1. NAME OF THE MEDICINAL PRODUCT

EYLEA, 40mg/ml solution for injection

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.

For the full list of excipients see section "List of excipients".

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colorless to pale yellow, iso-osmotic solution, pH 6.2.

4. CLINICAL PARTICULARS

4.1 Indication(s)

EYLEA is indicated for the treatment of

- neovascular (wet) age-related macular degeneration (wet AMD) (see section 5.1 “Pharmacodynamic properties”).
- macular edema secondary to retinal vein occlusion (branch RVO or central RVO).
- diabetic macular edema (DME).
- myopic choroidal neovascularization (myopic CNV)

4.2 Dosage and method of administration

EYLEA is for intravitreal injection only.

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

4.2.1 Dosage regimen

4.2.1.1 Neovascular (wet) age-related degeneration (wet AMD)

The recommended dose for EYLEA is 2 mg aflibercept, equivalent to 50 microlitres.

EYLEA treatment is initiated with one injection per month for three 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 two months or further extended, such as with using a treat-and-extend

dosing regimen, where treatment 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 injections visits.

Treatment intervals greater than 4 months (16 weeks) or shorter than 4 weeks between injections have not been studied (see section "Pharmacodynamic effects).

4.2.1.2 Macular edema secondary to retinal vein occlusion (branch RVO or central RVO)

The recommended dose for EYLEA is 2 mg aflibercept, equivalent to 50 microliters.

After the initial injection, treatment is given monthly until visual and/ or anatomic outcomes are stable. Three or more consecutive, monthly injections may be needed. The interval between two doses should not be shorter than one month.

If there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended.

If necessary, treatment may be continued and the interval may be extended based on visual and/ or anatomic outcomes (treat and extend regimen).

Usually, monitoring should be done at the injection visits. During treatment interval extension through to completion of therapy, the monitoring schedule should be determined by the treating physician based on the individual patient's response and may be more frequent than the schedule of injections.

4.2.1.3 Diabetic macular edema (DME)

The recommended dose for EYLEA is 2 mg aflibercept, equivalent to 50 microliters.

EYLEA treatment is initiated with one injection per month for five consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.

After the first 12 months of treatment with EYLEA, and based the physician's judgement of on visual and/or anatomic outcomes, the treatment interval may be extended, 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.

EYLEA may be dosed as frequently as once per month (4 weeks).

The schedule for monitoring should therefore be determined by the treating physician and may be more frequent than the schedule of injections.

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

Treatment intervals shorter than 4 weeks between injections have not been studied (see section 5.1).

4.2.1.4 Myopic choroidal neovascularization (myopic CNV)

The recommended dose for EYLEA is a single intravitreal injection of 2 mg aflibercept, equivalent to 50 microliters.

Additional doses should be administered only if visual and anatomic outcomes indicate that the disease persists. Recurrences are treated like a new manifestation of the disease. The monitoring schedule should be determined by the treating physician based on the individual patient's response. The interval between two doses should not be shorter than one month.

4.2.2 Additional information on special populations

4.2.2.1 Patients with hepatic and/or renal impairment:

No specific studies in patients with hepatic and/or renal impairment were conducted with EYLEA. Available data do not suggest a need for a dose adjustment with EYLEA in these patients (see section 5.2 "Pharmacokinetic properties").

4.2.2.2 Elderly population:

No special considerations are needed.

4.2.2.3 Pediatric population:

Safety and efficacy have not been established in children and adolescents. There is no relevant use of EYLEA in the pediatric population in the indication wet AMD.

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 microbicide (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.

The pre-filled syringe contains more than the recommended dose of 2 mg (equivalent to 50 microliters solution for injection). **The excess volume must 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 bubble 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”, “Instruction for use/handling”).

After injection any unused product must be discarded.

For handling of the medicinal product, see section 6.6 “Instructions for use / handling”.

4.3 Contraindications

- Hypersensitivity to the active substance aflibercept or to any of the excipients listed in section 6.1 “List of excipients”.
- Active or suspected ocular or periocular infection
- Active severe intraocular inflammation

4.4 Special warnings and precautions for use

Endophthalmitis

Intravitreal injections, including those with aflibercept, have been associated with endophthalmitis (see section 4.8 “Undesirable effects”). Proper aseptic injection technique must always be used when administering EYLEA. 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 EYLEA (see section 4.8 “Undesirable effects”). Special precaution is needed in patients with poorly controlled glaucoma (do not inject EYLEA while the intraocular pressure is ≥ 30 mmHg). In all cases both the intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately.

Immunogenicity

As this is a therapeutic protein, there is a potential for immunogenicity with EYLEA (see section 4.8). Patients should be instructed to report any signs or symptoms of intraocular inflammation, e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity.

Systemic effects

Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors, and there is a theoretical risk that these may relate to VEGF inhibition. There are limited data on safety in the treatment of patients with a history of stroke or transient ischaemic attacks (TIA) or myocardial infarction within the last 6 months. Caution should be exercised when treating such patients.

Other
As with other intravitreal anti-VEGF treatments for AMD the following also applies:

- The safety and efficacy of EYLEA therapy administered to both eyes concurrently have not been systematically studied.
- Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD, include a large and/or high pigment epithelial retinal detachment. When initiating EYLEA therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.
- Treatment should be withheld in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.
- 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 and treatment should not be resumed earlier than the next scheduled treatment in the event of:
    - a decrease in best-corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity;
    - a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50%, of the total lesion area.
- The dose should be withheld within the previous or next 28 days in the event of a performed or planned intraocular surgery.
- EYLEA should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus (see section 4.6).
- Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept (see section 4.6).
- There is limited experience with treatment of patients with ischemic, chronic CRVO. In patients presenting with clinical signs of irreversible ischemic visual function loss, the treatment is not recommended.

Populations with limited data

There is only limited experience in the treatment of subjects with DME due to Type 1 diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy. EYLEA has not been studied in patients with active systemic infections, or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with EYLEA in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed with EYLEA.

Adjunctive use of verteporfin photodynamic therapy (PDT) and EYLEA has not been studied, therefore, a safety profile is not established.

4.6 Fertility, Pregnancy and lactation

4.6.1 Pregnancy

There are no data on the use of aflibercept in pregnant women.
Studies in animals have shown embryo-fetal toxicity after high systemic administration (see section 5.3 "Preclinical safety data").

Although the systemic exposure after ocular administration is very low, EYLEA should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus.

4.6.2 Lactation

It is unknown whether aflibercept is excreted in human milk. A risk to the breast-fed child cannot be excluded. EYLEA is not recommended during breast-feeding. A decision must be made whether to discontinue breast-feeding or to abstain from EYLEA therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.6.3 Fertility

Results from animal studies with high systemic exposure indicate that aflibercept can impair male and female fertility (see section 5.3 "Preclinical safety data"). Such effects are not expected after ocular administration with very low systemic exposure.

4.7 Effects on ability to drive or use machines

Injection with EYLEA has a minor influence on the ability to drive and use machines due to possible temporary visual disturbances associated either with the injection or the eye examination. Patients should not drive or use machines until their visual function has recovered sufficiently.

4.8 Undesirable effects

4.8.1 Summary of the safety profile

A total of 3,102 patients treated with EYLEA constituted the safety population in the eight phase III studies. Among those, 2,501 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 2,400 intravitreal injections with EYLEA and included endophthalmitis, retinal detachment, cataract traumatic, vitreous haemorrhage, 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 EYLEA) were conjunctival hemorrhage (25%), eye pain (10.2 %), cataract (7.6%), intraocular pressure increased (7.5 %), vitreous detachment (7.4 %), and vitreous floaters (6.9 %).

4.8.2 Tabulated list of adverse reactions

The safety data described below include all adverse reactions 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 (pooled data of the phase III studies for the indications wet AMD, RVO, DME and myopic CNV) 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, Retinal degeneration, Vitreous haemorrhage, 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, Injection site irritation, Abnormal sensation in eye, Eyelid irritation, 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.

4.8.3 Description of selected adverse reactions

4.8.3.1 Arterial thromboembolic events

In the wet AMD phase III studies, there was an increased incidence of conjunctival haemorrhage in patients receiving anti-thrombotic agents. This increased incidence was comparable between patients treated with ranibizumab and EYLEA.

Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events, including stroke and

myocardial infarction, following intravitreal use of VEGF inhibitors.

A low incidence rate of arterial thromboembolic events was observed in the EYLEA 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.

