RISK MANAGEMENT PLAN

for

Yesafili® (aflibercept)

Data lock point (DLP) for RMP: 02-Aug-2023

Version Number: 1.3

Dated: 15-May-2025

[redacted]

Risk Management Plan – Aflibercept

Risk Management Plan for:	Aflibercept
RMP Version number:	1.3
Data lock point for this RMP:	02-Aug-2023
Date of final sign off:	15-May-2025
Rationale for submitting an updated RMP:	The Risk Management Plan, EU RMP version 1.3, Annex 6 of the RMP has been updated to align with Annex IID of the SmPC based on the supplementary information on EMA procedure EMA/VR/0000245097.
Summary of significant changes in this RMP:	Annex 6 of the RMP has been updated in alignment with Annex IID of the SmPC. Annex 8: Updated with all the above-mentioned changes.
Other RMP versions under evaluation • RMP version number • Submitted on • Procedure number	Not applicable
Details of the currently approved RMP • Version number • Approved with procedure • Date of approval (Opinion date)	 1.0 EMEA/H/C/006022 20-Jul-2023
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List of Abbreviations

Abbreviation	Explanation
ADA	Anti-Drug Antibodies
ATC Code	Anatomical Therapeutic Chemical Classification System Code
AUC	Area under the curve
AMD	Age-Related Macular Degeneration
BBL	Biocon Biologics Limited
BCVA	Best Corrected Visual Acuity
CHO	Chinese Hamster Ovary
CNV	Choroidal Neovascularisation
CP	Centralised Procedure
DLP	Data Lock Point
DME	Diabetic Macular Oedema
DNA	Deoxyribonucleic Acid
ETDRS	Early Treatment Diabetic Retinopathy Study
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
EURD	European Union Reference Date
FAS	Full Analysis Set
HCP	Healthcare Professional
INN	International Non-proprietary Name
IOP	Intra-Ocular Pressure
IV	Intravenous Administration
IVT	Intravitreal Administration
LOAEL	Lowest Observed Adverse Effect Level
MAH	Marketing Authorization Holder
OCT	Optical Coherence Tomography
PFS	Pre-filled Syringe
PL	Package leaflet
PlGF	Placental Growth Factor
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
ROP	Retinopathy Of Prematurity
RVO	Retinal Vein Occlusion
SC	Subcutaneous

SD-OCT	Spectral-Domain Optical Coherence Tomography
SmPC	Summary of product characteristics
TEAE	Treatment Emergent Adverse Event
VEGF	Vascular endothelial growth factor

Part I: Product(s) overview

Table 1: Product overview

Active substance (s) (INN or common name):	Aflibercept
Pharmacotherapeutic group (s): (Anatomical Therapeutic Chemical Classification System (ATC) Code):	Ophthalmologicals / Anti neovascularization agent (ATC code: S01LA05)
Marketing Authorisation Applicant:	Biosimilar Collaborations Ireland Limited (BCIL)
Medicinal products to which this RMP refers	1
Invented name (s) in the European Economic Area (EEA)	Yesafili (aflibercept) 40 mg/mL
Marketing authorisation procedure	Centralised/National
Brief Description of the Product	Aflibercept belongs to the pharmacotherapeutic group of ophthalmologicals / Anti neovascularization agent (ATC code: S01LA05). Yesafili (aflibercept) is a biosimilar medicinal product. Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1. Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors and thereby can inhibit the binding and activation of these cognate VEGF receptors. *Summary of mode of action:* Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of pro-angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via 2 receptor tyrosine kinases, VEGFR-1, and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leukocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation

	and excessive vascular permeability. PlGF can synergize with VEGF-A in these processes and is also known to promote leucocyte infiltration and vascular inflammation.
Hyperlink to the Product Information	PI available in section 1.3.1 of the dossier
Indication (s) in the EEA	Current: Aflibercept 40 mg/mL (2 mg dose) is indicated for adults for the treatment of: • Neovascular (wet) age-related macular degeneration (AMD) • Visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) • Visual impairment due to diabetic macular oedema (DME) • Visual impairment due to myopic choroidal neovascularisation (myopic CNV).
	Proposed: Not applicable
Dosage in the EEA	Current: *wet AMD:* The recommended dose for Aflibercept is 2mg aflibercept, equivalent to 0.05 mL. Aflibercept treatment is initiated with one injection per month for three consecutive doses. The treatment interval is then extended to two months. *Macular oedema secondary to RVO (branch RVO or central RVO):* The recommended dose for Aflibercept is 2 mg aflibercept equivalent to 0.05 mL. After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month. *Diabetic macular oedema:* The recommended dose for Aflibercept is 2 mg aflibercept equivalent to 0.05 mL. Aflibercept treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections. *Myopic choroidal neovascularization (myopic CNV):* The recommended dose for Aflibercept is a single intravitreal injection of 2 mg aflibercept equivalent to 0.05 mL. Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences should be treated as a new manifestation

	of the disease. The interval between two doses should not be shorter than one month. Aflibercept is for intravitreal injection only.
	Proposed: Not applicable
Pharmaceutical form (s) and strengths	Current: 1 mL solution for injection contains 40 mg aflibercept*. 1) 40 mg/mL Solution for injection (injection) in Vial 2mg/0.05mL. 2) 40mg/mL solution for injection in a Pre-filled Syringe (PFS). One pre-filled syringe contains 3.6 mg aflibercept in 90 microlitres (40 mg/mL) in isosmotic solution. Delivers a single dose of 2 mg/0.05 mL. *Fusion protein consisting of portions of human VEGF (Vascular Endothelial Growth Factor) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

Part II: Safety specification

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

Not applicable as this RMP pertains to a similar biologic. (Ref: In accordance with the Good Pharmacovigilance Practices (GVP) - Biological medicinal products "All parts of an RMP are required for a biosimilar, except for RMP part II, module SI "Epidemiology of the target population).

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

In line with current regulatory guidelines in biosimilar development, the nonclinical testing strategy was based on a stepwise approach to identify any potential differences between aflibercept (M710) and the reference product (Eylea®) in terms of efficacy and safety using the most sensitive non-clinical assays. No non-clinical toxicological studies were conducted with M710 provided the strong similarity data in physiochemical property, purity, and biological activity between M710 and Eylea® and the minimum local and systemic toxicity observed with Eylea® following intravitreal (IVT) administration. In response to a request from the Japanese Pharmaceuticals and Medical Device Agency (PMDA), two GLP-compliant single dose 14-day rabbit ocular PK studies were performed to compare the ocular PK profile between M710 and Eylea® sourced from Japan (JP-Eylea). In these studies, except for body weight, clinical signs of toxicity and mortality, other general and/or local ocular toxicological endpoints were not assessed. While the study reports of these studies are still under preparation, in-life observation revealed no treatment-related changes in body weight, clinical signs of toxicity or mortality following single intravitreal injection of M710 or JP-Eylea at dosage levels up to 1.2 mg/eye in both eyes. As such, the key safety findings from non-clinical studies are based solely upon the studies performed with the reference product (Eylea®) by the innovator.

Based on the sequence homology, monkey is the most relevant species for toxicity assessment for aflibercept. Given that significant immunogenic responses and resulting nephropathy were observed in rodent species (mice and rats) following repeated dosing, thus, repeat dose toxicity of aflibercept is evaluated only based on data obtained in monkeys. The important toxicological findings with the reference product Eylea® are summarized below in Table 2 in the order of types of toxicological studies.

Table 2: Summary of Important Non-Clinical Safety Findings

Important Nonclinical Safety Findings	Relevance to Human Usage
Acute-dose toxicity Acute toxicity studies were conducted with aflibercept by the innovator in rats following single intravenous (IV) administration at doses up to 500 mg/kg. Transient skin lesions and discoloration of the tail at the injection administration site were observed at 50 and 500 mg/kg. A moderate decrease in body weight gain accompanied by reduction in food consumption were noted.	Intravenous injection is not the intended clinical route of administration; the exposure levels with IV route of administration is multiple orders of magnitude higher than the systemic exposure at clinical intravitreal (IVT) dose, thus is not related to any additional risks.

