EU Risk Management Plan for Ahzantive (aflibercept)

RMP Version number: 1.0

Data lock point for this RMP: 10 Aug 2023

Date of final sign-off: 15 Nov 2024

Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation application submission

Summary of significant changes in this RMP: Not applicable

QPPV name[1]: Larissa Gutenmacher-Ruf

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

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Aflibercept
Pharmacotherapeutic group(s) (ATC Code)	S01LA05
Marketing Authorization Applicant	Formycon AG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Ahzantive (company code: FYB203)
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Aflibercept is a 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: It is designed to interfere with the increase in vascular permeability and growth of pathological new blood vessels that lead to retinal edema, ischemia and hemorrhage in diseases accompanied by ocular neovascularization.
	Important information about its composition: Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.
Hyperlink to the Product Information	Please refer to Module 1, Section 1.3.1: Proposed Product Information in Module 1.3.1
Indication(s) in the EEA	Current: Ahzantive is indicated for adults for the treatment of: - Neovascular (wet) age-related macular degeneration (AMD). - Visual impairment due to macular edema secondary to retinal vein occlusion (branch RVO or central RVO).

	- Visual impairment due to diabetic macular edema (DME). - Visual impairment due to myopic choroidal neovascularization (myopic CNV).
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current: In adult patients, the injection volume of Ahzantive is 50 microlitres (µL) (equivalent to 2 mg aflibercept). <u>Wet AMD</u> The recommended dose for Ahzantive is 2 mg aflibercept, equivalent to 50 microlitres. <u>Macular edema secondary to RVO</u> The recommended dose for Ahzantive is 2 mg aflibercept, equivalent to 50 microlitres. <u>Diabetic macular edema</u> The recommended dose for Ahzantive is 2 mg aflibercept, equivalent to 50 microlitres. <u>Myopic CNV</u> The recommended dose for Ahzantive is 2 mg aflibercept, equivalent to 50 microlitres.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Solution for injection in a vial. One vial contains 4 mg aflibercept in 100 microlitres (40 mg/mL) in iso-osmotic solution. Delivers a single dose of 2 mg/0.05 mL.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

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

According to Good Pharmacovigilance Practice (GVP) – Module V, this section is not applicable to biosimilar medicinal products.

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

Data from originator:

A comprehensive toxicology and safety pharmacology program was conducted for the originator Eylea. The monkey was identified as the only relevant species for repeated-dose studies with intravitreal (IVT) administration. Effects in non-clinical studies on repeated dose toxicity were observed only at systemic exposures considered substantially in excess of the maximum human exposure after intravitreal administration at the intended clinical dose indicating little relevance to clinical use.

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

Key safety findings (from non-clinical studies)	Relevance to human usage of aflibercept
• Potential to impair fertility Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous 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 curve (AUC) for free aflibercept observed at the 3 mg/kg intravenous dose, the systemic exposures were approximately 4,900-fold and 1,500-fold higher, respectively, than the exposure observed in adult patients after an intravitreal dose of 2 mg. All changes were reversible.	Results from animal studies with high systemic exposure indicate that aflibercept can impair male and female fertility. Such effects are not expected after ocular administration with very low systemic exposure.
• Potential to be embryo-fetotoxic An effect of aflibercept on intrauterine development was shown in embryo-fetal development studies in pregnant rabbits with intravenous (3 to 60 mg/kg) as well as subcutaneous (0.1 to 1 mg/kg) administration. The maternal no observed adverse effect level (NOAEL) was at the dose of 3 mg/kg or 1 mg/kg, respectively. A developmental NOAEL was not identified. At the 0.1 mg/kg dose, the systemic exposures based on C_{max} and cumulative AUC for free aflibercept were approximately 17- and 10-fold higher,	Although the systemic exposure after ocular administration is very low, aflibercept should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus. Aflibercept is not recommended in women of childbearing potential not using contraception. Appropriate contraception during the treatment and for at least 3 months after the last administration has to be indicated for women who could possibly become pregnant.

Key safety findings (from non-clinical studies)	Relevance to human usage of aflibercept
respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg.	
• Nasal cavities/sinuses Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at systemic exposures in excess of the maximum human exposure. At the NOAEL of 0.5 mg/eye in monkeys the systemic exposure was 42- and 56-fold higher based on C_{max} and AUC when compared to corresponding values observed in adult patients.	These findings were not confirmed in a targeted sub-study within the clinical phase III study VIEW 2 (adult patients). In the Phase III Study 20090 (FIREFLEYE) in preterm infants with retinopathy of prematurity (ROP), monitoring for nasal bleeding was included, since this patient population could be more sensitive with regard to changes of the nasal epithelium after IVT treatment with aflibercept and have a higher systemic exposure than adults. No cases of nasal bleeding were observed in this study, indicating therefore no relevance to human usage of aflibercept.

Source: Eylea RMP II SII and Eylea EU SmPC 09/2023

No signs of hepatotoxicity or nephrotoxicity in the non-clinical toxicology program of aflibercept were observed.

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

Data from the biosimilar:

Ahzantive (company code: FYB203) is developed as a biosimilar aflibercept to Eylea as the reference medicinal product. Like the originator Eylea, FYB203 is a glycosylated, disulfide-stabilized homodimeric recombinant fusion protein consisting of domain 2 of human vascular endothelial growth factor receptor 1 (VEGFR-1 D2) and domain 3 of VEGFR-2 (VEGFR-2 D3) fused to the Fc domain of human IgG1. *In vitro* data obtained with representative FYB203 drug substance and drug product batches from production scale demonstrated similar pharmacological results in binding assays and cell-based assays when compared to Eylea.

A Good Laboratory Practice (GLP)-compliant repeat dose toxicity study was performed for FYB203 to evaluate the toxicological effects of repeated IVT injections of FYB203 in comparison with EU-approved Eylea over a 5-week period in rabbits. The aim of this study was to evaluate the ocular and systemic tolerability/toxicity of FYB203 in comparison to Eylea after two repeated IVT injections into both eyes (2 x 50 µL; which equals 2 x 2000 µg/animal per injection) in rabbits. The respective vehicles served as controls.

Systemic tolerability/toxicity: Throughout the study period, no major clinical findings were recorded for any of the animals. Necropsy did not reveal any abnormal finding in any of the animals and no statistical difference was shown for gross weight of any of the measured organs, in comparison with vehicle controls. The histomorphological examination of rabbit organs from all rabbits did not reveal any morphological lesions which were considered to be related to the administration of the test item (FYB203), reference item (Eylea), or vehicle controls.

Ocular tolerability/toxicity: Mean intraocular pressure values were within normal values for all study animals following IVT injection of FYB203, EU-approved Eylea or vehicle items. No marked difference in ocular reactions were detected between FYB203, EU-approved Eylea, or vehicle control treated eyes. Analysis of full-field electroretinographic responses was performed on both treated eyes of all animals at baseline and on study days 8 and 20 on dark-adapted animals. No remarkable differences were

observed for all a-waves and b-waves at baseline and throughout the course of the study between FYB203, Eylea EU, or vehicle control treated eyes.

Ocular histopathology revealed numerous pathological findings in the examined eyes and adnexae (Harderian lacrimal gland). The most important finding was the occurrence of extremely severe anterior uveitis in two rabbits treated with FYB203 and in one rabbit treated with EU-approved Eylea. In addition, in three rabbits treated with FYB203 and in two rabbits treated with EU-approved Eylea, less severe anterior uveitis was observed. At study termination, none of the recovery animals and none of the vehicle control treated animals disclosed pathological findings.

Toxicokinetics: Concentrations of free aflibercept increased in plasma of all animals treated with FYB203 and Eylea. C_{max} of free aflibercept was detectable 72 hours after injection. For all animals, concentrations of the active substance declined over the following weeks (840 hours). Comparison of toxicokinetic profiles of free aflibercept in plasma indicated an approximately twofold difference between FYB203 and Eylea with FYB203 levels being lower when compared to the reference product. The different pharmacokinetic (PK) profile was likely caused by lower sialylation of FYB203 as compared to Eylea. However, the ocular distribution of FYB203 and Eylea was similar, and furthermore both aflibercept products had a similar toxicity profile. In Study FYB203-03-01, in patients with neovascular age-related macular degeneration (nAMD), similar systemic (plasma) free and total aflibercept exposure was observed for FYB203 versus Eylea in a subgroup of patients undergoing PK analyses.

Anti-drug antibody (ADA) formation: There were no differences in the rates of ADA formation between treatment groups. The formation of anti-aflibercept antibodies correlated well with the results of the ocular histopathology. Two out of four rabbits determined to be positive for the formation of ADAs following treatment with FYB203 showed signs of extremely severe anterior uveitis. In addition, one rabbit determined to be positive for the formation of ADAs following treatment with FYB203 showed signs of mild anterior uveitis. Two animals with mild anterior uveitis proved to be negative for the formation of ADAs. For rabbits treated with EU-approved Eylea, one out of five rabbits determined to be positive for the formation of ADAs showed signs of extremely severe anterior uveitis and one rabbit showed signs of mild anterior uveitis. The animal with mild anterior uveitis proved to be negative for the formation of ADAs. In Study FYB203-03-01, only 1 ADA-negative patient developed uveitis (see SVII.1).

In conclusion, in non-clinical studies, no clinically relevant differences in ocular and systemic toxicity and ocular pharmacokinetic parameters were noted between FYB203 and Eylea.

Summary of non-clinical safety concerns

Important identified risk	• None
Important potential risk	• Embryo-fetotoxicity
Missing information	• None

Part II: Module SIII - Clinical trial exposure

One comparative clinical trial in 433 patients was conducted to show similar efficacy and safety between the biosimilar (FYB203) and the reference product (Eylea). This was a Phase 3, randomized, double-masked, multi-center study comparing the efficacy and safety of the proposed aflibercept biosimilar (FYB203) to Eylea in patients with nAMD (FYB203-03-01, MAGELLAN-AMD). All eligible

patients were randomized in a 1:1 ratio to receive either FYB203 or EU-approved Eylea at a dose of 2 mg (0.05 mL of a 40 mg/mL solution). The treatment consisted of 1 IVT injection every 4 weeks for 3 consecutive doses starting at Baseline (Visit 1) through Week 8 (Visit 3) followed by 1 IVT injection every 8 weeks over a period of approximately 48 weeks (Visit 8), resulting in a total of 8 IVT injections per patient.

The study was conducted in 9 countries, where 77 sites screened at least 1 patient. 434 patients were randomized to receive treatment with FYB203 (215 patients) or Eylea (219 patients). After consent withdrawal by 1 patient randomized to Eylea, 433 patients started treatment with FYB203 (215 patients) and Eylea (218 patients). These 433 patients formed the safety analysis set (SAF). Demographics were comparable between the FYB203 and Eylea groups. Overall, there were fewer male patients (42.7%) than female patients (57.3%). Most patients were White (91.9%) and not Hispanic or Latino (98.2%). The mean (standard deviation [SD]) age of patients was 73.5 (7.71) years. Most patients were 65 years or older (90.3%). The primary efficacy endpoint analysis (Best Corrected Visual Acuity to Week 8) demonstrated therapeutic equivalence between FYB203 and Eylea. The secondary efficacy analyses showed similar results for both groups across all endpoints. FYB203 was safe and well tolerated and the safety profile of FYB203 was in line with the established safety profile of Eylea. The study demonstrated that FYB203 and Eylea have a highly similar safety and efficacy profile.

Summary information on the clinical trial exposure is provided in the tables below.

