9%)
17	0	9 (1.6%)	0	0	9 (1.6%)
18	0	5 (0.9%)	0	0	5 (0.9%)
19	0	3 (0.5%)	0	0	3 (0.5%)
20	0	2 (0.4%)	0	0	2 (0.3%)
21	0	2 (0.4%)	0	0	2 (0.3%)
22	0	2 (0.4%)	0	0	2 (0.3%)
23	0	1 (0.2%)	0	0	1 (0.2%)
25	0	1 (0.2%)	0	0	1 (0.2%)
32	0	1 (0.2%)	0	0	1 (0.2%)

Ranibizumab treatment is based on the actual treatment that patients have received. The summary only includes Genentech-supplied and commercially available ranibizumab administered to Study Eye, per the protocol following PDS implantation (PDS implantation, PDS refill-exchanges and supplemental intravitreal ranibizumab injection). Duration of treatment is defined as the time from first study treatment to treatment end date (as recorded in eCRF). For patients in the GX28228 / GR40548 Intravitreal to GR40549 group, only exposure data collected as part of GR40549 is included.

Program: /builds/studies/clinicalreporting/CDT3728_OtherAct_pool_SUR6M_2790423/programs/tlg/t_ex_eth.sas

Output: /ocean/harbour/CDT3728/OtherAct_pool_SUR6M/prod_SUR_CCOD_2SEP2025_snapshot_7NOV2025_v3/output/t_ex_eth_ALP_EMA_02SEP2025_3728.out

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PART II: MODULE SIV— POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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

Table 11 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be Included as Missing Information?	Rationale (if not Included as Missing Information)
Treated eye			
Active intraocular inflammation	Intraocular surgery could lead to worsening of the pre-existing active intraocular inflammation. Pre-existing inflammation could also confound the identification of intraocular inflammation of different etiology.	No	A contraindication in patients with active intraocular inflammation is included in the SmPC.
Subfoveal fibrosis, subfoveal atrophy	Late stage nAMD associated with fibrosis and atrophy is unlikely to allow for visual acuity improvements. This would often result in increased deterioration over time, which could confound study results.	No	This exclusion criterion is considered specific to the conduct of the clinical development program and does not justify the restriction of treatment recommendation in this population. It is at the prescriber's discretion to evaluate patients' eligibility for treatment, based on an individual case by case benefit-risk evaluation.
Subretinal hemorrhage (greater than 1.27 mm ² involving the center of the fovea) in the study eye	Large subretinal hemorrhages are a risk factor for development of fibrosis. As such, improvement of visual acuity is unlikely in this patient population, which could confound study results.	No	This exclusion criterion is considered specific to the conduct of the clinical development program and does not justify the restriction of treatment recommendation in this population. It is at the prescriber's discretion to evaluate patients' eligibility for treatment, based on an individual case by case benefit-risk evaluation.

Table 11 Important Exclusion Criteria in Pivotal Studies in the Development Program (cont.)

Criterion	Reason for Exclusion	Is it to be Included as Missing Information?	Rationale (if not Included as Missing Information)
Treated eye			
Requirement for continuous use of aspirin, NSAIDs, other anticoagulants, or antiplatelet therapy at the time of study entry	There is potentially a higher risk of vitreous hemorrhage and conjunctival hemorrhage with the PDS implant insertion surgery in patients using aspirin, NSAIDs, anticoagulant, or antiplatelet therapy.	No	A recommendation to temporarily interrupt oral antithrombotic medication prior to the implant insertion procedure is included in the SmPC. Vitreous hemorrhage is a PDS implant and PDS procedural complication, which is an important identified risk associated with the PDS (see Part II Module SVII 3.1), and any potential risk factors and any risk groups such as patients on antithrombotic therapy will be further characterized through routine pharmacovigilance activities, including a specific follow-up questionnaire (see Part III 1).
History of vitrectomy surgery, submacular surgery, or other surgical intervention for AMD	This patient population may present with modifications in the physiology/anatomy of the eye, with potential impact on visual acuity, which could confound study results. The objective of the clinical development program was to assess the safety and efficacy of the PDS in eyes previously treated with and responsive to anti-VEGF therapy, and without any other previous treatments for nAMD which could confound study results.	No	No change in the safety of the PDS implant procedure, the safety profile of the PDS, or the efficacy of the PDS is foreseen in this patient population. This concern is not considered to be a sufficient reason to limit physician options in treatment of this patient population. Instructions in the manufacturer's IFU are considered sufficient to mitigate the risks associated with implantation of the PDS implant in this population.

Table 11 Important Exclusion Criteria in Pivotal Studies in the Development Program (cont.)

Criterion	Reason for Exclusion	Is it to be Included as Missing Information?	Rationale (if not Included as Missing Information)
Treated eye			
Prior treatment with Visudyne®, external-beam radiation therapy, transpupillary thermotherapy or laser (any type) used for AMD treatment	Patients who underwent such treatments may present with different degrees of macular fibrosis or scar, which will impact visual acuity and could confound study results. The objective of the clinical development program was to assess the safety and efficacy of the PDS in eyes previously treated with and responsive to anti-VEGF therapy, and without any other previous treatments for nAMD which could confound study results.	No	A limited number of patients previously treated with Visudyne®, external-beam radiation therapy, transpupillary thermotherapy, or laser are expected to be administered PDS in the post-marketing setting. The impact on the benefit-risk profile when administering PDS in this population is considered low.
Retinal pigment epithelial tear	Retinal pigment epithelium tears are events that could lead to severe visual loss, which could confound study results.	No	This exclusion criterion is considered specific to the conduct of the clinical development program and does not justify the restriction of treatment recommendation in this population. No potential risk factors are foreseen when administering the PDS in this population.
History of vitreous hemorrhage	Chronic or recurrent vitreous hemorrhage is an event that could lead to severe visual loss, which could confound study results.	No	No warning or contraindication for this population is included in the SmPC. Patient evaluation for the risk of bleeding complications is considered part of routine assessment for surgery eligibility (part of routine ocular surgery practice).

Table 11 Important Exclusion Criteria in Pivotal Studies in the Development Program (cont.)

Criterion	Reason for Exclusion	Is it to be Included as Missing Information?	Rationale (if not Included as Missing Information)
Treated eye			
History of vitreous hemorrhage (cont.)			Vitreous hemorrhage is a PDS implant and PDS procedures complication, which is an important identified risk associated with PDS (see Part II Module SVII 3.1), however, patients with a history of vitreous hemorrhage are not considered a risk group. Administration of PDS in this patient population does not pose any additional risk factors for developing vitreous hemorrhage.
History of retinal tear, retinal detachment; or peripheral retinal breaks within 3 months prior to the randomization visit	Patients with history of retinal tear, retinal detachment; or peripheral retinal breaks within 3 months may present with pathological modification in the physiology/anatomy of the eye, with potential impact on the visual acuity, which could confound the study results. Furthermore, patients with history of retinal tears or detachment are at risk of subsequent retinal tears or detachment, which could confound the study safety outcomes.	No	Retinal tear and Retinal detachment are PDS implant and PDS procedures complication, which is an important identified risk associated with the PDS (see Part II Module SVII 3.1). Patients with a history of retinal tear and retinal detachment or peripheral retinal break are considered a risk group and are at increased risk of developing retinal detachments when implanted with PDS. The safety of PDS when administered in this risk group will be further characterized through routine pharmacovigilance activities, including a specific follow-up questionnaire (see Part III 1).

Table 11 Important Exclusion Criteria in Pivotal Studies in the Development Program (cont.)

Criterion	Reason for Exclusion	Is it to be Included as Missing Information?	Rationale (if not Included as Missing Information)
Treated eye			
Aphakia or absence of the posterior capsule. Previous violation of the posterior capsule is also an exclusion criterion unless it occurred as a result of yttrium-aluminum garnet laser posterior capsulotomy in association with prior, posterior chamber intraocular lens implantation	This patient population presents with pathological modification in the physiology/anatomy of the eye, with potential impact on the visual acuity, which could confound study results.	No	No warning or contraindication for this population is included in the SmPC since this is considered part of routine assessment of a patient's eligibility for surgery (part of routine ocular surgery practice). This concern is not considered to be a sufficient reason to limit physician options in treatment of this patient population.
Spherical equivalent of the refractive error demonstrating more than 8 diopters of myopia	This patient population may present with pathological modification in the physiology/anatomy of the eye, with potential impact on the visual acuity, which could confound study results. Furthermore, patients with high myopia may be at increased risk of ocular comorbidities, which could confound the study safety outcomes.	No	Patients with high myopia have a thin sclera and retina and are susceptible to retinal tears and detachments. Retinal detachment is a PDS implant and PDS procedures complication, which is an important identified risk associated with the PDS (see Part II Module SVII 3.1). Any potential risk factors and risk groups such as patients with high myopia will be further characterized through routine pharmacovigilance activities, including a specific follow-up questionnaire (see Part III 1). It is at the prescriber's discretion to evaluate patients' eligibility for treatment, based on an individual benefit-risk evaluation.

Table 11 Important Exclusion Criteria in Pivotal Studies in the Development Program (cont.)

Criterion	Reason for Exclusion	Is it to be Included as Missing Information?	Rationale (if not Included as Missing Information)
Treated eye			
Intraocular surgery (including cataract surgery) within 3 months preceding the randomization visit	Precautionary measure implemented in most vitreoretinal disease clinical trials to minimize confounding of the study safety outcomes.	No	This exclusion criterion is considered specific to the conduct of the clinical development program and does not justify the restriction of treatment recommendation in this population. It is at the prescriber's discretion to evaluate patients' eligibility for treatment, based on an individual case by case benefit-risk evaluation.
Uncontrolled ocular hypertension or glaucoma (defined as IOP 25 mmHg or a cup to disc ratio 0.8, despite treatment with anti-glaucoma medication) and any such condition the Investigator determines may require a glaucoma-filtering surgery during a patient's participation in the study	Uncontrolled IOP or glaucoma can confound efficacy and safety results. Glaucoma created irreversible visual field defects (hence abnormalities in the patient's vision) and uncontrolled IOP can lead to safety events during surgery or with an in-dwelling ocular implant. Furthermore, patients with glaucoma that would potentially require filtering surgery may affect conjunctival and scleral health.	No	This exclusion criterion is considered specific to the conduct of the clinical development program and does not justify the restriction of treatment recommendation in this population. It is at the prescriber's discretion to evaluate patients' eligibility for treatment, based on an individual case by case benefit-risk evaluation.
History of glaucoma-filtering surgery, tube shunts, or microinvasive glaucoma surgery	Glaucoma drainage devices are generally implanted in the same ocular area where the PDS should be implanted (i.e., the supero-temporal quadrant). As such, it is not expected that the PDS would be implanted in this patient population. Furthermore, the underlying disease (glaucoma) can confound efficacy and safety results.	No	This exclusion criterion is considered specific to the conduct of the clinical development program and does not justify the restriction of treatment recommendation in this population. It is at the prescriber's discretion to evaluate patients' eligibility for treatment, based on an individual case by case benefit-risk evaluation.

Table 11 Important Exclusion Criteria in Pivotal Studies in the Development Program (cont.)

Criterion	Reason for Exclusion	Is it to be Included as Missing Information?	Rationale (if not Included as Missing Information)
Treated eye			
History of corneal transplant	Performing intraocular surgery on patients with a history of corneal transplant could cause rejection and failure of the corneal transplant, especially if patients develop post-operative ocular inflammation. This would have potential impact on the visual acuity, which could confound the study results.	No	No warning or contraindication for this population is included in the SmPC since this is considered part of routine assessment of a patient's eligibility for surgery (part of routine ocular surgery practice). This concern is not considered to be a sufficient reason to limit physician options in treatment of this patient population.
Either eye			
Suspected or active ocular or periocular infections (e.g., infectious conjunctivitis, or endophthalmitis)	As part of standard clinical practice, ocular surgical interventions are not recommended in patients with active ocular infections in either eye. There is risk of contaminating intraocular structures leading to vision loss during the PDS implant insertion surgery in a patient with suspected or active ocular or periocular infection.	No	A contraindication in patients with active or suspected ocular or periocular infections is included in the SmPC.
Choroidal neovascularization due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia	The objective of the clinical development program was to assess the efficacy and safety of the PDS in patients with choroidal neovascularization secondary to nAMD. This exclusion criterion was meant to exclude patients with different pathologies that might have a different response to ranibizumab and limit interpretability of the results.	No	The PDS is indicated for the treatment of adult patients with nAMD, and thus should not be administered in patients with choroidal neovascularization due to other causes. The exclusion criterion of use in patients with choroidal neovascularization due to other causes in the fellow eye is considered specific to the conduct of the clinical development program and does not justify the restriction of treatment recommendation in this population.

Table 11 Important Exclusion Criteria in Pivotal Studies in the Development Program (cont.)

Criterion	Reason for Exclusion	Is it to be Included as Missing Information?	Rationale (if not Included as Missing Information)
Either eye			
History of idiopathic or autoimmune-associated uveitis	Patients with idiopathic or autoimmune-associated uveitis are likely to develop intraocular inflammation, and are as such, generally not recommended to undergo ocular surgical interventions. The risk of recurrent inflammation is high in this patient population, especially after an ocular surgery. Occurrence of such events can confound efficacy and safety results.	No	A contraindication in patients with active intraocular inflammation is included in the SmPC. No other warning or contraindication for this population is included in the SmPC since this is considered part of routine assessment of a patient's eligibility for surgery (part of routine ocular surgery practice). This concern is not considered to be a sufficient reason to limit physician options in treatment of this patient population.
Systemic conditions			
Current systemic treatment for a confirmed active systemic infection	A systemic infection could spread to the eye through systemic circulation and confound study results.	No	A warning for patients not to undergo a PDS procedure if they have a severe systemic infection is included in the SmPC.
History of stroke within the last 3 months prior to informed consent, uncontrolled atrial fibrillation within 3 months of informed consent, history of myocardial infarction within the last 3 months prior to informed consent	Precautionary measure implemented in most clinical trials to minimize the risk of thromboembolic events.	No	This exclusion criterion is considered specific to the conduct of the clinical development program and does not justify the restriction of treatment recommendation in this population. No potential risk factors are foreseen when administering PDS in this population.

AMD = age-related macular degeneration; IFU = Instructions for Use; IOP = intraocular pressure; nAMD = neovascular age-related macular degeneration; NSAID = non-steroidal anti-inflammatory drugs; PDS = Port Delivery System with ranibizumab; SmPC = Summary of Product Characteristics; VEGF = vascular endothelial growth factor.

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

The clinical trial development program for the PDS is unlikely to detect adverse reactions that are rare, caused by prolonged exposure, caused by cumulative exposure, or that have a long latency.

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

Information available for the use of ranibizumab in populations typically underrepresented in clinical trial development programs is provided in [Table 12](#).

Use in Pregnancy and Lactation

Given that the prevalence and incidence of nAMD increases with age, and the disease is becoming more prevalent in patients ≥ 75 years old ([Creuzot-Garcher et al. 2022](#), [Korva-Gurung et al. 2023](#), [Almony et al 2021](#), [Hu et al 2017](#), [Kim et al 2016](#)), there is a low likelihood that female patients receiving treatment for nAMD will be of childbearing potential.

Table 12 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	
Patients with hepatic impairment	Not included in the clinical development program.
Patients with renal impairment	In pharmacokinetic covariate analyses with data from Studies GX28228, GR40548, and GR40549 as of the CCOD 27 August 2021, 73% of PDS treated patients (266/364) had renal impairment (44% mild, 27% moderate, and 2% severe).
Patients with cardiovascular impairment ^a	Not included in the clinical development program.
Immunocompromised patients	Not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin or race	Clinical trial exposure data by ethnic origin are provided in Table 10 . Clinical trial exposure data by race are provided in Table 9 .
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.

Type of Special Population	Exposure
Other	
Patients with bilateral disease	In Studies GX28228, GR40548, and GR40549, as of the CCOD 2 September 2025, 54.8% of patients (316/577) had bilateral disease. The majority of patients with bilateral disease were treated with PDS in the study eye and intravitreal treatment in fellow eye. Fourteen patients received PDS in their fellow eye during treatment in Study GR40549.

Source: SmPC = Summary of Product Characteristics; [Annex 7B.1](#); [Annex 7B.2](#).

PDS = Port Delivery System with ranibizumab.

^a In the pivotal Study GR40548, patients with the following conditions were excluded:

- Uncontrolled blood pressure (defined as systolic blood pressure > 180 mmHg and/or
- Diastolic blood pressure > 110 mmHg, while a patient is at rest); If a patient's initial measurement exceeds these values, a second reading may be taken 30 or more minutes later. If the patient's blood pressure must be controlled by antihypertensive medication, the patient may become eligible if medication is taken continuously for at least 30 days prior to Day 1.
- History of stroke within the last 3 months prior to informed consent.
- Uncontrolled atrial fibrillation within 3 months of informed consent.
- History of myocardial infarction within the last 3 months prior to informed consent.

PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

Susvimo was first granted marketing approval in the US on 22 October 2021, which marks the international birth date (IBD). Of note, in the US, Susvimo is the tradename for the totality of the system (drug and device) and, to date, it is only commercialized in the US. Outside of the US, Susvimo will be the tradename of the drug part only and the devices will be marketed under a different tradename (Contivue). Susvimo is approved in Canada, Taiwan, Turkey, and Thailand but is not commercialized as the device applications are pending or not completed. Ranibizumab is marketed worldwide as a solution for intravitreal injection under different brand names (e.g., Lucentis®, Accentrix®) and is indicated for the treatment of nAMD and other ocular indications. The safety profile of the PDS, as presented in this RMP, is based mostly on data generated from the PDS clinical development program. Although appropriate for the safety profile of the drug, the available post-authorization exposure and safety data for ranibizumab solution for intravitreal injection do not directly support the identification or characterization of the specific safety concerns associated with the PDS implant and PDS procedures. Therefore, intravitreal ranibizumab post-authorization exposure data are not provided in this section.

SV.1.1 Method Used to Calculate Exposure

The following methodology was used to calculate the number of patients who received the PDS implant in the commercial setting and to calculate the number of patients who exited clinical trials and received subsequent refills in the commercial setting:

- commercial patient numbers were used
- the number of clinical trial exits that occurred prior to a given time period after launch was combined with total commercial patients during the same time period
- the number of clinical trial patients was calculated through the number of clinical trial exits during a given time period
- commercial refills were tracked through TM1 (internal Sales data of Genentech) based on OUTs (Product went out from Inventory) data (note that the number of completed refills is currently unknown) and the following assumptions were applied:
 - refills were given every 6 months from the month of the clinical trial exit for each patient
 - patients were not extended beyond 6 months and there was no patient drop off
 - no supplemental intravitreal injections of ranibizumab were administered.

SV.1.2 Exposure

Since the IBD (22 October 2021) until 12 June 2025, an estimated cumulative total of 772 patients have received Susvimo (560 patients have been implanted with a PDS implant and have received subsequent refills from marketing experience and 212 patients were confirmed to have exited clinical trials and have received refills for the PDS with ranibizumab in the marketing setting).

PART II: MODULE SVI— ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Drugs that have a potential for misuse for illegal purposes are expected to share general characteristics such as psychoactive, stimulant, or sedative effects, or less commonly, anabolic effects, or enhancement of hemoglobin levels. Based on the mechanism of action, and the specialized procedures associated with its use, it is unlikely that the PDS will be misused for illegal purposes.

PART II: MODULE SVII—IDENTIFIED AND POTENTIAL RISKS

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

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

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

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

- Hyphema

In the All PDS Population (N=577), 10 patients (1.7%) experienced hyphema. See [Annex 7B.3](#) for additional details. All events were mild or moderate in intensity, most of them occurred in the post-operative period (i.e., within 37 days after the surgery), and resolved spontaneously within one month. One event of sight threatening hyphema was reported in Study GX28228 (Ladder) in a patient who also experienced sight threatening corneal oedema and increased intraocular pressure due to vitreous hemorrhage.

Hyphema, which consists of the accumulation of blood in the anterior chamber, is a well-known complication in the immediate post-operative period after ocular surgery and is reported to happen in up to ~4% patients after vitreoretinal surgery ([Kung and Wu 2016](#)). Depending on the severity, hyphema may be associated with patient-reported symptoms such as decreased vision, sensitivity to light, blurry vision, or distortion. Uncomplicated hyphema may be managed medically, by means of topical treatment, as well as by general measures like elevating the head while sleeping, and limiting the physical activity, etc. In a small number of cases that are not adequately addressed with medical management, surgical intervention may be needed to remove the hemorrhage from the anterior chamber through paracentesis or anterior chamber irrigation. Vision recovery is generally expected following resolution of hyphema.

The hyphema rate observed in the PDS clinical development program is within the reported rates in the literature for posterior segment surgeries ([Kung and Wu 2016](#)).

Moreover, the course of the events in the development program led to no significant impact on vision. In clinical practice, the ophthalmologists and retinal surgeons expected to administer PDS are familiar with the management and treatment of hyphema as part of the standard post-operative care protocols. This includes evaluation of vision, hyphema evaluation, and monitoring the intraocular pressure.

Considering the clinical context and the safety data available to date from the clinical development program, routine pharmacovigilance activities are considered sufficient to monitor this AE in the post-marketing setting and routine risk minimization communications are considered sufficient to minimize the risk. As such, hyphema is not included in the RMP, as it is a known risk, that requires no further characterization and is followed up via routine pharmacovigilance.

Risks not considered important for other reasons

Increased intraocular pressure

Transient increase in intraocular pressure (IOP) has been reported soon after intravitreal administration of VEGF inhibitors ([Lucentis SmPC](#), [Eylea SmPC](#), [Beovu SmPC](#)). The potential mechanism of occurrence of transient IOP increase is presumed to be connected to the volume of bolus injection inserted into the vitreous, rather than to VEGF inhibitors. As the eyeball is a closed structure of approximately 4 mL volume with minimal room for expansion, a 0.05 mL bolus injected via intravitreal injection would result in a sudden increase in intraocular pressure.

Repeated injections could lead to sustained increase in intraocular pressure. Possible mechanisms for sustained IOP elevation after repeat injections include mechanical or functional damage to the trabecular meshwork, drug-induced inflammation, or patients may have an unknown predisposition for developing increased intraocular pressure following intravitreal injection ([Bressler et al. 2015](#), [Kiddee and Montriwet al. 2015](#)).

Increased intraocular pressure is not expected during or immediately after the PDS implant insertion procedure because per the IFU, the intraocular pressure is controlled by the surgeon through the use of the inserted infusion cannula and checked at the end of the surgery using digital palpation. Increased intraocular pressure is also not typically expected after the refill-exchange procedures, because no substantial bolus of the drug is delivered into the eye through the implant during the procedure. During the refill-exchange procedure, the infusion of new drug into the implant reservoir displaces old drug into a refill collection chamber in the refill needle. Because the implant is rigid, this procedure does not cause an increase in the volume within the eye.

In the Phase III pivotal Study GR40548, IOP-increased AEs in the study eye were observed in 5 of the 248 patients in the PDS arm; 2 of the 5 patients experienced IOP-increased AEs assessed by the investigator as related to study treatment. In

the ranibizumab intravitreal arm, 3 of the 167 patients had IOP-increased AEs; one of which experienced IOP-increased AEs assessed by the investigator as related to study treatment. In both study arms, all events were non-serious, and the majority were mild or moderate in severity and resolved with either medical or surgical treatment by the end of the study ([Study GR40548 Final Clinical Study Report \[CSR\]](#); [Annex 7B.4](#)).

Considering the potential mechanisms of occurrence and the available data from the PDS clinical development program, increased IOP is not expected to impact the benefit-risk profile of the PDS implant. Cases of increased IOP can be adequately monitored through routine pharmacovigilance activities. Therefore, increased IOP is not considered a risk important for inclusion in the RMP.

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

Important Identified Risk of PDS Implant and PDS Procedures Complications (Vitreous Hemorrhage, Conjunctival Bleb/Bleb Leak, Conjunctival Erosion, Conjunctival Retraction, Endophthalmitis, Retinal Tear and Retinal Detachment, Device Dislocation, and Traumatic Cataract)

Benefit-risk impact:

In the All PDS Population (N=577) from Studies GX28228, GR40548, and GR40549 in adult patients with nAMD, patients experienced complications associated with the PDS implant and PDS procedures, including vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear, retinal detachment, device dislocation, and traumatic cataract. These events are clinically relevant and require prompt identification and evaluation so that treatment may be provided as appropriate. Some complications require prompt intervention to reduce the risk of worsening and/or vision loss and to maximize recovery potential. The potential mechanisms of occurrence and risk factors have been identified and are presumed to be linked to the surgical technique for the PDS implant procedure.

Based on data as of 02 September 2025 from the clinical development program, the risk of the complications associated with the PDS implant and PDS procedures (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract) has been sufficiently characterized and will continue to be analyzed. Overall, the safety profile of the PDS was shown to be generally consistent with that expected for a novel therapeutic product including an ocular implantation surgery and refill-exchange procedure, with the types of post-surgical procedural events being similar to those observed with other ocular implants and ocular surgeries. The known risks associated with the initial surgical implantation procedure and the low risk of AEs associated with subsequent refill-exchanges as observed in the clinical development program, are expected to be adequately managed by surgical training, product labeling (including the

manufacturer's IFU), a Physician Guide, and Patient Educational Materials (see [Part V.2](#)). These measures will ensure that the associated risks are mitigated and managed appropriately and are therefore outweighed by the overall benefits of the PDS, including robust efficacy results and durability of effect, thereby alleviating treatment burden and optimizing long-term vision outcomes. Robust safety data collected in the post-marketing setting will aid in further characterizing this risk and further refining/optimizing the PDS surgical procedures, if required.

Important Identified Risk of Septum Dislodgement

Benefit-risk impact:

Septum dislodgement (including both full septum dislodgement and partial septum dislodgement) is a device deficiency where the septum (a component of the implant which ensures self-sealing, see [Figure 1](#)) has dislodged into the implant body. Although the silicone overmold covering the top of the device remains in place, the self-sealing properties of the device are impaired and in the presence of septum dislodgement, normal device functioning cannot be assured. Cases of septum dislodgement have been reported after refill-exchange procedures. These events are clinically relevant and may require additional medical and/or surgical management. Careful examination of the implant through the dilated pupil is required prior to and after the refill-exchange procedure to check the appearance of the implant and its components.

To mitigate the risk of septum dislodgement, the design of the septum component of implant was updated, resulting in a post-septum improved implant ([Figure 2](#)). Furthermore, an updated manufacturing process has been implemented for the refill needle, to add a layer of lubricant (cross-linked silicone).

In addition, close adherence to the most up-to-date PDS IFU document is required, including the following recommendations:

- If excessive resistance, withdraw the refill needle with gentle counter pressure with a moist cotton swab, orient and insert again.
- Do not twist when encountering conjunctiva and Tenon's capsule to gain access to the septum, as damage to the overlying tissue and to the septum of the device may result.

Based on the investigation of septum dislodgement, further details have been added to the IFU and the PDS Surgical Training Program (see [Part V.2](#)), as appropriate. Overall, the risk of septum dislodgement, is expected to be adequately mitigated and managed through the risk minimization activities in place: surgical training, product labeling (including the manufacturer's IFU), a Physician Guide, and Patient Educational Materials. Based on current knowledge and the changes implemented at the component and manufacturing level of the PDS implant to mitigate the risk of septum dislodgement, the overall benefit-risk for PDS patients remains favorable at this time.

Important Identified Risk: Intraocular Inflammation

Benefit-risk impact:

Intraocular inflammation (IOI) can range from a mild inflammation of the eye to sequelae leading to vision loss. Inflammation can occur due to potential immunogenicity, in reaction to the active substance or its excipients, or inflammatory response due to the invasive nature of the procedure. The intraocular anatomical location, severity, and duration of the event is commonly used to assess the risk associated with intraocular inflammation. The IOI events observed with the PDS implant are primarily associated with the implantation surgery.

Overall, in All PDS Population a total of 163 patients (28.2%) experienced 212 IOI events, of which iritis was the most commonly reported IOI event. The majority of IOI events were mild or moderate in severity and recovered within 30 days of event onset. No events of posterior uveitis (including retinitis or retinal vasculitis) or retinal occlusive vasculitis have been reported in the All PDS Population.

This risk is expected to be adequately managed by product labeling (including the manufacturer's IFU), a Physician Guide, and Patient Educational Materials (see [Part V.2](#)).

Important Potential Risk of Implant Damage during the PDS Procedures (other than Septum Dislodgement)

Benefit-risk impact:

Implant damage can result from inappropriate handling during the PDS procedures and may lead to AEs. In addition, implant damage could prevent successful refill-exchange procedures, and may require removal of the implant, thereby interfering with the patient's treatment.

Implant damage during the PDS procedures is rare and not expected when following the manufacturer's IFU. To date, septum dislodgement was the only event of implant damage during the PDS procedures seen in the PDS clinical development program. Septum dislodgement is an important identified risk for the PDS implant, further discussed in Part II, Module SVII.3 [Important Identified Risk: Septum Dislodgement](#). Based on the totality of the data as well as the risk minimization measures put in place by the Applicant ([Part V.2](#)), implant damage is not anticipated to impact the risk benefit profile of the PDS.

Missing Information of Long-term Safety

Benefit-risk impact:

As of 02 September 2025, the overall extent of exposure from clinical development program in the All PDS Population accounts for 577 patients. The follow-up duration of patients in All PDS Population is more than 7 years, with the majority of patients having >3 years of follow-up (84.9% [490/577]) or >4 years of follow-up

(75.2% [434/577]), and almost half having > 5 years of follow-up (48.0% [277/577]) (see [Table 6](#)). Therefore, the safety profile of PDS implant in clinical trial setting is considered well characterized and continues to be analyzed. However, limited long-term safety data are available in the post-marketing setting. PDS is designed for permanent use and is intended to continuously deliver ranibizumab treatment. It is therefore considered important to continue collecting long-term safety data in the post-marketing setting to contribute to the effectiveness of the proposed RMP.

Missing Information of Implant Removal-Related Risks

Benefit-risk impact:

As of 02 September 2025, in the All PDS Population (N=577) from Studies GX28228, GR40548, and GR40549 in adult patients with nAMD, a total of 70 patients had their PDS implant removed, of which 34 had no reimplantation. Of the 34 patients with no reimplantation, 26 experienced AEs in the study eye that led to implant removal. The implant removal procedures were generally well tolerated, and the majority of ocular AEs post-implant removal, were non-serious, mild and recovered/resolved. Failure to adhere to the manufacturer's IFU for the implant removal procedure may potentially lead to different complications, not all of which were observed in the clinical development program, as cases requiring implant removal were rare. Hence, there are still gaps in knowledge about the safety of the implant removal procedure. Limited data are available with respect to the severity, type of complications associated with the implant removal, pre-existing risk factors, long-term risk outcomes of the implant being removed. The implant removal-related risks need to be further characterized.

Missing information of Reimplantation-Related Risks

Benefit-risk impact:

The risks associated with reimplantation are not well characterized, due to the limited number of patients in the nAMD All PDS Population that underwent a reimplantation procedure (36/577 patients as of 02 September 2025: 29 following a septum dislodgement, and 7 for reasons other than septum dislodgement (device dislocation [3 patients], conjunctival erosion [2 patients], and hypotony [1 patient])). This limited experience poses challenges in fully understanding the potential complications and outcomes associated with reimplantation procedures. Therefore, it is important to continue monitoring and documenting reimplantation cases to better characterize these risks and refine guidelines for managing such procedures.

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

Not applicable.

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

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

Important Identified Risks: PDS Implant and PDS Procedures Complications (Vitreous Hemorrhage, Conjunctival Bleb/Bleb Leak, Conjunctival Erosion, Conjunctival Retraction, Endophthalmitis, Retinal Tear and Retinal Detachment, Device Dislocation, and Traumatic Cataract)

Potential mechanisms:

The complications associated with the PDS implant and PDS procedures differ in terms of occurrence, etiology, development, and patient impact. The potential mechanisms of occurrence have been identified for all complications and are presumed to be linked to the surgical technique for the PDS implant procedure (see [Table 13](#)).

Table 13 Potential Mechanisms for the PDS Implant and PDS Procedures Complications

Complication	Potential Mechanism
Vitreous hemorrhage	The implant insertion procedure includes an incision of the pars plana 4 millimeters posterior to the limbus. As the pars plana has a vascular component, intraocular bleeding after pars plana incision resulting in vitreous hemorrhage could occur. Additionally, incomplete cauterization of conjunctival and scleral blood vessels around the scleral wound before implant insertion, or improper diathermy of active bleeding within the scleral wound before implant insertion may also lead to vitreous hemorrhage.
Conjunctival bleb/bleb leak (subconjunctival thickening)	Conjunctival bleb is defined as encapsulated elevation of the conjunctiva above the implant flange, which may be secondary to subconjunctival thickening or fluid. Excessive length of the scleral incision or the improper seating of the implant upon completion of the implant insertion procedure may result in temporary leakage of vitreous fluid into the subconjunctival space, with subsequent elevation of the conjunctiva above the implant flange, creating a fluid-filled bleb. The subconjunctival fluid collection may activate inflammatory processes that could eventually promote development of a thickened Tenon's capsule, with subsequent elevation of the conjunctiva above the implant flange, resembling a conjunctival bleb. A conjunctival bleb may also result from a subconjunctival fluid collection while performing the refill-exchange procedure, if the needle is not fully inserted into the implant, or if excessive forces are applied to the eye, with subsequent vitreous fluid leak into the subconjunctival space.
Conjunctival erosion	Once the PDS implant is inserted in the eye, the implant flange lays in the subconjunctival space, slightly elevating the conjunctiva and Tenon's capsule. The contact between the implant flange and the Tenon's capsule/conjunctiva, and the repeated friction between the eye lid and the elevated conjunctiva may promote conjunctival erosion, and eventually lead to implant flange exposure.