4.8.3.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with EYLEA.

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 overdosage 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

Pharmacotherapeutic group: Ophthalmologicals/ Anti-neovascularization 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.

5.1.1 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, 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 is 0.5 pM and to human VEGF-A 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.

5.1.2 Pharmacodynamic effects

5.1.2.1 Neovascular (wet) age-related macular degeneration (wet AMD)

Wet AMD is characterized by pathological choroidal neovascularisation (CNV). Leakage of blood and fluid from CNV may cause retinal thickening or oedema and/or sub-/intra-retinal haemorrhage, resulting in loss of visual acuity.

In patients treated with EYLEA (one injection per month for three consecutive months, followed by one injection every 2 months), retinal thickness decreased soon after treatment initiation, and the mean CNV lesion size was reduced, consistent with the results seen with ranibizumab 0.5 mg every month.

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.

In the VIEW1 study there were mean decreases in retinal thickness on optical coherence tomography (OCT) (-130 and -129 microns at week 52 for the EYLEA 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively). Also at the 52 week time point, in the VIEW2 study there were mean decreases in retinal thickness on OCT (-149 and -139 microns for the EYLEA 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively).

The reduction of CNV size and reduction in retinal thickness were generally maintained in the second year of the studies.

The ALTAIR study enrolled patients with treatment naïve wet AMD, showing similar outcomes to the VIEW studies using 3 initial monthly EYLEA 2 mg injections, followed by one injection after 2 months, and then continued with a treat-and-extend regimen with variable treatment intervals (2- week or 4-week adjustments) up to a maximum 16 week interval according to pre-specified criteria.At week 52, there were mean decreases in central retinal thickness (CRT) on OCT of -134.4 and - 126.1 microns for the 2-week adjustment group and the 4-week adjustment group, respectively. The proportion of patients without fluid on OCT at week 52 were 68.3% and 69.1% in the 2- and 4-week adjustment groups, respectively.

The reduction in retinal thickness was generally maintained in both treatment arms in the second year of the ALTAIR study

The ARIES study was designed to explore the non-inferiority of an Eylea 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.

5.1.2.2 Macular edema secondary to central retinal vein occlusion (CRVO)

In CRVO, retinal ischemia occurs and signals the release of VEGF which in turn destabilizes the tight junctions and promotes endothelial cell proliferation. Up-regulation of VEGF is associated with the breakdown of the blood retina barrier and this increased vascular permeability results in retinal edema, stimulation of endothelial cell growth and neovascularization.

In patients treated with EYLEA (one injection every month for six months), there was consistent, rapid and robust response in morphology (central retinal thickness [CRT] as assessed by OCT). Improvements in mean CRT were maintained through week 24.

Retinal thickness on OCT at week 24 compared to baseline was a secondary efficacy variable in both the COPERNICUS and GALILEO studies. In both studies, the mean change in CRT from baseline to week 24 was statistically significant favoring EYLEA.

Table 2: Pharmacodynamic parameter at week 24, week 52 and week 76/100 (Full Analysis Set with LOCF) in COPERNICUS and GALILEO studies

Efficacy Outcomes	**COPERNICUS**					
	24 Weeks		**52 Weeks**		**100 Weeks**	
	Control (N = 73)	EYLEA 2 mg Q4 (N = 114)	Control [C]) (N = 73)	EYLEA 2 mg (N = 114)	Control [C,D]) (N = 73)	EYLEA[D]) 2 mg (N = 114)
Mean change in retinal thickness from baseline	-145	-457	-382	-413	-343	-390
Difference in LS mean[A,B,C,D]) (95% CI) p-value		-312 (-389, -234) p < 0.0001		-28 (-121, 64) p = 0.5460		-45 (-142, 53) p=0.3661

Efficacy Outcomes	**GALILEO**					
	24 Weeks		**52 Weeks**		**76 Weeks**	
	Control (N = 68)	EYLEA 2 mg Q4 (N = 103)	Control (N = 68)	EYLEA 2 mg (N = 103)	Control [E]) (N = 68)	EYLEA [E]) 2 mg (N = 103)

Mean change in retinal thickness from baseline	-169	-449	-219	-424	-306	-389
Difference in LS mean[A,B,E]) (95% CI) p-value		-239 (-286, -193) p < 0.0001		-167 (-217, -118) p < 0.0001		-44 (-99, 10) p=0.1122

A) Difference is EYLEA 2 mg Q4 minus control

B) LS: Least square mean difference and confidence interval (CI) based on an ANCOVA model with baseline value as covariate and 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)

C) In COPERNICUS study, control group patients could receive EYLEA on an as-needed basis as frequently as every 4 weeks during week 24 to week 52; patients had visits every 4 weeks

D) In COPERNICUS study, both control group and EYLEA 2mg patients received EYLEA 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

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

5.1.2.3 Macular edema secondary to branch retinal vein occlusion (BRVO)

In BRVO, retinal ischemia occurs and signals the release of VEGF which in turn destabilizes the tight junctions and promotes endothelial cell proliferation. Up-regulation of VEGF is associated with the breakdown of the blood retina barrier and this increased vascular permeability results in retinal edema, stimulation of endothelial cell growth and neovascularization.

In patients treated with EYLEA (one injection every month for six months), there was consistent, rapid and robust response in morphology (central retinal thickness [CRT] as assessed by OCT). There was a statistically significant improvement in the EYLEA 2 mg group in comparison to the control group at week 24 (-280 microns vs. -128 microns). At week 24 the dosing interval was extended to every 2 months, and anatomic outcomes were maintained.

Retinal thickness on OCT at week 24 compared to baseline was a secondary efficacy variable in the VIBRANT study. This decrease from baseline was maintained to week 52 favoring EYLEA.

Table 3: Pharmacodynamic parameter at week 24 and at week 52 (Full Analysis Set with LOCF) in VIBRANT study

Efficacy Outcomes	**VIBRANT**			
	24 Weeks		**52 Weeks**	
	EYLEA 2 mg Q4 (N = 91)	**Active Control (laser) (N = 90)**	**EYLEA 2 mg Q8 B) (N = 91)**	**Active Control C) (N = 90)**
Mean change in retinal thickness from baseline	-280	-128	-284	-249
Difference in LS mean (95% CI)[A)] p-value	-149 (-180, -117) p < 0.0001		-30 (-55, -4) p=0.0218	

A) EYLEA administered as 2 mg every 4 weeks through week 24.
Laser treatment administered on day 1.
Last observation carried forward (LOCF) method was used to impute missing data.

Difference was EYLEA group minus laser group. Point estimate , 95% confidence interval (CI), and p-value were based on an analysis of covariance (ANCOVA) model with baseline measurement as covariate and treatment group, region, and baseline Best Corrected Visual Acuity (BCVA ≤ 20/200 and BCVA > 20/200) as fixed factors.

B) From week 24 on the treatment interval in the EYLEA treatment group was extended for all subjects from 4 weeks to 8 weeks through week 48.

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

5.1.2.4 Diabetic macular edema (DME)

Diabetic macular edema is characterized by increased vasopermeability and damage to the retinal capillaries which may result in loss of visual acuity.

In patients treated with EYLEA, rapid and robust response in morphology (central retinal thickness [CRT]) as assessed by OCT was seen soon after treatment initiation. The mean change in CRT from baseline to week 52 was statistically significant favoring EYLEA and was maintained through week 100.

Table 4: Pharmacodynamic parameter at week 52 and week 100 (Full Analysis Set with LOCF) in VIVID^{DME} study

Efficacy Outcomes	**VIVID^{DME}**			**VIVID^{DME}**		
	52 Weeks			**100Weeks**		
	EYLEA 2 mg Q8 A) **(N = 135)**	**EYLEA 2 mg Q4**C) **(N = 136)**	**Active Control (laser) (N = 132)**	**EYLEA 2 mg Q8** A) **(N = 135)**	**EYLEA 2 mg Q4 (N = 136)**	**Active Control (laser) (N = 132)**
Mean change in CRT score from Baseline (SD)	-192.4 (149.89)	-195.0 (146.59)	-66.2 (138.99)	-195.8 (141.75)	-211.8 (150.87)	-85.7 (145.84)
Difference in LS mean A,B) (97.5% CI)	-142.8 (-179.3, -106.3)	-157.0 (-190.9, -123.1)		-126.8 (-164.6, -89.0)	-154.4 (-189.1, -119.7)	
p-value	p < 0.0001	p < 0.0001		p < 0.0001	p < 0.0001	

A) 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}).
EYLEA 2 mg Q8: From week 16 onwards the treatment interval in the EYLEA treatment group was extended for all subjects from 4 weeks to 8 weeks.

