EUROPEAN UNION RISK MANAGEMENT PLAN

PAVBLU® (ABP 938, aflibercept)

Marketing Authorization Applicant	Amgen Technology (Ireland) Unlimited Company Pottery Road, Dun Laoghaire Co. Dublin A96 F2A8 Ireland
Version:	1.0
Date:	28 January 2025
Supersedes:	None

Risk Management Plan (RMP) version to be assessed as part of this application

RMP version number:	1.0
Data lock point of this RMP:	06 April 2023
Date of final sign-off:	28 January 2025
Rationale for submitting an updated RMP:	Not applicable

Summary of significant changes in this RMP

Not applicable.

Other RMP versions under evaluation:	
RMP version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	Not applicable
Approved with procedure:	Not applicable
Date of approval (opinion date):	Not applicable
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm and MSc Ind Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization applicant's QPPV. The electronic signature is available on file.

Table of Contents

List of Tables

List of Annexes

List of Abbreviations

Term/Abbreviation	Explanation
AMD	age-related macular degeneration
AUC	area under the curve
BCVA	best corrected visual acuity
BLA	Biologics License Application
C_{max}	maximum concentration
CNV	choroidal neovascularisation
DME	diabetic macular oedema
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
Fc	fragment crystallizable
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IV	intravenous
IVT	intravitreal
NOAEL	no-observed-adverse-effect-level
PBRER	Periodic Benefit-Risk Evaluation Report
PI	Product Information
PL	package leaflet
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RVO	retinal vein occlusion
SC	subcutaneous
SmPC	Summary of Product Characteristics
US	United States
USPI	United States Prescribing Information
VEGF	vascular endothelial growth factor
VEGF-A	vascular endothelial growth factor-A
VEGFR	vascular endothelial growth factor receptor

Note to Reviewers: ABP 938 is being developed as a biosimilar candidate to Eylea® (aflibercept). Eylea (aflibercept) that is approved in, and sourced from, the United States (US) is referred to as "aflibercept (US)." Eylea (aflibercept) that is approved in, and sourced from, the European Union (EU) is referred to as "aflibercept (EU)." The comparator reference medicinal product Eylea is referred to as aflibercept in the ABP 938 studies to be consistent with the marketing application. In all other contexts in this document it is referred to as Eylea. The biosimilar candidate to Eylea is referred to as ABP 938 in the Amgen-sponsored studies to be consistent with the marketing application. In all other contexts in this document it is referred to as PAVBLU.

PART I: PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Aflibercept
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	S01LA05
Marketing authorization applicant	Amgen Technology (Ireland) Unlimited Company
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	PAVBLU®
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Aflibercept is a recombinant fusion protein consisting of portions of human vascular endothelial growth factor (VEGF) receptor (VEGFR) 1 and 2 extracellular domains fused to the fragment crystallizable (Fc) portion of human immunoglobulin (Ig) G1. Aflibercept is a specific blocker that binds and inactivates VEGF and the related molecule, placental growth factor.
Summary of mode of action	Vascular endothelial growth factor-A (VEGF-A) and placental growth factor are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. Vascular endothelial growth factor acts via 2 receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. Placental growth factor binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. Placental growth factor can synergize with VEGF-A in these processes, and is also known to promote leucocyte infiltration and vascular inflammation.
Important information about its composition	PAVBLU is produced in a Chinese hamster ovary cell line by recombinant DNA technology.
Hyperlink to the Product Information (PI)	The proposed PI is provided in Module 1.3.1.

Table 1. Product(s) Overview

Indication(s) in the EEA	
Current	PAVBLU 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)
Dosage in the EEA	
Current	The recommended dose for PAVBLU is 2 mg aflibercept, equivalent to 0.05 mL, by intravitreal (IVT) injection only. *Wet AMD* PAVBLU treatment is initiated with 1 injection per month for 3 consecutive doses. The treatment interval is then extended to 2 months. Based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at 2 months or further extended using a treat-and-extend dosing regimen, where injection intervals are increased in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. Treatment intervals greater than 4 months or shorter than 4 weeks between injections have not been studied. *Macular oedema secondary to RVO (branch RVO or central RVO)* After the initial injection, treatment is given monthly. The interval between 2 doses should not be shorter than 1 month. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, PAVBLU should be discontinued. Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a treat-and-extend regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly.

Table 1. Product(s) Overview

Dosage in the EEA	
Current (continued)	*Diabetic macular oedema* PAVBLU treatment is initiated with 1 injection per month for 5 consecutive doses, followed by 1 injection every 2 months. Based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at 2 months or individualized, such as with a treat-and-extend dosing regimen, where the treatment intervals are usually increased by 2-week increments to maintain stable visual and/or anatomic outcomes. There are limited data for treatment intervals longer than 4 months. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. Treatment intervals shorter than 4 weeks have not been studied. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, PAVBLU should be discontinued. *Myopic choroidal neovascularization* A single dose of PAVBLU treatment is recommended. 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 2 doses should not be shorter than 1 month.
Pharmaceutical form(s) and strength(s)	
Current:	PAVBLU is supplied as a clear to opalescent, colorless to slightly yellow, and iso-osmotic solution for injection in a pre-filled syringe and a vial: • One pre-filled syringe contains an extractable volume of at least 0.09 mL, equivalent to at least 3.6 mg aflibercept. This provides a usable amount to deliver a single dose of 0.05 mL containing 2 mg aflibercept to adult patients. • One vial contains an extractable volume of at least 0.1 mL, equivalent to at least 4 mg aflibercept. This provides a usable amount to deliver a single dose of 0.05 mL containing 2 mg aflibercept.
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)

As per the Guideline on Good Pharmacovigilance Practices Module V - Risk management systems (EMA/838713/2011 Rev 2) Module SI may be omitted from the EU RMP for new applications for similar biological products.

Part II: Module SII - Nonclinical Part of the Safety Specification

ABP 938 is being developed as a biosimilar candidate to Eylea (aflibercept), the reference medicinal product. ABP 938 and Eylea have the same amino acid sequence, route of administration (IVT injection), and product strength (40 mg/mL aflibercept); however, ABP 938 has a different formulation than Eylea that includes α,α-trehalose dihydrate and polysorbate 80. Both α,α-trehalose dihydrate and polysorbate 80 are well-known, compendial excipients that have been administered by the same route of administration at higher dose levels in other IVT drugs (Lucentis® [ranibizumab] or Beovu® [brolucizumab], respectively) approved for use in adult populations in the US and EU (Lucentis Summary of Product Characteristics [SmPC], October 2023; Beovu SmPC, September 2023; Beovu United States Prescribing Information [USPI], September 2023; Lucentis USPI, February 2024).

To evaluate the potential toxicity of ABP 938 and to qualitatively compare the toxicity and toxicokinetics of ABP 938 and aflibercept (EU), a 1-month IVT repeat-dose toxicology study in the female cynomolgus monkey was conducted with ABP 938 and Eylea (Study 119678). This animal model and route of administration were also used in the original aflibercept reference product toxicology assessment (Eylea Biologics License Application [BLA] 125387 Pharmacology Review, 2011). In this study, both eyes of each animal were administered saline control, ABP 938 at 1 mg/eye, or aflibercept (EU) at 1 mg/eye on study days 1 and 29 by IVT injection in a 25 μL dose volume. The 1 mg/eye dose level was selected to provide a human equivalent dose of 2 mg/eye to patients, adjusting for vitreous volume differences between cynomolgus monkeys and humans, and the IVT route of administration was selected as the intended route of administration in humans (Eylea USPI, December 2023; Emami et al, 2018). There were no observations of ocular or systemic toxicity in the female cynomolgus monkey administered ABP 938 and there were no apparent differences in the groups of cynomolgus monkeys administered saline, ABP 938, or aflibercept related to clinical observations, body weights, ophthalmic parameters, intraocular pressures, full-field electroretinography measurements, or clinical or anatomic pathology endpoints including histologic evaluation of both eyes from each animal (Study 119678). Single and transient clinical observations in 1 eye from animals in the ABP 938- or aflibercept (EU)-treated groups that were not present in the saline-treated animal groups included 0.5+ aqueous cells and white vitreous floaters with multifocal clear spheres. These observations were not considered treatment related due to the sporadic nature and

minor magnitude of the findings and attributed to the IVT injection procedure and the silicone droplets used to lubricate the syringes, respectively. The no-observed-adverse-effect-level (NOAEL) for ABP 938 was determined to be greater than 1 mg/eye, the highest dose level tested.

Based on the nonclinical assessment of ABP 938 and Eylea, ABP 938 is considered safe with no residual uncertainties regarding ocular or systemic safety for IVT administration in the intended patient populations.

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from ABP 938 studies		
Toxicity		
• Single and repeat-dose toxicity studies	There were no ocular or systemic toxicities observed with ABP 938 or aflibercept (EU) and no apparent differences between saline, 1 mg/eye ABP 938, or 1 mg/eye aflibercept (EU) when administered by IVT injection in both eyes of the female cynomolgus monkey in a 1-month repeat-dose toxicology study (2 total doses, 4-weeks apart). The 1 mg/eye dose level of ABP 938 is a human equivalent dose of 2 mg/eye to patients adjusting for vitreous volume differences between cynomolgus monkey and humans. There were no ABP 938- or aflibercept (EU)-related effects on clinical observations, body weights, ophthalmic parameters, intraocular pressures, full-field electroretinography measurements, or clinical or anatomic pathology endpoints and no histopathologic observations specific to the eye. Sporadic, minor, and transient clinical observations of ocular inflammation in 1 eye of an ABP 938 and aflibercept (EU), but not saline, treated animal, were considered procedurally related and not caused by ABP 938 or aflibercept (EU). The NOAEL for ABP 938 was greater than 1 mg/eye, the highest dose tested, based on no observed ocular or systemic toxicity in the female cynomolgus monkey.	The nonclinical repeat-dose IVT toxicology study with ABP 938 did not identify any areas of concern for human use. There were no observed differences in animals administered ABP 938 or aflibercept (EU) by IVT injection at a human equivalent dose level. The EU RMP for the reference medicinal product, Eylea, states that post-injection, sterile intraocular inflammation is a known risk following IVT injections, and the Eylea SmPC includes vitreous floaters as a common finding in patients (Eylea SmPC, June 2024; Eylea EU RMP v34.1, February 2024), which correlates to the transient (mild) episodes of ocular inflammation observed in 1 eye of ABP 938- or aflibercept (EU)-treated animals. The SmPC and USPI for the reference medicinal product, Eylea, acknowledge the findings of erosions and ulcerations of the respiratory epithelium that were observed in the nasal turbinates of monkeys administered higher doses of Eylea (2 or 4 mg/eye) by IVT injection and qualify these findings as having little relevance to clinical use due to the high systemic exposure needed to cause these effects in animals (Eylea SmPC, June 2024; Eylea USPI, December 2023).

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from ABP 938 studies (continued)		
Toxicity		
• Reproductive/ developmental toxicity	There were no reproductive or development toxicity studies and no chronic repeat-dose toxicology studies conducted in animals with ABP 938 consistent with recommendations in global guidance for biosimilar drug development.	Maternal and fetal toxicities were observed in embryo-fetal development studies in pregnant rabbits at high systemic exposures of Eylea achieved through parenteral (intravenous [IV]) route of administration (approximately 600-fold higher than the clinical exposure in a 2 mg IVT administered dose) (Eylea BLA 125387 Pharmacology Review, 2011). Based on the anti-VEGF mechanism of action for aflibercept and potential risk to human embryo-fetal development, ABP 938 should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus. There are no data regarding the effects of Eylea on human fertility (Eylea SmPC, June 2024). At systemic Eylea exposures approximately 1500 times higher than the systemic level observed in adult patients with an IVT dose of 2 mg, Eylea adversely affected female and male reproductive systems in a 6-month repeat-dose IV study in cynomolgus monkeys. The potential for VEGF inhibition to impair fertility is a known class effect of anti-VEGF drugs and is not specific to Eylea (Eylea BLA 125387 Pharmacology Review, 2011). As a biosimilar medicinal product, the same adverse effects should be expected with ABP 938 if similarly high systemic exposure levels were achieved in animals. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last IVT injection of Eylea (Eylea SmPC, June 2024). In line with the reference medicinal product, Eylea, embryo-fetotoxicity is included an important potential risk (Table 16).

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from ABP 938 studies (continued)		
Toxicity		
• Genotoxicity/ carcinogenicity	There were no genotoxicity or carcinogenicity studies conducted with ABP 938 or the reference product Eylea as they are not applicable for biotechnology-derived pharmaceuticals in accordance with International Conference on Harmonisation (ICH) S6 Guidance for Industry.	No studies have been conducted on the mutagenic or carcinogenic potential of Eylea (Eylea SmPC, June 2024). Other marketed drugs of a similar anti-VEGF mechanistic class have not been associated with neoplasia (Eylea BLA 125387 Pharmacology Review, 2011).
Safety pharmacology	There were no safety pharmacology studies conducted with ABP 938 in accordance with guidance for biosimilar drug development.	Eylea caused a rapid increase in blood pressure in telemeterized mice and rats when administered by subcutaneous (SC) injection. The duration of the blood pressure increase was dose proportional and resolved when systemic Eylea levels fell below approximately 1 μg/mL in both species; approximately 50-fold higher than the clinical exposure in patients administered 2 mg by IVT injection (Eylea BLA 125387 Pharmacology Review, 2011). As a biosimilar medicinal product, the same adverse effects on blood pressure would be expected with ABP 938 if similarly high exposure levels and experimental conditions were replicated in animal studies. There were no changes in electrocardiogram or blood pressure in cynomolgus monkeys in the repeat-dose IV toxicology studies with Eylea up to 6 months in duration (Eylea BLA 125387 Pharmacology Review, 2011).