Complication	Potential Mechanism
Conjunctival retraction	Conjunctival retraction has been defined as a recession or opening of the limbal and/or radial peritomy. Inadequate suturing of the conjunctiva and Tenon's capsule upon completion of the implant insertion procedure may result in incomplete conjunctival healing, dehiscence of the sutured conjunctival flap leading to retraction of the conjunctiva, and eventually, implant flange exposure.
Endophthalmitis	Endophthalmitis may result from migration of microorganisms into the implant and/or vitreous cavity. This can be as a result of implant exposure secondary to conjunctival retraction or erosion as seen in the PDS clinical development program but could also be a result of improper sterile technique during the PDS procedures.
Retinal tear and retinal detachment	During the implant insertion procedure, the vitreous gel is manipulated. As a result, movement of the vitreous gel could generate vitreoretinal tractions in areas of pre-existing vitreoretinal adhesions. These tractions may lead to the development of a retinal tear. A rhegmatogenous retinal detachment occurs when vitreous fluid migrates from the vitreous cavity into the subretinal space due to the presence of a retinal tear.
Device dislocation	The PDS implant is securely placed into a scleral incision at the pars plana, such that the implant body resides within the vitreous cavity, and the implant flange rests on the outer surface of the eye between the Tenon's capsule and sclera. Following the insertion procedure, the implant is covered by the conjunctiva and Tenon's capsule, providing an additional barrier to keep the implant secured into the eye. However, surgical technique not adherent to the IFU such as a scleral incision too large for the device to be securely seated on the sclera, or presence of an exposed implant flange could cause implant dislocation from the intended position in the sclera. The implant may dislocate or subluxate into the vitreous cavity, or extend outside the vitreous cavity into or beyond the subconjunctival space. Implant dislocation into the vitreous cavity could be potentially amplified by a loose-fitting implant, which could dislocate, for example, if excessive forces are applied to the eye with the refill needle during the refill-exchange procedure.
Traumatic cataract	Traumatic cataract could potentially result from improper insertion of the implant's distal tip in close proximity to the patient's lens, excessive force applied during the refill-exchange resulting in eye indentation, dislocation of the implant into the vitreous cavity, or surgical removal of the dislocated implant. Perpendicular entry of the implant is important to avoid contact between the implant and intraocular structures such as the lens.

IFU = Instructions for Use; PDS = Port Delivery System with ranibizumab;
SUN = Standardization of Uveitis Nomenclature.

Evidence source(s) and strength of evidence:

The important identified risk of PDS implant and PDS procedure complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, and device dislocation) is based on the safety data from Studies GX28228, GR40548, and GR40549 in adult patients with nAMD.

Characterization of the risk:

Please refer to [Table 14](#) for the overall frequency, severity, seriousness, and outcomes of the PDS implant and PDS procedure complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract). Most of the PDS implant and PDS procedure complications were of mild or moderate severity. The majority of the severe events were considered serious and related to study device or procedure; all of the events were considered resolved, resolved with sequelae, or resolving ([Annex 7B.5](#)).

In the Phase III pivotal Study GR40548, adverse reactions of vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment occurred more frequently in the PDS arm than in the intravitreal ranibizumab arm. In Study GR40548, adverse reactions of device dislocation only occurred in the PDS arm ([Study GR40548 Final CSR](#)).

The higher percentage of adverse reactions in the PDS arm was attributed to the surgical nature of the study, and the PDS implant and PDS procedures in particular ([Study GR40548 Final CSR](#)).

As expected, for most complications associated with the PDS implant and procedures, the frequency of occurrence seen in the PDS clinical development program was different than that seen in literature for other clinical trials and observational studies in nAMD population following treatment with anti-VEGF injections (see [Table 15](#)). However, complications were generally consistent with those expected for a novel therapeutic product including an ocular implantation surgery and refill-exchange procedure, with the types of post-surgical procedural events being similar to those observed with other ocular implants and ocular surgeries. The risk profile of PDS implantation surgery is similar to the surgical risk profile of other intraocular implants including Ahmed, Baerveldt and Retisert devices that are considered the closest ophthalmologic surgical analogs and the most similar comparator for the PDS safety profile, because of the unique aspects of surgical technique, the trans-scleral anatomic location and configuration, and the long-term safety profile of a permanent intraocular implant. These devices have been categorized as similar devices in this assessment (see [Table 15](#)).

Table 14 PDS Implant and PDS Procedures Complications: Overall Frequency, Severity, Seriousness, and Outcomes in the All PDS Population

Protocol: GX28228, GR40548, GR40549

Risk:	All (pooled) (N=577)
Number of patients with at least one AE	177 (30.7%)
95% CI for % of patients with at least one AE	(27.05%, 34.56%)
Total number of AEs	305
Number (%) of patients with at least one AE by worst severity:	
Mild	89 (15.4%)
Moderate	47 (8.1%)
Severe	41 (7.1%)
Number of patients with at least one serious AE	70 (12.1%)
Outcome:	
No. of pts with at least 1 AE resulted in fatal outcome	0
No. of pts with at least 1 AE Not Recovered/Not Resolved	21 (3.6%)
No. of pts with at least 1 AE Recovering/Resolving	2 (0.3%)
No. of pts with at least 1 AE Recovered/Resolved	165 (28.6%)
No. of pts with at least 1 AE Resolved with Sequelae	5 (0.9%)
No. of pts with at least 1 AE with Unknown outcome	0

AE = adverse event; CI = Confidence Interval; 95% CIs computed using the Wilson method.

Investigator text for adverse events (AEs) coded using MedDRA version 28.0.

Percentages are based on the N in the column headings. This table summary includes adverse events that started or worsened (for existing condition) on or after the date of PDS implantation.

Conjunctival Bleb/Conjunctival Filtering Bleb Leak refers to the group of PTs: Conjunctival bleb, Conjunctival Filtering Bleb Leak, Conjunctival Cyst, Implant Site Cyst.

Retinal Detachment refers to the group of PTs: Retinal Detachment, Rhegmatogenous Retinal Detachment, Tractional Retinal Detachment.

Program:

/builds/studies/clinicalreporting/CDT3728_OtherAct_pool_SUR6M_2790423/programs/tlg/
t_ae_risk_all.sas

Output: /ocean/harbour/CDT3728/OtherAct_pool_SUR6M/
prod_SUR_CCOD_2SEP2025_snapshot_7NOV2025_v3/output/
t_ae_risk_all_SEYE_ALP_EMA_02SEP2025_3728.out

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Table 15 Frequency of Occurrence of PDS Implant and PDS Procedures Complications in the All PDS 100 mg/mL Population compared to nAMD Patients Treated with Intravitreal Injections or other Similar Devices

MedDRA Preferred Term	All PDS Population	Literature Data
Vitreous haemorrhage	7.5%	0–17.7% incidence in patients with similar devices (Retisert, Ahmed and Baerveldt) (Kempen et al. 2017, Teixeira et al. 2012, Pakravan et al. 2014, Tang et al. 2016, Yazdani et al. 2016, Sastre-Ibanez et al. 2019, Gedde et al. 2012, Gedde et al. 2022, Tokumo et al. 2021, Budenz et al. 2016). < 1% incidence for the IVT treatment for nAMD (Hatamnejad et al. 2023).
Conjunctival bleb/bleb leak (subconjunctival thickening)	14.9%	8–22% incidence in patients with Ahmed implants (Elbaklish and Gomaa 2020, Li et al 2014).
Conjunctival erosion	8.7%	1–21.3% incidence in patients with similar devices (Retisert, Ahmed and Baerveldt) (Tamcelik et al. 2013, Mahdy et al. 2013, Yazdani et al. 2016, Choy et al. 2018, Pakravan et al. 2018, Rathi et al. 2018, Simsek and Bilgec 2019, Elbaklish and Gomaa 2020a, Gedde et al. 2012, Gedde et al. 2022, Tokumo et al. 2021 Oct, Budenz et al. 2016, Christakis et al. 2016, Elbaklish and Gomaa 2020b).
Conjunctival retraction	3.5%	1–4.5% incidence in patients with similar devices (Retisert, Ahmed and Baerveldt) (Pakravan et al. 2018 Nov, Tang et al. 2016 Jan 9, Yazdani et al. 2016 May, Gedde et al. 2022 Dec).
Endophthalmitis	2.8%	< 1–4.5% incidence in patients with similar devices (Retisert, Ahmed, and Baerveldt) (Budenz et al. 2016, Callanan et al. 2008, Christakis et al. 2016, Gedde et al. 2012, Gedde et al. 2022 Dec, Jaffe et al. 2006, Jaffe et al. 2016 Sep, Kempen et al. 2017, Pavesio et al. 2010, Pakravan et al. 2018 and Tamcelik et al. 2013). ≤ 0.94% incidence for the IVT treatment for nAMD (Finger et al. 2022, Patil et al. 2022, Hatamnejad et al. 2023, Rosenberg et al. 2023).

MedDRA Preferred Term	All PDS Population	Literature Data
Retinal tear and retinal detachment	2.1%	0–5% incidence in patients with similar devices (Retisert, Ahmed and Baerveldt) (Callanan et al. 2008 , Kempen et al. 2017 , Pavesio et al. 2010 , Jaffe et al. 2016 , Arcieri et al. 2015 , Gedde et al. 2012 , Gedde et al. 2022 , Christakis et al. 2016 , Barton et al. 2011 , , Barton et al 2014 , Budenz et al. 2016). 0.3–0.49% incidence for the IVT treatment for nAMD (Finger et al 2022 , Rosenberg et al. 2023).
Device dislocation	2.4%	11.6% incidence in patients with the intraocular implant Retisert (Holbrook et al. 2016).
Traumatic cataract	0.2%	Not available

MedDRA = Medical Dictionary for Regulatory Activities; nAMD = neovascular age-related macular degeneration; PDS = Port Delivery System with ranibizumab.

Source: t_aesi_OCU_SEYE_ALP_EMA_02SEP2025_3728, t_ae_OCU_SEYE_ALP_EMA_02SEP2025_3728 ([Annex 7B.5](#)).

The complications associated with the PDS implant and PDS procedures can occur at different times after the implant procedure, depending on the complication and etiology. Vitreous hemorrhage is expected to occur mostly on the same day or the day after the implant insertion procedure; conjunctival erosion/retraction is expected to be identified at a later point in time after implantation; endophthalmitis can have either early or late onset. Traumatic cataract can occur in phakic patients during PDS procedures if the implant touches the patient's lens and disrupts the lens fibers. Implant dislocation is expected to occur at a later point in time after implantation, and most likely in conjunction with a refill-exchange procedure. However, no exact pattern of occurrence has yet been identified based on data available to date from the clinical development program.

Some of the complications associated with the PDS implant and PDS procedures (e.g., non-clearing vitreous hemorrhage, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract) may require prompt treatment, including specialized medical/surgical care and could be reversible if diagnosed and treated in a timely manner. Other complications (e.g., conjunctival bleb/ conjunctival filtering bleb leak, and low grade/mild vitreous hemorrhage) may require close monitoring and can resolve without any intervention.

If undiagnosed and not treated in a timely manner, most complications associated with the PDS implant and PDS procedures could evolve to cause significant discomfort to the patient and have critical impact on the patient's vision and/or quality of life, especially if associated with an infection. A summary of the impact on the patient's quality of life, management strategies and long-term outcomes for each of the PDS implant and PDS procedures complications is included in [Table 16](#).

Table 16 Impact on Patients' Quality of Life, Management Strategies, and Long-Term Outcomes for the PDS Implant and PDS Procedures Complications

Complications	Characterization
Vitreous hemorrhage	Vitreous hemorrhage presents with progressive onset of painless decreased vision. The degree of visual loss can vary, including appearance of red-black floating spots/streaks, cobwebs, or haze in the vision; severe loss of vision is also possible. Visual recovery is expected in the case of spontaneously clearing vitreous hemorrhage. However, surgical intervention (e.g., vitrectomy) may be needed in the case of a non-clearing vitreous hemorrhage. If the view through the vitreous cavity is limited, and if possible, perform an ocular B-scan ultrasonography to evaluate the areas of the retina not directly visualized on examination, in addition to the assessments scheduled for that specific visit / standard clinical and diagnostic procedures.

Complications	Characterization
Conjunctival bleb/bleb leak (subconjunctival thickening)	Subconjunctival thickening (conjunctival bleb/bleb leak) presents with no to mild ocular discomfort (e.g., foreign body sensation, eye discharge, or watering). The vitreous fluid associated with a conjunctival bleb leak is expected to be resorbed spontaneously after the leak stops. The subconjunctival tissue thickening secondary to conjunctival bleb may be persistent. In time, persistent subconjunctival tissue thickening above the implant flange may obscure the septum and make it difficult to perform the refill-exchange procedure. Additional surgical and/or medical management may be required to avoid further complications, especially if the implant septum is no longer identifiable due to the conjunctival bleb (e.g., including surgery to revise the conjunctiva and excise the bleb).
Conjunctival erosion	Conjunctival erosion presents with no to mild ocular discomfort (i.e., foreign body sensation), especially in case the implant flange becomes exposed. In time, conjunctival erosion could increase the risk of ocular infection and could lead to ocular infections and/or endophthalmitis. For a suspected conjunctival erosion, consider applying topical fluorescein over the conjunctiva to confirm erosion on slit lamp examination with cobalt blue light (Seidel testing). If available, anterior segment OCT imaging may be considered by the physician to evaluate the tissues on the top of the flange. In case of confirmed or suspected conjunctival erosion, prescribe antibiotic drops as per standard of care. Watch and wait in case of small, localized erosion without flange exposure, if the surrounding tissue is well adhered to the sclera and there is no evidence of an active leak. Schedule for surgical repair in case of full-thickness erosion (i.e., exposing the flange), or evidence of an active leak with Seidel positivity.
Conjunctival retraction	Conjunctival retraction presents with no to mild ocular discomfort (e.g., foreign body sensation), which could increase if the implant flange is exposed. Exposure of the implant increases the risk of ocular infection and may lead to ocular infections and/or endophthalmitis. Prescribe antibiotic drops as per standard of care. In the case of minimal conjunctival retraction (with or without Tenon's capsule), without leakage or without potential risk of device exposure, it is possible to attempt a course of conservative management and observe the retraction. In the case of conjunctival retraction with leak or with the potential risk of device exposure or there is the concern for their development or progression of the retraction, schedule for surgical repair as soon as possible.

Complications	Characterization
Endophthalmitis	Endophthalmitis presents with sudden onset of decreased vision and severe eye pain that leads to an urgent visit to an ophthalmologist. Cases may develop with a variable degree of visual loss and different time of occurrence from the PDS-related procedures. These events are clinically relevant and require prompt treatment as per standard of care to reduce the risk of vision loss and to maximize recovery. Per standard of care, vitreous tap is performed (aqueous humor tap may be considered per physician's discretion or if no vitreous can be obtained with a needle tap) and the specimen is sent the laboratory for microbiology cultures. Standard of care treatment includes intravitreal antibiotics (e.g., vancomycin). In addition, a preservative-free saline flush of implant contents can be performed using a refill needle, followed by a flush of the implant with 100 µL (0.1 mL) of vancomycin 1 mg/0.1 mL using the refill needle. Appropriate sterility control before and during implant insertion surgery, and administration of standard of care pre- and post-operative eye topical medications should be used to minimize the risk of endophthalmitis.
Retinal tear and retinal detachment	Retinal detachment presents with sudden onset of painless decreased vision centrally or peripherally. The degree of visual loss varies depending on the severity, duration, and location of the retinal detachment. In many cases, individuals could experience severe loss of vision, especially if the macula is detached. Retinal tear may be asymptomatic or present with flashes of lights (photopsia); decreased vision centrally or peripherally may occur when a retinal tear evolves into retinal detachment. Retinal detachment and retinal tear are considered clinically relevant events with a possible outcome of permanent vision loss. Prompt treatment with a laser procedure for retinal tears or a surgical intervention (e.g., pneumatic retinopexy, pars plana vitrectomy, or laser photocoagulation) may be needed for management of retinal detachments.
Device dislocation	Implant dislocation usually presents with no to severe ocular discomfort (e.g., foreign body sensation) and/or increased lacrimation, depending on where the implant is dislocated. Progressive vision loss or disturbances could also occur, especially if it is associated with decreased intraocular pressure and/or inflammation, or retinal detachment. <u>Dislocation into the vitreous cavity</u> The implant may dislocate in the anterior vitreous behind the scleral wound, with secondary vitreous fluid leak underneath the Tenon's capsule through the scleral wound. If available, anterior segment OCT imaging may be considered by the physician to aid visualization of the implant and surrounding tissues. It is recommended to surgically remove the implant by performing a vitrectomy and implant removal procedure as soon as possible. An implant completely dislocated into the vitreous and removed should not be re-implanted because of the possibility of damage to the implant during implant removal surgery.