B) Difference is EYLEA group minus active control (laser) group

C) EYLEA administered 2 mg every 4 weeks.

Table 5: Pharmacodynamic parameter 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		
	EYLEA 2 mg Q8 [A)] (N = 151)	EYLEA 2 mg Q4[C)] (N = 154)	Active Control (laser) (N = 154)	EYLEA 2 mg Q8 [A)] (N = 151)	EYLEA 2 mg Q4 (N = 154)	Active Control (laser) (N = 154)
Mean change in CRT score from Baseline (SD)	-183.1 (153.50)	-185.9 (150.68)	-73.3 (176.72)	-191.1 (160.66)	-191.4 (180.01)	-83.9 (179.29)
Difference in LS mean [A, B)] (97.5% CI) p-value	-113.47 (-144.19, -82.75) p < 0.0001	-110.78 (-141.34, -80.22) p < 0.0001		-110.99 (-142.94, -79.04) p < 0.0001	-104.89 (-139.58, -70.21) p < 0.0001	

[A)] 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}.
EYLEA 2 mg Q8: From week 16 onwards the treatment interval in the EYLEA treatment group was extended for all subjects from 4 weeks to 8 weeks.
[B)] Difference is EYLEA group minus active control (laser) group
[C)] EYLEA administered 2 mg every 4 weeks.

The VIOLET study compared three different dosing regimens of Eylea 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. After the baseline visit of the VIOLET study, patients continued treatment with EYLEA 2 mg according to one of the dosing regimens:

- treat-and-extend (2T&E) where treatment intervals were maintained at a minimum of 8 weeks and gradually extended based on clinical and anatomical outcomes
- pro re nata (2PRN) where patients were observed every 4 weeks and injected when needed based on clinical and anatomical outcomes, and
- dosed every 8 weeks (2Q8) for the second and third year of treatment.

At week 52 of the study, i.e., after at least two years of treatment, the mean changes in CRT from baseline were -2.1, 2.2 and -18.8 microns for 2T&E, 2PRN, and 2Q8, respectively. At week 100, i.e., after at least three years of treatment, the mean changes in CRT from baseline were 2.3, -13.9 and -15.5 microns, respectively (see section 'Clinical efficacy').

5.1.2.5 Myopic choroidal neovascularization (myopic CNV)

Myopic choroidal neovascularization (myopic CNV) is a frequent cause of vision loss in adults with pathologic myopia. Eyes with pathologic myopia are elongated, often excessively, and have, in addition, pathologic tissue alterations such as retinal pigment epithelial thinning and defects, lacquer cracks and Bruch's membrane ruptures, choroidal neovascularization, subretinal hemorrhage, and choroidal atrophy. As a consequence of ruptures of Bruch's membrane, myopic CNV develops as a wound healing mechanism, and at the same time represents the most vision-threatening event in pathologic myopia.

In patients treated with EYLEA (one injection given at start of therapy, additional injection given in case of disease persistence or recurrence) retinal thickness assessed by OCT decreased soon after treatment initiation and the mean CNV lesion size was reduced. The mean change in CRT from baseline to week 24 was statistically significant favoring EYLEA.

Table 6: Pharmacodynamic parameter at week 24 and week 48 in MYRROR study (Full Analysis Set with LOCF[A)])

Efficacy Outcomes	**MYRROR**			
	24 Weeks		**48 Weeks**	
	EYLEA 2mg [B]) (N=90)	**Sham (N=31)**	**EYLEA 2mg[C]) (N=90)**	**Sham/EYLEA 2mg[D]) (N=31)**
Mean change in cerntral retinal thickness from baseline	-79	-4	-83	-57
Difference in LS mean [E,F,G,H)] (95% CI) p-value	-78 (-109, -47) p < 0.0001		-29 (-60,2) p= 0.0650	

[A)] LOCF: Last Observation Carried Forward
[B)] EYLEA 2mg administered at baseline and potentially every 4 weeks in case of disease persistence or recurrence.
[C)] EYLEA 2mg administered from Week 24 through Week 44 potentially every 4 weeks in case of disease persistence or recurrence
[D)] Mandatory injection of EYLEA 2mg at Week 24, thereafter potentially every 4 weeks in case of disease persistence or recurrence through Week 44.
[E)] Difference is EYLEA 2mg minus sham at Week 24, Difference is EYLEA 2mg minus sham/EYLEA 2mg at Week 48.
[F)] LS mean: Least square means derived from ANCOVA model
[G)] CI: Confidence Interval
[H)] 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.

5.1.3 Clinical efficacy

5.1.3.1 Neovascular (wet) age-related macular degeneration (wet AMD)

The safety and efficacy of EYLEA were assessed in two randomized, multi-centre, double-masked, active-controlled studies in patients with wet AMD. A total of 2,412 patients were treated and evaluable for efficacy (1,817 with EYLEA) 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) EYLEA administered at 2 mg every 8 weeks following 3 initial monthly doses (EYLEA 2Q8);
2) EYLEA administered at 2 mg every 4 weeks (EYLEA 2Q4);
3) EYLEA administered at 0.5 mg every 4 weeks (EYLEA 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 EYLEA 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, 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 EYLEA 2Q8 treatment group maintained vision compared to 94.4% patients in the ranibizumab 0.5Q4 group. EYLEA treatment was 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 EYLEA 2Q8 treatment group maintained vision compared to 94.4% patients in the ranibizumab 0.5Q4 group. EYLEA treatment was shown to be non-inferior and clinically equivalent to the ranibizumab 0.5Q4 group.

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

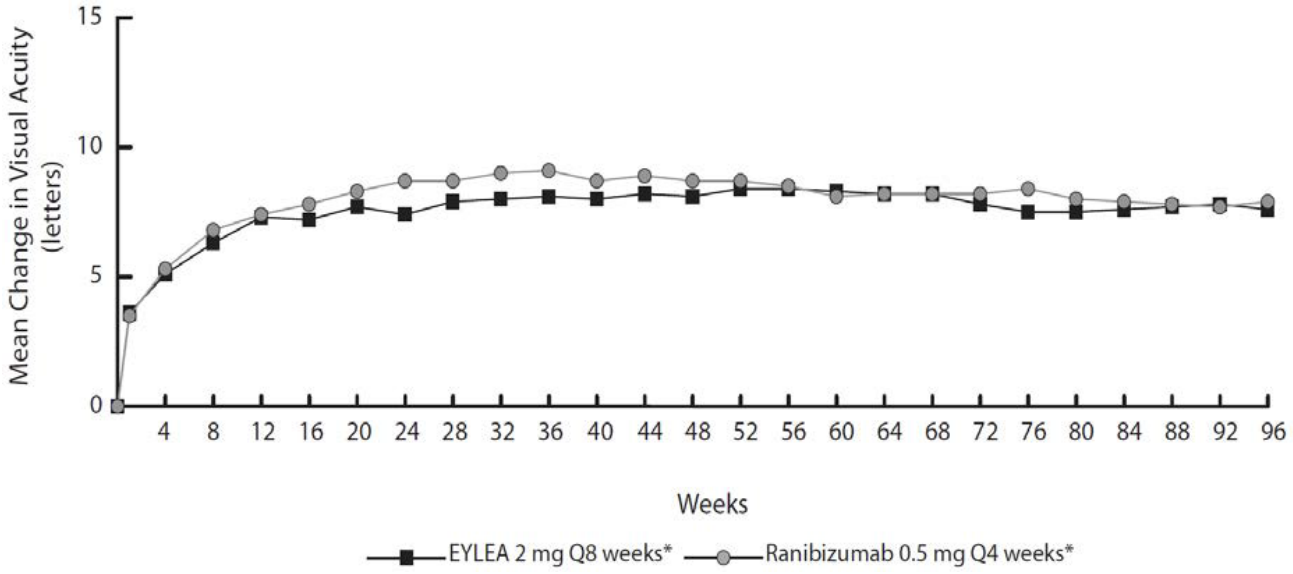
Table 7: Efficacy outcomes at week 52 (primary analysis) and week 96; combined data from the VIEW1 and VIEW2 studies[B)]

