EU Risk Management Plan
For
Eydenzelt
(CT-P42, aflibercept biosimilar)

RMP version to be assessed as part of this application:	
RMP Version number:	1.0
Data lock point for this RMP:	21 July 2023
Date of final sign-off:	02 January 2025
Rationale for submitting an updated RMP:	Not applicable
Summary of significant changes in this RMP:	Not applicable
Other RMP versions under evaluation: Not applicable	
RMP Version number:	-
Submitted on:	-
Procedure number:	-
Details of the currently approved RMP: Not applicable	
Approved with procedure:	-
Date of approval (opinion date):	-
QPPV name:	Oliver Wiedemann
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

Note: Throughout this document, symbols indicating proprietary names (®, ™) are not displayed. The appearance of product names without these symbols does not imply that these names are not protected.

Table of Contents

List of Tables

List of Abbreviations

Abbreviation/Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AMD	Age-related Macular Degeneration
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration Time Curve
BCVA	Best Corrected Visual Acuity
BRVO	Branch RVO
CHMP	Committee for Human Medicinal Products
CHO	Chinese Hamster Ovary
CI	Confidence Interval
C_{max}	Maximum Concentration
CNV	Choroidal Neovascularisation
CRVO	Central RVO
DME	Diabetic Macular Oedema
DNA	Deoxyribonucleic Acid
DR	Diabetic Retinopathy
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ETDRS	Early Treatment of Diabetic Retinopathy Study
EU	European Union
GD	Gestation Day
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
ICH	International Council for Harmonisation
IgG1	Immunoglobulin G1
INN	International Non-proprietary Names
IOI	Intraocular Inflammation
IOP	Intraocular Pressure
IV	Intravenous
IVT	Intravitreal
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No Observed Adverse Effect Level
OCT	Optical Coherence Tomography

PFS	Pre-Filled Syringe
PlGF	Placental Growth Factor
PL	Package Leaflet
PT	Preferred Term
PSUR	Periodic Safety Update Report
PY	Patient Year
RMP	Risk Management Plan
ROP	Retinopathy Of Prematurity
RPE	Retinal Pigment Epithelial
RVO	Retinal Vein Occlusion
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
TEAE	Treatment Emergent Adverse Event
VEGF	Vascular Endothelial Growth Factor

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Aflibercept
Pharmacotherapeutic group(s) (ATC Code)	Ocular vascular disorder agents, Antineovascularisation agents (S01LA05)
Marketing Authorisation Applicant	Celltrion Healthcare Hungary kft.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Eydenzelt
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	**Chemical class** Recombinant fusion protein consisting of portions of human Vascular Endothelial Growth Factor (VEGF) receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1. Aflibercept is a specific blocker that binds and inactivates VEGF and the related molecule, placental growth factor (PlGF).
	Summary of mode of action Aflibercept is designed to interfere with the increase in vascular permeability and growth of pathological new blood vessels that lead to retinal oedema, ischaemia and haemorrhage in diseases accompanied by ocular neovascularisation.
	Important information about its composition: Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant Deoxyribonucleic Acid (DNA) technology.
Hyperlink to the Product Information	CTD Module 1.3.1
Indication(s) in the EEA	Current: Eydenzelt is indicated in adults for the treatment of: • Neovascular (wet) age-related macular degeneration (AMD). • Visual impairment due to macular oedema secondary to retinal vein occlusion (branch retinal vein occlusion (RVO) or central RVO). • Visual impairment due to diabetic macular oedema (DME). • Visual impairment due to myopic choroidal neovascularisation (myopic CNV).
	Proposed: Not applicable

Dosage in the EEA	Current: The injection volume of Eydenzelt is 0.05 mL (equivalent to 2 mg aflibercept). <u>Wet AMD</u> The recommended dose of Eydenzelt is 2 mg aflibercept, equivalent to 0.05 mL. <u>Macular oedema secondary to RVO</u> The recommended dose of Eydenzelt is 2 mg aflibercept, equivalent to 0.05 mL. <u>DME</u> The recommended dose of Eydenzelt is 2 mg aflibercept, equivalent to 0.05 mL. <u>Myopic CNV</u> The recommended dose of Eydenzelt is 2 mg aflibercept, equivalent to 0.05 mL.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Solution for injection in a Pre-Filled Syringe (PFS). One PFS contains 3.6 mg aflibercept in 0.09 mL (40 mg/mL) in iso-osmotic solution. Delivers a single dose of 0.05 mL containing 2 mg aflibercept. Solution for injection in a vial. One vial contains 4 mg aflibercept in 0.1 mL (40 mg/mL) in iso-osmotic solution. Delivers a single dose of 0.05 mL containing 2 mg aflibercept.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Eydenzelt, biosimilar aflibercept and CT-P42 may be used interchangeably in this document to describe the investigational product to which this application refers.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

According to the Guideline on Good Pharmacovigilance Practices (GVP) Module V (EMA/838713/2011 Rev 2) this part of the Risk Management Plan (RMP) is not required for biosimilar medicinal products.

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

Table 2: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies) of CT-P42	Relevance to human usage
Repeat-dose toxicity of CT-P42 No CT-P42 or Eylea-related mortality; clinical observations; body weight change, Electrocardiogram (ECG) parameters, or blood pressure; clinical pathology effects; organ weight differences; macroscopic or microscopic differences; nor clinically important intraocular pressure differences were noted. Animals administered 2 mg/eye CT-P42 were noted to have slightly less ophthalmic inflammation than animals administered 2 mg/eye Eylea; although both test articles resulted in a mild to moderate anterior segment inflammatory response 2 days postdose. CT-P42 was not associated with loss of visual function on ERG and VEP assessment, nor was it distinguished from Eylea. Due to the mild severity of findings and the lack of impact on the health and wellbeing of animals administered 2 mg/eye CT-P42, effects for this dose were considered non-adverse and comparable to Eylea at the same dose level. Thus, the "No Observed Adverse Effect Level" (NOAEL) is 2 mg/eye CT-P42. **Repeat-dose toxicity of Eylea (RMP)** Repeated monthly intravitreal (IVT) administration of aflibercept to monkeys for up to 8 months was not associated with ocular effects considered adverse, with ocular findings in the study limited to inflammation that were generally mild and completely or mostly reversed by 4-weeks postdose. Erosions and ulcerations of the respiratory epithelium of the nasal turbinates were observed in individual animals treated at and above the clinical dose of 2 mg/eye and with mostly low severity (exception: 1 animal with moderate, one with marked severity) at the end of the dosing period. However, assessing adverse events in clinical trials on humans did not reveal any occurrence of these findings following repeated IVT dosing of aflibercept.	No direct safety concern for the use of aflibercept in the target population.

Potential to impair fertility Potential to be embryo-foetotoxic **Reproductive/Developmental toxicity of CT-P42** Reproductive toxicology studies comparing CT-P42 and Eylea have not been performed because they are not required according to the European Medicines Agency (EMA) guidance on biosimilar products (Committee for Human Medicinal Products [CHMP] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance - non-clinical and clinical issues [EMEA/CHMP/BMWP/42832/2005 Rev1] and Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues [EMA/CHMP/BMWP/403543/2010] **Reproductive/Developmental toxicity of Eylea (RMP)** Effects on male and female fertility were assessed as part of the 6-month studies in monkeys with intravenous (IV) administration of aflibercept at doses ranging from 3 to 30 mg/kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. Based on maximum concentration (C_{max}) and area under the concentration time curve (AUC) for free aflibercept observed at the 3 mg/kg IV dose, the systemic exposures were approximately 4,900-fold and 1,500-fold higher, respectively, than the exposures observed in humans after IVT administration of 2 mg and are, therefore, considered not relevant for the IVT use of aflibercept. All changes were reversible. No changes to reproductive organs were observed after IVT administration of aflibercept in monkeys. Based on its mechanism of action, aflibercept is expected to influence embryo-foetal development. This was shown in an embryo-foetal development study in pregnant rabbits with IV administration (3 to 60 mg/kg). At 60 mg/kg foetal resorptions, pregnancy disruptions and numerous foetal (external, visceral and skeletal) malformations were observed. The maternal (NOAEL) was the dose of 3 mg/kg, whereas the developmental NOAEL was not identified, since at 3 mg/kg still some signs of embryo-foetal toxicity were observed in one foetus. At the lowest dose of 3 mg/kg, systemic exposures of free aflibercept were approximately 600- to 2,000-fold in excess of the maximum human exposure after an IVT administration of 2 mg (based on AUC and C_{max}, respectively). In a combined early embryonic/embryo-foetal development study with aflibercept in pregnant rabbits with subcutaneous (SC) administration (0.1 to 1 mg/kg) starting at gestation day (GD) 1, no influence on maternal toxicity, gestation rate, post-implantation loss, placental weight, placental appearance, foetal sex distribution, or foetal weight was observed at all doses tested. The overall rate of cardiac ventricular septal defects (with/without malformation of major vessels), and skeletal malformations was slightly higher in aflibercept treated than control animals but showed no clear dose-dependency. A “spina bifida” was seen in a single foetus from each of 2 different dams that received 0.1 mg/kg during gestation. A “meningocele” was seen in 1 foetus from a single dam that received 1.0 mg/kg during gestation. Based on the results of this study, the maternal NOAEL was	Treatment with aflibercept is not recommended during pregnancy unless the potential benefit outweighs the potential risk to the foetus. Likewise, aflibercept is not recommended for women of childbearing potential not using contraception. Aflibercept is not recommended during breast-feeding.

Key Safety findings (from non-clinical studies) of CT-P42	Relevance to human usage
considered to be 1 mg/kg. The developmental NOAEL was not identified. Comparison of the systemic exposures observed in this study with mean exposures observed in humans following a 2 mg/eye dose indicate an exposure margin of approximately 10-fold (based on mean AUC for free aflibercept).	
Genotoxicity/Carcinogenicity of CT-P42 Genotoxicity/carcinogenicity studies comparing CT-P42 and Eylea have not been performed because they are not required according to the EMA guidance on similar biological medicinal products and monoclonal antibodies (EMEA/CHMP/BMWP/42832/2005 Rev1; EMA/CHMP/BMWP/403543/2010) **Genotoxicity/Carcinogenicity of Eylea (RMP)** In accordance with International Council for Harmonisation (ICH) guideline S6, no genotoxicity studies were conducted. Since aflibercept is a large molecule, it is not expected to interact directly with DNA or other chromosomal material. No studies explicitly targeting carcinogenicity were conducted. Based on studies performed so far, there is no evidence that aflibercept (or other VEGF-inhibitory compounds) act as growth factors or are immunosuppressive. Therefore, currently there is no reason to suspect that aflibercept has a tumorigenic potential.	Not applicable
General Safety Pharmacology of CT-P42 No specific safety pharmacology studies were performed. Safety end-points were incorporated into the monkey repeat-dose toxicity study (Study No. 8422306). No CT-P42- or Eylea-related clinical observations, blood pressure, or changes to ECG parameters were noted. This approach is compatible with CHMP guidance on similar biological medicinal products containing monoclonal antibodies, which states that safety pharmacology studies are not routinely required (CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues EMA/CHMP/BMWP/403543/2010). **General Safety Pharmacology of Eylea (RMP)** Effects of aflibercept on blood pressure and wound healing were only observed following systemic administration. Exposures after systemic administration were substantially above those following IVT injection. Therefore, IVT administration of aflibercept is not expected to exert appreciable effects on VEGF-mediated processes outside of the eye.	Not applicable

Key Safety findings (from non-clinical studies) of CT-P42	Relevance to human usage
Mechanisms for Drug Interactions of CT-P42 No drug interactions have been studied, although aflibercept is intended to be given to patients in combination with various other medicinal products. **Mechanisms for Drug Interactions of Eylea (European Public Assessment Report [EPAR])** Data from formal pharmacodynamic drug-drug interaction studies of Eylea with ophthalmic anaesthetic agents, antimicrobial agents and mydriatics are not available. Because topical ocular medications do not reach the posterior segment, drug-drug interactions with Eylea within this ocular compartment are highly unlikely.	Not applicable
Juvenile Toxicity Studies of CT-P42 Juvenile toxicity studies were not performed in line with the CHMP EMA guidance on similar biological medicinal products and monoclonal antibodies (EMEA/CHMP/BMWP/42832/2005 Rev1) and CHMP guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010). **Juvenile Toxicity Studies of Eylea (EPAR)** Eylea was administered IV at doses of 0, 0.5, 3, or 30 mg/kg/administration once weekly for 3 months in young, skeletally immature Cynomolgus monkeys, with reversibility of systemic findings evaluated after an additional 5 month recovery phase. Effects were seen in bone, kidney, ovaries, adrenal glands and systemic vascular proliferation. A NOAEL was not determined. Based on C_{max} and AUC0-168h for free Eylea observed at the 0.5 mg/kg IV dose, the lowest dose at which finding were observed, the exposure was 503-fold and 134-fold higher, respectively, than the systemic exposure observed in humans after an IVT dose of 2 mg/eye.	Not applicable

Conclusion on Non-Clinical Data

Non-clinical investigations comparing CT-P42 with the reference product have not shown them to behave differently from one another in any relevant respects when administered by IVT injection. No unexpected safety findings or signals were identified in the non-clinical programme for CT-P42.

Part II: Module SIII - Clinical trial exposure

The terms Eydenzelt and CT-P42 may be used interchangeably in this document.

The clinical development programme for Eydenzelt (CT-P42) includes one completed Phase 3 clinical study in patients with DME (Study CT-P42 3.1).

Study CT-P42 3.1 (equivalence study of CT-P42 to European Union (EU)-approved Eylea): a Phase 3, randomised, active-controlled, double-masked, parallel-group study to compare efficacy and safety of CT-P42 in comparison with Eylea in patients with diabetic macular oedema. This study consisted of 348 male and female patients with DME, aged 18 years and above, and randomly assigned in a 1:1 ratio to receive one of the following: 2 mg/0.05 mL CT-P42 or 2 mg/0.05 mL Eylea IVT injection. This study comprised 3 study periods (Screening Period, Main Study Period, and Extension Study Period). The maximum duration of the treatment was 56 weeks: a Main Study Period of 52 weeks, and an Extension Study Period of 4 weeks. In the Main Study Period, patients received 2 mg/0.05 mL of CT-P42 or Eylea IVT injection via a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses. A total of 31 patients who completed the Main Study Period up to Week 52, regardless of the treatment groups that they were randomised to, did participate in the open-label Extension Study Period. At Extension Week 0, all patients received a single dose of CT-P42 PFS.

A total of 348 patients were enrolled in Study CT-P42 3.1. Of those, 174 patients received CT-P42 and 174 patients received EU-approved Eylea. Out of 31 patients who participated in the Extension Study Period, 16 patients were from Eylea (Aflibercept reference product) treatment group in the Main Study Period. Exposure data of Study CT-P42 3.1 are presented in the following tables.

