1. NAME OF THE MEDICINAL PRODUCT

PAVBLU 40 mg/mL solution for injection in pre-filled syringe.
PAVBLU 40 mg/mL solution for injection in vial.

PAVBLU is a biosimilar medicine to the reference product EYLEA® (aflibercept). The evidence for comparability supports the use of PAVBLU for the listed indications.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One milliliter solution for injection contains 40 mg aflibercept*.

Each single-dose, pre-filled syringe or vial provides a usable amount to deliver a single-dose of 50 microliters containing 2 mg aflibercept.

* Fusion protein consisting of portions of human VEGF (Vascular Endothelial Growth Factor) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and produced in a Chinese hamster ovary (CHO) cells by recombinant DNA technology.

For a full list of excipients, see section "List of excipients".

3. PHARMACEUTICAL FORM

Solution for intravitreal injection.

Sterile, clear, colorless to slightly yellow, iso-osmotic solution, pH 6.2, preservative-free.

4. CLINICAL PARTICULARS

4.1 Indication(s)

PAVBLU is indicated for the treatment of
- neovascular (wet) age-related macular degeneration (wet AMD)
- visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- visual impairment due to diabetic macular edema (DME)
- visual impairment due to myopic choroidal neovascularization (myopic CNV)

4.2 Dosage and method of administration

PAVBLU is for intravitreal injection.

It must only be administered by a qualified physician experienced in administering intravitreal injections.

4.2.1 Dosage regimen

Neovascular (wet) age-related macular degeneration (wet AMD)
The recommended dose for PAVBLU is 2 mg aflibercept, equivalent to 0.05 mL (50 µL).

PAVBLU treatment is initiated with one injection per month for three consecutive doses. The treatment interval is then extended to two months.

Based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at two 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.

There is no requirement for monitoring between injections. Based on the physician's judgement the schedule of monitoring visits may be more frequent than the injection visits.

Treatment intervals greater than four months or shorter than 4 weeks between injections have not been studied (see section 5.4).

Macular oedema secondary to RVO (branch RVO or central RVO)
The recommended dose for PAVBLU is 2 mg aflibercept, (equivalent to 50 microliters).

After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one 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.

The monitoring and treatment schedule should be determined by the treating physician based on the individual patient's response.

Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography).

Diabetic macular edema (DME)
The recommended dose for PAVBLU is 2 mg aflibercept (equivalent to 50 microliters).

PAVBLU treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two 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 between injections have not been studied (see section 5.4).

The schedule for monitoring should be determined by the treating physician.

If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, PAVBLU should be discontinued.

Myopic choroidal neovascularization (myopic CNV)
The recommended dose for PAVBLU is a single intravitreal injection of 2 mg aflibercept (equivalent to 50 microliters).

Additional doses may be administered if visual and/or anatomic outcomes indicate that the disease persists. Recurrences are treated like a new manifestation of the disease.

The schedule for monitoring should be determined by the treating physician.

The interval between two doses should not be shorter than one month.

4.2.2 Additional information on special populations

Patients with hepatic and/or renal impairment
No specific studies in patients with hepatic and/or renal impairment have been conducted with aflibercept.

Available data do not suggest a need for a dose adjustment with PAVBLU in these patients.

Paediatric
Paediatric population
Safety and efficacy have not been established in children and adolescents. There is no relevant use of PAVBLU in the paediatric population in the indication wet AMD, CRVO, BRVO, DME and myopic CNV.

Elderly
No special considerations are needed for dosing as phase III clinical trials were conducted in this subpopulation (see section "5.4 Clinical Studies"). There is limited experience in patients older than 75 years with DME.

4.2.3 Method of administration

Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. In general, adequate anesthesia and asepsis, including topical broad spectrum microbiocide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface), have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended.

The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 microliters is then delivered; a different scleral site should be used for subsequent injections.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each pre-filled syringe or vial should only be used for the treatment of a single eye.

Extraction of multiple doses from a single vial or a pre-filled syringe may increase the risk of contamination and subsequent infection.

The pre-filled syringe contains more than the recommended dose of 2 mg aflibercept (equivalent to 50 microliters solution for injection). The extractable volume of the syringe is the amount that can be expelled from the syringe and is not to be used in total. For the PAVBLU pre-filled syringe, the extractable volume is at least 90 microliters. **The excess volume should be expelled before injecting the recommended dose** (see section "Instruction for use / handling").

Injecting the entire volume of pre-filled syringe could result in overdose. To expel the air bubbles along with excess medicinal product, slowly depress the plunger to **align the base of the plunger dome (not the tip of the dome) with the dosing line on the syringe** (equivalent to 50 microlitres i.e. 2 mg aflibercept) (see sections "Overdose" and "Instruction for use/handling").

The vial contains more than the recommended dose of 2 mg aflibercept (equivalent to 50 microlitres solution for injection). The extractable volume of the vial is the amount that can be withdrawn from the vial and is not to be used in total. For the PAVBLU vial, the extractable volume is at least 100 microliters. **The excess volume must be expelled before injecting the recommended dose** (see section "Instruction for use/handling").

Injecting the entire volume of the vial could result in overdose. To expel the air bubbles along with excess medicinal product, slowly depress the plunger so that the flat plunger edge aligns with the line that marks 50 microlitres on the syringe (equivalent to 50 microlitres i.e. 2 mg aflibercept) (see sections "Overdose" and "Instruction for use/handling").

After injection any unused product must be discarded.

For handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Ocular or periocular infection
- Active severe intraocular inflammation
- Known hypersensitivity to aflibercept or to any of the excipients

4.4 Special warnings and precautions for use

Endophthalmitis
Intravitreal injections, including those with aflibercept, have been associated with endophthalmitis (see section "Undesirable effects"). Proper aseptic injection technique must always be used when administering PAVBLU. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay and should be managed appropriately.

Increase in intraocular pressure
Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection, including with aflibercept (see section "Undesirable effects"). Special precaution is needed in patients with poorly controlled glaucoma. In all cases both intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately.

Other
As with other intravitreal anti-VEGF treatments for AMD, CRVO, BRVO, DME and myopic CNV the following also applies:

- The safety and efficacy of aflibercept therapy administered to both eyes concurrently have not been systematically studied.
- In the event of a retinal break the dose should be withheld and treatment should not be resumed until the break is adequately repaired.
- The dose should be withheld based on the clinical judgement of the treating physician, in the event of a performed or planned intraocular surgery.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction drug interaction studies have been performed with aflibercept .

4.6 Pregnancy and lactation

4.6.1 Pregnancy

There are no data on the use of aflibercept in pregnant women.

Studies in animals have shown reproductive toxicity after systemic administration (see section "Preclinical safety data").

PAVBLU should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus.

4.6.2 Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept.

4.6.3 Lactation

It is unknown whether aflibercept is excreted in human milk. A risk to the breast-fed child cannot be excluded.

PAVBLU is not recommended during breast-feeding. A decision must be made whether to discontinue breast-feeding or to abstain from PAVBLU therapy.

4.7 Effects on ability to drive or use machines

Patients may experience temporary visual disturbances after an intravitreal injection with PAVBLU and the associated eye examinations. They should not drive or use machines until visual function has recovered sufficiently.

4.8 Undesirable effects

Summary of the safety profile

A total of 3102 patients treated with aflibercept constituted the safety population in the eight phase III studies. Among those, 2501 patients were treated with the recommended dose of 2 mg.

Serious adverse reactions related to the injection procedure have occurred in less than 1 in 2400 intravitreal injections with aflibercept and included endophthalmitis, retinal detachment, cataract traumatic, cataract, vitreous detachment and intraocular pressure increased (see section "Special warnings and precautions for use").

The most frequently observed adverse reactions (in at least 5% of patients treated with aflibercept) were conjunctival haemorrhage, eye pain, cataract, intraocular pressure increased, vitreous detachment and vitreous floaters.

In wet AMD studies, these adverse reactions occurred with a similar incidence in the ranibizumab treatment group.

Tabulated list of adverse reactions
The safety data described below include all adverse reactions (serious and non-serious) from eight phase III studies with a reasonable possibility of causality to the injection procedure or medicinal product.

The adverse reactions are listed by system organ class and frequency using the following convention: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000).

Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 1. All Treatment-Emergent Adverse Drug Reactions Reported in Patients in Phase III Studies or During Post-Marketing Surveillance

System Organ Class	Very common	Common	Uncommon	Rare
Immune system disorders			Hypersensitivity***	
Eye disorders	Conjunctival hemorrhage Eye pain	Retinal pigment epithelial tear*, Detachment of the retinal pigment epithelium, Cataract, Cataract cortical, Cataract nuclear, Cataract subcapsular, Corneal erosion, Corneal abrasion, Intraocular pressure increased, Vision blurred, Vitreous floaters, Vitreous detachment, Injection site pain, Foreign body sensation in eyes, Lacrimation increased, Eyelid edema, Injection site hemorrhage, Punctate keratitis, Conjunctival hyperemia, Ocular hyperemia	Endophthalmitis**, Retinal detachment, Retinal tear, Uveitis, Iritis, Iridocyclitis, Lenticular opacities, Corneal epithelium defect, Anterior chamber flare, Corneal edema	Cataract traumatic, Vitritis, Hypopyon

* Conditions known to be associated with wet AMD. Observed in the wet AMD studies only.
** Culture positive and culture negative endophthalmitis.
*** During the post-marketing period, reports of hypersensitivity included rash, pruritus, urticaria, and isolated cases of severe anaphylactic/anaphylactoid reactions.

In addition 157 wet AMD patients were treated for up to 44 months in a long term extension of the phase I and phase II studies. The safety profile was consistent with that seen in the phase III wet AMD studies.

Description of selected adverse reactions

Arterial thromboembolic events
Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of ATEs, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors.

A low incidence rate of arterial thromboembolic events was observed in the aflibercept clinical trials in patients with AMD, DME, CRVO, BRVO and myopic CNV. Across indications no notable difference between the groups treated with aflibercept and the respective comparator groups were observed.

Comparability of PAVBLU with Eylea®
Adverse events were determined based on data from Study 20210034 (a randomized, open-label, two-arm study evaluating the effectiveness and safety of the PAVBLU PFS compared to aflibercept PFS when administered through IVT injection by a retina specialist in adult subjects with various chorioretinal vascular diseases (CVDs)), and from Study 20170542 (a randomized, double-blind, active-controlled study evaluating the efficacy, safety, and immunogenicity of PAVBLU compared with aflibercept in adult subjects with neovascular (wet) age-related macular degeneration (AMD)).

Study 20210034
In Study 20210034, a total of 48 subjects received a single IVT injection of either PAVBLU PFS (32 subjects) or aflibercept PFS (16 subjects) and were included in the safety analysis set.

The safety assessment comparing the PAVBLU PFS and aflibercept PFS (US) treatment groups looked at the incidence of ocular and non-ocular adverse events through the end-of-study (EOS).

Subjects in the PAVBLU PFS treatment group reported any ocular adverse event in the study eye by system organ class (SOC), with eye disorders occurring in 3 (9.4%) subjects and by the preferred terms of eye pain, halo vision and visual impairment with vitreous detachment reported in 1 (3.1%) subject. All ocular adverse events reported in the study eye were Common Terminology Criteria for Adverse Events (CTCAE) grade 1. There were no adverse events in the study eye reported by subjects in the aflibercept PFS (US) treatment group. Non-ocular adverse events occurred in 12.5% of subjects in both PFS treatment groups reported by SOC and preferred term. The SOC of musculoskeletal and connective tissue disorders had the highest incidence of non-ocular adverse events, being reported by 1 subject in each the of PFS treatment groups, with all other SOCs reported in 1 subject for each. The PAVBLU PFS treatment group reported CTCAE grade 2 events, by the preferred terms of hypercholesterolemia, hypertension, seasonal allergy, skin irritation and vitamin D deficiency, as well as CTCAE grade 1 spondylitis. The aflibercept (US) PFS treatment group reported CTCAE grade 1 events of arthralgia and diarrhea. For both treatment groups, the non-ocular adverse events by preferred term were reported in 1 subject each.

An overall summary of adverse events through the end-of-study (EOS) is shown in Table 2.

Table 2. Overall Summary of Adverse Events (Safety Analysis Set)

	PAVBLU PFS (N = 32) n (%)	Aflibercept (US) PFS (N = 16) n (%)
Any ocular adverse event in the study eye	3 (9.4)	0
Any non-ocular adverse event	4 (12.5)	2 (12.5)
Any ocular serious adverse event in the study eye	0	0
Any non-ocular serious adverse event	0	0
Any grade ≥ 3 adverse event	0	0
Any fatal adverse event	0	0
Any COVID-19 adverse event[a]	0	0
Any adverse event leading to discontinuation of study	0	0
Any investigational product related adverse event	0	0
Any study procedure related adverse event	1 (3.1)	0
Any device related adverse event	0	0
Any adverse event of interest	0	0

eCRF = electronic case report form; MedDRA = Medical Dictionary for Regulatory Activities; PFS = prefilled syringe; US = United States

Note: Only treatment-emergent adverse events were summarized by actual treatment received. For each category, subjects were included only once, even if they experienced multiple adverse events in that category.

[a] Adverse event data collected on the Adverse Events eCRF was used to identify COVID-19 adverse events using the COVID-19 Standardized MedDRA Query narrow search strategy.

The safety results showed an absence of clinically meaningful differences between the PAVBLU PFS and aflibercept PFS treatment groups based on an assessment of incidence of ocular and non-ocular adverse events through the EOS.

Study 20170542

In Study 20170542, all 576 subjects in the full analysis set (FAS) and safety analysis set were treated with investigational product in the study eye. The treatment groups through Week 8 and through Week 16 of the study were identified by the treatment received, of either PAVBLU (288 subjects) or aflibercept European Union (EU) (288 subjects). Post-week 16 treatment groups were identified by the treatment sequence received, of either PAVBLU/PAVBLU (273 subjects), aflibercept (EU)/PAVBLU (133 subjects), or aflibercept (EU)/aflibercept (EU) (136 subjects).

The number of doses administered to subjects, the mean total dose of investigational product received, and the total investigational product exposure duration were similar between PAVBLU and aflibercept (EU) treatment groups through Week 16 and across re-randomized treatment groups post-Week 16.

The safety assessment comparing the treatment groups looked at the incidence of subject level and eye level (study eye and fellow eye) adverse events. Adverse events through Week 16, and post-week 16 are summarized separately below.

Through Week 16

Subject Level

An overall summary of adverse events through Week 16 is shown in Table 3.

Most adverse events through Week 16 were CTCAE grade 1 or 2 in severity. Grade ≥ 3 adverse events were reported in 5 (1.7%) subjects in the PAVBLU treatment group and 9 (3.1%) subjects in the aflibercept (EU) treatment group.

Table 3. Overall Summary of Adverse Events Through Week 16 (Safety Analysis Set)

Adverse Event Category	PAVBLU (N = 288) n (%)	Aflibercept (EU) (N = 288) n (%)
Any adverse event	113 (39.2)	107 (37.2)
Any grade ≥ 3 adverse event	5 (1.7)	9 (3.1)
Any fatal adverse event	0 (0.0)	2 (0.7)
Any serious adverse event	6 (2.1)	9 (3.1)
Any adverse event leading to discontinuation of IP/study	1 (0.3)	4 (1.4)
Any EOI	6 (2.1)	3 (1.0)
Any adverse event leading to interruption of IP[a]	6 (2.1)	7 (2.4)

EOI = event of interest; EU = European Union; IP = investigational product
Note: Only treatment-emergent adverse events were summarized by actual treatment received. For each category, subjects were included only once, even if they experienced multiple adverse events in that category.
[a] Drug Interrupted was used for temporary modification of the dosing schedule.

Eye Level – Study Eye
All ocular adverse events in the study eye through Week 16 were CTCAE grade 1 or 2 in severity. An overall summary of ocular adverse events in the study eye through Week 16 is presented in Table 4.

Table 4. Overall Summary of Ocular Adverse Events in Study Eye Through Week 16 (Safety Analysis Set)

Adverse Event Category	PAVBLU (N = 288) n (%)	Aflibercept (EU) (N = 288) n (%)
Any ocular adverse event	46 (16.0)	49 (17.0)
Any grade ≥ 3 adverse event	0 (0.0)	0 (0.0)
Any serious adverse event	0 (0.0)	0 (0.0)
Any adverse event leading to discontinuation of IP/study	1 (0.3)	0 (0.0)
Any EOI	3 (1.0)	2 (0.7)
Any adverse event leading to interruption of IP[a]	1 (0.3)	1 (0.3)

EOI = event of interest; EU = European Union; IP = investigational product
Note: Only treatment-emergent adverse events were summarized by actual treatment received. For each category, subjects were included only once, even if they experienced multiple adverse events in that category.
[a] Drug Interrupted was used for temporary modification of the dosing schedule.

