Yesafili 40 mg/mL Solution for Injection in Pre-filled Syringe

NAME OF THE MEDICINAL PRODUCT

Yesafili 40 mg / ml Solution for Injection in Pre-filled Syringe.

Qualitative and Quantitative Composition

1 mL solution for injection contains 40 mg aflibercept*.
One pre-filled syringe contains an extractable volume of at least 0.09 mL, equivalent to at least 3.6 mg aflibercept. This provides a usable amount to deliver a single dose of 0.05 mL containing 2 mg aflibercept.

*Fusion protein consisting of portions of human VEGF (vascular endothelial growth factor) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

Excipients: Histidine, Histidine hydrochloride monohydrate, Polysorbate 20, Trehalose dihydrate, Water for injections.

Yesafili has been developed as Biosimilar Product to Eylea.

PHARMACEUTICAL FORM

Solution for intravitreal injection.
Sterile, clear, colourless to pale yellow, iso-osmotic solution, pH 6.2, preservative-free.

Yesafili is available in the following pack:
Pack size of 1 pre-filled syringe.

CLINICAL PARTICULARS

Therapeutic Indications

Yesafili 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 oedema (DME)
- Visual impairment due to myopic choroidal neovascularisation (myopic CNV)

Dosage and method of administration

Yesafili is for intravitreal injection.
It must only be administered by a qualified physician experienced in administering intravitreal injections.

Dosage regimen

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

Yesafili 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 Pharmacodynamic Properties).

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

Yesafili 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 Pharmacodynamic Properties).

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, Yesafili should be discontinued.

Myopic choroidal neovascularization (myopic CNV)
The recommended dose for Yesafili 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.

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

Paediatric

Paediatric population

Safety and efficacy have not been established in children and adolescents. There is no relevant use of Yesafili 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 Clinical Studies). There is limited experience in patients older than 75 years with DME.

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 mL 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 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 (equivalent to 50 microliters solution for injection). The excess volume should be expelled before injecting (see sections "Instruction for use / handling").

Injecting the entire volume of prefilled 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 dose line on the syringe (equivalent to 50 microlitres i.e. 2 mg aflibercept) (see sections “Overdose”, “Instruction for use/handling”).

After injection any unused product must be discarded.

For handling of the medicinal product before administration, see section Special Instructions for Use, Handling and Disposal

Contraindications

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

Special Warnings and Precautions for Use

Endophthalmitis

Intravitreal injections, including those with Yesafili, have been associated with endophthalmitis (see section "Undesirable effects"). Proper aseptic injection technique must always be used when administering Yesafili. 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 Yesafili (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 Yesafili 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.

Interaction with Other Medicinal Product

No formal drug interaction studies have been performed with Yesafili.

Pregnancy and lactation

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").

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

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 Yesafili.

Lactation

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

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

Undesirable effects

Summary of the safety profile

A total of 3102 patients treated with Yesafili constituted the safety population in the eighth 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 Yesafili 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 Yesafili) 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	Not known
Immune system disorders			Hypersensitivity***		
Eye disorders	Conjunctival haemorrhage, 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 oedema, Injection site haemorrhage, Punctate keratitis, Conjunctival hyperaemia, Ocular hyperaemia	Endophthalmitis**, Retinal detachment, Retinal tear, Uveitis, Iritis, Iridocyclitis, Lenticular opacities, Corneal epithelium defect, Anterior chamber flare, Corneal oedema	Cataract traumatic, Vitritis, Hypopyon	Scleritis****

* 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.
**** From post-marketing reporting

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.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity with Yesafili. Immunogenicity was evaluated in serum samples. The immunogenicity data reflects the percentage of patients whose test results were considered positive for antibodies to Yesafili 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 Yesafili was approximately 1% - 3% in all treatment groups. After dosing with Yesafili for up to 96 weeks (wet AMD), 76 weeks (CRVO), 52weeks (BRVO), 100 weeks (DME) or 48 weeks (myopic CNV) antibodies to Yesafili 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.

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 Special Instructions for Use, Handling and Disposal).

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties
Pharmacotherapeutic group: Ophthalmologicals / Antineovascularisation agents
ATC code: S01LA05

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1.

Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors and thereby can inhibit the binding and activation of these cognate VEGF receptors.