Important Nonclinical Safety Findings	Relevance to Human Usage
Repeated-dose toxicity Repeat dose toxicity studies were performed with Eylea® following intravitreal (IVT), IV, and subcutaneous (SC) route of administration in Cynomolgus monkeys (the most relevant species) for up to 8 months. In two pivotal IVT studies, mild to transient ocular inflammation as well as transient increase in intraocular pressure (IOP) were observed in both aflibercept and control groups. Except for erosions and ulcerations of the respiratory epithelium and chronic-active inflammation of the nasal turbinates noted at doses ≥2 mg/eye (equivalent to 708 x the plasma exposure at clinical dose on area under concentration-time curve (AUC) basis), no other treatment-related toxicities were observed. In a 6-month repeat-dose toxicity study, groups of Cynomolgus monkeys received 30-min intravenous infusion of aflibercept at 3-30 mg/kg followed by a 5-month recovery. There was one mortality (3 mg/kg dose) of a euthanized monkey due to marked anemia from nasal bleeding. Nose bleeding was observed in the remaining animals along with reduced body weight, activity, appetite, and sneezing. Female menses were absent or irregular and sperm morphology was irregular. Degenerative joint disease was observed at all dose levels and changes in hematology, and serum chemistry were related to the test article. Macro- and microscopic examination revealed treatment-related changes in bones, nasal cavities, adrenals, brain (choroid plexus), liver, kidneys, ovaries, and digestive systems. At the end of recovery period, principal findings including kyphosis, nasal cavity deformation, degenerative joint disease, and changes in the digestive system and the brain were still present. The lowest observed adverse effect level (LOAEL) of 3 mg/kg is approximately 1546 x the human systemic exposure at the recommended clinical dose on AUC basis. In a 13-week SC toxicity study, aflibercept at doses ≥1.5 mg/kg (the lowest dose tested) for 13 weeks was associated with slight increases in hemoglobin, hematocrit, and red	Transient increase in intraocular pressure (IOP) observed in monkeys after IVT injection is consistent with clinical observation in both M710 and Eylea® treated eyes. Given that the adverse effects on respiratory epithelium and nasal turbinates in monkeys occurred only at intravitreal doses ~708 x and were not observed at 56 x (AUC basis) the systemic exposure in patients at the recommended clinical IVT dose, no additional risks related such findings are inferred. Other systemic toxicities observed after IV or SC administration are not considered to be associated with clinical risks given the large safety margin over the therapeutical IVT dose.

Important Nonclinical Safety Findings	Relevance to Human Usage
blood cell (RBC) and increased urine protein and/or serum blood urine nitrogen (BUN) and histological findings in femoral growth plates (degeneration and disorganization), ovaries (decreased numbers of maturing follicles, granulosa cells, and/or thecal cells), and kidneys (increased glomerular mesangial matrix). Mean plasma concentration of free aflibercept at the highest dose group (30 mg/kg) was ≥510 µg/mL is multiple orders higher than C_{max} in patient (0.0193 µg/mL) after IVT administration of 2 mg/eye aflibercept.	
Genotoxicity and Carcinogenicity No genetic toxicology or carcinogenicity studies were performed with M710 nor for Eylea® by the innovator.	No additional risk is inferred
Reproductive/developmental toxicity No developmental or reproductive toxicology studies were performed with M710. Studies with Eylea® revealed adverse effects on male and female reproductive system in monkeys at the lowest observed adverse effect level (LOAEL) of 3 mg/kg intravenously (~1500 x the human plasma exposure at the clinical IVT dose on AUC basis) and embryofoetal toxicity in pregnant rabbits at the LOAEL of 0.1 mg/kg subcutaneously (~ 6 x the human plasma exposure at the clinical IVT dose on AUC basis).	The reproductive and developmental toxicity observed in animals is linked to the mechanism of action of aflibercept as an anti-VEGF agent (class effect). As such, aflibercept should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus.
Local tolerance No local tolerance studies were performed with M710 given the excipients used in M710 formulation are commonly used at the same exposure level by IVT injection. The local tolerance of Eylea® was assessed as part of the pivotal 8-month study in monkeys which demonstrated that aflibercept in the currently approved commercial formulation (Eylea®) was well tolerated, with only mild and transient inflammation observed in the anterior and vitreous humour.	The observation of transient intraocular inflammation may be linked to the clinically identified risk with reference product Eylea®.
Safety Pharmacology *Effects on blood pressure*	Given the low systemic exposure following IVT administration, no risks on

Important Nonclinical Safety Findings	Relevance to Human Usage
No dedicated safety pharmacology studies were performed with M710. While rapid increases in blood pressure was observed in telemetered mice and rats after a single SC administration of Eylea® at doses that resulted in plasma exposure level of free aflibercept >1µg/mL, such effect was absent at plasma concentration ≤1µg/mL (approximately 50-fold higher than the plasma concentration of free aflibercept of 0.0193µg/mL at clinical IVT dose). In monkeys, the most relevant species, no effects on blood pressure were observed at IV doses up to 30 mg/kg (multiple orders of the clinical IVT dose on AUC basis) for 6 months. *Inhibition of wound healing* As an anti-VEGF agent, aflibercept has been demonstrated to inhibit would healing in rabbit incision and excisional wound healing models. Eylea® at IV doses from 0.3-30 mg/kg dose-dependently impaired wound healing.	blood pressure or wound healing are inferred.
Other toxicity-related information or data *Immunogenicity* As immunogenicity studies conducted in animals are generally considered poor predictors of human immunogenicity, the applicant has not evaluated immunogenicity of M710 in any preclinical studies. Anti-aflibercept antibodies were detected in the serum of monkeys after IVT injection of the reference product (Eylea®) at monthly dose ≥ 0.5 mg/eye. However, there were no obvious correlation between the presence of antibodies and concentrations of free or bound aflibercept.	As with other therapeutic proteins, there is a potential for an immune response to aflibercept after IVT administration in patients. A low incidence of immunogenicity was observed in patients treated with M710 and Eylea®, which was not associated with efficacy or safety.

Conclusion from Non-clinical Overview:

Results from the nonclinical program demonstrate that the applicant's M710 is similar to Eylea® sourced from US, EU and Japan in terms of all primary and secondary pharmacological activities. Considering the similar nonclinical pharmacological data in combination with the known mechanisms of action driving the efficacy and safety of aflibercept, M710 is expected to produce a similar efficacy and safety profile when compared to Eylea®. The safety concerns inferred from non-clinical data with Eylea® are listed in the following Table 3 and are predictable for this drug substance class.

Table 3: Identified Safety Risks from Non-clinical Data

Important Identified Risks (confirmed by clinical data) • Transient increase in intraocular pressure (IOP) • Intraocular inflammation
Important potential risks • Embryofoetal toxicity
Important missing information • None

Part II: Module SIII - Clinical trial exposure

Aflibercept (M710 or MYL-1701P) has been developed as a similar biological medicinal product to Eylea® in accordance with EMA and the US FDA biosimilar guidelines. In accordance with the FDA and EMA guidance related to development of biosimilars, company development program has aimed to establish similarity of MYL-1701P to the reference product in terms of extensive structural and functional characterization using orthogonal techniques, efficacy and safety, systemic pharmacokinetics including immunogenicity, based on a comprehensive similarity exercise. Viatris (Ex-MAH) has conducted below clinical studies in adults patients with DME.

MYL-1701P-3001: A multi-center, randomized, double masked, active controlled, comparative clinical study to evaluate the efficacy and safety of MYL-1701P and Eylea® in subjects with diabetic macular edema. This study has been completed.

In total, 355 subjects received an injection for intravitreal at a dose of 2 mg every 4 weeks for a total of 5 injections, and then every 8 weeks (with optional doses at every 4 weeks) through the remainder of the 52-week treatment period, with the last dose at 48 weeks.

AFIL-IJZ-3002: A multi-center, extension study to evaluate the safety and efficacy of MYL-1701P in subjects with diabetic macular edema completed MYL-1701P-3001 study. This study has been completed.

A total of 52 subjects were enrolled: 29 subjects in the Treatment Continuation arm and 23 subjects in the Treatment Switch arm. Of 52 subjects, 46 (88.46%) subjects completed the study;25 (86.21%) subjects in the Treatment Continuation arm and 21 (91.30%) subjects in the Treatment Switch arm.

AFIL-IJZ-3001 (Stats: completed)

Study Design:

This was a multi-center, randomized, double-masked, active-controlled, comparative clinical study between MYL-1701P and US-licensed Eylea in subjects with DME treated up to 52 weeks. The maximum planned study duration from screening to end of study was up to 13 months/56 weeks approximately.