Eye Level – Fellow Eye
All ocular adverse events in the fellow eye through Week 16 were CTCAE grade 1 or 2 in severity, with the exception of a grade 3 ocular adverse event reported by 1 subject in the aflibercept (EU) treatment group.

An overall summary of ocular adverse events in the fellow eye through Week 16 is presented in Table 5.

Table 5. Overall Summary of Ocular Adverse Events in Fellow Eye Through Week 16 (Safety Analysis Set)

Adverse Event Category	PAVBLU (N = 288) n (%)[a]	Aflibercept (EU) (N = 288) n (%)[a]
Subjects treated with IP in fellow eye (N1)	18	16
Any ocular adverse event	3 (16.7)	5 (31.3)
Any grade ≥ 3 adverse event	0 (0.0)	1 (6.3)
Any serious adverse event	0 (0.0)	1 (6.3)
Any adverse event leading to discontinuation of IP/study	0 (0.0)	0 (0.0)
Any EOI	0 (0.0)	0 (0.0)
Any adverse event leading to interruption of IP[b]	0 (0.0)	1 (6.3)

EOI = event of interest; EU = European Union; IP = investigational product
Note: Only treatment-emergent adverse events were summarized by actual treatment received. For each category, subjects were included only once, even if they experienced multiple adverse events in that category.
[a] Percentage is calculated using the count (N1) as the denominator.
[b] Drug Interrupted was used for temporary modification of the dosing schedule.

Post-Week 16 (Re-randomized Subjects Who Were Treated After Re-randomization)
Subject Level
An overall summary of adverse events post-week 16 is presented in Table 6 for re-randomized and treated subjects.

Most adverse events post-week 16 were CTCAE grade 1 or 2 in severity. Grade ≥ 3 adverse events were reported in 23 (8.4%) subjects in the PAVBLU/PAVBLU treatment group, 13 (9.8%) subjects in the aflibercept (EU)/PAVBLU treatment group and 15 (11.0%) subjects in the aflibercept (EU)/aflibercept (EU) treatment group.

Table 6. Overall Summary of Adverse Events Post-Week 16 (Safety Analysis Set – Re-randomized and Treated)

Adverse Event Category	PAVBLU/ PAVBLU (N = 273) n (%)	Aflibercept (EU)/ PAVBLU (N = 133) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 136) n (%)
Any adverse event	144 (52.7)	76 (57.1)	72 (52.9)
Any grade ≥ 3 adverse event	23 (8.4)	13 (9.8)	15 (11.0)
Any fatal adverse event	2 (0.7)	2 (1.5)	0 (0.0)
Any serious adverse event	22 (8.1)	14 (10.5)	11 (8.1)
Any adverse event leading to discontinuation of IP/study	9 (3.3)	3 (2.3)	5 (3.7)
Any EOI	9 (3.3)	8 (6.0)	2 (1.5)
Any adverse event leading to interruption of IP[a]	26 (9.5)	9 (6.8)	4 (2.9)

EOI = event of interest; EU = European Union; IP = investigational product
Note: Only treatment-emergent adverse events were summarized by actual treatment received. For each category, subjects were included only once, even if they experienced multiple adverse events in that category.

[a] Drug Interrupted was used for temporary modification of the dosing schedule.

Eye Level – Study Eye
Most ocular adverse events in the study eye post-week 16 were CTCAE grade 1 or 2 in severity. Grade ≥ 3 ocular adverse events were reported in 1 (0.4%) subject in the PAVBLU/PAVBLU treatment group, 1 (0.8%) subject in the aflibercept (EU)/PAVBLU treatment group, and 3 (2.2%) subjects in the aflibercept (EU)/aflibercept (EU) treatment group.

An overall summary of ocular adverse events in the study eye post-week 16 is presented in Table 7 for re-randomized and treated subjects.

Table 7. Overall Summary of Ocular Adverse Events in Study Eye Post-Week 16 (Safety Analysis Set – Re-randomized and Treated in Study Eye)

Adverse Event Category	PAVBLU/ PAVBLU (N = 273) n (%)	Aflibercept (EU)/ PAVBLU (N = 133) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 136) n (%)
Any ocular adverse event	61 (22.3)	32 (24.1)	25 (18.4)
Any grade ≥ 3 adverse event	1 (0.4)	1 (0.8)	3 (2.2)
Any serious adverse event	0 (0.0)	0 (0.0)	2 (1.5)
Any adverse event leading to discontinuation of IP/study	2 (0.7)	0 (0.0)	3 (2.2)
Any EOI	3 (1.1)	4 (3.0)	1 (0.7)
Any adverse event leading to interruption of IP[a]	3 (1.1)	0 (0.0)	1 (0.7)

EOI = event of interest; EU = European Union; IP = investigational product
Note: Only treatment-emergent adverse events were summarized by actual treatment received. For each category, subjects were included only once, even if they experienced multiple adverse events in that category.
[a] Drug Interrupted was used for temporary modification of the dosing schedule.

Eye Level – Fellow Eye
All ocular adverse events in the fellow eye post-week 16 were CTCAE grade 1 or 2 in severity, with the exception of a grade 3 ocular adverse event reported by 1 subject in the not treated/PAVBLU treatment group.

An overall summary of ocular adverse events in the fellow eye post-week 16 is displayed in Table 8.

Table 8. Overall Summary of Ocular Adverse Events in Fellow Eye Post-Week 16 (Safety Analysis Set – Re-randomized and Treated in Fellow Eye)

Adverse Event Category	PAVBLU / PAVBLU (N = 18) n (%)	Aflibercept (EU)/ PAVBLU (N = 10) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 3) n (%)	Not Treated/ PAVBLU (N = 35) n (%)	Not Treated/ Aflibercept (EU) (N = 14) n (%)
Any ocular adverse event	5 (27.8)	3 (30.0)	1 (33.3)	21 (60.0)	9 (64.3)
Any grade ≥ 3 adverse event	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Any serious adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any adverse event leading to discontinuation of IP/study	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any EOI	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any adverse event leading to interruption of IP[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

EOI = event of interest; EU = European Union; IP = investigational product
Note: Only treatment-emergent adverse events were summarized by actual treatment received. For each category, subjects were included only once, even if they experienced multiple adverse events in that category.
[a] Drug Interrupted was used for temporary modification of the dosing schedule.

Immunogenicity of aflibercept
As with all therapeutic proteins, there is a potential for immunogenicity with aflibercept. Immunogenicity was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to aflibercept in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

In all phase III studies the pre-treatment incidence of immunoreactivity to aflibercept was approximately 1% - 3% in all treatment groups. After dosing with aflibercept for up to 96 weeks (wet AMD), 76 weeks (CRVO), 52 weeks (BRVO), 100 weeks (DME) or 48 weeks (myopic CNV) antibodies to aflibercept were detected in a similar percentage range of patients. In all studies, there were no differences in efficacy or safety between patients with or without immunoreactivity.

Immunogenicity of PAVBLU
One comparative clinical study (Study 20170542) was conducted to confirm low systemic exposure of unbound (free) drug concentrations following IVT administration of PAVBLU or aflibercept, and to compare the immunogenicity of PAVBLU to aflibercept in subjects with neovascular (wet) AMD. Therefore, comparison and analysis across studies were not performed.

Immunogenicity data are discussed below through Week 16, and post-week 16 and over the entire study for re-randomized and treated subjects.

Through Week 16
Through Week 16, a total of 9 (3.2%) subjects in the PAVBLU treatment group and 8 (2.8%) subjects in the aflibercept (EU) treatment group tested positive for pre-existing binding ADAs at baseline.

There were no subjects with a post-baseline result through Week 16 who tested positive for treatment-boosted ADAs (ie, binding antibody positive at baseline with a ≥ 4 × increase in magnitude post-baseline).

Through Week 16, 287 subjects in the PAVBLU treatment group and 284 subjects in the aflibercept (EU) treatment group had a post-baseline result. Of subjects with a post-baseline result through Week 16, 1 (0.3%) subject in the PAVBLU treatment group and 4 (1.4%) subjects in the aflibercept (EU) treatment group tested positive for the development of binding ADAs. Of these, the results were transient (ie, a negative result at the subject's last time point tested during the study period) for 0 (0.0%) and 3 (1.1%) subjects, respectively.

Post-Week 16 (Re-randomized Subjects Who Were Treated After Re-randomization)
Of the subjects with a post-baseline result after Week 16, 3 (1.1%) subjects in the PAVBLU / PAVBLU treatment group, 0 (0.0%) subjects in the aflibercept (EU)/PAVBLU treatment group, and 0 (0.0%) subjects in the aflibercept (EU)/aflibercept (EU) treatment group tested positive for the development of binding ADAs. These results were transient (ie, a negative result at the subject's last time point tested during the study period) for 2 (0.7%), 0 (0.0%), and 0 (0.0%) subjects, respectively.

The neutralizing activity against PAVBLU and aflibercept was not assessed, due to the low incidence of binding antidrug antibodies (ADAs) (1% to 3%) and neutralizing ADAs (0.11% to 0.17%) reported for Eylea® (aflibercept), resulting in no clinical impact on pharmacokinetics/pharmacodynamics, safety or efficacy across multiple indications [neovascular (wet) AMD, retinal vein occlusion (RVO), diabetic macular edema (DME) and myopic choroidal neovascularization (CNV)].

In addition, binding or neutralizing ADA formation in the periphery is unlikely to penetrate the blood-retinal barrier.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the test method and may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PAVBLU with the incidence of antibodies to other products may be misleading.

As with all therapeutic proteins, there is potential for immunogenicity. Differences in assay methodology for measuring immunogenicity prevent direct comparison of immunogenicity rates between PAVBLU and Eylea® or other biologics in different studies. In Study 20170542, binding anti-drug antibody (ADA) activity was determined using an electrochemiluminescence (ECL)-based bridging immunoassay to detect antibodies capable of binding to PAVBLU.

4.9 Overdose

In clinical trials, doses of up to 4 mg in monthly intervals and isolated cases of overdoses with 8 mg were generally well tolerated.

Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of an overdose, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated (see section "Instructions for use / handling").

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action
Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leukocytes. Excessive activation of these receptors by VEGF-A can result in

pathological neovascularization and excessive vascular permeability. PlGF can synergize with VEGF-A in these processes and is also known to promote leukocyte infiltration and vascular inflammation. A variety of ocular diseases are associated with pathologic neovascularization, vascular leakage, and/or can result in thickening and edema of the retina, which is thought to contribute to vision loss.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors. The equilibrium dissociation constant (K_D) for aflibercept binding to human VEGF-A_{165} is 0.5 pM and to human VEGF-A_{121} is 0.36 pM. The K_D for binding to human PlGF-2 is 39 pM.

In animal studies, aflibercept can prevent pathological neovascularization and vascular leakage in a number of different models of ocular disease. For example, intravitreal administration of aflibercept to monkeys prevented the development of significant choroidal neovascularization (CNV) following laser injury and reversed vascular leakage from established CNV lesions.

Comparability of PAVBLU with Eylea®
See section 5.4 Clinical Studies for Comparability of PAVBLU with Eylea® for more details.

5.2 Pharmacokinetic properties

Absorption / Distribution
Aflibercept is slowly absorbed from the eye into the systemic circulation after intravitreal administration and is predominately observed in the systemic circulation as an inactive, stable complex with VEGF; however only "free aflibercept" is able to bind endogenous VEGF.

In a pharmacokinetic sub-study with frequent sampling in AMD patients, maximum plasma concentrations of free aflibercept (systemic C_{max}) were low, with a mean of approximately 0.02 microgram/mL (range 0 to 0.054 microgram/mL) within 1 to 3 days after a 2-mg intravitreal injection and were undetectable two weeks following dosage in almost all patients. Aflibercept does not accumulate in the plasma when administered intravitreally every 4 weeks.

It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100-fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF (2.91 microgram/mL) in a study of healthy volunteers. Therefore, systemic pharmacodynamic effects such as blood pressure changes are unlikely.

These pharmacokinetic results were consistent in pharmacokinetic sub-studies in patients with CRVO, BRVO, DME or myopic CNV with mean C_{max} of free aflibercept in plasma in the range of 0.03 to 0.05 microgram/mL and individual values not exceeding 0.14 microgram/mL. Thereafter, plasma concentrations of free aflibercept declined to values below or close to the lower limit of quantitation generally within one week; undetectable concentrations were reached before the next administration after 4 weeks in all patients.

Elimination
As aflibercept is a protein-based therapeutic, no metabolism studies have been conducted.

Free aflibercept binds VEGF to form a stable, inert complex. As with other large proteins, both free and bound aflibercept are expected to be cleared by proteolytic catabolism.

Comparability of PAVBLU with Eylea®
Results from the PK substudy within Study 20170542 confirmed low systemic exposure of unbound (free) drug concentrations following IVT administration of PAVBLU or Eylea® (aflibercept) in subjects with neovascular (wet) AMD. These levels were below the concentration required to half-maximally bind systemic VEGF (2.91 mcg/mL) for a pharmacologically relevant reduction in endogenous systemic VEGF.

A PK substudy within Study 20170542 was conducted to provide descriptive information to confirm low systemic exposure of unbound (free) drug concentrations following IVT administration of PAVBLU or aflibercept. In clinical studies with Eylea® (aflibercept), systemic unbound (free) concentrations of aflibercept were low following IVT administration of Eylea® (aflibercept). Moreover, free aflibercept plasma concentrations were undetectable 2 weeks after dosing in all patients assessed (Eylea® USPI, 2023). Therefore, standard PK parameters (ie, area under the concentration time curve and maximum observed serum concentration) were considered not evaluable.

Subjects enrolled in Study 20170542 were not enrolled in the PK substudy if it was anticipated that the fellow eye would need to be treated prior to the Week 8 post-dose PK sample. If an enrolled PK substudy subject developed a requirement for fellow eye treatment prior to the Week 8 post-dose PK sample, no further PK samples were collected. If the need for treating the fellow eye was identified at the Week 8 visit, then the fellow eye was treated after the Week 8 post-dose PK sample had been drawn for those subjects included in the PK substudy.

These subjects were to have both pre-dose (at least 60 minutes before the day 1 dose) and post-dose (approximately 24 hours after the day 1 dose) PK samples collected, with an allowable window of 6 hours to +24 hours (ie, 18 hours to 48 hours after the day 1 dose), then post-dose at Week 8 (approximately 24 hours after the Week 8 dose) with an allowable window of -6 hours to +24 hours (ie, 18 hours to 48 hours post-dose).

A total of 49 subjects were enrolled in the PK substudy. Overall, 44 (89.8%) of the subjects enrolled in the PK substudy were included in the PK analysis set. Five (10.2%) of the subjects were excluded from the PK analysis set due to a missing reported concentration of either drug.

The median free drug serum concentrations at day 1 post-dose for the PAVBLU and aflibercept (EU) treatment groups were 24.95 ng/mL and 37.30 ng/mL, respectively. The median free drug serum concentrations at Week 8 post-dose for the PAVBLU and aflibercept (EU) treatment groups were 35.60 ng/mL and 74.10 ng/mL, respectively.

These concentrations are consistent with the mean C_{max} of free aflibercept reported for patients with neovascular (wet) AMD, RVO and DME following IVT administration of Eylea® (aflibercept) (Eylea® SmPC, 2023; Eylea® USPI, 2023). Although the median and geometric mean free drug concentrations at day 1 post-dose and Week 8 post-dose were higher for the aflibercept (EU) treatment group than the PAVBLU treatment group, these differences may be attributed to high variability in serum concentrations between subjects.

A summary of the unbound (free) drug concentrations following IVT administration of PAVBLU or aflibercept (EU) for subjects in the PK analysis set are provided in Table 9.