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from Eylea studies		
Toxicity		
• Single-dose toxicity studies	A moderate dose-related decrease in mean body weight and a slight decrease in mean food consumption was observed in male rats (only) administered Eylea at 50, 150, or 500 mg/kg in a single 30-minute IV infusion. Lesions at the injection site were reported in a few rats at 50 and 500 mg/kg. The NOAEL was considered to be > 500 mg/kg in females and a NOAEL was not identified in males due to the significant decrease in body weight gain (26%) that persisted at the end of a 2-week recovery period. The lethal dose of Eylea in rats is above 500 mg/kg when administered by IV injection (Eylea BLA 125387 Pharmacology Review, 2011).	As a biosimilar, the safety profile for ABP 938 is expected to be similar to the reference medicinal product, Eylea.
• Repeat-dose toxicity studies		
– Ocular	Eylea was administered by IVT injection, every 4 weeks, for 8 months to male and female cynomolgus monkeys at 500, 2000, or 4000 μg/eye in a consistent 50 μL dose volume using 10, 40, or 80 mg/mL concentration formulations, respectively. A mild and transient anterior segment and vitreous inflammatory response was detected at all dose levels and was not associated with other ocular abnormalities. In animals ≥ 2000 μg/eye, there was an increased incidence of epithelial erosion/ulceration, often accompanied by chronic-active inflammation of the nasal turbinates. There was substantial systemic exposure after IVT injection (in the μg/mL range) that was detectable at the end of the 6-month recovery period in animals in the high-dose group (Eylea BLA 125387 Pharmacology Review, 2011).	The SmPC and USPI for the reference medicinal product, Eylea, acknowledge the findings of erosions and ulcerations of the respiratory epithelium that were observed in the nasal turbinates of monkeys administered higher doses of Eylea (2 or 4 mg/eye) by IVT injection and qualify these findings as having little relevance to clinical use due to the high systemic exposure needed to cause these effects in animals (Eylea SmPC, June 2024; Eylea USPI, December 2023).

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from Eylea studies (continued)		
Toxicity		
• Repeat-dose toxicity studies		
– Systemic	The systemic toxicity of IV-administered Eylea was evaluated in multiple repeat-dose toxicology studies in the cynomolgus monkey up to 6 months in duration with a 5-month recovery period at 0, 3, 10, or 30 mg/kg dosed weekly for 15 weeks and reduced to every-other-week dosing for the final 12 weeks due to toxicity (decreased body weights). In the IV repeat-dose toxicology studies in cynomolgus monkeys with Eylea, there were consistent aflibercept-related effects on clinical pathology parameters (hematology, clinical chemistry), organ weights (multiple tissues), reduction in sperm motility and abnormal sperm morphology in males, and histopathology findings observed in the nasal cavities, various bones, kidneys, female reproductive system, digestive system (liver, gallbladder, duodenum, and stomach), adrenal glands, brain, thymus, and trachea with microvascular effects noted in most of these tissues and sporadically in the heart. There was partial recovery in some organs at the end of the recovery period. There was no NOAEL determined in the 6-month study in cynomolgus monkeys (Eylea BLA 125387 Pharmacology Review, 2011).	Effects in nonclinical studies on repeated dose toxicity were observed only at systemic exposures considered substantially in excess of the maximum human exposure after IVT administration at the intended clinical dose indicating little relevance to clinical use (Eylea SmPC, June 2024). Intravitreal injection of Eylea causes an increase in systemic plasma levels of Eylea. The adverse effects of systemic exposure to Eylea are associated with anti-angiogenic activity from Eylea's mechanism of action (anti-VEGF). The adverse findings in the repeat-dose toxicity studies in cynomolgus monkey with Eylea occurred at exposure levels at least 50-fold over the expected systemic exposure from a clinical dose (2 mg) of IVT administered Eylea.

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from Eylea studies (continued)		
Toxicity		
• Reproductive/ developmental toxicity	An embryo-fetal development toxicity study was conducted in pregnant rabbits at 0, 3, 15, or 60 mg/kg on gestation days 6, 9, 12, 15, and 18 by 30-minute IV infusion. Abortions, increased postimplantation loss, and early resorptions lowered the mean number of viable fetuses in dams at 60 mg/kg. External, visceral, and skeletal malformations associated with anti-angiogenic effects of aflibercept were observed in fetuses at $\geq$ 3 mg/kg. The maternal NOAEL was 3 mg/kg and the developmental NOAEL was $<$ 3 mg/kg. For the proposed indication that affects an older population ($\geq$ 50 years of age), no pre- and post-natal toxicity studies were required (Eylea BLA 125387 Pharmacology Review, 2011). An effect of aflibercept on intrauterine development was also shown in an embryo-fetal development study in pregnant rabbits with SC (0.1 to 1 mg/kg) administration. The maternal NOAEL was at the dose of 1 mg/kg. A developmental NOAEL was not identified. At the 0.1 mg/kg dose, the systemic exposures based on maximum concentration (C_{max}) and cumulative area under the curve (AUC) for free aflibercept were approximately 17- and 10-fold higher, respectively, when compared to corresponding values observed in humans after an IVT dose of 2 mg (Eylea SmPC, June 2024). Male and female fertility was evaluated as part of the 6-month IV toxicity study in monkeys. In females, there were absent or irregular menses associated with reductions in ovarian hormones, decreased ovary weights accompanied by markedly compromised luteal development, and uterine endometrial and myometrial atrophy and vaginal epithelial atrophy. In males, there was a pronounced reduction in sperm motility and increased morphological abnormalities in spermatozoa. The reproductive toxicities occurred down to the lowest dose level at 3 mg/kg. There was no NOAEL in this study (Eylea BLA 125387 Pharmacology Review, 2011).	Based on the anti-VEGF mechanism of action for aflibercept and the potential risk to human embryo-fetal development, Eylea should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus (Eylea SmPC, June 2024; Eylea USPI, December 2023). There are no data regarding the effects of Eylea on human fertility. At systemic Eylea exposures approximately 1500 times higher than the systemic level observed in adult patients with an IVT dose of 2 mg, Eylea adversely affected female and male reproductive systems in a 6-month repeat-dose IV study in cynomolgus monkeys (Eylea SmPC, June 2024; Eylea USPI, December 2023). Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last IVT injection of Eylea (Eylea SmPC, June 2024). In line with the reference medicinal product, Eylea, embryo-fetotoxicity is included an important potential risk (Table 16).

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from Eylea studies (continued)		
Toxicity		
• Genotoxicity/ carcinogenicity	There were no genotoxicity or carcinogenicity studies conducted with Eylea as they are not applicable for biotechnology-derived pharmaceuticals in accordance with ICH S6 Guidance for Industry.	No studies have been conducted on the mutagenic or carcinogenic potential of Eylea (Eylea SmPC, June 2024). Other marketed drugs of a similar anti-VEGF mechanistic class have not been associated with neoplasia (Eylea BLA 125387 Pharmacology Review, 2011).
Safety pharmacology		
• Cardiovascular system (including potential effect on the QT interval) and respiratory function	Single-dose SC injections of aflibercept at 0.5 to 25 mg/kg in Wistar-Kyoto rats and at 2.5 and 25 mg/kg in C57BL/6 mice produced rapid increases in blood pressure in telemetered animals. The maximal increases were evident at 2 to 4 days (Wistar-Kyoto rats) or 1 to 2 days postdose (C57BL/6 mice). The maximal elevation in blood pressure saturated at ≥ 10 mg/kg in rats but the duration of the blood pressure elevation was dose proportional throughout the full range of doses tested in both species (eg, approximately 7 days at 2.5 mg/kg, approximately 21 days at 25 mg/kg in mice) (Eylea BLA 125387 Pharmacology Review, 2011). There were no significant effects on respiratory function of conscious rats administered an IV infusion of Eylea over 30 minutes at 10, 50, or 250 mg/kg measured by whole body plethysmography up to 7 days after administration (Eylea BLA 125387 Pharmacology Review, 2011). There were no effects on electrocardiogram and blood pressure measured in the IV repeat-dose toxicology studies in the cynomolgus monkey dosed up to 30 mg/kg (highest dose tested), weekly for 15 weeks and reduced to every other week for the final 12 weeks due to decreased body weights (Eylea BLA 125387 Pharmacology Review, 2011).	Eylea caused increased systolic and diastolic blood pressure with a compensatory transient decrease in heart rate in telemeterized mice and rats when administered by SC injection. The duration of the blood pressure increase was dose proportional and returned to pre-treatment values when Eylea levels fell below approximately 1 μg/mL (approximately 50-fold the observed human exposure for a 2 mg IVT dose) (Eylea BLA 125387 Pharmacology Review, 2011).

Table 2. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Important nonclinical safety findings from Eylea studies (continued)		
Other toxicity-related information or data	Aflibercept did not demonstrate antibody-dependent cell-mediated cytotoxicity activities or mediate complement-dependent cytotoxicity in various in vitro cell based systems.	Not applicable.

Part II: Module SIII - Clinical Trial Exposure

Table 3. Total Subject Exposure to ABP 938 or Aflibercept in Clinical Trials by Indication and Duration (Safety Analysis Set)

	ABP 938		Aflibercept	
Indication	Cumulative Exposure < 6 months n (subj-yrs)	Cumulative Exposure ≥ 6 months n (subj-yrs)	Cumulative Exposure < 6 months n (subj-yrs)	Cumulative Exposure ≥ 6 months n (subj-yrs)
Comparative Clinical Study in Patients with (wet) Age-related Macular Degeneration (AMD)	25 (7.83)	396 (354.10)	154 (47.32)	134 (132.37)
Open-label, Clinical Usability Study with Pre-filled Syringe (PFS) in Patients with Chorioretinal Vascular Disease (CVD)	32 (2.59)	0 (0)	16 (1.37)	0 (0)
Total	57 (10.42)	396 (354.10)	170 (48.68)	134 (132.37)

n = number of subjects exposed to ABP 938 or aflibercept; subj-yrs = total subject-years of follow-up

Note: Data is from the completed PFS CVD Study 20210034 (completed on 06APR2023) and the completed Comparative Clinical AMD Study 20170542 (completed on 13MAR2023). For Comparative Clinical AMD Study 20170542, subjects were randomized to receive either ABP 938 or Aflibercept by intravitreal (IVT) injection every 4 weeks for the first 3 doses (ie, baseline/day 1, week 4, week 8); subjects were then re-randomized at week 16 such that subjects initially randomized to ABP 938 would continue to receive ABP 938 by IVT injection every 8 weeks from week 16 until week 48 and subjects initially randomized to Aflibercept would be re-randomized to either transit to ABP 938 or continue to receive Aflibercept by IVT injection every 8 weeks from week 16 until week 48.
For PFS CVD Study 20210034, subjects were randomized to receive a single IVT injection of ABP 938 or aflibercept.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

Source: t05-cum-subj-exp.rtf (Generated on: 12JUL2023 09:23)

Table 4. Total Subject Exposure to ABP 938 or Aflibercept in Clinical Trials by Age Group and Gender (Safety Analysis Set)

	ABP 938		Aflibercept	
Indication	< 65 years n (subj-yrs)	≥ 65 years n (subj-yrs)	< 65 years n (subj-yrs)	≥ 65 years n (subj-yrs)
Male				
Comparative Clinical Study in Patients with (wet) Age-related Macular Degeneration (AMD)	21 (18.26)	170 (143.63)	11 (6.87)	106 (69.28)
Open-label, Clinical Usability Study with Pre-filled Syringe (PFS) in Patients with Chorioretinal Vascular Disease (CVD)	7 (0.57)	12 (0.97)	5 (0.41)	9 (0.78)
Total	28 (18.84)	182 (144.60)	16 (7.28)	115 (70.07)
Female				
Comparative Clinical Study in Patients with (wet) AMD	16 (13.55)	214 (186.48)	15 (9.01)	156 (94.52)
Open-label, Clinical Usability Study with PFS in Patients with CVD	3 (0.26)	10 (0.79)	1 (0.09)	1 (0.08)
Total	19 (13.81)	224 (187.27)	16 (9.10)	157 (94.60)

n = number of subjects exposed to ABP 938 or aflibercept; subj-yrs = total subject-years of follow-up

Note: Data is from the completed PFS CVD Study 20210034 (completed on 06APR2023) and the completed Comparative Clinical AMD Study 20170542 (completed on 13MAR2023). For Comparative Clinical AMD Study 20170542, subjects were randomized to receive either ABP 938 or Aflibercept by intravitreal (IVT) injection every 4 weeks for the first 3 doses (ie, baseline/day 1, week 4, week 8); subjects were then re-randomized at week 16 such that subjects initially randomized to ABP 938 would continue to receive ABP 938 by IVT injection every 8 weeks from week 16 until week 48 and subjects initially randomized to Aflibercept would be re-randomized to either transit to ABP 938 or continue to receive Aflibercept by IVT injection every 8 weeks from week 16 until week 48.
For PFS CVD Study 20210034, subjects were randomized to receive a single IVT injection of ABP 938 or aflibercept.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

Source: t06-cum-subj-exp-age-sex.rtf (Generated on: 12JUL2023 09:24)

Table 5. Exposure to ABP 938 or Aflibercept in Clinical Trials by Dose Level and Indication (Safety Analysis Set)

	Exposure to ABP 938 in Days		Exposure to Aflibercept in Days		Exposure to ABP 938 in Subject-years		Exposure to Aflibercept in Subject-years	
Indication	2 mg Single Dose n (mean)	2 mg Q4W n (mean)	2 mg Single Dose n (mean)	2 mg Q4W n (mean)	2 mg Single Dose n (mean)	2 mg Q4W n (mean)	2 mg Single Dose n (mean)	2 mg Q4W n (mean)
Comparative Clinical Study in Patients with (wet) Age-related Macular Degeneration (AMD)	-	421 (314.0)	-	288 (227.9)	-	421 (0.86)	-	288 (0.62)
Open-label, Clinical Usability Study with Pre-filled Syringe (PFS) in Patients with Chorioretinal Vascular Disease (CVD)	32 (29.6)	-	16 (31.3)	-	32 (0.08)	-	16 (0.09)	-
Total	32 (29.6)	421 (314.0)	16 (31.3)	288 (227.9)	32 (0.08)	421 (0.86)	16 (0.09)	288 (0.62)

n = number of subjects exposed to ABP 938 or aflibercept; subj-yrs = total subject-years of follow-up; Q4W = every 4 weeks.