As per protocol version 2.0, a total of 324 eligible adult subjects with type 1 or 2 diabetes mellitus with central DME involvement and BCVA between 73 and 38 letter score (approximate Snellen equivalent 20/40 to 20/200) based on early treatment diabetic retinopathy study (ETDRS) chart in the study eye and with CRT ≥ 300 µm, as determined by spectral domain -

optical coherence tomography (SD-OCT), in the study eye, were planned to be randomized in 1:1 ratio to intravitreal treatment with MYL-1701P or Eylea. Thirty-one additional subjects were randomized based on pre-specified criteria as per protocol version 3.0 (due to missed/delayed dosing and/or study assessments because of the coronavirus disease 2019 (COVID-19) pandemic. Overall, 355 subjects were randomized in the study.

At study Week 8, the primary endpoint was assessed, and subjects continued to receive the assigned treatment until Week 48. An end of study visit was scheduled at Week 52.

Subjects received intravitreal injections of either MYL-1701P or Eylea throughout the 52-week treatment period, with planned doses at Study Day 1, Day 29 (week 4), Day 57 (Week 8), Day 85 (Week 12), Day 113 (Week 16), Day 169 (Week 24), and at Day 225 (Week 32), Day 281 (Week 40) and Day 337 (Week 48). In addition to the nine planned doses, study drug was also to be administered at Week 20, Week 28, Week 36 and Week 44 based on the current visual acuity, and or SD-OCT at that visit and in accordance with the "criteria for administering additional 4-weekly doses".

All subjects returned to clinic every 4 weeks for assessment of visual acuity (BCVA using ETDRS chart) and central retinal thickness (measured as central subfield thickness by SD-OCT) to assess efficacy and to guide treatment. There were additional visits during the study as specified in the study visit schedule for safety and pharmacokinetic evaluation.

Study recruited subjects from the US, Europe, Japan and India. Higher proportion (49.0%) of the subjects were recruited from Europe followed by India (21.7%), US (17.7%) and Japan (11.5%). In general, both treatment arms were similar in terms of ocular and non-ocular medical history. All subjects had history of diabetes mellitus (Type 1 or Type 2).

A total of 355 subjects were randomized with 179 subjects to the MYL-1701P arm and 176 subjects to the Eylea arm. A total of 172 (96.1%) subjects in the MYL-1701P arm and 173 (98.3%) in the Eylea arm completed the study up through Week 8, and a total of 168 (93.9%) subjects in the MYL-1701P arm and 172 (97.7%) subjects in the Eylea arm completed Week 24 of the study and a total of 161 (89.9%) subjects in the MYL-1701P arm and 158 (89.8%) subjects in the Eylea arm completed Week 52. There were 4 subjects in the Eylea arm, (3 subjects due to Death, and one subject Withdrew consent) who completed the study treatment but discontinued the study prior to completing Week 52/EOS visit.

Safety Summary:

Treatment exposure: The extent of exposure was similar between the two treatment arms in terms of dose and duration of treatment for MYL-1701P and Eylea.

TEAE: The incidence of was similar between the two treatment arms, 138 (77.5%) subjects in the MYL-1701P arm reported a total of 508 TEAEs and 138 (78.4%) subjects in the Eylea arm reported a total of 503 TEAEs. The most frequently reported TEAEs by SOC were eye disorders, infections and infestations, and investigations. The incidence of non-ocular TEAEs was similar between study arms. Most frequently reported non-ocular TEAEs by PT were hypertension, nasopharyngitis and urinary tract infection. The incidence of ocular TEAEs in the study eye was similar between study arms. Most frequently reported ocular TEAEs in study eye by PT included cataract, conjunctival haemorrhage, and intraocular pressure increased.

Overall, 5.9% to 10.6% of subjects in both arms were reported to have positive ADA at some visit across visits from baseline to Week 52. Around 10% of subjects were positive for ADA at baseline in both arms even before receiving study treatment. Most often ADA positivity was transient and positive at some visits and had low titers. The incidence of treatment induced

ADA or treatment boosted ADA was low in both arms. Overall, 2.8% subjects in MYL-1701P arm and 5.7% subjects in Eylea arm reported either treatment induced, or treatment boosted ADA. Five (2.8%) incidences of treatment induced ADA and no incidences of treatment boosted ADA were reported in the MYL-1701P arm; 8 (4.5%) incidences of treatment induced ADA and 2 (1.1%) incidences of treatment boosted ADA was reported in the Eylea arm.

Immunogenicity: A small proportion of patients that tested positive for ADA also tested positive for NAb. At baseline visit, one subject had NAb in the MYL-1701P arm and no subjects had NAb in the Eylea arm. At subsequent post-treatment visits, NAb positivity was observed in 0 to 1 subject in the MYL-1701P arm and 0 to 3 subjects in the Eylea arm. NAb positivity was mostly transient and present in specific visits in most cases. Overall, 2 subjects in MYL-1701P and 5 subjects in Eylea arm tested positive for NAb at least in one of the post-baseline visits. There were no subjects showing NAb in the treatment induced ADA positive subset. There were no subjects in the MYL-1701P arm and 1 subject (0.6%) in Eylea arm among subjects having treatment boosted ADA that tested positive for NAb.

No clinically meaningful differences observed in mean change in BCVA at Week 52 in ADA positive groups compared to ADA negative groups in both the arms and no specific comparisons could be made because of small sample size. No clinically relevant differences observed in the incidence and type of TEAE reported between the study treatment arms in the ADA positive subgroup. The number of ADA positive subjects in the PK subset was low (2 in MYL-1701P and 4 in Eylea) and hence a meaningful comparison of PK data in ADA positive and ADA negative sub-groups could not be made.

Overall, MYL-1701P and Eylea were well tolerated, and their safety profiles were similar with no significant safety concerns observed, and the safety profile was consistent with the known safety profile of Eylea in the target population.

AFIL-IJZ-3002 (Stats: completed)

Study Design:

This extension study (AFIL-IJZ-3002) was designed and conducted by Mylan (Ex-MAH) to further evaluate the safety, efficacy and immunogenicity of MYL-1701P among a group of subjects who successfully completed the parent study MYL-1701P-3001. All subjects that participated in the extension study received 3 doses of MYL-1701P, every 8 weeks. The total study duration was 24 weeks.

Number of Subjects (planned and analyzed): There was no formal sample size estimation performed. The extension study was open for all subjects from India who completed the parent study MYL-1701P-3001. It was expected that up to 100 subjects were to be considered for participation in the extension study.

A total of 52 subjects were enrolled: 29 subjects in the Treatment Continuation arm and 23 subjects in the Treatment Switch arm. Of 52 subjects, 46 (88.46%) subjects completed the study; 25 (86.21%) subjects in the Treatment Continuation arm and 21 (91.30%) subjects in the Treatment Switch arm.

All enrolled subjects were to receive three doses of the investigational product MYL-1701P at intervals of 8-weeks during visit 2 (Day 1), visit 3 (Week 8 ± 7 days) and visit 4 (Week 16 ± 7 days) in an open-label manner. All subjects were to return to the clinic every 8 weeks for dosing, safety and efficacy evaluations.

Eligible subjects who completed 52 weeks of MYL-1701P-3001 study from clinical sites in India (the parent study) were enrolled to the extension study (AFIL-IJZ-3002). Subjects who received MYL-1701P in the parent study continued to receive the same treatment (will be further referred as Treatment Continuation arm), while subjects who received Eylea in the parent study were switched to receive MYL-1701P (will be further referred as Treatment Switch arm).

A total of 55 subjects who had completed MYL-1701P-3001 study and willing to participate in extension study were screened; 3 subjects were screen failures. One subject in the Treatment Continuation arm did not meet the eligibility criteria and 2 subjects in the Treatment Switch arm withdrew consent.

A total of 52 subjects were enrolled: 29 subjects in the Treatment Continuation arm and 23 subjects in the Treatment Switch arm. Of 52 subjects, 46 (88.46%) subjects completed the study; 25 (86.21%) subjects in the Treatment Continuation arm and 21 (91.30%) subjects in the Treatment Switch arm. Four subjects in the Treatment Continuation arm and 2 subjects in the Treatment Switch arm discontinued the study.

All the 52 randomized subjects are included into the safety analysis set; 29 (100.0%) in the Treatment Continuation arm and 23 (100.0%) in the Treatment Switch arm.