Complications	Characterization
	<u>Urgent</u> surgical intervention is recommended if device dislocation is associated with the following events: • Positive Seidel test • Retinal detachment • Appositional choroidal detachments Topical, intravitreal, and/or systemic treatment may also be needed per standard of care in case of ocular infections, intraocular inflammation, hypotony, or other associated events. Prophylactic treatment to limit the risk of ocular infections may be needed in some cases. <u>Dislocation outside the vitreous cavity</u> The implant may entirely dislocate or sublunate outside the vitreous cavity into or beyond the subconjunctival space. If available, anterior segment OCT imaging may be considered by the physician to aid visualization of the implant flange and surrounding tissues. It is recommended to surgically intervene as soon as possible. • If the implant is sublunated into the subconjunctival space without extrusion through the conjunctiva and part of the implant body is still in the scleral wound, the implant may be seated back into its original position using the implant insertion tool. Do not handle the implant with forceps or tools other than the implant insertion tool as other tools could damage the implant. The oversized scleral wound should be sutured to reduce its length to 3.5 mm to provide tight fit of the implant. • If the implant is entirely dislocated into the subconjunctival space, removal of the implant is recommended followed by closure of the scleral wound with non-resorbable sutures. An implant removed from the subconjunctival space after dislocation should not be re-implanted because of the possibility of damage to the implant during implant removal surgery. <u>Urgent</u> surgical intervention is recommended if implant dislocation is associated with the following events: • Conjunctival opening with vitreous leak and implant expulsion (open globe) • Retinal detachment • Appositional choroidal detachments • Topical, intravitreal, and/or systemic treatment may also be needed per standard of care in case of ocular infections, intraocular inflammation, hypotony, or other associated events. Prophylactic treatment to limit the risk of ocular infections may be needed in some cases.
Traumatic cataract	Traumatic cataract may lead to rapid and progressive vision loss due to clouding of the lens, with the rate of lens clouding contingent on the integrity of the capsular bag of the lens. Once traumatic cataract becomes intumescent, it requires surgery to remove the patient's lens, or the patient is at risk of developing blindness.

PDS = Port Delivery System with ranibizumab; OCT = optical coherence tomography

Risk factors and risk groups:

The risk factors and risk groups identified for PDS implant and PDS procedures complications are included in [Table 17](#). Surgical-related risk factors are based on data available from the PDS clinical development program. Patient-related risk factors are presumed based on the potential mechanism of occurrence and the pathophysiology of the complication.

Table 17 Risk Factors and Risk Groups for the PDS Implant and PDS Procedures Complications

Complication	Risk Factors and Risk Groups
Vitreous hemorrhage	Patients on antithrombotic medication (e.g., oral anticoagulants, aspirin, non-steroidal anti-inflammatory drugs), or patients with coagulation abnormalities, may be at increased risk of vitreous hemorrhage. Vitreous hemorrhage may also occur due to the underlying disease. Surgery-related risk factors include insufficient laser ablation of the pars plana prior to incision, incomplete cauterization of conjunctival and scleral blood vessels around the scleral wound, or improper diathermy of active bleeding within the scleral wound before implant insertion.
Conjunctival bleb/bleb leak (subconjunctival thickening)	No risk group has been identified for the conjunctival bleb/bleb leak complication. Surgery-related risk factors include scleral incision greater than the recommended length in the IFU, as well as excessive suturing leading to long lasting conjunctival inflammation in the area around the implant flange. Refill-exchange-related risk factors include partial needle insertion into the implant, or excessive force applied to the eye while attempting to insert the needle.
Conjunctival erosion	It is presumed that patients with conjunctival allergies could be at increased risk of conjunctival erosions (e.g., due to potential eye rubbing creating tractional forces on the conjunctiva). Patients with thinner conjunctiva might also be at increased risk of conjunctival erosion. Surgery-related risk factors include improper coverage of the implant with Tenon's capsule, or loose-fitting implant due to scleral incision length wider than recommended in the manufacturer's IFU. Conjunctival erosion may also occur due to impaired conjunctival healing after a refill-exchange procedure (i.e., needle track-related erosion).

Complication	Risk Factors and Risk Groups
Conjunctival retraction	It is presumed that patients with conjunctival allergies could be at increased risk of conjunctival retraction (e.g., due to eye rubbing creating tractional forces on the conjunctiva). Patients with thinner conjunctiva might also be at increased risk of conjunctival retraction. Surgery-related risk factors include insufficient or partial reapposition of the conjunctiva and Tenon's capsule edges with sutures, either at the limbus, or in the radial cut.
Endophthalmitis	Patients with active or suspected ocular or periocular infections and patients with a severe systemic infection are at risk of endophthalmitis if they undergo PDS procedures. With respect to the implant insertion procedure or refill-exchange procedure, improper aseptic technique is a known risk factor, as well as conjunctival retraction or erosion with implant flange exposure. Furthermore, poor ocular hygiene or failure to use eye protection during high-risk activities constitutes additional risk factors for endophthalmitis after the implant insertion procedure.
Retinal tear and retinal detachment	It is presumed that patients with a thin retina (e.g., secondary to high myopia), peripheral vitreoretinal degenerations (e.g., lattice degeneration), abnormal vitreoretinal adhesions, or posterior vitreous detachment or any history of rhegmatogenous retinal detachment could be at increased risk of retinal tear and subsequent rhegmatogenous retinal detachment, especially after an eye trauma. Surgery-related risk factors include excessive vitreous prolapse or improper management of the vitreous prolapse after pars plana incision or after trocars removal.
Device dislocation	It is presumed that patients with eye trauma or very high intraocular pressure are at risk of device dislocation. In the clinical development program, most dislocation cases were associated with a longer than recommended incision (>3.7 mm before or after laser ablation of the pars plana) at the time of implantation. Most cases had evidence of "scleral discoloration" around the implant flange on images before the event of dislocation. The "scleral discoloration," which is seen as darkened areas most often around the outer corners of the implant flange, may demonstrate a transillumination defect and thus may represent an elongated scleral wound. Implant dislocations related to an elongated scleral wound can occur during the refill-exchange procedure as the force from the needle may lead to the movement of the implant. Intrinsic and extrinsic risk factors related to the patient could include thin conjunctiva, excessive eye rubbing, and eye trauma.
Traumatic cataract	No risk group has been identified for the traumatic cataract complications. The event might be linked to the direct trauma to the lens during the procedure.

IFU = Instructions for Use; PDS = Port Delivery System with ranibizumab.

Preventability:

Strict adherence to the manufacturer's IFU is required to minimize the risk of PDS implant and PDS procedures complications. These include:

- Appropriate pars plana laser ablation and scleral cauterization to minimize the risk of vitreous hemorrhage
- Appropriate scleral incision length, appropriate incorporation of conjunctiva and Tenon's capsule in peritomy closure, and appropriate seating of the refill needle during refill-exchange procedure to minimize risk of conjunctival bleb
- Appropriate incorporation of conjunctiva and Tenon's capsule in peritomy closure and appropriate placement of conjunctival sutures to avoid contact with the implant edge to minimize the risk of conjunctival erosion
- Appropriate suturing of the conjunctiva and Tenon's capsule to the limbus to minimize the risk of conjunctival retraction
- Appropriate sterile controls during implant insertion or refill-exchange procedures to minimize the risk of endophthalmitis
- Appropriate management of vitreous prolapse after pars plana incision to minimize the risk of retinal tear and retinal detachment
- Appropriate scleral incision length and appropriate targeting of the pars plana during laser ablation incision to minimize the risk of device dislocation.

Impact on the benefit-risk balance of the product:

The complications associated with the PDS implant and PDS procedures are clinically relevant and require prompt evaluation so that treatment may be provided as appropriate. Some complications require prompt intervention to reduce the risk of worsening and/or vision loss and to maximize recovery potential. The potential mechanisms of occurrence and risk factors have been identified and are presumed to be linked to the surgical technique for the PDS implant procedure.

Based on data available up to 02 September 2025 from the clinical development program, the risk of the complications associated with the PDS implant and PDS procedures has been sufficiently characterized and will continue to be analyzed. Overall, the safety profile of the PDS was shown to be generally consistent with that expected for a novel therapeutic product including an ocular implantation surgery and refill-exchange procedure, with the types of post-surgical procedural events being similar to those observed with other ocular implants and ocular surgeries. The known risks associated with the initial surgical implantation procedure and the low risk of AEs associated with subsequent refill-exchanges as observed in the clinical development program, are expected to be adequately managed by surgical training, product labeling (including the manufacturer's IFU), a Physician Guide, and Patient Educational Materials (see [Part V.2](#)). Robust safety data collected in the post-marketing setting will aid in further

characterizing this risk and further refining/optimizing the PDS surgical procedures, if required.

Public health impact:

Not yet established.

Important Identified Risk: Septum Dislodgement

Potential mechanisms¹:

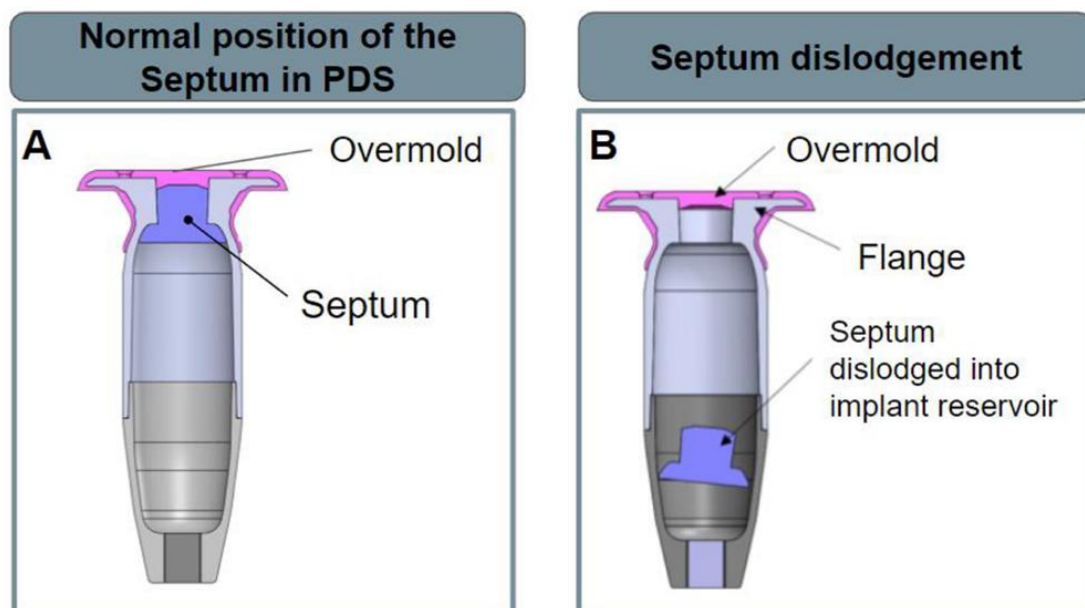
Following an increased incidence of cases of septum dislodgement reported with the Phase III implants in the Phase III clinical trials in 2022, a root cause analysis was conducted. The outcome of the analysis revealed that the main contributing factors leading to septum dislodgement were:

- Insufficient bonding between the septum and the overmold (see [Figure 1](#))
- Excessive insertion force from the refill needle during refill-exchange.

The root cause investigation also indicated that septum dislodgement into the implant may also occur due to improper refill-exchange technique (e.g., twisting/rotation motion while attempting to insert the refill needle).

¹ Risk management for the PDS implant and ancillary devices is performed in accordance with [ISO 14971](#) Medical Devices-Application of Risk Management to Medical Devices and with the company's internal risk management procedures *Quality Risk Management* and *Quality Risk Management Process*. Through the risk management process, hazards, hazardous situations, and harms relating to the PDS design, procedures, and use are identified, evaluated, and mitigated, when possible, through implementation of specific measures, including verification, validation, inspection, training, labeling, and other controls.

Figure 1 Schematic of Septum Dislodged into Implant Reservoir



PDS = Port Delivery System

Evidence source(s) and strength of evidence:

This important identified risk is based on the safety data from Studies GX28228, GR40548, and GR40549 in adult patients with nAMD.

Characterization of the risk

Refer to [Table 18](#) for the overall frequency, severity, seriousness, and outcomes of the events of septum dislodgement reported up to the CCOD of 02 September 2025. Of note, 3 additional patients in the All PDS Population experienced septum dislodgement. These events occurred before 14 June 2021 (i.e., with the pre-septum improved implant), when the electronic case report form (eCRF) was updated to collect device deficiency information. Only one had an AE reported (preferred term [PT] of device breakage), however, all 3 events were reported as product complaints. Overall, no distinct patterns of AEs were observed in patients with septum dislodgement, including no cases of endophthalmitis.

Table 18 Septum Dislodgement: Overall Frequency with 95% CI, Severity, Seriousness, and Outcomes for All PDS Population

Protocol: GX28228, GR40548, GR40549

Risk: Septum Dislodgement	All (pooled) (N=577)
Number of patients with at least one AE	59 (10.2%)
95% CI for % of patients with at least one AE	(8.01%, 12.97%)
Total number of AEs	59
Number (%) of patients with at least one AE by worst severity:	
Mild	42 (7.3%)
Moderate	14 (2.4%)
Severe	3 (0.5%)
Number of patients with at least one serious AE	58 (10.1%)
Outcome:	
No. of pts with at least 1 AE resulted in fatal outcome	0
No. of pts with at least 1 AE Not Recovered/Not Resolved	29 (5.0%)
No. of pts with at least 1 AE Recovering/Resolving	1 (0.2%)
No. of pts with at least 1 AE Recovered/Resolved	29 (5.0%)
No. of pts with at least 1 AE Resolved with Sequelae	0
No. of pts with at least 1 AE with Unknown outcome	0

AE = adverse event; CI = Confidence Interval; 95% CIs computed using the Wilson method. Investigator text for adverse events (AEs) coded using MedDRA version 28.0. Percentages are based on the N in the column headings. This table summary includes adverse events that started or worsened (for existing condition) on or after the date of PDS implantation. Septum Dislodgement (SD) is identified using AE Preferred Term = "Device issue" & Lower Level Term = "Device septum dislodgement".

Program: /builds/studies/clinicalreporting/CDT3728_OtherAct_pool_SUR6M_2790423/programs/tlg/
t_ae_risk_all.sas
Output: /ocean/harbour/CDT3728/OtherAct_pool_SUR6M/
prod_SUR_CCOD_2SEP2025_snapshot_7NOV2025_v3/output/
t_ae_risk_all_SEYE_ALP_SEPT_EMA_02SEP2025_3728.out
21JAN2026 12:47

According to [Holbrook et al. 2016](#), an implant dissociation has been associated with Retisert, wherein the fluocinolone acetonide implant is designed to allow sustained release of corticosteroid for approximately 2.5 years. The implant made of a non-biodegradable polymer consists of a suture strut that anchors the implant to the eye wall and a drug pellet containing fluocinolone acetonide, which is glued to the strut. The pellet can become unglued from the strut, which is referred to as a "dissociation." This device complication is a recognized one and closest in resemblance to the septum dislodgement of the PDS implant. An implant dissociation rate of 13.6% was reported in literature for the Retisert device ([Holbrook et al. 2016](#)).

A septum dislocated into the body of the implant could make the implant non-functional due to loss of the septum integrity and the ability to refill. These events are clinically relevant and may require additional medical and/or surgical management. Although septum dislodgements in and of themselves are not surgical emergencies, it is important to monitor disease activity while determining further treatment course.

Risk factors and risk groups

Patients implanted with the pre-septum improved implant are at higher risk of experiencing septum dislodgement than those who have received other versions of the implant.

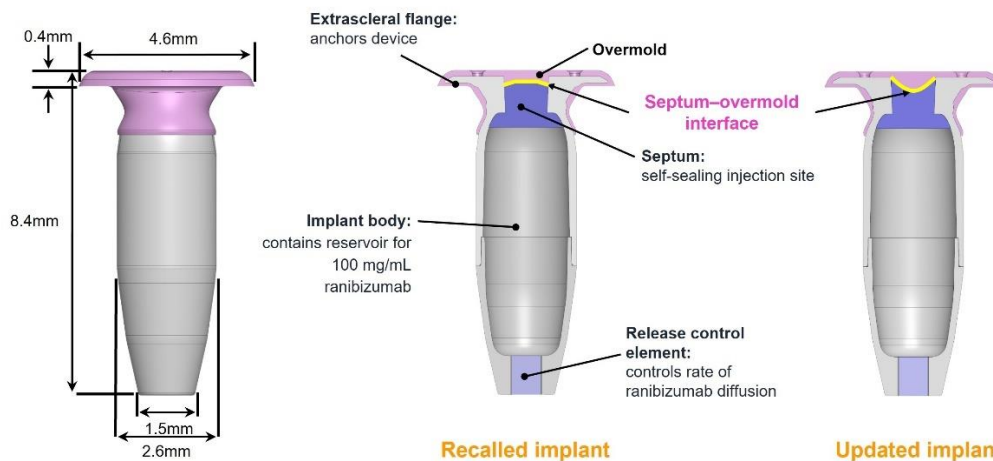
Preventability:

To mitigate the risk of septum dislodgement, the following updates were implemented at the component and manufacturing level:

- The changes to the implant consisted of a component-level internal geometry change to the septum, manufacturing process settings for epoxy levels and curing, and introduction of additional manufacturing controls to improve manufacturing robustness. Based on the changes made, the pre-change and post-change versions of the implant were distinguished as pre-septum-improved and post-septum-improved, respectively ([Figure 2](#))
- To reduce the force exerted by the refill needle on the septum during the refill-exchange procedure, a siliconized lubricant was added to the refill needle cannula, along with related manufacturing controls.