Note: Data is from the completed PFS CVD Study 20210034 (completed on 06APR2023) and the completed Comparative Clinical AMD Study 20170542 (completed on 13MAR2023). For Comparative Clinical AMD Study 20170542, subjects were randomized to receive either ABP 938 or Aflibercept by intravitreal (IVT) injection every 4 weeks for the first 3 doses (ie, baseline/day 1, week 4, week 8); subjects were then re-randomized at week 16 such that subjects initially randomized to ABP 938 would continue to receive ABP 938 by IVT injection every 8 weeks from week 16 until week 48 and subjects initially randomized to Aflibercept would be re-randomized to either transit to ABP 938 or continue to receive Aflibercept by IVT injection every 8 weeks from week 16 until week 48.
For PFS CVD Study 20210034, subjects were randomized to receive a single IVT injection of ABP 938 or aflibercept.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

Source: t07-exp-by-dose.rtf (Generated on: 19JUL2023 13:06)

Table 6. Total Subject Exposure to ABP 938 or Aflibercept in Clinical Trials by Product and Race/Ethnic Group (Safety Analysis Set)

Indication	ABP 938 n (subj-yrs)	Aflibercept n (subj-yrs)
Comparative Clinical Study in Patients with (wet) Age-related Macular Degeneration (AMD)		
Ethnic		
Hispanic or Latino	12 (8.04)	13 (8.30)
Not Hispanic or Latino	408 (352.88)	275 (171.39)
Unknown	1 (1.01)	0 (0)
Total	421 (361.93)	288 (179.69)
Race		
Asian	53 (47.45)	39 (23.92)
Japanese	14 (12.18)	17 (11.71)
Other	39 (35.27)	22 (12.21)
Black or African American	2 (1.70)	1 (0.31)
Multiple	1 (0.37)	0 (0)
White, Native Hawaiian or Other Pacific Islander	1 (0.37)	0 (0)
White	365 (312.41)	248 (155.46)
Total	421 (361.93)	288 (179.69)

n = number of subjects exposed to ABP 938 or aflibercept; subj-yrs = total subject-years of follow-up

Note: Data is from the completed PFS CVD Study 20210034 (completed on 06APR2023) and the completed Comparative Clinical AMD Study 20170542 (completed on 13MAR2023). For Comparative Clinical AMD Study 20170542, subjects were randomized to receive either ABP 938 or Aflibercept by intravitreal (IVT) injection every 4 weeks for the first 3 doses (ie, baseline/day 1, week 4, week 8); subjects were then re-randomized at week 16 such that subjects initially randomized to ABP 938 would continue to receive ABP 938 by IVT injection every 8 weeks from week 16 until week 48 and subjects initially randomized to Aflibercept would be re-randomized to either transit to ABP 938 or continue to receive Aflibercept by IVT injection every 8 weeks from week 16 until week 48.
For PFS CVD Study 20210034, subjects were randomized to receive a single IVT injection of ABP 938 or aflibercept.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

Source: t08-cum-subj-exp-ethnic-race.rtf (Generated on: 12JUL2023 09:25)

Table 6. Total Subject Exposure to ABP 938 or Aflibercept in Clinical Trials by Product and Race/Ethnic Group (Safety Analysis Set)

Indication	ABP 938 n (subj-yrs)	Aflibercept n (subj-yrs)
Open-label, Clinical Usability Study with Pre-filled Syringe (PFS) in Patients with Chorioretinal Vascular Disease (CVD)		
Ethnic		
Hispanic or Latino	9 (0.69)	4 (0.33)
Not Hispanic or Latino	22 (1.82)	12 (1.04)
Unknown	1 (0.08)	0 (0)
Total	32 (2.59)	16 (1.37)
Race		
American Indian or Alaska Native	1 (0.08)	1 (0.09)
Asian	1 (0.10)	0 (0)
Black or African American	2 (0.16)	0 (0)
White	28 (2.26)	14 (1.20)
Other	0 (0)	1 (0.08)
Total	32 (2.59)	16 (1.37)

n = number of subjects exposed to ABP 938 or aflibercept; subj-yrs = total subject-years of follow-up
Note: Data is from the completed PFS CVD Study 20210034 (completed on 06APR2023) and the completed Comparative Clinical AMD Study 20170542 (completed on 13MAR2023). For Comparative Clinical AMD Study 20170542, subjects were randomized to receive either ABP 938 or Aflibercept by intravitreal (IVT) injection every 4 weeks for the first 3 doses (ie, baseline/day 1, week 4, week 8); subjects were then re-randomized at week 16 such that subjects initially randomized to ABP 938 would continue to receive ABP 938 by IVT injection every 8 weeks from week 16 until week 48 and subjects initially randomized to Aflibercept would be re-randomized to either transit to ABP 938 or continue to receive Aflibercept by IVT injection every 8 weeks from week 16 until week 48.
For PFS CVD Study 20210034, subjects were randomized to receive a single IVT injection of ABP 938 or aflibercept.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
Source: t08-cum-subj-exp-ethnic-race.rtf (Generated on: 12JUL2023 09:25)

Table 6. Total Subject Exposure to ABP 938 or Aflibercept in Clinical Trials by Product and Race/Ethnic Group (Safety Analysis Set)

Indication	ABP 938 n (subj-yrs)	Aflibercept n (subj-yrs)
Total		
Ethnic		
Hispanic or Latino	21 (8.73)	17 (8.63)
Not Hispanic or Latino	430 (354.70)	287 (172.42)
Unknown	2 (1.09)	0 (0)
Total	453 (364.52)	304 (181.06)
Race		
American Indian or Alaska Native	1 (0.08)	1 (0.09)
Asian	54 (47.55)	39 (23.92)
Japanese	14 (12.18)	17 (11.71)
Other	39 (35.27)	22 (12.21)
Black or African American	4 (1.86)	1 (0.31)
Multiple	1 (0.37)	0 (0)
White, Native Hawaiian or Other Pacific Islander	1 (0.37)	0 (0)
White	393 (314.67)	262 (156.66)
Other	0 (0)	1 (0.08)
Total	453 (364.52)	304 (181.06)

n = number of subjects exposed to ABP 938 or aflibercept; subj-yrs = total subject-years of follow-up

Note: Data is from the completed PFS CVD Study 20210034 (completed on 06APR2023) and the completed Comparative Clinical AMD Study 20170542 (completed on 13MAR2023). For Comparative Clinical AMD Study 20170542, subjects were randomized to receive either ABP 938 or Aflibercept by intravitreal (IVT) injection every 4 weeks for the first 3 doses (ie, baseline/day 1, week 4, week 8); subjects were then re-randomized at week 16 such that subjects initially randomized to ABP 938 would continue to receive ABP 938 by IVT injection every 8 weeks from week 16 until week 48 and subjects initially randomized to Aflibercept would be re-randomized to either transit to ABP 938 or continue to receive Aflibercept by IVT injection every 8 weeks from week 16 until week 48.

For PFS CVD Study 20210034, subjects were randomized to receive a single IVT injection of ABP 938 or aflibercept.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

Source: t08-cum-subj-exp-ethnic-race.rtf (Generated on: 12JUL2023 09:25)

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

PAVBLU is being developed as a biosimilar for Eylea. Table 7 reflects the important exclusion criteria for PAVBLU.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
General exclusion criteria			
Pregnant or breastfeeding women and sexually active subjects and their partners who are of childbearing potential (ie, neither surgically sterile nor postmenopausal) and not agreeing to use adequate contraception	Studies of aflibercept in animals have shown embryo-fetal toxicity. Adverse embryo-fetal effects in rabbits included external, visceral, and skeletal malformations. A fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryo-fetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single IVT treatment at the recommended clinical dose (Eylea SmPC, June 2024; Eylea USPI, December 2023).	No	In line with the reference medicinal product, Eylea, embryo-fetotoxicity is included an important potential risk (Table 16). Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last IVT injection of aflibercept. Although the systemic exposure after ocular administration is very low, PAVBLU should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus. Based on very limited human data, aflibercept may be excreted in human milk at low levels. Aflibercept is a large protein molecule and the amount of medication absorbed by the infant is expected to be minimal. The effects of aflibercept on a breastfed newborn/infant are unknown. As a precautionary measure, breastfeeding is not recommended during the use of PAVBLU.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
General exclusion criteria (continued)			
Allergy or hypersensitivity to investigational product, to any of the excipients of ABP 938 or aflibercept, or to other study-related procedures/ medications (eg, anesthesia, antiseptic, fluorescein dye)	Hypersensitivity is a contraindication for ABP 938 and the reference medicinal product, Eylea.	No	PAVBLU is contraindicated in patients with hypersensitivity to the active substance aflibercept or to any of the excipients.
Active extraocular infection or history of extraocular infections as follows: (a) any active infection for which systemic anti-infectives were used within 4 weeks before randomization, or (b) recurrent or chronic infections or other active infection that, in the opinion of the investigator, might cause this study to be detrimental to the subject	To ensure that patient safety and evaluation of the safety profile in clinical studies was not affected.	No	The safety of PAVBLU is not expected to be different from the reference medicinal product, Eylea, in this patient population. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
General exclusion criteria (continued)			
Acute coronary event or stroke within 3 months before randomization	To ensure that patient safety and evaluation of the safety profile in clinical studies was not affected. Systemic adverse events including non-ocular hemorrhages and arterial thromboembolic events have been reported following IVT injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition (Eylea SmPC, June 2024).	No	Per the SmPC for the reference medicinal product, Eylea, there are limited data on safety in the treatment of patients with central RVO, branch RVO, DME, or myopic CNV with a history of stroke or transient ischemic attacks or myocardial infarction within the last 6 months and caution should be exercised when treating such patients (Eylea SmPC, June 2024). The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.
Uncontrolled, clinically significant systemic disease such as diabetes mellitus, hypertension, cardiovascular disease including moderate to severe heart failure (New York Heart Association class III/IV), renal disease, or liver disease	To ensure that patient safety and evaluation of the safety profile in clinical studies was not affected.	No	These conditions may occur in the target population. Per the SmPC for the reference medicinal product, Eylea, there is only limited experience in the treatment of subjects with DME due to type I diabetes or in diabetic patients with an HbA1c over 12%, and no experience of treatment in diabetic patients with uncontrolled hypertension (Eylea SmPC, June 2024). The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
General exclusion criteria (continued)			
Malignancy within 5 years EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, OR in situ breast ductal carcinoma	To ensure that evaluation of the safety profile in clinical studies was not affected.	No	The safety of PAVBLU is not expected to be different from the reference medicinal product, Eylea, in this patient population. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.
Exclusion criteria specific to the study eye only			
Total lesion size $>$ 12 disc areas (30.5 mm^2, including blood, scars, and neovascularization)	To ensure that patients have a sizable ocular disease, and that evaluation of the safety and efficacy outcomes in clinical studies can meet study primary and secondary objectives.	No	The safety of PAVBLU is not expected to be different from the reference medicinal product, Eylea, in this patient population. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.
Active CNV area (classic plus occult components) that is $<$ 50% of the total lesion area	To ensure that patients have a sizable ocular disease, and that evaluation of the safety and efficacy outcomes in clinical studies can meet study primary and secondary objectives.	No	The safety of PAVBLU is not expected to be different from the reference medicinal product, Eylea, in this patient population. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Exclusion criteria specific to the study eye only (continued)			
Scar, fibrosis, or atrophy involving the center of the fovea	To ensure that patients have a sizable ocular disease, and that evaluation of the safety and efficacy outcomes in clinical studies can meet study primary and secondary objectives.	No	The safety of PAVBLU is not expected to be different from the reference medicinal product, Eylea, in this patient population. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.
Presence of retinal pigment epithelium tears or rips involving the macula	To ensure patient safety and that evaluation of the safety and efficacy outcomes in clinical studies can meet study primary and secondary objectives.	No	Retinal pigment epithelium tears or rips involving the macula may occur as IVT injection-related adverse events. In line with the reference medicinal product, Eylea, retinal pigment epithelial tears is included an important identified risk (Table 12). The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.
History of any vitreous hemorrhage within 4 weeks before randomization	To ensure patient safety and that evaluation of the safety and efficacy outcomes in clinical studies can meet study primary and secondary objectives.	No	Vitreous hemorrhage may occur as an IVT injection-related adverse event. In line with the reference medicinal product, Eylea (Eylea SmPC, June 2024), vitreous hemorrhage is included as an adverse drug reaction in the SmPC for PAVBLU. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Exclusion criteria specific to the study eye only (continued)			
Presence of other causes of CNV, including pathologic myopia (spherical equivalent of 8 diopters or more negative or axial length of 25 mm or more), ocular histoplasmosis syndrome, angioid streaks, choroidal rupture, or multifocal choroiditis	These confounding factors were excluded to minimize data variability due to other conditions and data interpretation.	No	The reference medicinal product, Eylea, has been studied in Asian patients with myopic CNV, which is a frequent cause of vision loss in adults with pathologic myopia (Eylea SmPC, June 2024). The indications for PAVBLU are listed in Section 4.1 of the SmPC. In line with the reference medicinal product, Eylea (Eylea SmPC, June 2024), Section 4.4 of the PAVBLU SmPC states that in myopic CNV there is no experience with aflibercept in the treatment of non-Asian patients, patients who have previously undergone treatment for myopic CNV, and patients with extrafoveal lesions. The safety of PAVBLU is not expected to be different from the reference medicinal product, Eylea, in this patient population. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Exclusion criteria specific to the study eye only (continued)			
Prior vitrectomy or laser surgery of the macula (including photodynamic therapy or focal laser photocoagulation); any intraocular or periocular surgery within 3 months before randomization, except lid surgery, which may not have taken place within 4 weeks before randomization, as long as it is unlikely to interfere with the injection; prior trabeculectomy or other filtration surgery; or any concurrent intraocular condition other than neovascular (wet) AMD that, in the opinion of the investigator, requires planned medical or surgical intervention during the study or increases the risk to the subject beyond what is expected from standard procedures of intraocular injection, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety	To ensure patient safety and that evaluation of the safety and efficacy outcomes in clinical studies can meet study primary and secondary objectives.	No	In line with the reference medicinal product, Eylea, the dose of PAVBLU should be withheld within the previous or next 28 days in the event of a performed or planned intraocular surgery. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Exclusion criteria specific to the study eye only (continued)			
History of retinal detachment or macular hole of stage 2 and above	To ensure patient safety and that evaluation of the safety and efficacy outcomes in clinical studies can meet study primary and secondary objectives.	No	In line with the reference medicinal product, Eylea, treatment with PAVBLU should be withheld in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.
Any macular pathology that might limit vision (ie, vitreomacular traction or significant epiretinal membrane)	The condition was included as an exclusion criterion in order to minimize confounding factors on best corrected visual acuity (BCVA) assessments.	No	The safety of PAVBLU is not expected to be different from the reference medicinal product, Eylea, in this patient population. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.
Uncontrolled glaucoma (defined as intraocular pressure ≥ 25 mmHg despite treatment with antiglaucoma medication)	To ensure patient safety and that evaluation of the safety and efficacy outcomes in clinical studies can meet study primary and secondary objectives.	No	Increase in intraocular pressure may occur as an IVT injection-related adverse event. In line with the reference medicinal product, Eylea, transient intraocular pressure increase is included an important identified risk (Table 11). Special precaution is needed in patients with poorly controlled glaucoma (PAVBLU should not be injected while the intraocular pressure is ≥ 30 mmHg).