Of 52 randomized subjects, 49 subjects are included into FAS; 26 (89.66%) in Treatment Continuation arm and 23 (100.0%) in the Treatment Switch arm. Three (10.34%) subjects-(Subjects 105002, 113005 and 115009) from the Treatment Continuation arm were excluded from FAS as they did not have post-dose BCVA assessments for any of the visits.

The baseline demographic profile was comparable between treatment arms with respect to age, gender, race and ethnic origin. At Baseline, the ocular disease characteristics were evaluated through assessment of CRT, BCVA, and intraocular pressure (IOP), which were all similar between the two treatment arms in the study eye.

Safety Summary:

Treatment exposure: The extent of exposure to the study drug was similar between the two treatment arms with regards to duration of treatment. The proportion of subjects who received the first, second and third doses were similar in both the treatment arms.

TEAE: The incidence of TEAEs were similar between the treatment arms, 9 (31.03%) subjects in the Treatment Continuation arm and 7 (30.43%) subjects in Treatment Switch arm reported TEAEs. Only one (1.92%) subject in the Treatment Switch arm had at least one TEAE that was considered related to the IP. There was one Serious TEAE reported in the Treatment Switch arm and was considered as related to study drug.

All the TEAEs were mild or moderate in severity; in the Treatment Continuation arm, 7 (24.14%) subjects reported mild, and 3 (10.34%) subjects reported moderate TEAEs; while in the Treatment Switch arm, 5 (21.74%) subjects reported mild and 2 (8.70%) reported moderate TEAEs showing that the severity of TEAEs were comparable between the treatment arms.

All the TEAEs were considered to be unrelated to the investigational products except for one event (cerebral infarction) reported in the Treatment Switch arm. Cerebral infarction was the only one serious TEAE reported in the study which was in the Treatment Switch arm. There were no other serious TEAEs reported in either of the arms.

There were no reports of TEAEs leading to death injection procedure related TEAEs and TEAEs leading to discontinuation of study drug during the study.

Overall, there were 7 (13.46%) subjects who reported 11 ocular TEAEs; 4 (13.79%) subjects in the Treatment Continuation arm reported 5 ocular TEAEs and 3 (13.04%) subjects in the Treatment Switch arm reported 6 ocular TEAEs. Overall, the incidence of ocular TEAE was comparable between the two treatment arms. All the events had recovered or were recovering at the end of the study except for two events. One event by PT cataract, in each of the treatment arms had not recovered / not resolved at the end of the study.

Immunogenicity: Two (6.90%) subjects in the Treatment Continuation arm and 3 (13.04%) subjects in the Treatment Switch arm were ADA positive at the baseline of the extension study. The overall proportion of ADA positive subjects remained similar throughout the study period from 0% to 6.90% in the Treatment Continuation arm at post-baseline visits compared to 8.70% to 13.04% in the Treatment Switch arm. No incidence of treatment induced, or treatment boosted ADA or Nab reported during the study.

Overall, the safety profile was consistent with the known safety profile of Eylea and was in line with the safety profile noted in the previous global study (MYL-1701P-3001) in the target population. The switch from Eylea to MYL1701P was well tolerated, and safety profiles were similar between the two treatment arms with no safety signals or change in immunogenicity profile observed.

Cumulative subject exposure from completed clinical trials (MYL-1701P-3001 and MYL-1701P-3002) is provided below.

SIII. 1: Duration of exposure to MYL-1701P or Eylea® from completed clinical trial

Duration of Exposure	**Patients Overall**	**Patients exposed to MYL-1701P**	**Patients exposed to Eylea®**
8 weeks	345	172	173
24 weeks	340	168	172
52 weeks*	323	161	162

*Completed doses until 48 weeks
Note: 52 subjects from MYL-1701P-3001 study participated in the extension study (MYL-170P-3002) and received 3 doses of MYL-1701P, every 8 weeks. The total study duration was 24 weeks.

SIII.2- Cumulative patient exposure to MYL-1701P or Eylea® from completed clinical trial by Age Group and Gender

Age Group	**Patients n (%)**
Adults (<55)	70 (19.7%)
Adults (≥55 to <65)	137 (38.6%)
Elderly (≥65 to <75)	121 (34.1%)
Elderly (≥75)	27 (7.6%)
Total	**355 (100%)**
Gender	**Patients n (%)**
Male	216 (60.8%)
Female	139 (39.2%)
Total	**355 (100%)**

SIII.3- Cumulative patient exposure to MYL-1701P or Eylea® from completed clinical trial by Racial Group

Racial Group	Patients n (%)
American Indian or Alaska Native	0
Asian	120 (33.8%)
Black or African American	5 (1.4%)
Native Hawaiian or other Pacific Islander	1 (0.3%)
White	228 (64.2%)
Other/not reported	1 (0.3%)
Total	**355 (100%**

SIII.4- Cumulative patient exposure to MYL-1701P or Eylea® from

Ethnic Origin	Patients n (%)
Hispanic/Latino	12 (3.4%)
Not Hispanic/Latino	343 (96.6%)
Total	**355 (100%)**

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

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

A subject who met any of the following criteria was excluded from the study:

1. Subjects with known hypersensitivity to aflibercept or any of the excipients in MYL-1701P and Eylea®

2. Known hypersensitivity to fluorescein

3. Ocular media of insufficient quality to obtain fundus and OCT images

4. Subjects were excluded if any of the following conditions were met in the study eye:

    a. Subjects with a history of vitreoretinal surgery in study eye and/or including scleral buckling.

    b. Subjects who have had panretinal or macular laser photocoagulation within 3 months of randomization.

    c. Subjects with history of use of intraocular corticosteroids anytime in the past or periocular (subconjunctival, intra-scleral, sub-tenon or retrobulbar) corticosteroids within 4 months of randomization.

    d. Subjects who had reduced vision due to causes other than DME, with the exception of requirement for spherical correction, or mild cataract assessed by the Investigator as not interfering with assessment of BCVA or CRT.

    e. Subjects with active proliferative diabetic retinopathy.

    f. Subjects with active ocular inflammation.

g. Subjects who have had cataract or other intraocular surgery within 3 months of randomization or expected to undergo cataract surgery or capsulotomy during the study duration.

h. Subjects who have had laser capsulotomy within 3 months of randomization.

i. Subjects with aphakia, whether congenital or surgical.

j. Subjects with vitreous haemorrhage.

k. Subjects with visually significant vitreomacular traction or epiretinal membrane evident biomicroscopically or on OCT that is thought to affect central vision.

l. Subjects with myopia of spherical equivalent of ≥-8 diopters, prior to any possible refractive or cataract surgery.

m. Subjects with any other disease that might have compromised visual acuity or required medical or surgical intervention during the study period or could confound interpretation of the results (including retinal vascular occlusion, retinal detachment, macular hole or choroidal neovascularization of any cause).

n. Structural damage to the center of the macula that was likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia or organized hard exudates based on the Investigator's discretion with help of FA/FP and OCT.

o. Subjects with uncontrolled glaucoma (defined as intraocular pressure ≥ 25 mmHg despite treatment with antiglaucoma medication); subjects with controlled glaucoma may participate in the study. [For India - Subjects with a clinical diagnosis of glaucoma (controlled or uncontrolled)].

p. Surgery for glaucoma in the past or likely to be needed in the future.

q. Intraocular pressure ≥25 mm of Hg in the study eye

r. Prior treatment with verteporfin (photodynamic therapy)

5. Subjects were excluded if any of the following conditions were met in either eye:

a. Subjects with active iris neovascularization.

b. Subjects with preretinal fibrosis involving the macula.

c. Subjects with history of idiopathic or autoimmune uveitis.

d. Subjects with active or suspected ocular or peri-ocular infection including but not limited to infectious blepharitis, keratitis, scleritis, or conjunctivitis.

6. Subjects who received previous therapy with antiangiogenic drugs for either eye (pegaptanib, bevacizumab, ranibizumab, aflibercept).

7. Subjects who have received previous systemic antiangiogenic drugs (bevacizumab, aflibercept).

8. Subjects with 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.

9. Subjects who had planned to participate in another clinical study while enrolled in this study and/or who had received an investigational drug and/or device within 30 days or 5 half-lives, whichever is longer, prior to screening.

