**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use EYLEA safely and effectively. See full prescribing information for EYLEA.**

**EYLEA™ (aflibercept) Injection**
**For Intravitreal Injection**
**Initial U.S. Approval: 2011**

**RECENT MAJOR CHANGES**

- Indications and Usage, Macular Edema Following Central Retinal Vein Occlusion (CRVO) (1.2) 9/2012
- Dosage and Administration, Macular Edema Following Central Retinal Vein Occlusion (CRVO) (2.3) 9/2012
- Dosage and Administration, Preparation for Administration (2.4) 9/2012
- Contraindications, Hypersensitivity (4.3) 9/2012
- Warnings and Precautions, Thromboembolic Events (5.3) 9/2012

**INDICATIONS AND USAGE**

EYLEA is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Central Retinal Vein Occlusion (CRVO) (1.2)

**DOSAGE AND ADMINISTRATION**

For ophthalmic intravitreal injection only. (2.1)

**Neovascular (Wet) Age-Related Macular Degeneration (AMD)**

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.2)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks. (2.2)

**Macular Edema Following Central Retinal Vein Occlusion (CRVO)**

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly). (2.3)

**DOSAGE FORMS AND STRENGTHS**

40 mg/mL solution for intravitreal injection in a single-use vial (3)

**CONTRAINDICATIONS**

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

**WARNINGS AND PRECAUTIONS**

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. (5.1)
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection. (5.2)
- There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. (5.3)

**ADVERSE REACTIONS**

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure. (6.2)

**To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-855-395-3248 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: 9/2012**

**FULL PRESCRIBING INFORMATION: CONTENTS***

**1 INDICATIONS AND USAGE**
1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
1.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)
**2 DOSAGE AND ADMINISTRATION**
2.1 General Dosing Information
2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
2.3 Macular Edema Following Central Retinal Vein Occlusion (CRVO)
2.4 Preparation for Administration
2.5 Administration
**3 DOSAGE FORMS AND STRENGTHS**
**4 CONTRAINDICATIONS**
4.1 Ocular or Periocular Infections
4.2 Active Intraocular Inflammation
4.3 Hypersensitivity
**5 WARNINGS AND PRECAUTIONS**
5.1 Endophthalmitis and Retinal Detachments
5.2 Increase in Intraocular Pressure
5.3 Thromboembolic Events
**6 ADVERSE REACTIONS**
6.1 Injection Procedure
6.2 Clinical Studies Experience
6.3 Immunogenicity
**8 USE IN SPECIFIC POPULATIONS**
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
**11 DESCRIPTION**
**12 CLINICAL PHARMACOLOGY**
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
**13 NONCLINICAL TOXICOLOGY**
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
**14 CLINICAL STUDIES**
14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)
**16 HOW SUPPLIED/STORAGE AND HANDLING**
**17 PATIENT COUNSELING INFORMATION**

***Sections or subsections omitted from the full prescribing information are not listed**

# FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

EYLEA is indicated for the treatment of patients with:

### 1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

### 1.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

## 2 DOSAGE AND ADMINISTRATION

### 2.1 General Dosing Information

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY. EYLEA must only be administered by a qualified physician.

### 2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.1)*].

### 2.3 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly) [*see Clinical Studies (14.2)*].

### 2.4 Preparation for Administration

EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle.

**Vial**

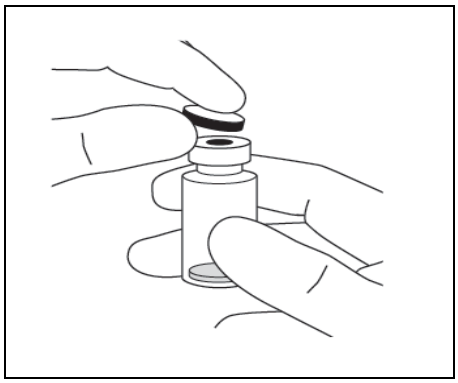
The glass vial is for single use only.