Table 3: Duration of exposure

INDICATION: Diabetic Macular Oedema (DME) (CT-P42 3.1)								
Duration of exposure	**CT-P42**						**Aflibercept reference product** (N=174)**	
	Total (N=190)		**CT-P42 only (N=174)**		**CT-P42 after administration of aflibercept reference product* (N=16)**			
	Persons (n)	**Person time (days)**	**Persons (n)**	**Person time (days)**	**Persons (n)**	**Person time (days)**	**Persons (n)**	**Person time (days)**
Duration <= 4 weeks	18	71	2	55	16	16	2	2
4 weeks < Duration <= 12 weeks	2	124	2	124	0	0	5	237
12 weeks < Duration <= 24 weeks	4	405	4	405	0	0	6	729
24 weeks < Duration <= 40 weeks	8	1657	8	1657	0	0	7	1480
40 weeks < Duration <= 52 weeks	143	48037	143	48037	0	0	136	45996
52 weeks < Duration	15	5958	15	5958	0	0	18	7082
Total	190	56252	174	56236	16	16	174	55526

Protocol Number: CT-P42 3.1.
Abbreviation: n=number of patients.
**Patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product in the main study period.*
***Patients exposed to aflibercept reference product during main study period is included in this column.*

INDICATION: Diabetic Macular Oedema (DME) (CT-P42 3.1)								
Duration of exposure	CT-P42						Aflibercept reference product** (N=174)	
	Total (N=190)		CT-P42 only (N=174)		CT-P42 after administration of aflibercept reference product* (N=16)			
	Persons (n)	Person time (days)	Persons (n)	Person time (days)	Persons (n)	Person time (days)	Persons (n)	Person time (days)

Person time (days) for each arm is calculated as follows.
CT-P42 only: Date of Last Exposure to Treatment – Date of First Exposure to Treatment + 1.
CT-P42 after administration of aflibercept reference product: Date of Last Exposure to CT-P42 Treatment – Date of First Exposure to CT-P42 Treatment + 1.
CT-P42 total: Duration from 'CT-P42 only' and 'CT-P42 after administration of aflibercept reference product'.
Aflibercept reference product: (Date of Last Exposure to Treatment – Date of First Exposure to Treatment + 1) or ([Date of First Exposure of CT-P42] – [Date of First Exposure to Treatment]).

Table 4: Exposure by Dose

INDICATION: Diabetic Macular Oedema (DME) (CT-P42 3.1)								
Number of treatment administration	CT-P42						Aflibercept reference product** (N=174)	
	Total (N=190)		CT-P42 only (N=174)		CT-P42 after administration of aflibercept reference product* (N=16)			
	Persons (n)	Person time (days)	Persons (n)	Person time (days)	Persons (n)	Person time (days)	Persons (n)	Person time (days)
1	16	16	0	0	16	16	2	2
2	3	119	3	119	0	0	2	62
3	2	152	2	152	0	0	3	175
4	1	91	1	91	0	0	2	183
5	2	222	2	222	0	0	2	221
6	5	1084	5	1084	0	0	5	832
7	6	1593	6	1593	0	0	5	1317
8	11	3535	11	3535	0	0	13	4362
9	130	43875	130	43875	0	0	140	48372
10	14	5565	14	5565	0	0	0	0
Total	190	56252	174	56236	16	16	174	55526
Total Cumulative Dose (mg) n	190	-	174	-	16	-	174	-
Total Cumulative Dose (mg) Mean	15.9	-	17.2	-	2.00	-	16.8	-
Total Cumulative Dose (mg) Median	18.0	-	18.0	-	2.00	-	18.0	-
Total Cumulative Dose (mg) Min	2	-	4	-	2	-	2	-
Total Cumulative Dose (mg) Max	20	-	20	-	2	-	18	-

Protocol Number: CT-P42 3.1.
Abbreviation: n=number of patients.
**Patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product in the main study period.*

***Patients exposed to aflibercept reference product during main study period is included in this column.*
Person time (days) for each arm is calculated as follows.
CT-P42 only: Date of Last Exposure to Treatment – Date of First Exposure to Treatment + 1.
CT-P42 after administration of aflibercept reference product: Date of Last Exposure to CT-P42 Treatment – Date of First Exposure to CT-P42 Treatment + 1.
CT-P42 total: Duration from 'CT-P42 only' and 'CT-P42 after administration of aflibercept reference product'.
Aflibercept reference product: (Date of Last Exposure to Treatment – Date of First Exposure to Treatment + 1) or ([Date of First Exposure of CT-P42] – [Date of First Exposure to Treatment]).

Table 5: Exposure by Age and Gender

INDICATION: Diabetic Macular Oedema (DME) (CT-P42 3.1)																
Age group	**CT-P42**												**Aflibercept reference product** (N=174)**			
	Total (N=190)				**CT-P42 only (N=174)**				**CT-P42 after administration of aflibercept reference product* (N=16)**							
	Persons (n)		**Person time (days)**		**Persons (n)**		**Person time (days)**		**Persons (n)**		**Person time (days)**		**Persons (n)**		**Person time (days)**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
18- 40	4	1	1403	344	4	1	1403	344	0	0	0	0	4	3	1360	710
41- 50	7	2	1750	750	7	2	1750	750	0	0	0	0	4	5	1340	1702
51- 64	65	27	19896	8025	61	26	19892	8024	4	1	4	1	51	28	15161	8983
≥ 65	41	43	11463	12621	35	38	11457	12616	6	5	6	5	37	42	12383	13887
Total	117	73	34512	21740	107	67	34502	21734	10	6	10	6	96	78	30244	25282

Protocol Number: CT-P42 3.1.
Abbreviation: n=number of patients, M=Male, F=Female.
**Patients who received a single dose of CT-P42 in the extension study period.after administration of aflibercept reference product in the main study period.*
***Patients exposed to aflibercept reference product during main study period is included in this column.*
Person time (days) for each arm is calculated as follows.
CT-P42 only: Date of Last Exposure to Treatment – Date of First Exposure to Treatment + 1.
CT-P42 after administration of aflibercept reference product: Date of Last Exposure to CT-P42 Treatment – Date of First Exposure to CT-P42 Treatment + 1.
CT-P42 total: Duration from 'CT-P42 only' and 'CT-P42 after administration of aflibercept reference product'.
Aflibercept reference product: (Date of Last Exposure to Treatment – Date of First Exposure to Treatment + 1) or ([Date of First Exposure of CT-P42] – [Date of First Exposure to Treatment]).

Table 6: Exposure by Race

INDICATION: Diabetic Macular Oedema (DME) (CT-P42 3.1)								
Race	CT-P42						Aflibercept reference product** (N=174)	
	Total (N=190)		CT-P42 only (N=174)		CT-P42 after administration of aflibercept reference product* (N=16)			
	Persons (n)	Person time (days)	Persons (n)	Person time (days)	Persons (n)	Person time (days)	Persons (n)	Person time (days)
Asian	62	18210	62	18210	0	0	62	18606
White	128	38042	112	38026	16	16	112	36920
Total	190	56252	174	56236	16	16	174	55526

Protocol Number: CT-P42 3.1.

Abbreviation: n=number of patients.

**Patients who received a single dose of CT-P42 in the extension study period.after administration of aflibercept reference product in the main study period.*

***Patients exposed to aflibercept reference product during main study period is included in this column.*

Person time (days) for each arm is calculated as follows.

CT-P42 only: Date of Last Exposure to Treatment – Date of First Exposure to Treatment + 1.

CT-P42 after administration of aflibercept reference product: Date of Last Exposure to CT-P42 Treatment – Date of First Exposure to CT-P42 Treatment + 1.

CT-P42 total: Duration from 'CT-P42 only' and 'CT-P42 after administration of aflibercept reference product'.

Aflibercept reference product: (Date of Last Exposure to Treatment – Date of First Exposure to Treatment + 1) or ([Date of First Exposure of CT-P42] – [Date of First Exposure to Treatment]).

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The important exclusion criteria from the pivotal clinical study, CT-P42 3.1, are presented below.

Patient who has only one functional eye, even if the eye met all other study requirements, or has and/or is likely to have amblyopia, amaurosis or ocular disorder with BCVA ≤ 34 ETDRS letter score (approximate Snellen equivalent of ≤ 20/200) in the fellow eye.

Reason for exclusion: This exclusion criterion is based on ethical concerns and technical requirements for the clinical study; as long as beneficial effects are not proven, the only remaining functional eye should not be exposed to an experimental drug. No safety concern was anticipated.

Is it considered to be included as missing information?: No

Rationale: Patients with above mentioned conditions were excluded from the clinical study for ethical reason. There are no safety concerns associated with this exclusion criterion and it is not a safety concern for the reference product, Eylea.

Patient who currently has, or has a history (where indicated) of ocular condition in the study eye including active proliferative DR, or pre-retinal fibrosis involving the macula, aphakia, vitreomacular traction or epiretinal membrane that is expected to affect central vision, iris neovascularization, vitreous haemorrhage, or tractional retinal detachment, ocular inflammation, uncontrolled glaucoma or filtration surgery for glaucoma in the past or likely to be needed in the future, intraocular pressure ≥25 mmHg, spherical equivalent of the refractive error of worse than -6 dioptres myopia, structural damage to the centre of the macula that is likely to preclude improvement in BCVA, concurrent and/or history of disease, other than DME, that could compromise visual acuity, require medical or surgical intervention during the study period, or could confound interpretation of the results or inability to obtain fundus or OCT images due to, but not limited to, insufficient media clarity or inadequate pupil dilation.

Reason for exclusion: Patients with above mentioned conditions were excluded from the clinical study as there is safety risk to the patient and also to prevent interference with safety and efficacy result.

Is it considered to be included as missing information?: No

Rationale: The precautions to be taken while using aflibercept in patients with active proliferative DR, retinal detachment, and uncontrolled glaucoma have been adequately described in the Summary of Product Characteristics (SmPC) (Section 4.4 ‘Special warnings and precautions for use’). Intraocular inflammation and Transient increase in intraocular pressure are identified risks of aflibercept and have adequately been described in the SmPC (Section 4.3 ‘Contraindications’ and Section 4.4. ‘Special warnings and precautions for use’).

Patient who currently has, or has a history (where indicated) of, ocular condition including one or more of the following in either eye: Concurrent and/or history of idiopathic or autoimmune uveitis, Evidence or suspicion of infection including blepharitis, keratitis, scleritis, or conjunctivitis.

Reason for exclusion: Patients with above mentioned conditions were excluded from the clinical study to prevent interference with safety study endpoints.

Is it considered to be included as missing information?: No

Rationale: Aflibercept is contraindicated in patients with active or suspected ocular or periocular infection, and in patients with active severe intraocular inflammation. Intraocular inflammation and periocular infection have adequately been described in the SmPC (Section 4.3 'Contraindication' and Section 4.4 'Special warnings and precautions for use').

Patient who currently has, or has a history of (where indicated), systemic condition including uncontrolled diabetes mellitus as defined by hemoglobin A1c >10%, uncontrolled blood pressure, history of vascular disease such as cerebrovascular accident, myocardial infarction, transient ischemic attack, or thromboembolic reaction including pulmonary embolism within 180 days prior to the first study drug administration, New York Heart Association Functional Classification Class III or IV heart failure, or severe uncontrolled cardiac disease (i.e., unstable angina), current treatment for serious systemic infection, history of recurrent significant infections, renal failure requiring dialysis or renal transplant, history of malignancies within 5 years prior to the first study drug administration, except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma *in situ*, history of other disease, metabolic dysfunction that contraindicates the use of the study drug or that might affect interpretation of the study results or render the patient at high risk for treatment complications, significant uncontrolled concomitant diseases including cardiovascular system, nervous system, pulmonary, renal, hepatic, endocrine, gastrointestinal disorders, or psychiatric condition.

Reason for exclusion: A history of systemic disease or infections may act as potentially confounding factors and may complicate the interpretation of safety endpoints. Moreover, patients with history of past or concurrent malignancy are prone to frequent hospitalisation, hence higher dropout rates.

Is it considered to be included as missing information?: No

Rationale: Aflibercept has not been studied in patients with active systemic infections, in diabetic patients with an HbA1c over 12% or diabetic patients with uncontrolled hypertension. Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. There are limited data on safety in the treatment of patients with Central RVO (CRVO), Branch RVO (BRVO), DME or myopic CNV with a history of stroke or transient ischaemic attacks or myocardial infarction within the last 6 months. This has adequately been described in the SmPC (Section 4.4 'Special warnings and precautions for use').

Patient who has one or more previous/concomitant treatments of the following: previous systemic or ocular treatment with aflibercept including potential biosimilars, previous treatment with ocular anti-angiogenic agents (e.g., pegaptanib sodium, bevacizumab, ranibizumab) in the study eye, administration of systemic anti-angiogenic agents and/or ocular anti-angiogenic agents in fellow (non-study) eye within 180 days prior to the first study

drug administration, previous use of intraocular or periocular corticosteroids including dexamethasone implant (e.g., Ozurdex) within 180 days, or fluocinolone acetonide implant (e.g., Iluvien) within 36 months prior to the first study drug administration in the study eye, laser photocoagulation (panretinal or macular) in the study eye within 90 days prior to the first study drug administration, more than two previous macular laser treatments, and/or focal laser scars in the fovea that could limit BCVA improvement in the study eye, history of vitreoretinal surgery including scleral bucking in the study eye, any intraocular surgery including cataract surgery in the study eye within 90 days prior to the first study drug administration or planned or expected during the study, Yttrium-aluminum-garnet capsulotomy in the study eye within 30 days prior to the first study drug administration, treatment with any investigational medicinal product and/or device within 30 days or 5 half-lives, whichever is longer, prior to the first study drug administration

Reason for exclusion: The exclusion criteria for prior or concomitant treatment and prior surgery are based on technical requirements for the reduction of confounding factor impact on efficacy measurements.

Is it considered to be included as missing information?: No

Rationale: No interaction studies have been performed for aflibercept. This has adequately been described in the SmPC (Section 4.5 'Interaction with other medicinal products and other forms of interaction').

Patient with a hypersensitivity to immunoglobulin products, or patient who has allergies to any of the excipients or components of study drug, any other human proteins, or diagnostic process (e.g., anaesthetics, topical broad-spectrum microbicides, fluorescein).

Reason for exclusion: Patients with significant hypersensitivity to any component of the medicinal products were excluded from the clinical development programme for safety reasons. Patients with a known hypersensitivity would be at a higher risk of subsequent serious systemic hypersensitivity reactions with re-exposure.

Is it considered to be included as missing information?: No

Rationale: Aflibercept is contraindicated in patients with hypersensitivity to the active substance aflibercept or to any of the excipients.

Hypersensitivity to aflibercept (or any component of the excipients) is a known risk of aflibercept and has adequately been described in the SmPC (Section 4.3 'Contraindication' and Section 4.4 'Special warnings and precautions for use').

Female patient who is currently pregnant or breastfeeding.

Reason for exclusion: Female patients who are pregnant or breastfeeding were excluded from the clinical development programme for safety reasons, to minimise risk to pregnant women and nursing mothers and their children.

Is it considered to be included as missing information?: No

Rationale: The safety of aflibercept is not known in these populations, and there is risk of possible embryo-foetal toxicity based on non-clinical studies. Embryo-foetotoxicity is an important potential risk of aflibercept.