Efficacy Outcome	**EYLEA 2Q8[E)]** (EYLEA 2mg every 8 weeks following 3 initial monthly doses) **(N = 607)**		**Ranibizumab 0.5Q4** (ranibizumab 0.5 mg every 4 weeks) **(N = 595)**	
	Week 52[G)]	Week 96[G)]	52 Weeks[G)]	96 Weeks[G)]
Mean number of injections from baseline	7.6	11.2	12.3	16.5
Mean number of injections during second year (Week 52 to 96)		4.1		4.6
Proportion of patients with maintained visual acuity (< 15 letters of BCVA[A)] loss) (Per Protocol Set)	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 from baseline as measured by ETDRS[A)] letter score	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 who gained at least 15 letters of vision 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

[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 EYLEA group minus the value of the ranibizumab group. A positive value favours EYLEA.
[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 EYLEA to ranibizumab
[G)] Beginning at week 52, all groups were treated using a modified quarterly treatment paradigm where patients could be dosed as frequently as every 4 weeks but not less frequently than every 12 weeks based upon pre-specified retreatment criteria

Figure 1: Mean change in visual acuity from baseline to week 96; combined data from the VIEW1 and VIEW2 studies



*) From Baseline to Week 52, EYLEA was dosed every 8 weeks following 3 initial monthly doses. From Baseline to Week 52, ranibizumab 0.5 mg was dosed every 4 weeks. Beginning at Week 52, all groups were treated using a modified quarterly treatment paradigm where patients could be dosed as frequently as every 4 weeks but not less frequently than every 12 weeks based upon pre-specified retreatment criteria.

The proportion of patients at week 96 gaining at least 15 letters from baseline was 33.44% in the EYLEA 2Q8 group, and 31.60% in ranibizumab 0.5Q4 group.

In combined data analysis of the VIEW1 and VIEW2 studies EYLEA 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 EYLEA 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.

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

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.

In the second year of the studies, efficacy was generally maintained through the last assessment at week 96 and 2-4% of patients required all injections on a monthly basis, and a third of patients required at least one injection with a treatment interval of only one month.

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

All patients received 3 monthly doses of EYLEA 2 mg, followed by one injection after a 2 month interval. At week 16, patients were randomized 1:1 into two treatment groups: 1) EYLEA treat-and-extend with 2-week adjustments and 2) EYLEA 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 group). 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 orbeyond 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 prior 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.

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% and 54.5% of the patients (2- and 4-week adjustment) were extended to a treatment interval of 16 weeks at least once. Of these patients, 96.2% and 77.6% (2- and 4-week adjustment) required no additional adjustment of their treatment interval, meaning that a 16-week interval was maintained until the end of the study. By week 96, 41.5% and 46.3% of all patients (2- and 4-week adjustment) had achieved the maximum 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.

Ocular and systemic safety profiles were similar to the safety observed in the pivotal studies VIEW1 and VIEW2.

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.

Elderly Population

In the clinical studies, approximately 89% (1,616/1,817) of the patients randomized to treatment with EYLEA were 65 years of age or older and approximately 63% (1,139/1,817) were 75 years of age or older.

5.1.3.2 Macular edema secondary to central retinal vein occlusion (CRVO)

The safety and efficacy of EYLEA were assessed in two randomised, 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 EYLEA) in the two studies COPERNICUS and GALILEO. In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg EYLEA 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) until week 52. Starting from this timepoint all patients were offered treatment if they met pre-specified criteria.

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 favour of EYLEA in both studies. In both pivotal studies the maximal improvement in visual acuity was achieved at month 3 with subsequent stabilisation of the effect on visual acuity and central retinal thickness until month 6. The statistically significant difference was maintained through week 52.

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

Table 8: 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**	
	Control (N = 73)	**EYLEA 2 mg Q4 (N = 114)**	**Control[E)] (N = 73)**	**EYLEA 2 mg (N = 114)**	**Control[E,F)] (N = 73)**	**EYLEA[F)] 2 mg (N = 114)**
Proportion of patients who gained at least 15 letters in BCVA[C)] from baseline	12%	56%	30%	55%	23.3%	49.1%
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
Mean change in BCVA as measured by ETDRS[C)] letter score from baseline (SD)	-4.0 (18.0)	17.3 (12.8)	3.8 (17.1)	16.2 (17.4)	1.5 (17.7)	13.0 (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

Efficacy Outcomes	**GALILEO**					
	24 Weeks		**52 Weeks**		**76 Weeks**	
	Control (N = 68)	**EYLEA 2 mg Q4 (N= 103)**	**Control (N = 68)**	**EYLEA 2 mg (N = 103)**	**Control[G)] (N = 68)**	**EYLEA[G)] 2 mg (N = 103)**
Proportion of patients who gained at least 15 letters in BCVA[C)] from baseline	22%	60%	32%	60%	29.4%	57.3%
Weighted difference[A,B,E)] (95% CI)		38.3% (24.4, 52.1)		27.9% (13.0, 42.7)		28.0% (13.3, 42.6)

p-value		p < 0.0001		p = 0.0004		p=0.0004
Mean change in BCVA as measured by ETDRS[C)] letter score from baseline (SD)	3.3 (14.1)	18.0 (12.2)	3.8 (18.1)	16.9 (14.8)	6.2 (17.7)	13.7 (17.8)
Difference in LS mean[A,C,D,E)] (95% CI)		14.7 (10.8, 18.7)		13.2 (8.2, 18.2)		7.6 (2.1, 13.1)
p-value		p < 0.0001		p < 0.0001		p=0.0070

A) Difference is EYLEA 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

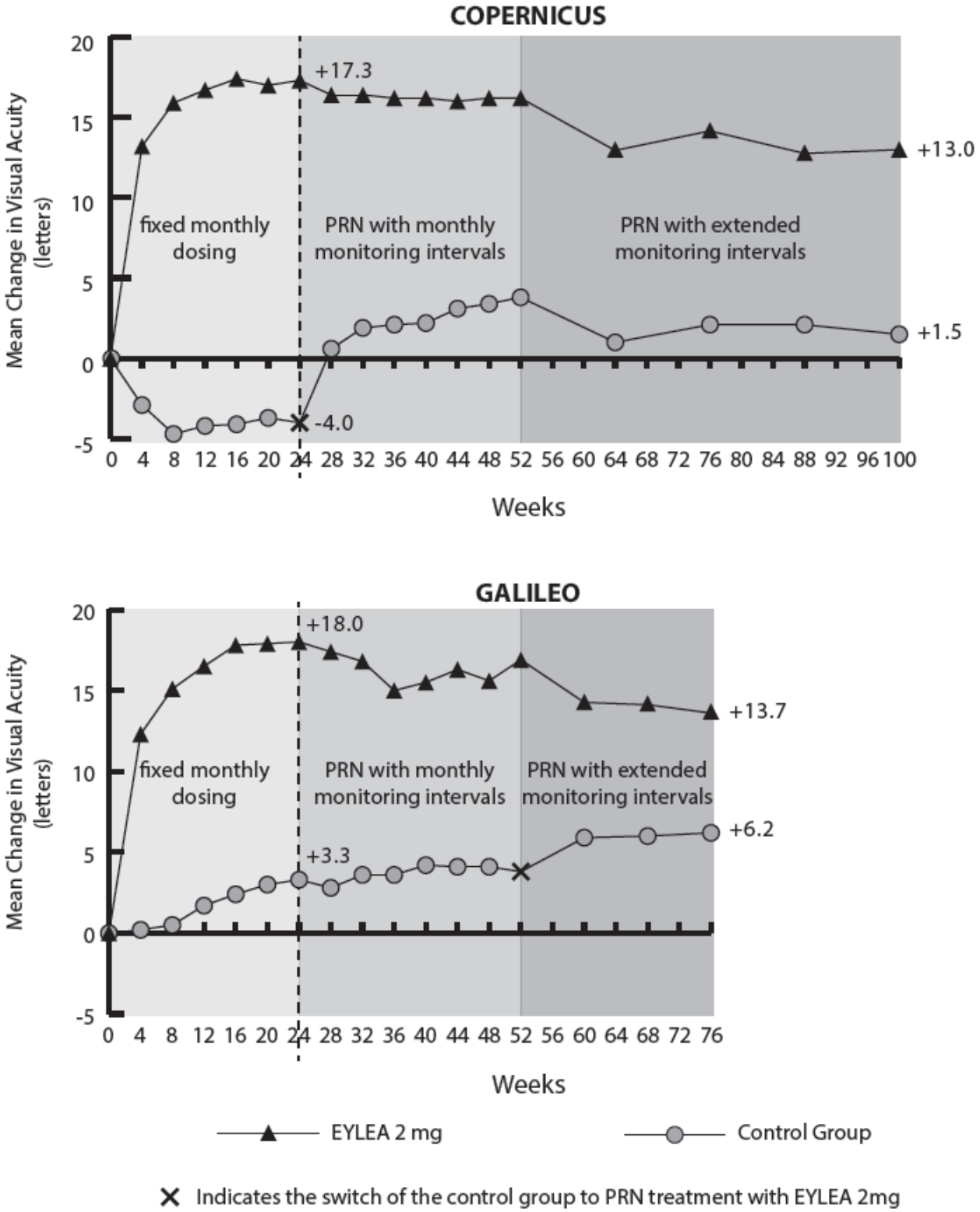
D) LS mean difference and confidence interval based on an ANCOVA model with factors treatment group, region (America vs. rest of the world for COPERNICUS and Europe vs. Asia/Pacific for GALILEO) and baseline BCVA category (> 20/200 and ≤ 20/200)