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Exclusion criteria specific to the study eye only (continued)			
Aphakia or pseudophakia with complete absence of posterior capsule (unless it occurred as a result of an yttrium aluminum garnet [YAG] posterior capsulotomy)	To ensure patient safety and that evaluation of the safety and efficacy outcomes in clinical studies can meet study primary and secondary objectives.	No	The safety of PAVBLU is not expected to be different from the reference medicinal product, Eylea, in this patient population. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.
Previous therapeutic radiation in the region of the eye	To ensure patient safety and that evaluation of the safety and efficacy outcomes in clinical studies can meet study primary and secondary objectives.	No	The safety of PAVBLU is not expected to be different from the reference medicinal product, Eylea, in this patient population. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.
History of corneal transplant or corneal dystrophy	To ensure patient safety and that evaluation of the safety and efficacy outcomes in clinical studies can meet study primary and secondary objectives.	No	Corneal erosion, abrasion, oedema, and epithelium defect may occur in patients treated with PAVBLU. In line with the reference medicinal product, Eylea (Eylea SmPC, June 2024), corneal erosion, corneal abrasion, corneal oedema, and corneal epithelium defect are included as adverse drug reactions in the SmPC for PAVBLU. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Exclusion criteria specific to the study eye only (continued)			
Significant media opacities, including cataract, which might interfere with visual acuity or assessment of safety	To ensure patient safety and that evaluation of the safety and efficacy outcomes in clinical studies can meet study primary and secondary objectives.	No	Cataract may occur as an IVT injection-related adverse event. In line with the reference medicinal product, Eylea, cataract (especially of traumatic origin) is included an important identified risk (Table 13).
Exclusion criteria applicable to either eye			
History or clinical evidence of uveitis, diabetic retinopathy, DME, or any other vascular disease affecting the retina, other than neovascular (wet) AMD	To ensure that evaluation of the safety profile in clinical studies was not affected.	No	The reference medicinal product, Eylea, has been studied in patients with DME as a consequence of diabetic retinopathy (Eylea SmPC, June 2024). Uveitis may occur in patients treated with PAVBLU. In line with the reference medicinal product, Eylea (Eylea SmPC, June 2024), uveitis is included as an adverse drug reaction in the SmPC for PAVBLU. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.
Active intraocular inflammation or active or suspected ocular or periocular infection, within 2 weeks before randomization	This is a contraindication for ABP 938 and the reference medicinal product, Eylea.	No	PAVBLU is contraindicated in patients with active or suspected ocular or periocular infection and patients with active severe intraocular inflammation. In line with the reference medicinal product, Eylea, endophthalmitis (likely infectious origin) (Table 9) and intraocular inflammation (Table 10) are included as important identified risks.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Exclusion criteria applicable to either eye (continued)			
Active scleritis or episcleritis or presence of scleromalacia	The condition was included as an exclusion criterion in order to minimize confounding factors on BCVA assessments.	No	Although no data are provided in the Eylea SmPC about active scleritis or episcleritis or presence of scleromalacia, the safety of PAVBLU is not expected to be different from the reference medicinal product, Eylea, in this patient population. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.
Washouts and nonpermitted treatments			
Any prior ocular or systemic treatment, including another investigational product or surgery for neovascular (wet) AMD (including anti-VEGF therapy), except dietary supplements or vitamins	To ensure that patient safety and evaluation of the safety profile in clinical studies was not affected.	No	In line with the reference medicinal product, Eylea, the dose of PAVBLU should be withheld within the previous or next 28 days in the event of a performed or planned intraocular surgery. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Washouts and nonpermitted treatments (continued)			
Prior systemic anti-VEGF treatment as follows: (a) investigational or approved anti-VEGF therapy systemically within 3 months before randomization, or (b) aflibercept, ziv-aflibercept, or a biosimilar of aflibercept/ ziv-aflibercept systemically at any time	To ensure that patient safety and efficacy and evaluation of the safety and efficacy outcomes in clinical studies was not affected.	No	Per the Eylea SmPC, in the VIVID^{DME} and VISTA^{DME} studies, 36 (9%) and 197 (43%) patients received prior anti-VEGF therapy, respectively, with a 3-month or longer washout period. Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor were similar to those seen in patients who were VEGF inhibitor naïve (Eylea SmPC, June 2024). The safety of PAVBLU is not expected to be different from the reference medicinal product, Eylea, in this patient population. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.
Any IVT therapy, including adrenocorticotropic hormone or intramuscular or IV corticosteroids, within 4 weeks before randomization. The use of long-acting steroids, either systemically or intraocularly, in the 3 months before randomization	To ensure that patient safety and evaluation of the safety profile in clinical studies was not affected.	No	Although no data are provided in the Eylea SmPC about prior IVT therapy, the safety of PAVBLU is not expected to be different from the reference medicinal product, Eylea, in this patient population. The use of PAVBLU in this patient group should be based on a benefit-risk assessment by the treating physician in consultation with the patient.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

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

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 8. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	There are no adequate and well-controlled studies in pregnant women with Eylea (Eylea USPI, December 2023). Pregnant women were not included in studies with ABP 938.
Breastfeeding women	Based on very limited human data, aflibercept may be excreted in human milk at low levels (Eylea SmPC, June 2024). Breastfeeding women were not included in studies with ABP 938.
Patients with relevant comorbidities	
Patients with hepatic impairment	Not included in the ABP 938 clinical development program. Exposure data for patients with hepatic impairment in the Eylea clinical development program is unknown (Eylea SmPC, June 2024).
Patients with renal impairment	Not included in the ABP 938 clinical development program. In the Eylea clinical development program, pharmacokinetic analysis of a subgroup of patients (n = 492) in 1 wet AMD study, of which 43% had renal impairment (mild n = 120, moderate n = 74, and severe n = 16), revealed no differences with respect to plasma concentrations of free aflibercept after IVT administration every 4 or 8 weeks. Similar results were seen in patients in an RVO study and in patients in a DME study. No dose adjustment based on renal impairment status is needed for either wet AMD, RVO, or DME patients (Eylea USPI, December 2023).
Patients with cardiovascular impairment	Patients with moderate to severe heart failure were not included in the ABP 938 clinical development program. Exposure data for patients with cardiovascular impairment or disorders in the Eylea clinical development program is limited (Eylea SmPC, June 2024).
Immunocompromised patients	Not included in the ABP 938 clinical development program. Exposure data for immunocompromised patients in the Eylea clinical development program is unknown (Eylea SmPC, June 2024).

Table 8. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Patients with relevant comorbidities (continued)	
Patients with a disease severity different from inclusion criteria in clinical trials	Exposure data for patients with a disease severity different from inclusion criteria in clinical studies in the Eylea or ABP 938 clinical development program is unknown (Eylea SmPC, June 2024).
Population with relevant different ethnic origin	Overall, 393 subjects (314.67 subject-years), 54 subjects (47.55 subject-years), 4 subjects (1.86 subject-years), 1 subject (0.08 subject-years), and 1 subject (0.37 subject-years) of White, Asian, Black or African American, American Indian or Alaska Native, and multiple race were exposed to ABP 938, respectively (see Table 6). In the Eylea development program, patients of various different racial and/or ethnic origins were exposed to Eylea 40 mg/mL (2 mg dose); the majority of exposed patients, however, were White (66.0%) (Eylea EU RMP v34.1, February 2024).
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other	
Patients ≥ 65 years of age	In the clinical studies, approximately 76% of patients randomized to treatment with Eylea were ≥ 65 years of age and approximately 46% were ≥ 75 years of age (Eylea USPI, December 2023), which is comparable to the ABP 938 clinical development program. No dosage modification is required in the elderly (Eylea USPI, December 2023).

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

PAVBLU has not been authorized for marketing in any country.

SV.1.1 Method Used to Calculate Exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Postauthorization Use From Business Partners

Not applicable.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No evidence to suggest a potential for drug abuse or misuse has been observed in the clinical studies to date for PAVBLU. The reference medicinal product, Eylea, is not associated with any abuse potential.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

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

Not applicable. PAVBLU is a biosimilar product; therefore, the safety concerns from the EU RMP of the reference medicinal product, Eylea, are reflected in this RMP as the risks are expected to be similar.

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

Not applicable. PAVBLU is a biosimilar product; therefore, the list of safety concerns considered important is aligned with the list of safety concerns from the EU RMP of the reference medicinal product, Eylea.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable, as this is an initial marketing authorization application.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

The safety concerns for PAVBLU are presented as per the EU RMP of Eylea with the following exceptions:

- the missing information ‘long-term safety of aflibercept in preterm infants with retinopathy of prematurity’ was not included as PAVBLU 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 PAVBLU is not available in this formulation and dose.

No new safety concerns were identified in the PAVBLU clinical program.

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

Table 9. Important Identified Risk: Endophthalmitis (Likely Infectious Origin)

Potential mechanisms	The IVT injection procedure can implant pathogens into the eye if there is a break in sterile technique. Source of pathogenic agents is in most cases the patient's conjunctival bacterial flora.
Evidence source(s) and strength of evidence	This important identified risk is included per the reference medicinal product Eylea. Evidence source: Eylea SmPC, June 2024.
Characterization of the risk	
Frequency	**ABP 938 study:** There were no adverse events of endophthalmitis (likely infectious origin)[a] reported in the randomized, double-masked, comparative clinical study of ABP 938 efficacy and safety compared to aflibercept (Eylea®) in subjects with neovascular AMD (Study 20170542). **Eylea studies:** A total of 3102 patients constituted the safety population in the eight phase 3 studies of Eylea, of which 2501 patients were treated with the recommended dose of 2 mg. Serious ocular adverse reactions in the study eye related to the injection procedure, which included endophthalmitis, occurred in less than 1 in 1900 IVT injections. Endophthalmitis (culture positive and negative) was reported as an uncommon adverse reaction in phase 3 studies or during postmarketing surveillance (Eylea SmPC, June 2024).
Severity	No adverse events of endophthalmitis (likely infectious origin)[a] were reported in Study 20170542; however, if occurred, severity data for ABP 938 are expected to be comparable to Eylea.
Reversibility	Endophthalmitis may resolve with appropriate treatment. If left untreated, endophthalmitis may lead to loss of vision.
Long-term outcomes	Long-term outcome data are not available for PAVBLU, but are expected to be comparable to Eylea.
Impact on quality of life	Endophthalmitis can cause permanent loss of vision if it is not diagnosed at an early stage and appropriately treated. Vision loss as such constitutes a substantial burden for the involved subject.
Risk factors and risk groups	Improper aseptic technique increases the risk of intraocular inflammation.