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 leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergize with VEGF-A in these processes and is also known to promote leucocyte infiltration and vascular inflammation. 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 (KD) for aflibercept binding to human VEGF- A165 is 0.5 pM and to human VEGF-A121 is 0.36 pM. The KD 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.

Clinical Studies

wet AMD

The safety and efficacy of aflibercept were assessed in two randomised, multi-centre, double-masked, active-controlled studies in patients with wet AMD (VIEW1 and VIEW2) with a total of 2412 patients treated and evaluable for efficacy (1817 with aflibercept).

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 initially randomised dose 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 year of the studies.

In both studies, the primary efficacy endpoint was the proportion of patients in the Per Protocol Set who maintained vision, i.e. losing fewer than 15 letters of visual acuity at week 52 from 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 Table 2 and Figure 1 below:

Table 2: Efficacy outcomes at week 52 (primary analysis) and week 96; combined data from the VIEW1 and VIEW2 studies[B])

Efficacy Outcome	**Aflibercept 2Q8** [E)] (aflibercept 2 mg every 8 weeks following 3 initial monthly doses) **(N=607)**		**Ranibizumab 0.5Q4** (ranibizumab 0.5 mg every 4 weeks) **(N=595)**	
	Week 52	Week 96	Week 52	Week 96
Mean number of injections from baseline	7.6	11.2	12.3	16.5
Mean number of injections from week 52 to 96		4.2		4.7
Proportion of patients with < 15 letters loss from baseline (PPS [A)])	95.33%[B)]	92.42%	94.42%[B)]	91.60%
Difference [C)] (95 % CI)[D)]	0.9% (- 1.7, 3.5)[F)]	0.8% (- 2.3, 3.8)[F)]		
Mean change in BCVA as measured by ETDRS [A)] letter score from baseline	8.40	7.62	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)		
Proportion of patients with ≥ 15 letters gain from baseline	30.97%	33.44%	32.44%	31.60%
Difference [C)] (95 % CI)[D)]	- 1.5% (- 6.8, 3.8)	1.8% (- 3.5, 7.1)		

[A)] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
LS: Least square means derived from ANCOVA
PPS: Per Protocol Set

[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 PPS

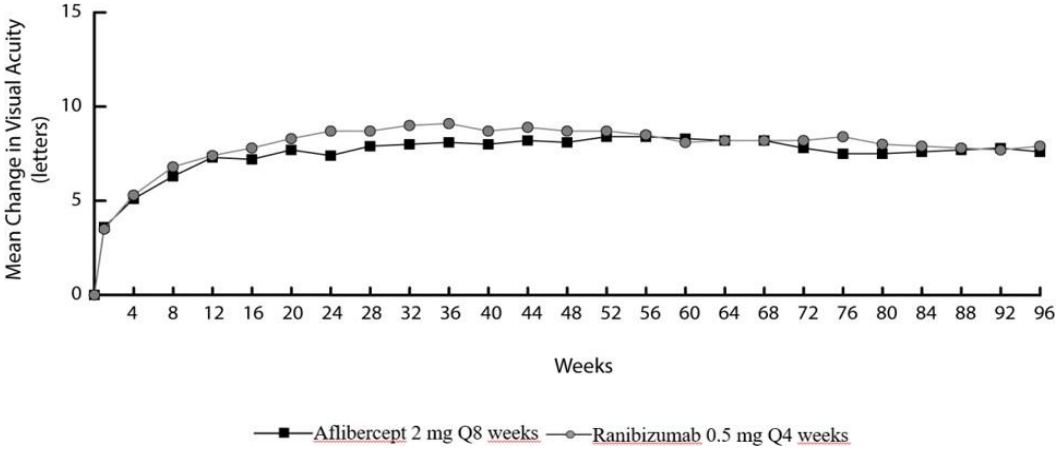
[C)] The difference is the value of the aflibercept group minus the value of the ranibizumab group. A positive value favours aflibercept

[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 VIEW1 and VIEW2, 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).

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, randomised, open-label study in 247 Japanese patients with treatment naïve 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 monthly doses of aflibercept 2 mg for 3 months, followed by one injection after a further 2-month interval. At week 16, patients were randomised 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 treatment 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, respectively. Over the 2-year treatment period patients received an average of 10.4 injections.