Table SIII.1: Number of administered IVT injections until Week 56 in MAGELLAN-AMD, SAF

Number of injections	**FYB203 (N=215)** **n (%)**	**Eylea (N=218)** **n (%)**	**Total (N=433)** **n (%)**
1 injection	1 (0.5)	1 (0.5)	2 (0.5)
2 injections	3 (1.4)	2 (0.9)	5 (1.2)
3 injections	1 (0.5%)	5 (2.3%)	6 (1.4%)
4 injections	4 (1.9%)	1 (0.5%)	5 (1.2%)
5 injections	3 (1.4%)	0 (0.0%)	3 (0.7%)
6 injections	7 (3.3%)	2 (0.9%)	9 (2.1%)
7 injections	13 (6.0%)	8 (3.7%)	21 (4.8%)
8 injections	183 (85.1%)	199 (91.3%)	382 (88.2%)

IVT = intravitreal; SAF = safety analysis set; N, n = number of patients

Source: 14.3.1.5 End of Text Tables

Table SIII.2: Treatment duration until Week 56 [days] in MAGELLAN-AMD, SAF

Statistic	**FYB203** **(N=215)**	**Eylea** **(N=218)**	**Total** **(N=433)**
Mean (SD)	320.2 (60.01)	326.0 (57.92)	323.1 (58.97)
Median	337.0	337.0	337.0
Min–Max	1 - 372	1 - 372	1 - 372
Q1–Q3	334.0 - 338.0	336.0 - 339.0	336.0 - 338.0

SAF = safety analysis set; N, n = number of patients; SD = standard deviation; Min = minimum; Max = maximum; Q1 = first quartile; Q3 = third quartile

Source: 14.3.1.2 End of Text Tables

Table SIII.3: Sex, age group and race in MAGELLAN-AMD, SAF

Category	Sub-category	FYB203 (N=215) n (%)	Eylea (N=218) n (%)	Total (N=433) n (%)
Sex	Males	94 (43.7)	91 (41.7)	185 (42.7)
	Females	121 (56.3)	127 (58.3)	248 (57.3)
Age group	50-64 years	17 (7.9)	25 (11.5)	42 (9.7)
	65 to 75 years	105 (48.8)	111 (50.9)	216 (49.9)
	>75 to 84 years	76 (35.3)	69 (31.7)	145 (33.5)
	≥85	17 (7.9)	13 (6.0)	30 (6.9)
Race	White	197 (91.6)	201 (92.2)	398 (91.9)
	Black or African American	0 (0.0)	0 (0.0)	0 (0.0)
	Asian	17 (7.9)	16 (7.3)	33 (7.6)
	American Indian or Alaska native	0 (0.0)	0 (0.0)	0(0.0)
	Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
	Other	1 (0.5)	1 (0.5)	2 (0.5)
	Not reported	0 (0.0)	0 (0.0)	0 (0.0)

SAF = safety analysis set; N, n = number of patients

Source: 14.1.5.1.1 End of Text Tables

Table SIII.4: Age group and race in male patients in MAGELLAN-AMD, SAF

Category	Sub-category	FYB203 (N=94) n (%)	Eylea (N=91) n (%)	Total (N=185) n (%)
Age group	50-64 years	9 (9.6)	9 (9.9)	18 (9.7)
	65 to 75 years	47 (50.0)	52 (57.1)	99 (53.5)
	>75 to 84 years	32 (34.0)	25 (27.5)	57 (30.8)
	≥85	6 (6.4)	5 (5.5)	11 (5.9)
Race	White	80 (85.1)	80 (87.9)	160 (86.5)
	Black or African American	0 (0.0)	0 (0.0)	0 (0.0)
	Asian	13 (13.8)	11 (12.1)	24 (13.0)
	American Indian or Alaska native	0 (0.0)	0 (0.0)	0 (0.0)
	Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
	Other	1 (1.1)	0 (0.0)	1 (0.5)
	Not reported	0 (0.0)	0 (0.0)	0 (0.0)

SAF = safety analysis set; N, n = number of patients

Source: 14.1.5.3.1 End of Text Tables

Table SIII.5: Age group and race in female patients in MAGELLAN-AMD, SAF

Category	Sub-category	FYB203 (N=121) n (%)	Eylea (N=127) n (%)	Total (N=248) n (%)
Age group	50-64 years	8 (6.6)	16 (12.6)	24 (9.7)
	65 to 75 years	58 (47.9)	59 (46.5)	117 (47.2)
	>75 to 84 years	44 (36.4)	44 (34.6)	88 (35.5)
	≥85	11 (9.1)	8 (6.3)	19 (7.7)
Race	White	117 (96.7)	121 (95.3)	238 (96.0)
	Black or African American	0 (0.0)	0 (0.0)	0 (0.0)
	Asian	4 (3.3)	5 (3.9)	9 (3.6)
	American Indian or Alaska native	0 (0.0)	0 (0.0)	0 (0.0)
	Native Hawaiian or other pacific islander	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	1 (0.8)	1 (0.4)
	Not reported	0 (0.0)	0 (0.0)	0 (0.0)

SAF = safety analysis set; N, n = number of patients
Source: 14.1.5.3.1 End of Text Tables

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

SIV.1 Exclusion criteria in pivotal clinical study within the development program

The pivotal clinical study in the FYB203 clinical development program is MAGELLAN-AMD. Important exclusion criteria of this study are discussed in the following.

Study eye requiring immediate treatment

Reason for exclusion: Any condition in the study eye that requires immediate treatment.

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

Rationale: Safety/well-being of patients who cannot await completion of screening period to receive treatment.

Any prior treatment with IVT anti-VEGF agent (e.g. bevacizumab, aflibercept, ranibizumab) or any investigational products to treat AMD, in either eye

Reason for exclusion: Use of these agents could interfere with interpretation of the clinical outcomes.

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

Rationale: To study aflibercept only in treatment-naïve patients.

History of vitrectomy, macular surgery or other surgical intervention for AMD in the study eye

Reason for exclusion: Vitreoretinal surgery is associated with the removal of the vitreous gel; thus, it may influence the pharmacodynamics of an intraocular pharmacological treatment. Precautionary measure due to limited data in patients with vitrectomized eyes. Macular surgery and other surgical

interventions may also hinder interpretation of study outcomes, e.g. foveal center point or foveal central subfield assessment.

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

Rationale: To exclude confounding factors that may hinder interpretation of study results.

History of IVT or periocular injections of corticosteroids or device implantation within six months prior to randomization in the study eye

Reason for exclusion: The use of corticosteroids has a potential impact on the efficacy results, can cause morphology changes of the eye, and may affect the biosimilarity evaluation.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

Prior treatment with verteporfin (photodynamic therapy), transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e.g. focal laser photocoagulation) in the study eye

Reason for exclusion: Precautionary measure. Use of these agents could interfere with interpretation of the clinical outcomes.

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

Rationale: To study aflibercept only in treatment-naïve patients.

Any other intraocular surgery (including cataract surgery) in the study eye within three months prior to randomization

Reason for exclusion: According to the summary of product characteristics (SmPC) of the reference product, the aflibercept dose should be withheld 28 days before and after planned intraocular surgery.

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

Rationale: Precautionary measure.

Sub- or intra-retinal hemorrhage that comprises more than 50% of the entire lesion in the study eye

Reason for exclusion: Large sub- or intra-retinal hemorrhage can confound the assessment of the extent and size of the neovascular lesion that needs treatment. Furthermore, it is listed as special warning in the SmPC of the originator.

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

Rationale: Not to include patient with disease features that would confound or make the results difficult to interpret.

Irreversible structural damage involving the center of fovea (e.g. advanced fibrosis >50% of the total lesion in the study eye or atrophy) in the study eye that was considered sufficient to irreversibly impair visual acuity (VA)

Reason for exclusion: These anatomic characteristics are representative of pre-existing pathology, which make interpretation of patient data obtained during a clinical trial difficult and may confound study results.

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

Rationale: Aflibercept is unlikely to have an effect in patients with pre-existing pathology from late stage disease.

CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia

Reason for exclusion: CNV with other origins may have a potential impact on best corrected visual acuity and other functional parameters and eventually could interfere with the interpretation of the clinical outcomes.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

Retinal pigment epithelial tear involving the macula in the study eye

Reason for exclusion: Retinal pigment epithelial tear is listed as common adverse drug reaction in the SmPC of the reference medicinal product. Worsening of the condition due to the injection procedure is possible.

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

Rationale: To exclude the risk of worsening the condition.

History of full-thickness macular hole (stage 2 and above by clinical examination or full thickness macular hole by SD-OCT [Spectral Domain Optical Coherence Tomography] imaging of any size) in the study eye

Reason for exclusion: A patient's macular hole may cause a decline in visual acuity, an important endpoint for safety and efficacy of an intervention for intraocular use. Therefore, the presence of a macular hole could confound efficacy outcomes. The section "4.4 Special warning and precautions for use" of the Eylea SmPC includes the recommendation to suspend the treatment in patients with stage 3 or 4 macular hole.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

History of or current retinal detachment in the study eye

Reason for exclusion: Precautionary measure. These anatomic characteristics are representative of pre-existing pathology, which make interpretation of patient data obtained during a clinical trial difficult and may confound study results.

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

Rationale: To exclude patients with pre-existing pathology, which makes interpretation of patient data obtained during a clinical trial difficult and may confound study results.

Current vitreous hemorrhage in the study eye

Reason for exclusion: Precautionary measure. This anatomic characteristic is representative of pre-existing pathology, which makes interpretation of patient data obtained during the clinical trial difficult and may confound study results.

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

Rationale: To exclude patients with pre-existing pathology, which make interpretation of patient data obtained during a clinical trial difficult and may confound study results.

Spherical equivalent of the refractive error in the study eye demonstrating more than 6 diopters of myopia

Reason for exclusion: Refractive errors with high diopter values can make interpretation of patient data obtained during the clinical trial difficult and may confound study results.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

For patients who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye cannot exceed 6 diopters of myopia

Reason for exclusion: Refractive errors with high diopter values can make interpretation of patient data obtained during the clinical trial difficult and may confound study results.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

History of or current corneal transplant in the study eye

Reason for exclusion: Corneal transplant may confound study results and make interpretation of patient data obtained during a clinical trial difficult.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

Aphakia in the study eye. Absence of an intact posterior capsule is allowed if it occurred as a result of yttrium aluminum garnet laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation

Reason for exclusion: Aphakia is a potential confounding factor which may impact biosimilarity assessment

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

Active or recent (within 4 weeks prior to randomization) intraocular inflammation of clinical significance in either eye such as active infections of the anterior segment (excluding mild blepharitis) including conjunctivitis, keratitis, scleritis, uveitis, or endophthalmitis

Reason for exclusion: There is a risk of worsening of an ongoing inflammatory process, or masking inflammation due to another cause. In addition, active intraocular inflammation may be associated with an increased intraocular pressure (IOP); administering an intraocular injection when there is ongoing inflammation is contraindicated.

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

Rationale: Active severe intraocular inflammation is a contraindication mentioned in the SmPC of the originator.

Uncontrolled ocular hypertension or glaucoma in the study eye (defined as IOP ≥30 mmHg, despite treatment with anti-glaucomatous medication)

Reason for exclusion: Precautionary measure. Increased IOP and uncontrolled glaucoma is a general contraindication to any invasive intraocular procedure due to known possible associated complications.

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

Rationale: Injection of additional volume to the vitreous in patients with increased IOP or uncontrolled glaucoma should generally be avoided to avoid consequences of additional raised IOP including a temporary increase associated with the procedure.

Ocular disorders in the study eye (i.e. retinal detachment, pre-retinal membrane of the macula or cataract with significant impact on VA) at the time of Screening that may confound interpretation of study results and compromise VA

Reason for exclusion: Ocular disorders may confound interpretation of study results and compromise visual acuity.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

Any concurrent intraocular condition in the study eye (e.g. glaucoma, cataract or diabetic retinopathy) that, in the opinion of the Principal Investigator or his/her delegate, would either require surgical intervention during the study to prevent or treat visual loss that might result from that condition or affect interpretation of study results

Reason for exclusion: Any condition which may lead to loss of vision or associated potential complications could confound the outcomes of efficacy and safety in the clinical trial.