This safety concern has been adequately described in the SmPC (Section 4.4 'Special warnings and precautions for use' and Section 4.6 'Fertility, pregnancy and lactation') which states that aflibercept should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus and women of childbearing potential should use effective contraception during treatment and for at least 3 months after the last IVT injection of aflibercept.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

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

Eydenzelt has been studied in DME. 190 patients with DME (in Study CT-P42 3.1) have been treated with CT-P42 in the clinical development programme. The median treatment duration for patients with DME treated with CT-P42 was 337 days, and the longest duration of exposure is 421 days. The median treatment duration for patients with DME treated with Eylea was 337 days and the longest duration of exposure is 406 days.

In addition to DME, the reference product Eylea is approved for the treatment of Neovascular (wet) AMD, Visual impairment due to macular oedema secondary to RVO (BRVO or CRVO), Visual impairment due to myopic CNV in adults and Retinopathy of prematurity in preterm infants.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 7: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Paediatric patients	The safety and efficacy of CT-P42 have not been established in children and adolescents. There is no relevant use of aflibercept in the paediatric population for the indications of wet AMD, CRVO, BRVO, DME and myopic CNV.
Elderly patients	The safety and efficacy of aflibercept in elderly patients was studied in the clinical trial CT-P42 3.1. A total of 84 patients ≥ 65 years of age were exposed to CT-P42 in Study CT-P42 3.1 (Table 5). There is no evidence that elderly patients need special considerations while using aflibercept.
Pregnant or Breastfeeding women	Not included in the clinical development programme of CT-P42. There were no confirmed cases of pregnancy reported in the Study CT-P42 3.1 in women treated with aflibercept.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Patients with hepatic impairment were not studied in the clinical development programme of CT-P42.
Patients with renal impairment	Patients with renal impairment were not studied in the clinical development programme of CT-P42.
Patients with cardiovascular impairment	Patients with cardiovascular impairment were not studied in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	Not studied in the clinical development programme of CT-P42.
Population with relevant different race	Patients exposed to either CT-P42 or Aflibercept reference product in Study CT-P42 3.1 were White (64.4%) or Asian (35.6%) (Table 6). There is no evidence to suggest that race may impact either safety or efficacy for aflibercept.
Subpopulations carrying relevant genetic polymorphisms	There are no known relevant genetic polymorphisms.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable as the product has not received marketing authorisation yet in any jurisdiction.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

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

Potential for misuse for illegal purposes

Based on the mechanism of action of Eydenzelt and its indications, the potential for misuse or abuse for illegal purposes is negligible.

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:

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

   None.

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

   None.

3. **Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation 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 authorised):**

   Eydenzelt has been shown to have quality, safety and efficacy comparable to the reference product Eylea. The safety profile of Eydenzelt is similar to that of the reference product and has been adequately described in the product information.

   The following risks are labelled in the product information for the reference product and are not important safety concerns for either Eylea or Eydenzelt:

   Visual acuity reduced, Retinal haemorrhage, Conjunctival haemorrhage, Eye pain, Detachment of the retinal pigment epithelium, Retinal degeneration, Vitreous haemorrhage, Cataract, Cataract cortical, Cataract nuclear, Cataract subcapsular, Corneal erosion, Corneal abrasion, Retinal detachment, Retinal tear, Iritis, Uveitis, Iridocyclitis, Lenticular opacities, Corneal epithelium defect, Injection site irritation, Abnormal sensation in eye, Blindness, Vitritis, Hypopyon, Vision blurred, Vitreous floaters, Vitreous detachment, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid oedema, Injection site haemorrhage, Punctate keratitis, Conjunctival hyperaemia, Ocular hyperaemia, Eyelid irritation, Anterior chamber flare, and Corneal oedema.

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

   None.

5. **Other reasons for considering the risks not important:**

   None.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

In the RMP of the reference product Eylea, there are two additional missing information items, which has not been presented in this Eydenzelt RMP, namely, long-term safety of aflibercept in preterm infants with retinopathy of prematurity (ROP) and exposure with bilateral 8 mg dose aflibercept therapy.

Eydenzelt is not intended to be used for the treatment of ROP and is not indicated for this condition. The recommended dosage for Eydenzelt is 2 mg whilst it is 0.4 mg, 2 mg, and 8 mg for Eylea. The formulation of Eydenzelt is not suitable for use in infants with ROP. Off-label use has been included as a potential risk for Eydenzelt.

Important identified risk: Endophthalmitis (likely infectious origin)

Risk-benefit impact:

Endophthalmitis is inflammation of inner layers of the eye, resulting from infection with microorganisms. Endophthalmitis may occur during treatment with aflibercept. The infection may occur either through direct introduction of microorganisms into the eye (exogenous infection) or through spreading of microorganisms from other areas of the body (endogenous infection). In cases of inflammation where no pathogens can be identified (no/negative culture growth of microorganisms observed), the condition may be characterised as “sterile endophthalmitis” or “non-infectious endophthalmitis”. Because of the risk of severe vision loss, treatment should be initiated as soon as possible, and, depending on cause and severity, may consist of topical and IVT application of antibiotics, corticosteroids, and surgical removal of matter and infected structures (drainage, vitrectomy). The risk of endophthalmitis (and other intraocular infections) cannot be completely excluded but minimised through strict aseptic and sterile conditions when administering Eydenzelt.

The proportion of patients exposed to the reference product Eylea, who experienced endophthalmitis in the study eye in clinical studies with Eylea, was low (range from 0% to 0.9% in the VIEW 1 extension study). No events related to endophthalmitis were reported in the clinical development programme of Eydenzelt. Although the incidence is low, endophthalmitis is a serious complication of IVT injection as it may lead to severe vision loss and requires immediate medical treatment.

The risk of endophthalmitis can be minimised by use of proper aseptic technique during the IVT injection procedure. Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. The patients should report any symptoms of endophthalmitis (e.g., eye pain, redness of the eye, photophobia, blurring of vision) to their doctors in order to enable the treating physician to introduce appropriate countermeasures in due time.

According to the SmPC of the reference product Eylea and Eydenzelt, endophthalmitis is a treatment-emergent Adverse Drug Reaction (ADR) with ‘uncommon’ frequency. The benefits of an effective treatment with Eydenzelt outweigh the risk of endophthalmitis, which can be managed by observing strict aseptic technique during administration of Eydenzelt.

Important identified risk: Intraocular inflammation

Risk-benefit impact:

Intraocular inflammation (other than endophthalmitis) refers to inflammation of defined structures of the inner eye (e.g., iritis, uveitis, iridocyclitis). Besides endophthalmitis/intraocular inflammation with an infectious origin, there are other types of inflammation where no pathogens can be identified (either no culture performed or negative culture growth); the condition may be characterised as "sterile" inflammatory condition. The cause of a sterile inflammation, independently of the administered drug, remains uncertain, and may be of multifactorial origin. Intraocular inflammation generally constitutes a serious condition, which may lead to generalised eye inflammation and risk of blindness.

The proportion of patients exposed to the reference product Eylea, who experienced intraocular inflammation (grouped term) in the study eye in the clinical studies with Eylea, ranged from 0% to 2.6% (VIEW 1 & 2 AMD studies). Intraocular inflammation (e.g., iritis, uveitis) is an uncommon adverse event related to IVT injections which may cause vision loss if not treated immediately. Although most intraocular inflammation is of infection origin, in some cases no pathogens can be identified. Such cases of intraocular inflammation are categorised as acute onset sterile intraocular inflammation.

According to the SmPC of Eydenzelt, the frequency of inflammatory conditions iritis, uveitis, iridocyclitis are 'uncommon' and vitritis and hypopyon is 'rare'. The risk of intraocular inflammation can be minimised by use of proper aseptic technique during the IVT injection procedure. Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. The use of Eydenzelt is contraindicated in patient with active severe intraocular inflammation. The patients should report any symptoms of intraocular inflammation (e.g., pain, photophobia, or redness) to their doctors in order to enable the treating physician to start treatment in due time. The benefits of an effective treatment with Eydenzelt outweigh the risk of intraocular inflammation following the IVT injection, which can be managed by observing strict aseptic, atraumatic technique during administration of Eydenzelt.

Important identified risk: Transient intraocular pressure increase

Risk-benefit impact:

Chronically elevated intraocular pressure is a major risk factor for glaucoma, which can lead to loss of nerve fibres in the optic nerve with the subsequent risk of blindness. Many different factors may be responsible for the development of glaucoma, and increased intraocular pressure is not a mandatory prerequisite for the development of glaucoma (e.g., normal-tension glaucoma).

The proportion of patients exposed to the reference product Eylea, who experienced an increase in intraocular pressure (grouped term) in the study eye in the clinical studies with Eylea ranged from 2.8% (VIVID-JAPAN DME study) to 13.6% (CRVO studies GALILEO & COPERNICUS), but the vast majority of these events resolved without treatment.

Systematic measurements of intraocular pressure during the course of the clinical studies did not indicate a trend towards sustained intraocular pressure increase. "Intraocular pressure increased" is a common ADR. Transient intraocular pressure increase is an important identified risk of the reference product Eylea, based on the incidence of elevated intraocular pressure from clinical studies as well as post-marketing data. Transient increase in the intraocular pressure is a recognised adverse event of IVT injection. The added volume of the injection fluid causes a transient elevation in pressure and usually subsides when the injection fluid is resorbed. According to the SmPC of the reference product Eylea and Eydenzelt, Transient intraocular pressure increase is a common

ADR of aflibercept. Patients should be monitored for elevation in intraocular pressure, immediately after the IVT injection.

This safety concern does not have an impact on the benefit-risk balance of Eydenzelt as the elevation in intraocular pressure is not sustained. The benefits of an effective treatment with Eydenzelt outweigh the apparent risk of transient intraocular pressure increase, which usually resolves without treatment or long-term complications.

Important identified risk: Retinal pigment epithelial tears

Risk-benefit impact:

The retinal pigment epithelium is the external layer of the retina, and a tear in this layer of the retina is known as Retinal pigment epithelial (RPE) tears. These tears may be self-healing, or may require laser coagulation. RPE tears may be caused by AMD, or trauma during IVT injection, or the cause may be unknown. No events related to RPE tear was reported in the clinical development programme of Eydenzelt.

In the clinical development program of the reference product Eylea, up to 1.9% of patients with underlying wet AMD who were treated with Eylea developed RPE tear, while none of the patients treated for other Eylea indications (CRVO, BRVO, myopic CNV, DME) had developed RPE tear. The total incidence of RPE tears with Eylea in the AMD Phase III trials was in line with the known background incidences from literature; and the absence of RPE tear in the clinical studies investigating the non-AMD indications of Eylea suggests that RPE tear development caused by IVT treatment with Eylea is rather unlikely.

As per the SmPC of the reference product Eylea and Eydenzelt, RPE tear is a commonly reported adverse event.

The benefits of an effective treatment with Eydenzelt outweigh the apparent risk of RPE tears, for which effective risk management strategies are available.

Important identified risk: Cataract (especially of traumatic origin)

Risk-benefit impact:

Cataract is a gradually progressive opacification of the clear eye lens, which may be caused by various factors including age, congenital cataract, systemic disease, endocrine disease, alcohol use, smoking, poor nutrition, sun exposure or traumatic injury. The proportion of patients exposed to the reference product Eylea, who experienced traumatic cataract in the study eye in the clinical studies with Eylea, ranged from 0% to 2.8% (VIVID-DME & VISTA-DME).

According to the SmPC of the reference product Eylea and Eydenzelt, various forms of cataract (cortical, nuclear, subcapsular) are common ADRs. Another form of cataract, traumatic cataract, is a rare adverse event and it may be prevented by following correct procedure of IVT injection. Traumatic cataract is an important identified risk.

The benefits of an effective treatment with Eydenzelt outweigh the apparent risk of cataract (especially of traumatic origin), which can be managed by observing strict atraumatic technique during administration of Eydenzelt.

Important potential risk: Medication errors

Risk-benefit impact:

The medication error providing the greatest source of potential safety concern is overdose. Eydenzelt PFS and vial contain an excess volume which exceeds the recommended net dose of 2 mg aflibercept per injection. Thus, injecting the entire volume of the PFS or vial would result in overdose. However, Eydenzelt will be administered only by qualified physicians, thus reducing the risk of inappropriate dosing and administration. In the clinical development programme of the reference product Eylea, no events of overdose were reported. This safety concern does not have an impact on the benefit-risk balance of Eydenzelt. The PFS presentation limits the risk of potential overdose due to the volume deliverable from the syringe. 'Medication errors' is considered as a potential risk, which is, however, completely avoidable by proper adherence to the dosing recommendations.

The benefits of an effective treatment with Eydenzelt outweigh the apparent risk of 'Medication errors' for which effective risk management strategies are available.

Important potential risk: Off-label use and misuse

Risk-benefit impact:

Off-label use is the therapeutic use of a medicinal product for indications other than the approved indications, or use in any indication in a fashion that is not recommended in the product information. As with other drugs, Eydenzelt might be intentionally used off-label.

Intentional off-label use in the context of multiple use of single use product (vial splitting) has been observed with the reference product Eylea, when the Eylea vial is approved for single eye use only. Additionally, Eydenzelt is not indicated for paediatric use unlike the reference product Eylea, which has the risk of off-label use in paediatric indication.

Since the clinical experience with Eydenzelt in such off-label use is limited (in particular in terms of efficacy and safety), any case of off-label use may be considered a potential risk.

There is no evidence to suggest that off-label use of aflibercept may be associated with safety concerns that are not also associated with IVT injection, when administered in full compliance with the recommendations in the product information.

The benefits of an effective treatment with Eydenzelt outweigh the risk of off-label use and misuse.

Important potential risk: Embryo-foetotoxicity

Risk-benefit impact:

Eydenzelt may cause embryo-foetal toxicity due to its mechanism of action of inhibiting angiogenesis. In non-clinical studies conducted for the reference product Eylea where extremely high doses were given to female rabbits, dose-related increases were seen in foetal resorptions, pregnancy disruptions and numerous foetal (external, visceral and skeletal) malformations. The use of Eydenzelt is not recommended in pregnant women unless the potential benefit outweighs the potential risk to the foetus.

This safety concern does not have an impact on the benefit-risk balance of Eydenzelt based on the currently available data. The benefits of an effective treatment with Eydenzelt outweigh the apparent risk of embryo-foetotoxicity for which effective risk management strategies are available.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable as this is an initial RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

Since Eydenzelt is a biosimilar, all risks except the missing information, long-term safety of aflibercept in preterm infants with retinopathy of prematurity (ROP) and exposure with bilateral 8mg dose aflibercept therapy, have been included based on the safety profile of the reference medicinal product Eylea, for all indications: Wet AMD, Macular oedema secondary to RVO, DME and Myopic CNV.

SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risk: Endophthalmitis (likely infectious origin) (Medical Dictionary for Regulatory Activities [MedDRA] Preferred Term [PT] Endophthalmitis)

Potential mechanisms:

Improper aseptic technique during the IVT injection procedure can introduce pathogens into the eye. The source of pathogens is in most cases the patient's conjunctival bacterial flora.