ARIES was a 104 -week multicentre, randomised, open-label, active-controlled study in 269 patients with treatment naïve 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 than15 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 VIEW 1 and VIEW 2.

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-center, double- masked, sham-controlled studies in patients with macular edema secondary to CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with aflibercept) in the two studies COPERNICUS and GALILEO. Patient ages ranged from 22 to 89 years with a mean of 64 years. 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 CRT 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 Table 3 and Figure 2 below.

Table 3: 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						GALILEO					
	24 Weeks		52 Weeks		100 Weeks		24 Weeks		52 Weeks		76 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)	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 with ≥ 15 letters gain from baseline	56%	12%	55%	30%	49.1%	23.3%	60%	22%	60%	32%	57.3%	29.4%
Weighted difference[A,B,E] (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		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[C] 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)	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,E] (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		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.

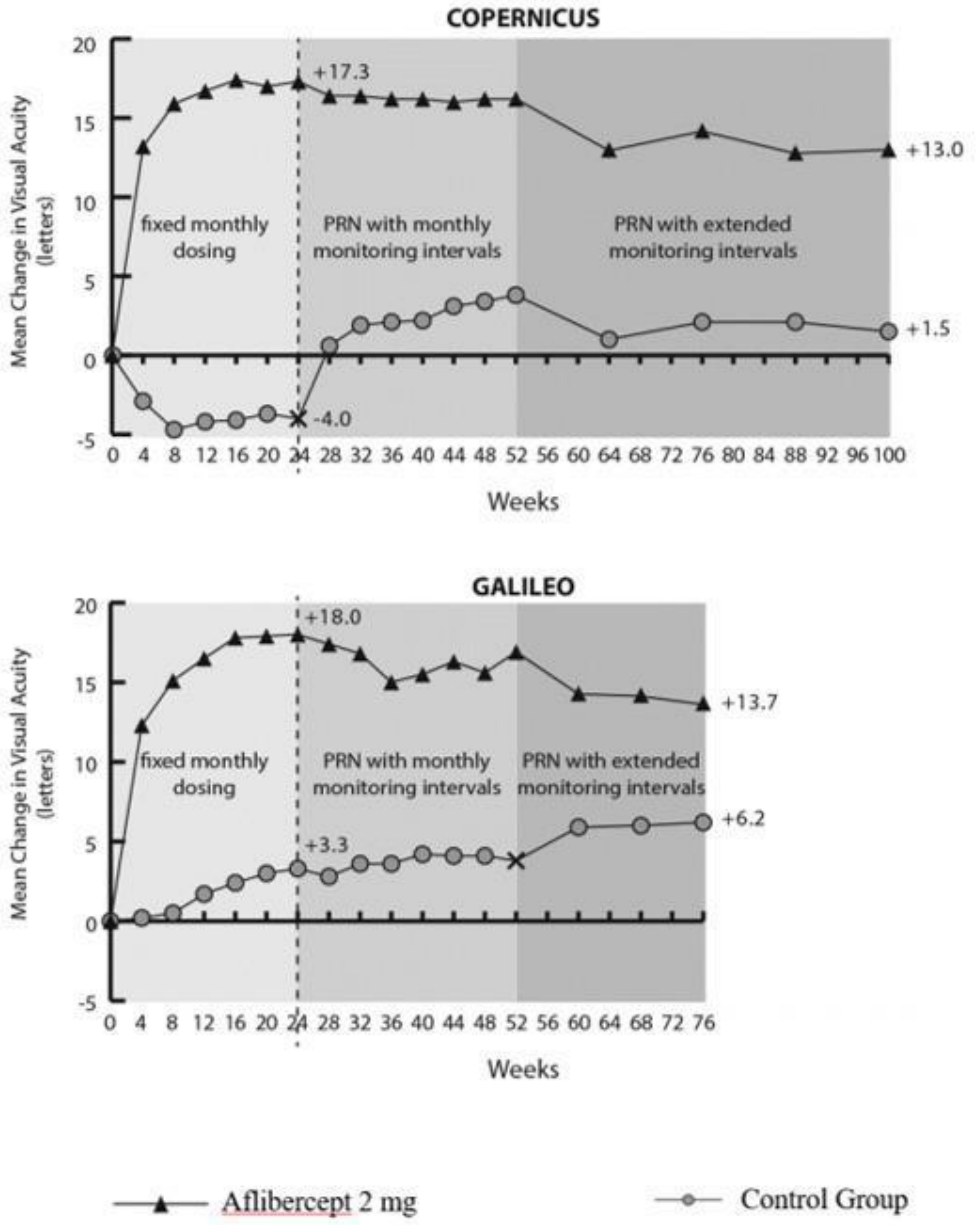


Figure 2: Mean change from baseline to week 76/100 in visual acuity by treatment group for the COPERNICUS and GALILEO studies (full analysis set)

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 subgroups of perfused and non-perfused patients.

In combined data analysis of GALILEO and COPERNICUS, 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 assessment at 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 randomised, multi-centre, double-masked, active-controlled study in patients with macular oedema secondary to BRVO (VIBRANT) which included Hemi-Retinal Vein Occlusion. A total of 181 patients were treated and evaluable for efficacy (91 with aflibercept). 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 2mg, if at least one pre-specified rescue criterion was met. Aflibercept rescue treatment consisted of a fixed regimen with 2mg 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 (Active Control/ aflibercept 2 mg group), which resulted in improvement of visual acuity by about 5 letters from week 24 to 52.