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

Rationale: Precautionary measure and to exclude confounding factors that may hinder the interpretation of study results.

Use of other investigational drugs (excluding vitamins, minerals) within 30 days or 5 half-lives prior to randomization, whichever is longer

Reason for exclusion: General exclusion criterion to avoid potential risk factors and unknown side effects.

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

Rationale: Standard exclusion in clinical trials to exclude confounding effects.

Systemic treatment with anti-VEGF agent (e.g. bevacizumab) within 90 days prior randomization

Reason for exclusion: General exclusion criterion to avoid potential risk factors and side effects

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

Rationale: Precautionary measure

Any type of advanced, severe or unstable disease, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change

Reason for exclusion: Exclusion of any diseases that may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk.

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

Rationale: Precautionary measure.

Stroke or myocardial infarction within six months prior to randomization

Reason for exclusion: Precautionary measure based on effects which have been identified following intravenous administration of VEGF inhibitors.

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

Rationale: Precautionary measure to exclude patients with a recent major cardiovascular event.

Presence of uncontrolled systolic blood pressure >160 mmHg or uncontrolled diastolic blood pressure >100 mmHg within 4 weeks prior to randomization

Reason for exclusion: Precautionary measure as systemic conditions such as uncontrolled hypertension are serious risks impacting the patient's overall health. When the patient is undergoing treatment for serious systemic conditions, study participation and required follow-up visits may be difficult to make.

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

Rationale: To exclude patients with poor control of high blood pressure that may impact overall health and their ability to meet the requirements for study visits and assessments.

Known hypersensitivity to the investigational medicinal product (aflibercept or any component of the aflibercept formulation) or to drugs of similar chemical class or to fluorescein or any other component of fluorescein formulation

Reason for exclusion: To avoid a hypersensitivity reaction in predisposed patients.

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

Rationale: Precautionary measure.

Current or planned use of systemic medications known to be toxic to the lens, retina, or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, and ethambutol

Reason for exclusion: Substances that are toxic to the lens can make the assessment and following interpretation of patient data obtained during the clinical trial difficult and may confound study results.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

History of recurrent significant infections and/or current treatment for active systemic infection

Reason for exclusion: A systemic infection could spread into the eye through hematogenous circulation and confound study results. Also, the presence of systemic infection may put the patient at higher risk for infection related to the intraocular injection.

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

Rationale: Precautionary measure.

Any diagnosis and/or signs of nAMD requiring treatment with an IVT anti-VEGF agent (e.g. aflibercept, bevacizumab, ranibizumab) within the screening period or the expectation, in the opinion of the Principal Investigator or his/her delegate, to need such treatment in the fellow eye throughout the study

Reason for exclusion: Treatment of the fellow eye should not be withheld if it is crucial. However, fellow eye treatment during the clinical trial may have an impact on the pharmacokinetic results and confound their interpretation.

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

Rationale: To exclude confounding factors that may hinder the interpretation of study results.

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

Rare adverse drug reactions detected during the clinical development program for Eylea (in wet AMD, CRVO, BRVO, DME, and myopic CNV patients) were eye disorders such as traumatic cataract, vitritis, and hypopyon. Based on the experience from the long exposure during the clinical development of Eylea, it is unlikely that a rare adverse reaction will impact the benefit/risk balance of aflibercept in the target population.

Aflibercept is slowly absorbed from the eye into the systemic circulation after intravitreal administration and is predominately observed in the systemic circulation as an inactive stable complex with VEGF. As with other large proteins, both free and bound aflibercept are expected to be cleared by proteolytic catabolism. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than a 100-fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF (2.91 µg/mL) in a study of healthy volunteers. Adverse events due to cumulative effects are not anticipated (source: Eylea RMP v35.1 Table SIV.2a).

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

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

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	No pregnancies occurred in the FYB203 clinical trial development program. As aflibercept belongs to the class of anti-VEGF therapies, which are potentially teratogenic, embryo-fetotoxicity has been identified as an important potential risk. Based on very limited human data, aflibercept may be excreted in human milk at low levels. Aflibercept is a large protein molecule and the amount of medication absorbed by the infant is expected to be minimal. The effects of aflibercept on a breast-fed newborn/infant are unknown.

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	The active moiety in aflibercept is a large protein. The metabolism and excretion of such molecules is generally by means other than the renal or hepatic pathways. No specific studies in patients with hepatic and/or renal impairment have been conducted with aflibercept. Available data do not suggest a need for a dose adjustment with Ahzantive in these patients.
Population with relevant different ethnic origin	In the MAGELLAN-AMD study, most patients were white (91.9%); 7.6% were Asian.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other	The originator included pediatric patients (indication ROP) in the clinical development program. The safety and efficacy of Eylea in children and adolescents below 18 years of age for indications other than ROP have not been studied. There is no relevant use of aflibercept in the pediatric population for the indications of wet AMD, CRVO, BRVO, DME, and myopic CNV. There is a high percentage of elderly patients in the clinical development program of FYB203 (Table SIII.3).

Part II: Module SV - Post-authorisation experience

Not applicable.

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

Potential for misuse for illegal purposes

No potential for misuse or use for illegal purposes are currently anticipated with the use of FYB203.

Part II: Module SVII - Identified and potential risks

FYB203 and the reference product Eylea were well tolerated in Study FYB203-03-01 in patients with nAMD (MAGELLAN-AMD). There were no clinically remarkable differences in the incidence and nature of treatment-emergent adverse events (TEAEs). The overall evaluation of tolerability and safety confirmed the known safety profile for aflibercept. Therefore, the same identified and potential risks of Eylea published in the Eylea risk management summary are applied for FYB203.

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

Not applicable. Biosimilarity of FYB203 to Eylea was demonstrated. The overall evaluation of tolerability and safety of FYB203 confirmed the known safety profile for aflibercept.

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

Not applicable.

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

The safety concerns in this initial RMP submission for FYB203 are identical to the current safety concerns of Eylea (RMP version 35.1).

Important identified risks associated with the use of FYB203:

- Endophthalmitis (likely infectious origin)
- Intraocular inflammation
- Transient intraocular pressure increase
- Retinal pigment epithelia tears
- Cataract (especially of traumatic origin)

Important potential risks associated with the use of FYB203:

- Medication errors
- Off-label use and misuse
- Embryo-fetotoxicity

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

Not applicable.

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

Details on important identified/potential risks (potential mechanisms, evidence source(s) and strength of evidence, characterization of the risk, risk factors and risk groups, preventability, impact on the risk-benefit balance of the product, and public health impact, references, all as applicable) are adapted from the Eylea RMP version 35.1.

In the subsection 'characterization of the risk', for the originator Eylea, proportion of subjects with relevant events are presented as given in the Eylea RMP version 35.1. The percentage of subjects with one or more events associated with a specific important identified or potential risk is provided for all clinical indications, AMD, CRVO, BRCO, DME, and myopic CNV (mCNV) (except for ROP). Important identified and potential risks refer to safety data of Eylea in the following studies (for their design and efficacy data refer to [applicable reference], retrieved via PubMed):

- AMD: Pooled data of the pivotal Phase III AMD randomized controlled studies VIEW 1 and VIEW 2 (96 weeks) [Schmidt-Erfurth et al. 2014], open-label VIEW 1 extension study (VGFT-

OD-0910) [Kaiser et al. 2017], Phase III AMD randomized controlled study SIGHT (52 weeks) [Li et al. 2017], Phase IV AMD study ALTAIR (52 weeks) [Ohji et al. 2020];

- CRVO: pooled data of the Phase III CRVO randomized controlled studies GALILEO and COPERNICUS (76/100 weeks) [Pielen et al. 2017];
- BRVO: Phase III BRVO randomized controlled study VIBRANT (52 weeks) [Clark et al. 2016];
- DME: pooled data of the pivotal Phase III DME randomized controlled studies VIVID-DME and VISTA-DME (148 weeks) [Heier et al. 2016]; randomized, controlled Phase III DME study VIVID-EAST (52 weeks) [Chen et al. 2020]; single-arm, open-label study Phase III DME study VIVID-JAPAN (52 weeks) [Terasaki et al. 2019];
- mCNV: Phase III myopic CNV randomized controlled study MYRROR (48 weeks) [Ikuno et al. 2015].

For FYB203, data are presented for patients with neovascular age-related macular degeneration (Study FYB203-03-01 [MAGELLAN-AMD], N=433). Medical Dictionary for Regulatory Activities (MedDRA) search terms used for retrieval of patients with events belonging to the respective safety concern are identical to those described in the Eylea RMP version 35.1 and are specified in Annex 7.3.

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

Important identified risk: Endophthalmitis

Potential mechanisms:

The intravitreal injection procedure can implant pathogens into the eye if there is a break in sterile technique. Source of pathogenic agents is in most cases the patient's conjunctival bacterial flora.

Evidence source(s) and strength of evidence:

Inflammation of the inner structures of the eye (in particular the vitreous body, which fills the globe) may occur as a result of an infection with microorganisms, either through direct traumatic injury of the eye (exogenous infection) or through spreading of microorganisms from other areas of the body (endogenous infection). This pathogen-caused inner eye (intraocular) infection is called endophthalmitis. In cases of inflammation where no pathogens can be identified (no/negative culture growth of microorganisms observed), the condition may be characterized as "sterile endophthalmitis" or "non-infectious endophthalmitis".

Infectious endophthalmitis can possibly lead to a loss of vision and sometimes even to the loss of the eye itself.

Characterization of the risk:

A systematic review of 278 publications was published in 2011 to identify adverse events associated with anti-VEGF injections. Endophthalmitis was reported after anti-VEGF injections with incidence rates below or equal to 0.04 (95% confidence interval [CI]: 0.02-0.08), 0.05 (95% CI: 0.03-0.10) per 100 injections for ranibizumab and bevacizumab, respectively [van der Reis et al. 2011]. Endophthalmitis following IVT injections of anti-VEGF agents is an uncommon but potentially devastating complication [Sachdeva et al. 2016].

Endophthalmitis can cause permanent loss of vision if it is not diagnosed at an early stage and appropriately treated. Vision loss as such constitutes a substantial burden for the involved subject.

Originator: For Eylea (source: RMP version 35.1), reported frequencies in the study eye from clinical trials are given as absolute number (of exposed patients) and percentage:

- In *adults* in the indication nAMD
    - VIEW 1 and VIEW 2 (96 weeks): 5 of 1,824 (0.3%)
    - VIEW 1 long-term extension study: 3 of 323 (0.9%)
    - SIGHT (52 weeks): 0
    - ALTAIR (52 weeks): 0
- In *adults* in the indication CRVO
    - COPERNICUS and GALILEO (pooled data 76/100 weeks): 1 of 317 (0.3%)
- In *adults* in the indication BRVO
    - VIBRANT (52 weeks): 0
- In *adults* in the indication mCNV
    - MYRROR (48 weeks): 0
- In *adults* in the indication DME
    - VIVID-DME and VISTA-DME (pooled data, 148 weeks). 3 of 821 (0.4%)
    - VIVID-EAST (52 weeks): 0
    - VIVID-Japan (52 weeks): 0

Post-marketing surveillance (PMS) data Eylea (source RMP version 35.1): Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period until 30 September 2017, the reporting rate of endophthalmitis cases (N=844) was 0.05 cases per 1,000 sold vials (0.005%) and 0.36 cases per 1,000 patient years (0.036%), respectively.

Biosimilar: In MAGELLAN-AMD there were no cases of endophthalmitis.