Evidence source(s) and strength of evidence:

Endophthalmitis is a condition in which the inside of the eye becomes inflamed due to the presence of harmful bacteria or other germs. This can happen when these germs get inside the eye from the outside (exogenous) or from other parts of the body (endogenous). Endophthalmitis is the most serious avoidable complication of anti-VEGF agent IVT injections. Although the incidence is low, endophthalmitis is considered serious complication as it may lead to severe vision loss and requires immediate medical treatment (Simakurthy et al., 2022). Post IVT injection, endophthalmitis is most commonly caused by a type of bacteria called coagulase-negative staphylococci, followed by streptococci (McCannel, 2011). The incidence of endophthalmitis in the clinical development programme of the reference product Eylea was very low. No events related to endophthalmitis were reported in the clinical development programme of Eydenzelt. According to the literature reports the incidence of endophthalmitis ranges from 0.01% to 0.26% after IVT injection of anti-VEGF agents (Menchini et al., 2018).

Characterisation of the risk:

There were no TEAEs reported for endophthalmitis (likely infectious origin) in the CT-P42 group (190 patients) and the reference product group (174 patients) in Study CT-P42 3.1.

Risk factors and risk groups:

Improper aseptic technique while administering aflibercept into the eye increases the risk of endophthalmitis.

Preventability:

The risk of intraocular inflammation, especially if caused by microorganisms may be minimised. The administration of aflibercept must be done under strictly sterile conditions to avoid introduction of pathogens into the inner eye. Moreover, the single use PFS or vial is not used to

extract multiple doses, which prevents contamination. Aflibercept must only be administered by a qualified physician experienced in administering IVT injections.

Impact on the risk-benefit balance of the product:

This important identified risk does not have an impact on the positive risk-benefit balance of the reference product Eylea. Hence, the benefit-risk balance is favourable for aflibercept for the treatment of wet AMD, Macular oedema secondary to RVO, DME and Myopic CNV.

Public health impact:

Severe intraocular infection/inflammation such as endophthalmitis can cause permanent loss of vision, if it is not rapidly diagnosed and appropriately treated. This condition is likely to impact the ability to work and to increase the dependency on caregivers. The incidence of infective endophthalmitis is low when IVT injection is conducted aseptically. The impact on public health is, therefore, likely to be correspondingly low.

Important identified risk: Intraocular inflammation (MedDRA PT Non-infectious Endophthalmitis)

Potential mechanisms:

The aetiology of sterile intraocular inflammations, independently of the administered drug, remains uncertain, and a multifactorial origin has been proposed. Needle trauma *per se* might cause an inflammatory reaction. Additionally, inflammation secondary both to IVT triamcinolone acetonide and to IVT bevacizumab (or other anti-VEGF agents) that manifest with acute and painless vision loss is usually interpreted as being primarily toxic and sterile. In these patients, visual acuity improves progressively as the intraocular inflammation reduces without specific treatment. However, since there remains a substantial uncertainty on the cause, the complication is often treated, in addition to corticosteroids and non-steroidal anti-inflammatory drug, like an acute (infective) endophthalmitis with antibiotics because of the poor visual prognosis of this intraocular infection in the absence of antibiotic therapy.

Evidence source(s) and strength of evidence:

Intraocular inflammation is inflammation inside the eye associated with IVT injections of anti-VEGF agents including aflibercept, and when no germs or pathogen can be identified, it is termed ‘sterile’ intraocular inflammation. Post-injection, sterile intraocular inflammation is a known risk, following injections into the eye, of anti-VEGFs and for other IVT applied drugs. The onset of the inflammation is typically within the first 5 days of IVT injection.

The proportion of patients who experienced intraocular inflammation in the study eye in the clinical studies with Eylea ranged from 0% to 2.6% (VIEW 1 & 2 AMD studies).

Characterisation of the risk:

Frequency with 95 % CI for 100 PY:

TEAEs in both study and fellow eyes

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	2	2	0	2
N of Patients with TEAEs [1]	2 (1.1%)	2 (1.1%)	0	2 (1.1%)
Incidence of TEAEs per 100 PY	1.299	1.299	0.000	1.316
95% CI for Incidence of TEAEs per 100 PY	(0.157, 4.691)	(0.157, 4.692)	(0.000, 8421.020)	(0.159, 4.752)

Source: Study CT-P42 3.1
From the MedDRA dictionary, version 25.1.
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; PY = Patient Year; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
***TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
Patient Year is calculated as follows:

CT-P42 total: Duration from 'CT-P42 only' and 'CT-P42 after administration of aflibercept reference product'
CT-P42 only: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25
CT-P42 after administration of aflibercept reference product: (Date of Last Exposure to CT-P42 Treatment - Date of First Exposure to CT-P42 Treatment +1) / 365.25
Aflibercept reference product: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25 or (Date of First Exposure to CT-P42 Treatment - Date of First Exposure to Treatment) / 365.25

TEAEs in study eye

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	1	1	0	1
N of Patients with TEAEs [1]	1 (0.5%)	1 (0.6%)	0	1 (0.6%)
Incidence of TEAEs per 100 PY	0.649	0.649	0.000	0.658

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
95% CI for Incidence of TEAEs per 100 PY	(0.016, 3.618)	(0.016, 3.619)	(0.000, 8421.020)	(0.017, 3.665)

Source: Study CT-P42 3.1
From the MedDRA dictionary, version 25.1.
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; PY = Patient Year; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
***TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
Patient Year is calculated as follows:

CT-P42 total: Duration from 'CT-P42 only' and 'CT-P42 after administration of aflibercept reference product'
CT-P42 only: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25
CT-P42 after administration of aflibercept reference product: (Date of Last Exposure to CT-P42 Treatment - Date of First Exposure to CT-P42 Treatment +1) / 365.25
Aflibercept reference product: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25 or (Date of First Exposure to CT-P42 Treatment - Date of First Exposure to Treatment) / 365.25

TEAEs in fellow eye

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	1	1	0	2
N of Patients with TEAEs [1]	1 (0.5%)	1 (0.6%)	0	2 (1.1%)
Incidence of TEAEs per 100 PY	0.649	0.649	0.000	1.316

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
95% CI for Incidence of TEAEs per 100 PY	(0.016, 3.618)	(0.016, 3.619)	(0.000, 8421.020)	(0.159, 4.752)

Source: Study CT-P42 3.1
From the MedDRA dictionary, version 25.1.
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; PY = Patient Year; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
***TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
Patient Year is calculated as follows:

CT-P42 total: Duration from 'CT-P42 only' and 'CT-P42 after administration of aflibercept reference product'
CT-P42 only: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25
CT-P42 after administration of aflibercept reference product: (Date of Last Exposure to CT-P42 Treatment - Date of First Exposure to CT-P42 Treatment +1) / 365.25
Aflibercept reference product: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25 or (Date of First Exposure to CT-P42 Treatment - Date of First Exposure to Treatment) / 365.25

Frequency with Severity, Seriousness and Outcome:

TEAEs in both study and fellow eyes

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	2	2	0	2
N of Patients with TEAEs [1]	2 (1.1%)	2 (1.1%)	0	2 (1.1%)
95% CI for proportion of patients with TEAEs	(0.13, 3.75)	(0.14, 4.09)	(0.00, 20.59)	(0.14, 4.09)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	0	0	0	1 (0.6%)
Grade 2	2 (1.1%)	2 (1.1%)	0	1 (0.6%)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [3]				

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Serious	0	0	0	0
Non-serious	2 (1.1%)	2 (1.1%)	0	2 (1.1%)
Outcomes [4]				
Missing	0	0	0	0
Recovered	2 (1.1%)	2 (1.1%)	0	2 (1.1%)
Recovering	0	0	0	0
Did not recover	0	0	0	0
Fatal	0	0	0	0

Source: Study CT-P42 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
*** TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
NOTE: For each AE, location is collected by either Oculus Dexter (right eye), Oculus Sinister (left eye), or Oculus Uterque (both eyes). The total number of TEAEs does not represent the sum of TEAEs in each category (study eye and fellow eye).
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted:
Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted:
Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted:
Outcomes: Fatal > Did not recover > Recovering > Recovered > Missing
From the MedDRA dictionary, version 25.1.

TEAEs in study eye

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	1	1	0	1
N of Patients with TEAEs [1]	1 (0.5%)	1 (0.6%)	0	1 (0.6%)
95% CI for proportion of patients with TEAEs	(0.01, 2.90)	(0.01, 3.16)	(0.00, 20.59)	(0.01, 3.16)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	0	0	0	0

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Grade 2	1 (0.5%)	1 (0.6%)	0	1 (0.6%)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [3]				
Serious	0	0	0	0
Non-serious	1 (0.5%)	1 (0.6%)	0	1 (0.6%)
Outcomes [4]				
Missing	0	0	0	0
Recovered	1 (0.5%)	1 (0.6%)	0	1 (0.6%)
Recovering	0	0	0	0
Did not recover	0	0	0	0
Fatal	0	0	0	0

Source: Study CT-P42 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
*** TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
NOTE: For each AE, location is collected by either Oculus Dexter (right eye), Oculus Sinister (left eye), or Oculus Uterque (both eyes). The total number of TEAEs does not represent the sum of TEAEs in each category (study eye and fellow eye).
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted:
Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted:
Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted:
Outcomes: Fatal > Did not recover > Recovering > Recovered > Missing
From the MedDRA dictionary, version 25.1.

TEAEs in fellow eye

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	1	1	0	2

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			**Aflibercept reference product** (N=174)**
	Total (N=190)	**CT-P42 only (N=174)**	**CT-P42 after administration of aflibercept reference product* (N=16)**	
N of Patients with TEAEs [1]	1 (0.5%)	1 (0.6%)	0	2 (1.1%)
95% CI for proportion of patients with TEAEs	(0.01, 2.90)	(0.01, 3.16)	(0.00, 20.59)	(0.14, 4.09)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	0	0	0	1 (0.6%)
Grade 2	1 (0.5%)	1 (0.6%)	0	1 (0.6%)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [3]				
Serious	0	0	0	0
Non-serious	1 (0.5%)	1 (0.6%)	0	2 (1.1%)
Outcomes [4]				
Missing	0	0	0	0
Recovered	1 (0.5%)	1 (0.6%)	0	2 (1.1%)
Recovering	0	0	0	0
Did not recover	0	0	0	0
Fatal	0	0	0	0

Source: Study CT-P42 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
*** TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
NOTE: For each AE, location is collected by either Oculus Dexter (right eye), Oculus Sinister (left eye), or Oculus Uterque (both eyes). The total number of TEAEs does not represent the sum of TEAEs in each category (study eye and fellow eye).
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted:
Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted:
Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted:
Outcomes: Fatal > Did not recover > Recovering > Recovered > Missing
From the MedDRA dictionary, version 25.1.

Overall, there were four non-serious (4) TEAEs related to intraocular inflammation; two (2) each in the CT-P42 group and the reference product group. The incidence of TEAEs per 100 PY in the

CT-P42 group was 1.299 (95% CI: 0.157, 4.691) and in the reference product group was 1.316 (95% CI: 0.159, 4.752).

Of the two (2) TEAEs in the CT-P42 group, one (1) was in the study eye and one (1) was in the fellow eye.

Of the four (4) patients who experienced TEAEs related to intraocular inflammation, two (2 [1.1%], 95% CI: 0.13, 3.75) patients in the CT-P42 group experienced two Grade 2 events and 2 (2 [1.1%], 95% CI: 0.14, 4.09) patients in the reference product group experienced one Grade 1 and one Grade 2 event. All four TEAEs related to intraocular inflammation were reported as "recovered" at the end of trial period.

Risk factors and risk groups:

Improper technique while administering aflibercept increases the risk of intraocular inflammation.

Preventability:

The risk of intraocular inflammation may be minimised. The administration of aflibercept must be done using meticulous technique under strict aseptic and sterile conditions. Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections.

Impact on the risk-benefit balance of the product: This important identified risk does not have an impact on the positive risk-benefit balance of aflibercept based on its low incidence.

Public health impact:

Severe intraocular inflammation can cause permanent loss of vision, if it is not diagnosed at an early stage and appropriately treated. Vision loss as such constitutes a substantial burden for the involved subject. The incidence of intraocular inflammation is low when IVT injection is conducted competently. The impact on public health is, therefore, likely to be correspondingly low.

Important identified risk: Transient intraocular pressure increase (MedDRA PT Intraocular pressure increased)

Potential mechanisms:

Transient elevation in intraocular pressure is attributed to an increase in vitreous volume (volume effect) after an IVT injection. Another proposed mechanism is decrease in nitric oxide levels via inhibition of nitric oxide synthase, resulting in downstream movement of potassium and calcium in trabecular meshwork cells, alteration of trabecular meshwork cell contractility, and ultimately decreased aqueous outflow through intercellular spaces resulting in increased outflow resistance in the eye (Levin et al., 2021).

Evidence source(s) and strength of evidence:

Intraocular pressure is the pressure exerted by the fluid inside the eye. Increased intraocular pressure is a risk factor in the development of glaucoma. Transient intraocular pressure increase is a recognised adverse event of IVT anti-VEGF injections. Glaucoma is characterised by a loss of nerve fibres in the eye with the subsequent risk of blindness. However, many different factors may be responsible for the development of glaucoma. When medicine is injected into the eye, it can cause a temporary increase in pressure inside the eye until the extra fluid is absorbed. This is because the medicine is dissolved in a certain amount of liquid, and the injection can cause a temporary increase in the amount of fluid in the eye.

In the clinical development programme of the reference product Eylea, the proportion of patients who experienced an increase in intraocular pressure in the study eye ranged from 2.8% (VIVID-JAPAN DME study) to 13.6% (CRVO studies GALILEO & COPERNICUS).