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 2
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

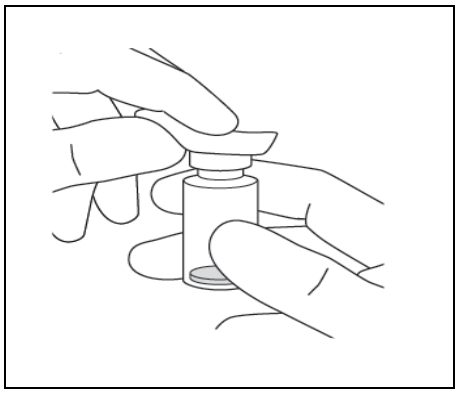
1. Remove the protective plastic cap from the vial (see Figure 1).

**Figure 1:**



2. Clean the top of the vial with an alcohol wipe (see Figure 2).

**Figure 2:**

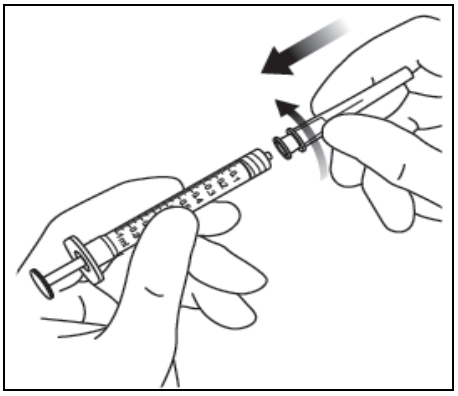


3. Remove the 19-gauge x 1½-inch, 5-micron, filter needle from its pouch and remove the 1-mL syringe supplied in the carton from its pouch. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip (see Figure 3).



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 3
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

**Figure 3:**



4. 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 bottom edge of the vial.

5. 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 (see Figures 4a and 4b).

**Figure 4a:**

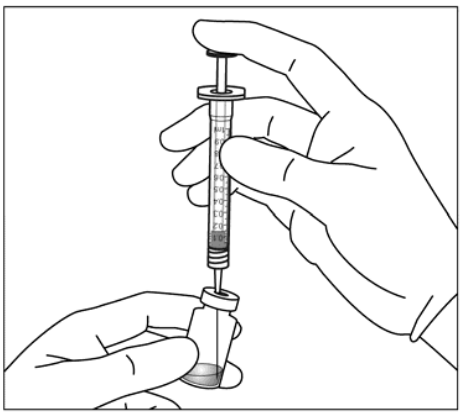
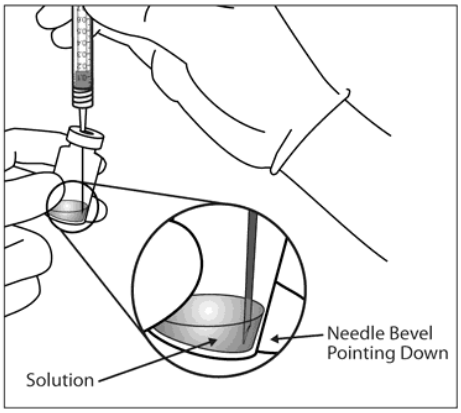


**Figure 4b:**




6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

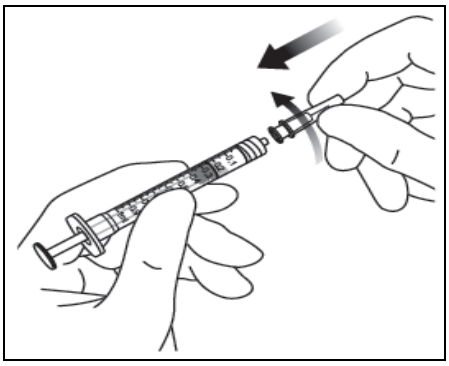
7. Remove the filter needle from the syringe and properly dispose of the filter needle.
**Note**: Filter needle is **not** to be used for intravitreal injection.



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 4
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

8. Remove the 30-gauge x ½-inch injection needle from the plastic pouch and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 5).