Risk factors and risk groups:

Improper aseptic technique increases the risk of intraocular inflammation.

Preventability:

The risk of intraocular inflammation, especially if caused by pathogens, cannot be completely excluded, but may be minimized. In the scope of intravitreal injections of drugs for the treatment of wet AMD, CRVO, BRVO, DME, and myopic CNV, (by which pathogens might be inadvertently carried into the inner eye), it is absolutely crucial to work under strict aseptic and sterile conditions. Thus, only experienced and appropriately trained ophthalmologists should be charged with the injections.

Moreover, patients should report to their doctors any signs or symptoms of intraocular inflammation (e.g., visual acuity decreased, pain, photophobia, or redness) in order to enable the treating physician to introduce appropriate countermeasures in due time.

Impact on the risk-benefit balance of the product:

An educational program is performed as an additional risk minimization measure to raise patients' awareness on identified and potential risks. The effectiveness of this program was verified with a post-authorization safety study (Eylea SN 16526). Furthermore, a specific questionnaire is used to gain more knowledge about this risk.

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

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.

Important identified risk: Intraocular inflammation

Potential mechanisms:

In a certain percentage the intraocular inflammation is culture-negative. However, there are some difficulties in the definition and diagnosis of "sterile" endophthalmitis or intraocular inflammation. Many infectious cases are not diagnosed as such as no tap is performed, or tap is performed, but culture is false negative. Vice versa, true sterile cases may be false positive in culture (e.g. due to contamination of the medium) and thus misdiagnosed as infectious.

The etiology of sterile intraocular inflammations, independently of the administered drug, remains uncertain, and a multifactorial origin has been proposed. Needle trauma per se might cause a certain inflammatory reaction. Inflammation secondary both to IVT triamcinolone acetonide and to IVT bevacizumab (or other anti-VEGF agents) that manifest with acute and painless vision loss is usually interpreted as being primarily toxic and sterile. In these patients, visual acuity improves progressively as the intraocular inflammation reduces without any specific treatment. However, since there remains a substantial uncertainty on origin, the complication is often treated - on top of steroids and non-steroidal anti-inflammatory drug (NSAID) - like an acute (infectious) endophthalmitis with antibiotics because of the devastating visual prognosis of this intraocular infection in the absence of antibiotic therapy [Marticorena et al. 2012].

Two types of inflammation are seen with intravitreal injections, acute onset sterile inflammation and delayed onset inflammatory vasculitis. Acute onset inflammation can be subcategorized into subclinical anterior chamber inflammation and sterile uveitis/endophthalmitis. Inflammatory vasculitis is only associated with brolucizumab, suspected to be an auto-immune type IV hypersensitivity reaction, and occurred in 3.3% of injections according to the post hoc review of the HAWK/HARRIER data [Monés et al 2022]. In addition, silicone oil from syringes can induce immunogenic protein aggregates. Agitation of the syringe, freeze thawing, shipping and improper storage prior to injection may increase the amount of silicone oil released from the syringe [Anderson et al 2021].

Evidence source(s) and strength of evidence:

Next to endophthalmitis/intraocular inflammations with an infectious origin, there are inflammations where no pathogens can be identified (either no culture performed or negative culture growth), the condition may be characterized as "sterile" inflammatory condition. The cause of a sterile inflammation, independently of the administered drug, remains uncertain, and a multifactorial origin cannot be discarded. An intraocular inflammation generally constitutes a serious condition, which may lead to generalized eye inflammation and risk of blindness. Treatment should be initialized as soon as possible, and, depending on cause and severity, may consist of topical and intravitreal application of antibiotics, corticosteroids, and surgical removal of matter and infected structures (drainage, vitrectomy).

Characterization of the risk:

Post-injection, sterile intraocular inflammation is a known risk following intravitreal injections of anti-VEGFs and for other intravitreally applied drugs. Incidence rates reported in the literature vary and have been reported to occur in clusters corresponding to administration dates. Moshfeghi et al.

described 12 cases (11 patients) out of 60,322 anti-VEGF injections (bevacizumab n=7; ranibizumab n=5) that developed post-injection inflammation (0.02% per injection), 5 cases (4 patients) were culture-negative (0.008%) [Moshfeghi et al. 2011]. Day et al. conducted a retrospective, longitudinal case-control study using the Medicare 5% claims database. Based on an evaluation of 40,903 intravitreal injections of anti-VEGF agents in wet AMD, an endophthalmitis rate of 0.09% (38 cases) and a uveitis rate of 0.11 % (45 cases) were reported [Day et al. 2011], whether cases were culture-positive or -negative is not reported. Chong et al. reported 44 cases of sterile inflammation after intravitreal injection of bevacizumab (0.27% of 16,166 injections). Seventeen inflammatory reactions were clustered around specific dates, which suggests a possible relation to drug preparation, though a specific cause remains unclear [Chong et al 2010].

A recent review reported that subclinical anterior chamber inflammation can occur at rates as high as 19% after intravitreal anti-VEGF injection. Rates of sterile uveitis/endophthalmitis range from 0.05% to 4.4% depending on the anti-VEGF agent (aflibercept (0.05-2.1%) [Anderson et al 2021].

Severe intraocular infection/inflammation can cause permanent loss of vision if it is not diagnosed at an early stage and appropriately treated. Vision loss as such constitutes a substantial burden for the involved subject.

Originator: For Eylea (source: RMP version 35.1), reported frequencies of intraocular inflammation (grouped term) in the study eye from clinical trials are given as absolute number (of Eylea-exposed patients) and percentage:

- In *adults* in the indication nAMD
    - VIEW 1 and VIEW 2 (pooled data, 96 weeks): 46 of 1,824 (2.5%)
    - VIEW 1 long-term extension study: 6 of 323 (1.9%)
    - SIGHT (52 weeks): 1 of 299 (0.3%)
    - ALTAIR (52 weeks): 0
- In *adults* in the indication CRVO
    - COPERNICUS and GALILEO (pooled data 76/100 weeks): 5 of 317 (1.6%)
- In *adults* in the indication BRVO
    - VIBRANT (52 weeks): 1 of 158 (0.6%)
- In *adults* in the indication mCNV
    - MYRROR (48 weeks): 1 of 116 (0.9%)
- In *adults* in the indication DME
    - VIVID-DME and VISTA-DME (pooled data, 148 weeks). 20 of 821 (2.4%)
    - VIVID-EAST (52 weeks): 0
    - VIVID-Japan (52 weeks): 1

PMS data Eylea (source RMP version 35.1): Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period until 30 September 2017, the reporting rate of intraocular inflammation cases (N=1,047) was 0.07 cases per 1,000 sold vials (0.007%) and 0.45 cases per 1,000 patient years (0.045%), respectively.

Biosimilar: In MAGELLAN-AMD (56 weeks), intraocular inflammation occurred in 9 of 433 (2.1%) patients with a similar incidence in both treatment groups. MedDRA search terms are specified in Annex 7.3. Details are shown in the following table.

SVII.1 Intraocular inflammation in MAGELLAN-AMD by PT, worst severity, seriousness, worst outcome and relationship, SAF (N=433)

TEAE category	**Details**	**FYB203 (N=215) n (%)**	**Eylea (N=218) n (%)**
Grouped term	Intraocular inflammation	5 (2.3)	4 (1.8)
Included PTs:	Iritis	1 (0.5)	3 (1.4)
	Iridocyclitis	2 (0.9)	1 (0.5)
	Vitritis	1 (0.5)	1 (0.5)
	Anterior chamber cell	1 (0.5)	0 (0.0)
	Uveitis	1 (0.5)	0 (0.0)
Worst severity	mild	4 (1.9)	2 (0.9)
	moderate	0 (0.0)	2 (0.9)
	severe	1 (0.5)[a,b]	0 (0.0)
Seriousness	Serious	1 (0.5)[a,b]	0
Worst outcome	Recovered/Resolved	4 (1.9)	4 1.8)
	Recovered/Resolved with sequelae	1 (0.5)[a,b]	0 (0.0)
	Recovering/resolving	0 (0.0)	0 (0.0)
	Not recovered/resolved	0 (0.0)	0 (0.0)
	Unknown	0 (0.0)	0 (0.0)
	Fatal	0 (0.0)	0 (0.0)
Relationship to study drug / study procedure	Probably related	1 (0.5)[a,b] / 1 (0.5)[a,b]	0 (0.0) / 1 (0.5)[a,c]
	Possibly related	2 (0.9)[c,d] / 2 (0.9)[c,d]	3 (1.4)[c,d] / 2 (0.9)[c,d]
	Unlikely to be related	0 (0.0) / 0 (0.0)	0 (0.0) / 1 (0.5)
	Unrelated	2 (0.9) / 2 (0.9)	1 (0.5) / 0 (0.0)
	Unknown	0 (0.9) / 0 (0.0)	0 (0.0) / 0 (0.0)

SAF =safety analysis set; TEAE = treatment-emergent adverse event; N or n = number of patients; PT = MedDRA preferred term

[a] iridocyclitis; [b] uveitis; [c] iritis; [d] vitritis (note: 1 patient may have more than 1 event)

Source: Magellan Clinical Study Report

Risk factors and risk groups:

Improper aseptic technique increases the risk of intraocular inflammation.

Preventability:

Measures other than aseptic injection techniques to prevent infectious reactions are not known to minimize the risk of intraocular inflammation. It is crucial to work under strict aseptic and sterile conditions. Thus, only experienced and appropriately trained ophthalmologists should be charged with the injection procedure.

Moreover, patients should report to their doctors any signs or symptoms of intraocular inflammation (e.g. visual acuity decreased, pain, photophobia, or redness) as soon as possible in order to enable the treating physician to introduce appropriate countermeasures in due time.

Impact on the risk-benefit balance of the product:

An educational program is performed as an additional risk minimization measure to raise patients' awareness on identified and potential risks. The effectiveness of this program was verified with a post-authorization safety study (Eylea SN 16526). Furthermore, a specific questionnaire is used to gain more knowledge about this risk.

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

Public health impact:

Severe intraocular infection/inflammation can cause permanent loss of vision if it is not rapidly diagnosed and appropriately treated. This condition is likely to impact the ability to work and to increase the dependency on caregivers.

Important identified risk: Transient intraocular pressure increase

Potential mechanisms:

Transient intraocular pressure (IOP) increase is attributed to an increase in vitreous volume (volume effect).

Evidence source(s) and strength of evidence:

Due to the filling of the eye-ball with liquids (i.e. aqueous and vitreous humor), there is an inherent pressure in the eye, which is measured in the same unit as the blood pressure is (i.e. in millimeter Mercury; mmHg). Normal pressure in the inner eye is approximately 10-21 mmHg. Elevated eye pressure is a major risk factor for a condition called "glaucoma", which is characterized by a loss of nerve fibers in the optic nerve with the subsequent risk of blindness. However, many different factors may be responsible for the development of glaucoma, and increased intraocular pressure is not a mandatory prerequisite for the development of glaucoma (e.g. the condition of normal-tension glaucoma is well-known). In the scope of intravitreal injections, it is easily comprehensible that the volume load caused by the application of the drug, which is dissolved in a certain amount of injection liquid, will lead to a transient increase of intraocular pressure at least until the surplus fluid will have been resorbed from the inner eye.

Characterization of the risk:

Transient IOP increase is usually a mild reaction which is compensated within 0.5 to 1 hours after injection so that IOP normalises back to baseline values [Bakri et al. 2009; Kotliar et al 2007].