While these device changes were implemented for the implant and refill needle, the key attributes for these devices, such as intended use, user steps, manufacturing sites, packaging configuration, and sterilization processes remain unchanged.

Figure 2 Component-Level Changes and Manufacturing Process Improvements Implemented to Strengthen the Septum–Overmold Bond



- In addition, appropriate handling and insertion of the refill needle into the septum (avoid twisting and/or rotation) is required to minimize the risk of septum dislodgement.

Impact on the benefit-risk balance of the product:

In the presence of septum dislodgement, the self-sealing properties of the device are impaired and normal device functioning cannot be assured. The instances of septum dislodgement in the clinical development program have been evaluated to determine potential causality. Based on the investigation of these occurrences the IFU and the PDS Surgical Training Program have been updated to further address this risk (see [Part V.2](#)), as appropriate. Based on the current knowledge and the changes implemented at the component and manufacturing level of the PDS implant to mitigate the risk of septum dislodgement, the overall benefit-risk for PDS patients remains favorable at this time. If septum dislodgement is observed or suspected, prior to a refill-exchange, the refill-exchange procedure should not be performed because normal device functioning cannot be assured after septum dislodgement. Removal of the PDS implant can be performed at the physician's discretion, should the benefit of removal outweigh the risk of the procedure. As the patient can no longer undergo refill-exchange, the physician should monitor the patient for signs of disease activity. Per physician's clinical judgment, the patient may start treatment with a locally approved intravitreal anti-VEGF agent, irrespective of the decision to remove the PDS implant or not.

It should be noted that the benefits and risks of retaining, removing, or removing and replacing an implant with a dislodged septum are not well characterized. For further details, implant-removal and reimplantation related risks are considered missing information and are addressed in Part II [SVII.3.2](#).

Public health impact:

Not yet established.

Important Identified Risk: Intraocular Inflammation

Intraocular inflammation is a broad category, which typically consists of the following sub-categories: anterior uveitis (i.e., iritis, iridocyclitis), intermediate uveitis (i.e., vitritis), posterior uveitis, panuveitis, and events which were not otherwise specified (i.e., eye inflammation) according to the Standardization of Uveitis Nomenclature (SUN) classification ([Jabs et al. 2005](#)).

Of note, endophthalmitis is covered under the important identified risk of PDS implant and PDS procedures and complications (See Part II, [Module SVII.3.1](#)).

Potential mechanism:

A sterile, inflammatory process within the eye can occur after ocular surgeries or intravitreal injections. The exact mechanism for this inflammatory process may not always be clear for each individual case. However, it could be associated with patient susceptibility to immunologic reactions, noninfectious contamination (e.g., endotoxins), immunogenic properties of ranibizumab, protein aggregation or change in conformation, or others.

Post-procedural IOI was defined as any event of IOI occurring within 37 days after implantation, refill, explantation, and reimplantation.

Evidence source(s) and strength of evidence:

This important identified risk is based on the safety data from Studies GX28228, GR40548, and GR40549 in adult patients with nAMD.

Characterization of the risk:

Please refer to [Table 19](#) for the overall frequency, severity, seriousness, and outcomes of IOIs.

Table 19 Intraocular Inflammation (IOI): Overall Frequency with 95% CI, Severity, Seriousness, and Outcomes for All PDS Population

Protocol: GX28228, GR40548, GR40549

Risk: Intraocular Inflammation (Excluding Endophthalmitis)		All (pooled) (N=577)
Number of patients with at least one AE		163 (28.2%)
95% CI for % of patients with at least one AE		(24.73%, 32.06%)
Total number of AEs		212
Number (%) of patients with at least one AE by worst severity:		
Mild		141 (24.4%)
Moderate		20 (3.5%)
Severe		2 (0.3%)
Number of patients with at least one serious AE		0
Outcome:		
No. of pts with at least 1 AE resulted in fatal outcome		0
No. of pts with at least 1 AE Not Recovered/Not Resolved		2 (0.3%)
No. of pts with at least 1 AE Recovering/Resolving		0
No. of pts with at least 1 AE Recovered/Resolved		163 (28.2%)
No. of pts with at least 1 AE Resolved with Sequelae		0
No. of pts with at least 1 AE with Unknown outcome		0
AE = adverse event; NOS = not otherwise specified; CI = Confidence Interval; 95% CIs computed using the Wilson method. Investigator text for adverse events (AEs) coded using MedDRA version 28.0. Percentages are based on the N in the column headings. This table summary includes adverse events that started or worsened (for existing condition) on or after the date of PDS implantation. Intraocular inflammation events are defined as: Anterior Uveitis (Iritis, Iridocyclitis, Anterior cyclitis, Anterior Chamber Cell, Anterior Chamber Flare, Anterior Chamber Inflammation, and A.U. NOS / Other [LLT = "anterior uveitis" and PT not in any of the above]), Intermediate Uveitis (Pars Planitis, Posterior Cyclitis, Hyalitis, Vitritis, and Vitreous haze), Posterior Uveitis (Choroiditis, Chorioretinitis, Retinochoroiditis, Retinitis, Neuroretinitis, Retinal Vasculitis, and P.I.U. NOS / Other [LLT = "posterior uveitis" with PT not in any of the above]), Panuveitis (Panuveitis NOS / Other [LLT = "panuveitis" with PT not in any of the above]), and Not otherwise specified (Eye inflammation, Uveitis, Post procedural inflammation, Incision site inflammation, Inflammation of wound, Ocular vasculitis).		
Program: /builds/studies/clinicalreporting/CDT3728_OtherAct_pool_SUR6M_2790423/programs/tlg/t_ae_risk_all.sas Output: /ocean/harbour/CDT3728/OtherAct_pool_SUR6M/prod_SUR_CCOD_2SEP2025_snapshot_7NOV2025_v3/output/t_ae_risk_all_SEYE_ALP_IOI_EMA_02SEP2025_3728.out 21JAN2026 12:49		

Overall, the most frequently reported type of IOI in the study eye was iritis. The majority of patients who experienced IOIs recovered within 30 days of the onset date (154/175 patients, [Annex 7B.6](#)). No events of posterior uveitis (including retinitis or retinal vasculitis) or retinal occlusive vasculitis have been reported in the All PDS Population.

In the Phase III pivotal Study GR40548 the incidence of IOI events was similar amongst patients who were positive for anti-ranibizumab antibodies and those who were negative ([Study GR40548 Final CSR](#)).

Intraocular inflammation commonly occurs post-operatively in similar ocular surgeries such as glaucoma device surgeries. In a 5-year post-operative follow-up of patients undergoing tube-shunt surgery for management of glaucoma, the rate of current/recurrent iritis was 6.2–7% for Ahmed Glaucoma Valve placement surgery and 5.5–12% for Baerveldt Glaucoma Implant placement surgery ([Bundez et al. 2016](#); [Christakis et al. 2016](#)). Iritis was the only post-operative type of intraocular inflammation observed post-tube-shunt surgery ([Bundez et al. 2016](#); [Christakis et al. 2016](#)).

Intraocular inflammation is expected to occur shortly after the implant insertion surgery, and it generally resolves with standard of care topical treatment. Intraocular inflammation, in particular iritis or iridocyclitis, is a sterile process that may cause decreased vision, photophobia, and pain and may progress to include intermediate uveitis with floaters. Cases occur mostly after PDS implant insertion and are expected to resolve within 30 days of surgery with topical antimicrobial/corticosteroids treatment, as standard of care treatment after major ocular surgeries. Treatment (refill-exchange) should be delayed until resolution of the intraocular inflammation. The administration of standard of care topical medications should be used to minimize risk of intraocular inflammation.

Risk factors and risk groups:

Patients with known history of inflammation from uveitis, as well as on chronic treatment with pro-inflammatory drugs (such as prostaglandins) may be more at risk of IOI if they undergo ocular surgeries, including PDS procedures.

Preventability:

Appropriate standard of care post-operative topical treatment following implant insertion or refill-exchange procedures to minimize the risk of IOI.

Impact on the benefit-risk balance of the product:

Intraocular inflammation can range from a mild inflammation of the eye to severe with sequelae leading to vision loss. Symptoms can consist of blurred vision, floaters, pain, and photophobia. Pain is significantly associated with severe vitreous or anterior

chamber inflammation. As part of standard post-operative care, topical antibiotics, cycloplegics, or systemic corticosteroids can be administered. More invasive interventions have also been employed, including vitreous tap, intraocular or periorbital steroids, and pars plana vitrectomy ([Agrawal et al. 2013](#); [Cox et al. 2021](#)).

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

Public health impact:

Not yet established.

Information on Important Potential Risks

Important Potential Risk: Implant Damage during the PDS Procedures (other than Septum Dislodgement)

Potential mechanisms²:

Damage to the implant can potentially be caused by inappropriate handling during the PDS procedures, or inappropriate use of the ancillary devices in conjunction with the implant. This could include:

- Septum damage due to improper user technique relative to maintaining contact between refill needle soft stop and the conjunctiva on top of the implant septum
- Septum or flange damage due to poor alignment of the refill needle with the implant during the refill-exchange procedure
- Septum damage due to improper user technique relative to maintaining perpendicularity of refill needle to eye globe during insertion or withdrawal of the refill needle
- Flange damage prior to implant insertion due to handling of the implant with inappropriate surgical instruments (e.g., forceps)
- Implant septum or flange damage caused by use of a bent needle.

² Risk management for the PDS implant and ancillary devices is performed in accordance with [ISO 14971](#) Medical Devices-Application of Risk Management to Medical Devices and with the company's internal risk management procedures *Quality Risk Management* and *Quality Risk Management Process*. Through the risk management process, hazards, hazardous situations, and harms relating to the PDS design, procedures, and use are identified, evaluated, and mitigated, when possible, through implementation of specific measures, including verification, validation, inspection, training, labeling, and other controls.

Evidence source(s) and strength of evidence:

This potential risk is based on the known potential risk associated with any type of medical device.

Characterization of the risk:

Implant damage can occur at any time during the use of the PDS. Based on available clinical data, the frequency of occurrence cannot be established.

No instances of implant damage have been reported, apart from septum dislodgement which is categorized as an important identified risk (Part II, Module SVII.3 [Important Identified Risk: Septum Dislodgement](#)).

The potential outcomes of a damaged implant would differ in terms of severity and impact to the patient, depending on the extent of the damage and the parts of the implants that are affected.

A damaged septum or flange could cause conjunctival erosion or could increase the risk of endophthalmitis. A damaged flange could cause implant seating issues or even dislocation. Any damage to the body of the implant or release control element could lead to inappropriate dosing or even disease progression.

Should the implant become damaged in a way that affects its functionality or effectiveness, it may restrict a patient's access to treatment via the PDS. In such cases, removal of the implant might be required.

Implant damage can potentially be associated with an AE. In such cases, patients may require immediate specialized medical care. The complications associated with implant damage may result in permanent vision loss, may require a surgical procedure to resolve, and/or require implant removal. Failure to diagnose and treat these complications in a timely manner may lead to permanent damage to the eye and potentially blindness.

Risk factors and risk groups:

Not yet established.

Preventability:

Strict adherence to the manufacturer's IFU and the PDS Surgical Training Program (see Part [V.2](#)) are expected to minimize the risk of implant damage during the PDS procedures.

Impact on the benefit-risk balance of the product:

No instances of implant damage have been reported, apart from septum dislodgement which is categorized as an important identified risk (Part II, Module SVII.3 [Important Identified Risk: Septum Dislodgement](#)). Implant damage may have minor or potentially important safety impact depending on the characteristics of the damage. However, based on the totality of the data, as well as the risk minimization measures put in place by the Applicant (Part [V.2](#)), implant damage is not anticipated to impact the risk benefit profile of the PDS.

Public health impact:

Cannot yet be established.

SVII.3.2. Presentation of the Missing Information

Missing Information: Long-term safety

Evidence source:

As of 02 September 2025, the overall extent of exposure in the All PDS Population accounts for 577 patients, with a maximum duration of exposure of more than 7 years with 84.9% (490/577) having >3 years of follow-up, 75.2% [434/577] having >4 years of follow-up, and almost half having >5 years of follow-up (48.0% [277/577]); see [Table 6](#). The overall safety profile in clinical trial setting is considered well characterized, manageable, and largely consistent with that of ranibizumab intravitreal injection for the approved nAMD indication. No new safety signals were identified. The safety profile of PDS in clinical trial setting will continue to be monitored. However, despite the extensive data from clinical trials, there is limited long-term safety data in the post-marketing setting.

Anticipated risk/consequence of the missing information:

PDS is designed for permanent use and is intended to continuously deliver ranibizumab treatment. The occurrence of most complications appears to be linked to the surgical technique for the PDS implant insertion procedure. Strict adherence to the current IFU is required to minimize procedure-related risks. Long-term safety of PDS implant will be analyzed through routine pharmacovigilance activities. In addition, this safety concern will be evaluated in the long-term extension study GR40549 (Portal) (see Part [III.2](#) for additional information).

Missing Information: Implant Removal-Related Risks

Evidence source:

As of 02 September 2025, a total of 70 patients in All PDS Population (N=577) from Studies GX28228, GR40548, and GR40549 in adult patients with nAMD had their PDS implant removed. In the majority of these patients (61/70 patients), the implant was

removed because of an AE. A total of 34/70 patients were explanted with no reimplantation, of which 26 experienced AEs in the study eye that led to implant removal (see [Annex 7B.7](#)). The implant removal procedures were generally well tolerated, and the majority of ocular AEs post-implant removal, were non-serious, mild and resolved. The most common AEs leading to implant removal in patients explanted with no reimplantation included: rhegmatogenous retinal detachment, wound secretion, ectropion, device breakage, conjunctival erosion, conjunctival retraction, endophthalmitis, and device dislocation (see [Annex 7B.7](#)).

Anticipated risk/consequence of the missing information

Implant removal can be performed at the physician's discretion in consultation with the patient should it be determined that the benefit of removal outweighs the risk of the procedure.

Removal of the PDS implant is performed using the PDS explant tool that is provided separately. This consists of a set of forceps with customized, contoured tips designed to grasp underneath the implant flange and securely pull the implant for removal. Removal of the PDS implant is performed by incising and dissecting the conjunctiva and Tenon's capsule, as well as any fibrous capsule over the implant flange, and gently grasping the implant underneath both sides of the flange using the explant tool to remove the implant from the eye. The scleral wound is sutured closed, followed by conjunctiva and Tenon's capsule closure.

Removal of the PDS implant requires a surgical procedure, and is, as such, associated with certain risks. Failure to adhere to the manufacturer's IFU for the removal procedure may potentially lead to development of different complications, not all of which were observed in the clinical development program. During the removal procedure, contact between the implant and the intraocular structures, such as the lens, may lead to traumatic cataract, and vitreous adhesion to the implant may lead to retinal detachment. Complete scleral wound suturing, as well as complete closure of conjunctiva and Tenon's capsule across the surgical site are critical steps to minimize potential post-removal complications. Aseptic conditions and use of topical antimicrobial/anti-inflammatory treatment per standard of care before and after surgery is imperative to minimize the risk of endophthalmitis.

In the clinical development program, if clinically indicated, the implant removal procedure was performed and was generally well tolerated. However, cases requiring implant removal were limited. As such, there are still gaps in knowledge about the safety of the implant removal procedure. Limited data are available with respect to the severity, type of complications associated with the implant removal, pre-existing risk factors, long-term risk outcomes of the implant being removed.

Implant removal-related risks will be analyzed through routine pharmacovigilance activities. In addition, this safety concern is under evaluation in the long-term extension study GR40549 (Portal) (see Part [III.2](#) for additional information).

Missing Information: Reimplantation-related risks

Evidence source:

The risks associated with reimplantation are not well characterized, due to the limited number of patients in the nAMD All PDS Population that underwent a reimplantation procedure (a total of 36 patients: 29 following a septum dislodgement and 7 for reasons other than septum dislodgement: device dislocation [3 patients], conjunctival erosion [2 patients], and hypotony [1 patient]) (see [Annex 7B.7](#)). As of 02 September 2025, none of the patients who had a reimplantation due to septum dislodgement needed another explantation. However, three patients who underwent reimplantation due to device dislocation (2 patients) and hypotony (1 patient) were re-explanted. The reasons the re-explantation was performed were conjunctival retraction, conjunctival filtering bleb leak, and physician decision after a bleb leak respectively. No ocular SAEs were reported post-explantation. Following explantation, these patients were treated per standard of care.