Table 9. Summary of Pharmacokinetic Concentrations (ng/mL) (Study 20170542 PK Analysis Set)

Visit **Statistic**	**PAVBLU** **(N = 18)**	**Aflibercept (EU)** **(N = 26)**
Baseline		
n	16	22
Mean (SD)	0.00 (0.00)	0.00 (0.00)
Median	0.00	0.00
Minimum, maximum	0.0, 0.0	0.0, 0.0
Day 1 post-dose		
n	16	22
Mean (SD)	33.28 (38.225)	58.41 (50.011)

Visit Statistic	PAVBLU (N = 18)	Aflibercept (EU) (N = 26)
Median	24.95	37.30
Minimum, maximum	0.0, 139.0	0.0, 220.0
m	10	21
GeoMean	44.98	46.75
GeoCV (%)	65.5	85.6
Geometric LS mean	52.90	51.97
Ratio of geometric LS means (PAVBLU/Aflibercept [EU])	1.0179	
90% CI for ratio of geometric LS means	(0.6342, 1.6337)	
Week 8 post-dose		
n	15	23
Mean (SD)	58.03 (53.111)	75.83 (36.743)
Median	35.60	74.10
Minimum, maximum	0.0, 192.0	25.4, 173.0
m	14	23
GeoMean	47.37	67.44
GeoCV (%)	84.5	54.3
Geometric LS mean	47.68	66.55
Ratio of geometric LS means (PAVBLU/Aflibercept [EU])	0.7165	
90% CI for ratio of geometric LS means	(0.4926, 1.0421)	

BCVA = best corrected visual acuity; CSR = clinical study report; EU = European Union; GeoCV = geometric coefficient of variation; GeoMean = geometric mean; LS = least squares; m = number of subjects with a non-zero concentration; n = number of subjects with non-missing values; PK = pharmacokinetics

Note: Lower limit of quantification was < 15.0 ng/mL. Pharmacokinetic concentrations below the lower limit of quantification were assigned a value of 0 and were excluded from the calculations of GeoMean, GeoCV, geometric LS mean, geometric mean ratio, and 90% CI (calculated only if m ≥ 5). The geometric LS mean, ratio of geometric LS means, and 90% CI were estimated based on ANCOVA model adjusted for the actual stratification factors of geographic region (East Asia, Europe, North America) and baseline BCVA (BCVA < 64 letters, BCVA ≥ 64 letters). Post-dose samples were collected approximately 24 hours after the day 1 dose, with an allowable window of: -6 hours to +24 hours (ie, 18 hours to 48 hours after day 1 dose). PK sample collection window 1 day after Week 8 dose: -6 hours to +24 hours (ie, 18 hours to 48 hours after Week 8 dose).

The results of the PK substudy within Study 20170542 confirmed low systemic exposure of unbound (free) drug concentrations following IVT administration of PAVBLU or aflibercept in subjects with neovascular (wet) AMD. These levels were below the concentration required to half-maximally bind systemic VEGF (2.91 mcg/mL) for a pharmacologically relevant reduction in endogenous systemic VEGF (Eylea® Public Assessment Report, 2012; Eylea® USPI, 2023).

5.3 Preclinical safety data

Effects in non-clinical studies on repeated dose toxicity were observed only at systemic exposures considered substantially in excess of the maximum human exposure after intravitreal administration at

the intended clinical dose indicating little relevance to clinical use.

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept.

An effect of aflibercept on intrauterine development was shown in embryo-fetal development studies in pregnant rabbits with intravenous (3 to 60 mg/kg) as well as subcutaneous (0.1 to 1 mg/kg) administration. The maternal 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 basedon 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 intravitreal dose of 2 mg.

5.4 Clinical Studies

Neovascular (wet) age-related macular degeneration (wet AMD)
The safety and efficacy of aflibercept were assessed in two randomized, multi-centre, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2).

In each study, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens:
1) Aflibercept administered at 2 mg every 8 weeks following 3 initial monthly doses (Aflibercept 2Q8);
2) Aflibercept administered at 2 mg every 4 weeks (Aflibercept 2Q4);
3) Aflibercept administered at 0.5 mg every 4 weeks (Aflibercept 0.5Q4); and
4) Ranibizumab administered at 0.5 mg every 4 weeks (Ranibizumab 0.5Q4).

Patient ages ranged from 49 to 99 years with a mean of 76 years.

In the second year of the studies, patients continued to receive the dosage strength to which they were initially randomized but on a modified dosing schedule guided by assessment of visual and anatomic outcomes with a protocol-defined maximum dosing interval of 12 weeks. During the second year of the studies, 90% of patients originally treated with aflibercept 2Q8 received 6 doses or less and 72% received 4 doses or less among those patients completing the second yearof the studies.

In both studies, the primary efficacy endpoint was the proportion of patients in the Per Protocol Set who maintained vision, defined as losing fewer than 15 letters of visual acuity at Week 52 compared to baseline.

In the VIEW1 study, at Week 52, 95.1% of patients in the aflibercept 2Q8 treatment group, 95.1% of patients in the aflibercept 2Q4 treatment group, and 95.9% of patients in the aflibercept 0.5Q4 treatment group maintained vision compared to 94.4% patients in the ranibizumab 0.5Q4 group. All aflibercept treatment groups were shown to be non-inferior and clinically equivalent to the ranibizumab 0.5Q4 group.

In the VIEW2 study, at Week 52, 95.6% of patients in the aflibercept 2Q8 treatment group, 95.6% of patients in the aflibercept 2Q4 treatment group, and 96.3% of patients in the aflibercept 0.5Q4 treatment group maintained vision compared to 94.4% patients in the ranibizumab 0.5Q4 group. All aflibercept treatment groups were shown to be non-inferior and clinically equivalent to the ranibizumab 0.5Q4 group.

The ARIES study was designed to explore the non-inferiority of an aflibercept 2 mg treat-and-extend dosing regimen initiated immediately after administration of 3 initial monthly injections and one additional injection after 2 months vs. a treat-and-extend dosing regimen initiated after one year of treatment. For patients requiring a more frequent than Q8 dosing at least once over the course of the study, CRT remained higher, but the mean decrease in CRT from baseline to Week 104 was -160.4 microns, similar to the patients treated at Q8 or less frequent intervals.

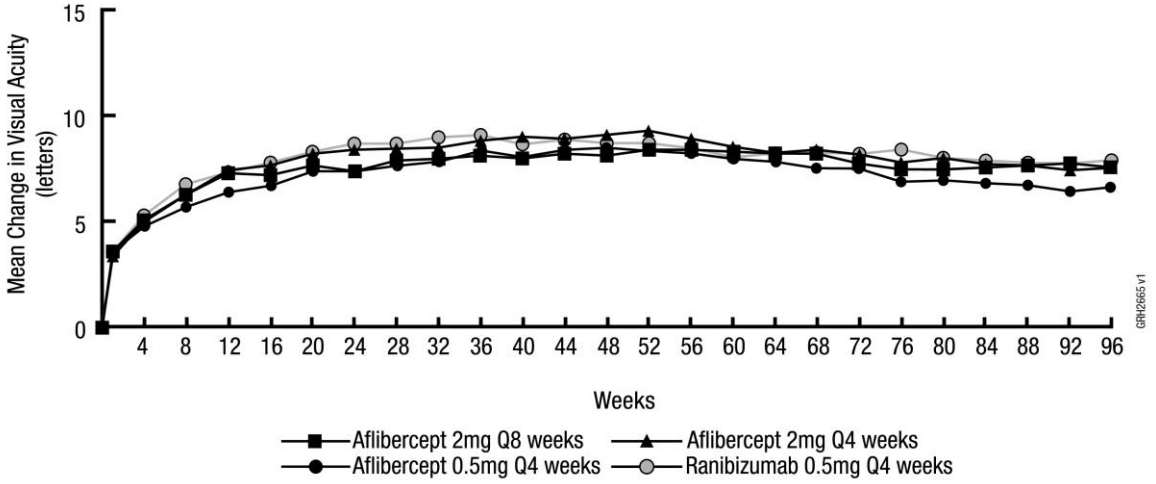
Detailed results from the combined analysis of both studies are shown in the Table and Figure below.

Table 10. Efficacy Outcomes at Week 52 (Primary Analysis) and Week 96; Combined Data from the VIEW1 and VIEW2 studies[B)]

Efficacy Outcome	Aflibercept 2 mg Q8[E)] (N = 607)		Aflibercept 2 mg Q4 (N = 613)		Aflibercept 0.5 mg Q4 (N = 597)		Ranibizumab 0.5 mg Q4 (N = 595)	
	52 weeks	96 weeks	52 weeks	96 weeks	52 weeks	96 weeks	52 weeks	96 weeks
Mean number of injections	7.6	11.2	12.3	16.0	12.2	16.2	12.3	16.5
Proportion of patients with maintained visual acuity (< 15 letters of BCVAA) loss) (Per Protocol Set)	95.33% [B)]	92.42%	95.35% [B)]	92.17%	96.10% [B)]	91.46%	94.42%[B)]	91.60%
Difference[C)] (95% CI)[D)]	0.9% (-1.7, 3.5)[F)]	0.8% (-2.3, 3.8)[F)]	0.9% (-1.7, 3.5)[F)]	0.6% (-2.5, 3.6)[F)]	1.7% (-0.9, 4.2)[F)]	-0.2% (-3.3, 3.0)[F)]		
Mean change in BCVA from baseline as measured by ETDRS[A)] letter score	8.40	7.62	9.26	7.60	8.29	6.59	8.74	7.89
Difference in LS[A)] mean change (ETDRS letters)[C)] (95% CI)[D)]	-0.32 (-1.87, 1.23)	-0.25 (-1.98, 1.49)	0.60 (-0.94, 2.14)	-0.20 (-1.93, 1.53)	-0.43 (-1.99, 1.12)	-1.28 (-3.02, 0.46)		
Proportion of patients who gained at least 15 letters of vision from baseline	30.97%	33.44%	33.44%	31.16%	29.82%	28.14%	32.44%	31.60%
Difference[C)] (95% CI)[D)]	-1.5% (-6.8, 3.8)	1.8% (-3.5, 7.1)	1.0% (-4.3, 6.3)	-0.4% (-5.6, 4.8)	-2.7% (-7.9, 2.6)	-3.5 (-8.7, 1.7)		

[A)] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LS: Least square means derived from ANCOVA
[B)] Full Analysis Set (FAS), Last Observation Carried Forward (LOCF) for all analyses except proportion of patients with maintained visual acuity at Week 52 which is Per Protocol Set (PPS)
[C)] The difference is the value of the aflibercept group minus the value of the ranibizumab group. A positive value favors aflibercept
[D)] Confidence interval (CI) calculated by normal approximation
[E)] After treatment initiation with three monthly doses
[F)] A confidence interval lying entirely above -10% indicates a non-inferiority of aflibercept to ranibizumab

Figure 1. Mean Change in Visual Acuity from Baseline to Week 96 for the Combined Data from the VIEW1 and VIEW2 Studies



Decreases in mean CNV area were evident in all dose groups in both studies.

In combined data analysis of the VIEW1 and VIEW2 studies aflibercept at all doses (2Q8, 2Q4, and 0.5Q4) demonstrated clinically meaningful changes from baseline in pre-specified secondary efficacy endpoint National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in Best Corrected Visual Acuity (BCVA).

No clinically meaningful differences were found between aflibercept and the reference product ranibizumab in changes of NEI VFQ-25 total score and subscales (near activities, distance activities, and vision-specific dependency) at Week 52 from baseline.

In the second year of the studies, efficacy was generally maintained through the last assessment at Week 96. Over the 2 year period, patients in the aflibercept 2Q8 group received an average of 11.2 doses and patients in the ranibizumab group received an average of 16.5 doses.

Efficacy results in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, lesion type, lesion size) in each study and in the combined analysis were consistent with the results in the overall populations.

ALTAIR was a 96 week multicentre, randomized, open-label phase 4 study in 247 Japanese patients with treatment naive wet AMD, designed to assess the efficacy and safety of aflibercept following two different adjustment intervals (2-weeks and 4-weeks) of a treat-and-extend dosing regimen.

All patients received 3 monthly doses of aflibercept 2 mg, followed by one injection after a 2-month interval. At Week 16, patients were randomized 1:1 into two treatment groups: 1) aflibercept treat-and-extend with 2-week adjustments and 2) aflibercept treat-and-extend with 4-week adjustments. Extension or shortening of the interval was decided based on visual and/or anatomic criteria defined by protocol with a maximum treatment interval of 16 weeks for both groups.

The primary efficacy endpoint was mean change in BCVA from baseline to Week 52. The secondary efficacy endpoints were the proportion of patients who did not lose ≥ 15 letters and the proportion of patients who gained at least 15 letters of BCVA from baseline to Week 52.

At Week 52, patients in the treat-and-extend arm with 2-week adjustments gained a mean of 9.0 letters from baseline as compared to 8.4 letters for those in the 4-week adjustment group [LS mean difference in letters (95% CI): -0.4 (-3.8,3.0), ANCOVA]. The proportion of patients who did not lose ≥ 15 letters in the two treatment arms was similar (96.7% in the 2-week and 95.9% in the 4-week

adjustment groups). The proportion of patients who gained ≥ 15 letters at Week 52 was 32.5% in the 2-week adjustment group and 30.9% in the 4-week adjustment group. The proportion of patients who extended their treatment interval to 12 weeks or beyond was 42.3% in the 2-week adjustment group and 49.6% in the 4-week adjustment group. Furthermore, in the 4-week adjustment group 40.7% of patients were extended to 16-week intervals. At the last visit up to Week 52, 56.8% and 57.8% of patients in the 2-week and 4-week adjustment groups, respectively had their next injection scheduled at an interval of 12 weeks or beyond. Ocular and systemic safety profiles were similar to the safety observed in the pivotal studies VIEW1 and VIEW2.

In the second year of the study, efficacy was generally maintained up to and including the last assessment at Week 96, with a mean gain from baseline of 7.6 letters for the 2-week adjustment group and 6.1 letters for the 4-week adjustment group. The proportion of patients who extended their treatment interval to 12 weeks or beyond was 56.9% in the 2-week adjustment group and 60.2% in the 4-week adjustment group. At the last visit prior to Week 96, 64.9% and 61.2% of patients in the 2-week and 4-week adjustment groups, respectively, had their next injection scheduled at an interval of 12 weeks or beyond.

Between Week 16 and 96, 43.1% (n = 53) and 54.5% (n = 67) of the patients (2-week and 4-week adjustment groups respectively) were extended to a maximum treatment interval of 16 weeks at least once. Of these patients, 96.2% (n = 51 of 53) patients in the 2-week adjustment group and 77.6% (n = 52 of 67) patients in the 4-week adjustment group maintained a 16-week treatment interval until the end of the study. During the 96 week study period, 41.5% (n = 51) and 46.3% (n = 57) of patients in the 2-week and 4-week adjustment groups respectively had a final treatment interval of 16 weeks.

During the second year of treatment patients in both the 2-week and 4-week adjustment groups received an average of 3.6 and 3.7 injections. Over the 2 year treatment period patients received an average of 10.4 injections.

ARIES was a 104-week multicentre, randomized, open-label, active-controlled study in 269 patients with treatment naive wet AMD, designed to assess the non-inferiority in terms of efficacy as well as the safety of a treat-and-extend dosing regimen initiated after 3 consecutive monthly doses followed by extension to a 2 monthly treatment interval vs. a treat-and-extend dosing regimen initiated after the first year of treatment.

The ARIES study also explored the percentage of patients that required more frequent treatment than every 8 weeks based on the investigator's decision. Out of the 269 patients 62 patients received more frequent dosing at least once during the course of the study. Such patients remained in the study and received treatment according to the investigator's best clinical judgement but not more frequently than every 4 weeks and their treatment intervals could be extended again afterwards. The average treatment interval after the decision to treat more frequently was 6.1 weeks. Week 104 BCVA was lower in patients requiring more intensive treatment at least once over the course of the study compared with patients who did not and the mean change in BCVA from baseline to end of the study was +2.3 ± 15.6 letters. Among the patients treated more frequently, 85.5% maintained vision, i.e. lost less than 15 letters, and 19.4% gained 15 letters or more. The safety profile of patients treated more frequently than every 8 weeks was comparable to the safety data in VIEW1 and VIEW2.

Geriatric patients
In the VIEW pivotal wet AMD studies, approximately 89% (1616/1817) of the patients randomized to treatment with aflibercept were 65 years of age or older and approximately 63% (1139/1817) were 75 years of age or older.

Macular oedema secondary to central retinal vein occlusion (CRVO)
The safety and efficacy of aflibercept were assessed in two randomized, multi-centre, double-masked, sham-controlled studies in patients with macular oedema secondary to CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with aflibercept) in the two studies COPERNICUS and GALILEO. In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg aflibercept

administered every 4 weeks (2Q4) or the control group receiving sham injections every 4 weeks for a total of 6 injections.