Originator: For Eylea (source: RMP version 35.1), reported frequencies of transient intraocular pressure increase (grouped term) in the study eye from clinical trials are given as absolute number (of Eylea-exposed patients) and percentage, if available:

- In *adults* in the indication nAMD
    - VIEW 1 and VIEW 2 (pooled data, 96 weeks): 142 of 1,824 (7.8%)
    - VIEW 1 long-term extension study: 16 of 323 (5.0%)
    - SIGHT (52 weeks): 17 of 299 (5.7%)
    - ALTAIR (52 weeks): 0
- In *adults* in the indication CRVO
    - COPERNICUS and GALILEO (pooled data 76/100 weeks): 43 of 317 (13.6%)
- In *adults* in the indication BRVO
    - VIBRANT (52 weeks): 5 of 158 (3.2%)
- In *adults* in the indication mCNV
    - MYRROR (48 weeks): 0

- In *adults* in the indication DME
    - VIVID-DME and VISTA-DME (pooled data, 148 weeks). 100 of 821 (12.2%)
    - VIVID-EAST (52 weeks): 11 of 299 (3.7%)
    - VIVID-Japan (52 weeks): 2 of 72 (2.8%)

PMS data Eylea (source RMP version 35.1): Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period until 30 September 2017, the reporting rate of cases associated with IOP increase (N=250) was 0.02 cases per 1,000 sold vials (0.002%) and 0.11 cases per 1,000 patient years (0.011 %), respectively.

Biosimilar: In MAGELLAN-AMD (56 weeks), intraocular pressure increased occurred in 18 of 433 (4.2%) of patients with a similar frequency in both treatment groups. MedDRA search terms are specified in Annex 7.3. Details are shown in the following table.

SVII.2 Incidence of intraocular pressure increase in MAGELLAN-AMD by PT, worst severity, seriousness, worst outcome and relationship, SAF (N=433)

TEAE category	**Details**	**FYB203 (N=215) n (%)**	**Eylea (N=218) n (%)**
Grouped term	Intraocular pressure increased	9 (4.2)	9 (4.1)
Included PTs:	Intraocular pressure increased	8 (3.7)	9 (4.1)
	Ocular hypertension	1 (0.5)	0 (0.0)
Worst severity	mild	5 (2.3)	6 (2.8)
	moderate	4 (1.9)	3 (1.4)
	severe	0 (0.0)	0 (0.0)
Seriousness	Serious	0	0
Worst outcome	Recovered/Resolved	8 (3.7)	8 (3.7)
	Recovered/Resolved with sequelae	0 (0.0)	0 (0.0)
	Recovering/resolving	1 (0.5)	1 (0.5)
	Not recovered/resolved	0 (0.0)	0 (0.0)
	Unknown	0 (0.0)	0 (0.0)
	Fatal	0 (0.0)	0 (0.0)
Relationship to study drug / study procedure	Probably related	0 (0.0) / 7 (3.3)	2 (0.9) / 7 (3.2)
	Possibly related	0 (0.0) / 0 (0.0)	3 (1.4) / 1 (0.5)
	Unlikely to be related	1 (0.5) / 0 (0.0)	0 (0.0) / 0 (0.0)
	Unrelated	7 (3.3) / 2 (0.9)	4 (1.8) / 1 (0.5)
	Unknown	1 (0.5) / 0 (0.0)	0 (0.0) / 0 (0.0)

SAF = safety analysis set; TEAE = treatment-emergent adverse event; N or n = number of patients; PT = MedDRA preferred term

Source: Magellan Clinical Study Report

Risk factors and risk groups:

Patients with glaucoma.

Increased intraocular pressure is a known adverse drug reaction on treatment with intravitreal corticosteroids.

Preventability:

Intraocular pressure should be checked after each injection. As the transient increase in eye pressure is an inherent result of the procedure-related volume load in the scope of intravitreal injections, there

is no reasonable chance to avoid this effect. However, this effect is usually transient, and there is no robust evidence so far that pressure increases following intravitreal injections (even after multiple injections) could become durable or may lead to clinically relevant glaucoma.

Impact on the risk-benefit balance of the product:

An educational program is performed as an additional risk minimization measure to raise patients' awareness on identified and potential risks. The effectiveness of this program was verified with a post-authorization safety study (Eylea SN 16526).

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 tears

Potential mechanisms:

Development of retinal pigment epithelial (RPE) tears after anti-VEGF intravitreal injection has been attributed to a decline in intercellular adherence, thereby increasing susceptibility to tearing of the RPE layer [Singh and Sears 2006].

Evidence source(s) and strength of evidence:

The retinal pigment epithelium is the outer layer of the retina. Tears in that layer may occur secondary to AMD, following intravitreal injections, or for unknown reasons. These tears may be self-sealing or may require sealing by laser coagulation.

Characterization of the risk:

RPE tear is a potentially vision threatening complication of retinal pigment epithelial detachment (PED) associated with neovascular age-related macular degeneration. RPE tear has been reported to occur spontaneously and after treatment with anti-vascular growth endothelial factor agents. The incidence of RPE tears ranged from 0.61% to 12.3% in patients with neovascular AMD treated with anti-VEGF injections of ranibizumab or bevacizumab (review in [Rachitskaya and Goldhardt 2015]). RPE tears have also been reported in patients with wet AMD in the absence of treatment, particularly when a PED is present. Incidence rates for spontaneous RPE tears ranged between 2-6% of eyes with nAMD [Chan et al. 2010; Chang and Sarraf 2007; Salz et al. 2010; Sastre-Ibáñez et al 2019]. For eyes with nAMD and vascularized PED incidences up to approximately a quarter are reported, 10-15% according to [Salz et al 2010], and 0.4-27% according to [Sastre-Ibáñez et al 2019].

RPE tears may lead to a loss of vision (and thus to legal blindness).

Originator: For Eylea (source: RMP version 35.1), reported frequencies of retinal pigment epithelia tear in the study eye from clinical trials are given as absolute number (of Eylea-exposed patients) and percentage:

- In *adults* in the indication nAMD
    - VIEW 1 and VIEW 2 (pooled data, 96 weeks): 35 of 1,824 (1.9%)
    - VIEW 1 long-term extension study: 2 of 323 (0.6%)
    - SIGHT (52 weeks): 1 of 299 (0.3%)

  - ALTAIR (52 weeks): 3 of 254 (1.2%)
- In *adults* in the indication CRVO
  - COPERNICUS and GALILEO (pooled data 76/100 weeks): 0
- In *adults* in the indication BRVO
  - VIBRANT (52 weeks): 0
- In *adults* in the indication mCNV
  - MYRROR (48 weeks): 0
- In *adults* in the indication DME
  - VIVID-DME and VISTA-DME (pooled data, 148 weeks). 0
  - VIVID-EAST (52 weeks): 0
  - VIVID-Japan (52 weeks): 0

PMS data Eylea (source RMP version 35.1): Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period until 30 September 2017, the reporting rate of of RPE tear cases (N=159) was 0.01 cases per 1,000 sold vials (0.001 %) and 0.07 cases per 1,000 patient years (0.007%), respectively.

Biosimilar: In MAGELLAN-AMD (56 weeks), retinal pigment epithelial tears occurred in 7 of 433 (1.6%) patients with a similar frequency in both treatment groups. MedDRA search terms are specified in Annex 7.3. Details are shown in the following table.

SVII.3 Incidence of retinal pigment epithelial tears in MAGELLAN-AMD by PT, worst severity, seriousness, worst outcome and relationship, SAF (N=433)

TEAE category	**Details**	**FYB203 (N=215) n (%)**	**Eylea (N=218) n (%)**
Grouped term	Retinal pigment epithelial tears	4 (1.9)	3 (1.4)
Included PTs:	Retinal pigment epithelia tear	4 (1.9)	3 (1.4)
Worst severity	mild moderate severe	1 (0.5) 2 (0.9) 1 (0.5)	2 (0.9) 1 (0.5) 0 (0.0)
Seriousness	Serious	0	0
Worst outcome	Recovered/Resolved Recovered/Resolved with sequelae Recovering/resolving Not recovered/resolved Unknown Fatal	0 (0.0) 0 (0.0) 1 (0.5) 3 (1.4) 0 (0.0) 0 (0.0)	0 (0.0) 1 (0.5) 0 (0.0) 2 (0.9) 0 (0.0) 0 (0.0)
Relationship to study drug / study procedure	Probably related Possibly related Unlikely to be related Unrelated Unknown	3 (1.4) / 0 (0.0) 0 (0.0) / 0 (0.0) 0 (0.0) / 1 (0.5) 1 (0.5) / 3 (1.4) 0 (0.0) / 0 (0.0)	1 (0.5) / 0 (0.0) 0 (0.0) / 0 (0.0) 0 (0.0) / 1 (0.5) 2 (0.9) / 2 (0.9) 0 (0.0) / 0 (0.0)

SAF; safety analysis set; TEAE = treatment-emergent adverse event; N or n = number of patients; PT = MedDRA preferred term

Source: Magellan Clinical Study Report

Risk factors and risk groups:

Wet AMD with pigment epithelial detachment; treatment of neovascularization. The vast majority of RPE tears have a pre-existing vascularized PED and the most important predisposing risk factor appears to be PED size as measured by basal diameter and vertical height (review in [Salz et al 2010]).

Preventability:

The underlying mechanisms resulting in RPE tears following intravitreal injection are not yet understood and thus, no preventive measure are currently known.

Impact on the risk-benefit balance of the product:

An educational program is performed as an additional risk minimization measure to raise patients' awareness on identified and potential risks. The effectiveness of this program was verified with a post authorization safety study (Eylea SN 16526).

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

Important identified risk: Cataract (especially of traumatic origin)

Potential mechanisms:

Related to IVT procedure.

Evidence source(s) and strength of evidence:

Generally, clouding of the usually clear eye lens is called a cataract. Cataract may occur spontaneously (particularly in the elderly), as a side effect of certain drugs, or following outside influences such as irradiation or mechanical injury (traumatic cataract).

If the needle used to inject aflibercept touched the lens in the patient's eye this could cause such a traumatic cataract. There is currently no evidence that the occurrence of a traumatic cataract is increased on treatment with aflibercept. However, as this might be a hypothetical result of the lens perforation, it has been included as potential important risk.

Characterization of the risk:

Originator: For Eylea (source: RMP version 35.1), reported frequencies of cataract (grouped term) in the study eye from clinical trials are given as absolute number (of Eylea-exposed patients) and percentage, crude incidence and injection-related as assessed by the Investigator:

- In *adults* in the indication nAMD
    - VIEW 1 and VIEW 2 (pooled data, 96 weeks):
      233 of 1,824 (12.8%), injection-related 14 (0.8%)
    - VIEW 1 long-term extension study: 45 of 323 (13.9%), injection-related 0
    - SIGHT (52 weeks): 12 of 299 (4.0%), injection-related 3 (1.0%)
    - ALTAIR (52 weeks): 3 of 254 (1.2%), injection-related 0

- In *adults* in the indication CRVO
    - COPERNICUS and GALILEO (pooled data 76/100 weeks): 24 of 317 (7.6%), injection-related 1
- In *adults* in the indication BRVO
    - VIBRANT (52 weeks): 7 of 158 (4.4%), injection-related 1
- In *adults* in the indication mCNV
    - MYRROR (48 weeks): 1 of 116 (0.9%), injection-related 0
- In *adults* in the indication DME
    - VIVID-DME and VISTA-DME (pooled data, 148 weeks): 188 of 821 (22.9%), injection-related 23 (2.8%)
    - VIVID-EAST (52 weeks): 6 of 299 (2.0%), injection-related 0
    - VIVID-Japan (52 weeks): 1 of 72 (1.4%), injection-related 0

PMS data Eylea (source RMP version 35.1): Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period until 30 September 2017, the reporting rate of cataract cases (N=713) was 0.04 cases per 1,000 sold vials (0.004%) and 0.31 cases per 1,000 patient years (0.031 %), respectively.