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of the table.

Table 9. Important Identified Risk: Endophthalmitis (Likely Infectious Origin)

Preventability	The risk of intraocular inflammation, especially if caused by pathogens, cannot be completely excluded, but may be minimized. In the scope of IVT injections of drugs for treatment of wet AMD, central RVO, branch RVO, myopic CNV, or DME (by which pathogens might be inadvertently carried into the inner eye), it is absolutely crucial to work under strict aseptic and sterile conditions. Thus, only experienced and appropriately trained ophthalmologists should be charged with the injections. Moreover, patients should report to their doctors any signs or symptoms of intraocular inflammation (eg, visual acuity decreased, pain, photophobia, or redness) in order to enable the treating physician to introduce appropriate countermeasures in due time. Additional risk minimization measures are provided to mitigate this risk, which include a prescriber guide and video (see Part V.2 for details).
Impact on the risk-benefit balance of the product	The risk of endophthalmitis (likely infectious origin) has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. This risk can be minimized through product labeling, single-use product packaging, and use of the prescriber guide and video. The patient guide (and audio version) provides additional awareness for patients on this risk. Furthermore, a specific questionnaire is used to gain more knowledge about this risk.
Public health impact	Severe intraocular infection/inflammation such as endophthalmitis can cause permanent loss of vision, if it is not rapidly diagnosed and appropriately treated. This condition is likely to impact the ability to work and to increase the dependency on caregivers. The public health impact is not expected to be greater than the reference medicinal product Eylea.

Page 2 of 2

AMD = age-related macular degeneration; CNV = choroidal neovascularization; DME = diabetic macular oedema; IVT = intravitreal; RVO = retinal vein occlusion; SmPC = Summary of Product Characteristics

[a] For identification of events suggestive of endophthalmitis (likely infectious origin), the following search strategy was utilized: Preferred Terms (PTs) endophthalmitis, Candida endophthalmitis, mycotic endophthalmitis, eye infection, eye infection bacterial, eye infection fungal, eye infection chlamydial, eye infection staphylococcal, eye infection intraocular.

Table 10. Important Identified Risk: Intraocular Inflammation

Potential mechanisms	In a certain percentage the intraocular inflammation is culture-negative. However, there are some difficulties in the definition and diagnosis of "sterile" endophthalmitis or intraocular inflammation. Many infectious cases are not diagnosed as such as no tap is performed, or tap is performed, but culture is false negative. Vice versa, true sterile cases may be false positive in culture (eg, due to contamination of the medium) and thus misdiagnosed as infectious. The etiology of sterile intraocular inflammations, independently of the administered drug, remains uncertain, and a multifactorial origin has been proposed. Needle trauma per se might cause a certain inflammatory reaction. Inflammation secondary both to IVT triamcinolone acetonide and to IVT bevacizumab (or other anti-VEGF agents) that manifest with acute and painless vision loss is usually interpreted as being primarily toxic and sterile. In these patients, visual acuity improves progressively as the intraocular inflammation reduces without any specific treatment. However, since there remains a substantial uncertainty on origin, the complication is often treated - on top of steroids and nonsteroidal anti-inflammatory drugs - like an acute (infectious) endophthalmitis with antibiotics because of the devastating visual prognosis of this intraocular infection in the absence of antibiotic therapy (Eylea EU RMP v34.1, February 2024).
Evidence source(s) and strength of evidence	This important identified risk is included per the reference medicinal product Eylea. Evidence sources: ABP 938 clinical study of neovascular (wet) AMD and Eylea SmPC, June 2024.
Characterization of the risk	
Frequency	**ABP 938 study:** In Study 20170542, the subject incidence of adverse events of intraocular inflammation[a] was 3 of 421 subjects (0.7%; 95% CI: 0.1, 2.1) while receiving ABP 938 treatment and 2 of 288 subjects (0.7%; 95% CI: 0.1, 2.5) while receiving aflibercept treatment. **Eylea studies:** In phase 3 studies or during postmarketing surveillance, vitreous floaters were reported as a common adverse reaction; endophthalmitis (which included both culture positive and negative endophthalmitis), iritis, uveitis, iridocyclitis, and anterior chamber flare were reported as uncommon adverse reactions; and vitritis and hypopyon were reported as rare adverse reactions (Eylea SmPC, June 2024).
Severity	In Study 20170542, the adverse events of intraocular inflammation[a] were reported as moderate in all 3 subjects receiving ABP 938 treatment and mild in both subjects receiving aflibercept treatment. All events were resolved without sequelae.
Reversibility	Intraocular inflammation may resolve with appropriate treatment. If left untreated, intraocular inflammation may lead to loss of vision.
Long-term outcomes	Long-term outcome data are not available for PAVBLU, but are expected to be comparable to Eylea.

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of the table.

Table 10. Important Identified Risk: Intraocular Inflammation

Characterization of the risk (continued)	
Impact on quality of life	Severe intraocular infection/inflammation can cause permanent loss of vision, if it is not diagnosed at an early stage and appropriately treated. Vision loss as such constitutes a substantial burden for the involved subject.
Risk factors and risk groups	Improper aseptic technique increases the risk of intraocular inflammation.
Preventability	Measures other than aseptic injection techniques to prevent infectious reactions are not known to minimize the risk of intraocular inflammation. It is crucial to work under strict aseptic and sterile conditions. Thus, only experienced and appropriately trained ophthalmologists should be charged with the injection procedure. Moreover, patients should report to their doctors any signs or symptoms of intraocular inflammation (eg, visual acuity decreased, pain, photophobia, or redness) as soon as possible in order to enable the treating physician to introduce appropriate countermeasures in due time. Additional risk minimization measures are provided to mitigate this risk, which include a prescriber guide and video (see Part V.2 for details).
Impact on the risk-benefit balance of the product	The risk of intraocular inflammation has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. This risk can be minimized through product labeling, single-use product packaging, and use of the prescriber guide and video. The patient guide (and audio version) provides additional awareness for patients on this risk. Furthermore, a specific questionnaire is used to gain more knowledge about this risk.
Public health impact	Severe intraocular infection/inflammation can cause permanent loss of vision, if it is not rapidly diagnosed and appropriately treated. This condition is likely to impact the ability to work and to increase the dependency on caregivers. The public health impact is not expected to be greater than the reference medicinal product Eylea.

AMD = age-related macular degeneration; EU RMP = European Union Risk Management Plan; IVT = intravitreal; SmPC = Summary of Product Characteristics; VEGF = vascular endothelial growth factor

[a] For identification of events suggestive of intraocular inflammation, the following search strategy was utilized: Preferred Terms (PTs) anterior chamber cell, anterior chamber flare, anterior chamber inflammation, aqueous fibrin, autoimmune uveitis, chorioretinitis, choroiditis, cyclitis, eye inflammation, hypopyon, intermediate uveitis, iridocyclitis, iritis, non-infectious endophthalmitis, ocular vasculitis, pseudoendophthalmitis, retinal vasculitis, retinitis, uveitis, vitreal cells, vitritis.

Table 11. Important Identified Risk: Transient Intraocular Pressure Increase

Potential mechanisms	Transient intraocular pressure increase is attributed to an increase in vitreous volume (volume effect).
Evidence source(s) and strength of evidence	This important identified risk is included per the reference medicinal product Eylea. Evidence sources: ABP 938 clinical study of neovascular (wet) AMD and Eylea SmPC, June 2024.
Characterization of the risk	
Frequency	**ABP 938 study:** In Study 20170542, the subject incidence of adverse events of transient intraocular pressure increase[a] was 11 of 421 subjects (2.6%; 95% CI: 1.3, 4.6) while receiving ABP 938 treatment and 2 of 288 subjects (0.7%; 95% CI: 0.1, 2.5) while receiving aflibercept treatment. **Eylea studies:** Increases in intraocular pressure were seen within 60 minutes of IVT injection of Eylea. Intraocular pressure increase was reported as a common adverse reaction in phase 3 studies or during postmarketing surveillance. In clinical studies, intraocular pressure increase occurred in 8% of patients treated with Eylea (Eylea SmPC, June 2024).
Severity	In Study 20170542, all adverse events of transient intraocular pressure increase[a] were reported as mild or moderate in subjects receiving ABP 938 treatment and aflibercept treatment. Most events were resolved without sequelae; the outcome was reported as not resolved in 3 subjects in the ABP 938 treatment group.
Reversibility	Transient intraocular pressure increase may resolve with appropriate treatment. If left untreated, transient intraocular pressure increase may lead to deterioration of visual acuity.
Long-term outcomes	Long-term outcome data are not available for PAVBLU, but are expected to be comparable to Eylea.
Impact on quality of life	Transient intraocular pressure increase is usually a mild reaction which is compensated within 0.5 to 1 hours after injection so that intraocular pressure normalizes back to baseline values. Most patients recovered without sequelae.
Risk factors and risk groups	Patients with glaucoma. Increased intraocular pressure is a known adverse drug reaction of treatment with IVT corticosteroids.
Preventability	Intraocular pressure should be checked after each injection. As the transient increase of eye pressure is an inherent result of the procedure-related volume load in the scope of IVT injections, there is no reasonable chance to avoid this effect. However, this effect is usually transient, and there is no robust evidence so far that pressure increases following IVT injections (even after multiple injections) could become durable or may lead to clinically-relevant glaucoma. Additional risk minimization measures are provided to mitigate this risk, which include a prescriber guide and video (see Part V.2 for details).

Footnotes, including abbreviations, are defined on the last page of the table.

Table 11. Important Identified Risk: Transient Intraocular Pressure Increase

Impact on the risk-benefit balance of the product	The risk of transient intraocular pressure increase has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. This risk can be minimized through product labeling, single-use product packaging, and use of the prescriber guide and video. The patient guide (and audio version) provides additional awareness for patients on this risk. Furthermore, a specific questionnaire is used to gain more knowledge about this risk.
Public health impact	Due to the transient and usually mild nature of the condition, no impact of this safety concern on public health issues is expected. The public health impact is not expected to be greater than the reference medicinal product Eylea.

Page 2 of 2

AMD = age-related macular degeneration; IVT = intravitreal; SmPC = Summary of Product Characteristics

[a] For identification of events suggestive of transient intraocular pressure increase, the following search strategy was utilized: Preferred Terms (PTs) intraocular pressure increased, ocular hypertension, angle closure glaucoma, borderline glaucoma, glaucoma, glaucoma traumatic, normal tension glaucoma, open angle glaucoma, phacolytic glaucoma, pseudophakic glaucoma, uveitic glaucoma, glaucomatous optic disc atrophy.

Table 12. Important Identified Risk: Retinal Pigment Epithelial Tears

Potential mechanisms	Development of retinal pigment epithelial tears after anti-VEGF IVT injection has been attributed to a decline in intercellular adherence, thereby increasing susceptibility to tearing of the retinal pigment epithelial layer.
Evidence source(s) and strength of evidence	This important identified risk is included per the reference medicinal product Eylea. Evidence sources: ABP 938 clinical study of neovascular (wet) AMD and Eylea SmPC, June 2024.
Characterization of the risk	
Frequency	**ABP 938 study:** In Study 20170542, the subject incidence of adverse events of retinal pigment epithelial tears[a] was 4 of 421 subjects (1.0%; 95% CI: 0.3, 2.4) while receiving ABP 938 treatment and 5 of 288 subjects (1.7%; 95% CI: 0.6, 4.0) while receiving aflibercept treatment. **Eylea studies:** Retinal pigment epithelial tear was reported as a common adverse reaction in phase 3 studies or during postmarketing surveillance; this event was observed in the wet AMD studies only (Eylea SmPC, June 2024).
Severity	In Study 20170542, all adverse events of retinal pigment epithelial tears[a] were reported as mild or moderate in subjects receiving ABP 938 treatment and aflibercept treatment. The outcome was reported as not resolved for all events.
Reversibility	Retinal pigment epithelial tears may resolve with appropriate treatment. If left untreated, retinal pigment epithelial tears may lead to loss of vision.
Long-term outcomes	Long-term outcome data are not available for PAVBLU, but are expected to be comparable to Eylea.
Impact on quality of life	Retinal pigment epithelial tears may lead to a loss of vision (and thus to legal blindness).
Risk factors and risk groups	Wet AMD with pigment epithelial detachment; treatment of neovascularization.
Preventability	The underlying mechanisms resulting in retinal pigment epithelial tears following IVT injection are not yet understood and thus, no preventive measures are currently known.

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of the table.