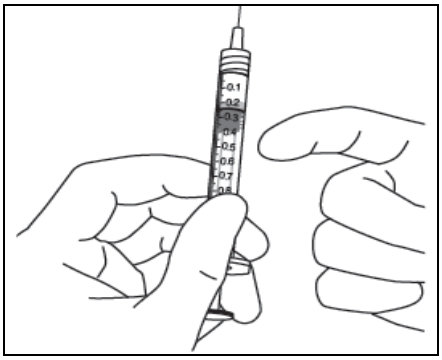
**Figure 5:**



9. When ready to administer EYLEA, remove the plastic needle shield from the needle.

10. 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 (see Figure 6).

**Figure 6:**



11. To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.05 mL on the syringe (see Figures 7a and 7b).



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 5
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

**Figure 7a:**

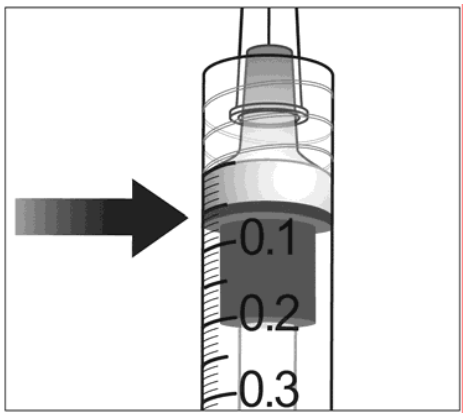
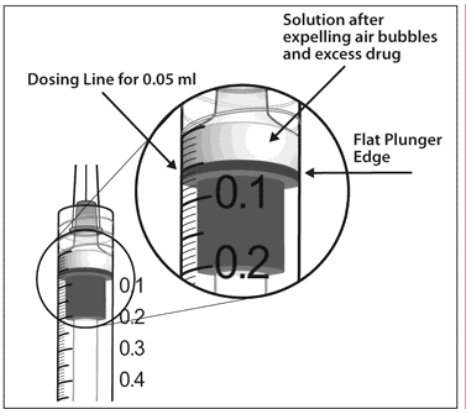



**Figure 7b:**




## 2.5 Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

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 needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay [*see Patient Counseling Information (17)*].

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

# 3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution for intravitreal injection.



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 6
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

# 4 CONTRAINDICATIONS

## 4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

## 4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

## 4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as severe intraocular inflammation.

# 5 WARNINGS AND PRECAUTIONS

## 5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.5) and Patient Counseling Information (17)*].

## 5.2 Increase in Intraocular Pressure

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.5)*].

## 5.3 Thromboembolic Events

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence in the VIEW1 and VIEW2 wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA [*see Clinical Studies (14.1)*]. The incidence in the COPERNICUS and GALILEO CRVO studies during the first 6 months was 0% (0/218) in patients treated with EYLEA 2 mg every 4 weeks compared with 1.4% (2/142) in patients receiving sham treatment [*see Clinical Studies (14.2)*].



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 7
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

# 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions (5)* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

## 6.1 Injection Procedure

Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis, traumatic cataract, increased intraocular pressure, and vitreous detachment.

## 6.2 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2042 patients treated with EYLEA constituted the safety population in four phase 3 studies. Among those, 1441 patients were treated with the recommended dose of 2 mg.

### Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months [*see Clinical Studies (14.1)*].

**Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies**

| Adverse Reactions | EYLEA (N=1824) | Active Control (ranibizumab) (N=595) |
|---|---|---|
| Conjunctival hemorrhage | 25% | 28% |
| Eye pain | 9% | 9% |
| Cataract | 7% | 7% |