After 6 monthly injections, patients received treatment only if they met pre-specified retreatment criteria, except for patients in the control group in the GALILEO study who continued to receive sham (control to control).

Patient ages ranged from 22 to 89 years with a mean of 64 years.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at Week 24 compared to baseline.

Change in visual acuity at Week 24 compared to baseline was a secondary efficacy variable in both COPERNICUS and GALILEO studies.

The difference between treatment groups was statistically significant in favor of aflibercept in both studies. In both pivotal studies the maximal improvement in visual acuity was achieved at month 3 with subsequent stabilization of the effect on visual acuity and central retinal thickness until month 6. The statistically significant difference was maintained through Week 52. A difference was maintained through Week 76/100.

Detailed results from the analysis of both studies are shown in the Table and Figure below.

Table 11. Efficacy Outcomes at Week 24, Week 52 and Week 76/100 (Full Analysis Set with LOCF[C]) in COPERNICUS and GALILEO Studies

Efficacy Outcomes	**COPERNICUS**					
	24 Weeks		**52 Weeks**		**100 Weeks**	
	Aflibercept 2 mg Q4 (N = 114)	**Control (N = 73)**	**Aflibercept 2 mg (N = 114)**	**Control[E] (N = 73)**	**Aflibercept[F] 2 mg (N = 114)**	**Control[E,F] (N = 73)**
Proportion of patients who gained at least 15 letters in BCVA[C] from baseline	56%	12%	55%	30%	49.1%	23.3%
Weighted difference[A,B,E,F] (95% CI) p-value	44.8% (33.0, 56.6) p < 0.0001		25.9% (11.8, 40.1) p = 0.0006		26.7% (13.1, 40.3) p = 0.0003	
Mean change in BCVA as measured by ETDRS[C] letter score from baseline (SD)	17.3 (12.8)	-4.0 (18.0)	16.2 (17.4)	3.8 (17.1)	13.0 (17.7)	1.5 (17.7)
Difference in LS mean[A,C,D,E,F] (95% CI) p-value	21.7 (17.4, 26.0) p < 0.0001		12.7 (7.7, 17.7) p < 0.0001		11.8 (6.7, 17.0) p < 0.0001	

Efficacy Outcomes	GALILEO					
	24 Weeks		52 Weeks		76 Weeks	
	Aflibercept 2 mg Q4 (N = 103)	Control (N = 68)	Aflibercept 2 mg (N = 103)	Control (N = 68)	Aflibercept[G] 2 mg (N = 103)	Control[G] (N = 68)
Proportion of patients who gained at least 15 letters in BCVA[C] from baseline	60%	22%	60%	32%	57.3%	29.4%
Weighted difference[A,B,G] (95% CI) p-value	38.3% (24.4, 52.1) p < 0.0001		27.9% (13.0, 42.7) p = 0.0004		28.0% (13.3, 42.6) p = 0.0004	
Mean change in BCVA as measured by ETDRS[C] letter score from baseline (SD)	18.0 (12.2)	3.3 (14.1)	16.9 (14.8)	3.8 (18.1)	13.7 (17.8)	6.2 (17.7)
Difference in LS mean[A,C,D,G] (95% CI) p-value	14.7 (10.8, 18.7) p < 0.0001		13.2 (8.2, 18.2) p < 0.0001		7.6 (2.1, 13.1) p = 0.0070	

[A] Difference is aflibercept 2 mg Q4 weeks minus control

[B] Difference and confidence interval (CI) are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)

[C] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LOCF: Last Observation Carried Forward
SD: Standard deviation
LS: Least square means derived from ANCOVA

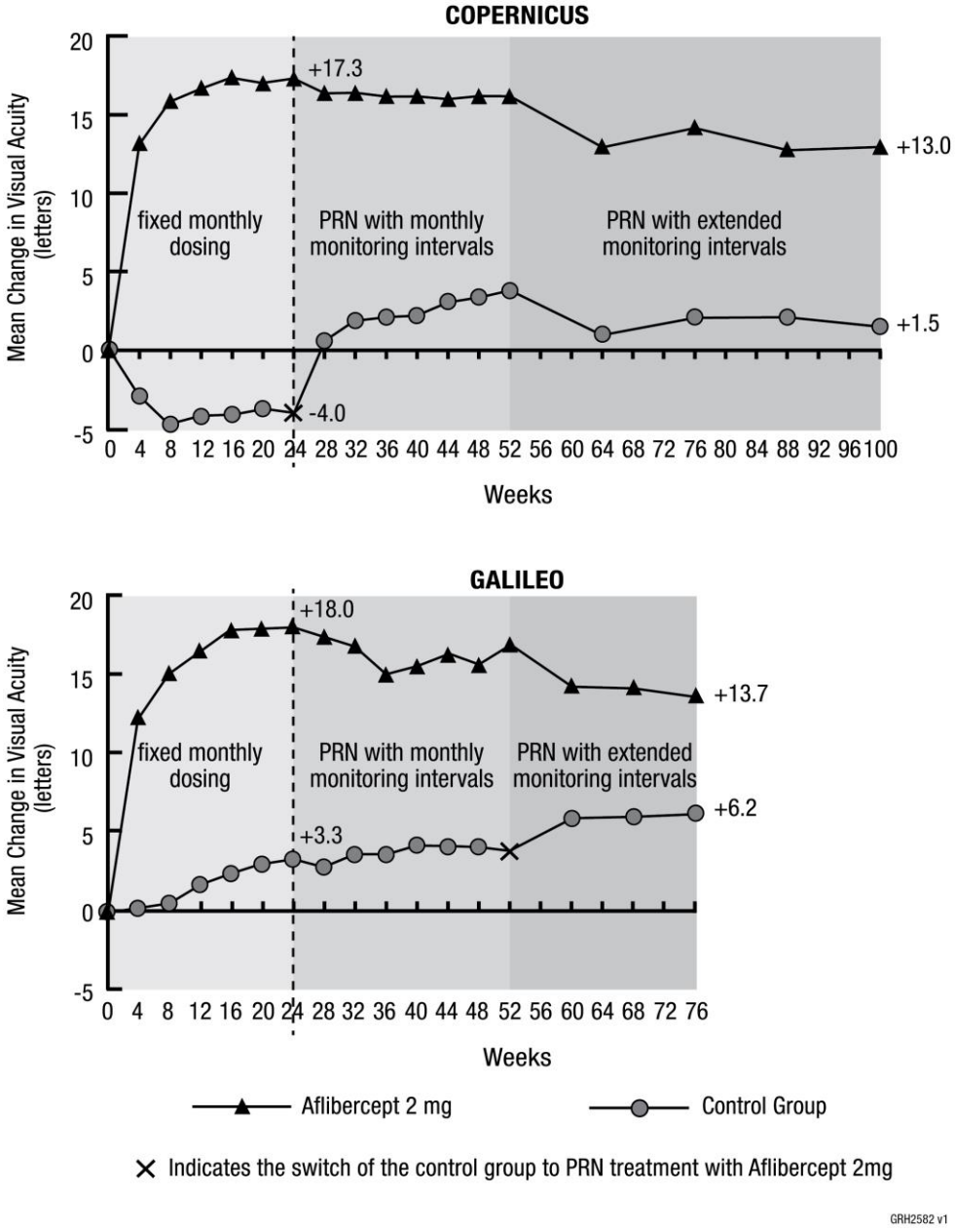
[D] LS mean difference and confidence interval based on an ANCOVA model with factors treatment group, region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)

[E] In COPERNICUS study, control group patients could receive aflibercept on an as-needed basis as frequently as every 4 weeks during Week 24 to Week 52; patients had visits every 4 weeks

[F] In COPERNICUS study, both control group and aflibercept 2 mg patients received aflibercept 2 mg on an as-needed basis as frequently as every 4 weeks starting from Week 52 to Week 96; patients had mandatory quarterly visits but may have been seen as frequently as every 4 weeks if necessary

[G] In GALILEO study, both control group and aflibercept 2 mg patients received aflibercept 2 mg on an as-needed basis every 8 weeks starting from Week 52 to Week 68; patients had mandatory visits every 8 weeks

Figure 2. Mean Change from Baseline to Week 76/100 in Visual Acuity by Treatment Group for the COPERNICUS and GALILEO Studies (Full Analysis Set)



The proportion of perfused patients in the aflibercept group at baseline was 67.5% (n = 77) in the COPERNICUS study and 86.4% (n = 89) in the GALILEO study. In the 2 studies, the percent of perfused patients was maintained or increased through Week 76/100.

The beneficial effect of aflibercept treatment on visual function was similar in the baseline subgroupsof perfused and non-perfused patients.

In combined data analysis of the COPERNICUS and GALILEO studies, aflibercept demonstrated clinically meaningful changes from baseline in pre-specified secondary efficacy endpoint National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The magnitude of these changes was similar to that seen in published studies, which corresponded to a 15-letter gain in Best Corrected Visual Acuity (BCVA).

In the extension phase of the studies, efficacy was largely maintained through the last assessmentat

Week 100 for COPERNICUS and Week 76 for GALILEO. After the initial monthly dosing phase, patients randomized to start on aflibercept received an average of 6.0 doses from Week 24 - 100 in COPERNICUS and 3.7 doses from Week 24-76 in GALILEO.

Treatment effects in all evaluable subgroups (e.g. age, gender, race, baseline visual acuity, retinal perfusion status, CRVO duration) in each study were in general consistent with the results in the overall populations.

Geriatric patients
In the CRVO studies, approximately 52% (112/217) of the patients randomized to treatment with aflibercept were 65 years of age or older, and approximately 18% (38/217) were 75 years of age or older.

Macular oedema secondary to branch retinal vein occlusion (BRVO)
The safety and efficacy of aflibercept were assessed in a randomized, multi-centre, double-masked, active-controlled study in patients with macular oedema secondary to BRVO which included Hemi-Retinal Vein Occlusion. A total of 181 patients were treated and evaluable for efficacy (91 with aflibercept) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg aflibercept administered every 4 weeks (2Q4) with a total of 6 injections or laser photocoagulation administered at baseline (laser control group). Patients in the laser control group could receive additional laser photocoagulation (called “rescue laser treatment”) beginning at Week 12, if at least one pre-specified rescue treatment criterion was met. The minimum interval between laser photocoagulation treatments was 12 weeks. After Week 24, patients in the aflibercept group received 2 mg every 8 weeks through Week 48, and patients in the control group could receive treatment with aflibercept 2 mg, if at least one pre-specified rescue criterion was met. Aflibercept rescue treatment consisted of a fixed regimen with 2 mg aflibercept administered every 4 weeks (2Q4) for 3 treatment intervals followed by intravitreal injections every 8 weeks through Week 48.

Patient ages ranged from 42 to 94 years with a mean of 65 years.

In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at Week 24 compared to baseline. At Week 24, the aflibercept group was superior to laser control for the primary endpoint.

Change in visual acuity at Week 24 compared to baseline was a secondary efficacy variable in the VIBRANT study. The difference between treatment groups was statistically significant in favor of aflibercept. The course of visual improvement was rapid and maximal improvement was achieved at Week 12 with subsequent stabilization of the effect on visual acuity and central retinal thickness until Week 24.

Visual and anatomic outcomes were maintained with administration of aflibercept 2 mg every 8 weeks beginning at Week 24 in the aflibercept treatment group.

In the laser group 67 patients received rescue treatment with aflibercept beginning at Week 24. In this treatment group visual acuity improved by about 5 letters from Week 24 to 52.

Detailed results from the analysis of the VIBRANT study are shown in Table and Figure below.

Table 12. Efficacy Outcomes at Week 24 and Week 52 (Full Analysis Set with LOCF) in VIBRANT Study

Efficacy Outcomes	VIBRANT			
	24 Weeks		52 Weeks	
	Aflibercept 2 mg Q4 (N = 91)	Active Control (laser) (N = 90)	Aflibercept 2 mg Q8 (N = 91)[D]	Active Control[E] (N = 90)
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	52.7%	26.7%	57.1%	41.1%
Weighted Difference[A,B] (%) (95% CI) p-value	26.6% (13.0, 40.1) p = 0.0003		16.2% (2.0, 30.5) p = 0.0296	
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	17.0 (11.9)	6.9 (12.9)	17.1 (13.1)	12.2 (11.9)
Difference in LS mean[A,C] (95% CI) p-value	10.5 (7.1, 14.0) p < 0.0001		5.2 (1.7, 8.7) p = 0.0035	

[A] Difference is aflibercept 2 mg Q4 weeks minus Laser Control

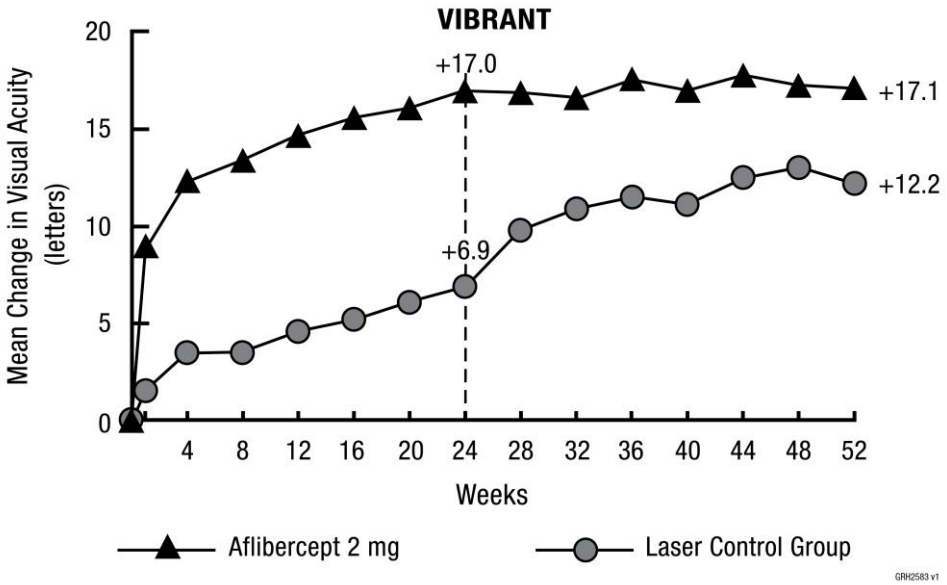
[B] Difference and 95% CI are calculated using Mantel-Haenszel weighting scheme adjusted for region (North America vs. Japan) and baseline BCVA category (> 20/200 and ≤ 20/200)

[C] LS mean difference and 95% CI based on an ANCOVA model with treatment group, baseline BCVA category (> 20/200 and ≤ 20/200) and region (North America vs. Japan) as fixed effects, and baseline BCVA as covariate

[D] From Week 24 on the treatment interval in the aflibercept treatment group was extended for all subjects from 4 weeks to 8 weeks through Week 48

[E] Beginning at Week 24 subjects in the Laser Group could receive rescue treatment with aflibercept, if they met at least one pre-specified eligibility criterion. At total of 67 subjects in this group received aflibercept rescue treatment. The fixed regimen for aflibercept rescue was three times aflibercept 2 mg every 4 weeks followed by injections every 8 weeks

Figure 3. Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 52 in VIBRANT Study (Full Analysis Set, LOCF)



The proportion of perfused patients in the aflibercept group at baseline was 60.4% (n = 55) in the aflibercept group. At Week 24 this proportion increased 80.2% (n = 65) and was sustained at Week 52 (77.9%, n = 67). The proportion of perfused patients that started on grid laser photocoagulationwas 68.9% (n = 62) at baseline. Perfusion at the Week 24 primary endpoint in the laser group was67.1% (n = 55). Patients in the laser group were eligible for rescue treatment with aflibercept beginning at Week 24 according to pre-specified criteria. At Week 52, 78.0% (n = 64) were perfusedat this time. The beneficial effect of aflibercept treatment on visual function was similar in the baseline groups with perfused and non-perfused patients.

Treatment effects in evaluable subgroups (e.g., age, gender, and baseline retinal perfusion status)in the study were in general consistent with the results in the overall populations.

Geriatric patients
In the BRVO study, approximately 58% (53/91) of the patients randomized to treatment with aflibercept were 65 years of age or older, and approximately 23% (21/91) were 75 years of age or older.

Diabetic macular edema (DME)
The safety and efficacy of aflibercept were assessed in two randomized, multi-centre, double-masked, active-controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Of those, 576 were randomized to the aflibercept groups in two studies (VIVID^{DME} and VISTA^{DME}). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens:

1) Aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (Aflibercept 2Q8);
2) Aflibercept administered 2 mg every 4 weeks (Aflibercept 2Q4); and
3) Macular laser photocoagulation (active control).