Anticipated risk/consequences of the missing information:

This limited experience poses challenges in fully understanding the potential complications and outcomes associated with reimplantation procedures. Reimplantation may be necessary in cases of device failure or complications, and the lack of comprehensive data makes it difficult to predict the frequency and severity of associated risks.

Therefore, it is imperative to continue monitoring and documenting reimplantation cases to better characterize these risks and refine guidelines for managing such procedures. Reimplantation-related risks will be further evaluated in the GR40549 (Portal) main study and its re-implantation substudy (see Part [III.2](#) for additional information).

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 20 Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	PDS implant and PDS procedure complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract) Septum dislodgement Intraocular inflammation
Important potential risks	Implant damage during the PDS procedures (other than septum dislodgement)
Missing information	Long-term safety Implant removal-related risks Reimplantation-related risks

PDS = Port Delivery System with ranibizumab.

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

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine Pharmacovigilance Activities beyond Adverse Reaction Reporting and Signal Detection:

Specific follow-up questionnaire for the following important identified and potential risks:

- PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract)
- Septum dislodgement
- Intraocular inflammation
- Implant damage during the PDS procedures (other than septum dislodgement)

This follow-up questionnaire is designed to collect key information from post-marketing case reports on the following aspects:

- Duration of device implantation
- Details about refills and any additional surgical corrections performed
- Additional clinical information on reported events.

While the follow-up questionnaire represents the complete form, only the sections relevant to the specific reported event, such as endophthalmitis, will be sent to the reporter. This targeted approach ensures efficient and accurate data collection while minimizing the burden on healthcare professionals.

The follow-up questionnaire is provided in [Annex 4](#).

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

In addition to the routine pharmacovigilance activities, three post-authorization safety studies are ongoing or planned:

- A long-term extension study (GR40549; Portal) where patients with nAMD from the Phase II and Phase III parent studies are being followed up for additional safety data collection (see [Table 21](#)). The duration of this study will allow for collection, in Study GR40549, of a total of 240 weeks of follow-up safety data for patients from Studies GX28228 (Ladder) and GR40548 (Archway), and 144 weeks for patients from Study WR42221 (Velodrome), starting from the date of enrollment in GR40549 study.
- A re-implantation substudy in association with study GR40549 (Portal) to evaluate the safety of reimplantation of the PDS implant and the refill-exchange procedures following reimplantation in patients who experienced septum

dislodgement while in the main study or after having exited the main study (Table 22).

- A non-interventional, secondary data use study (Study GR46011; SightARC) to evaluate the safety of Susvimo (ranibizumab administered via the PDS implant) in nAMD patients treated in routine clinical practice (Table 23).

Table 21 Study GR40549 (Portal)

Study/activity short name and title: Study GR40549 (Portal): A Multicenter, Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of the PDS in Patients with nAMD
Rationale and study objectives: The objective of this study is to evaluate the long-term safety and tolerability of the PDS (100 mg/mL) in patients with nAMD, including further characterizing: • The risk of PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract) • The risk of septum dislodgement • The risk of post-surgical intraocular inflammation • The risk of implant damage during the PDS procedures (other than septum dislodgement) • The missing information on implant removal-related risks • The missing information on reimplantation-related risks • The missing information on long term safety
Study design: This is a global, multicenter, open-label, visual assessor-masked, multiple-cohort extension study designed to evaluate the long-term safety and tolerability of ranibizumab 100 mg/mL delivered via the PDS, with refill-exchanges administered Q24W or Q36W to patients who elect to enroll in the extension study from the parent studies.
Study populations: Patients with nAMD who have either completed Phase II Study GX28228 (Ladder), Phase III Study GR40548 (Archway), Phase IIIb Study WR42221 (Velodrome), or completed Week 24 visit in Study WR42221 but were not eligible to be randomized. Patients rolled over from Study GX28228 (Ladder) and Study GR40548 (Archway) are followed up to allow the collection of 240 weeks of safety data.
Milestones: Clinical Study Report: Q4 2030

LPLV = last patient last visit; nAMD = neovascular age-related macular degeneration; PDS = Port Delivery System with ranibizumab.

Table 22 Re-implantation substudy in association with Study GR40549 (Portal)

Study/activity short name and title: A Re-implantation Substudy in Association with Study GR40549 (Portal): a Multicenter, Open-Label Study to Evaluate the Safety of Re-implanting the PDS in Patients with nAMD
Rationale and study objectives: This substudy will evaluate the safety of the reimplantation of PDS implant and the refill-exchange procedures following reimplantation in patients, previously enrolled in the main study, who experienced septum dislodgement while in the main study or after having exited the main study.
Study design: This substudy is a non-randomized, uncontrolled, open-label study to evaluate the safety of reimplanting the new updated PDS implant and the refill-exchange procedures following reimplantation in patients who experienced septum dislodgement while in the main study or after having exited the main study.
Study populations: Patients who previously participated in the main study in the US will be enrolled in this substudy and will be followed for a maximum of 72 weeks
Milestones: Clinical Study Report corresponding to the LPLV for the Study GR40549 (Portal) patients in the re-implantation substudy: Q4 2028

LPLV = last patient last visit; nAMD = neovascular age-related macular degeneration;
PDS = Port Delivery System with ranibizumab.

Table 23 Study GR46011 (SightARC)

Study/activity short name and title: Study GR46011 (SightARC): A Non-Interventional, Secondary Data Use Study to Evaluate the Safety of Susvimo (Ranibizumab Administered via the PDS Implant) in nAMD Patients Treated in Clinical Practice
Rationale and study objectives: This retrospective, non-interventional study will utilize secondary data from one or more existing data sources to estimate the incidence of ocular safety outcomes and PDS-specific surgical and procedural complications associated with Susvimo in routine clinical practice. The study aims to further characterize safety outcomes of Susvimo, including endophthalmitis, retinal tear and retinal detachment, and will use patients treated with other approved IVT medications as a contextualizing reference cohort for these outcomes. Additionally, it aims to evaluate PDS-specific surgical and procedural complications (including vitreous hemorrhage, conjunctival bleb complications, conjunctival erosion, conjunctival retraction, and device dislocation) of patients receiving Susvimo, using both direct diagnostic codes and indirect procedural/medication proxy codes.
Study design: A retrospective, non-interventional study of patients treated for nAMD in clinical practice using secondary data from one or more existing data sources. A comprehensive Feasibility Assessment will be conducted following marketing authorization approval in the EU of data sources to evaluate the ability to identify exposure and relevant outcomes. Patients treated with standard IVT anti-VEGF therapies will serve as a contextualizing reference cohort for ocular safety outcomes (endophthalmitis, retinal tear and retinal detachment). Surgical and procedural complications associated with the PDS implant and procedure (including vitreous hemorrhage, conjunctival bleb complications, conjunctival erosion, conjunctival retraction, and device dislocation) will be characterized solely within the Susvimo treated cohort as determined by the feasibility assessment.
Study populations: Patients treated for nAMD
Milestones: First Annual Monitoring Report: Q4 2027 Interim Study Report: Within 12 months of first and intermediate extractions* Final Report: Within 12 months of last extraction*

nAMD = neovascular age-related macular degeneration; PDS = Port Delivery System with ranibizumab.

*First, intermediate, and last data extractions will occur within 6 months, 30 months, and 54 months of analysis trigger, respectively.

The tabulated summary of the ongoing pharmacovigilance study program is provided in [Annex 3](#).

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 24 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 3 —Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk minimization activities				
Study GR40549 (Portal): A Multicenter, Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of the PDS in Patients with nAMD	To evaluate the long-term safety and tolerability of the PDS in patients with nAMD	- PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract) - Septum dislodgement - Intraocular inflammation - Implant damage during the PDS procedures (other than septum dislodgement) - Implant removal-related risks - Reimplantation-related risks - Long term safety	Clinical Study Report	Q4 2030
Re-implantation Substudy in Association with Study GR40549 (Portal): a Multicenter, Open-Label Study to Evaluate the Safety of Re-implanting the PDS in Patients with nAMD	To evaluate the safety of the reimplantation of PDS implant and the refill-exchange procedures following reimplantation	Reimplantation-related risks	Clinical Study Report corresponding to the LPLV for the Study GR40549 (Portal) patients in the re-implantation substudy	Q4 2028

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Study GR46011 (SightARC): A Non-Interventional, Secondary Data Use Study to Evaluate the Safety of Susvimo (Ranibizumab Administered via the PDS Implant) in nAMD Patients Treated in Clinical Practice	To evaluate the incidence of ocular safety outcomes and PDS-specific surgical and procedural complications associated with Susvimo in routine clinical practice in nAMD patients	PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb complications, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, and device dislocation)	First annual monitoring report Interim study report Final report	Q4 2027 Within 12 months of first and intermediate extractions* Within 12 months of last extraction*

CHMP = Committee for Medicinal Products for Human Use; nAMD = neovascular age-related macular degeneration; LPLV = last patient last visit; NCA = National Competent Authority; PDS = Port Delivery System with ranibizumab; PRAC = Pharmacovigilance Risk Assessment Committee.

* First, intermediate, and last data extractions will occur within 6 months, 30 months, and 54 months of analysis trigger, respectively.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing imposed efficacy studies with Susvimo.

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

RISK MINIMIZATION PLAN

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 25 Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract)	Routine risk communication: • SmPC Sections 4.2, 4.4, and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Requirement for strict adherence to the manufacturer's IFU for the initial fill and implant insertion procedure, refill-exchange procedure, and the implant removal procedure is included in Section 4.4 of the SmPC (Special warnings and precautions for use). Warning to temporarily interrupt antithrombotic medication prior to the implant insertion procedure is included in Section 4.4 of the SmPC (Special warnings and precautions for use). Other risk minimization measures beyond the Product Information: Pack size Legal status Restricted medical prescription Section 4.2 of the EU SmPC states: The initial fill and implant procedure and implant removal procedure must be performed in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures. The implant refill-exchange procedure should be performed under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures.

Safety Concern	Routine Risk Minimization Activities
Septum dislodgement	Routine risk communication: • SmPC Sections 4.2, 4.4, and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Requirement for strict adherence to the manufacturer's IFU for the initial fill and implant insertion procedure, refill-exchange procedure, and the implant removal procedure is included in Section 4.4 of the SmPC (Special warnings and precautions for use). Other risk minimization measures beyond the Product Information: Pack size Legal status Restricted medical prescription Section 4.2 of the EU SmPC states: The initial fill and implant procedure and implant removal procedure must be performed in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures. The implant refill-exchange procedure should be performed under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures.
Intraocular inflammation	Routine risk communication: • SmPC Sections 4.2, 4.3, 4.4, and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: None. Other risk minimization measures beyond the Product Information Pack size Legal status Restricted medical prescription Section 4.2 of the EU SmPC states: The initial fill and implant procedure and implant removal procedure must be performed in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures. The implant refill-exchange procedure should be performed under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures.

Safety Concern	Routine Risk Minimization Activities
Implant damage during the PDS procedures (other than septum dislodgement)	Routine risk communication: • SmPC Section 4.2 • PL Section 2 • PL Section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Requirement for strict adherence to the manufacturer's IFU for the initial fill and implant insertion procedure, refill-exchange procedure, and the implant removal procedure is included in Section 4.4 of the SmPC (Special warnings and precautions for use). Other risk minimization measures beyond the Product Information: Pack size Legal status Restricted medical prescription Section 4.2 of the EU SmPC states: The initial fill and implant procedure and implant removal procedure must be performed in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures. The implant refill-exchange procedure should be performed under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures.
Long-term safety	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other risk minimization measures beyond the Product Information: None.
Implant removal-related risks	Routine risk communication: • SmPC Sections 4.2, 4.4 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: Requirement for strict adherence to the manufacturer's IFU for the implant removal procedure is included in Section 4.4 of the SmPC (Special Warnings and Precautions). Other risk minimization measures beyond the Product Information: Pack size Legal status Restricted medical prescription

Safety Concern	Routine Risk Minimization Activities
	Section 4.2 of the EU SmPC states: The initial fill and implant procedure and implant removal procedure must be performed in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures. The implant refill-exchange procedure should be performed under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures.
Reimplantation-related risks	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other risk minimization measures beyond the Product Information Legal status Restricted medical prescription Section 4.2 of the EU SmPC states: The initial fill and implant procedure and implant removal procedure must be performed in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures. The implant refill-exchange procedure should be performed under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures.

IFU = Instructions for Use; PDS = Port Delivery System with ranibizumab; PL = Patient Leaflet; SmPC = Summary of Product Characteristics.

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

Table 26 Additional Risk Minimization Measures: Physician Guide

Additional Risk Minimization Measure	Physician Guide
Objective(s)	To ensure consistency of the surgical procedure and of outcomes in the post-marketing setting, aiming to minimize the • Risk of PDS implant and PDS procedure complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, and device dislocation) • Risk of septum dislodgement • Risk of intraocular inflammation • Risk of traumatic cataract • Risk of implant damage during the PDS procedures (other than septum dislodgement)

Additional Risk Minimization Measure	Physician Guide
Rationale for the additional risk-minimization activity	Treatment with the PDS involves an initial surgical implantation procedure. Subsequent procedures are primarily refill-exchange and potential implant removal if required. It is acknowledged that implantation (and implant removal, if required) of the PDS and refill-exchange have their own inherent risks. While the implant and refill-exchange procedures are generally well tolerated, surgical risks exist, and surgeon training is crucial for continued safety. Precision on implant and refill-exchange procedures is a critical success factor and strict adherence to the manufacturer's IFU is essential for prevention of the risks of PDS implant and procedure complications and implant damage during the PDS procedures. The Physician Guide is aimed to establish consistency in following the IFU and confidence in the surgical procedures associated with PDS, and the ocular implant In addition, ongoing surgical support tailored to physicians performing the PDS procedures will be made available as needed.
Target audience and planned distribution path	Ophthalmologists experienced in vitreoretinal surgery who intend to perform the PDS implant insertion procedure, implant removal procedure, and refill-exchange procedure and to ophthalmologists who intend to perform the refill-exchange procedure for PDS. It will be provided by the surgical device liaison upon the delivery of the training, prior to performing any procedure with PDS.
Plans for evaluating the effectiveness of the interventions and criteria for success	How effectiveness will be measured: • Measuring and tracking the number of surgeons trained • Evaluation of the following reporting rates through routine pharmacovigilance including spontaneous reporting: – PDS implant and PDS procedure complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract) – Septum dislodgment – Intraocular inflammation – Implant damage during the PDS procedure (other than septum dislodgment) Milestones for reporting: • Periodically in PBRERs

IFU = Instructions for Use; PDS = Port Delivery System with ranibizumab; nAMD = neovascular age-related macular degeneration; PBRER = Periodic Benefit-Risk Evaluation Report.

Table 27 Additional Risk Minimization Measure: Patient Educational Materials

Additional Risk Minimization Measure	Patient Educational Materials
Objective(s)	Patient Education Materials will promote awareness of the information contained within the Susvimo Package Leaflet and the PDS manufacturer's IFU, which are intended to inform patients and their caregivers about the risks and potential adverse events, with the objective to minimize the following risks and their impact on the patients: • Risk of PDS implant and procedure complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract) • Risk of septum dislodgement • Risk of intraocular inflammation • Risk of implant damage during the PDS procedures (other than septum dislodgement)
Rationale for the additional risk-minimization activity	Patient Educational Materials will enable patients and their caregivers to receive education on the key recommendations to be followed during the treatment with Susvimo (i.e., how to prepare for treatment, steps to follow after treatment), with the aim of minimizing the worsening of adverse reactions relevant to the risks of PDS implant and procedure complications and of implant damage. The Patient Educational Materials will instruct patient and/or caregiver on the early recognition of key signs and symptoms both after the initial implant insertion procedure, following each refill-exchange procedure, and for the entire duration of the treatment with Susvimo. The intent is that the Patient Education Materials will also encourage patient and/or caregiver to seek immediate treatment by contacting the treating physician in a prompt manner, with the aim of optimizing the time to intervention, appropriate management of the adverse reactions, minimizing the risk of vision loss or further worsening of the adverse reaction, and maximizing recovery potential.
Target audience and planned distribution path	The Patient Educational Materials are targeted to use in adult patients with nAMD treated with Susvimo via the PDS implant and it is provided to the physician to be provided to the patient.
Plans for evaluating the effectiveness of the interventions and criteria for success	How effectiveness will be measured: • Measuring and tracking the distribution of the Patient Educational Materials Milestones for reporting: • Periodically in PBRERs

IFU = Instructions for Use; PDS = Port Delivery System with ranibizumab; nAMD = neovascular age-related macular degeneration; PBRER = Periodic Benefit-Risk Evaluation Report.