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 8
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

| Adverse Reactions | EYLEA (N=1824) | Active Control (ranibizumab) (N=595) |
|---|---|---|
| Vitreous detachment | 6% | 6% |
| Vitreous floaters | 6% | 7% |
| Intraocular pressure increased | 5% | 7% |
| Conjunctival hyperemia | 4% | 8% |
| Corneal erosion | 4% | 5% |
| Detachment of the retinal pigment epithelium | 3% | 3% |
| Injection site pain | 3% | 3% |
| Foreign body sensation in eyes | 3% | 4% |
| Lacrimation increased | 3% | 1% |
| Vision blurred | 2% | 2% |
| Retinal pigment epithelium tear | 2% | 1% |
| Injection site hemorrhage | 1% | 2% |
| Eyelid edema | 1% | 2% |
| Corneal edema | 1% | 1% |

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were retinal detachment, retinal tear, and endophthalmitis. Hypersensitivity has also been reported in less than 1% of the patients treated with EYLEA.

**Macular Edema Following Central Retinal Vein Occlusion (CRVO)**

The data described below reflect exposure to EYLEA in 218 patients with macular edema following CRVO treated with 2 mg dose in 2 double-masked, controlled clinical studies (COPERNICUS and GALILEO) for 6 months [*see Clinical Studies (14.2)*].

**Table 2: Most Common Adverse Reactions (≥1%) in CRVO Studies**

| Adverse Reactions | EYLEA (N=218) | Control (N=142) |
|---|---|---|
| Eye pain | 13% | 5% |
| Conjunctival hemorrhage | 12% | 11% |
| Intraocular pressure increased | 8% | 6% |
| Corneal erosion | 5% | 4% |
| Vitreous floaters | 5% | 1% |



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 9
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

| Adverse Reactions | EYLEA (N=218) | Control (N=142) |
|---|---|---|
| Conjunctival hyperemia | 5% | 3% |
| Foreign body sensation in eyes | 3% | 5% |
| Vitreous detachment | 3% | 4% |
| Lacrimation increased | 3% | 4% |
| Injection site pain | 3% | 1% |
| Vision blurred | 1% | <1% |

Less common adverse reactions reported in <1% of the patients treated with EYLEA were cataract, eyelid edema, corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

## 6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD and CRVO studies, the pre-treatment incidence of immunoreactivity to EYLEA was 1% to 3% across treatment groups. After dosing with EYLEA for 52 weeks (wet AMD), or 24 weeks (CRVO), antibodies to EYLEA were detected in a similar percentage range of patients. Both in the wet AMD and in the CRVO studies, there were no differences in efficacy or safety between patients with or without immunoreactivity.

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered during organogenesis in pregnant rabbits at intravenous doses of 3 to 60 mg/kg. A series of external, visceral, and skeletal malformations were observed in the fetuses. The maternal No Observed Adverse Effect Level (NOAEL) was 3 mg/kg, whereas the fetal NOAEL was below 3 mg/kg. At this dose, the systemic exposures based on $C_{max}$ and AUC for free aflibercept were approximately 2900 times and 600 times higher, respectively, when compared to corresponding values observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 10
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

## 8.3 Nursing Mothers

It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

## 8.4 Pediatric Use

The safety and effectiveness of EYLEA in pediatric patients have not been established.

## 8.5 Geriatric Use

In the clinical studies, approximately 85% (1728/2034) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 58% (1177/2034) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

# 11 DESCRIPTION

EYLEA (aflibercept) is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept is produced in recombinant Chinese hamster ovary (CHO) cells.

EYLEA is a sterile, clear, and colorless to pale yellow solution. EYLEA is supplied as a preservative-free, sterile, aqueous solution in a single-use, glass vial designed to deliver 0.05 mL (50 microliters) of EYLEA (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2).

# 12 CLINICAL PHARMACOLOGY

## 12.1 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 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. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors.



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 11
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

## 12.2 Pharmacodynamics

**Neovascular (Wet) Age-Related Macular Degeneration (AMD)**

In the clinical studies anatomic measures of disease activity improved similarly in all treatment groups from baseline to week 52. Anatomic data were not used to influence treatment decisions. [*see Clinical Studies (14.1)*].