E) In COPERNICUS study, control group patients could receive EYLEA 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 EYLEA 2mg patients received EYLEA 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 EYLEA 2mg patients received EYLEA 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 EYLEA group was high in the GALILEO study at baseline (86.4%; n = 89). Perfusion at week 24 primary endpoint was 91.8% (n = 89). The patients were largely able to maintain their perfusion status until week 76 (84.3%; n = 75). The number of perfused patients that started on sham was 79.4% (n = 54) at baseline. Perfusion at week 24 primary endpoint was 85.5% (n = 47). Patients in the sham group were switched to EYLEA according to pre-specified criteria at week 52, 83.7% (n = 41) were perfused at this time. The patients were able to maintain their perfusion status until week 76 (84.0%; n = 42).

The proportion of perfused patients in the EYLEA group in the COPERNICUS study at baseline was 67.5% (n = 77). Perfusion at week 24 primary endpoint was 87.4%; (n = 90). After week 24, patients in the EYLEA group were treated according to pre-specified criteria. At week 100, 76.8 % (n = 76) of patients were perfused. The percentage of perfused patients that started on sham was 68.5% (n = 50) at baseline. Perfusion at week 24 primary endpoint was 58.6% (n = 34). Patients in the sham arm were eligible to receive EYLEA from week 24. The proportion of perfused patients increased to 83.9% (n = 47) at week 52 and was largely maintained until week 100 (78%; n = 39).
The beneficial effect of EYLEA treatment on visual function was similar in the baseline subgroups of perfused and non-perfused patients.

In combined data analysis of the GALILEO and COPERNICUS studies, EYLEA 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).

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.

Elderly population

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

5.1.3.3 Macular edema secondary to branch retinal vein occlusion (BRVO)

The safety and efficacy of EYLEA were assessed in a randomized, multi-center, double-masked, active-controlled study in patients with macular edema secondary to BRVO which included Hemi-Retinal Vein Occlusion. A total of 181 patients were treated and evaluable for efficacy (91 with EYLEA) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg EYLEA 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 EYLEA group received 2 mg every 8 weeks through week 48, and patients in the control group could receive treatment with EYLEA 2mg, if at least one pre-specified rescue criterion was met. EYLEA rescue treatment consisted of a fixed regimen with 2mg EYLEA 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 EYLEA 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

EYLEA. 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 EYLEA 2 mg every 8 weeks beginning at week 24 in the EYLEA treatment group.

In the laser group 67 patients received rescue treatment with EYLEA 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 9: Efficacy outcomes at week 24, and at week 52 (Full Analysis Set with LOCF) in the VIBRANT study

Efficacy Outcomes	**VIBRANT**			
	24 Weeks		**52 Weeks**	
	EYLEA 2mg Q4 (N = 91)	**Active Control (laser) (N = 90)**	**EYLEA 2mg 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 EYLEA 2 mg Q4 weeks minus Laser Control

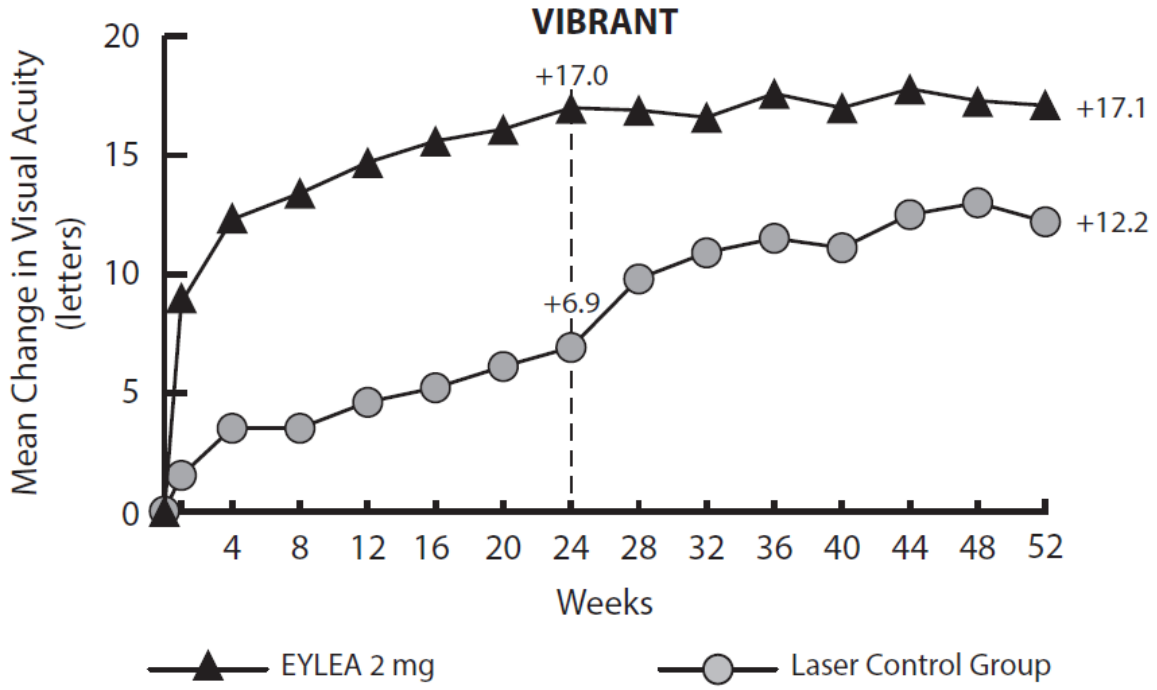
B) Difference and 95% CI are calculated using Mantel-Haenszel weighting scheme adjusted for region (North America vs. Japan) and baseline BCVA category (> 20/200 and ≤ 20/200)

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 EYLEA 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 EYLEA, if they met at least one pre-specified eligibility criterion. At total of 67 subjects in this group received EYLEA rescue treatment. The fixed regimen for EYLEA rescue was three times EYLEA 2mg 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 EYLEA group at baseline was 60.4% (n = 55) in the EYLEA 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 EYLEA 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 EYLEA 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.

Elderly Population

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

5.1.3.4 Diabetic macular edema (DME)

The safety and efficacy of EYLEA 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 EYLEA 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) EYLEA administered 2 mg every 8 weeks following 5 initial monthly injections (EYLEA 2Q8);
2) EYLEA administered 2 mg every 4 weeks (EYLEA 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 EYLEA groups could receive laser and patients in the laser group could receive EYLEA.

Patient ages ranged from 23 to 87 years with a mean of 63 years. The majority of patients in both studies had Type II diabetes.