10. Subject who was receiving treatment for a serious systemic infection.

11. Subjects with uncontrolled diabetes mellitus as defined by HbA1c ≥10% at screening

12. Subjects with uncontrolled hypertension defined as systolic blood pressure >160 mmHg or diastolic blood pressure >95 mmHg.

13. Subjects with a history of cerebrovascular accident or myocardial infarction within 6 months of randomization.

14. Subjects with renal failure requiring dialysis or renal transplant.

15. Subjects who had only one functional eye, even if the eye met all other study requirements, or who had an ocular condition on the fellow eye with a poorer prognosis than the study eye.

16. Presence or history of malignant neoplasm (including lymphoproliferative disease), except for adequately treated basal cell carcinoma and cervical carcinoma in situ; or any malignancy with complete remission of more than 5 years.

17. Subjects with a history or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, psychiatric disease, or any other condition, that in the opinion of the Investigator would jeopardize the safety of the subject or the validity of the study results.

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, or adverse reactions with a long latency or those caused by prolonged or cumulative exposure. Therefore, the clinical trials data and post marketing experience gained with the reference product is considered to relevantly complement the data gathered for MYL-1701P. Consequently, publicly available information on the reference product is carefully reviewed for this RMP and safety concerns identified for the reference product, if any, are addressed in this document.

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

Table 4: Exposure of special populations included or not in clinical trial development programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding Women	
Patients with Relevant Comorbidities Patients with Hepatic Impairment Patients with Renal Impairment Patients with Cardiovascular Impairment Immunocompromised Patients	Subjects with a history or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, psychiatric disease, or any other condition, that in the opinion of the Investigator would jeopardize the safety of the subject or the validity of the study results were excluded.

Patients with a Disease Severity Different from Inclusion Criteria in Clinical Trials	
Population with Relevant Different Ethnic Origin	Aflibercept has been studied in subject populations that included men and women of a variety of racial backgrounds and ages in clinical trials; no safety signals were identified for any particular racial groups in clinical trials or in post-marketing surveillance.
Subpopulations Carrying Relevant Genetic Polymorphisms	Not included in the clinical development program.
Children	The safety and efficacy of Aflibercept in children and adolescents below 18 years of age have not been studied.

Part II: Module SV - Post-authorisation experience

Not applicable. MYL-1701P, 40mg/ml solution for injection, was issued with a valid EU marketing authorisation on 15-Sep-2023, United Kingdom on 09-Nov-2023 and United States on 20-May-2024 but is not marketed in any country at present. It is a biosimilar product to the reference product Eylea® which was approved in EU on 21-Nov-2012.

SV.1 Post-authorisation exposure

Not applicable.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

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

SVI.1 Potential for misuse for illegal purposes

The product is restricted by prescription only. This is not a substance abuse drug and there is no potential for misuse of aflibercept (M710 or MYL-1701P) for illegal purposes.

SVI.2 Potential for Transmission of Infectious Agents

MYL-1701P is sterile medicinal product. It is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology. It is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1. During manufacturing, regulated processes and controls minimize any risk of microbiological contamination. Further, the product is tested for sterility at release, and integrity of the container closure system during storage has been demonstrated. There is no potential for transmission of infectious agents for the medicinal product itself. The product information

clearly advises that aflibercept should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution.

Overall, no particular risk for transmission of infectious agents is seen.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

The following safety concerns were identified in the initial RMP submission according to EMEA/ H/C/006022.

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

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

Not applicable, as all risks from reference product RMP have been considered in this RMP.

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

Not applicable, as all risks from reference product RMP have been considered in this RMP.

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

The safety concerns for Yesafili (aflibercept) follow the same safety concerns of the reference biologics RMP, with the following exceptions: long-term safety of aflibercept in preterm infants with retinopathy of prematurity as a missing information, as Yesafili (aflibercept) is currently not proposed for the treatment of preterm infants with retinopathy of prematurity, hence this missing formation was removed.

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

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

Not applicable, as this RMP for aflibercept (M710 or MYL-1701P) follows the same safety concerns as the safety concerns of the reference substance RMP.

SVII.3.2. Presentation of the Missing Information

The safety concerns for aflibercept (M710 or MYL-1701P) follows the same safety concerns as the safety concerns of the reference biologics RMP with the following exceptions:

- the missing information 'long-term safety of aflibercept in preterm infants with retinopathy of prematurity' was removed from the list of safety concerns, as Yesafili (aflibercept) is not currently indicated for the treatment of preterm infants with retinopathy of prematurity.

- the missing information 'exposure with bilateral 8 mg aflibercept therapy' was not included as Yesafili is not available in this formulation and dose.

Part II: Module SVIII - Summary of the safety concerns

Table 5: Summary of safety concerns

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

* The reported missing information in Eylea® RMP version 35.1 "Exposure with bilateral 8 mg aflibercept therapy" was not included as BBL do not have aflibercept 114.3 mg/mL (8mg) dosage.

*The reported missing information in Yesafili RMP version 1.2, "Long-term safety of aflibercept in preterm infants with ROP", was not included as BBL Yesafili (aflibercept) is not currently proposed for the treatment of preterm infants with retinopathy of prematurity (ROP).

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

The Pharmacovigilance System Master File contains details of the system and processes that the MAH has in place to identify and characterise the risks recognised in the safety specification.

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Routine pharmacovigilance activities including AE collection and reporting, PSURs and signal detection will be carried out.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific Adverse Reaction Follow-up Questionnaires	
Safety Concern	**Purpose/Description**
Endophthalmitis (likely infectious origin) and intraocular inflammation.	Specific questionnaire to obtain comprehensive and standardized follow-up information about cases suspicious for endophthalmitis and intraocular inflammation
Transient intraocular pressure increase	Specific questionnaire to obtain comprehensive and standardized follow-up information related to intraocular pressure increase following the use of the pre-filled syringe.

The forms are provided in Annex 4 - Specific Adverse Drug Reaction Follow-up Forms of the RMP.

Traceability:

BBL acknowledges the need for traceability to be fully integrated in different healthcare settings and that infrastructure may vary between countries. A key requirement for pharmacovigilance of biologicals is the need to ensure continuous product and batch traceability in the clinical use. Communication should emphasize the importance of providing the product name (or INN and the name of marketing authorization holder) and the batch number(s) when reporting suspected adverse reactions. In line with international guidance on biological medicinal products, reporting drug name and batch number is mentioned in appropriate sections of BBL's Aflibercept product information/labels and included in the product packaging. This information is therefore available to be recorded and reported at all levels in the supply chain from the manufacturer release to prescription, dispensing and patient information.

Aflibercept will mainly be supplied in the hospital setting. A statement is presented in the product information/label reminding Healthcare Professionals (HCPs) on the type of the medicinal product (Biosimilar) and the need to clearly record both, the trade name and batch number in the patient's healthcare records. For the BBL's Aflibercept biosimilar, in all countries, no matter if middle or low income, INN and batch number can be found on the package.

According to international guidelines for the use of Biosimilars, BBL has a process in place to cover the requirements of traceability. Pharmacovigilance activities of biosimilar Aflibercept follow established standard procedures laid down by BBL to collect initial and follow up information. If any missing batch number or product name in the initial report received, then separate follow up will be made to the reporter. Adequacy of the data and proper assessment will be ensured. BBL performs diligent follow up on national level to obtain trade name and batch number to distinguish the reports of the BBL products to identify batch-related issues and product specific safety concerns.

Other Forms of Routine Pharmacovigilance Activities			
Activity	**Safety Concern(s)**	**Objective/Description**	**Milestones**
For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible.	All safety concerns	To monitor if there are any batch-specific issues in the post marketing environment.	Not applicable

III.2 Additional pharmacovigilance activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable, as routine pharmacovigilance only is proposed and there are no studies or other additional activities from the pharmacovigilance plan, whether ongoing, planned or completed.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

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

The safety information in the proposed product information is aligned to the reference medicinal product (Eylea®).