Characterisation of the risk:

Frequency with 95 % CI for 100 PY:

TEAEs in both study and fellow eyes

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			**Aflibercept reference product** (N=174)**
	Total (N=190)	**CT-P42 only (N=174)**	**CT-P42 after administration of aflibercept reference product* (N=16)**	
Total N of TEAEs	5	5	0	11
N of Patients with TEAEs [1]	3 (1.6%)	3 (1.7%)	0	6 (3.4%)
Incidence of TEAEs per 100 PY	3.247	3.247	0.000	7.236
95% CI for Incidence of TEAEs per 100 PY	(1.054, 7.576)	(1.054, 7.579)	(0.000, 8421.020)	(3.612, 12.947)

Source: Study CT-P42 3.1
From the MedDRA dictionary, version 25.1.
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; PY = Patient Year; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
***TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
Patient Year is calculated as follows:

CT-P42 total: Duration from 'CT-P42 only' and 'CT-P42 after administration of aflibercept reference product'
CT-P42 only: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25
CT-P42 after administration of aflibercept reference product: (Date of Last Exposure to CT-P42 Treatment - Date of First Exposure to CT-P42 Treatment +1) / 365.25
Aflibercept reference product: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25 or (Date of First Exposure to CT-P42 Treatment - Date of First Exposure to Treatment) / 365.25

TEAEs in study eye

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	5	5	0	10
N of Patients with TEAEs [1]	3 (1.6%)	3 (1.7%)	0	6 (3.4%)
Incidence of TEAEs per 100 PY	3.247	3.247	0.000	6.578
95% CI for Incidence of TEAEs per 100 PY	(1.054, 7.576)	(1.054, 7.579)	(0.000, 8421.020)	(3.154, 12.097)

Source: Study CT-P42 3.1
From the MedDRA dictionary, version 25.1.
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; PY = Patient Year; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
***TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
Patient Year is calculated as follows:

CT-P42 total: Duration from 'CT-P42 only' and 'CT-P42 after administration of aflibercept reference product'
CT-P42 only: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25
CT-P42 after administration of aflibercept reference product: (Date of Last Exposure to CT-P42 Treatment - Date of First Exposure to CT-P42 Treatment +1) / 365.25
Aflibercept reference product: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25 or (Date of First Exposure to CT-P42 Treatment - Date of First Exposure to Treatment) / 365.25

TEAEs in fellow eye

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	0	0	0	1
N of Patients with TEAEs [1]	0	0	0	1 (0.6%)
Incidence of TEAEs per 100 PY	0.000	0.000	0.000	0.658

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
95% CI for Incidence of TEAEs per 100 PY	(0.000, 2.395)	(0.000, 2.396)	(0.000, 8421.020)	(0.017, 3.665)

Source: Study CT-P42 3.1
From the MedDRA dictionary, version 25.1.
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; PY = Patient Year; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
***TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
Patient Year is calculated as follows:
CT-P42 total: Duration from 'CT-P42 only' and 'CT-P42 after administration of aflibercept reference product'
CT-P42 only: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25
CT-P42 after administration of aflibercept reference product: (Date of Last Exposure to CT-P42 Treatment - Date of First Exposure to CT-P42 Treatment +1) / 365.25
Aflibercept reference product: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25 or (Date of First Exposure to CT-P42 Treatment - Date of First Exposure to Treatment) / 365.25

Frequency with Severity, Seriousness and Outcome:

TEAEs in both study and fellow eyes

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	5	5	0	11
N of Patients with TEAEs [1]	3 (1.6%)	3 (1.7%)	0	6 (3.4%)
95% CI for proportion of patients with TEAEs	(0.33, 4.54)	(0.36, 4.96)	(0.00, 20.59)	(1.28, 7.35)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	2 (1.1%)	2 (1.1%)	0	3 (1.7%)
Grade 2	0	0	0	3 (1.7%)
Grade 3	1 (0.5%)	1 (0.6%)	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			**Aflibercept reference product** ** **(N=174)**
	Total (N=190)	**CT-P42 only (N=174)**	**CT-P42 after administration of aflibercept reference product*** **(N=16)**	
Seriousness [3]				
Serious	0	0	0	0
Non-serious	3 (1.6%)	3 (1.7%)	0	6 (3.4%)
Outcomes [4]				
Missing	0	0	0	0
Recovered	2 (1.1%)	2 (1.1%)	0	6 (3.4%)
Recovering	1 (0.5%)	1 (0.6%)	0	0
Did not recover	0	0	0	0
Fatal	0	0	0	0

Source: Study CT-P42 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
*** TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
NOTE: For each AE, location is collected by either Oculus Dexter (right eye), Oculus Sinister (left eye), or Oculus Uterque (both eyes). The total number of TEAEs does not represent the sum of TEAEs in each category (study eye and fellow eye).
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted:
Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted:
Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted:
Outcomes: Fatal > Did not recover > Recovering > Recovered > Missing
From the MedDRA dictionary, version 25.1.

TEAEs in study eye

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	5	5	0	10
N of Patients with TEAEs [1]	3 (1.6%)	3 (1.7%)	0	6 (3.4%)
95% CI for proportion of patients with TEAEs	(0.33, 4.54)	(0.36, 4.96)	(0.00, 20.59)	(1.28, 7.35)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	2 (1.1%)	2 (1.1%)	0	4 (2.3%)
Grade 2	0	0	0	2 (1.1%)
Grade 3	1 (0.5%)	1 (0.6%)	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [3]				
Serious	0	0	0	0
Non-serious	3 (1.6%)	3 (1.7%)	0	6 (3.4%)
Outcomes [4]				
Missing	0	0	0	0
Recovered	2 (1.1%)	2 (1.1%)	0	6 (3.4%)
Recovering	1 (0.5%)	1 (0.6%)	0	0
Did not recover	0	0	0	0
Fatal	0	0	0	0

Source: Study CT-P42 3.1

Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; TEAE = Treatment Emergent Adverse Event.

**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*

*** TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*

NOTE: For each AE, location is collected by either Oculus Dexter (right eye), Oculus Sinister (left eye), or Oculus Uterque (both eyes). The total number of TEAEs does not represent the sum of TEAEs in each category (study eye and fellow eye).

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.

[2] Only the most severe event is counted:

Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing

[3] Only the most serious event is counted:

Seriousness: Serious > Non-serious

[4] Only the most severe outcome is counted:

Outcomes: Fatal > Did not recover > Recovering > Recovered > Missing

From the MedDRA dictionary, version 25.1.

TEAEs in fellow eye

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	0	0	0	1
N of Patients with TEAEs [1]	0	0	0	1 (0.6%)
95% CI for proportion of patients with TEAEs	(0.00, 1.92)	(0.00, 2.10)	(0.00, 20.59)	(0.01, 3.16)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	0	0	0	0
Grade 2	0	0	0	1 (0.6%)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [3]				
Serious	0	0	0	0
Non-serious	0	0	0	1 (0.6%)
Outcomes [4]				
Missing	0	0	0	0
Recovered	0	0	0	1 (0.6%)
Recovering	0	0	0	0
Did not recover	0	0	0	0
Fatal	0	0	0	0

Source: Study CT-P42 3.1

Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; TEAE = Treatment Emergent Adverse Event.

**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*

*** TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*

NOTE: For each AE, location is collected by either Oculus Dexter (right eye), Oculus Sinister (left eye), or Oculus Uterque (both eyes). The total number of TEAEs does not represent the sum of TEAEs in each category (study eye and fellow eye).

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.

[2] Only the most severe event is counted:

Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing

[3] Only the most serious event is counted:

Seriousness: Serious > Non-serious

[4] Only the most severe outcome is counted:

Outcomes: Fatal > Did not recover > Recovering > Recovered > Missing

From the MedDRA dictionary, version 25.1.

Overall, sixteen (16) non-serious TEAEs related to transient intraocular pressure increase were reported: five (5) TEAEs in three (3) patients in the CT-P42 group and eleven (11) TEAEs in six (6) patients in the reference product group. The incidence of TEAEs per 100 PY in CT-P42 group was 3.247 (95% CI: 1.054, 7.576), and in the reference product group was 7.236 (3.612, 12.947).

All five (5) TEAEs reported in the CT-P42 group were in the study eye. Of the eleven (11) TEAEs in the reference product group, ten (10) were in the study eye and one (1) was in the fellow eye.

Of the nine (9) patients who experienced TEAEs related to transient intraocular pressure increase, three (3 [1.6%], 95% CI: 0.33, 4.54) patients in the CT-P42 group experienced two Grade 1 and one Grade 3 TEAEs and six (6 [3.4%], 95% CI: 1.28, 7.35) patients in the reference product group experienced three Grade 1 and three Grade 2 events. Out of nine (9) patients, eight (8) patients were reported as “recovered” and one (1) patient was reported as “recovering” at the end of trial period.

Risk factors and risk groups:

Patients with a medical history of glaucoma are at an increased risk of transient increase in intraocular pressure following IVT injection. Increased intraocular pressure is also a known adverse event of treatment with IVT corticosteroids and other medicines that may be injected into the eye.

Preventability:

Intraocular pressure should be checked after each injection into the eye as the transient increase of eye pressure is a result of the volume of the injection into the eye. This effect is usually transient, and there is no evidence that pressure increases following IVT injections (even after multiple injections) could become durable or may lead to glaucoma.

Impact on the risk-benefit balance of the product:

This important identified risk does not have an impact on the positive risk-benefit balance of aflibercept.

Public health impact:

Due to the transient and usually mild nature of the condition, no impact of this safety concern on public health issues is expected.

Important identified risk: Retinal pigment epithelial tear (MedDRA PT Retinal pigment epithelial tear)

Potential mechanisms:

RPE tears after anti-VEGF IVT injection may develop due to decreased intercellular adherence, thereby increasing susceptibility to RPE tears (Singh et al., 2006). It has been suggested that anti-VEGF treatment augments the contraction of the choroidal neovascular membrane thus increasing the likelihood of RPE tear (Ersoz et al., 2017).

Evidence source(s) and strength of evidence:

The retinal pigment epithelium is the external layer of the retina which may develop tears. These tears are sometimes self-sealing; however, they may require sealing by laser coagulation. The incidence of RPE tear has significantly increased with the use of anti-VEGF agents injected into the eye (Ersoz et al., 2017).

In the clinical development programme of the reference product Eylea, up to 1.9% of patients with underlying wet AMD who were treated with Eylea developed a tear of the retina, whilst none of the patients with underlying CRVO, BRVO, myopic CNV, or DME developed a tear of the retina.

Characterisation of the risk:

There were no TEAEs reported for RPE tear in the CT-P42 group (190 patients) and the reference product group (174 patients) in Study CT-P42 3.1.

Risk factors and risk groups:

Risk factors for RPE tear may include wet AMD with pigment epithelial detachment; treatment of neovascularisation.

Preventability:

The underlying mechanisms causing RPE tears following IVT injection are not yet completely understood and thus, no preventive measure is currently known.

Impact on the risk-benefit balance of the product:

This important identified risk does not have an impact on the positive risk-benefit balance of the aflibercept.

Public health impact:

The potential public health impact of this safety concern is considered to be low, due to the low frequency of serious or severe events in clinical trials of the reference product Eylea.

Important identified risk: Cataract (especially of traumatic origin) (MedDRA PT Cataract traumatic)

Potential mechanisms:

Traumatic cataract may develop after IVT procedure as a result of lens capsule rupture with seepage of aqueous humour into lens fibres. If there is no capsule rupture, it is suspected that the traumatic forces damage lens fibres, ultimately resulting in cataract formation (Sharma et al., 2016).

Evidence source(s) and strength of evidence:

Cataract is a term for clouding or opacification of the eye lens. It is a gradually progressive condition which may cause vision loss. Cataract may develop due to multiple reasons including age, sun exposure, congenital cataract, generalised disease, endocrine disease, alcohol use, smoking, poor nutrition or traumatic injury. Traumatic cataract is a common consequence of eye trauma and may cause significant visual impairment. If the needle used to inject aflibercept touches the lens in the patient's eye this could be a cause of traumatic cataract.

The proportion of reference product Eylea-exposed patients who experienced traumatic cataract in the study eye in the clinical studies with Eylea ranged from 0% to 2.8% (VIVID-DME & VISTA-DME).

Characterisation of the risk:

Frequency with 95 % CI for 100 PY:

TEAEs in both study and fellow eyes

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			**Aflibercept reference product[**] (N=174)**
	Total (N=190)	**CT-P42 only (N=174)**	**CT-P42 after administration of aflibercept reference product[*] (N=16)**	
Total N of TEAEs	8	8	0	10
N of Patients with TEAEs [1]	7 (3.7%)	7 (4.0%)	0	10 (5.7%)
Incidence of TEAEs per 100 PY	5.194	5.196	0.000	6.578
95% CI for Incidence of TEAEs per 100 PY	(2.243, 10.235)	(2.243, 10.238)	(0.000, 8421.020)	(3.154, 12.097)

Source: Study CT-P42 3.1
From the MedDRA dictionary, version 25.1.
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; PY = Patient Year; TEAE = Treatment Emergent Adverse Event.
[*]TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.
[**]TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
Patient Year is calculated as follows:

CT-P42 total: Duration from 'CT-P42 only' and 'CT-P42 after administration of aflibercept reference product'
CT-P42 only: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25
CT-P42 after administration of aflibercept reference product: (Date of Last Exposure to CT-P42 Treatment - Date of First Exposure to CT-P42 Treatment +1) / 365.25
Aflibercept reference product: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25 or (Date of First Exposure to CT-P42 Treatment - Date of First Exposure to Treatment) / 365.25

TEAEs in study eye

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	5	5	0	7
N of Patients with TEAEs [1]	4 (2.1%)	4 (2.3%)	0	7 (4.0%)
Incidence of TEAEs per 100 PY	3.247	3.247	0.000	4.605
95% CI for Incidence of TEAEs per 100 PY	(1.054, 7.576)	(1.054, 7.579)	(0.000, 8421.020)	(1.851, 9.487)

Source: Study CT-P42 3.1
From the MedDRA dictionary, version 25.1.
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; PY = Patient Year; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
***TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
Patient Year is calculated as follows:

CT-P42 total: Duration from 'CT-P42 only' and 'CT-P42 after administration of aflibercept reference product'
CT-P42 only: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25
CT-P42 after administration of aflibercept reference product: (Date of Last Exposure to CT-P42 Treatment - Date of First Exposure to CT-P42 Treatment +1) / 365.25
Aflibercept reference product: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25 or (Date of First Exposure to CT-P42 Treatment - Date of First Exposure to Treatment) / 365.25

TEAEs in fellow eye

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	3	3	0	5
N of Patients with TEAEs [1]	3 (1.6%)	3 (1.7%)	0	5 (2.9%)
Incidence of TEAEs per 100 PY	1.948	1.948	0.000	3.289

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
95% CI for Incidence of TEAEs per 100 PY	(0.402, 5.693)	(0.402, 5.694)	(0.000, 8421.020)	(1.068, 7.675)

Source: Study CT-P42 3.1
From the MedDRA dictionary, version 25.1.
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; PY = Patient Year; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
***TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
Patient Year is calculated as follows:
CT-P42 total: Duration from 'CT-P42 only' and 'CT-P42 after administration of aflibercept reference product'
CT-P42 only: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25
CT-P42 after administration of aflibercept reference product: (Date of Last Exposure to CT-P42 Treatment - Date of First Exposure to CT-P42 Treatment +1) / 365.25
Aflibercept reference product: (Date of Last Exposure to Treatment - Date of First Exposure to Treatment +1) / 365.25 or (Date of First Exposure to CT-P42 Treatment - Date of First Exposure to Treatment) / 365.25

Frequency with Severity, Seriousness and Outcome:

TEAEs in both study and fellow eyes

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	8	8	0	10
N of Patients with TEAEs [1]	7 (3.7%)	7 (4.0%)	0	10 (5.7%)
95% CI for proportion of patients with TEAEs	(1.49, 7.44)	(1.63, 8.11)	(0.00, 20.59)	(2.79, 10.32)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	2 (1.1%)	2 (1.1%)	0	6 (3.4%)
Grade 2	3 (1.6%)	3 (1.7%)	0	4 (2.3%)
Grade 3	1 (0.5%)	1 (0.6%)	0	0
Grade 4	1 (0.5%)	1 (0.6%)	0	0
Grade 5	0	0	0	0

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			**Aflibercept reference product[**] (N=174)**
	Total (N=190)	**CT-P42 only (N=174)**	**CT-P42 after administration of aflibercept reference product[*] (N=16)**	
Seriousness [3]				
Serious	0	0	0	0
Non-serious	7 (3.7%)	7 (4.0%)	0	10 (5.7%)
Outcomes [4]				
Missing	0	0	0	0
Recovered	1 (0.5%)	1 (0.6%)	0	2 (1.1%)
Recovering	0	0	0	3 (1.7%)
Did not recover	6 (3.2%)	6 (3.4%)	0	5 (2.9%)
Fatal	0	0	0	0

Source: Study CT-P42 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
*** TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
NOTE: For each AE, location is collected by either Oculus Dexter (right eye), Oculus Sinister (left eye), or Oculus Uterque (both eyes). The total number of TEAEs does not represent the sum of TEAEs in each category (study eye and fellow eye).
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted:
Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted:
Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted:
Outcomes: Fatal > Did not recover > Recovering > Recovered > Missing
From the MedDRA dictionary, version 25.1.