Biosimilar: In MAGELLAN-AMD (56 weeks), cataract occurred in 26 of 433 (6.0%) patients with a comparable incidence in both treatment groups, none assessed as related to study drug and one related to study procedure (possibly related, FYB203 group). MedDRA search terms are specified in Annex 7.3. Details are shown in the following table.

SVII.4 Incidence of cataracts in MAGELLAN-AMD by PT, worst severity, seriousness, worst outcome and relationship, SAF (N=433)

TEAE category	**Details**	**FYB203 (N=215) n (%)**	**Eylea (N=218) n (%)**
Cataract (grouped term)		14 (6.5)	12 (5.5)
Included PTs:	Cataract	11 (5.1)	10 (4.6)
	Cataract cortical	1 (0.5)	1 (0.5)
	Cataract nuclear	1 (0.5)	1 (0.5)
	Cataract subcapsular	2 (0.9)	0 (0.0)
Worst severity	mild	10 (4.7)	9 (4.1)
	moderate	4 (1.9)	3 (1.4)
	severe	0 (0.0)	0 (0.0)
Seriousness	Serious	0	0
Worst outcome	Recovered/Resolved	2 (0.9)	3 (1.4)
	Recovered/Resolved with sequelae	1 (0.5)	0 (0.0)
	Recovering/resolving	5 (2.3)	3 (1.4)
	Not recovered/resolved	6 (2.8)	6 (2.8)
	Unknown	0 (0.0)	0 (0.0)
	Fatal	0 (0.0)	0 (0.0)

TEAE category	Details	FYB203 (N=215) n (%)	Eylea (N=218) n (%)
Relationship to study drug / study procedure	Probably related Possibly related Unlikely to be related Unrelated Unknown	0 (0.0) / 0 (0.0) 0 (0.0) / 1 (0.5) 5 (2.3) / 1 (0.5) 9 (4.2) / 12 (5.6) 0 (0.0) / 0 (0.0)	0 (0.0) / 0 (0.0) 0 (0.0) / 0 (0.0) 3 (1.4) / 0 (0.0) 9 (4.1) / 12 (5.5) 0 (0.0) / 0 (0.0)

SAF = safery analysis set; TEAE = treatment-emergent adverse event; N or n = number of patients; PT = MedDRA preferred term

Source: Magellan Clinical Study Report

Risk factors and risk groups:

Cataract is a known adverse drug reaction on treatment with corticosteroids (following topical as well as systemic administration) [Gaballa et al 2021].

Preventability:

By correct IVT procedure and a correct angle of the needle while injecting a cataract could be prevented. This is common knowledge of injecting physicians.

Impact on the risk-benefit balance of the product:

An educational program is performed as an additional risk minimization measure to raise patients' awareness on identified and potential risks. The effectiveness of this program was verified with a post-authorization safety study (Eylea SN 16526).

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

Public health impact:

Patients experiencing (traumatic) cataract may require cataract surgery.

Important potential risk: Medication errors

Potential mechanisms:

Not applicable.

Evidence source(s) and strength of evidence:

Although FYB203 is provided in a vial, there is an excess volume which exceeds the recommended net dose of 2 mg aflibercept per injection. Thus, injection of more than the recommended dose results in overdose. However, this numerical overdose is limited, and the drug will be administered only by qualified physicians (not by patients), and this reduces the risk of inappropriate dosing and administration as well. Nevertheless, it was decided to consider ‘medication error’ a potential risk of treatment, which is, however, completely avoidable by proper adherence to the dosing recommendations.

Characterization of the risk:

Originator: For Eylea (source: RMP version 35.1), reported frequencies of medication errors (grouped term) in the study eye from clinical trials are given as absolute number (of Eylea-exposed patients) and percentage:

- In *adults* in the indication nAMD
    - VIEW 1 and VIEW 2 (pooled data, 96 weeks): 5 of 1,824 (0.3%)[2]
    - VIEW 1 long-term extension study: 0
    - SIGHT (52 weeks): 0
    - ALTAIR (52 weeks): 0
- In *adults* in the indication CRVO
    - COPERNICUS and GALILEO (pooled data 76/100 weeks): 0
- In *adults* in the indication BRVO
    - VIBRANT (52 weeks): 0
- In *adults* in the indication mCNV
    - MYRROR (48 weeks): 0
- In *adults* in the indication DME
    - VIVID-DME and VISTA-DME (pooled data, 148 weeks). 1 of 821 (unintentional overdose of concomitant tramadol)
    - VIVID-EAST (52 weeks): 0
    - VIVID-Japan (52 weeks): 0

PMS data Eylea (source RMP version 35.1): In view of the large number of vials sold by 15 SEP 2017 (almost 16 million), there is no indication that medication errors might be a relevant issue of treatment with Eylea in routine care. Numerically, the reporting rate of cases with medication error (N=3,245) was 0.20 cases per 1,000 sold vials (0.020%) and 1.40 cases per 1,000 patient years of exposure (0.140%), respectively. The 5 most frequently reported preferred term events were "inappropriate schedule of drug administration" (1,476 events), "drug dose omission" (583 events), "product use issue" (523 events), "multiple use of single-use product" (263 events), and "product use in unapproved indication" (172 events). Vial/dose fractioning (coded to PT "multiple use of single-use product") is a common practice in some countries, and it might be supported by some health insurances. This PT was reported in 263 cases (with 263 events) and more than half of these cases (138 cases) were invalid, while 125 cases were valid. Most of the valid cases were associated with intraocular inflammations/infections which is an established and labelled adverse drug reaction (ADR) of the Eylea injection. For these cases it remains unknown whether the procedure of vial splitting contributed to the development of an intraocular infection. Overall, no increase in reporting rates for reported intraocular inflammations/infections was observed over the years worldwide, and to date, the reported number of cases with vial fractioning is considered low.

Biosimilar: In MAGELLAN-AMD (56 weeks), no medication errors occurred.

Risk factors and risk groups:

Not applicable.

Preventability:

Instructions on the correct drug preparation and administration will be given in the SmPC in order to minimise the risk of accidental medication errors.

[2] PT Drug administration error: 1, PT Overdose: 4. In 4 additional cases, ‘overdose’ was not reported as event, but as explanation for the event ‘intraocular pressure increase’.

Impact on the risk-benefit balance of the product:

An educational program is performed as an additional risk minimization measure to raise patients' awareness on identified and potential risks. The effectiveness of this program was verified with a post-authorization safety study (Eylea SN 16526).

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

Public health impact:

There is no life-threatening potential when aflibercept is administered by an incorrect route.

Important potential risk: Off-label use and misuse

Potential mechanisms:

Not applicable.

Evidence source(s) and strength of evidence:

As with other drugs, FYB203 might be intentionally used other than recommended, or in clinical conditions outside the approved indications. Since the clinical experience with aflibercept preparations in such off-label use will be limited (in particular in terms of efficacy and safety), any case of off-label use will be considered a potential risk. Since aflibercept must be administered by a qualified physician experienced in administering intravitreal injections, the risk of misuse is regarded as very low.

Characterization of the risk:

Originator: PMS data Eylea (source RMP version 35.1): By 15 SEP 2017, there were 1,846 recorded cases (including 1,925 events) of off-label use and misuse. Considering the sales figures and the estimated cumulative patient exposure in the post-marketing period until 30 SEP 2017, the reporting rate of off-label cases (N=1,846) was 0.12 cases per 1,000 sold vials (0.012%) and 0.80 cases per 1,000 patient years (0.080%), respectively.

Biosimilar: Not applicable.

Risk factors and risk groups:

Not applicable.

Preventability:

Off-label ophthalmic use has been reported with currently marketed VEGF inhibitors, e.g. for bevacizumab for the treatment of wet AMD [Conrad et al. 2008] or DME [Nagasawa et al. 2009], [Scott et al. 2007]. Off-label use of ranibizumab has been reported for ophthalmic diseases other than wet AMD such as DME [Pieramici et al. 2008] or retinal vein occlusion [Spaide et al. 2008] before market authorization was granted in the respective indications. There are also reports on off-label use of bevacizumab and ranibizumab in rarer diseases such as myopic CNV (in countries where myopic CNV is not labelled), or ROP (reviewed in [Andreoli and Miller 2007]). Aflibercept may have been used in the past to treat some cases of retinopathy of prematurity [Mutlu and Sarici 2013]. In general, as for the majority of possible indications for anti-VEGF therapy approved medications are available, the potential for off-label use is considered minimal. Additionally, non-approved indications are currently being investigated in various studies to establish safety and efficacy in these therapeutic areas.

Most neovascular and VEGF dependent retina diseases including particularly AMD are diseases of the adult. Therefore, the potential for off-label use in the pediatric population is expected to be very limited due to the nature of pediatric ophthalmic diseases. The number of such cases is considered very low and their care is provided by pediatric ophthalmologists who are tertiary care based and experienced in the care of these infants. Only Eylea pre-filled syringe in combination with the pediatric dosing device PICLEO is currently indicated for treatment of preterm infants with ROP. Ahzantive is provided only as vial and is indicated for use in adult patients only. Considering this, the risk for off-label use of the vial in this setting is assessed as minimal.

Intentional misuse, as such, is difficult to prevent because of the user's deliberate decision to deviate from the provided instructions. However, intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections.

Impact on the risk-benefit balance of the product:

An educational program is performed as an additional risk minimization measure to raise patients' awareness on identified and potential risks. The effectiveness of this program was verified with a post-authorization safety study (Eylea SN 16526).

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

Public health impact:

Not applicable.

Important potential risk: Embryo-fetotoxicity

Potential mechanisms:

An embryo-fetal toxicity study was performed in the rabbit with intravenous dosing of aflibercept (Eylea) at doses which provided systemic exposures over 670-fold higher than that observed with IVT dosing using the clinical dose of 2 mg. The study identified dose-related increases in fetal resorptions, pregnancy disruptions and numerous fetal (external, visceral and skeletal) malformations. These effects were thought to be due to the antiangiogenic effect of aflibercept. See also Table SII.1.

Evidence source(s) and strength of evidence:

Testing of aflibercept in animals was performed as a standard part of the development of Eylea. It was noted that aflibercept given in extremely high doses to animals (by far exceeding the doses which would be given to humans) might have an adverse influence on prenatal development (i.e. during the embryonic or fetal development period; so-called embryo-fetotoxicity). Therefore, embryo-fetotoxicity is regarded as a potential risk of treatment with aflibercept. However, IVT aflibercept is injected locally and at a dose that is distinctively lower than the exposure in animals under which the critical events were observed. So far, there is no relevant indication that treatment with IVT aflibercept might be associated with embryo-fetotoxicity.

Characterization of the risk:

Originator: For Eylea (source: RMP version 35.1) up to 15 September 2017, 8 pregnancies from clinical trials and 12 from post-marketing experience. Overall, these few pregnancy cases currently reported both in clinical studies and in post-marketing use do not give any rise to assume that treatment with Eylea might be associated with relevant embryo-fetotoxic effects. Based on currently available non-clinical data, no individual impact in terms of risk to the treated population is apparent.

Biosimilar: In MAGELLAN-AMD (56 weeks), no drug exposure via parent occurred.

Risk factors and risk groups:

Patients at risk are women of childbearing potential.

Preventability:

Treatment with FYB203 is not recommended during pregnancy, unless the potential benefit outweighs the potential risk to the fetus.

Impact on the risk-benefit balance of the product:

An educational program is performed as an additional risk minimization measure to raise patients' awareness on identified and potential risks. The effectiveness of this program was verified with a post-authorization safety study (Eylea SN 16526).

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

Public health impact:

Based on currently available non-clinical data, no public health impact in terms of risk to the treated population is apparent.