Beginning at Week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept.

Patient ages ranged from 23 to 87 years with a mean of 63 years.

In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52 as measured by ETDRS letter score. Both aflibercept 2Q8 and aflibercept 2Q4 groups were shown to have efficacy that was statistically significantly superior to the laser control group. This benefit was maintained through Week 100.

Detailed results from the analysis of the VIVID[DME] and VISTA[DME] studies are shown in Tables and Figures below.

Table 13. Efficacy Outcomes at Week 52 and Week 100 (Full Analysis Set with LOCF) in VIVID[DME] Study

Efficacy Outcomes	VIVID[DME] 52 Weeks			VIVID[DME] 100 Weeks		
	Aflibercept 2 mg Q8[A)] (N = 135)	Aflibercept 2 mg Q4 (N = 136)	Active Control (laser) (N = 132)	Aflibercept 2 mg Q8[A)] (N = 135)	Aflibercept 2 mg Q4 (N = 136)	Active Control (laser) (N = 132)
Mean change in BCVA as measured by ETDRS[E)] letter score from Baseline (SD)	10.7 (9.32)	10.5 (9.55)	1.2 (10.65)	9.4 (10.53)	11.4 (11.21)	0.7 (11.77)
Difference in LS mean[B, C, E)] (97.5% CI) p-value	9.1 (6.3, 11.8) p < 0.0001	9.3 (6.5, 12.0) p < 0.0001		8.2 (5.2, 11.3) p < 0.0001	10.7 (7.6, 13.8) p < 0.0001	
Proportion of patients who gained at least 10 letters in BCVA[E)] from Baseline	53.3%	54.4%	25.8%	49.6%	58.1%	25.0%
Adjusted Difference[D, C,E)] (97.5% CI) p-value	27.5 (14.6, 40.5) p < 0.0001	28.7 (15.8, 41.6) p < 0.0001		24.6 (11.9, 37.3) p < 0.0001	33.1 (20.3, 45.9) p < 0.0001	
Proportion of patients who gained at least 15 letters in BCVA[E)] from Baseline	33.3%	32.4%	9.1%	31.1%	38.2%	12.1%
Adjusted Difference[D, C, E)] (97.5% CI) p-value	24.2% (13.5, 34.9) p < 0.0001	23.3% (12.6, 33.9) p < 0.0001		19.0% (8.0, 29.9) p = 0.0001	26.1% (14.8, 37.5) p < 0.0001	
Proportion of patients with an improvement of > = 2 steps on the ETDRS DRSS[E,F)] from Baseline	27.7%	33.3%	7.5%	32.6%	29.3%	8.2%

Efficacy Outcomes	VIVID^{DME} 52 Weeks			VIVID^{DME} 100 Weeks		
	Aflibercept 2 mg Q8$^{A)}$ (N = 135)	**Aflibercept 2 mg Q4 (N = 136)**	**Active Control (laser) (N = 132)**	**Aflibercept 2 mg Q8$^{A)}$ (N = 135)**	**Aflibercept 2 mg Q4 (N = 136)**	**Active Control (laser) (N = 132)**
Adjusted Difference$^{D,C)}$ (97.5% CI)	19.3 (6.6, 32.1)	25.8 (12.2, 39.4)		24.4 (11.3, 37.4)	20.9 (7.7, 34.2)	
p-value	p = 0.0006	p < 0.0001		p< 0.0001	p = 0.0004	
Mean change in NEI VFQ-25$^{E)}$ near activities subscale from Baseline	5.29 (19.058)	5.73 (18.932)	3.54 (16.768)	6.97 (19.280)	8.17 (20.193)	4.8 (15.433)
Difference in LS mean$^{B, C, E)}$ (97.5% CI)	-1.21 (-5.79, 3.37)	2.41 (-2.01, 6.82)		-0.74 (-5.25, 3.78)	3.64 (-0.70, 7.98)	
p-value	p = 0.5537	p = 0.2208		p = 0.7144	p = 0.0596	
Mean change in NEI VFQ-25$^{E)}$ distance activities subscale from Baseline	5.32 (18.475)	0.94 (16.487)	2.26 (15.923)	4.94 (20.253)	4.62 (17.618)	2.2 (16.684)
Difference in LS mean$^{B, C, E)}$ (97.5% CI)	-0.37 (-4.79, 4.05)	-1.19 (-5.29, 2.91)		-1.30 (-6.00, 3.39)	2.57 (-1.73, 6.86)	
p-value	p = 0.8498	p = 0.5138		p = 0.5325	p = 0.1792	

A) After treatment initiation with 5 monthly injections

B) LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, region (Europe/Australia vs. Japan) had been included as a factor for VIVID^{DME}, and history of MI and/or CVA as a factor for VISTA^{DME}

C) Difference is aflibercept group minus active control (laser) group

D) Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by region (Europe/Australia vs. Japan) for VIVID^{DME} and medical history of MI or CVA for VISTA^{DME}

E) BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LOCF: Last Observation Carried Forward
SD: Standard deviation
LS: Least square means derived from ANCOVA
DRSS: Diabetic Retinopathy Severity Scale
CI: Confidence interval
NEI VFQ-25: National Eye Institute Visual Function Questionnaire

F) VIVID^{DME}: based on the patients with gradable images at baseline and post-baseline (Week 52: n = 83 (aflibercept 2 mg Q8), n = 81 (aflibercept 2 mg Q4), n = 80 (laser) ; Week 100: n = 86 (aflibercept 2 mg Q8), n = 82 (aflibercept 2 mg Q4), n = 85 (laser))

Table 14. Efficacy Outcomes at Week 52 and Week 100 (Full Analysis Set with LOCF) in VISTA[DME] Study

Efficacy Outcomes	VISTA[DME]			VISTA[DME]		
	52 Weeks			100 Weeks		
	Aflibercept 2 mg Q8[A)] (N = 151)	Aflibercept 2 mg Q4 (N = 154)	Active Control (laser) (N = 154)	Aflibercept 2 mg Q8[A)] (N = 151)	Aflibercept 2 mg Q4 (N = 154)	Active Control (laser) (N = 154)
Mean change in BCVA as measured by ETDRS[E)] letter score from Baseline (SD)	10.7 (8.21)	12.5 (9.54)	0.2 (12.53)	11.1 (10.70)	11.5 (13.75)	0.9 (13.94)
Difference in LS mean[B, C, E)] (97.5% CI) p-value	10.45 (7.73, 13.17) p < 0.0001	12.19 (9.35, 15.04) p < 0.0001		10.14 (6.96, 13.32) p < 0.0001	10.64 (7.09, 14.18) p < 0.0001	
Proportion of patients who gained at least 10 letters in BCVA[E)] from Baseline	58.3%	64.9%	19.5%	59.6%	63.6%	27.9%
Adjusted Difference[D, C,E)] (97.5% CI) p-value	38.8 (27.2, 50.3) p < 0.0001	45.9 (34.7, 57.0) p < 0.0001		31.6 (19.5, 43.7) p < 0.0001	36.2 (24.3, 48.1) p < 0.0001	
Proportion of patients who gained at least 15 letters in BCVA[E)] from Baseline	31.1	41.6	7.8	33.1	38.3	13.0
Adjusted Difference[D, C, E)] (97.5% CI) p-value	23.3 (13.5, 33.1) p < 0.0001	34.2 (24.1, 44.4) p < 0.0001		20.1 (9.6, 30.6) p < 0.0001	25.8 (15.1, 36.6) p < 0.0001	
Proportion of patients with an improvement of >= 2 steps on the ETDRS DRSS[E)] from Baseline	29.1	33.8	14.3	37.1	37.0	15.6
Adjusted Difference[D,C)] (97.5% CI) p-value	14.9 (4.4, 25.4) p = 0.0017	19.7 (9.0, 30.4) p < 0.0001		21.5 (10.4, 32.5) p = 0.0001	21.7 (10.8, 32.6) p < 0.0001	

Efficacy Outcomes	VISTA[DME] 52 Weeks			VISTA[DME] 100 Weeks		
	Aflibercept 2 mg Q8[A)] (N = 151)	**Aflibercept 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**	**Aflibercept 2 mg Q8[A)] (N = 151)**	**Aflibercept 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**
Mean change in NEI VFQ-25[E)] near activities subscale from Baseline	9.4 (18.50)	9.0 (20.60)	5.4 (20.44)	12.8 (21.36)	10.9 (23.12)	8.1 (22.10)
Difference in LS mean[B, C, E)] (97.5% CI) p-value	4.36 (-0.21, 8.93) p = 0.0323	5.19 (0.33, 10.04) p = 0.0168		5.05 (0.12, 9.98) p = 0.0218	4.59 (-0.73, 9.90) p = 0.0529	
Mean change in NEI VFQ-25[E)] distance activities subscale from Baseline	7.3 (19.32)	8.6 (20.99)	6.7 (19.85)	8.5 (20.35)	10.9 (22.05)	6.1 (20.42)
Difference in LS mean[B, C, E)] (97.5% CI) p-value	1.65 (-2.83, 6.13) p = 0.4067	2.86 (-1.82, 7.54) p = 0.1702		3.57 (-0.96, 8.11) p = 0.0772	5.80 (0.97, 10.64) p = 0.0072	

[A)] After treatment initiation with 5 monthly injections

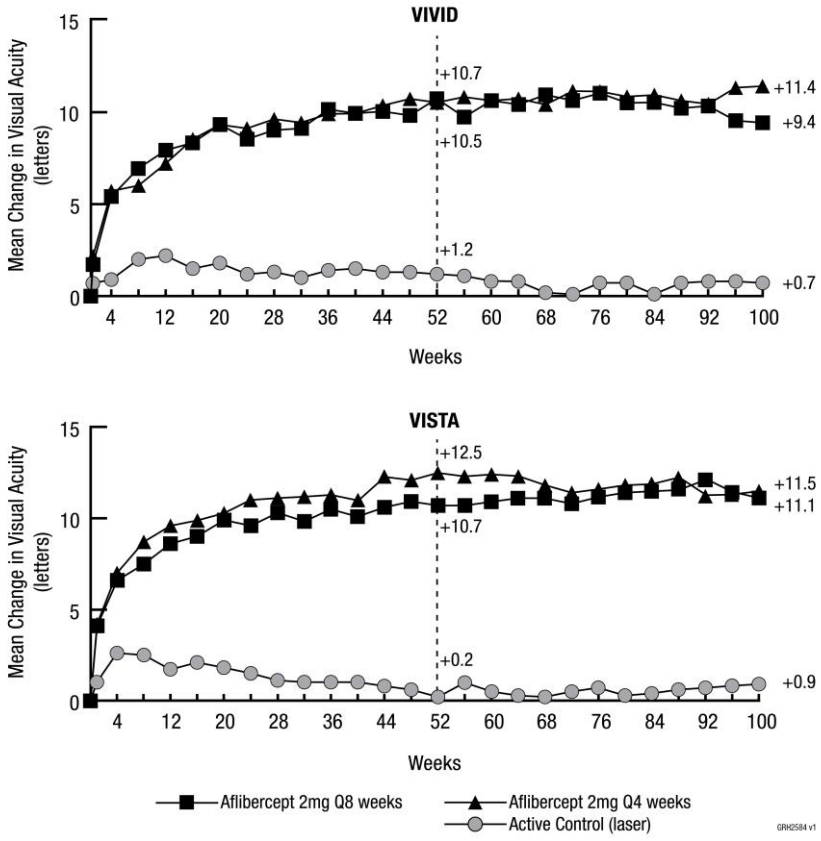
[B)] LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, region (Europe/Australia vs. Japan) had been included as a factor for VIVID[DME], and history of MI and/or CVA as a factor for VISTA[DME]

[C)] Difference is aflibercept group minus active control (laser) group

[D)] Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by region (Europe/Australia vs. Japan) for VIVID[DME] and medical history of MI or CVA for VISTA[DME]

[E)] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LOCF: Last Observation Carried Forward
SD: Standard deviation
LS: Least square means derived from ANCOVA
DRSS: Diabetic Retinopathy Severity Scale
CI: Confidence interval
NEI VFQ-25: National Eye Institute Visual Function Questionnaire

Figure 4. Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 100 in VIVID^{DME} and VISTA^{DME} Studies



At Week 52, 33.3% and 33.8% of 2Q4 patients, 27.7% and 29.1% of 2Q8 patients, and 7.5% and 14.3% of laser control patients in the VIVID^{DME} and VISTA^{DME} studies, respectively experienced an improvement in the severity of diabetic retinopathy, as measured by a ≥ 2 step improvement in the diabetic retinopathy severity scale (DRSS). This improvement was maintained through Week 100 (details see Table 14).

Treatment effects in evaluable subgroups (e.g. age, gender, race, baseline HbA1c, baseline visual acuity, prior anti-VEGF therapy) in each study and in the combined analysis were generally consistent with the results in the overall populations.

In the VIVID^{DME} and VISTA^{DME} studies, 36 (8.9%) and 197 (42.9%) 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 prior to study participation were similar to those seen in patients who were VEGF inhibitor naive prior to study participation.

Patients with bilateral disease were eligible to receive anti-VEGF treatment in their fellow eye. In the VISTA^{DME} study, 217 (70.7%) of aflibercept patients received bilateral aflibercept injections through Week 100; in the VIVID^{DME} study, 97 (35.8%) of aflibercept patients received a different anti-VEGF treatment in their fellow eye.

An independent comparative trial (DRCR.net Protocol T) utilised a flexible dosing regimen based on strict OCT and vision re-treatment criteria. In the aflibercept treatment group (n = 224) at Week 52, this treatment regimen resulted in patients receiving a mean of 9.2 injections, which is similar to the administered number of doses in the aflibercept 2Q8 group in VIVID^{DME} and VISTA^{DME}, while overall efficacy of the aflibercept treatment group in Protocol T was comparable to the aflibercept 2Q8 group in VIVID^{DME} and VISTA^{DME}. A 13.3 mean letter gain with 42% of patients gaining at least 15 letters

in vision from baseline was observed in Protocol T. Safety outcomes demonstrated that overall incidence of ocular and non-ocular adverse events (including ATEs) were comparable across all treatment groups in each of the studies and between the studies.

The VIOLET study compared three different dosing regimens of aflibercept 2 mg for treatment of DME after at least one year of treatment at fixed intervals, where treatment was initiated with 5 consecutive monthly doses followed by dosing every 2 months. At Week 52 and Week 100 of the study, i.e. second and third year of treatment, the mean changes in CRT were clinically similar for treat-and-extend (2T&E), *pro re nata* (2PRN) and 2Q8, respectively, -2.1, 2.2 and -18.8 microns at Week 52, and 2.3,-13.9 and -15.5 microns at Week 100.

VIOLET, a 100-week multicentre, randomized, open-label, active-controlled study in patients with DME compared three different dosing regimens of aflibercept 2 mg for treatment of DME after at least one year of treatment at fixed intervals, where treatment was initiated with 5 consecutives monthly doses followed by dosing every 2 months. The study evaluated non-inferiority of aflibercept 2 mg dosed according to a treat-and-extend regimen (2T&E where injections intervals were kept at a minimum of 8 weeks and gradually extended based on clinical and anatomical outcomes) and aflibercept 2 mg dosed as-needed (2PRN where patients were observed every 4 weeks and injected when needed based on clinical and anatomical outcomes), compared to aflibercept 2 mg dosed every 8 weeks (2Q8) for the second and third year of treatment.

The primary efficacy endpoint (change in BCVA from baseline to Week 52) was 0.5 ± 6.7 letters in the 2T&E group and 1.7 ± 6.8 letters in the 2PRN group compared to 0.4 ± 6.7 letters in the 2Q8 group, achieving statistical non-inferiority ($p < 0.0001$ for both comparisons; NI margin 4 letters). The changes in BCVA from baseline to Week 100 were consistent with the Week 52 results: -0.1 ± 9.1 letters in the 2T&E group and 1.8 ± 9.0 letters in the 2PRN group compared to 0.1 ± 7.2 letters in the 2Q8 group. The mean number of injections over 100 weeks were 12.3, 10.0 and 11.5 for 2Q8fix, 2T&E and 2PRN, respectively.

Ocular and systemic safety profiles in all 3 treatment groups were similar to those observed in the pivotal studies VIVID and VISTA.

In the T&E group, the increments and decrements for the injection intervals were at the investigator's discretion: increments of 2 weeks were recommended in the study.