TEAEs in study eye

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	5	5	0	7
N of Patients with TEAEs [1]	4 (2.1%)	4 (2.3%)	0	7 (4.0%)
95% CI for proportion of patients with TEAEs	(0.58, 5.30)	(0.63, 5.78)	(0.00, 20.59)	(1.63, 8.11)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	2 (1.1%)	2 (1.1%)	0	5 (2.9%)
Grade 2	1 (0.5%)	1 (0.6%)	0	2 (1.1%)
Grade 3	1 (0.5%)	1 (0.6%)	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [3]				
Serious	0	0	0	0
Non-serious	4 (2.1%)	4 (2.3%)	0	7 (4.0%)
Outcomes [4]				
Missing	0	0	0	0
Recovered	0	0	0	0
Recovering	0	0	0	3 (1.7%)
Did not recover	4 (2.1%)	4 (2.3%)	0	4 (2.3%)
Fatal	0	0	0	0

Source: Study CT-P42 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
*** TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
NOTE: For each AE, location is collected by either Oculus Dexter (right eye), Oculus Sinister (left eye), or Oculus Uterque (both eyes). The total number of TEAEs does not represent the sum of TEAEs in each category (study eye and fellow eye).
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted:
Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted:
Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted:
Outcomes: Fatal > Did not recover > Recovering > Recovered > Missing
From the MedDRA dictionary, version 25.1.

TEAEs in fellow eye

INDICATION: Diabetic Macular Oedema (CT-P42 3.1)				
	CT-P42			Aflibercept reference product** (N=174)
	Total (N=190)	CT-P42 only (N=174)	CT-P42 after administration of aflibercept reference product* (N=16)	
Total N of TEAEs	3	3	0	5
N of Patients with TEAEs [1]	3 (1.6%)	3 (1.7%)	0	5 (2.9%)
95% CI for proportion of patients with TEAEs	(0.33, 4.54)	(0.36, 4.96)	(0.00, 20.59)	(0.94, 6.58)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	0	0	0	3 (1.7%)
Grade 2	2 (1.1%)	2 (1.1%)	0	2 (1.1%)
Grade 3	0	0	0	0
Grade 4	1 (0.5%)	1 (0.6%)	0	0
Grade 5	0	0	0	0
Seriousness [3]				
Serious	0	0	0	0
Non-serious	3 (1.6%)	3 (1.7%)	0	5 (2.9%)
Outcomes [4]				
Missing	0	0	0	0
Recovered	1 (0.5%)	1 (0.6%)	0	2 (1.1%)
Recovering	0	0	0	1 (0.6%)
Did not recover	2 (1.1%)	2 (1.1%)	0	2 (1.1%)
Fatal	0	0	0	0

Source: Study CT-P42 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of Patients; TEAE = Treatment Emergent Adverse Event.
**TEAEs occurred during Extension study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
*** TEAEs occurred during Main study period in patients who received a single dose of CT-P42 in the extension study period after administration of aflibercept reference product is included in this column.*
NOTE: For each AE, location is collected by either Oculus Dexter (right eye), Oculus Sinister (left eye), or Oculus Uterque (both eyes). The total number of TEAEs does not represent the sum of TEAEs in each category (study eye and fellow eye).
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted:
Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted:
Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted:
Outcomes: Fatal > Did not recover > Recovering > Recovered > Missing
From the MedDRA dictionary, version 25.1.

Overall, there were eighteen (18) non-serious TEAEs related to cataract (especially of traumatic origin); eight (8) in the CT-P42 group, and ten (10) in the reference product group. The incidence of TEAEs per 100PY in CT-P42 group was 5.194 (95% CI: 2.243, 10.235) and in the reference product group was 6.578 (95% CI: 3.154, 12.097).

Of the eight (8) TEAEs in the CT-P42 group, five (5) were in the study eye and three (3) were in the fellow eye.

The four (4) patients who experienced TEAEs related to cataract in the study eye in CT-P42 group were, two (2) Grade 1, one (1) Grade 2 and one (1) Grade 3; all non-serious events; all four (4) "did not recover". The seven (7) patients who experienced TEAEs related to cataract in the study eye in the reference product group were, five (5) Grade 1 and two (2) Grade 2; all non-serious events; three (3) were "recovering" and four (4) "did not recover" at the end of trial period. The proportion of patients with TEAEs in the study eye in the CT-P42 group was 2.1% (95% CI: 0.58, 5.30) and in the reference product group was 4.0% (95% CI: 1.63, 8.11).

Risk factors and risk groups:

Cataract is a known side effect of treatment with IVT corticosteroids. Other risk factors include age, sun exposure, generalised disease, endocrine disease, alcohol use, smoking, poor nutrition, or injury to the lens of the eye.

Preventability:

Eydenzelt should always be injected a qualified physician experienced in IVT injection. Using the correct IVT injection procedure and a correct angle of the needle while injecting, could prevent traumatic cataract.

Impact on the risk-benefit balance of the product:

This important identified risk does not have an impact on the positive risk-benefit balance of the aflibercept considering the rare frequency of occurrence of traumatic cataract associated with aflibercept IVT injection.

Public health impact:

The impact on public health would be expected to be minimal because traumatic cataract associated with aflibercept is a rare adverse event.

Important potential risks: Medication errors (MedDRA SMQ Medication errors)

Potential mechanisms:

Not applicable.

Evidence source(s) and strength of evidence:

The medication error providing the greatest source of potential safety concern is overdose. Eydenzelt PFS and vial contain an excess volume which exceeds the recommended net dose of 2 mg aflibercept per injection. Thus, injecting the entire volume of the PFS or vial would result in overdose. However, Eydenzelt will be administered only by qualified, appropriately experienced physicians, thus reducing the risk of inappropriate dosing and administration. In the clinical development programme of aflibercept, no clinically meaningful events of overdose were reported. Medication error can be avoided by adhering to the dosing recommendations.

Characterisation of the risk:

There were no TEAEs reported in either CT-P42 or the reference product group related to medication errors.

Risk factors and risk groups:

Not applicable

Preventability:

Medication errors can be minimised by following the correct method of administration as mentioned in the SmPC of Eydenzelt.

Impact on the risk-benefit balance of the product:

This important potential risk does not have an impact on the positive risk-benefit balance of the aflibercept.

Public health impact:

This safety concern is not expected to have an impact on public health.

Important potential risks: Off-label use and misuse (MedDRA PT Off label use)

Potential mechanisms:

Not applicable

Evidence source(s) and strength of evidence:

Off-label use is the therapeutic use of a medicinal product for indications other than the approved indications. As with other drugs, aflibercept might intentionally be used off-label. Eydenzelt is not indicated for paediatric use unlike the reference product Eylea, which has the risk of off-label use in paediatric indication. Since the clinical experience with aflibercept in such off-label use will be limited (in particular in terms of efficacy and safety), any case of off-label use will be considered a potential risk.

Characterisation of the risk:

There were no TEAEs reported in either CT-P42 or the reference product group related to Off-label use and misuse.

Risk factors and risk groups:

Eydenzelt might intentionally be used off-label for the treatment of retinopathy of prematurity (ROP) in preterm infants.

Preventability:

In general, as for the majority of possible indications for anti-VEGF therapy approved medications are available, the potential for off-label use is considered minimal. Additionally, non-approved indications are currently being investigated in various studies to establish safety and efficacy in these therapeutic areas. As approved treatments are available for the possible indications for anti-VEGF agents, the potential for off label use in unapproved indications is considered low.

Intentional misuse cannot be prevented.

Impact on the risk-benefit balance of the product:

This important potential risk does not have an impact on the positive risk-benefit balance of aflibercept.

Public health impact:

Not applicable.

Important potential risks: Embryo-foetotoxicity (MedDRA SMQ Congenital, familial and genetic disorders)

Potential mechanisms:

Aflibercept may cause embryo-foetal toxicity due to its mechanism of action i.e., anti-angiogenic effect. In the non-clinical studies conducted for the reference product Eylea, dose-related increases were seen in foetal resorptions, pregnancy disruptions and numerous foetal (external, visceral and skeletal) malformations.

Evidence source(s) and strength of evidence:

The evidence source for this safety concern is the embryo-foetal toxicity study conducted for the reference product Eylea. In this non-clinical study extremely high doses of Eylea were given to rabbits and it was observed that such high doses of Eylea have a negative impact on the development of the foetus. However, Eylea is injected locally and at a dose that is distinctively lower than the exposure in animals under which the critical events were observed.

Characterisation of the risk:

There were no TEAEs reported in either CT-P42 or the reference product group related to Embryo-foetotoxicity.

Risk factors and risk groups:

Women of childbearing potential are at risk of experiencing embryo-foetal toxicity.

Preventability:

Aflibercept should not be used during pregnancy unless the potential benefit outweighs the risk to the foetus. The risk can be prevented by appropriate effective contraceptive measures.

Impact on the risk-benefit balance of the product:

This important potential risk does not have an impact on the positive risk-benefit balance of aflibercept.

Public health impact:

Based on currently available data and preventability, the public health impact in terms of risk to the treated population remains minimal.

SVII.3.2. Presentation of the missing information

There is no missing information available for inclusion in the list of safety concerns in the RMP.

Part II: Module SVIII - Summary of the safety concerns

Table 8: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Endophthalmitis (likely infectious origin) • Intraocular inflammation • Transient intraocular pressure increase • Retinal pigment epithelial tears • Cataract (especially of traumatic origin)
Important potential risks	• Medication errors • Off-label use and misuse • Embryo-foetotoxicity
Missing information	None

Note: The missing information 'Long-term safety of aflibercept in preterm infants with retinopathy of prematurity', is not included in this table because Eydenzelt is not indicated in preterm infants for the treatment of Retinopathy of Prematurity. The missing information 'Exposure with bilateral 8mg dose aflibercept therapy' is not included as well because Eydenzelt is only available as 2mg dose.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Specific AE follow-up questionnaires will be used to collect further data to help further characterise and/or closely monitor each of the respective safety concerns specified below. Targeted follow-ups with specific checklist are applicable for the following risks:

- Endophthalmitis (likely infectious origin)
- Intraocular inflammation
- Transient intraocular pressure increase

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional pharmacovigilance activities

Not applicable as there are no additional pharmacovigilance activities planned for Eydenzelt.

III.3 Summary Table of additional Pharmacovigilance activities

Table 9: Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestone	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				

Study Status	Summary of objectives	Safety concerns addressed	Milestone	Due dates
None				

Part IV: Plans for Post-authorisation Efficacy Studies

Not applicable, since there are no post authorisation efficacy studies planned for Eydenzelt.

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Safety concern	Routine risk minimisation activities
Endophthalmitis (likely infectious origin) (Important identified risk)	Routine risk communication: SmPC Sections 4.2, 4.3, 4.4 and 4.8. PL Sections – 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Treatment with Eydenzelt is contraindicated in patients with Ocular or periocular infection and active severe intraocular inflammation (SmPC Section 4.3). • Recommendation for administering the drug, and monitoring and reporting any symptoms suggestive of endophthalmitis following the IVT injection of Eydenzelt is given in SmPC Section 4.2 and 4.4. • Guidance is given in PL Section 2 for patients to recognise early signs and symptoms of infection and how to manage this risk. • Information is given in PL Section 3 for patients about how the doctor will disinfect the eye before injection to prevent infection. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections.
Intraocular inflammation (Important identified risk)	Routine risk communication: SmPC Sections 4.2, 4.3, 4.4 and 4.8. PL Sections – 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Treatment with Eydenzelt is contraindicated in patients with active severe intraocular inflammation (SmPC Section 4.3). • Recommendation for administering the drug, and monitoring and reporting any symptoms of intraocular inflammation, is given in SmPC Section 4.2 and 4.4. • Guidance is given in PL Section 2 for patients to recognise early signs and symptoms of infection or inflammation and how to manage this risk. Information is given in PL Section 3 for patients about how the doctor will disinfect the eye before injection to prevent infection. Other routine risk minimisation measures beyond the Product Information:

Safety concern	Routine risk minimisation activities
	Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections.
Transient intraocular pressure increase (Important identified risk)	Routine risk communication: SmPC Sections 4.2, 4.4, 4.8 and 4.9. PL Sections - 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for physicians for administering the drug, and monitoring and management of intraocular pressure, immediately following IVT injection is given in SmPC Section 4.2 and 4.4. • Information is given in SmPC Section 4.2, that the excess volume must be expelled before injecting the recommending dose. • Advice in provided in SmPC Section 4.9 about monitoring and management of intraocular pressure increase caused by overdose. • Information is given in PL Section 2 for patients regarding the increase in eye pressure within 60 minutes of Eydenzelt injection and that the doctor will monitor the eye pressure after each injection. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections.
Retinal pigment epithelial tears (Important identified risk)	Routine risk communication: SmPC Sections 4.4 and 4.8. PL Sections – 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance for physicians regarding the caution to be used in patients with risk factors for retinal pigment epithelial tears is mentioned in SmPC Section 4.4. • Guidance is given in PL Section 2 for patients regarding the risk factors for retinal pigment epithelial tears and the caution to be followed while giving Eydenzelt in such cases. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections.
Cataract (especially of traumatic origin) (Important identified risk)	Routine risk communication: SmPC Sections 4.2, 4.4 and 4.8. PL Sections – 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimisation activities
	• Recommendation for physicians for administering the drug is given in SmPC Section 4.2. Special precaution to physicians for using proper aseptic injection techniques when administering Eydenzelt and monitoring for symptoms during the week following the injection are provided in SmPC Section 4.4. • Advice to instruct adult patients to report any symptoms suggestive of traumatic cataract without delay is mentioned in SmPC Section 4.4. • Guidance is given in PL Section 2 for patients to recognise and report immediately, the symptoms of inflammation inside the eye. • Information is given in PL Section 3 for patients about how the doctor will disinfect the eye to prevent infection. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections.
Medication errors (Important potential risk)	Routine risk communication: SmPC Sections 4.2, 4.9 and 6.6 PL Sections - 1 and 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation is provided in the SmPC Section 4.2 regarding the correct method of administration of Eydenzelt to minimise the risk of drug administration error. • Advice in provided in SmPC Section 4.9 about monitoring and management of overdose. • Detailed and illustrated instructions for the use of the PFS is provided in SmPC Section 6.6 and PL Section 'information intended for HCPs only', in order to minimise the risk of drug administration error. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections.
Off-label use and misuse (Important potential risk)	Routine risk communication: SmPC Sections 4.1, 4.3, 4.4 and 4.6 PL Sections – 1, 2 and 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation on conditions in which treatment is contraindicated or should be withheld/discontinued are provided in SmPC Sections 4.3 and 4.4. • Recommendation for use in pregnancy and brestfeeding is given in SmPC Section 4.6.