Detailed results from the analysis of the VIBRANT study are shown in Table 4 and Figure 3 below.

Table 4: 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 (laser)/aflibercept 2 mg[E] (N = 90)
Proportion of patients with ≥ 15 letters gain 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.

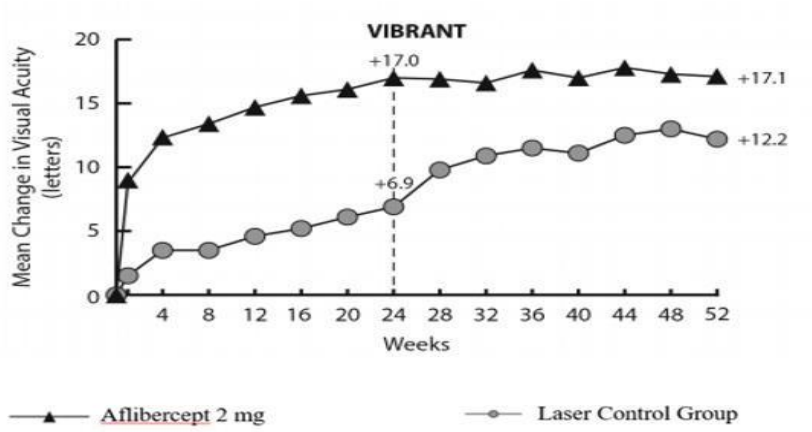


Figure 3: Mean change in BCVA as measured by ETDRS letter score from baseline to week 52 in VIBRANT Study (Full Analysis Set, LOCF)

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 to 80.2 % (n = 65) and was sustained at week 52 (77.9%, n=67). The proportion of perfused patients that started on grid laser photocoagulation was 68.9% (n = 62) at baseline. Perfusion at the week 24 primary endpoint in the laser group was 67.1% (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 perfused at 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 oedema (DME)
The safety and efficacy of aflibercept were assessed in two randomized, multi-center, 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 studies, 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 control 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 and both aflibercept 2Q8 and aflibercept 2Q4 groups demonstrated statistical significance and were superior to the 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 Table 5 and Figure 4 below.

Table 5: Efficacy outcomes at week 52 and week 100 (full analysis set with LOCF) in VIVID[DME] and VISTA[DME] studies

Efficacy Outcomes	VIVID[DME]						VISTA[DME]					
	52 Weeks			100 Weeks			52 Weeks			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)	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	10.7	10.5	1.2	9.4	11.4	0.7	10.7	12.5	0.2	11.1	11.5	0.9
Difference in LS mean [B,C,E] (97.5% CI)	9.1 (6.3, 11.8)	9.3 (6.5, 12.0)		8.2 (5.2, 11.3)	10.7 (7.6, 13.8)		10.45 (7.7, 13.2)	12.19 (9.4, 15.0)		10.1 (7.0, 13.3)	10.6 (7.1, 14.2)	
Proportion of patients with ≥ 15 letters gain from Baseline	33%	32%	9%	31.1%	38.2%	12.1%	31%	42%	8%	33.1%	38.3%	13.0%
Adjusted Difference [D,C,E] (97.5% CI)	24% (13.5, 34.9)	23% (12.6, 33.9)		19.0% (8.0, 29.9)	26.1% (14.8, 37.5)		23% (13.5, 33.1)	34% (24.1, 44.4)		20.1% (9.6, 30.6)	25.8% (15.1, 36.6)	