Geriatric patients
In the DME phase III studies, approximately 47% (268/576) of the patients randomized to treatment with aflibercept were 65 years of age or older, and approximately 9% (52/576) were 75 years of age or older.

MYOPIC choroidal neovascularization (myopic CNV)
The safety and efficacy of aflibercept were assessed in a randomized, multi-centre, double-masked, sham-controlled study in patients with myopic choroidal neovascularization (myopic CNV). A total of 121 patients were treated and evaluable for efficacy (90 with aflibercept). Patients were randomly assigned in a 3:1 ratio to either 2 mg aflibercept administered once at study start (with additional injections given in case of disease persistence or reoccurrence) or the control group receiving sham injections. In total 6 injections were possible until the Week 24 primary endpoint assessment.

After the first 6 months, patients initially randomized to sham were eligible to receive the first dose of aflibercept at Week 24. Following this, patients in this former sham arm but also patients in the arm initially randomized to active treatment continued to be eligible for additional injections in case of disease persistence or recurrence.

Patient ages ranged from 27 to 83 years with a mean of 58 years.

The primary efficacy endpoint was the change in visual acuity at Week 24 compared to baseline.

The confirmatory secondary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at Week 24 compared to baseline.

The difference between treatment groups was statistically significant in favor of aflibercept for the primary and confirmatory secondary efficacy endpoints at Week 24. Differences for both endpoints were maintained through Week 48.

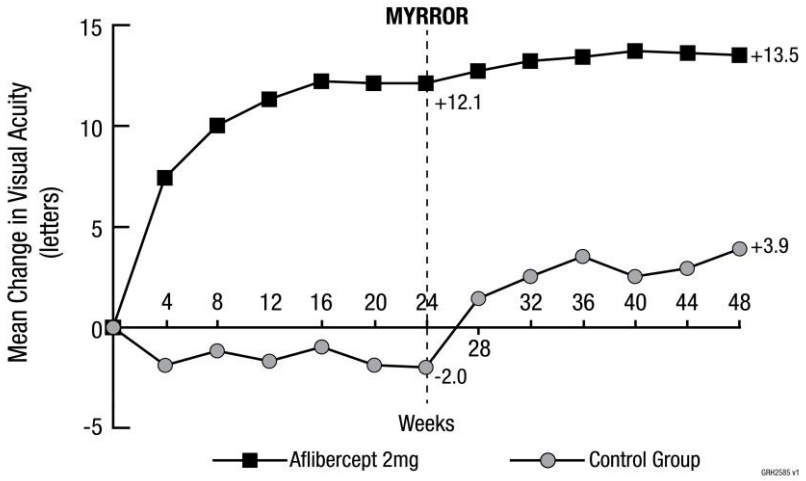
Detailed results from the analysis are shown in Table and Figure below.

Table 15. Efficacy Outcomes at Week 24 (Primary Analysis) and Week 48 in MYRROR Study (Full Analysis Set with LOCF[A)])

Efficacy Outcomes	MYRROR			
	24 Weeks		48 Weeks	
	Aflibercept 2 mg[B)] (N = 90)	Sham (N = 31)	Aflibercept 2 mg[C)] (N = 90)	Sham/Aflibercept 2 mg[D)] (N = 31)
Mean change in BCVA letter score as measured by ETDRS from baseline (SD)[E)]	12.1 (8.3)	-2.0 (9.7)	13.5 (8.8)	3.9 (14.3)
Difference in LS mean[F,G,H,I)] (95% CI) p-value	14.1 (10.8, 17.4) p < 0.0001		9.5 (5.4, 13.7) p< 0.0001	
Proportion of patients who gained at least 15 letters in BCVA[E)] from baseline	38.9%	9.7%	50.0%	29.0%
Weighted difference[F, H, J)] (95% CI) p-value	29.2% (14.4, 44.0) p = 0.0001		21.0% (1.9, 40.1) p = 0.0308	

[A)] LOCF: Last Observation Carried Forward
[B)] Aflibercept 2 mg administered at baseline and potentially every 4 weeks in case of disease persistence or recurrence
[C)] Aflibercept 2 mg administered from Week 24 through Week 44 potentially every 4 weeks in case of disease persistence or recurrence
[D)] Mandatory injection of aflibercept 2 mg at Week 24, thereafter potentially every 4 weeks in case of disease persistence or recurrence through Week 44
[E)] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
SD: Standard Deviation
[F)] Difference is aflibercept 2 mg minus sham at Week 24 and aflibercept 2 mg minus sham/aflibercept 2 mg at Week 48
[G)] LS mean: Least square means derived from ANCOVA model
[H)] CI: Confidence Interval
[I)] LS mean difference and 95% CI based on an ANCOVA model with treatment group and country (country designations) as fixed effects, and baseline BCVA as covariant
[J)] Difference and 95% CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for country (country designations)

Figure 5. Mean Change from Baseline to Week 48 in Visual Acuity by Treatment Group for the MYRROR Study (Full Analysis Set, LOCF)



Treatment effects in all evaluable subgroups were in general consistent with the results in the overall populations.

Geriatric patients
In the myopic CNV study, approximately 36% (33/91) of the patients randomized to treatment with aflibercept were 65 years of age or older, and approximately 10% (9/91) were 75 years of age or older.

Comparative study between PAVBLU and Eylea® (Study 20170542)
Study 20170542 was designed as a randomized, double-masked, active-controlled comparative study in adult subjects with neovascular (wet) AMD. The primary objective of Study 20170542 was to assess the efficacy of PAVBLU compared to aflibercept (EU). Study subjects were dosed based on the product labeling for Eylea® (aflibercept) for treatment of patients with neovascular (wet) AMD (Eylea® SmPC, 2023; Eylea® USPI, 2023).Through Week 16, 579 subjects (290 subjects in the PAVBLU treatment group and 289 subjects in the aflibercept [EU] treatment group) were randomized (stratified by geographic region [East Asia, Europe, North America] and disease severity [best corrected visual acuity (BCVA) < 64 letters vs ≥ 64 letters) in a masked 1:1 ratio to receive 2 mg (0.05 mL) of either PAVBLU or aflibercept [EU] at a dose of 2 mg IVT injection every 4 weeks for the first 12 weeks, followed by 2 mg IVT injection every 8 weeks. Subjects who were unable to complete the Week 16 visit were discontinued from the study and asked to return to complete an EOS visit within 28 days of discontinuing the study. At Week 16, of the 542 (99.8%) subjects, 273 (100%) subjects continued to receive PAVBLU and 269 subjects in the initial aflibercept [EU] treatment group were re-randomized at a masked 1:1 ratio to either continue to receive aflibercept (EU) (136 [100%] subjects) or to transition and receive PAVBLU (133 [99.3%] subjects) by IVT injection every 8 weeks from Week 16 until Week 48. An EOS visit was conducted at Week 52 for subjects that completed the study.

The primary efficacy endpoint was a change from baseline in BCVA as measured by ETDRS letter score at Week 8. The clinical similarity of the primary efficacy endpoint was determined by assessing changes in visual acuity (the measure of the ability of the eye to distinguish shapes and the details of objects at a given distance) using the ETDRS chart (a chart with a series of 5 letters of equal difficulty on each row with standardized spacing between letters and rows, for a total of 14 lines [70 letters]). Published studies have shown that repeated monthly IVT dosing of Eylea® (aflibercept) over 8 weeks demonstrated significant reductions in retinal thickness and improvements in visual acuity (Brown et al, 2011; Heier et al, 2012). At Week 8, the observed mean (SD) change from baseline in BCVA as measured by ETDRS letter score was 6.4 (8.18) in the PAVBLU treatment group and 6.5 (8.97) in the aflibercept (EU) treatment group (Table 16).

Table 16. Analysis of Change from Baseline in BCVA at Week 8 (as Observed) (Full Analysis Set)

Visit Statistic	PAVBLU (N = 288) BCVA	PAVBLU (N = 288) Change From Baseline	Aflibercept (EU) (N = 288) BCVA	Aflibercept (EU) (N = 288) Change From Baseline
Week 8				
n	279	279	281	281
Mean (SD)	65.4 (12.36)	6.4 (8.18)	64.2 (13.09)	6.5 (8.97)
95% CI of mean	(63.9, 66.9)	(5.4, 7.4)	(62.7, 65.7)	(5.4, 7.5)
Difference between means[a]		0.1		
90% CI[a]		(-1.1, 1.3)		

BCVA = best corrected visual acuity; EU = European Union
[a] Estimated using ANCOVA model adjusted for the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA as covariates.

The point estimate of the LS mean difference in change from baseline in BCVA as measured by ETDRS letter score at Week 8 between the treatment groups was 0.1 with a 2-sided 90% CI of (-1.1, 1.3) (Table 16). The 90% CI was within the pre-specified similarity margin of (-3, 3), thus supporting a demonstration of no clinically meaningful differences between PAVBLU and aflibercept (EU).

Sensitivity analyses were performed to assess the robustness of the primary efficacy analysis result. The analysis of covariance (ANCOVA) described above for the primary efficacy endpoint was repeated using the per-protocol (PP) analysis set based on observed cases, and using the FAS based on last observation carried forward imputation. In addition, a mixed model repeated-measures analysis was performed for day 1 through Week 8 based on the FAS. The results of the sensitivity analyses are summarized in Table 17.

Table 17. Sensitivity Analysis of Change from Baseline in BCVA at Week 8

Population Statistic	PAVBLU BCVA	PAVBLU Change From Baseline	Aflibercept (EU) BCVA	Aflibercept (EU) Change From Baseline
PP analysis set, as observed: ANCOVA, n/N	265/265	265/265	265/265	265/265
Mean (SD)	65.4 (12.43)	6.4 (8.31)	64.5 (13.21)	6.7 (8.96)
Difference (PAVBLU – aflibercept [EU]) between means of change from baseline[a]		-0.1		
90% CI[a]		(-1.3, 1.1)		
95% CI[a]		(-1.6, 1.4)		
FAS with LOCF: ANCOVA, n/N	288/288	288/288	288/288	288/288
Mean (SD)	65.2 (12.39)	6.3 (8.22)	64.0 (13.12)	6.5 (9.02)
Difference (PAVBLU – aflibercept [EU]) between means of change from baseline[a]		0.0		

Population Statistic	PAVBLU BCVA	PAVBLU Change From Baseline	Aflibercept (EU) BCVA	Aflibercept (EU) Change From Baseline
90% CI[a]		(-1.2, 1.2)		
95% CI[a]		(-1.4, 1.4)		
FAS, repeated measures mixed model, n/N		279/288		281/288
LS Mean (SE)		6.4 (0.51)		6.4 (0.51)
Difference (PAVBLU – aflibercept [EU]) between LS means of change from baseline[b]		0.0		
90% CI[b]		(-1.1, 1.1)		
95% CI[b]		(-1.3, 1.3)		
FAS: stepwise selected covariates, n/N		279/288		281/288
Mean (SD)		6.4 (8.18)		6.5 (8.97)
Difference (PAVBLU – aflibercept [EU]) between means[c]		0.1		
90% CI[c]		(-1.1, 1.3)		
95% CI[c]		(-1.3, 1.5)		

BCVA = best corrected visual acuity; BMI = body mass index; CNV = choroidal neovascularization; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; EU = European Union; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; PP = per-protocol

[a] Estimated using ANCOVA model adjusted for the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA as covariates.

[b] Estimated using a repeated-measures mixed model including the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA, treatment, visit, and treatment-by-visit interaction in the model, with visit as a categorical variable. A compound symmetry covariance structure was used.

[c] Estimated using a final ANCOVA model adjusted for the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA. A general linear model for the mean difference in change from baseline in BVCA at Week 8 was fit using proc GLM with stepwise selection of the following covariates: age, age category, race, sex, ethnicity, height, weight, BMI, duration of disease, BCVA ETDRS letter score, CNV area size, CST, and fellow eye treated prior to Week 8. A covariate with p-value < 0.25 entered the model and a covariate with a p-value < 0.1 stayed in the model. The stratification factors of geographic region and baseline BCVA value were forced into the model.

An analysis using the FAS was conducted to explore the impact of other baseline covariates on BCVA change from baseline to Week 8 in addition to the stratification factors of region and baseline BCVA value. In addition, tipping point analyses were performed using the FAS to explore the sensitivity of the primary analysis results to violations in assumptions about missing data.

Table 18 displays the estimated mean difference and 90% CIs between the PAVBLU treatment group and the aflibercept (EU) treatment group for change from baseline in BCVA at Week 8, with varying assumptions regarding differences in each treatment group between outcomes in subjects with missing change from baseline in BCVA at Week 8 data and outcomes in subjects with data. The 90% CIs for all assumptions were within the margin of (3, 3) and were consistent with the results from the primary efficacy analysis. Therefore, the tipping point analysis supports the findings of the primary efficacy analyses in the study.

Table 18. Tipping Point Analysis of Change from Baseline in BCVA at Week 8 With 90% Confidence Interval (Full Analysis Set)

Shift in Change from Baseline BCVA PAVBLU	Shift in Change from Baseline BCVA (Aflibercept [EU])						
	-6	-4	-2	0	+2	+4	+6
-6	-0.0 (-1.2, 1.2)	-0.1 (-1.2, 1.1)	-0.1 (-1.3, 1.1)	-0.1 (-1.3, 1.0)	-0.2 (-1.4, 1.0)	-0.2 (-1.4, 0.9)	-0.3 (-1.5, 0.9)
-4	0.1 (-1.1, 1.2)	-0.0 (-1.2, 1.2)	-0.0 (-1.2, 1.1)	-0.1 (-1.3, 1.1)	-0.1 (-1.3, 1.0)	-0.2 (-1.3, 1.0)	-0.2 (-1.4, 0.9)
-2	0.1 (-1.1, 1.3)	0.1 (-1.1, 1.2)	0.0 (-1.1, 1.2)	-0.0 (-1.2, 1.1)	-0.1 (-1.2, 1.1)	-0.1 (-1.3, 1.1)	-0.2 (-1.3, 1.0)
0	0.2 (-1.0, 1.3)	0.1 (-1.0, 1.3)	0.1 (-1.1, 1.2)	0.0 (-1.1, 1.2)	-0.0 (-1.2, 1.2)	-0.1 (-1.2, 1.1)	-0.1 (-1.3, 1.1)
+2	0.2 (-0.9, 1.4)	0.2 (-1.0, 1.4)	0.1 (-1.0, 1.3)	0.1 (-1.1, 1.3)	0.1 (-1.1, 1.2)	0.0 (-1.2, 1.2)	-0.0 (-1.2, 1.1)
+4	0.3 (-0.9, 1.5)	0.3 (-0.9, 1.4)	0.2 (-1.0, 1.4)	0.2 (-1.0, 1.3)	0.1 (-1.0, 1.3)	0.1 (-1.1, 1.2)	0.0 (-1.1, 1.2)
+6	0.4 (-0.8, 1.5)	0.3 (-0.8, 1.5)	0.3 (-0.9, 1.4)	0.2 (-0.9, 1.4)	0.2 (-1.0, 1.3)	0.1 (-1.0, 1.3)	0.1 (-1.1, 1.3)

BCVA = best corrected visual acuity; EU = European Union

Note: Multiple imputation was performed using PROC MI generating 10 imputed datasets by imputing missing data assuming monotone missing pattern and that subjects with missing data have, on average, worse or better efficacy compared to those who have values. Each set of imputed datasets were analyzed using Proc GLM adjusting for stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA. Results from all imputed datasets were combined together and analyzed using proc MIANALYZE. Point estimates and 90% confidence intervals are presented for each scenario.

Subgroup analyses of the primary efficacy endpoint were repeated at each level of the following factors: geographic region (East Asia, Europe, North America), disease severity (baseline BCVA < 64 letters vs ≥ 64 letters), age (< 65 years vs ≥ 65 years), race (white vs non-white), gender, and subjects with fellow eye treated prior to Week 8 (yes vs no).

In general, results for all subgroups were consistent with results from the primary efficacy analysis.

The secondary endpoints for Study 20170542 were the proportion of subjects who maintained vision at Week 52, where a subject was classified as maintaining vision if he/she lost fewer than 15 letters in ETDRS letter score compared to baseline; change from baseline in BCVA as measured by ETDRS letter score over the study duration; proportion of subjects who gained at least 10 letters of vision at Week 8 and proportion of subjects who gained at least 15 letters of vision at Week 52 as compared to baseline; and change from baseline in CNV area as measured by fluorescein angiography (FA) and central subfield thickness (CST) as measured by spectral domain optical coherence tomography (SD OCT) over the study duration.