Safety concern	Routine risk minimisation activities
	• Contraindications, conditions in which treatment should be withheld/discontinued, and recommendation on use during pregnancy/breastfeeding are mentioned in PL Section 2. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections.
Embryo-foetotoxicity (Important potential risk)	Routine risk communication: SmPC Sections 4.4, 4.6 and 5.3 PL Section – 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation and advice is given in SmPC Section 4.4 and 4.6 regarding the use during pregnancy and breastfeeding, and regarding the use of effective contraception during treatment. • Advice is given in PL Section 2 for patients regarding the use during pregnancy and breastfeeding, and use of effective contraception during treatment. • Advice is given in PL Section 2 for patients to inform the doctor if the patient is pregnant or planning to get pregnant before using Eydenzelt. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections.

V.2. Additional Risk Minimisation Measures

V.2.1 Educational programme

Besides the routine risk minimisation activities (SmPC and patient information), additional activity, specifically an educational programme is considered to be necessary for the important identified risks of endophthalmitis (likely infectious origin), intraocular inflammation, transient intraocular pressure increase, retinal pigment epithelium tears, cataract (especially of traumatic origin), as well as for the important potential risk of medication errors, off-label use and misuse, embryo-foetotoxicity. Generally, the educational material covers the indications wet AMD, CRVO, BRVO, myopic CNV and DME.

V.2.1.1 Objectives and rationale for the additional risk minimisation activity

To inform patients and physicians about risks in order to minimise their occurrence and consequences in routine care. Educational material also includes guidance on the IVT injection procedure to re-train physicians in order to minimise injection-related adverse reactions. The following risks are addressed in the Educational Material: endophthalmitis/intraocular inflammation, transient intraocular pressure increase, RPE tear, cataract, medication error, off label use and misuse, and embryo-foetotoxicity.

V.2.1.2 Target audience and planned distribution path

The target audience are healthcare professionals specialised in IVT injections of VEGF as well as patients to be treated. The key messages of the educational materials (provided in Part VII Annex 6) will be distributed as paper version and/or through a digital communication method (digital platform) to the target audience(s). The feasibility and implementation of the planned distribution path will be agreed upon with and after liaising with the national health authorities in the member states, as required per GVP Module XVI addendum.

V.2.1.3 Plans to evaluate the effectiveness of the interventions and criteria for success

Signal detection will be performed on the reports received at Celltrion. The applied trend analysis tool will compare relative reported frequencies (actual versus historic) as per ADR type according to internal procedure. Obtained ratios, equal or above a value of 3 will be considered a signal and subjected to further signal verification activities. This method will allow the identification of relative changes in reporting frequency, e.g., caused by a decrease in the effectiveness of risk minimisation measures or in the case of emerging new risk factors and represents a pragmatic quantitative means of monitoring at least secular changes in the frequency of reporting of serious preventable ADRs.

V.3 Summary of risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Endophthalmitis (likely infectious origin) (Important identified risk)	Routine risk minimisation measures: • *SmPC Sections 4.3 and 4.8.* • *SmPC Sections 4.2 and 4.4 where recommendations for administering the drug, monitoring and reporting any symptoms suggestive of endophthalmitis following the IVT injection of Eydenzelt are included.* • *PL Sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Intraocular inflammation (Important identified risk)	Routine risk minimisation measures: • *SmPC Sections 4.3 and 4.8.* • *SmPC Sections 4.2 and 4.4 where recommendations for monitoring and reporting any symptoms of intraocular inflammation are included.* • *PL Sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients'and physicians' awareness on identified and potential risks (prescriber guide and patient guide).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaire Additional pharmacovigilance activities: None
Transient intraocular pressure increase (Important identified risk)	Routine risk minimisation measures: • *SmPC Sections 4.8 and 4.9.* • *SmPC Section 4.2 and 4.4 where guidance for physicians for monitoring and management of intraocular pressure, immediately following IVT injection are included.* • *PL Sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Retinal pigment epithelial tears (Important identified risk)	Routine risk minimisation measures: • *SmPC Section 4.8.* • *SmPC Section 4.4 where caution to be used in patients with risk factors for retinal pigment epithelial tears is mentioned.* • *PL Sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide andpatient guide).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Cataract (especially of traumatic origin) (Important identified risk)	Routine risk minimisation measures: • *SmPC Sections 4.2, 4.8.* • *SmPC Section 4.4 where advice to physicians for using proper aseptic injection techniques when administering Eydenzelt and monitoring for symptoms during the week following the injection is provided. Additionally, the Section 4.4 advises to instruct adult patients to report any symptoms suggestive of traumatic cataract without delay.* • *PL Sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Medication errors (Important potential risk)	Routine risk minimisation measures: • *SmPC Section 4.9.* • *SmPC Section 4.2 where the correct method of administration of Eydenzelt is provided in detail to minimise risk of drug administration error. Section 4.9 provides information on monitoring and management of overdose.* • *SmPC Section 6.6. where detailed and illustrated instructions are provided for the use of the PFS.* • *PL Sections 1 and 3* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Off-label use and misuse (Important potential risk)	Routine risk minimisation measures: • *SmPC Sections 4.1, 4.6.* • *SmPC Sections 4.3 and 4.4 where recommendation on conditions in which treatment is contraindicated or should be withheld/discontinued are provided.* • *PL Sections 1, 2 and 3* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Embryo-foetotoxicity (Important potential risk)	Routine risk minimisation measures: • *SmPC Sections 4.6 and 5.3.* • *SmPC Section 4.4 which advises that Eydenzelt should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus.* • *PL Section 2* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Eydenzelt (biosimilar aflibercept)

This is a summary of the risk management plan (RMP) for Eydenzelt. The RMP details important risks of Eydenzelt, how these risks can be minimised.

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

This summary of the RMP for Eydenzelt should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European public assessment report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Eydenzelt's RMP.

I. The medicine and what it is used for

Eydenzelt is authorised in adults for Neovascular (wet) age-related macular degeneration (AMD), Visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), Visual impairment due to diabetic macular oedema (DME), Visual impairment due to myopic choroidal neovascularisation (myopic CNV) (see SmPC of Eydenzelt for the full indication). Eydenzelt is not authorised for treatment of retinopathy of prematurity in preterm infants.

It contains aflibercept as the active substance and it is given as intravitreal (IVT) injection. The following pharmaceutical forms are currently available:

- Solution for injection in a Pre-Filled Syringe (PFS). One PFS contains 3.6 mg aflibercept in 0.09 mL (40 mg/mL). Delivers a single dose of 0.05 mL containing 2 mg aflibercept.
- Solution for injection in a vial. One vial contains 4 mg aflibercept in 0.1 mL (40 mg/mL). Delivers a single dose of 0.05 mL containing 2 mg aflibercept.

The dosage of Eydenzelt is one injection per month for three consecutive doses for wet AMD (2 mg aflibercept, equivalent to 0.05 mL). The treatment interval is then extended to two months. Eydenzelt is given once in a month (2 mg aflibercept, equivalent to 0.05 mL) for branch RVO or central RVO. For DME, it is given once in a month for five consecutive doses, followed by one injection every two months. Eydenzelt is given as a single IVT injection of 2 mg aflibercept equivalent to 0.05 mL for myopic CNV.

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

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise 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 authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

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

In the case of Eydenzelt, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including 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 Eydenzelt is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

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

List of important risks and missing information	
Important identified risks	Endophthalmitis (likely infectious origin) Intraocular inflammation Transient intraocular pressure increase Retinal pigment epithelial tears Cataract (especially of traumatic origin)
Important potential risks	Medication errors Off-label use and misuse Embryo-foetotoxicity
Missing information	None

Note: The missing information 'Long-term safety of aflibercept in preterm infants with retinopathy of prematurity', is not included in this table because Eydenzelt is not indicated in preterm infants for the treatment of Retinopathy of Prematurity. The missing information 'Exposure with bilateral 8mg dose aflibercept therapy' is not included as well because Eydenzelt is only available as 2mg dose.

II.B Summary of important risks

Important identified risk: Endophthalmitis (likely infectious origin)	
Evidence for linking the risk to medicine	Endophthalmitis is a condition in which the inside of the eye becomes inflamed due to the presence of harmful bacteria or other germs. This can happen when these germs get inside the eye from the outside (exogenous) or from other parts of the body (endogenous). Endophthalmitis is a serious problem that can occur after injections given into the eye. It is the most serious avoidable complication of anti-VEGF agent IVT injections. Although the incidence is low, endophthalmitis is considered serious complication as it may lead to severe vision loss and requires immediate medical treatment. Post IVT injection, endophthalmitis is most commonly caused by a type of bacteria called coagulase-negative staphylococci, followed by streptococci. The incidence of endophthalmitis in the clinical development programme of the reference product Eylea was very low. No events related to endophthalmitis were reported in the clinical development programme of Eydenzelt. According to the literature reports the incidence of endophthalmitis ranges from 0.01% to 0.26% after IVT injection of anti-VEGF agents.
Risk factors and risk groups	Improper aseptic technique while administering Eydenzelt into the eye increases the risk of endophthalmitis.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC Sections 4.3 and 4.8.* • *SmPC Sections 4.2 and 4.4 where recommendations for administering the drug, monitoring and reporting any symptoms suggestive of endophthalmitis following the IVT injection of Eydenzelt are included.* • *PL Sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).

Important identified risk: Intraocular inflammation	
Evidence for linking the risk to medicine	Intraocular inflammation is inflammation inside the eye associated with IVT injections of anti-VEGF agents including Eydenzelt, and when no germs or pathogen can be identified, it is termed 'sterile' intraocular inflammation. Post-injection, sterile intraocular inflammation is a known risk, following injections into the eye, of anti-VEGFs and for other intravitreally applied drugs. The onset of the inflammation is typically within the first 5 days of IVT injection. The proportion of patients who experienced intraocular inflammation in the study eye in the clinical studies with Eylea ranged from 0% to 2.6% (VIEW 1 & 2 AMD studies).
Risk factors and risk groups	Improper technique while administering Eydenzelt increases the risk of intraocular inflammation.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC Sections 4.3 and 4.8.* • *SmPC Sections 4.2 and 4.4 where recommendations for monitoring and reporting any symptoms of intraocular inflammation are included.* • *PL Sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients'and physicians' awareness on identified and potential risks (prescriber guide and patient guide).
Important identified risk: Transient intraocular pressure increase	
Evidence for linking the risk to medicine	Intraocular pressure is the pressure exerted by the fluid inside the eye. Increased intraocular pressure is a risk factor in the development of glaucoma. Transient intraocular pressure increase is a recognised adverse event of IVT anti-VEGF injections. Glaucoma is characterised by a loss of nerve fibres in the eye with the subsequent risk of blindness. However, many different factors may be responsible for the development of glaucoma. When medicine is injected into the eye, it can cause a temporary increase in pressure inside the eye until the extra fluid is absorbed. This is because the medicine is dissolved in a certain amount of liquid, and the injection can cause a temporary increase in the amount of fluid in the eye. In the clinical development programme of the reference product Eylea, the proportion of patients who experienced an increase in intraocular pressure in the study eye ranged from 2.8% (VIVID-JAPAN DME study) to 13.6% central RVO ([CRVO] studies GALILEO & COPERNICUS).

Risk factors and risk groups	Patients with a medical history of glaucoma are at an increased risk of transient increase in intraocular pressure following IVT injection. Increased intraocular pressure is also a known side effect of treatment with IVT corticosteroids and other medicines that may be injected into the eye.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC Sections 4.8 and 4.9.* • *SmPC Section 4.2 and 4.4 where guidance for physicians for monitoring and management of intraocular pressure, immediately following IVT injection are included.* • *PL Sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).
Important identified risk: Retinal pigment epithelial tears	
Evidence for linking the risk to medicine	The retinal pigment epithelium is the external layer of the retina which may develop tears. These tears are sometimes self-sealing however, they may require sealing by laser coagulation. The incidence of RPE tear has significantly increased with the use of anti-VEGF agents injected into the eye. In the clinical development programme of the reference product Eylea, up to 1.9% of patients with underlying wet AMD who were treated with Eylea developed a tear of the retina, whilst none of the patients with underlying CRVO, branch RVO, myopic CNV, or DME developed a tear of the retina.
Risk factors and risk groups	Risk factors for RPE tear may include wet AMD with pigment epithelial detachment; treatment of neovascularisation.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC Section 4.8.* • *SmPC Section 4.4 where caution to be used in patients with risk factors for retinal pigment epithelial tears is mentioned.* • *PL Sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures:

	Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide andpatient guide).
Important identified risk: Cataract (especially of traumatic origin)	
Evidence for linking the risk to medicine	Cataract is a term for clouding or opacification of the eye lens. It is a gradually progressive condition which causes significant blindness around the world. Cataract may develop due to multiple reasons including age, sun exposure, congenital cataract, generalised disease, endocrine disease, alcohol use, smoking, poor nutrition or traumatic injury. Traumatic cataract is a common consequence of eye trauma and may cause significant visual impairment. If the needle used to inject aflibercept touches the lens in the patient's eye this could be a cause of traumatic cataract. The proportion of reference product Eylea-exposed patients who experienced traumatic cataract in the study eye in the clinical studies with Eylea ranged from 0% to 2.8% (VIVID-DME & VISTA-DME).
Risk factors and risk groups	Cataract is a known side effect of treatment with IVT corticosteroids. Other risk factors include age, sun exposure, generalised disease, endocrine disease, alcohol use, smoking, poor nutrition, or injury to the lens of the eye.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> • *SmPC Sections 4.2, 4.8.* • *SmPC Section 4.4 where advice to physicians for using proper aseptic injection techniques when administering Eydenzelt and monitoring for symptoms during the week following the injection is provided. Additionally, the section 4.4 advises to instruct adult patients to report any symptoms suggestive of traumatic cataract without delay.* • *PL Sections 2 and 4* <u>Legal status:</u> Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. <u>Additional risk minimisation measures:</u> Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).
Important potential risks: Medication errors	
Evidence for linking the risk to medicine	The medication error providing the greatest source of potential safety concern is overdose. Eydenzelt PFS and vial contain an excess volume which exceeds the recommended net dose of 2 mg aflibercept per injection. Thus, injecting the entire volume of the PFS or vial would result in overdose. However, this numerical overdose is limited, and Eydenzelt will be administered only by qualified physicians, thus reducing the risk of inappropriate dosing and

	administration as well. Medication error can be avoided by adhering to the dosing recommendations.
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures: • *SmPC Section 4.9.* • *SmPC Section 4.2 where the correct method of administration of Eydenzelt is provided in detail to minimise risk of drug administration error. Section 4.9 provides information on monitoring and management of overdose.* • *SmPC Section 6.6 where detailed and illustrated instructions are provided for the use of the PFS.* • *PL Sections 1 and 3* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).
Important potential risks: Off-label use and misuse	
Evidence for linking the risk to medicine	Off-label use is the therapeutic use of a medicinal product for indications other than the approved indications. As with other drugs, Eydenzelt might be intentionally used off-label. Eydenzelt is not indicated for paediatric use unlike the reference product Eylea, which has the risk of off-label use in paediatric indication. Since the clinical experience with Eydenzelt in such off-label use will be limited (in particular in terms of efficacy and safety), any case of off-label use will be considered a potential risk. The risk of misuse is regarded as very low since Eydenzelt does not have dependence potential. The risk is considered an important potential risk based on the safety profile of the reference product Eylea.
Risk factors and risk groups	Eydenzelt might intentionally be used off-label for the treatment of retinopathy of prematurity (ROP) in preterm infants.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC Sections 4.1, 4.6.* • *SmPC Sections 4.3 and 4.4 where recommendation on conditions in which treatment is contraindicated or should be withheld/discontinued are provided.*