**Macular Edema Following Central Retinal Vein Occlusion (CRVO)**

Reductions in mean retinal thickness were observed in COPERNICUS and GALILEO at Week 24 compared to baseline. Anatomic data were not used to influence treatment decisions. [*see Clinical Studies (14.2)*].

## 12.3 Pharmacokinetics

EYLEA is administered intravitreally to exert local effects in the eye. In patients with wet AMD or CRVO, following intravitreal administration of EYLEA, a fraction of the administered dose is expected to bind with endogenous VEGF in the eye to form an inactive aflibercept: VEGF complex. Once absorbed into the systemic circulation, aflibercept presents in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., aflibercept: VEGF complex).

*Absorption/Distribution*

Following intravitreal administration of 2 mg per eye of EYLEA to patients with wet AMD and CRVO, the mean $C_{max}$ of free aflibercept in the plasma was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL) and 0.05 mcg/mL (range 0 to 0.081 mcg/mL), respectively and was attained in 1 to 3 days. The free aflibercept plasma concentrations were undetectable two weeks post-dosing in all patients. Aflibercept did not accumulate in plasma when administered as repeated doses intravitreally every 4 weeks. It is estimated that after intravitreal administration of 2 mg to patients, the mean maximum plasma concentration of free aflibercept is more than 100 fold lower than the concentration of aflibercept required to half-maximally bind systemic VEGF.

The volume of distribution of free aflibercept following intravenous (I.V.) administration of aflibercept has been determined to be approximately 6L.

*Metabolism/Elimination*

Aflibercept is a therapeutic protein and no drug metabolism studies have been conducted. Aflibercept is expected to undergo elimination through both target-mediated disposition via binding to free endogenous VEGF and metabolism via proteolysis. The terminal elimination half-life (t1/2) of free aflibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 12
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

**Specific Populations**

*Renal Impairment*

Pharmacokinetic analysis of a subgroup of patients (n=492) in one wet AMD study, of which 43% had renal impairment (mild n=120, moderate n=74, and severe n=16), revealed no differences with respect to plasma concentrations of free aflibercept after intravitreal administration every 4 or 8 weeks. Similar results were seen in patients in a CRVO study. No dose adjustment based on renal impairment status is needed for either wet AMD or CRVO patients.

# 13 NONCLINICAL TOXICOLOGY

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. 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. In addition, females showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy. A No Observed Adverse Effect Level (NOAEL) was not identified. Based on $C_{max}$ and AUC for free aflibercept observed at the lowest dose used of 3 mg/kg, the systemic exposures were approximately 4900 times and 1500 times higher, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible.

## 13.2 Animal Toxicology and/or Pharmacology

Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at intravitreal doses of 2 or 4 mg/eye. At the NOAEL of 0.5 mg/eye in monkeys, the systemic exposure was 42 times and 56 times higher based on $C_{max}$ and AUC, respectively, than the exposure observed in humans after an intravitreal dose of 2 mg. Similar effects were not seen in clinical studies [*see Clinical Studies (14)*].

# 14 CLINICAL STUDIES

## 14.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 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 2 mg every 8 weeks following 3 initial monthly doses (EYLEA 2Q8);



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 13
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); 3) EYLEA 0.5 mg administered every 4 weeks (EYLEA 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). Patient ages ranged from 49 to 99 years with a mean of 76 years.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Data are available through week 52. Both EYLEA 2Q8 and EYLEA 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group.

Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in Table 3 and Figure 8 below.