The endpoints of proportion of subjects who maintained vision at Week 52 and proportion of subjects who gained at least 15 letters of vision at Week 52 were included as endpoints in clinical studies to assess the efficacy of Eylea® (aflibercept) in neovascular (wet) AMD subjects (Eylea® USPI, 2023). Therefore, these endpoints were also assessed in Study 20170542. A change from baseline in BCVA as measured by ETDRS letter score over the study duration, proportion of subjects who gained at least 10 letters of vision at Week 8, change in CNV area and CST from baseline over study duration were

also included as secondary endpoints in Study 20170542.

Results for the analysis of proportion of subjects who maintained vision at Week 52 for the re-randomized subjects in the FAS with observed data are summarized in Table 19. The proportion of subjects who maintained vision was similar across the treatment groups at Week 52.

Table 19. Analysis of Proportion of Subjects Who Maintained Vision at Week 52 (as Observed) (Study 20170542 Full Analysis Set - Re-randomized)

Visit Statistic	PAVBLU/ PAVBLU (N = 273)	Aflibercept (EU)/ PAVBLU (N = 134)	Aflibercept (EU)/ Aflibercept (EU) (N = 136)
Week 52			
Subjects who maintained vision, n/N1 (%)	240/251 (95.6)	118/123 (95.9)	122/125 (97.6)
95% CI for proportion	(93.1, 98.2)	(92.5, 99.4)	(94.9, 100.0)
Risk difference (%)[a]	-2.1	-1.7	
90% CI for risk difference (%)[a]	(-5.2, 2.2)	(-6.2, 2.8)	
95% CI for risk difference (%)[a]	(-5.9, 3.4)	(-7.4, 4.0)	

BCVA = best corrected visual acuity; CSR = clinical study report; ETDRS = Early Treatment Diabetic Retinopathy Study; EU = European Union; n = the number of subjects meeting the criteria at Week 52; N1 = the number of subjects having available data at Week 52.

Note: A subject was classified as maintaining vision if he/she lost fewer than 15 letters in ETDRS letter score, assessed on the study eyes, compared to baseline.

Note: The risk differences for subjects who maintained vision and the corresponding CIs in the ABP 938/ABP 938 and aflibercept (EU)/ABP 938 columns are for ABP 938/ABP 938 minus aflibercept (EU)/aflibercept (EU) and aflibercept (EU)/ABP 938 minus aflibercept (EU)/aflibercept (EU), respectively.

[a] Estimated using the stratified Newcombe confidence limits (with Mantel-Haenszel weights) adjusting for stratification factors geographic region (East Asia, Europe, North America) and baseline BCVA (BCVA < 64 letters, BCVA ≥ 64 letters).

Results from the analyses of change from baseline in BCVA as measured by ETDRS letter score at Weeks 4, 8 and 16 for the FAS with observed data are summarized in Table 20. Change from baseline in BCVA was similar between the two treatment groups through Week 16.

Table 20. Analysis of Change from Baseline in BCVA by Visit – Through Week 16 (as Observed) (Study 20170542 Full Analysis Set)

	PAVBLU (N = 288)		Aflibercept (EU) (N = 288)	
Visit Statistic	BCVA	Change From Baseline	BCVA	Change From Baseline
Baseline				
n	288		288	
Mean (SD)	58.9 (10.68)		57.6 (11.74)	
Week 4				
n	285	285	282	282

Visit Statistic	PAVBLU (N = 288) BCVA	PAVBLU (N = 288) Change From Baseline	Aflibercept (EU) (N = 288) BCVA	Aflibercept (EU) (N = 288) Change From Baseline
Mean (SD)	63.8 (11.07)	5.0 (6.53)	62.0 (12.82)	4.5 (8.17)
Difference between means[a]		0.65		
90% CI[a]		(-0.4, 1.6)		
95% CI[a]		(-0.5, 1.8)		
Week 8				
n	279	279	281	281
Mean (SD)	65.4 (12.36)	6.4 (8.18)	64.2 (13.09)	6.5 (8.97)
Difference between means[a]		0.11		
90% CI[a]		(-1.1, 1.3)		
95% CI[a]		(-1.3, 1.5)		
Week 16				
n	281	281	277	277
Mean (SD)	65.8 (12.52)	6.8 (8.61)	64.6 (13.04)	7.2 (9.26)
Difference between means[a]		-0.17		
90% CI[a]		(-1.4, 1.1)		
95% CI[a]		(-1.6, 1.3)		

BCVA = best corrected visual acuity; CSR = clinical study report; EU = European Union

[a] Estimated using ANCOVA model with treatment, the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA as covariates.

Results from the analyses of change from baseline in BCVA as measured by ETDRS letter score over the entire study for re-randomized subjects in the FAS with observed data, with a change from baseline in BCVA, was similar between the treatment groups over the entire study.

Results from the analysis of proportion of subjects who gained ≥ 10 letters at Week 8 are summarized in Table 21. The proportion of subjects who gained ≥ 10 letters was similar between the two treatment groups at Week 8.

Table 21. Analysis of Proportion of Subjects Who Gained ≥ 10 Letters from Baseline at Week 8 (as Observed) (Study 20170542 Full Analysis Set)

Visit Statistic	PAVBLU (N = 288)	Aflibercept (EU) (N = 288)
Week 8		
Subjects who gained ≥ 10 letters from baseline, n/N1 (%)	82/279 (29.4)	92/281 (32.7)
95% CI for proportion	(24.1, 34.7)	(27.3, 38.2)
Risk difference (PAVBLU – aflibercept [EU]) (%)[a]	-3.4	

Visit Statistic	PAVBLU (N = 288)	Aflibercept (EU) (N = 288)
90% CI for risk difference (%)[a]	(-9.8, 3.1)	
95% CI for risk difference (%)[a]	(-11.0, 4.3)	

BCVA = best corrected visual acuity; CSR = clinical study report; EU = European Union; n = the number of subjects meeting the criteria at Week 8; N1 = the number of subjects having available data at Week 8

[a] Estimated using the stratified Newcombe confidence limits (with Mantel Haenszel weights) adjusting for stratification factors geographic region (East Asia, Europe, North America) and baseline BCVA (BCVA < 64 letters, BCVA ≥ 64 letters).

Results from the analysis of proportion of subjects who gained ≥ 15 letters at Week 52 are summarized in Table 22. The proportion of subjects who gained ≥ 15 letters was similar across the treatment groups at Week 52.

Table 22. Analysis of Proportion of Subjects Who Gained ≥ 15 Letters from Baseline at Week 52 (as Observed) (Study 20170542 Full Analysis Set - Re-randomized)

Visit Statistic	PAVBLU / PAVBLU (N = 273)	Aflibercept (EU)/ PAVBLU (N = 134)	Aflibercept (EU)/ Aflibercept (EU) (N = 136)
Week 52			
Subjects who gained ≥ 15 letters from baseline, n/N1 (%)	61/251 (24.3)	30/123 (24.4)	37/125 (29.6)
95% CI for proportion	(19.0, 29.6)	(16.8, 32.0)	(21.6, 37.6)
Risk difference (%)[a]	-5.3	-5.2	
90% CI for risk difference (%)[a]	(-13.6, 2.5)	(-14.4, 4.2)	
95% CI for risk difference (%)[a]	(-15.2, 4.0)	(-16.1, 6.0)	

BCVA = best corrected visual acuity; CSR = clinical study report; EU = European Union; n = the number of subjects meeting the criteria at Week 52; N1 = the number of subjects having available data at Week 52.

Note: The risk differences for subjects who gained ≥ 15 letters from baseline and the corresponding CIs in the PAVBLU/PAVBLU and aflibercept (EU)/PAVBLU columns are for PAVBLU/PAVBLU minus aflibercept (EU)/aflibercept (EU) and aflibercept (EU)/PAVBLU minus aflibercept (EU)/aflibercept (EU), respectively.

[a] Estimated using the stratified Newcombe confidence limits (with Mantel-Haenszel weights) adjusting for stratification factors geographic region (East Asia, Europe, North America) and baseline BCVA (BCVA < 64 letters, BCVA ≥ 64 letters).

Results from the analyses of change from baseline in CNV area size as measured by FA over the entire study for re randomized subjects in the FAS with observed data are summarized in Table 23. Change from baseline in CNV area size was similar between the treatment groups over the entire study.

Table 23. Analysis of Change from Baseline in CNV Area Size by Visit – Entire Study (as Observed) (Study 20170542 Full Analysis Set – Re-randomized)

	PAVBLU/PAVBLU (N = 273)		Aflibercept (EU)/PAVBLU (N = 134)		Aflibercept (EU)/Aflibercept (EU) (N = 136)	
Visit Statistic	**CNV Area Size (mm^2)**	**Change From Baseline**	**CNV Area Size (mm^2)**	**Change From Baseline**	**CNV Area Size (mm^2)**	**Change From Baseline**
Baseline						
n	273		134		136	
Mean (SD)	8.550 (5.7413)		9.167 (5.3255)		9.490 (5.0549)	
Week 8						
n	255	255	130	130	127	127
Mean (SD)	3.601 (4.3070)	-4.962 (5.1604)	4.004 (4.9665)	-5.169 (4.6943)	4.028 (4.1565)	-5.479 (5.1023)
Difference between means[a]		-0.048		0.105		
90% CI[a]		(-0.734, 0.638)		(-0.682, 0.891)		
95% CI[a]		(-0.866, 0.770)		(-0.833, 1.042)		
Week 16						
n	245	245	125	125	121	121
Mean (SD)	4.261 (5.1050)	-4.089 (5.3668)	4.492 (5.3074)	-4.751 (4.8814)	4.373 (4.8033)	-5.174 (5.2280)
Difference between means[a]		0.431		0.245		
90% CI[a]		(-0.367, 1.229)		(-0.667, 1.158)		
95% CI[a]		(-0.521, 1.383)		(-0.842, 1.333)		
Week 24						
n	242	242	118	118	119	119
Mean (SD)	4.072 (4.7763)	-4.323 (5.5972)	4.069 (5.4950)	-5.121 (5.2776)	4.335 (4.8535)	-5.308 (5.6238)
Difference between means[a]		0.197		-0.116		
90% CI[a]		(-0.625, 1.019)		(-1.065, 0.834)		
95% CI[a]		-0.783, 1.177)		(-1.248, 1.017)		

Visit Statistic	PAVBLU/PAVBLU (N = 273)		Aflibercept (EU)/PAVBLU (N = 134)		Aflibercept (EU)/Aflibercept (EU) (N = 136)	
	CNV Area Size (mm^2)	Change From Baseline	CNV Area Size (mm^2)	Change From Baseline	CNV Area Size (mm^2)	Change From Baseline
Week 52						
n	234	234	114	114	119	119
Mean (SD)	2.185 (3.7203)	-6.276 (6.2690)	2.764 (4.8173)	-6.434 (5.2445)	2.237 (3.6345)	-7.280 (5.8262)
Difference between means[a]		0.156		0.647		
90% CI[a]		(-0.561, 0.872)		(-0.186, 1.479)		
95% CI[a]		(-0.699, 1.010)		(-0.346, 1.639)		

BCVA = best corrected visual acuity; CNV = choroidal neovascularization; CSR = clinical study report; EU = European Union

Note: The differences between means of change from baseline and the corresponding CIs in the PAVBLU/PAVBLU and aflibercept (EU)/PAVBLU columns are for PAVBLU/PAVBLU minus aflibercept (EU)/aflibercept (EU) and aflibercept (EU)/PAVBLU minus aflibercept (EU)/aflibercept (EU), respectively.

[a] Estimated using ANCOVA model with treatment, baseline CNV measurement and the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA (BCVA < 64 letters, BCVA ≥ 64 letters) as covariates.

Results for the analyses of change from baseline in CST as measured by SD OCT over the entire study for re-randomized subjects in the FAS with observed data are summarized in Table 24. Change from baseline in CST was similar between the treatment groups over the entire study.

Table 24. Analysis of Change from Baseline in CST by Visit – Entire Study (as Observed) (Study 20170542 Full Analysis Set – Re-randomized)

Visit Statistic	PAVBLU/ PAVBLU (N = 273)		Aflibercept (EU)/ PAVBLU (N = 134)		Aflibercept (EU)/ Aflibercept (EU) (N = 136)	
	CST (mcm)	Change From Baseline	CST (mcm)	Change From Baseline	CST (mcm)	Change From Baseline
Baseline						
n	273		134		136	
Mean (SD)	439.4 (130.35)		458.8 (127.12)		440.3 (126.90)	
Week 4						
n	270	270	131	131	136	136
Mean (SD)	303.2 (81.16)	-136.5 (108.91)	310.5 (87.97)	-149.7 (107.01)	297.3 (74.54)	-143.1 (107.32)
Difference between means[a]		6.2		6.3		
90% CI[a]		(-5.6, 17.9)		(-7.4, 20.0)		

	PAVBLU/ PAVBLU (N = 273)		Aflibercept (EU)/ PAVBLU (N = 134)		Aflibercept (EU)/ Aflibercept (EU) (N = 136)	
Visit Statistic	CST (mcm)	Change From Baseline	CST (mcm)	Change From Baseline	CST (mcm)	Change From Baseline
95% CI[a]		(-7.9, 20.2)		(-10.1, 22.7)		
Week 8						
n	269	269	132	132	134	134
Mean (SD)	290.9 (82.60)	-145.9 (106.24)	291.7 (78.45)	-167.4 (118.52)	289.1 (78.48)	-146.3 (110.39)
Difference between means[a]		1.3		-5.1		
90% CI[a]		(-11.0, 13.5)		(-19.3, 9.1)		
95% CI[a]		(-13.3, 15.9)		(-22.1, 11.9)		
Week 16						
n	273	273	134	134	135	135
Mean (SD)	314.1 (102.79)	-125.2 (124.81)	315.6 (93.53)	-143.2 (121.93)	312.1 (89.88)	-127.3 (103.35)
Difference between means[a]		1.9		-3.8		
90% CI[a]		(-12.9, 16.6)		(-20.9, 13.3)		
95% CI[a]		(-15.7, 19.4)		(-24.2, 16.5)		
Week 24						
n	265	265	128	128	133	133
Mean (SD)	308.7 (96.69)	-130.8 (125.63)	310.4 (89.55)	-151.2 (118.21)	308.9 (88.18)	-131.7 (102.98)
Difference between means[a]		0.1		-6.0		
90% CI[a]		(-14.1, 14.4)		(-22.6, 10.6)		
95% CI[a]		(-16.9, 17.1)		(-25.8, 13.8)		
Week 32						
n	262	262	131	131	132	132
Mean (SD)	303.0 (94.48)	-133.2 (122.93)	304.7 (84.97)	-154.8 (114.22)	305.2 (87.02)	-134.1 (116.02)
Difference between means[a]		-1.2		-7.0		
90% CI[a]		(-15.3, 12.9)		(-23.3, 9.3)		
95% CI[a]		(-18.1, 15.6)		(-26.5, 12.5)		
Week 40						
n	257	257	124	124	130	130
Mean (SD)	300.6 (90.40)	-132.3 (113.25)	302.4 (78.49)	-155.7 (119.95)	301.7 (91.16)	-135.6 (119.07)

	PAVBLU/ PAVBLU (N = 273)		Aflibercept (EU)/ PAVBLU (N = 134)		Aflibercept (EU)/ Aflibercept (EU) (N = 136)	
Visit Statistic	**CST (mcm)**	**Change From Baseline**	**CST (mcm)**	**Change From Baseline**	**CST (mcm)**	**Change From Baseline**
Difference between means[a]		0.2		-6.5		
90% CI[a]		(-13.7, 14.1)		(-22.8, 9.8)		
95% CI[a]		(-16.4, 16.8)		(-25.9, 12.9)		
Week 48						
n	251	251	123	123	125	125
Mean (SD)	299.8 (94.71)	-132.3 (124.15)	299.7 (79.60)	-157.8 (121.23)	293.8 (80.58)	-141.1 (112.29)
Difference between means[a]		7.0		-0.5		
90% CI[a]		(-7.4, 21.4)		(-17.3, 16.2)		
95% CI[a]		(-10.2, 24.2)		(-20.5, 19.5)		
Week 52						
n	250	250	123	123	125	125
Mean (SD)	274.2 (64.35)	-157.1 (114.25)	280.3 (68.53)	-177.4 (122.22)	272.8 (65.06)	-159.1 (108.82)
Difference between means[a]		1.6		2.3		
90% CI[a]		(-9.3, 12.5)		(-10.5, 15.0)		
95% CI[a]		(-11.4, 14.7)		(-12.9, 17.4)		

BCVA = best corrected visual acuity; CST = central subfield thickness; CSR = clinical study report; EU = European Union

Note: The differences between means of change from baseline and the corresponding CIs in the PAVBLU/PAVBLU and aflibercept (EU)/PAVBLU columns are for PAVBLU/PAVBLU minus aflibercept (EU)/aflibercept (EU) and aflibercept (EU)/PAVBLU minus aflibercept (EU)/aflibercept (EU), respectively.