V.1. Routine Risk Minimisation Measures

Table 6: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important Identified Risks	
Endophthalmitis (likely infectious origin)	Routine risk communication: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet (PL) sections 2, 3 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Warning in section 4.4, intravitreal injections, including those with aflibercept, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above-mentioned events without delay. Other risk minimisation measures beyond the Product Information: Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections.
Intraocular Inflammation	Routine risk communication: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet section 2, 3 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Warning in section 4.4, intravitreal injections, including those with aflibercept, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract. 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. Other risk minimisation measures beyond the Product Information:

	Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections.
Transient intraocular pressure increase	Routine risk communication: SmPC sections 4.2, 4.4, 4.8, and 4.9 Package Leaflet section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Warning in section 4.4, increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with aflibercept. Special precaution is needed in patients with poorly controlled glaucoma (do not inject aflibercept 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. Excess volume from Aflibercept PFS/vial must be expelled/discarded prior to administration. Other risk minimisation measures beyond the Product Information: Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections.
Retinal pigment epithelial tears	Routine risk communication: SmPC sections 4.4 and 4.8 Package Leaflet section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Warning in section 4.4, 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. Other risk minimisation measures beyond the Product Information: Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections.
Cataract (especially of traumatic origin)	Routine risk communication: SmPC sections 4.2, 4.4 and 4.8 Package Leaflet section 2, 3 and 4

	Routine risk minimisation activities recommending specific clinical measures to address the risk: Warning in section 4.4, intravitreal injections, including those with aflibercept, have been associated with iatrogenic traumatic cataract. 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. Other risk minimisation measures beyond the Product Information: Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections.
Important Potential Risks	
Medication errors	Routine risk communication: SmPC sections 4.2, 4.9 and 6.6 Package Leaflet section 1 and 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Waning in section 4.2 (Posology and methods of administration) Verbal instruction is provided for the handling of the pre-filled syringe/vial in order to minimize the risk of drug administration error. Warning in section 4.9 (Overdose): Association between overdose and IOP increase is mentioned. Instruction for the use of the pre-filled syringe in the adult population is provided in section 6.6. Other risk minimisation measures beyond the Product Information: Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections.
Off-label use and misuse	Routine risk communication: SmPC sections 4.1, 4.3, 4.4 and 4.6 Package Leaflet section 1, 2 and 3 Routine risk minimisation activities recommending specific clinical measures to address the risk: Warning in section 4.3 (Contraindication), conditions in which treatment should be withheld/discontinued/not recommended are included in section 4.4 and conditions of use in pregnancy and breastfeeding are included in section 4.6. Other risk minimisation measures beyond the Product Information:

	Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections.
Embryo-fetotoxicity	Routine risk communication: SmPC sections 4.4, 4.6 and 5.3 Package Leaflet section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Warning in section 4.4 and 4.6, instruction for pregnancy and women of childbearing potential are mentioned. Other risk minimisation measures beyond the Product Information: Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections.
Missing information	
None	

V.2. Additional Risk Minimisation Measures

In line with the reference product, this medicine has additional risk minimisation measures for the following risks:

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

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 medication errors, off-label use and misuse, embryo-fetotoxicity. Generally, the educational material covers the indications wet AMD, CRVO, BRVO, myopic CNV, and DME.

The Educational Material will cover all approved dosage (40mg/mL) and approved formats (vials and PFS).

The updated Educational Material for HCPs includes highlighted information regarding the treatment of women of childbearing potential, information on the injection procedure with respect to unnecessary dilation of the eye, with the need for vision and intraocular pressure evaluation after the injection as well as the potential for medication misuse, particularly re-use of the vial.

Objectives of Additional Risk Minimisation Activities:

To address the above mentioned important identified and potential risks, the MAH proposes Prescriber Guide and Patient Guide to educate HCPs, patients/caregivers about specific risks, their early symptoms and the best course of action to be taken when these appear, beyond the recommendation contained in the Product Information.

Rationale for the Additional Risk Minimisation Activity:

Aflibercept is a biosimilar medicinal product to Eylea®. As a biosimilar, aflibercept has the same risks and hence needs to follow the same risk minimisation measures as the reference product. Details of the additional risk minimisation measures regarding the prescriber and patient guide are included above and in Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable).

Target Audience and Planned Distribution Path:

Appropriate method of distribution and target group will be agreed with national competent authorities prior to launch.

Plans for Evaluating the Effectiveness of the Interventions and Criteria for Success:

The company will monitor effectiveness of risk minimisation measures by routine pharmacovigilance activities during PSUR preparation (as per the EURD list), signal detection activity and medical review, as per internal procedures. The incidence of adverse reactions will be compared with those described in the SmPC. If there is an increased incidence of adverse reactions or if the reports are different in seriousness, severity or outcome to that described in the SmPC, labelling changes or risk minimisation will be considered. Additionally, effectiveness of additional RMMs will be evaluated on annual basis after MA approval.

Results of Effectiveness Evaluation:

Not applicable.

Rationale for Proposing to Remove Additional Risk Minimisation Measures:

Not applicable.

V.3 Summary of risk minimisation measures and Pharmacovigilance Activities

Table 7: Summary table of risk minimisation activities and pharmacovigilance activities by safety concern

Safety concern	Routine risk minimisation measures	Pharmacovigilance Activities
Important Identified Risks		
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 risk minimisation measures beyond the Product Information:** Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Prescriber guide and video; patient guide and its audio version	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific questionnaire to be used for endophthalmitis **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 risk minimisation measures beyond the Product Information:** Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific questionnaire to be used for intraocular inflammation **Additional pharmacovigilance activities:** None

	Additional risk minimization measures: Educational program: Prescriber guide and video; patient guide and its audio version	
Transient intraocular pressure increase	**Routine risk minimization measures:** SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2, 3 and 4 **Other risk minimisation measures beyond the Product Information:** Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Prescriber guide and video; patient guide and its audio version	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific questionnaire to be used for IOP increase following the use of the Yesafili pre-filled syringe. **Additional pharmacovigilance activities:** None
Retinal pigment epithelial tears	**Routine risk minimization measures:** SmPC sections 4.4, and 4.8 Package Leaflet sections 2, and 4 **Other risk minimisation measures beyond the Product Information:** Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections. **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

	Educational program: Prescriber guide and video; patient guide and its audio version	
Cataract (especially of traumatic origin)	**Routine risk minimization measures:** SmPC sections 4.2, 4.4 and 4.8 Package Leaflet section 2, 3 and 4 **Other risk minimisation measures beyond the Product Information:** Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Prescriber guide and video; patient guide and its audio version	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important Potential Risks		
Medication errors	**Routine risk minimization measures:** SmPC sections 4.2, 4.9 and 6.6 Package Leaflet section 1 and 3 **Other risk minimisation measures beyond the Product Information:** Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections. **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

	Educational program: Prescriber guide and video; patient guide and its audio version	
Off-label use and misuse	**Routine risk minimization measures:** SmPC sections 4.1, 4.3, 4.4 and 4.6 Package Leaflet section 1, 2, and 3 **Other risk minimisation measures beyond the Product Information:** Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Prescriber guide and video; patient guide and its audio version	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Embryo-fetotoxicity	**Routine risk minimization measures:** SmPC sections 4.4, 4.6 and 5.3 Package Leaflet section 2 **Other risk minimisation measures beyond the Product Information:** Medicine's legal status: Restricted medical prescription; Aflibercept must only be administered by a qualified health care professional experienced in administering intravitreal injections. **Additional risk minimization measures:** 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

	of women of child-bearing potential, and the need for appropriate contraception in women of childbearing potential. Educational program: Prescriber guide and video; patient guide and its audio version	
Missing Information		
None		

Part VI: Summary of the risk management plan

Summary of Risk Management Plan for Yesafili (Aflibercept)

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

Yesafili (Aflibercept) 40 mg/mL solution for injection and pre-filled syringe's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

This summary of the RMP for Yesafili (Aflibercept) should be read in the context of all the 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 Yesafili (Aflibercept)'s RMP.

I. The medicine and what it is used for

Yesafili (Aflibercept) is indicated for adults for the treatment of

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

It contains aflibercept as the active substance and it is given by intravitreal injection only.

The following pharmaceutical forms are currently available:

- Aflibercept 40 mg/mL (2 mg dose): Solution for injection in a vial. One vial contains 4 mg aflibercept in 100 microliters in iso-osmotic solution. Delivers a single dose of 2 mg/0.05 mL.
- Aflibercept 40 mg/mL (2 mg dose): Solution for injection in a pre-filled syringe. One pre-filled syringe contains 3.6 mg aflibercept in 90 microliters in iso-osmotic solution. Delivers a single dose of 2 mg/0.05 mL.