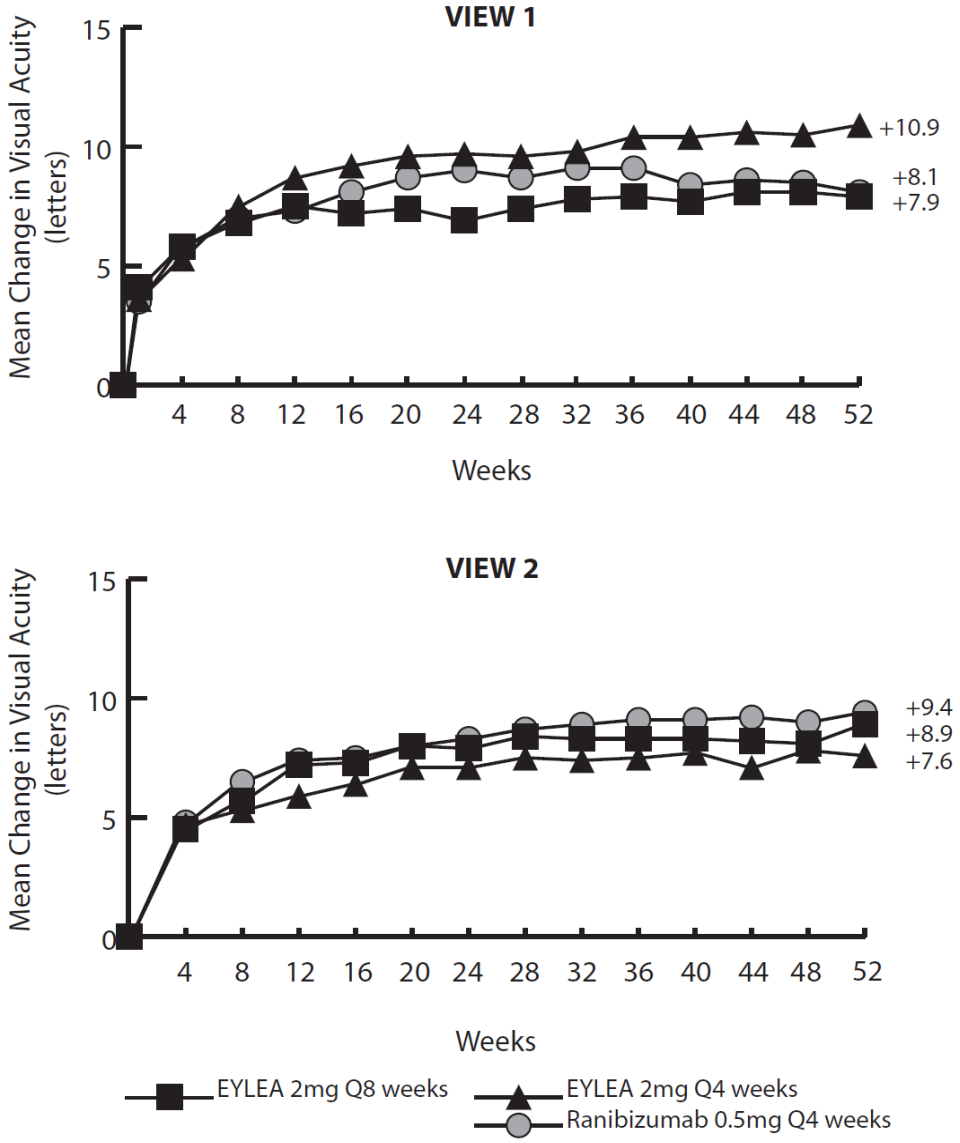
**Table 3: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies**

| | **VIEW1** | | | **VIEW2** | | |
|---|---|---|---|---|---|---|
| | EYLEA 2 mg Q8 weeks [a] | EYLEA 2 mg Q4 weeks | ranibizu-mab 0.5 mg Q4 weeks | EYLEA 2 mg Q8 weeks [a] | EYLEA 2 mg Q4 weeks | ranibizu-mab 0.5 mg Q4 weeks |
| Full Analysis Set | N=301 | N=304 | N=304 | N=306 | N=309 | N=291 |
| **Efficacy Outcomes** | | | | | | |
| Proportion of patients who maintained visual acuity (%) (<15 letters of BCVA loss) | 94% | 95% | 94% | 95% | 95% | 95% |
| Difference[b] (%) (95.1% CI) | 0.6 (-3.2, 4.4) | 1.3 (-2.4, 5.0) | | 0.6 (-2.9, 4.0) | -0.3 (-4.0, 3.3) | |
| Mean change in BCVA as measured by ETDRS letter score from Baseline | 7.9 | 10.9 | 8.1 | 8.9 | 7.6 | 9.4 |
| Difference[b] in LS mean (95.1% CI) | 0.3 (-2.0, 2.5) | 3.2 (0.9, 5.4) | | -0.9 (-3.1, 1.3) | -2.0 (-4.1, 0.2) | |
| Number of patients who gained at least 15 letters of vision from Baseline (%) | 92 (31%) | 114 (38%) | 94 (31%) | 96 (31%) | 91 (29%) | 99 (34%) |
| Difference[b] (%) (95.1% CI) | -0.4 (-7.7, 7.0) | 6.6 (-1.0, 14.1) | | -2.6 (-10.2, 4.9) | -4.6 (-12.1, 2.9) | |