SVII.3.2. Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

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

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

To optimize the data collection for defined medical conditions, a specific follow-up questionnaire will be used for endophthalmitis and intraocular inflammation (see Annex 4.1). This specific questionnaire will be used to follow-up on any post-marketing or study reports causing suspicion of these events in order to standardize and increase the completeness of reports.

Table Part III.1 Routine pharmacovigilance activities / questionnaires

Questionnaire	Objectives	Important identified risk
Specific questionnaire to be used for any post-marketing or study reports suspicious for endophthalmitis and intraocular inflammation (see Annex 4.1)	Specific questionnaire to obtain comprehensive and standardized follow-up information about cases suspicious for endophthalmitis and intraocular inflammation	Endophthalmitis (likely infectious origin) and intraocular inflammation

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 Additional pharmacovigilance activities

Not applicable.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorization efficacy studies

There are no planned or ongoing post authorization efficacy studies.

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

Risk Minimization Plan

V.1. Routine risk minimization measures

The following tables provide, per safety concern, an overview of the applied routine and additional risk minimization measures (quoted text parts are taken from the EU SmPC/Package Leaflet [PL] and are aligned to the originator).

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

Safety concern	Routine risk minimization activities
Endophthalmitis (likely infectious origin)	**Routine risk communication:** SmPC section 4.2 (Posology and method of administration) SmPC section 4.3 (Contraindications) SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) Package Leaflet section 2 (What you need to know before you are given Ahzantive) Package Leaflet section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • In SmPC Section 4.2 (Posology and method of administration), a comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • In SmPC Section 4.2 (Posology and method of administration) and Package Leaflet section 2 (What you need to know before you are given Ahzantive), the following text is provided for adults: *"Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay".* • *"Active or suspected ocular or periocular infection"* and *"active severe intraocular inflammation"* are listed in SmPC Section 4.3 (Contraindications) and Package Leaflet section 2 (What you need to know before you are given Ahzantive). • The following text is provided in SmPC Section 4.4 (Special warnings and precautions for use): *"Intravitreal injections, including those with aflibercept, have been associated with ... <endophthalmitis> ... (see section 4.8). Proper aseptic injection techniques must always be used when administering aflibercept. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Adult patients should be instructed to*

	report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay". • The following text is included in the Package Leaflet section 2 (What you need to know before you are given Ahzantive*): "if you develop an infection or inflammation inside the eye (endophthalmitis) or other complications, you may have eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, and increased sensitivity to light. It is important to have any symptoms diagnosed and treated as soon as possible*." • The following text is included in Package Leaflet section 3 (How you will be given Ahzantive): *Before the injection your doctor will use a disinfectant eyewash to clean your eye carefully to prevent infection.* **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections.
Intraocular inflammation	**Routine risk communication:** SmPC section 4.2 (Posology and method of administration) SmPC section 4.3 (Contraindications) SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) Package Leaflet section 2 (What you need to know before you are given Ahzantive) Package Leaflet section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • In SmPC Section 4.2 (Posology and method of administration), a comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • "*Active or suspected ocular or periocular infection*" and "*active severe intraocular inflammation*" are listed in SmPC Section 4.3 (Contraindications) and Package Leaflet section 2 (What you need to know before you are given Ahzantive). • The following text is provided in SmPC Section 4.4 (Special warnings and precautions for use): *"Intravitreal injections, including those with aflibercept, have been associated with ... <intraocular inflammation> ... (see section 4.8). Proper aseptic injection techniques must always be used when administering aflibercept. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs. Adult patients should be instructed to*

	report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay". • The following text is provided in SmPC Section 4.4 (Special warnings and precautions for use): *"As this is a therapeutic protein, there is a potential for immunogenicity with aflibercept (see section 4.8). Patients should be instructed to report any signs or symptoms of intraocular inflammation,e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity."* • The following text is included in the Package Leaflet section 2 (What you need to know before you are given Ahzantive): *"if you develop an infection or inflammation inside the eye (endophthalmitis) or other complications, you may have eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, and increased sensitivity to light. It is important to have any symptoms diagnosed and treated as soon as possible."* • The following text is included in Package Leaflet section 3 (How you will be given Ahzantive): *"Before the injection your doctor will use a disinfectant eyewash to clean your eye carefully to prevent infection."* **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections.
Transient intraocular pressure increase	**Routine risk communication:** SmPC section 4.2 (Posology and method of administration) SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) SmPC section 4.9 (Overdose) Package Leaflet section 2 (What you need to know before you are given Ahzantive) Package Leaflet section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • In SmPC Section 4.2 (Posology and method of administration), a comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • The following text is provided in SmPC Section 4.2 (Method of administration): *"Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available".*

	• The following text is provided in SmPC Section 4.4 (Special warnings and precautions for use): *"Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with aflibercept (see section 4.8). Special precaution is needed in patients with poorly controlled glaucoma (do not inject Ahzantive while the intraocular pressure is ≥30 mmHg). In all cases, both the intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately".* • The following text is included in the Package Leaflet section 2 (What you need to know before you are given Ahzantive): *"injections with Ahzantive may cause an increase in eye pressure (intraocular pressure) in some patients within 60 minutes of the injection. Your doctor will monitor this after each injection."* • The following text is provided in SmPC Section 4.9 (Overdose): *"Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdose, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated (see section 6.6)"*. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections.
Retinal pigment epithelial tears	**Routine risk communication:** SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) Package Leaflet section 2 (What you need to know before you are given Ahzantive) Package Leaflet section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • The following text is provided in SmPC Section 4.4 (Special warnings and precautions for use): *"Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD, include a large and/or high pigment epithelial retinal detachment. When initiating aflibercept therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears."* • The following text is included in the Package Leaflet section 2 (What you need to know before you are given Ahzantive): *"your doctor will check whether you have other risk factors that may increase the chance of a tear or detachment of one of the layers at the back of the eye (retinal detachment or tear, and retinal pigment epithelial detachment or tear), in which case aflibercept must be given with caution"*.

	Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections.
Cataract (especially of traumatic origin)	**Routine risk communication:** SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.8 (Undesirable effects) Package Leaflet section 2 (What you need to know before you are given Ahzantive) Package Leaflet section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • In SmPC Section 4.2 (Posology and method of administration), a comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • The following text is provided in SmPC Section 4.4 (Special warnings and precautions for use): *"Intravitreal injections, including those with aflibercept, have been associated with ... and iatrogenic traumatic cataract (see section 4.8). Proper aseptic injection techniques must always be used when administering aflibercept. Adult patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay*". • The following text is included in the Package Leaflet section 2 (What you need to know before you are given Ahzantive): *"if you develop an infection or inflammation inside the eye (endophthalmitis) or other complications, you may have eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, and increased sensitivity to light. It is important to have any symptoms diagnosed and treated as soon as possible."* • The following text is included in Package Leaflet section 3 (How you will be given Ahzantive): *"Before the injection your doctor will use a disinfectant eyewash to clean your eye carefully to prevent infection."* **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections.
Medication errors	**Routine risk communication:** SmPC section 4.2 (Posology and methods of administration) SmPC section 4.9 (Overdose)

	Package Leaflet section 1 (What Ahzantive is and what it is used for) Package Leaflet section 3 (How you will be given Ahzantive) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • In SmPC Section 4.2 (Posology and methods of administration) and Package Leaflet section 'information intended for HCPs only', a detailed verbal instruction is provided for the handling of the vial in order to minimise the risk of drug administration error. • The following text is provided in SmPC Section 4.9 (Overdose) in order to emphasise the association between overdose and intraocular pressure increase increase: *"Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdose, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated (see section 6.6)"*. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections.
Off-label use and misuse	**Routine risk communication:** SmPC section 4.1 (Therapeutic indications) Package Leaflet section 1 (What Ahzantive is and what it is used for) Package Leaflet section 3 (How you will be given Ahzantive) **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Contraindications are listed in SmPC Section 4.3 (Contraindications) and Package Leaflet section 2 (What you need to know before you are given Ahzantive) • Conditions in which treatment should be withheld/discontinued/not recommended are included in the SmPC section 4.4 and Package Leaflet section 2 (What you need to know before you are given Ahzantive) • Conditions of use in pregnancy and breastfeeding are included in the SmPC section 4.6 and Package Leaflet section 2 (What you need to know before you are given Ahzantive) **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections.
Embryo-fetotoxicity	**Routine risk communication:**

	SmPC section 4.4 (Special warnings and precautions for use) SmPC section 4.6 (Fertility, pregnancy and lactation) SmPC section 5.3 (Preclinical safety data) Package Leaflet section 2 (What you need to know before you are given Ahzantive) **Routine risk minimization activities recommending specific clinical measures to address the risk:** The following statements are provided in SmPC Section 4.4 (Special warnings and precautions for use) and Package Leaflet section 2 (What you need to know before you are given Ahzantive: *"Aflibercept should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept."* • The following statements are provided in SmPC Section 4.6 (Fertility, pregnancy and lactation): Women of childbearing potential: *"Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept."* Pregnancy: *"There are no data on the use of aflibercept in pregnant women. Studies in animals have shown embryo-foetal toxicity. Although the systemic exposure after ocular administration is very low, aflibercept should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus"*. • The following statements are provided in the Package Leaflet section 2 (What you need to know before you are given Ahzantive): *"Women of childbearing potential have to use effective contraception during treatment and for at least three further months after the last injection of Ahzantive. There is no experience of using Ahzantive in pregnant women. Ahzantive should not be used during pregnancy unless the potential benefit outweighs the potential risk to the unborn child. If you are pregnant or planning to become pregnant, discuss this with your doctor before treatment with Ahzantive."* **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections.

V.2. Additional risk minimization measures

Educational program

Besides routine risk minimization activities (SmPC and patient information), additional activity, specifically an educational program, is considered to be necessary for the important identified risks of

endophthalmitis (likely infectious origin), intraocular inflammation, transient intraocular pressure increase, retinal pigment epithelium tears, and cataract (especially of traumatic origin), as well as for the important potential risk of embryo-fetotoxicity. Generally, the educational material covers the indications wet AMD, CRVO, BRVO, myopic CNV, and DME.

Objectives and rationale for the additional risk minimization activity

To inform patients and physicians about risks in order to minimize their occurrence and consequences in routine care. Educational material also includes guidance on the IVT injection procedure to re-train physicians in order to minimize injection-related adverse reactions (adult population). The following risks are addressed in the Educational Material: endophthalmitis/intraocular inflammation, transient intraocular pressure increase, RPE tear, cataract, and embryo-fetotoxicity.

Target audience and planned distribution path

The target audience are health-care professionals (HCPs) specialized in intravitreal injections of anti-VEGF agents as well as patients to be treated. The key messages of the educational materials (provided in Part VII Annex 6) will be distributed through a digital communication method (digital platform) to the target audience(s). Paper version will be provided upon request from health-care professional, if needed. 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 requested per GVP Module XVI addendum.

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

Success of the proposed risk minimization measures will be evaluated by the criterion of a consistent spontaneous reporting rate of events concerning safety concerns at the time of the periodic safety update report (PSUR). Educational materials for adult patients have been in place for the reference product Eylea since its launch, and since further studies to assess continued effectiveness are not considered to be required for the reference product, the same is considered for the biosimilar product.

Removal of additional risk minimization activities

Not applicable.