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 EYLEA 2Q8 and EYLEA 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 10: Efficacy Outcomes at week 52 and week 100(Full Analysis Set with LOCF) in VIVID^{DME} study

Efficacy Outcomes	**VIVID^{DME}**			**VIVID^{DME}**		
	52 Weeks			**100 Weeks**		
	EYLEA 2 mg Q8 [A)] (N = 135)	**EYLEA 2 mg Q4 (N = 136)**	**Active Control (laser) (N = 132)**	**EYLEA 2 mg Q8 [A)] (N = 135)**	**EYLEA 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	

Efficacy Outcomes	**VIVID[DME]**			**VIVID[DME]**		
	52 Weeks			**100 Weeks**		
	EYLEA 2 mg Q8 [A)] (N = 135)	**EYLEA 2 mg Q4 (N = 136)**	**Active Control (laser) (N = 132)**	**EYLEA 2 mg Q8 [A)] (N = 135)**	**EYLEA 2 mg Q4 (N = 136)**	**Active Control (laser) (N = 132)**
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% (18.0, 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%
Adjusted Difference [D,C)] (97.5% CI) p-value	19.3 (6.6, 32.1) p = 0.0006	25.8 (12.2, 39.4) p < 0.0001		24.4 (11.3, 37.4) p<0.0001	20.9 (7.7, 34.2) p=0.0004	
See Table for Mean Change in CRT from Baseline						
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) p-value	-1.21 (-5.79, 3.37) p = 0.5537	2.41 (-2.01, 6.82) p = 0.2208		-0.74 (-5.25, 3.78) p = 0.7144	3.64 (-0.70, 7.98) 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)

Efficacy Outcomes	VIVID^{DME}			VIVID^{DME}		
	52 Weeks			100 Weeks		
	EYLEA 2 mg Q8 [A)] (N = 135)	EYLEA 2 mg Q4 (N = 136)	Active Control (laser) (N = 132)	EYLEA 2 mg Q8 [A)] (N = 135)	EYLEA 2 mg Q4 (N = 136)	Active Control (laser) (N = 132)
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 EYLEA 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 (EYLEA 2mg Q8), n=81 (EYLEA 2mg Q4), n=80 (laser): week 100: n=86 (EYLEA 2mg Q8), n=82 (EYLEA 2mg Q4), n=85 (laser))

Table 11: 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		
	EYLEA 2 mg Q8 [A)] (N = 151)	EYLEA 2 mg Q4 (N = 154)	Active Control (laser) (N = 154)	EYLEA 2 mg Q8 [A)] (N = 151)	EYLEA 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)	10.45 (7.73, 13.17)	12.19 (9.35, 15.04)		10.14 (6.96, 13.32)	10.64 (7.09, 14.18)	
p-value	p < 0.0001	p < 0.0001		p < 0.0001	p < 0.0001	

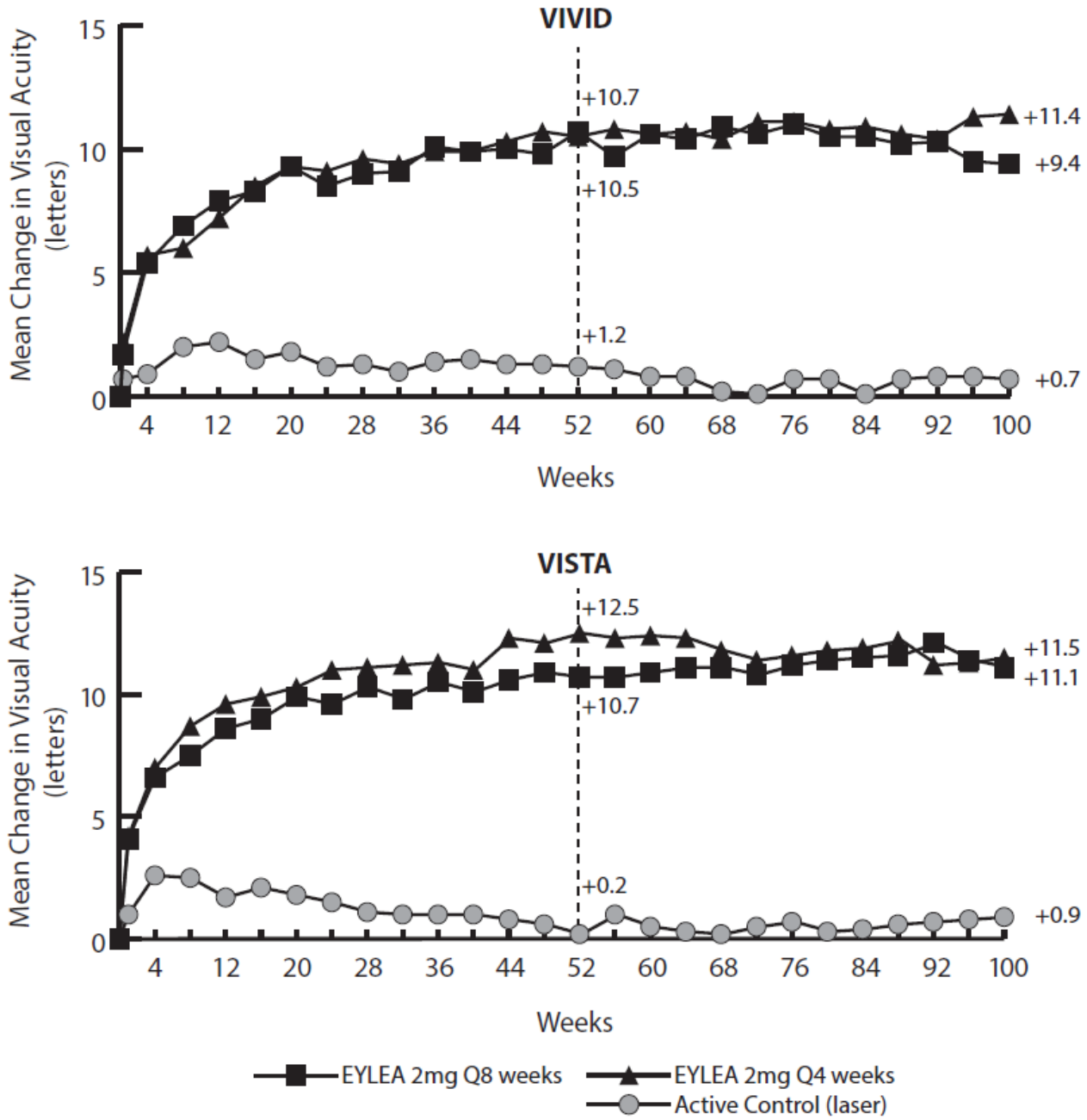
Efficacy Outcomes	**VISTA[DME]**			**VISTA[DME]**		
	52 Weeks			**100 Weeks**		
	EYLEA 2 mg Q8 [A)] (N = 151)	**EYLEA 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**	**EYLEA 2 mg Q8 [A)] (N = 151)**	**EYLEA 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**
Proportion of patients who gained 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	
See Table 5 for Mean Change in CRT from Baseline						
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)

Efficacy Outcomes	**VISTA^{DME}**			**VISTA^{DME}**		
	52 Weeks			**100 Weeks**		
	EYLEA 2 mg Q8 [A)] **(N = 151)**	**EYLEA 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**	**EYLEA 2 mg Q8** [A)] **(N = 151)**	**EYLEA 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**
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)

Efficacy Outcomes	**VISTA^{DME}**			**VISTA^{DME}**		
	52 Weeks			**100 Weeks**		
	EYLEA 2 mg Q8 [A)] **(N = 151)**	**EYLEA 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**	**EYLEA 2 mg Q8** [A)] **(N = 151)**	**EYLEA 2 mg Q4 (N = 154)**	**Active Control (laser) (N = 154)**
Difference in LS mean [B, C, E)] (97.5% CI)	1.65 (-2.83, 6.13)	2.86 (-1.82, 7.54)		3.57 (-0.96, 8.11)	5.80 (0.97, 10.64)	
p-value	p = 0.4067	p = 0.1702		p = 0.0772	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 EYLEA 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 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 11).

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 naïve 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 EYLEA patients received bilateral EYLEA injections through week 100; in the VIVID^{DME} study, 97 (35.8%) of EYLEA patients received a different anti-VEGF treatment in their fellow eye.

An independent comparative trial (DRCR.net Protocol T) utilised a 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 Eylea 2Q8 group in VIVID^{DME} and VISTA^{DME}, while overall efficacy of the aflibercept treatment group in Protocol T was comparable to the Eylea 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. Ocular and systemic safety profiles (including ATEs) were similar to VIVID^{DME} and VISTA^{DME}.

- VIOLET was a 100-week multicenter, randomized, open-label, active controlled study in 463 patients with DME. Patients were randomized in a 1:1:1 ratio to three regimens of EYLEA 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 ofEYLEA 2 mg dosed according to a treat-and-extend regimen (2T&E) where treatment intervals were maintained at a minimum of 8 weeks and gradually extended based on clinical and anatomical outcomes. The increments and decrements for the treatment intervals were at the investigator's discretion; increments of 2 weeks were recommended in the study, and
- EYLEA 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 EYLEA 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 10.0, 11.5 and 12.3 for 2T&E, 2PRN and 2Q8, 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.