Table 12. Important Identified Risk: Retinal Pigment Epithelial Tears

Impact on the risk-benefit balance of the product	The risk of retinal pigment epithelial tears has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. The product labeling, prescriber guide and video, and patient guide (and audio version) provide additional awareness for physicians and patients on this risk.
Public health impact	The potential public health impact of this safety concern is considered to be low, due to the low frequency of serious or severe events in clinical trials. The public health impact is not expected to be greater than the reference medicinal product Eylea.

AMD = age-related macular degeneration; IVT = intravitreal; SmPC = Summary of Product Characteristics; VEGF = vascular endothelial growth factor

[a] For identification of events suggestive of retinal pigment epithelial tears, the following search strategy was utilized: Preferred Term (PT) retinal pigment epithelial tear.

Table 13. Important Identified Risk: Cataract (Especially of Traumatic Origin)

Potential mechanisms	Related to IVT procedure.
Evidence source(s) and strength of evidence	This important identified risk is included per the reference medicinal product Eylea. Evidence sources: ABP 938 clinical study of neovascular (wet) AMD and Eylea SmPC, June 2024.
Characterization of the risk	
Frequency	**ABP 938 study:** In Study 20170542, the subject incidence of adverse events of cataract (especially of traumatic origin)[a] was 13 of 421 subjects (3.1%; 95% CI: 1.7, 5.2) while receiving ABP 938 treatment and 7 of 288 subjects (2.4%; 95% CI: 1.0, 4.9) while receiving aflibercept treatment. **Eylea studies:** Serious ocular adverse reactions in the study eye related to the injection procedure, which included cataract traumatic and cataract, occurred in less than 1 in 1900 IVT injections. In clinical studies, cataract occurred in 8% of patients treated with Eylea. In phase 3 studies or during postmarketing surveillance, cataract, cataract cortical, cataract nuclear, and cataract subcapsular were reported as common adverse reactions; lenticular opacities was reported as an uncommon adverse reaction; and cataract traumatic was reported as a rare adverse reaction (Eylea SmPC, June 2024).
Severity	In Study 20170542, most adverse events of cataract (especially of traumatic origin)[a] were reported as mild or moderate, with 1 severe event reported in each treatment group. The outcome was reported as not resolved for most events although some events in each treatment group were resolved without sequelae.
Reversibility	Traumatic cataract may resolve with appropriate treatment. If left untreated, traumatic cataract may lead to loss of vision.
Long-term outcomes	Long-term outcome data are not available for PAVBLU, but are expected to be comparable to Eylea.
Impact on quality of life	Development of cataract may impair vision and thus may require cataract surgery in order to remove the lens opacification.
Risk factors and risk groups	Cataract is a known adverse drug reaction of treatment with IVT corticosteroids.
Preventability	By correct IVT procedure and a correct angle of the needle while injecting, a cataract could be prevented. This is common knowledge of injecting physicians. Additional risk minimization measures are provided to mitigate this risk, which include a prescriber guide and video (see Part V.2 for details).

Footnotes, including abbreviations, are defined on the last page of the table.

Table 13. Important Identified Risk: Cataract (Especially of Traumatic Origin)

Impact on the risk-benefit balance of the product	The risk of cataract (especially of traumatic origin) has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. This risk can be minimized through product labeling and use of the prescriber guide and video. The patient guide (and audio version) provides additional awareness for patients on this risk.
Public health impact	Patients experiencing (traumatic) cataract may require cataract surgery. The public health impact is not expected to be greater than the reference medicinal product Eylea.

Page 2 of 2

AMD = age-related macular degeneration; IVT = intravitreal; SmPC = Summary of Product Characteristics

[a] For identification of events suggestive of cataract (especially of traumatic origin), the following search strategy was utilized: Preferred Terms (PTs) atopic cataract, cataract, cataract cortical, cataract diabetic, cataract nuclear, cataract operation, cataract subcapsular, cataract traumatic, intraocular lens implant, lens capsulotomy, lens discolouration, lens extraction, lenticular opacities, lenticular operation, posterior lens capsulotomy, radiation cataract, toxic cataract.

Table 14. Important Potential Risk: Medication Errors

Potential mechanisms	Not applicable.
Evidence source(s) and strength of evidence	This important potential risk is included per the reference medicinal product Eylea. Evidence source: Eylea SmPC, June 2024.
Characterization of the risk	
Frequency	**ABP 938 study:** There were no adverse events of medication errors[a] reported in Study 20170542. **Eylea studies:** In clinical studies, doses of up to 4 mg in monthly intervals have been used and isolated cases of overdoses with 8 mg occurred. No data on adverse events related to medication errors following Eylea IVT injection are available (Eylea SmPC, June 2024).
Severity	No data are available; however, severity data for ABP 938 are expected to be comparable to Eylea.
Reversibility	Effects associated with overdose, such as increased intraocular pressure with increased injection volume, may resolve with appropriate treatment. If left untreated, increased intraocular pressure may lead to deterioration of visual acuity.
Long-term outcomes	Long-term outcome data are not available for PAVBLU, but are expected to be comparable to Eylea.
Impact on quality of life	There is no life-threatening potential when PAVBLU is administered by an incorrect route.
Risk factors and risk groups	Not applicable.
Preventability	Instructions on the correct drug preparation and administration will be given in the SmPC and the educational program in order to minimize the risk of accidental medication errors. The use of pre-filled syringes limits any potential overdose to the volume in the syringe, so there can be no 10-fold overdose with the pre-filled syringe. Additional risk minimization measures are provided to mitigate this risk, which include a prescriber guide and video (see Part V.2 for details).

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of the table.

Table 14. Important Potential Risk: Medication Errors

Impact on the risk-benefit balance of the product	The risk of medication errors has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. This risk can be minimized through product labeling, single-use product packaging, and use of the prescriber guide and video.
Public health impact	There is no life-threatening potential when Eylea is administered by an incorrect route. The public health impact is not expected to be greater than the reference medicinal product Eylea.

IVT = intravitreal; SmPC = Summary of Product Characteristics

[a] For identification of events suggestive of medication errors, the following search strategy was utilized: Medication errors Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ; narrow scope).

Table 15. Important Potential Risk: Off-label Use and Misuse

Potential mechanisms	Not applicable.
Evidence source(s) and strength of evidence	This important potential risk is included per the reference medicinal product Eylea. Evidence source: Eylea SmPC, June 2024.
Characterization of the risk	
Frequency	**ABP 938 study:** Not applicable. **Eylea studies:** There are no data on adverse events related to off-label use and misuse of Eylea (Eylea SmPC, June 2024).
Severity	No data available.
Reversibility	No data available.
Long-term outcomes	No data available.
Impact on quality of life	Not applicable.
Risk factors and risk groups	Not applicable.
Preventability	Off-label ophthalmic use has been reported with currently marketed VEGF inhibitors, eg, for bevacizumab for the treatment of wet AMD or DME. Off-label use of ranibizumab has been reported for ophthalmic diseases other than wet AMD such as DME or RVO before market authorization was granted in the respective indications. There are also reports on off-label use of bevacizumab and ranibizumab in rarer diseases such as myopic CNV (in countries where myopic CNV is not labelled), or retinopathy of prematurity (Eylea EU RMP v34.1, February 2024). In general, as for the majority of possible indications for anti-VEGF therapy approved medications are available, the potential for off-label use is considered minimal. Most neovascular and VEGF-dependent retina diseases including particularly AMD are diseases of the adult. Therefore, the potential for off-label use in the pediatric population is expected to be very limited due to the nature of pediatric ophthalmic diseases. However, there might be exceptions to be considered. In some rare cases, diabetic retinopathy may occur in adolescents. Some ophthalmologists tend to use off-label anti-VEGF drugs in this disease instead of the approved therapy. Myopic CNV, central RVO, and branch RVO may also very rarely occur in adolescents and may be treated off-label with any IVT anti-VEGF drug, including PAVBLU. PAVBLU may be also used to treat some cases of retinopathy of prematurity (Eylea EU RMP v34.1, February 2024). The number of such cases is considered very low, and their care is provided by pediatric ophthalmologists who are tertiary care based and experienced in the care of these infants.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 15. Important Potential Risk: Off-label Use and Misuse

Preventability (continued)	Intentional misuse, as such, is difficult to prevent because of the user's deliberate decision to deviate from the provided instructions. However, there is no known dependence potential of PAVBLU. Additional risk minimization measures are provided to mitigate this risk, which include a prescriber guide (see Part V.2 for details).
Impact on the risk-benefit balance of the product	The risk of off-label use and misuse has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. This risk can be minimized through product labeling and use of the prescriber guide.
Public health impact	Not applicable. The public health impact is not expected to be greater than the reference medicinal product Eylea.

Page 2 of 2

AMD = age-related macular degeneration; CNV = choroidal neovascularization; DME = diabetic macular oedema; EU RMP = European Union Risk Management Plan; IVT = intravitreal; RVO = retinal vein occlusion; SmPC = Summary of Product Characteristics; VEGF = vascular endothelial growth factor

Table 16. Important Potential Risk: Embryo-fetotoxicity

Potential mechanisms	No studies evaluating the reproductive toxicity of ABP 938 have been conducted. An effect of aflibercept on intrauterine development was shown in embryo-fetal development studies in pregnant rabbits with IV (3 to 60 mg/kg) as well as SC (0.1 to 1 mg/kg) administration. The maternal NOAEL was at the dose of 3 mg/kg or 1 mg/kg, respectively. A developmental NOAEL was not identified. At the 0.1 mg/kg dose, the systemic exposures based on C_{max} and cumulative AUC for free aflibercept were approximately 17- and 10-fold higher, respectively, when compared to corresponding values observed in humans after an IVT dose of 2 mg (Eylea SmPC, June 2024). Adverse embryo-fetal effects in rabbits included external, visceral, and skeletal malformations. A fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryo-fetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single IVT treatment at the recommended clinical dose (Eylea SmPC, June 2024; Eylea USPI, December 2023).
Evidence source(s) and strength of evidence	This important potential risk is included per the reference medicinal product Eylea. Evidence sources: Eylea SmPC, June 2024, and Eylea USPI, December 2023.
Characterization of the risk	
Frequency	**ABP 938 study:** No pregnancies were reported in Study 20170542. **Eylea studies:** There are no data on the use of aflibercept in pregnant women (Eylea SmPC, June 2024).
Severity	No data available.
Reversibility	No data available.
Long-term outcomes	No data available.
Impact on quality of life	Based on currently available nonclinical data, no individual impact in terms of risk to the treated population is apparent.
Risk factors and risk groups	Patients at risk are women of childbearing potential.
Preventability	Treatment with PAVBLU is not recommended during pregnancy, unless the potential benefit outweighs the potential risk to the fetus. Additional risk minimization measures are provided to mitigate this risk, which include a prescriber guide (see Part V.2 for details).

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of the table.

Table 16. Important Potential Risk: Embryo-fetotoxicity

Impact on the risk-benefit balance of the product	The risk of embryo-fetotoxicity has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. This risk can be minimized through product labeling and use of the prescriber guide. The patient guide (and audio version) provides additional awareness for patients on this risk.
Public health impact	Based on currently available nonclinical data, no public health impact in terms of risk to the treated population is apparent. The public health impact is not expected to be greater than the reference medicinal product Eylea.

Page 2 of 2

AUC = area under the curve; C_{max} = maximum concentration; IV = intravenous; IVT = intravitreal; NOAEL = no-observed-adverse-effect-level; SC = subcutaneous; SmPC = Summary of Product Characteristics; USPI = United States Prescribing Information

SVII.3.2 Presentation of the Missing Information

Not applicable.

Part II: Module SVIII - Summary of the Safety Concerns

Table 17. 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

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 18 and Table 19.

Table 18. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Report of suspected aflibercept-associated adverse event: endophthalmitis and intraocular inflammation (IOI)	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.
Report of suspected aflibercept-associated adverse event: increase in intraocular pressure (IOP) with pre-filled syringes (PFS)	Transient intraocular pressure increase	Specific questionnaire to obtain comprehensive and standardized follow-up information related to intraocular pressure increase following the use of the PAVBLU pre-filled syringe.

Table 19. Other Forms of Routine Pharmacovigilance Activities

Description of Activity	Safety Concern(s)	Objectives	Milestones
For traceability purposes, brand name, batch number, and lot 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 postmarketing environment.	Not applicable

III.2 Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance activities.

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned PAVBLU category 1 to 3 studies.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

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

Risk Minimization Plan

The safety information in the proposed PAVBLU SmPC is aligned to the reference medicinal product, Eylea.

V.1 Routine Risk Minimization Measures

Table 20. (Table Part V.1) 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 minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2: A comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • SmPC Section 4.2 and PL Section 2: Suggestive symptoms of endophthalmitis are mentioned. • "*Ocular or periocular infection*" and "*active severe intraocular inflammation*" are listed in SmPC Section 4.3 and PL Section 2. • SmPC Section 4.4: Instructions for aseptic injection techniques, monitoring, and instructions for patients are mentioned. • PL section 2: Description of symptoms potentially indicative of endophthalmitis are given. Other risk minimization measures beyond the PI: • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections.

Table 20. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks (continued)	
Intraocular inflammation	Routine risk communication: • SmPC Sections 4.2, 4.3, 4.4, and 4.8 • PL Sections 2, 3, and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • In SmPC Section 4.2, a comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • "*Ocular or periocular infection*" and "*active severe intraocular inflammation*" are listed in SmPC Section 4.3 and PL Section 2. • SmPC Section 4.4: Instructions for aseptic injection techniques, monitoring, and instructions for patients are given. • SmPC Section 4.4: Potential for immunogenicity with PAVBLU is mentioned (see Section 4.8). Monitoring of symptoms is advised. • PL Section 2: Description, monitoring, and early treatment of symptoms are mentioned. • PL Section 3: Description on pre-injection use of disinfectant for cleaning measures provided. Other risk minimization measures beyond the PI: • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections.