[A] After treatment initiation with 5 monthly injections

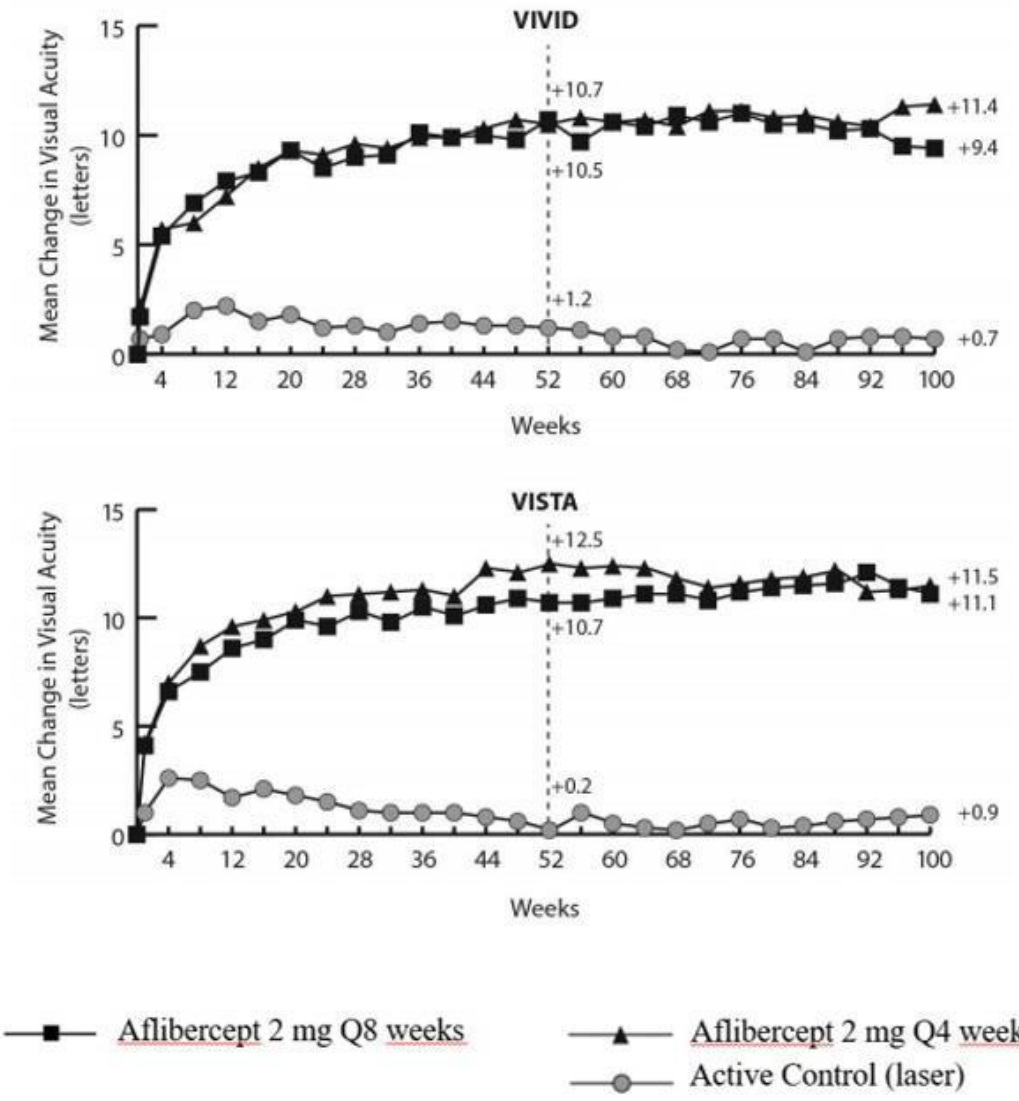
[B] LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, region (Europe/Australia vs. Japan) had been included as factor for VIVID[DME], and history of MI and/or CVA as a factor for VISTA[DME]

[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; LS: Least square means derived from ANCOVA; CI: Confidence interval

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 5).