Details of the proposed additional risk minimization activities are provided in [Annex 6](#).

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 28 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
PDS implant and PDS procedure complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract)	Routine risk minimization measures: SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable Effects PL Section 2 What you need to know before you are given Susvimo PL Section 4 Possible side effects Requirement for strict adherence to the manufacturer's IFU for the initial fill and implant insertion procedure, refill-exchange procedure, and the implant removal procedure is included in Section 4.4 of the SmPC (Special warnings and precautions for use). Warning to temporarily interrupt antithrombotic medication prior to the implant insertion procedure is included in Section 4.4 of the SmPC (Special warnings and precautions for use). Pack size Legal status Restricted medical prescription Restriction to perform the initial fill and implant procedure, and implant removal procedure in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures, and restriction to perform the implant refill-exchange procedure under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures in Section 4.2 of the SmPC.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: Study GR40549 (Portal) Study GR46011 (SightARC)*

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimization measures: Physician Guide Patient Educational Materials	
Septum Dislodgement	Routine risk minimization measures SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable Effects PL Section 2 What you need to know before you are given Susvimo PL Section 4 Possible side effects Requirement for strict adherence to the manufacturer's IFU for the initial fill and implant insertion procedure, refill-exchange procedure, and the implant removal procedure is included in Section 4.4 of the SmPC (Special warnings and precautions for use). Pack size Legal status Restricted medical prescription Section 4.2 of the EU SmPC states: The initial fill and implant procedure and implant removal procedure must be performed in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures. The implant refill-exchange procedure should be performed under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures. Additional risk minimization measures: Physician Guide Patient Educational Materials	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: Study GR40549 (Portal)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Intraocular inflammation	Routine risk minimization measures SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.3 Contraindications SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable Effects PL Section 2 What you need to know before you are given Susvimo PL Section 4 Possible side effects Pack size Legal status Restricted medical prescription Section 4.2 of the EU SmPC states: The initial fill and implant procedure and implant removal procedure must be performed in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures. The implant refill-exchange procedure should be performed under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures. Additional risk minimization measures: Physician Guide Patient Educational Materials	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: Study GR40549 (Portal)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Implant damage during the PDS procedures (other than septum dislodgement)	Routine risk minimization measures: SmPC Section 4.2 Posology and Method of Administration PL Section 2 What you need to know before you are given Susvimo PL Section 4 Possible side effects Strict adherence to the manufacturer's IFU in Section 4.4 of the SmPC (Special warnings and precautions for use). Pack size Legal status Restricted medical prescription Restriction to perform the initial fill and implant procedure, and implant removal procedure in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures, and restriction to perform the implant refill-exchange procedure under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures in Section 4.2 of the SmPC. Additional risk minimization measures: Physician Guide Patient Educational Materials	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: Study GR40549 (Portal)
Long-term safety	Routine risk minimization measures: None Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: Study GR40549 (Portal)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Implant removal-related risks	Routine risk minimization measures: SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Special Warnings and Precautions for Use PL Section 2 What you need to know before you are given Susvimo Requirement for strict adherence to the manufacturer's IFU for the implant removal procedure is included in Section 4.4 of the SmPC (Special Warnings and Precautions). Pack size Legal status Restricted medical prescription Restriction to perform the initial fill and implant procedure, and implant removal procedure in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures, and restriction to perform the implant refill-exchange procedure under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures in Section 4.2 of the SmPC. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: Study GR40549 (Portal)
Reimplantation-related risks	Routine risk minimization measures Legal status Restricted medical prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaires Additional pharmacovigilance activities: Study GR40549 (Portal)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Restriction to perform the initial fill and implant procedure, and implant removal procedure in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures, and restriction to perform the implant refill-exchange procedure under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures in Section 4.2 of the SmPC. Additional risk minimization measures: None	Re-implantation substudy in association with study GR40549 (Portal)

IFU = Instructions for Use; PDS = Port Delivery System with ranibizumab; PL = Patient Leaflet; SmPC = Summary of Product Characteristics.

* Study GR46011 (SightARC) aims to further characterize the following aspects of the important identified risk, PDS implant and PDS procedure complications: vitreous hemorrhage, conjunctival bleb complications, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, and device dislocation.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR SUSVIMO® (PORT DELIVERY SYSTEM WITH RANIBIZUMAB 100 MG/ML)

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

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

This summary of the RMP for Susvimo should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of 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 Susvimo's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Susvimo is authorized for use in adult patients for the treatment of neovascular (wet) age-related macular degeneration (see SmPC for the full indication). It contains ranibizumab as the active substance, and recommended dose is 2 mg in 0.02 mL continuously delivered via the ocular implant with refills every 24 weeks (approximately 6 months).

Further information about the evaluation of Susvimo's benefits can be found in Susvimo's EPAR, including in its plain-language summary, available on the EMA Web site, under the medicine's [Web page](#).

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

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

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

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorized pack size — The amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly.
- The medicine's legal status — The way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

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

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

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including a Periodic Safety Update Report (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 Susvimo is not yet available, it is listed under “missing Information” below.

II.A List of Important Risks and Missing Information

Important risks of Susvimo 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 Susvimo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information about the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract) Septum dislodgement Intraocular inflammation
Important potential risks	Implant damage during the PDS procedures (other than septum dislodgement)
Missing information	Long-term safety Implant removal-related risks Reimplantation-related risks

PDS = Port Delivery System with ranibizumab.

II.B Summary of Important Risks

Important Identified Risk: PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract)							
Evidence for linking the risk to the medicine	This identified risk is based on the safety data from Studies GX28228, GR40548, and GR40549 in adult patients with nAMD.						
Risk factors and risk groups	The risk factors and risk groups identified for PDS implant and PDS procedures complications are included below. Surgical-related risk factors are based on data available from the PDS clinical development program. Patient-related risk factors are presumed based on the potential mechanism of occurrence and the pathophysiology of the complication. <table border="1"> <thead> <tr> <th>Complication</th><th>Risk Factors and Risk Groups</th></tr> </thead> <tbody> <tr> <td>Vitreous hemorrhage</td><td>Patients on antithrombotic medication (e.g., oral anticoagulants, aspirin, non-steroidal anti-inflammatory drugs), or patients with coagulation abnormalities, may be at increased risk of vitreous hemorrhage. Vitreous hemorrhage may also occur due to the underlying disease. Surgery-related risk factors include insufficient laser ablation of the pars plana prior to incision, incomplete cauterization of conjunctival and scleral blood vessels around the scleral wound, or improper diathermy of active bleeding within the scleral wound before implant insertion.</td></tr> <tr> <td>Conjunctival bleb/bleb leak (subconjunctival thickening)</td><td>No risk group has been identified for the conjunctival bleb/bleb leak complication. Surgery-related risk factors include scleral incision greater than the recommended length in the IFU, as well as excessive suturing leading to long lasting conjunctival inflammation in the area around the implant flange. Refill-exchange-related risk factors include partial needle insertion into the implant, or excessive force applied to the eye while attempting to insert the needle.</td></tr> </tbody> </table>	Complication	Risk Factors and Risk Groups	Vitreous hemorrhage	Patients on antithrombotic medication (e.g., oral anticoagulants, aspirin, non-steroidal anti-inflammatory drugs), or patients with coagulation abnormalities, may be at increased risk of vitreous hemorrhage. Vitreous hemorrhage may also occur due to the underlying disease. Surgery-related risk factors include insufficient laser ablation of the pars plana prior to incision, incomplete cauterization of conjunctival and scleral blood vessels around the scleral wound, or improper diathermy of active bleeding within the scleral wound before implant insertion.	Conjunctival bleb/bleb leak (subconjunctival thickening)	No risk group has been identified for the conjunctival bleb/bleb leak complication. Surgery-related risk factors include scleral incision greater than the recommended length in the IFU, as well as excessive suturing leading to long lasting conjunctival inflammation in the area around the implant flange. Refill-exchange-related risk factors include partial needle insertion into the implant, or excessive force applied to the eye while attempting to insert the needle.
Complication	Risk Factors and Risk Groups						
Vitreous hemorrhage	Patients on antithrombotic medication (e.g., oral anticoagulants, aspirin, non-steroidal anti-inflammatory drugs), or patients with coagulation abnormalities, may be at increased risk of vitreous hemorrhage. Vitreous hemorrhage may also occur due to the underlying disease. Surgery-related risk factors include insufficient laser ablation of the pars plana prior to incision, incomplete cauterization of conjunctival and scleral blood vessels around the scleral wound, or improper diathermy of active bleeding within the scleral wound before implant insertion.						
Conjunctival bleb/bleb leak (subconjunctival thickening)	No risk group has been identified for the conjunctival bleb/bleb leak complication. Surgery-related risk factors include scleral incision greater than the recommended length in the IFU, as well as excessive suturing leading to long lasting conjunctival inflammation in the area around the implant flange. Refill-exchange-related risk factors include partial needle insertion into the implant, or excessive force applied to the eye while attempting to insert the needle.						

Important Identified Risk: PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract)

	Conjunctival erosion	It is presumed that patients with conjunctival allergies could be at increased risk of conjunctival erosions (e.g., due to potential eye rubbing creating tractional forces on the conjunctiva). Patients with thinner conjunctiva might also be at increased risk of conjunctival erosion. Surgery-related risk factors include improper coverage of the implant with Tenon's capsule, or loose-fitting implant due to scleral incision length wider than recommended in the manufacturer's IFU. Conjunctival erosion may also occur due to impaired conjunctival healing after a refill-exchange procedure (i.e., needle track-related erosion).
	Conjunctival retraction	It is presumed that patients with conjunctival allergies could be at increased risk of conjunctival retraction (e.g., due to eye rubbing creating tractional forces on the conjunctiva). Patients with thinner conjunctiva might also be at increased risk of conjunctival retraction. Surgery-related risk factors include insufficient or partial reapposition of the conjunctiva and Tenon's capsule edges with sutures, either at the limbus, or in the radial cut.
	Endophthalmitis	Patients with active or suspected ocular or periocular infections and patients with a severe systemic infection are at risk of endophthalmitis if they undergo PDS procedures. With respect to the implant insertion procedure or refill-exchange procedure, improper aseptic technique is a known risk factor, as well as conjunctival retraction or erosion with implant flange exposure. Furthermore, poor ocular hygiene or failure to use eye protection during high-risk activities constitutes additional risk factors for endophthalmitis after the implant insertion procedure.

Important Identified Risk: PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract)		
	Retinal tear and retinal detachment	It is presumed that patients with a thin retina (e.g., secondary to high myopia), peripheral vitreoretinal degenerations (e.g., lattice degeneration), abnormal vitreoretinal adhesions, or posterior vitreous detachment, or any history of rhegmatogenous retinal detachment could be at increased risk of rhegmatogenous retinal detachment, especially after an eye trauma. Surgery-related risk factors include excessive vitreous prolapse or improper management of the vitreous prolapse after pars plana incision or after trocars removal.
	Device dislocation	It is presumed that patients with eye trauma or very high intraocular pressure are at risk of device dislocation. In the clinical development program, most dislocation cases were associated with a longer than recommended incision (>3.7 mm before or after laser ablation of the pars plana) at the time of implantation. Most cases had evidence of "scleral discoloration" around the implant flange on images before the event of dislocation. The "scleral discoloration," which is seen as darkened areas most often around the outer corners of the implant flange, may demonstrate a transillumination defect and thus may represent an elongated scleral wound. Implant dislocations related to an elongated scleral wound can occur during the refill-exchange procedure as the force from the needle may lead to the movement of the implant. Intrinsic and extrinsic risk factors related to the patient could include thin conjunctiva, excessive eye rubbing, and eye trauma.

Important Identified Risk: PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract)		
	Traumatic cataract	No risk group has been identified for the traumatic cataract complications. The event might be linked to the direct trauma to the lens during the procedure
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable Effects PL Section 2 What you need to know before you are given Susvimo PL Section 4 Possible side effects Requirement for strict adherence to the manufacturer's IFU for the initial fill and implant insertion procedure, refill-exchange procedure, and the implant removal procedure is included in Section 4.4 of the SmPC (Special warnings and precautions for use). Warning to temporarily interrupt antithrombotic medication prior to the implant insertion procedure is included in Section 4.4 of the SmPC (Special warnings and precautions for use). Pack size Legal status Restricted medical prescription Restriction to perform the initial fill and implant procedure, and implant removal procedure in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures, and restriction to perform the implant refill-exchange procedure under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures in Section 4.2 of the SmPC. Additional risk minimization measures: Physician Guide Patient Educational Materials	
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: Study GR40549 (Portal) Study GR46011 (SightARC)*	

Important Identified Risk: PDS implant and PDS procedures complications (vitreous hemorrhage, conjunctival bleb/bleb leak, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, device dislocation, and traumatic cataract)	
	See Section II.C of this summary for an overview of the post-authorization development plan.

IFU = Instructions for Use; nAMD = neovascular age-related macular degeneration; PDS = Port Delivery System with ranibizumab; PL = Patient Leaflet; SmPC = Summary of Product Characteristics.

*Study GR46011 (SightARC) aims to further characterize the following aspects of the important identified risk, PDS implant and PDS procedure complications: vitreous hemorrhage, conjunctival bleb complications, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, and device dislocation.

Important Identified Risk: Septum Dislodgement	
Evidence for linking the risk to the medicine	This important identified risk is based on the safety data from Studies GX28228, GR40548, and GR40549 in adult patients with nAMD.
Risk factors and risk groups	Patients implanted with the Phase III implants are at higher risk of experiencing septum dislodgement than those who have received other versions of the implant.
Risk minimization measures	Routine risk minimization measures SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable Effects PL Section 2 What you need to know before you are given Susvimo PL Section 4 Possible side effects Requirement for strict adherence to the manufacturer's IFU for the initial fill and implant insertion procedure, refill-exchange procedure, and the implant removal procedure is included in Section 4.4 of the SmPC (Special warnings and precautions for use). Pack size Legal status Restricted medical prescription Section 4.2 of the EU SmPC states: The initial fill and implant procedure and implant removal procedure must be performed in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures. The implant refill-exchange procedure should be performed under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures.

Important Identified Risk: Septum Dislodgement	
	Additional risk minimization measures: Physician Guide Patient Educational Materials
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: Study GR40549 (Portal) See Section II.C of this summary for an overview of the post-authorization development plan.

IFU = Instructions for Use; PDS = Port Delivery System with ranibizumab; PL = Patient Leaflet; SmPC = Summary of Product Characteristics.

Important Identified Risk: Intraocular Inflammation	
Evidence for linking the risk to the medicine	This important identified risk is based on the safety data from Studies GX28228, GR40548, and GR40549 in adult patients with nAMD.
Risk factors and risk groups	Patients with known history of inflammation from uveitis, as well as on chronic treatment with pro-inflammatory drugs (such as prostaglandins) may be more at risk of IOI if they undergo ocular surgeries, including PDS procedures.
Risk minimization measures	Routine risk minimization measures SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.3 Contraindications SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable Effects PL Section 2 What you need to know before you are given Susvimo PL Section 4 Possible side effects Pack size Legal status Restricted medical prescription Section 4.2 of the EU SmPC states: The initial fill and implant procedure and implant removal procedure must be performed in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures. The implant refill-exchange procedure should be performed under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures.

Important Identified Risk: Intraocular Inflammation	
	Additional risk minimization measures: Physician Guide Patient Educational Materials
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: Study GR40549 (Portal) See Section II.C of this summary for an overview of the post-authorization development plan.

IFU = Instructions for Use; IOI = Intraocular Inflammation; PDS = Port Delivery System with ranibizumab; PL = Patient Leaflet; SmPC = Summary of Product Characteristics.

Important Potential Risk: Implant damage during the PDS procedures (other than Septum Dislodgement)	
Evidence for linking the risk to the medicine	This potential risk is based on the known potential risk associated with any type of medical device.
Risk factors and risk groups	Not yet established
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.2 Posology and Method of Administration PL Section 2 What you need to know before you are given Susvimo PL Section 4 Possible side effects Strict adherence to the manufacturer's IFU in Section 4.4 of the SmPC (Special warnings and precautions for use). Pack size Legal status Restricted medical prescription Restriction to perform the initial fill and implant procedure, and implant removal procedure in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures, and restriction to perform the implant refill-exchange procedure under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures in Section 4.2 of the SmPC. Additional risk minimization measures: Physician Guide Patient Educational Materials

Important Potential Risk: Implant damage during the PDS procedures (other than Septum Dislodgement)	
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: Study GR40549 (Portal) See Section II.C of this summary for an overview of the post-authorization development plan.

IFU = Instructions for Use; PDS = Port Delivery System with ranibizumab; PL = Patient Leaflet; SmPC = Summary of Product Characteristics.

Missing Information: Long-term Safety	
Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: Study GR40549 (Portal) See Section II.C of this summary for an overview of the post-authorization development plan.