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

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

Important risks of Yesafili (Aflibercept), together with measures to minimise 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 addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including the Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Yesafili (Aflibercept) is not yet available, it is listed under 'missing information' below.

In the case of Yesafili (Aflibercept) 40 mg/mL, these routine measures are supplemented with additional risk minimization measures, mentioned under relevant risk below.

II.A List of important risks and missing information

Important risks of Yesafili (Aflibercept) 40 mg/mL are risks that need special risk management activities to further investigate or minimise 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 Yesafili (Aflibercept) 40 mg/mL. 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/use in special patient populations etc.).

Table 8: Summary of safety concerns

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

* The reported missing information in Eylea® RMP version 35.1 "Exposure with bilateral 8 mg aflibercept therapy" was not included as BBL do not have aflibercept 114.3 mg/mL (8mg) dosage.

II.B Summary of important risks

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

Table 9: Important Identified Risk: Endophthalmitis (likely infectious origin)

Important identified risk: Endophthalmitis (likely infectious origin)	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Eylea®, this safety concern has been classified as important identified risk. This risk was identified from in the 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 group	Improper aseptic technique increases the risk of intraocular inflammation
Risk minimisation 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. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimisation measures: Educational Program: Prescriber guide and video, patient guide and its audio version: Beyond routine risk minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on endophthalmitis (likely infectious origin).

Table 10: Important Identified Risk: Intraocular inflammation

Important Identified Risk: Intraocular inflammation	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Eylea®, this safety concern has been classified as important identified risk. This risk was identified in the 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 section 2, 3 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational program: Prescriber guide and video, patient guide and its audio version: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on endophthalmitis (likely infectious origin).

Table 11: Important identified Risk: Transient intraocular pressure increase

Important Identified Risks: Transient intraocular pressure increase	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Eylea®, this safety concern has been classified as important identified risk. This risk was identified in the data from clinical trials, post-marketing surveillance and literature. Transient IOP increase is attributed to an increase in vitreous volume after aflibercept 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 minimisation 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. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational program: Prescriber guide and video, patient

	guide and its audio version: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on transient intraocular pressure increase.

Table 12: Important identified Risk: Retinal pigment epithelial tears

Important Identified Risk: Retinal pigment epithelial tears	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Eylea®, this safety concern has been classified as important identified risk. This risk was identified in the data from clinical trials, post-marketing surveillance and literature. Development of 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 particularly in patients with wet AMD.
Risk factors and risk groups	Wet AMD with pigment epithelial detachment; treatment of neovascularization
Risk minimisation 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. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimisation measures: Educational Program: Prescriber guide and video, patient guide and its audio version: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on retinal pigment epithelial tears.

Table 13: Important Identified risks: Cataract (especially of traumatic origin)

Important identified risks: Cataract (especially of traumatic origin)	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Eylea®, this safety concern has been classified as important identified risk. This risk was identified in the 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 minimisation 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. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimisation measures: Educational program: Prescriber guide and video, patient guide and its audio version: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on cataract (especially of traumatic origin).

Table 14: Important Potential risks: Medication errors

Important Potential risk: Medication errors	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Eylea®, this safety concern has been classified as an important potential risk. The drug will be administered only by qualified physicians (not by patients), and this reduces the risk of inappropriate dosing and administration as well. Proper adherence to the instructions for adequate PFS preparation and use minimizes medication errors.
Risk factors and risk groups	Not applicable
Risk minimization measures	Routine risk minimisation measures: • SmPC sections 4.2, 4.9 and 6.6 • Package Leaflet section 1 and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimisation measures: Educational program: Prescriber guide and video, patient guide and its audio version: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on medication errors.

Table 15: Important potential risks: Off-label use and misuse

Important potential risk: Off-label use and misuse	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Eylea®, this safety concern has been classified as important potential risk. As with other drugs, Aflibercept 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 Aflibercept in such off-label use will be limited (in particular in terms of efficacy and safety), any case of off-label use will be considered a potential risk. Since Aflibercept 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 minimisation 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. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimisation measures: Educational program: Prescriber guide and video, patient guide and its audio version: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on off label use.

Table 16: Important potential risks: Embryo-fetotoxicity

Important potential risk: Embryo-fetotoxicity	
Evidence for linking the risk to the medicine	In line with the RMP of the reference product Eylea®, this safety concern has been classified as important potential risk. This risk was identified in the data from clinical trials, post-marketing surveillance and literature. An embryo-foetal 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 foetal resorptions, pregnancy disruptions and numerous foetal (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 minimisation 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. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimisation measures: Educational program: Prescriber guide and video, patient guide and its audio version: 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.

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Yesafili (Aflibercept) 40 mg/mL solution for injection in a vial or PFS.

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

There are no studies required for Yesafili (Aflibercept) 40 mg/mL solution for injection in a vial or PFS.

Part VII: Annexes

List of Annexes

Annex 4 – Specific adverse event follow-up forms

Annex 4.1: Endophthalmitis and intraocular inflammation (IOI)

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

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

Annex 4 – Specific adverse event follow-up forms

Annex 4.1: Targeted Follow-Up forms for Endophthalmitis and intraocular inflammation (IOI)

Annex 4.2: Targeted Follow-Up forms for Intraocular pressure (IOP) increase following the use of the Aflibercept pre-filled syringe

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Aflibercept (Vials/PFS) Questionnaire – Intraocular Inflammation/Endophthalmitis

BBL Case ID:			
SECTION I- REFERENCE 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: (at onset of event)	**Gender: male ☐ female ☐**	**Weight: unit:**	**Height: unit:**
Is the patient pregnant?	☐ Yes ☐ No **If yes, how many weeks:** **Date of LMP:**		**(DD-MMM-YYYY)**
SECTION III- PRODUCT INFORMATION (Aflibercept)			
Therapy Date *(dd/mm/yyyy):* ☐ **Ongoing**		**Number of Aflibercept doses before the event:**	
Indication:		**If other indication, specify**	
Eye injected/dose: OS: ☐ 2mg OD: ☐ 2mg			

Vial	**PFS (Pre-filled Syringe)**
Lot/Batch Number **OS: _____ Expiry Date: _____** **OD: _____ Expiry Date: _____**	**PFS Lot/Batch number:** **OS: _____ Expiry Date: _____** **OD: _____ Expiry Date: _____**
Was the same vial used for more than one patient? ☐ Yes ☐ No **If yes, did an event occur in other patients?** ☐ Yes ☐ No **If yes, how many _____**	**Was the same PFS used for more than one patient?** ☐ Yes ☐ No **If yes, did an event occur in other patients?** ☐ Yes ☐ No **If yes, how many _____**
Was the vial aliquoted in several syringes? ☐ Yes ☐ No **Was the vial multipunctured?** ☐ Yes ☐ No	
Was the supplied filter needle used? ☐ Yes ☐ No ☐ Unknown	
Date of Injection preparation (dd/mm/yyyy): **Time of Injection preparation**(hh:mm):	**Date of Injection preparation** (dd/mm/yyyy): **Time of Injection preparation**(hh:mm):
What was used for Injection? __ **Injection needle Batch No:** **Brand of the needle: OS: _____ OD _____** **Syringe (Luer Lock: ☐ Yes ☐ No)** ☐ Glass ☐ Plastic **Batch No: _____** **Brand of the syringe: OS _____ OD _____**	**What was used for Injection?** **Injection needle Batch No:** **Brand of the needle: OS: _____ OD _____**

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Aflibercept (Vials/PFS) Questionnaire – Intraocular Inflammation/Endophthalmitis

Where was the syringe for injection prepared? ☐ Off-site pharmacy ☐ On-site pharmacy ☐ Treatment/Examining Room	**Was the PFS stored according to the instruction for storage provided by the manufacturer?** ☐ Yes ☐ No **If No, please explain deviation of the storage condition**
If prepared in pharmacy, provide the 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)*	**or how long after injection did the event occur** *(approx.):*	**Stop date** *(dd/mm/yyyy):*	**Outcome** *(recovered, not recovered, Improved, recovered with sequelae, fatal, unknown)*

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

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

Clinical presentation:

Treatment of adverse event

Treatment provided: ☐ Yes ☐No If yes, specify ➜	☐ **Antibiotics:**	☐ **Steroids** (regimen details):	☐ **Surgery vitrectomy):** **Date:**	☐ **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 Aflibercept**
☐ **Related to intravitreal injection procedure**
☐ **Not related/Unrelated to Aflibercept or intravitreal injection procedure**