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 (9%) and 197 (43%) patients received prior anti-VEGF therapy, respectively, with a 3-month or longer washout period. Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor were similar to those seen in patients who were VEGF inhibitor naïve prior to study participation.

Patients with bilateral disease were eligible to receive anti-VEGF treatment in their fellow eye if assessed necessary by the physician. In the VISTA^{DME} study, 217 (70.7%) of aflibercept patients

received bilateral aflibercept injections until week100; 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 incidences 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 - 18.8microns at week 52, and 2.3, -13.9 and -15.5 microns at week 100.

VIOLET, a 100-week multicentre, randomised, 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 consecutive 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 2T&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 neovascularisation (myopic CNV)
The safety and efficacy of aflibercept were assessed in a randomized, multi-center, 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 patient 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 of the MYRROR study are shown in Table 6 and Figure 5 below.

Table 6: 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 (N = 90)	Sham (N = 31)	Aflibercept 2 mg (N = 90)	Sham/ Aflibercept 2 mg (N = 31)
Mean change in BCVA [B)] as measured by ETDRS letter score from baseline (SD) [B)]	12.1 (8.3)	-2.0 (9.7)	13.5 (8.8)	3.9 (14.3)
Difference in LS mean [C,D,E)] (95% CI)	14.1 (10.8, 17.4)		9.5 (5.4, 13.7)	
Proportion of patients with ≥15 letters gain from baseline	38.9%	9.7%	50.0%	29.0%
Weighted difference [D,F)] (95% CI)	29.2% (14.4, 44.0)		21.0% (1.9, 40.1)	

[A)] LOCF: Last Observation Carried Forward
[B)] BCVA: Best Corrected Visual Acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
SD: Standard Deviation
[C)] LS mean: Least square means derived from ANCOVA model
[D)] CI: Confidence Interval
[E)] 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.
[F)] Difference and 95% CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for country (country designations)

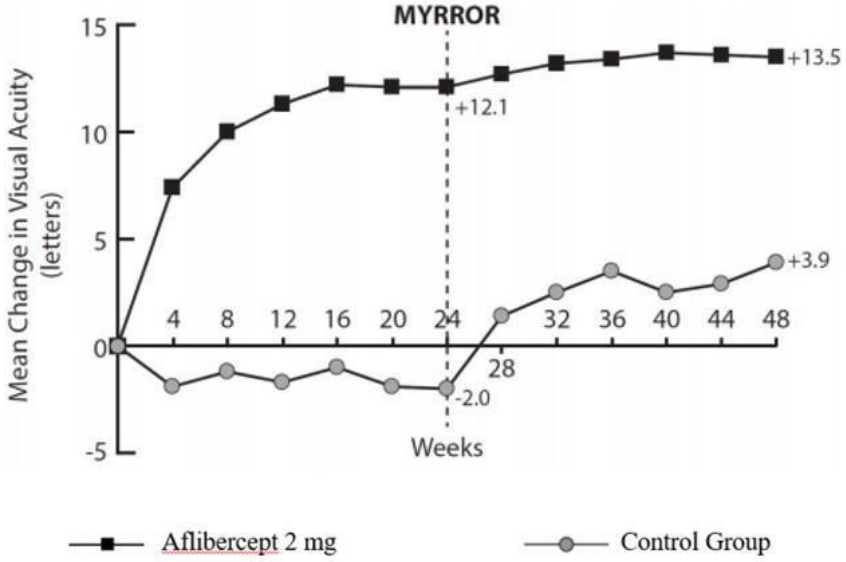


Figure 5: Mean change from baseline to week 48 in visual acuity by treatment group for the MYRROR study (full analysis set, LOCF)

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.