Elderly Population

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

5.1.3.5 Myopic choroidal neovascularization (myopic CNV)

The safety and efficacy of EYLEA 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 EYLEA). Patients were randomly assigned in a 3:1 ratio to either 2 mg EYLEA 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 EYLEA 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 EYLEA for the primary and confirmatory secondary efficacy endpoints at Week 24. Differences for both endpoints were maintained through Week 48.

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

Table 12: Efficacy outcomes at week 24 (primary analysis) and in week 48 in MYRROR study (Full Analysis Set with LOCF[A]))

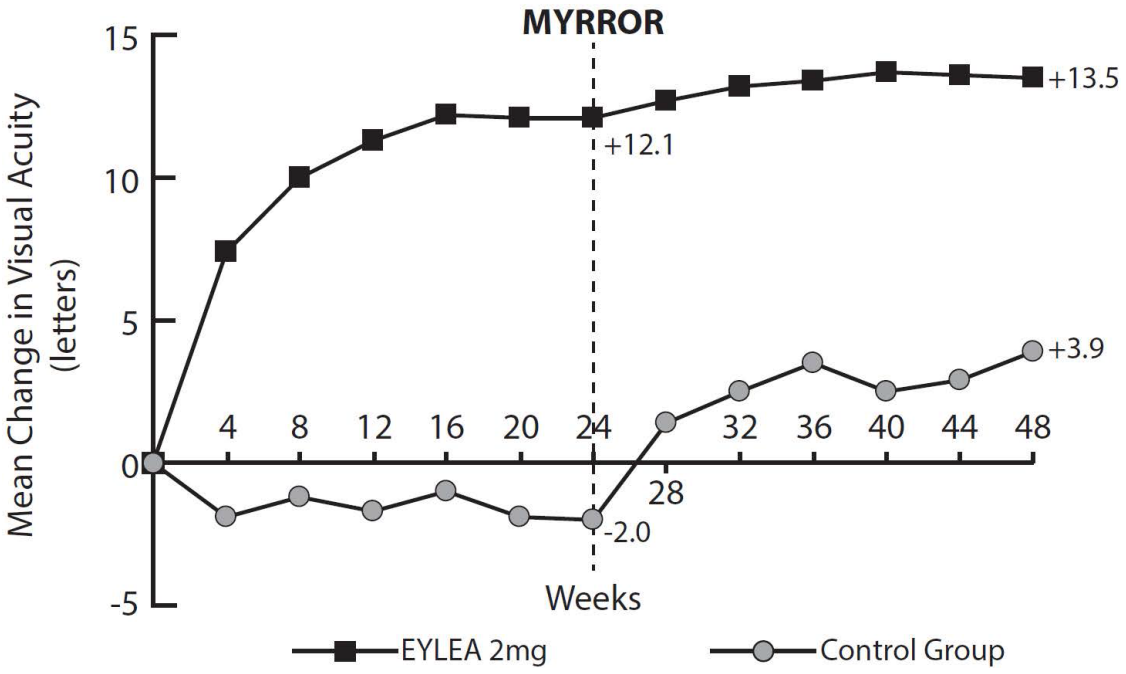
Efficacy Outcomes	**MYRROR**			
	24 Weeks		**48 Weeks**	
	EYLEA 2mg[B]) (N = 90)	**Sham (N = 31)**	**EYLEA 2mg[C]) (N = 90)**	**Sham/ EYLEA 2mg[D]) (N = 31)**
Mean change in BCVA letter score as measured by ETDRS from baseline (SD) [E])	12.1 (8.3)	-2.0 (9.7)	13.5 (8.8)	3.9 (14.3)
Difference in LS mean [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)] EYLEA 2mg administered at baseline and potentially every 4 weeks in case of disease persistence or recurrence.

[C)] EYLEA 2mg administered from Week 24 through Week 44 potentially every 4 weeks in case of disease persistence or recurrence
[D)] Mandatory injection of EYLEA 2mg 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 EYLEA 2mg minus sham at Week 24 and EYLEA 2mg minus sham/EYLEA 2mg 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.

Elderly Population

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

5.2 Pharmacokinetic properties

EYLEA is administered directly into the vitreous to exert local effects in the eye.

5.2.1 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 in 6 patients 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.

The mean maximum plasma concentration of free aflibercept is approximately 50 to 500 times below the aflibercept concentration required to inhibit the biologic activity of systemic VEGF by 50% in animal models, in which blood pressure changes were observed after circulating levels of free aflibercept attained approximately 10 microgram/ml and returned to baseline when levels fell below approximately 1 microgram/ml. 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 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.

5.2.2 Elimination

As EYLEA 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.

5.2.3 Additional information on special populations

5.2.3.1 Renal impairment

No special studies in patients with renal impairment have been conducted with EYLEA.

Pharmacokinetic analysis of patients in the VIEW2 study, of which 40% had renal impairment (24% mild, 15% moderate, and 1% severe), revealed no differences with respect to plasma concentrations of active drug after intravitreal administration every 4 or 8 weeks.

Similar results were seen in patients with CRVO in the GALILEO study.

Similar results were seen in patients with DME in the VIVID^{DME} study.

Similar results were seen in patients with myopic CNV in the MYRROR study.

5.2.3.2 Patients with hepatic impairment
No special or formal studies in patients with hepatic impairment have been conducted with EYLEA.

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.

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at systemic exposures in excess of the maximum human exposure. The systemic exposure based on C_{max} and AUC for free aflibercept were approximately 200- and 700-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg. At the No Observed Adverse Effect Level (NOAEL) of 0.5 mg/eye in monkeys the systemic exposure was 42- and 56-fold higher based on C_{max} and AUC, respectively.

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

An effect on Aflibercept on intrauterine development was shown embryo-fetal development study in pregnant rabbits with intravenous administration (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 1 mg/kg, respectively. A developmental NOAEL was not identified. At the 0.1 mg/kg dose, the systemic exposures based on C_{max} and cumulative AUC for free aflibercept were approximately 17- and 10-fold higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg.

Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at doses ranging from 3 to 30 mg/kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. Based on C_{max} and AUC for free aflibercept observed at the 3 mg/kg intravenous dose, the systemic exposures were approximately 4,900-fold and 1,500-fold higher, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20

Sodium phosphate, monobasic, monohydrate

Sodium phosphate, dibasic, heptahydrate

Sodium chloride

Sucrose

Water for injection

6.2 Incompatibilities

EYLEA must not be mixed with other medicinal products.

6.3 Shelf life

Please refer to labels.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C / 36°F to 46 °F). Do not freeze.
Keep the pre-filled syringe in its blister pack and in the outer carton in order to protect from light. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Pre-filled syringes:
Each carton includes a sealed blister pack with a sterile pre-filled type I glass syringe, containing a target fill volume of 177 microliter solution for injection, sealed with an elastomeric plunger stopper and an elastomeric tip cap that is part of a closure system with Luer lock adaptor. The syringe has a pre-attached plunger rod and a finger plate.

Vials:
Each carton includes a type I glass vial containing a fill volume of 278 microliter solution for injection with an elastomeric rubber stopper, and an 18 G filter needle.

Not all presentations may be marketed.

6.6 Instructions for use / handling

The pre-filled syringe and the vial are for single use in one eye only. 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 aflibercept (equivalent to 50 microliters). The excess volume must be discarded prior to the administration.

Prior to administration visually inspect the solution for injection. Do not use the vial or 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, the unopened vial or blister pack of EYLEA may be stored at room temperature (25 °C / 77°F) for up to 24 hours. After opening the vial or blister pack, proceed under aseptic conditions.

BD Blunt Filter (Fill) Needle, **not** for skin injection
Do **not** autoclave the BD Blunt Filter (Fill) Needle.
The filter needle is non-pyrogenic. Do **not** use it if individual packaging is damaged.
Discard the used BD Blunt Filter (Fill) Needle in approved sharps collector.
Caution: Re-use of the filter needle may lead to infection or other illness/injury.

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

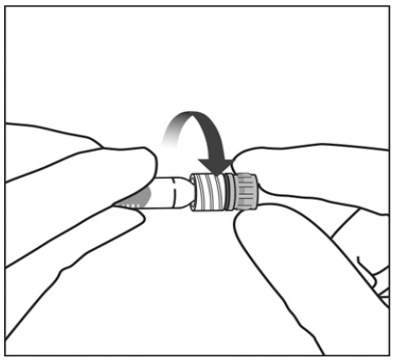
Pre-filled syringe:

1. When ready to administer EYLEA, open the carton and remove the sterilized blister pack.

Carefully peel open the blister pack ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.