Table 20. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks (continued)	
Transient intraocular pressure increase	Routine risk communication: • SmPC Sections 4.2, 4.4, 4.8, and 4.9 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • In SmPC Section 4.2, a comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • SmPC Section 4.2: Appropriate monitoring for elevation in intraocular pressure is mentioned. Special precaution in patients with poorly controlled glaucoma is mentioned. • SmPC Section 4.4: Excess volume from the 2 mg PAVBLU pre-filled syringe/vial must be expelled/discarded prior to administration. • PL Section 2: Injections with PAVBLU may cause an increase in eye pressure. • SmPC Section 4.9: Effect of overdosing, monitoring, and treatment of intraocular pressure by the physician are mentioned. Other risk minimization measures beyond the PI: • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections.

Table 20. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks (continued)	
Retinal pigment epithelial tears	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4: A description of risk factors is given for retinal pigment epithelial tear in wet AMD patients and advice to be cautious when initiating PAVBLU therapy in patients with this risk factor. • PL Section 2: Check of risk factors for retinal tear/detachment, retinal pigment epithelial tear/detachment by the physician is mentioned. Other risk minimization measures beyond the PI: • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections.
Cataract (especially of traumatic origin)	Routine risk communication: • SmPC Sections 4.2, 4.4, and 4.8 • PL Sections 2, 3, and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • In SmPC Section 4.2, a comprehensive description of the injection procedure (including short-term follow-up) is provided in order to ensure high-quality standard of the intervention. • SmPC Section 4.4: Instructions for aseptic injection techniques, monitoring, and instructions for patients are mentioned. • PL Section 2: Description, monitoring, and early treatment of symptoms are mentioned. • PL Section 3: Description on pre-injection use of disinfectant for cleaning measures provided. Other risk minimization measures beyond the PI: • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections.

Table 20. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks	
Medication errors	Routine risk communication: • SmPC Sections 4.2, 4.9, and 6.6 • PL Sections 1 and 3 Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 and PL Section 'information intended for healthcare professionals only': Instructions are provided for the handling of the pre-filled syringe/vial in order to minimize the risk of drug administration error. • SmPC Section 4.9: Association between overdose and intraocular pressure increase is mentioned. • SmPC Section 6.6 and PL Section 'information intended for healthcare professionals only': Instruction for the use of the pre-filled syringe is provided. Other risk minimization measures beyond the PI: • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections.
Off-label use and misuse	Routine risk communication: • SmPC Sections 4.1, 4.3, 4.4, and 4.6 • PL Sections 1, 2, and 3 Routine risk minimization activities recommending specific clinical measures to address the risk: • Contraindications are listed in SmPC Section 4.3 and PL Section 2. • Conditions in which treatment should be withheld/discontinued/not recommended are included in SmPC Section 4.4 and PL Section 2. • Conditions of use in pregnancy and breastfeeding are included in SmPC Section 4.6 and PL Section 2. Other risk minimization measures beyond the PI: • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections.

Table 20. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks (continued)	
Embryo-fetotoxicity	Routine risk communication: • SmPC Sections 4.4, 4.6, and 5.3 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 and PL Section 2: Instructions for pregnancy and women of childbearing potential are mentioned. • SmPC Section 4.6: Instructions for pregnancy and women of childbearing potential are mentioned. • PL Section 2: Instructions for pregnancy and women of childbearing potential are mentioned. Other risk minimization measures beyond the PI: • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections.

Page 6 of 6

V.2 Additional Risk Minimization Measures

Table 21. Additional Risk Minimization Measure: Prescriber Guide and Video

Objectives	To inform physicians about risks in order to minimize their occurrence and consequences in routine care. To instruct physicians on the correct preparation and administration of PAVBLU in order to minimize injection-related adverse reactions. Include guidance on the IVT injection procedure using the PAVBLU pre-filled syringe in order to minimize injection-related adverse reactions. To remind physicians to monitor patients for visual acuity and increased intraocular pressure after injection. The following risks are addressed in the prescriber guide and video: endophthalmitis (likely infectious origin), intraocular inflammation, transient intraocular pressure increase, retinal pigment epithelial tears, cataract (especially of traumatic origin) and medication errors. The prescriber guide also addresses the following risks: off-label use and misuse, and embryo-fetotoxicity.
Rationale for the additional risk minimization activity	These additional risk minimization activities are proposed to align with the reference medicinal product, Eylea, to inform healthcare professionals regarding the main risks associated with PAVBLU treatment. The risks of endophthalmitis (likely infectious origin) and intraocular inflammation can be minimized by ensuring proper aseptic technique when preparing the injection and during the injection itself, using recommended antiseptic agents, and monitoring the patient after the injection. Measures to minimize the risks of transient intraocular pressure increase and medication errors include properly priming the syringe by removing excess volume and air bubbles before administration and monitoring the patient's vision and intraocular pressure after the injection. The risk of retinal pigment epithelial tears can be minimized by monitoring the patient after the injection. The physician should measure for the correct site of injection and use the correct injection technique to minimize the risk of cataract (especially of traumatic origin). To minimize the risk of off-label use and misuse, physicians should be reminded to use PAVBLU only for treatment of the approved indications at the approved dose. PAVBLU should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus, and effective contraception should be used during treatment and for at least 3 months after the last IVT injection to minimize the risk of embryo-fetotoxicity.

Table 21. Additional Risk Minimization Measure: Prescriber Guide and Video

Target audience and planned distribution path	Healthcare professionals specialized in IVT injections of anti-VEGF agents.
Plans to evaluate the effectiveness of the interventions and criteria for success	The effectiveness of the prescriber guide and video will be assessed using routine pharmacovigilance including signal detection on a regular basis and reporting in scheduled Periodic Benefit-Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR) or earlier, if required.
Evaluation of the effectiveness of risk minimization activities	Not yet assessed.

Table 22. Additional Risk Minimization Measure: Patient Guide "Your Guide to PAVBLU" and its Audio Version

Objectives	To inform patients about risks in order to minimize their occurrence and consequences in routine care. To increase patients' awareness of the key signs and symptoms of serious adverse events and when to seek urgent attention. To provide a reminder that female patients of childbearing potential should use effective contraception if using PAVBLU. The patient guide "Your guide to PAVBLU" and its audio version contain information for patients on the following key risks of PAVBLU: • Endophthalmitis (likely infectious origin) • Intraocular inflammation • Transient intraocular pressure increase • Retinal pigment epithelial tears • Cataract (especially of traumatic origin) • Medication errors • Off-label use and misuse • Embryo-fetotoxicity
Rationale for the additional risk minimization activity	This additional risk minimization activity is proposed to align with the reference medicinal product, Eylea, to ensure patients have a good understanding of the risks associated with PAVBLU treatment and seek immediate medical attention if they experience any of the key signs and symptoms. The audio guide supports patients who may have limited eyesight due to the conditions being treated.
Target audience and planned distribution path	Patients who are treated with PAVBLU will receive the patient guide from the treating healthcare professional.
Plans to evaluate the effectiveness of the interventions and criteria for success	The effectiveness of the patient guide will be assessed using routine pharmacovigilance including signal detection on a regular basis and reporting in scheduled PBRER/PSUR or earlier, if required.
Evaluation of the effectiveness of risk minimization activities	Not yet assessed.

V.3 Summary of Risk Minimization Measures

Table 23. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization 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 • PL Sections 2, 3, and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific questionnaire to be used for any postmarketing reports suspicious for endophthalmitis and intraocular inflammation • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Intraocular inflammation	Routine risk minimization measures: • SmPC Sections 4.2, 4.3, 4.4, and 4.8 • PL Sections 2, 3, and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific questionnaire to be used for any postmarketing reports suspicious for endophthalmitis and intraocular inflammation • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

Table 23. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Transient intraocular pressure increase	Routine risk minimization measures: • SmPC Sections 4.2, 4.4, 4.8, and 4.9 • PL Sections 2 and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific questionnaire to be used for any postmarketing report regarding intraocular pressure increase following the use of the PAVBLU pre-filled syringe • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Retinal pigment epithelial tears	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

Table 23. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Cataract (especially of traumatic origin)	Routine risk minimization measures: • SmPC Sections 4.2, 4.4, and 4.8 • PL Sections 2, 3, and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Medication errors	Routine risk minimization measures: • SmPC Section 4.2, 4.9, and 6.6 • PL Sections 1 and 3 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise physicians' awareness on medication error (prescriber guide and video; patient guide "Your guide to PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

Table 23. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks (continued)		
Off-label use and misuse	Routine risk minimization measures: • SmPC Sections 4.1, 4.3, 4.4, and 4.6 • PL Sections 1, 2, and 3 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on off-label use (prescriber guide and patient guide "Your guide to PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Embryo-fetotoxicity	Routine risk minimization measures: • SmPC Sections 4.4, 4.6, and 5.3 • PL Section 2 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on the potential risk of embryo-toxicity and to underline information on treatment of women of childbearing potential, and the need for appropriate contraception in women of childbearing potential (prescriber guide and patient guide "Your guide to PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Missing Information		
None		

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the risk management plan (RMP) for PAVBLU is presented below.

Summary of Risk Management Plan for PAVBLU (aflibercept)

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

PAVBLU's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how PAVBLU should be used.

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

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

I. The Medicine and What it is Used for

PAVBLU is authorized 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), and visual impairment due to myopic choroidal neovascularisation (myopic CNV; see SmPC for the full indication). It contains aflibercept as the active substance and it is given by intravitreal injection (injection into the eye). The following pharmaceutical forms are currently available:

- Solution for injection in a pre-filled syringe. One pre-filled syringe contains an extractable volume of at least 0.09 mL, equivalent to at least 3.6 mg aflibercept. This provides a usable amount to deliver a single dose of 0.05 mL containing 2 mg aflibercept to adult patients.
- Solution for injection in a vial. One vial contains an extractable volume of at least 0.1 mL, equivalent to at least 4 mg aflibercept. This provides a usable amount to deliver a single dose of 0.05 mL containing 2 mg aflibercept.

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

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL 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 public (eg, with or without prescription) can help to minimize its risks.

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

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

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

II.A. List of Important Risks and Missing Information

Important risks of PAVBLU are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of PAVBLU. 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 (eg, on the long-term use of the medicine).

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

II.B. Summary of Important Risks

Important identified risk:	Endophthalmitis (likely infectious origin)
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medicinal product Eylea. Evidence source: Eylea SmPC, June 2024.
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 • PL Sections 2, 3, and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to PAVBLU," and its audio version).

Important identified risk:	Intraocular inflammation
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medicinal product Eylea. Evidence sources: ABP 938 clinical study of neovascular (wet) AMD and Eylea SmPC, June 2024.
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 • PL Sections 2, 3, and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to PAVBLU," and its audio version).

Important identified risk:	Transient intraocular pressure increase
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medicinal product Eylea. Evidence sources: ABP 938 clinical study of neovascular (wet) AMD and Eylea SmPC, June 2024.
Risk factors and risk groups	Patients with glaucoma. Increased intraocular pressure is a known adverse drug reaction of treatment with intravitreal corticosteroids.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.2, 4.4, 4.8, and 4.9 • PL Sections 2 and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to PAVBLU," and its audio version).

Important identified risk:	Retinal pigment epithelial tears
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medicinal product Eylea. Evidence sources: ABP 938 clinical study of neovascular (wet) AMD and Eylea SmPC, June 2024.
Risk factors and risk groups	Wet AMD with pigment epithelial detachment; treatment of neovascularization.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to PAVBLU," and its audio version).

Important identified risk:	Cataract (especially of traumatic origin)
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medicinal product Eylea. Evidence sources: ABP 938 clinical study of neovascular (wet) AMD and Eylea SmPC, June 2024.
Risk factors and risk groups	Cataract is a known adverse drug reaction of treatment with intravitreal corticosteroids.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.2, 4.4, and 4.8 • PL Sections 2, 3, and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to PAVBLU," and its audio version).

Important potential risk:	Medication errors
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medicinal product Eylea. Evidence source: Eylea SmPC, June 2024.
Risk factors and risk groups	Not applicable.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2, 4.9, and 6.6 • PL Sections 1 and 3 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise physicians' awareness on medication error (prescriber guide and video; patient guide "Your guide to PAVBLU," and its audio version).

Important potential risk: Off-label use and misuse	
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medicinal product Eylea. Evidence source: Eylea SmPC, June 2024.
Risk factors and risk groups	Not applicable.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.1, 4.3, 4.4, and 4.6 • PL Sections 1, 2, and 3 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on off-label use (prescriber guide and patient guide "Your guide to PAVBLU," and its audio version).

Important potential risk: Embryo-fetotoxicity	
Evidence for linking the risk to the medicine	This important identified risk is included per the reference medicinal product Eylea. Evidence sources: Eylea SmPC, June 2024, and Eylea USPI, December 2023.
Risk factors and risk groups	Patients at risk are women of childbearing potential.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4, 4.6, and 5.3 • PL Section 2 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on the potential risk of embryo-toxicity and to underline information on treatment of women of childbearing potential, and the need for appropriate contraception in women of childbearing potential (prescriber guide and patient guide "Your guide to PAVBLU," and its audio version).