STUDY MYL-1701P-3001

Study MYL-1701P-3001 was a multicenter, randomized, double masked, active controlled, comparative clinical study to demonstrate that no clinically meaningful differences exist between MYL-1701P and US-licensed Eylea regarding efficacy, safety, and immunogenicity in subjects with Diabetic Macular Edema (DME). Study MYL-1701P-3001 enrolled subjects with DME following type 1 or type 2 diabetes mellitus, with baseline CRT of ≥300 μm and BCVA at 4 m from 73 to 38 letters (ETDRS chart) equivalent to Snellen visual acuity of 20/40 to 20/200 in the study eye.

MYL-1701P (a proposed biosimilar to Eylea, reference aflibercept) or Eylea for intravitreal injection, administered at a dose of 2 mg (0.05 mL) every 4 weeks for a total of 5 injections, and then every 8 weeks (with optional doses to continue at every 4 weeks) through the remainder of the 52-week treatment period, with the last dose at 48 weeks.

A total of 355 subjects were randomized with 179 subjects to the MYL-1701P arm and 176 subjects to the Eylea arm. A total of 172 (96.1%) subjects in the MYL-1701P arm and 173 (98.3%) in the Eylea arm completed the study up through Week 8, and a total of 161 (89.9%) subjects in the MYL-1701P arm and 158 (89.8%) subjects in the Eylea arm completed Week 52.

The primary efficacy endpoint was the mean change from baseline in BCVA as assessed by ETDRS letter score, at Week 8. The primary analysis was performed on the ITT and PP analysis set (Table 7 and Table 8). The adjusted mean difference for mean change in BCVA from baseline through Week 8 for ITT and PP analysis set were 0.04 and -0.19 letters respectively, which corresponding to 95% CI of -1.40, 1.47 and -1.66, 1.27 respectively. Both ITT and PP analysis set results were well within the predefined equivalence margin of [-3, 3].

Table 7: Analysis of Mean Change in BCVA from Baseline to Week 8 by MMRM - ITT Set

Statistics [a]	MYL-1701P (N=179)	Eylea (N=176)
Visit 5 (Week 8) – Primary Endpoint		
Subjects with value at baseline and this week	163	165
Adjusted mean (SE)	6.60 (0.548)	6.56 (0.548)
95% CI	(5.52, 7.68)	(5.48, 7.64)
Adjusted mean difference (SE)		0.04 (0.730)
95% CI		(-1.40, 1.47)

Results for differences displayed in Eylea-column, difference defined as MYL-1701P minus Eylea. N=number of subjects in the treatment group analysis set. [a] Statistics are from a linear mixed model for repeated measures including treatment, Visit, Treatment*Visit and Region as fixed effects with baseline BCVA as a covariate. The unstructured co-variance matrix was used to adjust for the within-subject error variance. Estimation will use restricted maximum likelihood, and the denominator degrees of freedom will use the Kenward- Roger estimate. CI=Confidence interval, SE=Standard error

Table 8: Analysis of Mean Change in BCVA from Baseline to Week 8 by MMRM - PP Set

Statistics [a]	MYL-1701P (N=165)	Eylea (N=161)
Visit 5 (Week 8) – Primary Endpoint		
Subjects with value at baseline and this week	158	154
Adjusted mean (SE)	6.61 (0.556)	6.80 (0.565)
95% CI	(5.52, 7.70)	(5.69, 7.91)
Adjusted mean difference (SE)		-0.19 (0.745)
95% CI		(-1.66, 1.27)

Results for differences displayed in Eylea-column, difference defined as MYL-1701P minus Eylea. N=number of subjects in the treatment group analysis set. [a] Statistics are from a linear mixed model for repeated measures including treatment, Visit, Treatment*Visit and Region as fixed effects with baseline BCVA as a covariate. The unstructured co-variance matrix was used to adjust for the within-subject error variance. Estimation will use restricted maximum likelihood, and the denominator degrees of freedom will use the Kenward-Roger estimate. CI=Confidence interval, SE=Standard error.

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 Cmax) 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 a 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 Cmax 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 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.

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 1mg/kg) administration. The maternal NOAEL was at the dose of 3 mg/kg or 1mg/kg, respectively. A developmental NOAEL was not identified. At the 0.1mg/kg dose, the systemic exposures based on Cmax 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.

PHARMACEUTICAL PARTICULARS

Shelf Life
Please refer to carton/label.