Missing Information: Implant Removal-Related Risks	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Special Warnings and Precautions for Use PL Section 2 What you need to know before you are given Susvimo Requirement for strict adherence to the manufacturer's IFU for the implant removal procedure is included in Section 4.4 of the SmPC (Special Warnings and Precautions).

Missing Information: Implant Removal-Related Risks	
	Pack size Legal status Restricted medical prescription Restriction to perform the initial fill and implant procedure, and implant removal procedure in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures, and restriction to perform the implant refill-exchange procedure under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures in Section 4.2 of the SmPC. Additional risk minimization measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: Study GR40549 (Portal) See Section II.C of this summary for an overview of the post-authorization development plan.

PDS = Port Delivery System with ranibizumab; PL = Patient Leaflet; SmPC = Summary of Product Characteristics.

Missing Information: Reimplantation-related risks	
Risk minimization measures	Routine risk minimization measures: Legal status Restricted medical prescription Restriction to perform the initial fill and implant procedure, and implant removal procedure in an operating room setting by an ophthalmologist experienced in vitreoretinal surgery and trained in the implant procedures, and restriction to perform the implant refill-exchange procedure under strict aseptic conditions in an outpatient setting by an ophthalmologist trained in the implant refill-exchange procedures in Section 4.2 of the SmPC. Additional risk minimization measures: None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaires Additional pharmacovigilance activities: Study GR40549 (Portal) Re-implantation substudy in association with study GR40549 (Portal)

II.C Post-Authorization Development Plan

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

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

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

Study short name: Study GR40549 (Portal)

Purpose of the study: To evaluate the long-term safety and tolerability of the PDS (100 mg/mL) in patients with nAMD, including the evaluation of the safety concerns associated with the PDS.

Study short name: Re-implantation substudy in association with study GR40549 (Portal)

Purpose of the study: To evaluate the safety of the reimplantation of PDS implant and the refill-exchange procedures following reimplantation in patients, previously enrolled in the main study, who experienced septum dislodgement while in the main study or after having exited the main study.

Study short name: Study GR46011 (SightARC)

Purpose of the study: To estimate the incidence of the following ocular safety outcomes and PDS-specific surgical and procedural complications associated with Susvimo in routine clinical practice in nAMD patients: vitreous hemorrhage, conjunctival bleb complications, conjunctival erosion, conjunctival retraction, endophthalmitis, retinal tear and retinal detachment, and device dislocation.

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ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

	Guided Questionnaire for Susvimo Ocular events	Version 5.0
		Page 1 / 7
		AER:

You have received this questionnaire because you have reported ocular events with Susvimo. Please provide additional information below, if available to you. By providing this information, you are actively participating in safety monitoring of Susvimo use.

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

Instructions for Completion:

- *Please provide as much detail as possible.*
- *Use the checkboxes where applicable.*

Patient Information					
Initials:		Sex:	☐ Male ☐ Female	☐ Unknown ☐ Undifferentiated	
Year of Birth:		or Age at time of the event:		☐ Year(s) ☐ Month(s)	
Height (cm):		Weight (kg):		Ethnicity:	
Relevant Medical/Ocular History	Condition	Status	Start Date (DD-MMM-YYYY)	End Date (DD-MMM-YYYY)	
Concomitant medications:					

Product Information - Susvimo			
Indication		Which eye has an implant?	
Date of Implantation (DD-MMM-YYYY)		Date of last refill if applicable (DD-MMM-YYYY)	
Dose and Unit		Total number of refills received to date if applicable:	
Lot Number and Expiration Date			

Product Information -- Any other suspect drug associated with adverse event

	Guided Questionnaire for Susvimo Ocular events	Version 5.0
		Page 2 / 7
		AER:

Name of product	Indication	Route of administration	Start date (DD-MMM-YYYY)	Stop date (DD-MMM-YYYY)	Dose and Unit	Lot Number and Expiration Date

Description of the event:

Date of event (dd/mm/yyyy): ____/____/____

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

Was the reported adverse event associated with, or caused by, a medication error that occurred during or as a result of the use of the device or the medical procedure? ☐ Yes ☐ No

Please check adverse event that applies and provide the relevant information:

Please provide appropriate assessment details in the Assessment Section.

☐ **Conjunctival bleb/bleb leak** Event occurred in: ☐ Right eye ☐ Left eye ☐ Both eyes

Was there any intervention (i.e., surgical) required? ☐ Yes ☐ No ☐ Unknown

If yes, please specify: _____

Was there a Visual Acuity drop compared to last visit? ☐ Yes ☐ No ☐ Unknown

If yes, how deep was the loss? Please specify: _____

Other relevant information: _____

Please provide appropriate assessment details in the Assessment Section.

☐ **Conjunctival Retraction** Event occurred in: ☐ Right eye ☐ Left eye ☐ Both eyes

Implant flange exposed ☐ Yes ☐ No

Was there any intervention (i.e., surgical) required? ☐ Yes ☐ No ☐ Unknown

If yes, please specify: _____

Was there a Visual Acuity drop compared to last visit? ☐ Yes ☐ No ☐ Unknown

If yes, how deep was the loss? Please specify: _____

Other relevant information: _____

Please provide appropriate assessment details in the Assessment Section.

☐ **Conjunctival Erosion** Event occurred in: ☐ Right eye ☐ Left eye ☐ Both eyes

Implant flange exposed ☐ Yes ☐ No

Was there any intervention (i.e., surgical) required? ☐ Yes ☐ No ☐ Unknown

If yes, please specify: _____



Guided Questionnaire for Susvimo Ocular events

Version 5.0

Page 3 / 7

AER:

Was there a Visual Acuity drop compared to last visit? ☐ Yes ☐ No ☐ Unknown

If yes, how deep was the loss? Please specify: _____

Other relevant information: _____

Please provide appropriate assessment details in the Assessment Section.

☐ **Vitreous Hemorrhage** Event occurred in: ☐ Right eye ☐ Left eye ☐ Both eyes

Is the patient taking any concurrent antithrombotic therapy? ☐ Yes ☐ No ☐ Unknown

If yes, please specify: _____

Was there any intervention (i.e., surgical) required? ☐ Yes ☐ No ☐ Unknown

If yes, please specify: _____

Was there a Visual Acuity drop compared to last visit? ☐ Yes ☐ No ☐ Unknown

If yes, how deep was the loss? Please specify: _____

Other relevant information: _____

Please provide appropriate assessment details in the Assessment Section.

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

Date of implant insertion surgery in the affected eye: _____

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

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

Was there any intervention (i.e., surgical) required? ☐ Yes ☐ No ☐ Unknown

If yes, please specify: _____

Was this event associated with any conjunctival erosion or retraction? ☐ Yes ☐ No ☐ Unknown

If yes, please specify: _____

Date of last refill-exchange in the affected eye: _____

Did patient receive post refill-exchange topical antibiotics? ☐ Yes ☐ No ☐ Unknown (If yes, for how many days?)

Were sterile gloves used during refill-exchange? ☐ Yes ☐ No ☐ Unknown

Was a sterile drape used during refill-exchange? ☐ Yes ☐ No ☐ Unknown

Was eye speculum used during refill-exchange? ☐ Yes ☐ No ☐ Unknown

Was broad-spectrum microbicide used in preparation for the refill-exchange? ☐ Yes ☐ No ☐ Unknown

Pathogen identified: _____

Was there a Visual Acuity drop compared to last visit? ☐ Yes ☐ No ☐ Unknown

If yes, how deep was the loss? Please specify: _____

Other relevant information: _____

Please provide appropriate assessment details in the Assessment Section.

☐ **Retinal detachment** Event occurred in: ☐ Right eye ☐ Left eye ☐ Both eyes

Type of retinal detachment (Circle applicable: rhegmatogenous, exudative/serous, tractional)



Guided Questionnaire for Susvimo Ocular events

Version 5.0

Page 4 / 7

AER:

Location of retinal detachment? _____

Is the macula involved by retinal detachment? _____

Is a new retinal tear present? ☐ Yes ☐ No ☐ Unknown

If yes, please provide the location: _____

Was there any intervention (i.e., surgical) required? ☐ Yes ☐ No ☐ Unknown

If yes, please specify: _____

Is eye highly myopic (i.e., > -6 diopters)? ☐ Yes ☐ No ☐ Unknown

If yes, how many diopters? _____

Posterior vitreous detachment? ☐ Yes ☐ No ☐ Unknown

If yes, when? _____

Lattice degeneration? ☐ Yes ☐ No ☐ Unknown

If yes, when? _____

Prior eye surgery? (e.g. cataract or other surgery) ☐ Yes ☐ No ☐ Unknown

If yes, when? _____

Prior diagnosis of retinal tear? ☐ Yes ☐ No ☐ Unknown

If yes, location, when, and how was it treated?

Prior diagnosis of retinal detachment? ☐ Yes ☐ No ☐ Unknown

If yes, location, when, and how was it treated?

Did the retinal detachment already occur in the other eye? ☐ Yes ☐ No ☐ Unknown

If yes, location, when, and how was it treated?

Was there a Visual Acuity drop compared to last visit? ☐ Yes ☐ No ☐ Unknown

If yes, how deep was the loss? Please specify: _____

Other relevant information:

Please provide appropriate assessment details in the Assessment Section.

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

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

retinitis	posterior uveitis	cells in the anterior chamber/vitreous	uveitis	iritis	iridocyclitis	vitritis	intermediate uveitis
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Was there any intervention (i.e., surgical) required? ☐ Yes ☐ No ☐ Unknown

If yes, please specify: _____

Prior intraocular inflammation? ☐ Yes ☐ No ☐ Unknown

If yes, please describe the inflammation, in which eye it occurred, when it occurred and treatment given:

Systemic condition(s) known to be associated with uveitis? (e.g. infection, autoimmune diseases, HLAB27 positivity)?

☐ Yes ☐ No ☐ Unknown

If yes, when? Please describe:

Was there a Visual Acuity drop compared to last visit? ☐ Yes ☐ No ☐ Unknown



Guided Questionnaire for Susvimo Ocular events

Version 5.0

Page 5 / 7

AER:

If yes, how deep was the loss? Please specify: _____

Other relevant information: _____

Please provide appropriate assessment details in the Assessment Section.

☐ **Device (implant) dislocation** Event occurred in: ☐ Right eye ☐ Left eye ☐ Both eyes

Date of last refill-exchange in the affected eye: _____

Implant was dislocated: ☐ Into the vitreous cavity ☐ Outside the vitreous cavity

Did implant dislocation occur during a refill-exchange? ☐ Yes ☐ No ☐ Unsure

Was there any intervention (i.e., surgical) required? ☐ Yes ☐ No ☐ Unknown

If yes, please specify: _____

Was there a Visual Acuity drop compared to last visit? ☐ Yes ☐ No ☐ Unknown

If yes, how deep was the loss? Please specify: _____

Other relevant information: _____

Please provide appropriate assessment details in the Assessment Section.

☐ **Septum Dislodgement** Event occurred in: ☐ Right eye ☐ Left eye ☐ Both eyes

Date of last refill-exchange in the affected eye: _____

Was there any intervention (i.e., surgical) required? ☐ Yes ☐ No ☐ Unknown

If yes, please specify: _____

Was there a Visual Acuity drop compared to last visit? ☐ Yes ☐ No ☐ Unknown

If yes, how deep was the loss? Please specify: _____

Other relevant information: _____

Please provide appropriate assessment details in the Assessment Section.

☐ **Traumatic cataract** Event occurred in: ☐ Right eye ☐ Left eye ☐ Both eyes

Date of last refill-exchange in the affected eye: _____

Was there any intervention (i.e., surgical) required? ☐ Yes ☐ No ☐ Unknown

If yes, please specify: _____

Was there a Visual Acuity drop compared to last visit? ☐ Yes ☐ No ☐ Unknown

If yes, how deep was the loss? Please specify: _____

Other relevant information: _____

Please provide appropriate assessment details in the Assessment Section.

☐ **Implant damage (excluding septum dislodgement)** Event occurred in: ☐ Right eye ☐ Left eye ☐ Both eyes

Date of last refill-exchange in the affected eye: _____

Was there any intervention (i.e., surgical) required? ☐ Yes ☐ No ☐ Unknown

If so, please specify: _____

Was there a Visual Acuity drop compared to last visit? ☐ Yes ☐ No ☐ Unknown

If yes, how deep was the loss? Please specify: _____

	Guided Questionnaire for Susvimo Ocular events	Version 5.0 Page 6 / 7 AER:
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Other relevant information:

Please indicate any actions taken with the suspected medication: (Check all that apply)		
☐ Dose not changed	☐ Drug Interrupted	☐ Drug withdrawn
☐ Implant removal (Explantation) If this is checked, please provide the date: (dd/mm/yyyy): ____/____/____	☐ Not applicable	☐ Other (please explain):
Do any of the following criteria apply as a consequence of the event?		What is the final outcome?
☐ Resulted in Death Cause of Death: _____ Date of death: ____/____/____ (dd/mm/yyyy)	☐ Involved or prolonged inpatient hospitalization Date of admission: ____/____/____ (dd/mm/yyyy) Date of discharge: ____/____/____ (dd/mm/yyyy)	☐ Recovered/Resolved ☐ Recovered/Resolved with sequelae ☐ Recovering/Resolving ☐ Not Recovered/Not Resolved ☐ Fatal ☐ Outcome unknown
☐ Congenital anomaly or birth defect Provide details: _____	☐ Medically significant (An adverse event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other serious outcomes)	
☐ Persistence of significant disability or incapacity (A substantial disruption of a person's ability to conduct normal life functions, resulting in significant, persistent or permanent change, impairment, damage or disruptions in the patient's body function, physical activities and/or quality of life)	☐ Permanent impairment of a body structure or a body function incl. chronic disease ☐ Life-threatening at the time the event(s) occurred (Any adverse event where the patient was at immediate risk of death at the time the adverse event occurred)	
☐ None of the above		

Assessment of Suspect Drug-Event Relationship:
FOR POST-MARKETING, CLINICAL TRIALS, POST-MARKETING STUDIES/REGISTRY CASES ONLY:
Provide your evaluation of the relationship of the Roche product to the reported adverse event(s) by checking one of the assessments:
AE suspected to be caused by the drug? ☐ Yes ☐ No ☐ Unknown ☐ N/A
Adverse event suspected to be related to the device? ☐ Yes ☐ No (If yes, please check one of the following)
☐ Implant ☐ Insertion tool ☐ Initial fill needle ☐ Refill needle ☐ Explant tool
Adverse event suspected to be related to the procedure? ☐ Yes ☐ No (If yes, please check one of the following)
☐ Initial fill ☐ Implant insertion ☐ Refill-exchange ☐ Explantation

Reporter Information

	Guided Questionnaire for Susvimo Ocular events	Version 5.0 Page 7 / 7 AER:
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Reporter Name		Occupation	
E-mail Address		Phone Number	
Signature			

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES

Draft Key Messages of the Additional Risk-Minimization Measures

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

The MAH shall provide information on implant insertion procedure, implant removal procedure, and refill-exchange procedure to ophthalmologists experienced in vitreoretinal surgery, with the aim to establish consistency in following the instructions for use and confidence in the surgical procedures associated with Susvimo. The refill-exchange procedure information will also be provided to ophthalmologists who will perform the refill-exchange procedure for Susvimo. The MAH shall also provide patient educational materials.

The MAH shall ensure that, following discussions and agreements with the National Competent Authorities in each Member State where Susvimo is marketed, at launch and after launch, all ophthalmological clinics where Susvimo is expected to be used are provided with an up-to-date physician guide.

TABLE OF CONTENTS

1.	HEALTHCARE PROFESSIONALS.....	3
1.1	Physician Guide.....	3
2.	PATIENTS/CAREGIVERS	4
2.1	Patient Educational Materials	4

1. HEALTHCARE PROFESSIONALS

1.1 PHYSICIAN GUIDE

The physician guide will contain the following elements:

- Physician information
- Instructional video and pictograms on vitreoretinal surgery and performing the port delivery system (PDS) procedures
- Patient guide

The physician information will include the following key elements:

- Sterile techniques to minimize risk of infection
- Techniques for the vitreoretinal surgery and performing the PDS procedures
- Patient monitoring after the vitreoretinal surgery and the PDS procedures
- Key signs and symptoms of vitreoretinal surgery related adverse events
- Management of adverse events related to vitreoretinal surgery and performing the PDS procedures

2. PATIENTS/CAREGIVERS

2.1 PATIENT EDUCATIONAL MATERIALS

The patient guide is provided in written and audio format, and will include the following key elements:

- How to prepare for Susvimo treatment
- What are the steps following treatment with Susvimo
- Key signs and symptoms of adverse events including endophthalmitis
- When to seek urgent attention from the health care provider

Signature Page for RIM-PVG-210711 v1.0

Approval Task	 Deputy EU QPPV 17-Jul-2026 12:56:39 GMT+0000
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Approval Task	 Company Signatory 17-Jul-2026 14:42:36 GMT+0000
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