[a] Estimated using ANCOVA model with treatment, baseline CST measurement and the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA (BCVA < 64 letters, BCVA ≥ 64 letters) as covariates.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 80
Sucrose
α,α-Trehalose dihydrate
Water for injections

6.2 Incompatibilities

PAVBLU must not be mixed with other medicinal products.

6.3 Shelf life

Please refer to label.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.
The unopened blister in the outer carton or vial may be stored outside the refrigerator up to 30°C for up to 3 days. After opening the blister or vial, proceed under aseptic conditions.

6.5 Nature and contents of container

Pre-filled syringes:
Solution in a cyclic olefin polymer Luer-lock pre-filled syringe marked with a dosing line, with an elastomeric rubber plunger stopper, elastomeric rubber tip cap and polypropylene rigid shield. Each pre-filled syringe contains an extractable volume of at least 0.09 mL. Pack size of 1 pre-filled syringe.

Vials:
Solution in a vial (type I glass) with a stopper (elastomeric rubber). Each vial contains an extractable volume of at least 0.1 mL. Pack size of 1 vial.

6.6 Instructions for use / handling

Pre-filled syringe
The pre-filled syringe is for single use in one eye only. Extraction of multiple doses from a pre-filled syringe may increase the risk of contamination and subsequent infection.

Do not open the sterile pre-filled syringe blister outside the clean administration room. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

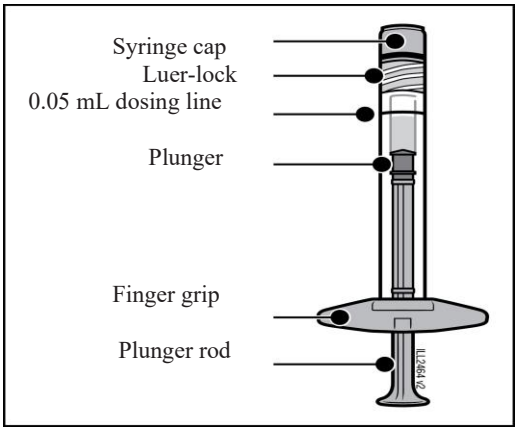
The pre-filled syringe contains more than the recommended dose of 2 mg aflibercept (equivalent to 0.05 mL). See following section “Instructions for use of pre-filled syringe”.

The solution should be inspected visually for any foreign particulate matter and/or discolouration or any variation in physical appearance prior to administration. In the event of either being observed, discard the medicinal product. Do not use if the packaging is open or damaged.

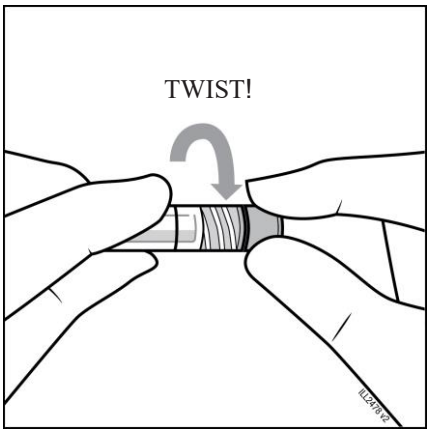
For the intravitreal injection, a 30 G × ½ inch injection needle should be used.

Instructions for use of pre-filled syringe:

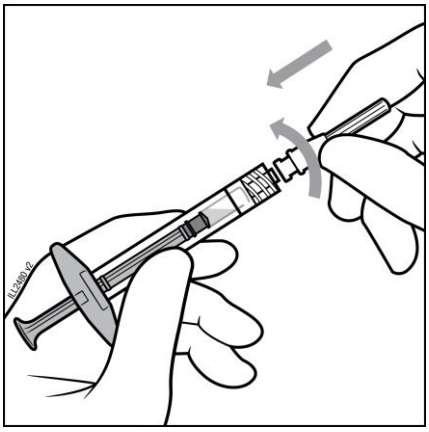
To prepare the pre-filled syringe for administration, follow all steps below.

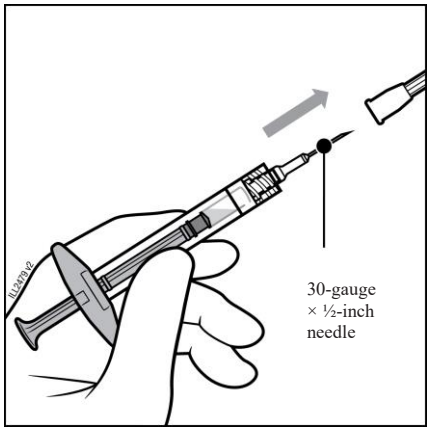


1. When ready to administer PAVBLU, open the carton and remove the sterilised blister. Carefully peel open the blister ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.
2. Using aseptic technique, remove the syringe from the sterilised blister.
3. To remove the syringe cap, hold the syringe in one hand while using the other hand to grasp the syringe cap with the thumb and fore finger. Please note: You should twist off (do not snap off) the syringe cap.



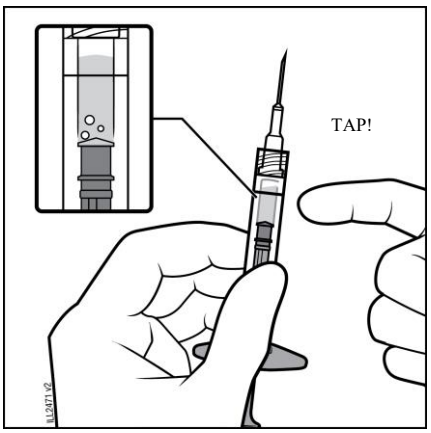
4. Using aseptic technique, firmly twist the injection needle onto the Luer-lock syringe tip.





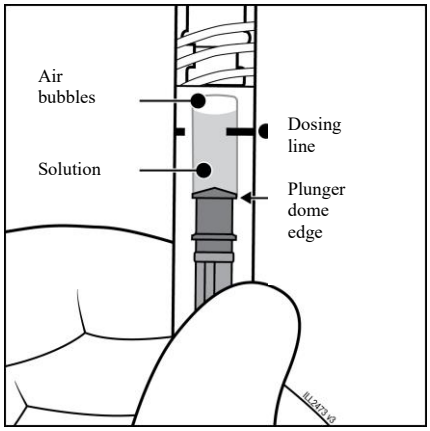
Note: When ready to administer PAVBLU, remove the plastic needle shield from the needle and place in a sharps container.

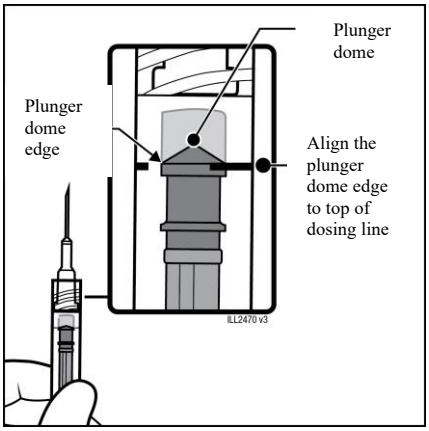
5. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



6. The excess volume must be discarded prior to administration. Eliminate all bubbles and **expel excess medicinal product by slowly depressing the plunger to align the base of the plunger dome (not the tip of the dome) with the dosing line on the syringe** (equivalent to 0.05 mL i.e. 2 mg aflibercept).

   Note: This accurate positioning of the plunger is very important, because incorrect plunger positioning can lead to delivering more or less than the labelled dose.





7. Inject while pressing the plunger carefully and with constant pressure. Do not apply additional pressure once the plunger has reached the bottom of the syringe. **Do not administer any residual solution observed in the syringe.**

8. The pre-filled syringe is for single use only. Extraction of multiple doses from a pre-filled syringe may increase the risk of contamination and subsequent infection.
   Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Vial

The vial is for single use in one eye only.

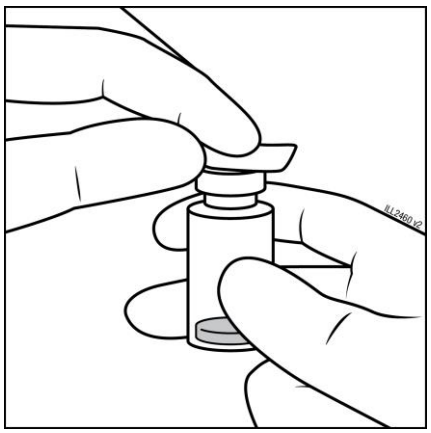
The vial contains more than the recommended dose of 2 mg aflibercept (equivalent to 0.05 mL). The excess volume must be discarded prior to administration.

The solution should be inspected visually for any foreign particulate matter and/or discolouration or any variation in physical appearance prior to administration. In the event of either being observed, discard the medicinal product. Do not use if the packaging is open or damaged.

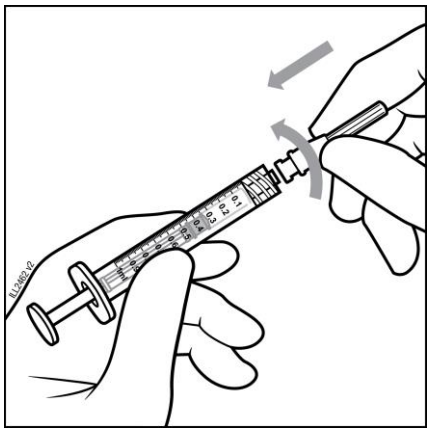
For the intravitreal injection, a 30 G × ½ inch injection needle should be used.

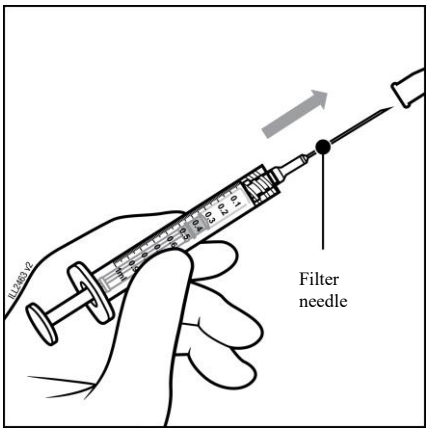
Instructions for use of vial:

1. Remove the plastic cap and disinfect the outer part of the rubber stopper of the vial.



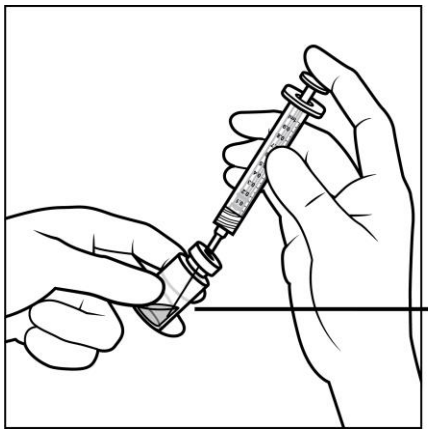
2. Attach a 18 G, 5-micron filter needle to a 1 mL sterile, Luer-lock syringe.

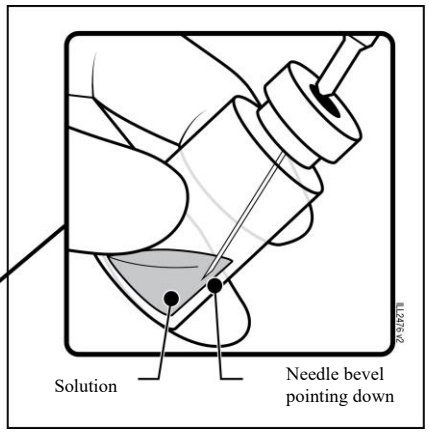




Note: When ready to withdraw PAVBLU, remove the plastic needle shield from the needle and place in a sharps container.

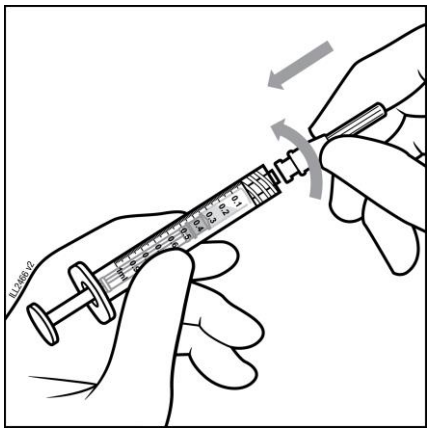
3. Push the filter needle into the centre of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.
4. Using aseptic technique withdraw all of the PAVBLU vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid.

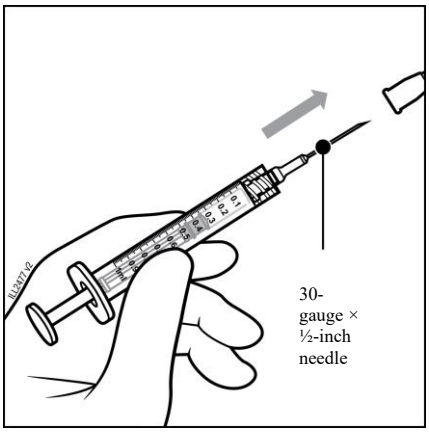




5. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
6. Remove the filter needle and properly dispose of it.
   Note: Filter needle is not to be used for intravitreal injection.

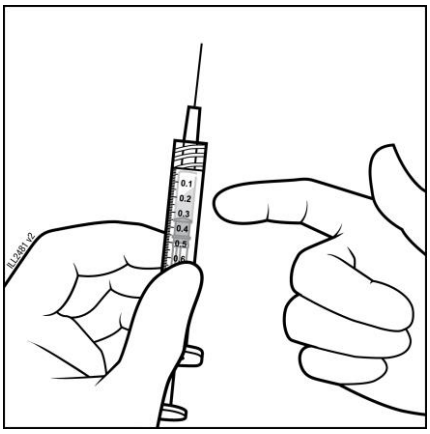
7. Using aseptic technique, firmly twist a 30 G × ½ inch injection needle onto the Luer-lock syringe tip.



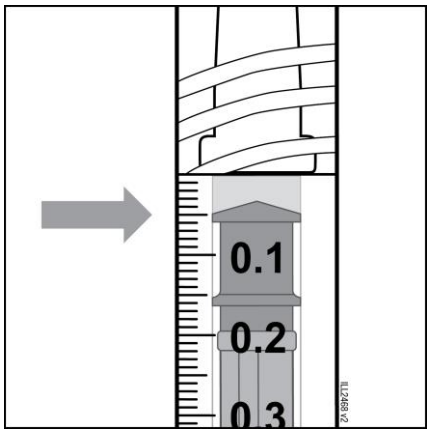


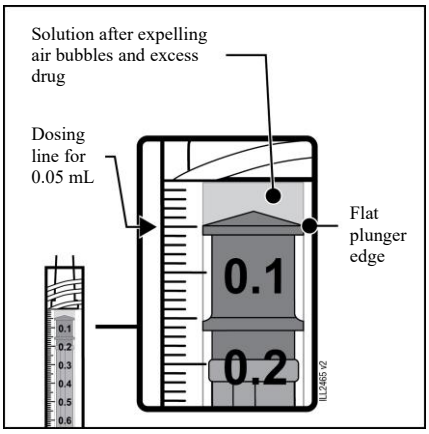
Note: When ready to administer PAVBLU, remove the plastic needle shield from the needle and place in a sharps container.

8. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



9. Eliminate all bubbles and expel excess medicinal product by slowly depressing the plunger so that the flat plunger edge aligns with the line that marks 0.05 mL on the syringe.





10. The vial is for single use only. Extraction of multiple doses from a single vial may increase the risk of contamination and subsequent infection.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PRODUCT REGISTRATION HOLDER:
Amgen Biopharmaceuticals Malaysia Sdn Bhd
Common Ground, 1 Powerhouse,
Horizon Penthouse, No. 1,
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47800 Petaling Jaya, Selangor, Malaysia.

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Feb 2026
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