Alternative explanation (e.g., underlying disease/condition predisposing to the event):

Action taken with product

	Date from *(dd/mm/yyyy)*	**Date to** *(dd/mm/yyyy)*
☐ **Dose not changed**	**N/A**	**N/A**
☐ **Stopped**		**N/A**
☐ **Dose reduced**		**New dose:**
☐ **Interrupted**		
☐ **Unknown**	**N/A**	**N/A**
Did the event abate/stop after treatment stopped? ☐ **YES** ☐ **NO** ☐ **UNK**		**Did the event reoccur upon resuming treatment?** ☐ **YES** ☐ **NO** ☐ **UNK**

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Aflibercept (Vials/PFS) Questionnaire – Intraocular Inflammation/Endophthalmitis

SECTION IV - RELEVANT CLINICAL SYMPTOMS *(to AE of Interest)* Please Indicate which eye was affected		
Signs or Symptom	**Start Date**	**Stop Date**

Additional Questions:

Did the patient experience the 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 injection**	**Indication**	**Similar event occurred? If yes, Please specify**
☐ **Anti VGEF** Please specify ☐ **OS** ☐ **OD** ☐ **OU**			☐			
☐ **Others** Please specify ☐ **OS** ☐ **OD** ☐ **OU**			☐			

SECTION VI- RELAVANT MEDICAL HISTORY/ RISK FACTORS (relevant to the reported event)

Condition	**Start Date** *(dd/mm/yyyy)*	**Stop Date** *(dd/mm/yyyy)*	**Ongoing?**
☐ **Diabetes**			☐
☐ **Autoimmune disease, please specify:**			☐
☐ **Malignancy, please specify:**			☐
☐ **Immunodeficiency, please specify:**			☐
☐ **Other, please specify:**			☐

SECTION VII: ADDITIONAL INFORMATION (COMMENTS) *(e.g. gender information if not male/female):*

Cause of Death	**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.

SECTION VIII: REPORTER'S DETAILS

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.	**Signature and Date**
Name/Initials:	
Occupation:	
☐ **Physician** ☐ **Pharmacist** ☐ **Nurse** ☐ **Other Healthcare Professional** ☐ **Patient/Consumer**	

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Questionnaire Aflibercept- Increase in Intraocular pressure (IOP) with Pre-filled syringes (PFS) of Aflibercept

BBL Case ID:		
REPORTER INFORMATION		
Name:		☐ Physician ☐ Nurse ☐ Others
Email:		**Telephone**
Institution Name and address		**Fax:**
PATIENT INFORMATION		
Initials: *(leave empty for study participants)*	**Gender: male ☐ female ☐**	**Age group** *(at onset of events)*
PRODUCT INFORMATION (Aflibercept)		
Number of aflibercept doses before the event:	**Dose information:** **OS** ☐ **2.0mg** **OD** ☐ **2.0mg**	**PFS batch number(s):** **OS:** _____ **Expiry Date:** _____ **OD:**_____ **Expiry Date:** _____
Indication:		
ADVERSE EVENT INFORMATION		
Intraocular Pressure (IOP) Increase onset date *(dd/mm/yyyy):*	**Last Injection date before event onset** *(dd/mm/yyyy):*	
Was the IOP value measured pre-injection? ☐ **No** ☐ **Yes, if yes, please provide** • IOP value(s) (mmHg) • Time/minutes pre-injection and date • Method		
Was the IOP value measured post-injection? ☐ **No** ☐ **Yes, if yes, please provide** • IOP value(s) (mmHg) • Time/minutes pre-injection and date • Method		
How long did the increased IOP last after the injection?		
Outcome of IOP increase event	☐ **recovering/resolving** ☐ **recovered/resolved without sequelae** ☐ **recovered/resolved with sequelae,** **please detail sequelae**_____ ☐ **not recovered/not resolved** ☐ **unknown**	
Did patient experience any other clinical sign or symptom in the context of post-injection IOP increase? ☐ **No** ☐ **Yes** **if yes, which other medical conditions / symptoms were experienced and what is the outcome of the event?** Please indicate the outcome in box to the right	**Outcome of the events (please indicate event in parenthesis)** ☐ **recovering/resolving (event(s)**_____ ☐ **recovered/resolved without sequelae (event(s)**_____ ☐ **recovered/resolved with sequelae (event(s)**_____ ☐ **not recovered/not resolved (event(s)**_____ ☐ **unknown (event(s)**_____	

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Questionnaire Aflibercept- Increase in Intraocular pressure (IOP) with Pre-filled syringes (PFS) of Aflibercept

	☐ not applicable
Was post injection fundoscopy performed? ☐ No ☐ Yes if yes, please provide the results and post-injecting timing	
Was there any intervention done to treat increased IOP? ☐ No ☐ Yes if yes, please specify the measures taken including date and time	
Does the patient have a history of glaucoma, ocular hypertension or glaucoma surgery or take anti-glaucoma medication in the injected or the fellow eye? ☐ No ☐ Yes if yes, please provide details	☐ OS ☐ OD ☐ OU Details:
Has the patient's anterior chamber angle been assessed in the eye(s) with IOP increase? ☐ No ☐ Yes if yes, please detail the result, date: timing (pre- or post-injection):	By which method? Is the angle open, narrow, or closed? ☐ OS ☐ OD Details:
Did the patient use corticosteroids or any other medication, they could potential increase IOP? ☐ No ☐ Yes if yes, please specify drug name and indications	
Does the patient have any of the following co-morbid conditions (please check all that apply)? ☐ Diabetes ☐ High blood pressure ☐ Low blood pressure ☐ Retinal ischemia ☐ CRAO ☐ BRAO ☐ Eye trauma ☐ Eye surgeries ☐ Myopia ☐ Pseudo exfoliation syndrome ☐ Pigment dispersion syndrome ☐ Corneal arcus present, details:	
PFS Details:	
Who prepared the Aflibercept PFS injection (e.g., physician, nurse, other)? **Was the individual specifically trained on the Aflibercept PFS ☐ No ☐ Yes**	
Who conducted the Aflibercept injection with the PFS (e.g., physician, nurse)? **Was the individual specifically trained on the Aflibercept PFS ☐ No ☐ Yes**	
Was the 30G needle used for injections? ☐ Yes ☐ No **If no, which needle size was used? Brand of injection needle if known:**	
For adult patients only: Where all bubbles eliminated/expelled, excess drug expelled, and the plunger correctly adjusted to the dose line before injection (moving the base of blunger dome (not the tip) to dosing line)? **☐ Yes ☐ No If no, please provide the details:**	

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Questionnaire Aflibercept- Increase in Intraocular pressure (IOP) with Pre-filled syringes (PFS) of Aflibercept

Was there any difficulty in preparing the PFS according to the instructions prior to the injection?
☐ No ☐ Yes
If yes, please explain:

Was there any physical or handling abnormality observed with the syringe/PFS ?
☐ No ☐ Yes
If yes, please specify:

For this event, did you see any foreign particles, discoloration or change in physical appearance of the Aflibercept solution? ☐ No ☐ Yes
If yes, provide details:

For this event, have you injected, or attempted to inject, the residual volume which remained in the syringe after completion of injection?
☐ No ☐ Yes
If yes, provide details:

Other anti-VEGF treatment:

Did the patient have previous intravitreal injections? ☐ No ☐ Yes **If yes, please fill the adjacent columns to the right:**	**Aflibercept** ☐ **Vial** ☐ **PFS** ☐ **Other Intravitreal injections**	**Was IOP increase also observed after previous intraocular injections?** ☐ No ☐ Yes **If yes, provide details:**

Further notes (free text)

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements. **Name/Initials:** **Occupation:** ☐ **Physician** ☐ **Pharmacist** ☐ **Nurse** ☐ **Other Healthcare Professional** ☐ **Patient/Consumer**	**Signature**

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Annex 6 - Details of proposed additional risk minimisation measures (if applicable)

The MAH has agreed to provide EU educational material for Yesafili. Prior to launch and during the product's lifecycle in each Member State the MAH will agree the final educational material with the National Competent Authority.

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

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

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

- Techniques for the intravitreal injection including use of a 30 G needle and angle of injection.
- The vial and the pre-filled syringe are for single use only.
- The need to expel excess volume of the syringe before injecting Yesafili 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 Yesafili.

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

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