Storage
Store in a refrigerator (2°C - 8°C). Do not freeze.
Store in the original package in order to protect from light.

The unopened blister may be stored outside the refrigerator below 25°C for up to 72 hours. After opening the blister, proceed under aseptic conditions.

Nature and Contents of Container

Solution in pre-filled syringe (type I glass) marked with a dosing line, with plunger stopper (elastomeric rubber) and Luer lock adaptor with a tip cap (elastomeric rubber). Each pre-filled syringe contains an extractable volume of at least 0.09 mL. Pack size of 1 pre-filled syringe.

Incompatibilities
Yesafili must not be mixed with other medicinal products.

Special Instructions for Use, Handling and Disposal

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*".

Prior to administration visually inspect the solution for injection. Do not use the pre-filled syringe if particulates, cloudiness, or discoloration are visible. Do not use if any part of the pre-filled syringe is damaged or loose, or if the syringe cap is detached from the Luer-lock.

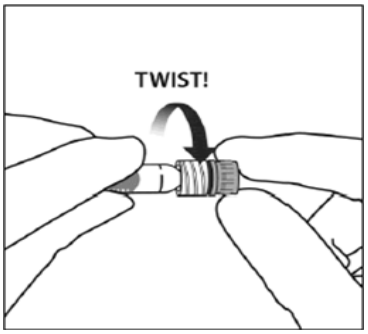
Prior to usage, an unopened blister may be stored outside the refrigerator below 25°C for up to 72 hours. After opening the blister, proceed under aseptic conditions.

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

Instructions for Use

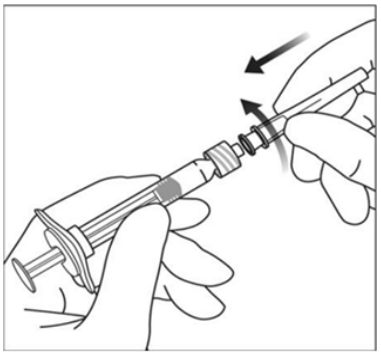
To prepare the pre-filled syringe for administration follow all steps below.

1. When ready to administer Yesafili, 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.

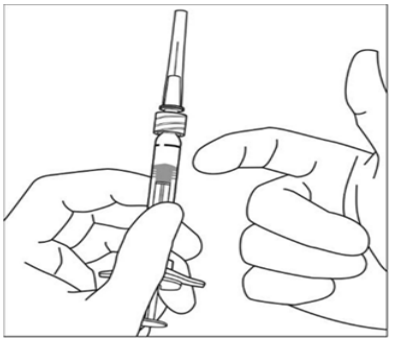


Note: You should twist off (do not snap off) the syringe cap.

4. To avoid compromising the sterility of the product, do not pull back on the plunger.
5. Using aseptic technique, firmly twist the injection needle onto the Luer-lock syringe tip.



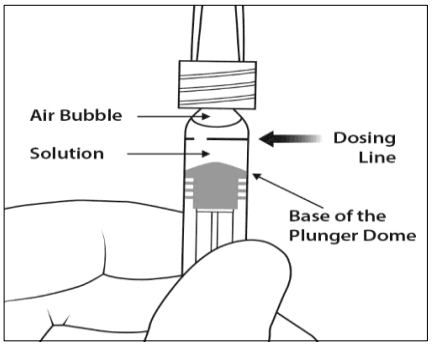
6. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.

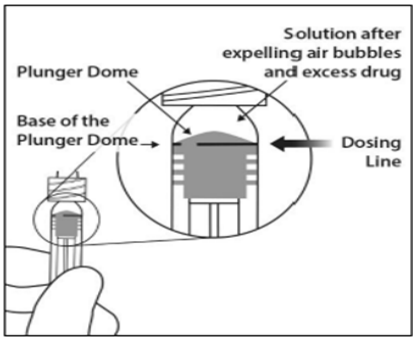


7. The excess volume must be discarded prior to administration. Eliminate all bubbles and **expel excess medicinal product by slowly depressing the plunger to align the base of the plunger dome (not the tip of the dome) with the dosing line on the syringe** (equivalent to 0.05 mL i.e. 2 mg aflibercept).

   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.





8. 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.
9. 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.

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