	• *PL Sections 1, 2 and 3* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).
Important potential risks: Embryo-foetotoxicity	
Evidence for linking the risk to medicine	The evidence source for this safety concern is the embryo-foetal toxicity study conducted for the reference product Eylea. In this non-clinical study extremely high doses of Eylea were given to rabbits and it was observed that such high doses of Eylea have a negative impact on the development of the foetus. However, Eylea is injected locally and at a dose that is distinctively lower than the exposure in animals under which the critical events were observed.
Risk factors and risk groups	Women of childbearing potential are at risk of experiencing embryo-foetal toxicity.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC Sections 4.6 and 5.3.* • *SmPC Section 4.4 which advises that Eydenzelt should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus.* • *PL Section 2* Legal status: Restricted medical prescription (Prescription only medicine). Eydenzelt must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimisation measures: Educational programme: Beyond routine risk minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and patient guide).

Abbreviations: AMD: Age-related Macular Degeneration, CNV: Choroidal Neovascularisation, DME: Diabetic Macular Oedema, EPAR: European Public Assessment Report, IVT: Intravitreal, PFS: Pre-Filled Syringe, PL: Package Leaflet, PSUR: Periodic Safety Update Report, RPE: Retinal Pigment Epithelial, RVO: Retinal Vein Occlusion, SmPC: Summary of Product Characteristics, VEGF: Vascular Endothelial Growth Factor.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Eydenzelt.

II.C.2 Other studies in post-authorisation development plan

There are no other studies in post-authorisation development plan of Eydenzelt.

Part VII: Annexes

Table of contents

Annex 4 – Specific adverse drug reaction follow-up forms

- Endophthalmitis and intraocular inflammation (IOI) following the use of Eydenzelt
- Intraocular pressure increase following the use of the Celltrion Eydenzelt pre-filled syringe

Annex 4.1: Endophthalmitis and Intraocular Inflammation (IOI) following the use of Eydenzelt

Section I – REFERENCE ID		
Case ID:	STUDY ID:	PATIENT ID:
Section II – REPORTER/PATIENT INFORMATION		
REPORTER: ☐ Physician ☐ Nurse ☐Other (specify): _____		
REPORTER CONTACT INFORMATION		
Name:		
Institution/Practice Name:		
Phone:		Fax:
Address:		
Email:		

PATIENT INFORMATION				
Age (years): (at onset of event)	Age group:	Gender: male female	Weight: unit: Kg/lbs	Height: unit: Kg/lbs

Section III – PRODUCT INFORMATION (Eydenzelt)	
Therapy date: (dd/mm/yyyy) ☐ Ongoing	Number of Eydenzelt doses before the event:
Indication:	If other indication, specify:
☐ Eye injected/dose: OS ☐ 2mg OD ☐ 2mg	

Vial	PFS (Pre-filled syringe)
Lot/Batch number: OS: _____ Expiry date: _____ OD: _____ Expiry date: _____	PFS Lot/Batch number: OS: _____ Expiry date: _____ OD: _____ Expiry date: _____
Was the same vial used for more than one patient? ☐ Yes ☐ No If yes, did an event occur in other patients? ☐ Yes ☐ No If yes, how many? _____	Was the same PFS used for more than one patient? ☐ Yes ☐ No If yes, did an event occur in other patients? ☐ Yes ☐ No If yes, how many? _____
Was the vial aliquoted in several syringes? ☐ Yes ☐ No Was the vial multipunctured? ☐ Yes ☐ No	
Was the supplied filter needle used?	

☐ Yes ☐ No ☐ Unknown	
Date of injection preparation(dd/mm/yyyy): Time of injection preparation(hh:mm):	Date of injection preparation(dd/mm/yyyy): Time of injection preparation(hh:mm):
What was used for injection? ☐ Injection needle Batch No: _____ Brand of the needle: OS_____, OD_____ ☐ Syringe (Luer lock: yes no) ☐ Glass ☐ Plastic Batch No: _____ Brand of the syringe: OS_____, OD_____	What was used for injection? ☐ Injection needle Batch No: _____ Brand of the needle, if known: OS_____, OD_____
Where was the syringe for injection prepared? ☐ Off-site pharmacy ☐ On-site pharmacy ☐ Treatment/Examining room	Was the PFS stored according to the instructions for storage provided by the Manufacturer? ☐ Yes ☐ No
If prepared in pharmacy, provide the name and contact details:	If No, please explain deviation of storage condition
How many hours did the prepared syringe stay at room temperature prior to administration? _____	

Section IV – ADVERSE EVENT INFORMATION

Event (as reported term) ☐ OS ☐ OD ☐ OU	Start date / time (dd/mm/yyyy/hh:mm)	or how much time after injection did the event occur (approx.):	Stop date (dd/mm/yyyy):	Outcome (recovered, not recovered, recovered with sequelae, recovering, fatal)

If stop date is unknown, provide the approximate event duration (days):

If AE resolved/ is resolving, did the visual acuity (VA) recover to:
☐ same level before AE started
☐ VA is worse

Clinical presentation:

Treatment of adverse event

Treatment provided: ☐ Yes ☐ No If yes, specify →	☐ Antibiotics:	☐ Steroids (regimen details):	☐ Surgery (vitrectomy): Date: (dd/mm/yyyy)	☐ Unknown

☐Culture taken on: From: ☐ OS ☐ OD ☐ OU ☐ Culture not taken/unknown	☐ Positive for: ☐ OS ☐ OD ☐ OU	☐ Negative for: ☐ OS ☐ OD ☐ OU

Reporter causality comment:

The event is considered:
☐ Related to Eydenzelt
☐ Related to intravitreal injection procedure
☐ Not related to Eydenzelt or intravitreal injection procedure

Alternative explanation (e.g. underlying disease/condition predisposing to the event):						
Action taken with product:						
	Date from (dd/mm/yyyy)			Date to (dd/mm/yyyy)		
☐ Dose not changed	N/A			N/A		
☐ Stopped				N/A		
☐ Dose reduced					New dose:	
☐ Interrupted						
☐ Unknown	N/A			N/A		
Did the event abate/stop after treatment stopped? ☐ Yes ☐ No ☐ UNK				Did the event reoccur upon resuming treatment: ☐ Yes ☐ No ☐ UNK		
Section V – RELEVANT CLINICAL SYMPTOMS (to AE of interest) Please indicate which eye was affected						
Signs or symptoms	Start Date (dd/mm/yyyy)			Stop Date (dd/mm/yyyy)		
Additional Questions: Did the patient experience the same event(s) in the past: ☐ Yes ☐ No If yes, please provide relevant details:						
Section VI – RELEVANT (intravitreal) CONCOMITANT / HISTORICAL MEDICATION						
Drug Name	From (dd/mm/yyyy)	To (dd/mm/yyyy)	Ongoing	Dose/ number of injections	Indication	Similar event occurred? If yes, please specify
☐Anti VEGF Please specify: _____ ☐ OS ☐ OD ☐ OU			☐			
☐Other Please specify: _____ ☐ OS ☐ OD ☐ OU			☐			
Section VII – RELEVANT MEDICAL HISTORY / RISK FACTORS (relevant to the reported event)						
Condition				Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)	Ongoing
☐ Diabetes						☐

☐ Autoimmune disease, please specify: _____			☐
☐ Malignancy, please specify: _____			☐
☐ Immunodeficiency, please specify: _____			☐
☐ Other, please specify: _____			☐

Section VIII– ADDITIONAL INFORMATION (COMMENTS) (e.g. gender information if not male/female):

Cause of death (If selected outcome was fatal)	Date of death (dd/mm/yyyy)	Autopsy done	Autopsy details (continue with SECTION IV)
		☐	

This section can also be used to provide information on any of the sections above. Please note the relevant section number below.

Annex 4.2: Intraocular pressure increase following the use of the Celltrion Eydenzelt pre-filled syringe

Reporter Information	Name: Email:	_____		☐Physician ☐Nurse ☐Other
Institution name and address			Telephone: Fax:	
Patient Information	Initials* *(leave empty for study participants)*:	☐ ♂ Male ☐ ♀ Female	Age *(at onset of event)*	
Product Information	Number of Eydenzelt doses before the event _____	Dose information: OS: ☐ 2mg OD: ☐ 2mg	PFS batch number(s): OS: _____ Expiry date: _____ OD: _____ Expiry date: _____	
	Indication:			
Adverse Event (AE) Information		Intraocular Pressure (IOP) Increase onset date:	Last injection date before event onset:	
Was the IOP value measured pre-injection? ☐No ☐Yes, if yes, please provide • IOP value(s) (mmHg) • Time/minutes pre-injection and date • Method				
Was the IOP value measured post-injection? ☐No ☐Yes, if yes, please provide • IOP value(s) (mmHg) • Time/minutes pre-injection and dates • Method				
How long did the increased IOP last after the injection?				
Outcome of IOP increase event	☐recovering/resolving ☐recovered/resolved without sequelae ☐recovered/resolved with sequelae, please detail sequelae: ☐not recovered/not resolved ☐unknown			

Did the patient experience any other clinical sign or symptom in the context of post-injection IOP increase? ☐No ☐Yes, if yes, which other medical conditions/symptoms were experienced and what is the outcome of the events? Please indicate outcome in box to the right.	Outcome of events (please indicate event in parenthesis): ☐recovering/resolving (event(s): _____) ☐recovered/resolved (event(s): _____) ☐recovered/resolved with sequelae, (event(s): _____) ☐not recovered/not resolved (event(s): _____) ☐unknown (event(s): _____) ☐not applicable
Was post injection fundoscopy performed? ☐No ☐Yes, if yes, please provide results and post-injection timing	
Was there any intervention done to treat increased IOP? ☐No ☐Yes, if yes, please specify the measures taken including date and time	
Does the patient have a history of glaucoma, ocular hypertension or glaucoma surgery or take anti-glaucoma medication in the injected or the fellow eye? ☐No ☐Yes, if Yes, please provide details	☐OS ☐OD ☐OU Details:
Has the patient's anterior chamber angle been assessed in the eye(s) with IOP increase? ☐No ☐Yes, if Yes, please detail result, date, timing (pre- or post-injection):	By which method? Is the angle open, narrow or closed? ☐OS ☐OD Details:
Did the patient use corticosteroids or any other medication that could potentially increase IOP? ☐No ☐Yes, if yes, please specify the drug names and indications	
Does the patient have any of the following co-morbid conditions (please check all that apply)? ☐diabetes ☐high blood pressure ☐low blood pressure ☐retinal ischemia ☐CRAO ☐BRAO ☐eye trauma ☐eye surgeries ☐myopia ☐pseudo exfoliation syndrome ☐pigment dispersion syndrome ☐corneal arcus present, details:	
PFS details	
Who prepared the Eydenzelt PFS injection (e.g., physician, nurse, other)? Was the individual specifically trained on the Eydenzelt PFS? ☐No ☐Yes	

Who conducted the Eydenzelt injection with the PFS (e.g., physician, nurse)? Was the individual specifically trained on the Eydenzelt PFS? ☐No ☐Yes		
Was the 30G needle used for injections? ☐Yes ☐No; If no which needle size was used? Brand of injection needle, if known:		
Were all the bubbles eliminated/expelled, excess drug expelled, and the plunger correctly adjusted to the dose line before injection (moving the base of plunger dome (not the tip) to dosing line)? ☐Yes ☐No, if No please provide details:		
Was there any difficulty in preparing the PFS according to the instructions prior to the injection? ☐No ☐Yes, if yes, please explain		
Was there any physical or handling abnormality observed with the syringe/PFS? ☐No ☐Yes, if yes, please explain:		
For this event, did you see any foreign particles, discoloration or change in physical appearance of the Eydenzelt solution? ☐No ☐Yes, if yes provide details:		
For this event, have you injected, or attempted to inject, the residual volume which remained in the syringe after completion of injection? ☐No ☐Yes, if yes provide details:		
Other anti VEGF treatment:		
Did the patient have previous intravitreal injections? ☐No ☐Yes If, yes please fill adjacent columns to the right	Eydenzelt: ☐Vial ☐PFS Other intravitreal injections ☐	Was IOP increase also observed after previous intraocular injections? ☐No ☐Yes, please detail:
Further notes *(free text)*:		

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Eydenzelt (Aflibercept) EU Educational Material – KEY MESSAGES

The Marketing Authorisation Holder (MAH) will provide EU Educational Material for Eydenzelt. Prior to launch and during the product's lifecycle in each Member State, the MAH will agree the final Educational Material with the National Competent Authority. The MAH ensures that, following discussions and agreement with the National Competent Authorities in each Member State where Eydenzelt is marketed, ophthalmological clinics where Eydenzelt is expected to be used are provided with an updated physician information pack containing the following elements:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information packs

The physician information in the educational material contains the following key elements:

- Techniques for the intravitreal injection including use of a 30 G needle, and angle of injection
- Confirmation that the pre-filled syringe and the vial are for single use only
- The need to expel excess volume of the syringe before injecting Eydenzelt to avoid overdose
- Patient monitoring after intravitreal injection including monitoring for visual acuity and increase of intraocular pressure post-injection
- Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, intraocular inflammation, increased intraocular pressure, retinal pigment epithelial tear and cataract
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eydenzelt

The patient information pack of the educational material includes a patient information guide and its audio version. The patient information guide contains following key elements:

- Patient information leaflet
- Who should be treated with Eydenzelt
- How to prepare for Eydenzelt treatment
- What are the steps following treatment with Eydenzelt
- Key signs and symptoms of serious adverse events including endophthalmitis, intraocular inflammation, intraocular pressure increased, retinal pigment epithelial tear and cataract
- When to seek urgent attention from their health care provider
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eydenzelt