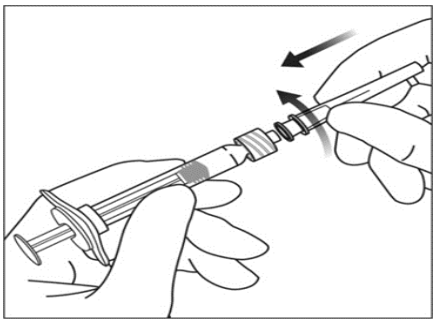
2. Using aseptic technique, remove the syringe from the sterilized blister pack.

3. To remove the syringe cap, hold the syringe in one hand while using your other hand to grasp the syringe cap with the thumb and fore finger. Please note: Twist off (do not snap off),the syringe cap.

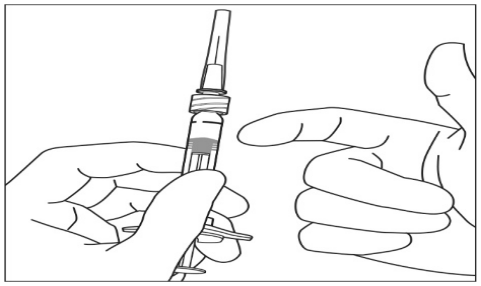


4. To avoid compromising the sterility of the product, do not pull back on the plunger.

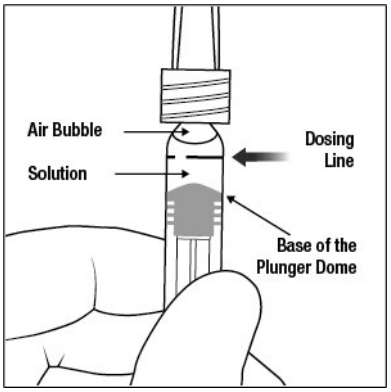
5. Using aseptic technique, firmly twist the injection needle onto the Luer-lock syringe tip.

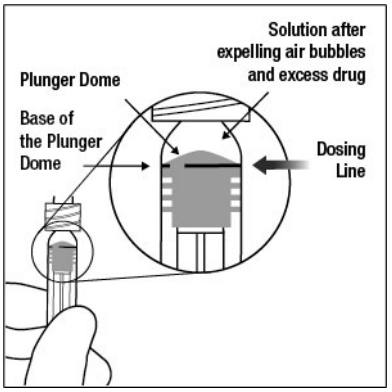


6. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.



7. To eliminate all bubbles and to expel excess drug, 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 microliters 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 labeled dose.



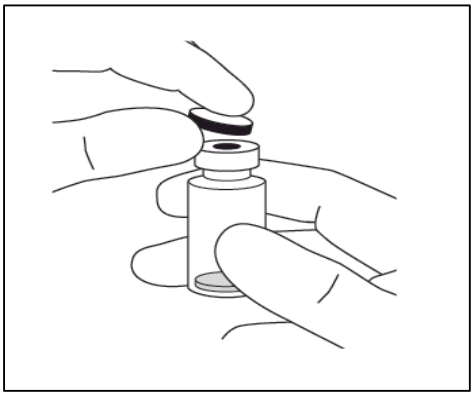


8. Inject by pressing the plunger carefully and with constant pressure until the stop. Do not apply additional pressure once the plunger has reached the bottom of the syringe. **Do not administer any residual solution observed in the syringe.**

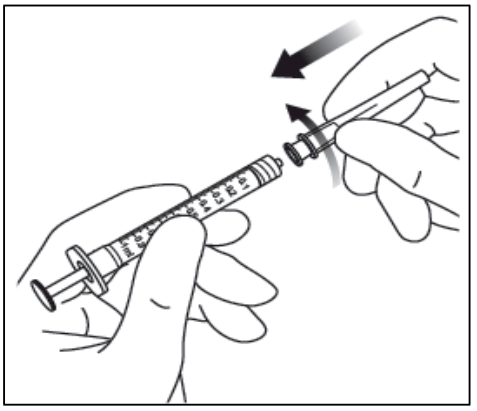
9 The pre-filled syringe is for single use only. After injection any unused product must be discarded.

Vials:

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

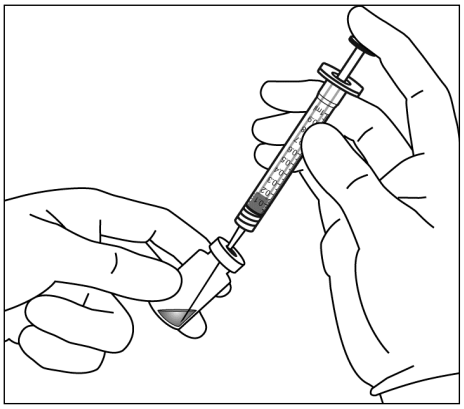


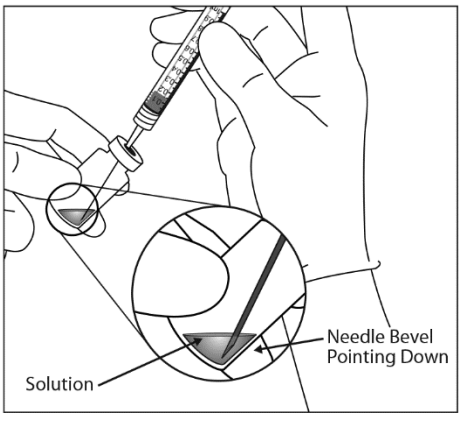
2. Attach the 18 G, 5-micron filter needle supplied in the carton to a 1-ml sterile, Luer-lock syringe.



3. Push the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or the bottom edge of the vial.

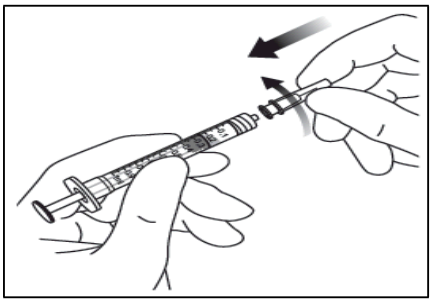
4. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid.





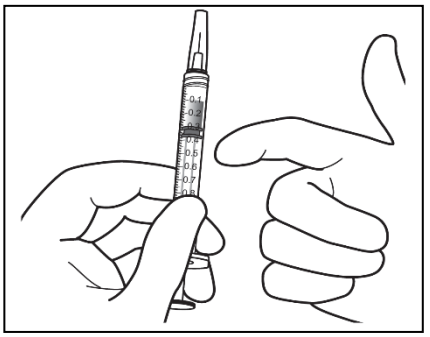
5. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle. After injection any unused product must be discarded.

6. Remove the filter needle and properly dispose of it. **Note**: Filter needle is **not** to be used for intravitreal injection.

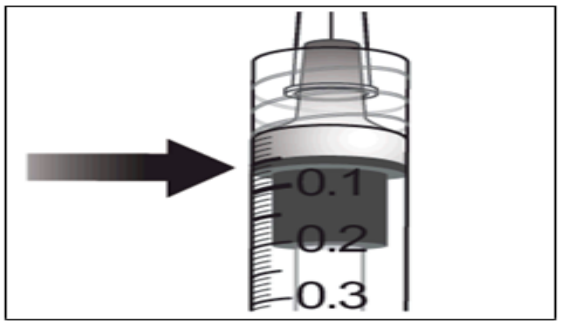


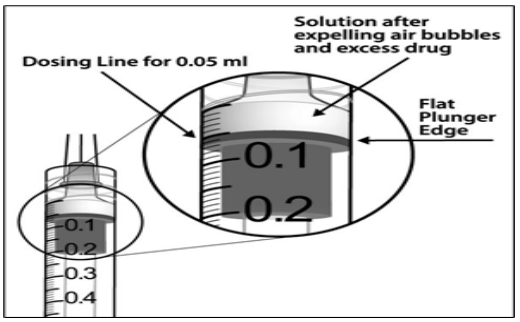
7. Using aseptic technique, firmly twist a 30 G x ½ inch injection needle to the Luer-lock syringe tip.

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 drug by slowly depressing the plunger so that the flat plunger edge aligns with the line that marks 0.05 ml on the syringe.





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