V.3 Summary of risk minimization measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Endophthalmitis (likely infectious origin)	**Routine risk minimization measures:** SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2,3 and 4 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific questionnaire to be used for any post-marketing or study reports suspicious for endophthalmitis and intraocular inflammation (see Annex 4.1)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).	**Additional pharmacovigilance activities:** None
Intraocular inflammation	**Routine risk minimization measures:** SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2,3 and 4 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific questionnaire to be used for any post-marketing or study reports suspicious for endophthalmitis and intraocular inflammation (see Annex 4.1) **Additional pharmacovigilance activities:** None
Transient intraocular pressure increase	**Routine risk minimization measures:** SmPC sections 4.2, 4.4, 4.8 and 4.9 Package Leaflet sections 2 and 4 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).	
Retinal pigment epithelial tears	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 Package Leaflet sections 2 and 4 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None
Cataract (especially of traumatic origin)	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 and 4.8 Package Leaflet sections 2, 3 and 4 **Other routine risk minimization measures beyond the Product Information:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).	**Additional pharmacovigilance activities:** None
Medication errors	**Routine risk minimization measures:** SmPC sections 4.2, 4.9 and 6.6 Package Leaflet sections 1 and 3 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise physicians' awareness on medication error (prescriber guide and video;patient guide "Your guide to Ahzantive", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None
Off-label use and misuse	**Routine risk minimization measures:** SmPC sections 4.1. 4.3, 4.4 and 4.6 Package Leaflet sections 1, 2 and 3	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on off-label use (prescriber guide and video;patient guide "Your guide to Ahzantive", and its audio version).	**Additional pharmacovigilance activities:** None
Embryo-fetotoxicity	**Routine risk minimization measures:** SmPC sections 4.4, 4.6 and 5.3 Package Leaflet section 2 **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on the potential risk of embryo-toxicity and to underline information on treatment of women of child-bearing potential, and the need for appropriate contraception in women of childbearing potential (prescriber	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	guide and video; patient guide "Your guide to Ahzantive", and its audio version).	

Part VI: Summary of the risk management plan

Summary of risk management plan for Ahzantive (aflibercept)

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

Ahzantive's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how FYB203 should be used.

This summary of the RMP for Ahzantive 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 Ahzantive's RMP.

I. The medicine and what it is used for

Ahzantive is indicated for adults for the treatment of

- neovascular (wet) age-related macular degeneration (AMD),
- visual impairment due to macular edema secondary to retinal vein occlusion (branch RVO or central RVO),
- visual impairment due to diabetic macular edema (DME), and
- visual impairment due to myopic choroidal neovascularization (myopic CNV; see SmPC for the full indication).

Ahzantive contains aflibercept as the active substance and it is given by intravitreal injection. The following pharmaceutical form is currently available: solution for injection in a vial. One vial contains 4 mg aflibercept in 100 microliters (40 mg/mL) in iso-osmotic solution and, after preparation, delivers a single dose of 2 mg/0.05 mL.

Further information about the evaluation of Ahzantive’s benefits can be found in Ahzantive’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Ahzantive, together with measures to minimize such risks are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

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

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

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

II.A List of important risks and missing information

Important risks of Ahzantive are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered to patients. 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 Ahzantive. 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-fetotoxicity
Missing information	• None

II.B Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product.

Important identified risk: Endophthalmitis (likely infectious origin)	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. The intravitreal injection procedure can implant pathogens into the eye if there is a break in sterile technique. Source of pathogenic agents is in most cases the patient's conjunctival bacterial flora.
Risk factors and risk groups	Improper aseptic technique increases the risk of intraocular inflammation.
Risk minimization measures	Routine risk minimization measures:

	SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2, 3 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).

Important identified risk: Intraocular inflammation	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. Post-injection, sterile intraocular inflammation is a known risk following intravitreal injections of anti-VEGFs and for other intravitreally applied drugs.
Risk factors and risk groups	Improper aseptic technique increases the risk of intraocular inflammation
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2, 3 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).

Important identified risk: Transient intraocular pressure increase

Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. Transient intraocular pressure increase is attributed to an increase in vitreous volume after Ahzantive injection (volume effect).
Risk factors and risk groups	Patients with glaucoma. Increased intraocular pressure is a known adverse drug reaction on treatment with intravitreal corticosteroids.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.4, 4.8 and 4.9 Package Leaflet sections 2 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).

Important identified risk: Retinal pigment epithelial tears	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. Development of retinal pigment epithelial tears after anti-VEGF intravitreal injection has been attributed to a decline in intercellular adherence, thereby increasing susceptibility to tearing of the RPE layer particularly in patients with wet AMD.
Risk factors and risk groups	Wet AMD with pigment epithelial detachment; treatment of neovascularization.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.4 and 4.8 Package Leaflet sections 2 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures:

	Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).

Important identified risk: Cataract (especially of traumatic origin)	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature. Related to IVT procedure.
Risk factors and risk groups	Cataract is a known adverse drug reaction on treatment with IVT corticosteroids.
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 4.8 Package Leaflet sections 2, 3 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).

Important potential risk: Medication error	
Evidence for linking the risk to the medicine	Although Ahzantive is provided in a vial, there is an excess volume which exceeds the recommended net dose of 2 mg aflibercept per injection. Thus, injection of more than the recommended dose results in overdose. However, this numerical overdose is limited, and the drug will be administered only by qualified physicians (not by patients), and this reduces the risk of inappropriate dosing and administration as well. Nevertheless, it was decided to consider 'medication error' a potential risk of treatment, which is, however, completely avoidable by proper adherence to the dosing recommendations.
Risk factors and risk groups	Not applicable.
Risk minimization measures	Routine risk minimization measures:

	SmPC sections 4.2, 4.9 and 6.6 Package Leaflet sections 1 and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise physicians' awareness on medication error (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).

Important potential risk: Off-label use and misuse	
Evidence for linking the risk to the medicine	As with other drugs, Ahzantive might be intentionally used other than recommended, or in clinical conditions outside the approved indications (so-called off-label use). Since the clinical experience with Ahzantive in such off-label use will be limited (in particular in terms of efficacy and safety), any case of off-label use will be considered a potential risk. Since Ahzantive has no dependence potential, the risk of misuse is regarded as very low.
Risk factors and risk groups	Not applicable
Risk minimization measures	Routine risk minimization measures: SmPC section 4.1, 4.3, 4.4 and 4.6 Package Leaflet sections 1, 2 and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on off-label use (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).

Important potential risk: Embryo-fetotoxicity	
Evidence for linking the risk to the medicine	Data from clinical trials, post-marketing surveillance and literature.

	An embryo-fetal toxicity study was performed in the rabbit with IV dosing of aflibercept at doses which provided systemic exposures over 670-fold higher than that observed with IVT dosing using the clinical dose of 2 mg. The study identified dose-related increases in fetal resorptions, pregnancy disruptions and numerous fetal (external, visceral and skeletal) malformations. These effects were thought to be due to the antiangiogenic effect of aflibercept.
Risk factors and risk groups	Patients at risk are women of childbearing potential.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4, 4.6 and 5.3 Package Leaflet sections 2 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on the potential risk of embryo-toxicity and to underline information on treatment of women of child-bearing potential, and the need for appropriate contraception in women of childbearing potential (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).

II.C Post-authorization development plan

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

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

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

There are no ongoing or planned additional pharmacovigilance activities for Ahzantive.

Part VII: Annexes

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Annex 4 – Specific adverse drug reaction follow-up forms

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Annex 4.1: Endophthalmitis and intraocular inflammation (IOI)

Note: This questionnaire is utilized in conjunction with standard case follow-up procedures to obtain complete case information.

Annex 4.1 Endophthalmitis and intraocular inflammation (IOI) following the use of Ahzantive 40 mg/mL (2 mg dose)

Targeted Follow-up Questionnaire:
Aflibercept Endophthalmitis and Intraocular Inflammation (Version 2/ Jul-2024)

In addition to collecting routine information for these adverse events (AEs), please ensure the following information is provided and/or confirmed.

SECTION I - REFERENCE ID			
MAH 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)	**Gender: male female**	**Weight:** **unit:**	**Height:** **unit:**
SECTION III – PRODUCT INFORMATION			
PRODUCT NAME:			
Therapy date: *(dd/mm/yyyy):* ☐ **ongoing**			
Indication: **If other indication, specify:**		**Number of doses before the event:**	
Eye injected: ☐ **OS** ☐ **OD** ☐ **OU**			
If both eyes were injected, indicate if the same vial was used: ☐ **Yes** ☐ **No** **If no, please provide Batch number per eye: OS_____ OD_____**			
Vial			
Lot/Batch number:			
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 vial aliquoted in several syringes? ☐ Yes ☐ No	Was the vial multi-punctured? ☐ Yes ☐ No	
Date and time of injection preparation:		
What was used for injection? ☐ Injection needle Batch No: _____ ☐ Syringe (Luer lock: yes no) ☐ Glass ☐ Plastic Batch No: _____		
Where was the syringe for injection prepared? ☐ Off-site pharmacy ☐ On-site pharmacy ☐ Treatment/Examining room	If prepared in pharmacy, provide the name and contact details: _____	
How many hours did the prepared syringe stay at room temperature prior to administration? _____		

SECTION IV – ADVERSE EVENT INFORMATION

Event (as reported term) ☐ OS ☐ OD ☐ OU	**Start date / time** (dd/mm/yyyy/hh:mm): **<u>or</u> how much time after injection did the event occur** (approx.):	**Stop date** (dd/mm/yyyy): **If stop date is unknown, provide the approximate event duration (days):**	**Outcome** □ recovered □ not recovered □ improved □ recovered with sequelae □ fatal □ unknown
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:	☐ **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 product**			

☐ **Related to intravitreal injection procedure** ☐ **Not related to product or intravitreal injection procedure**			
Alternative explanation (e.g. underlying disease/condition pre-disposing 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**	
RELEVANT CLINICAL SYMPTOMS (To AE of interest); please indicate which eye was affected:			
Symptom		**Start date:**	**Stop date:**
Additional question: **Did the patient experience te same event(s) in the past:** ☐ **Yes** ☐ **No** **If yes, please provide relevant details:**			

SECTION V – RELEVANT (intravitreal) CONCOMITANT / HISTORICAL MEDICATION						
Drug Name	**From** (dd/mm/yyyy)	**To** (dd/mm/yyyy)	**Ongoing**	**Dose/ number of injections**	**Indication**	**Similar event occurred? If yes, please specify**
☐ **Anti VEGF** Please specify: _____ ☐ **OS** ☐ **OD** ☐ **OU**			☐			

☐ **Other** Please specify: _____ ☐ **OS** ☐ **OD** ☐ **OU**			☐			

SECTION VI – RELEVANT MEDICAL HISTORY / RISK FACTORS *(relevant to the reported event)*			
Condition	**Start date**	**Stop date**	**Ongoing**
☐ **Diabetes**			□
☐ **Autoimmune disease, please specify:** _____			
☐ **Malignancy, please specify:** _____			□
☐ **Immunodeficiency, please specify:** _____			□
☐ **Other, please specify:** _____			□

SECTION VII: ADDITIONAL INFORMATION (COMMENTS) (e.g. gender information if not male/female)			
Cause of death (if selected outcome was fatal)	**Date of death** (dd/mm/yyyy))	**Autopsy done**	**Autopsy details** (continue with SECTION IV)
		☐	
This section can also be used to provide information on any of the sections above. Please note the relevant section number below.			

Annex 6 – Details of proposed additional risk minimization activities

The MAH has agreed to provide EU Educational Material for Ahzantive. Prior to launch in each Member State the MAH shall agree the final educational material with the National Competent Authority.

The MAH ensures that, following discussions and agreements with the National Competent Authorities in each Member State where Ahzantive is marketed, ophthalmological clinics where Ahzantive is expected to be used for the treatment of adult patients are provided with an updated physician information pack containing the following elements:

- Physician information booklet
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information pack

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 vial is for single use in adults only
- The need to expel excess volume of the syringe before injecting Ahzantive 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 Ahzantive

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

- Patient information leaflet
- Who should be treated with Ahzantive
- How to prepare for Ahzantive treatment
- What are the steps following treatment with Ahzantive
- 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 Ahzantive