II.C. Postauthorization Development Plan

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

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

II.C.2. Other Studies in Postauthorization Development Plan

There are no studies required for PAVBLU.

PART VII: ANNEXES

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Follow-up forms

Follow-up Form Title	Version Number	Date of Follow-up Version
Report of suspected aflibercept-associated adverse event: endophthalmitis and intraocular inflammation (IOI)	-	06 November 2023
Report of suspected aflibercept-associated adverse event: increase in intraocular pressure (IOP) with pre-filled syringes (PFS)	-	06 November 2023

AMGEN

Report of Suspected AFLIBERCEPT-Associated Adverse Event: Endophthalmitis and Intraocular Inflammation (IOI)

Date of this Report (dd/mm/yyyy) | AER #

This form is subject to applicable laws governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Amgen does not wish to receive information through which a patient can be identified therefore please do not provide any information other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

1. PATIENT INFORMATION

Date of birth or Patient identifier: | Patient initials (confidential): | Patient age at time of event: | Gender: ☐ Male ☐ Female

Weight: ____ Lbs ____ Kg Height: ____ In ____ Cm

2. AFLIBERCEPT THERAPY

Therapy date (dd/mm/yyyy): ____ ☐ Ongoing Doses before event: ____

Indication: ____ Eye injected: ☐ OS ☐ OD ☐ OU

Both eyes injected: ☐ No ☐ Yes ☐ Same vial/PFS used for both eyes

Provide batch number per eye: OS ____ OD ____

VIAL: Lot/Batch Number

Was the same vial used for more than one patient? ☐ No ☐ Yes

If yes, did an event occur in other patients? ☐ No ☐ Yes

If yes, how many patients? ____

Was the vial aliquoted in several syringes? ☐ No ☐ Yes

Was the vial multipunctured? ☐ No ☐ Yes

Was the supplier filter needle used? ☐ No ☐ Yes ☐ Unknown

Date/Time of injection preparation: ____

What was used for injection? ☐ Injection needle: Batch #: ____

☐ Syringe: ☐ Glass ☐ Plastic ☐ Luer Lock

Batch # ____

Where was the syringe for injection prepared?

☐ Off-site pharmacy ☐ On-site pharmacy ☐ Treatment/Examining room

Provide pharmacy name/contact details: ____

Specify hours the prepared syringe stayed at room temperature prior to administration: ____

PRE-FILLED SYRINGE (PFS): Lot/Batch Number

Was the same PFS used for more than one patient? ☐ No ☐ Yes

If yes, did an event occur in other patients? ☐ No ☐ Yes

If yes, how many patients? ____

Date/Time of injection preparation: ____

☐ Injection needle: Batch #: ____

3. ADVERSE EVENT INFORMATION (provide details)

DIAGNOSIS WITH CLINICAL PRESENTATION: ____ ☐ OS ☐ OD ☐ OU

Start date and time (dd/mm/yyyy, hh:mm): ____ Stop date (dd/mm/yyyy): ____

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

OUTCOME: ☐ Recovering/Resolving ☐ Recovered/Resolved without sequelae ☐ Not Recovered/Not Resolved ☐ Unknown

☐ Recovered/Resolved with sequelae (detail sequelae): ____

If resolving/resolved, did the visual acuity (VA) recover to the same level before the event started? ☐ Yes ☐ No, VA is worse

TREATMENT (check all that apply, provide details, regimen, dates):

☐ Antibiotics: ____ ☐ Surgery (vitrectomy): ____

☐ Steriods: ____ ☐ Other (specify): ____

Was a culture taken? ☐ No ☐ Yes ☐ Unknown Culture results: ____ ☐ OS ☐ OD ☐ OU

Did the event abate/stop after treatment stopped? ☐ No ☐ Yes ☐ Unknown ____

Did the event reoccur upon resuming treatment? ☐ No ☐ Yes ☐ Unknown ____

ACTION TAKEN WITH AFLIBERCEPT:

☐ Dose not changed ☐ Unknown

☐ Stopped (provide date): ____

☐ Dose reduced (provide date, duration, new dose): ____

☐ Interrupted (provide date, duration): ____

(Continued on next page)

AMGEN

Report of Suspected AFLIBERCEPT-Associated Adverse Event: Endophthalmitis and Intraocular Inflammation (IOI)

Date of this Report (dd/mm/yyyy) | AER #

4. RELEVANT CLINICAL SYMPTOMS (Indicate dates dd/mm/yyyy)

Symptom: _____ Start date: _____ Stop date: _____ ☐OS ☐OD ☐OU

Symptom: _____ Start date: _____ Stop date: _____ ☐OS ☐OD ☐OU

Symptom: _____ Start date: _____ Stop date: _____ ☐OS ☐OD ☐OU

Symptom: _____ Start date: _____ Stop date: _____ ☐OS ☐OD ☐OU

Symptom: _____ Start date: _____ Stop date: _____ ☐OS ☐OD ☐OU

Did the patient experience the same events in the past? ☐ No ☐ Yes, provide details: _____

5. RELEVANT (intravitreal) CONCOMITANT / HISTORICAL MEDICATION (Specify drug name, indicate dates dd/mm/yyyy)

Anti-VEGF: _____ Start date: _____ Stop date: _____ Dose: _____ Indication: _____ ☐OS ☐OD ☐OU

Drug name: _____ Start date: _____ Stop date: _____ Dose: _____ Indication: _____ ☐OS ☐OD ☐OU

Drug name: _____ Start date: _____ Stop date: _____ Dose: _____ Indication: _____ ☐OS ☐OD ☐OU

Drug name: _____ Start date: _____ Stop date: _____ Dose: _____ Indication: _____ ☐OS ☐OD ☐OU

Did a similar event occur with any of these concomitant medications? ☐ No ☐ Yes, provide details: _____

6. MEDICAL HISTORY / RISK FACTORS (Specify details, indicate dates dd/mm/yyyy)

☐ Diabetes: _____ Start date: _____ Stop date: _____ ☐Ongoing

☐ Autoimmune disease: _____ Start date: _____ Stop date: _____ ☐Ongoing

☐ Immunodeficiency: _____ Start date: _____ Stop date: _____ ☐Ongoing

☐ Other: _____ Start date: _____ Stop date: _____ ☐Ongoing

☐ Other: _____ Start date: _____ Stop date: _____ ☐Ongoing

7. NOTES

_____

_____

_____

REPORTER CAUSALITY COMMENT:

This event is considered:
- ☐ Related to aflibercept
- ☐ Not related to aflibercept
- ☐ Related to intravitreal injection procedure
- ☐ Not related to intravitreal injection procedure
- ☐ Alternative explanation (eg, underlying disease/condition predisposing to the event)

_____

RETURN TO AMGEN VIA SECURE EMAIL OR FAX AT:

Fax:

Email:

REPORTER NAME: _____

☐ Physician ☐ Nurse ☐ Other (specify) _____

Address: _____

City: _____ State/Province: _____

Country: _____ Postal Code: _____

Email: _____

Phone/Fax (indicate, include country code): _____

Signature: _____

Title/Organization: _____ Date: _____

(Continued from previous page)

AMGEN

Report of Suspected AFLIBERCEPT-Associated Adverse Event: Increase in Intraocular Pressure (IOP) With Pre-Filled Syringes (PFS)

Date of this Report (dd/mm/yy y) | AER #

1. PATIENT INFORMATION

Date of birth or Patient identifier: | Patient initials (confidential): | Patient age at time of event: | Gender: ☐ Male ☐ Female

Weight: ____ Lbs ____ Kg Height: ____ In ____ Cm

2. AFLIBERCEPT THERAPY

Indication: ____ Eye Injected: ☐OS ☐OD ☐OU

Number of doses before the event: ____

Date of expiry (dd/mm/yyyy): | PFS Batch number(s)

3. ADVERSE EVENT INFORMATION

Intraocular pressure (IOP) increase event onset date (dd/mm/yyyy): ____ Last injection date before event onset (dd/mm/yyyy): ____

Was the IOP value measured pre-injection?
☐ No ☐ Yes, provide: IOP value(s) (mmHg) ____ Time in minutes before injection: ____ Date(s) ____ Method ____

Was the IOP value measured post-injection?
☐ No ☐ Yes, provide: IOP value(s) (mmHg) ____ Time in minutes after injection: ____ Date(s) ____ Method ____

How long did the increased IOP last after injection? ____

Outcome of IOP increase event: ☐ Recovering/Resolving ☐ Recovered/Resolved without sequelae ☐ Not Recovered/Not Resolved ☐ Unknown
☐ Recovered/Resolved with sequelae (detail sequelae) ____

Did the patient experience any other clinical sign or symptom in the context of post-injection IOP increase? ☐ No ☐ Yes; provide information on other clinical symptoms/medical conditions experienced and provide outcome of events: ____

☐ Recovering/Resolving event(s) ____ ☐ Recovered/Resolved event(s) ____

☐ Recovered/Resolved event(s) with sequelae (detail sequelae) ____

☐ Not Recovered/Not Resolved event(s) ____ ☐ Unknown ☐ Not applicable

Was post-injection fundoscopy performed?
☐ No ☐ Yes, provide post-injection time in minutes: ____ Fundoscopy results: ____

Was there any intervention done to treat increased IOP?
☐ No ☐ Yes, specify the measures taken: ____ Date (dd/mm/yyyy) ____ Time (hr/min) ____

4. MEDICAL HISTORY / ADDITIONAL DETAILS

Does the patient have a history of glaucoma, ocular hypertension, glaucoma surgery, or take glaucoma medication in the injected or fellow eye?
☐ No ☐ Yes, provide details: ____ ☐OS ☐OD ☐OU

Has the patient's anterior chamber angle been assessed in the eye(s) with IOP increase?
☐ No ☐ Yes; provide details: ____ Date (dd/mm/yyyy) ____ Time (hr/min) ____ ☐ Pre-injection ☐ Post-injection
By which method: ____ Angle: ☐ Open ☐ Narrow ☐ Closed Eye: ☐ OS ☐ OD

Concomitant medications that could potentially increase IOP (eg, corticosteriods). Provide drug name(s), indications, details, dates (dd/mm/yyyy):

Name: ____ Start date: ____ Stop date: ____ Dosage: ____ Indication: ____

Name: ____ Start date: ____ Stop date: ____ Dosage: ____ Indication: ____

Name: ____ Start date ____ Stop date: ____ Dosage: ____ Indication: ____

Co-morbid conditions (check all that apply):

☐ Diabetes ☐ High blood pressue ☐ Retinal ischemia ☐ Eye trauma ☐ Psuedo exfoliation syndrome ☐ Corneal arcus present (details):
☐ Myopia ☐ Low blood pressure ☐ BRAO ☐ CRAO ☐ Eye surgeries ☐ Pigment dispersion syndrome ____

Other anti-VEGF treatment: Did the patient have previous intravitreal injections?
☐ No ☐ Yes, provide details: Drug name: ____ ☐ Vial ☐ PFS
Was IOP increase observed after previous injections? ☐ No ☐ Yes, provide details: ____

AMGEN

Report of Suspected AFLIBERCEPT-Associated Adverse Event: Increase in Intraocular Pressure (IOP) With Pre-Filled Syringes (PFS)

Date of this Report (dd/mm/yyyy)	AER #

5. PRE-FILLED SYRINGE (PFS) DETAILS

Who prepared the aflibercept dose (eg, nurse)?_____ Was the individual specifically trained on the aflibercept PFS? ☐ No ☐ Yes

Who administered the aflibercept injection with the PFS?_____ Was the individual specifically trained on the aflibercept PFS? ☐ No ☐ Yes

Was the 30G needle used for injection(s)? ☐ Yes ☐ No, specify needle size used:_____ Brand of injection needle:_____

Were all the bubbles eliminated/expelled, excess drug expelled, and the plunger correctly adjusted to the dose line before injection (moving the base of plunger dome [not the tip] to dosing line)? ☐ Yes ☐ No, provide details:_____

Was there any difficulty in preparing the PFS according to the instructions prior to the injection?

☐ No ☐ Yes, provide details:_____

Was there any physical or handling abnormality observed with the syringe?

☐ No ☐ Yes, provide details:_____

For this event, did you see any foreign particles, discoloration or change in physical appearance of the aflibercept solution?

☐ No ☐ 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, provide details:_____

6. NOTES

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

RETURN TO AMGEN VIA SECURE EMAIL OR FAX AT:

Fax:

Email:

REPORTER Name:_____

☐ Physician ☐ Nurse ☐ Other (specify)_____

Address:_____

City:_____ State/Province:_____

Country:_____ Postal Code:_____

Email:_____

Phone/Fax (indicate and nclude country code):_____

Signature:_____

Title/Organization:_____ Date:_____

Annex 6. Details of Proposed Additional Risk Minimization Activities (if Applicable)

Draft key messages of the additional risk minimization measures

The Marketing Authorization Holder (MAH) agrees to provide European Union educational material for PAVBLU. 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 PAVBLU is marketed, ophthalmological clinics where PAVBLU is expected to be used are provided with a physician information pack containing the following elements:

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

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

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

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 PAVBLU
- How to prepare for PAVBLU treatment
- What are the steps following treatment with PAVBLU

- 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 healthcare provider
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use PAVBLU