BCVA = Best Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCF = Last Observation Carried Forward (baseline values are not carried forward); 95.1% confidence intervals were presented to adjust for safety assessment conducted during the study.

[a] After treatment initiation with 3 monthly doses
[b] EYLEA group minus the ranibizumab group

**Figure 8: Mean Change in Visual Acuity from Baseline to Week 52 in VIEW1 and VIEW2 Studies**




## 14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, sham-controlled studies in patients with macular edema following CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with EYLEA) in the two studies



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 15
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

(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 sham injections (control group) administered every 4 weeks for a total of 6 injections. 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 compared to baseline. At week 24, the EYLEA 2 mg Q4 group was superior to the control group for the primary endpoint.

Results from the analysis of the COPERNICUS and GALILEO studies are shown in Table 4 and Figure 9 below.

**Table 4: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in COPERNICUS and GALILEO Studies**

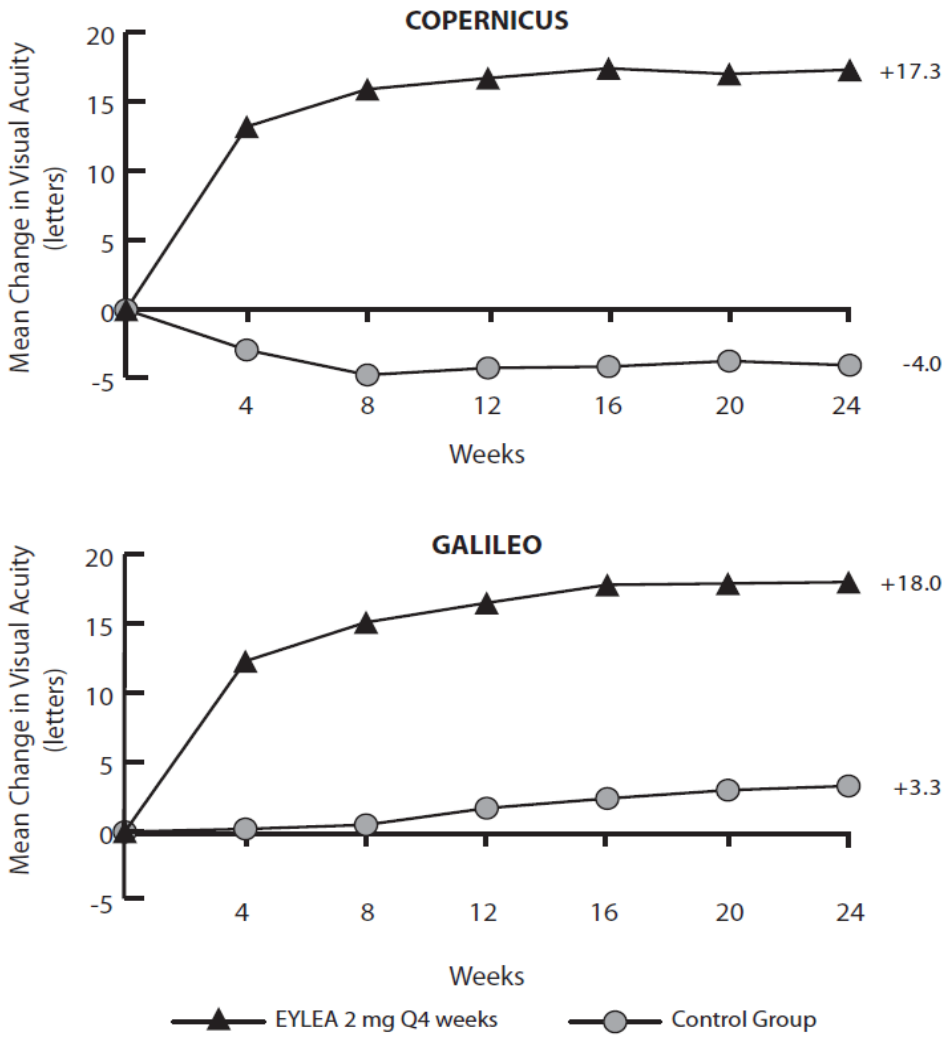
| | **COPERNICUS** | | **GALILEO** | |
|---|---|---|---|---|
| | Control | EYLEA 2 mg Q4 weeks | Control | EYLEA 2 mg Q4 weeks |
| | N=73 | N=114 | N=68 | N=103 |
| **Efficacy Outcomes** | | | | |
| Proportion of patients who gained at least 15 letters in BCVA from Baseline (%) | 12% | 56% | 22% | 60% |
| Weighted Difference [a,b] (%) (95.1% CI) | | 44.8%[c] (32.9, 56.6) | | 38.3%[c] (24.4, 52.1) |
| Mean change in BCVA as measured by ETDRS letter score from Baseline (SD) | -4.0 (18.0) | 17.3 (12.8) | 3.3 (14.1) | 18.0 (12.2) |
| Difference in LS mean [a,d] (95.1% CI) | | 21.7[c] (17.3, 26.1) | | 14.7[c] (10.7, 18.7) |

[a] Difference is EYLEA 2 mg Q4 weeks minus Control
[b] Difference and CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for baseline factors; 95.1% confidence intervals were presented to adjust for the multiple assessments conducted during the study.
[c] $p<0.01$ compared with control
[d] LS mean and CI based on an ANCOVA model



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 16
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

**Figure 9: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in COPERNICUS and GALILEO Studies**




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

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Each Vial is for single eye use only. EYLEA is supplied in the following presentation [*see Dosage and Administration (2.4) and (2.5)*].



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 17
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

| NDC NUMBER | CARTON TYPE | CARTON CONTENTS |
|---|---|---|
| 61755-005-02 | Vial | one single-use, sterile, 3-mL, glass vial containing a 0.278 mL fill of 40 mg/mL EYLEA<br>one 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents<br>one 30-gauge x ½-inch injection needle for intravitreal injection<br>one 1-mL syringe for administration<br>one package insert |

**Storage**

EYLEA should be refrigerated at 2°C to 8ºC (36°F to 46ºF). Do Not Freeze. Do not use beyond the date stamped on the carton and container label. Protect from light. Store in the original carton until time of use.

## 17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patient should seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Patients should be advised not to drive or use machinery until visual function has recovered sufficiently.



Regeneron Pharmaceuticals, Inc. Exhibit 2161 Page 18
Samsung Bioepis Co., Ltd. and Biocon Biologics Inc. v. Regeneron Pharmaceuticals, Inc. IPR2023-00739

REGENERON

Manufactured by:

Regeneron Pharmaceuticals, Inc.

777 Old Saw Mill River Road

Tarrytown, NY 10591-6707

U.S. License Number 1760

EYLEA™ is a trademark of Regeneron Pharmaceuticals, Inc.

© 2012, Regeneron Pharmaceuticals, Inc.

All rights reserved.

V X.0

Issue Date: 9/2012

Initial U.S. Approval: 2011

Regeneron U.S. Patents 7,306,799; 7,531,173; 7,608,261; 7,070,959; 7,374,757; 7,374,758, and other pending patents