

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125387Orig1s060

Trade Name: EYLEA

Generic or Proper Name: Aflibercept

Sponsor: Regeneron Inc.

Approval Date: August 12, 2019

Indication: EYLEA is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)

CENTER FOR DRUG EVALUATION AND RESEARCH

125387Orig1s060

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



BLA 125387/S-060

APPROVAL LETTER

Regeneron Pharmaceuticals, Inc.
Attention: Candace Drumma
Senior Manager Cmc Regulatory Affairs
81 Columbia Turnpike, Bldg 85
Rensselaer, NY 12144

Dear Ms. Drumma:

Please refer to your Supplemental Biologics License Application (sBLA) dated and received April 12, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Eylea (afibercept) injection, 2 mg/0.05 mL.

We acknowledge receipt of your amendment dated April 12, 2019, which constituted a complete response to our October 15, 2018, action letter.

This Prior Approval supplemental biologics license application provides for the addition of a new sterile 2 mg/0.05 mL single-dose pre-filled syringe (PFS) presentation for afibercept drug product. The PFS is filled at (b) (4)

sterilized blister pack ((b) (4)

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the prescribing information) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled *SPL Standard for Content of Labeling Technical Qs and As* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels submitted on October 9, 2018 and trade carton labeling submitted on July 24, 2019 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125387/S-060.**" Approval of this submission by FDA is not required before the labeling is used.

This information will be included in your biologics license application file.

If you have any questions, call Andrew Shiber, Regulatory Business Process Manager, at (301) 796 - 4798.

Sincerely,

{See appended electronic signature page}

Kathleen A. Clouse, Ph.D.
Director
Division of Biotechnology Review and Research I
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure(s):

Content of Labeling
Carton and Container Labeling

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125387Orig1s060

LABELING

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 Use
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

- Indications and Usage (1) 5/2019
- Dosage and Administration (2) X/201X
- Warnings and Precautions, Thromboembolic Events (5.3) 8/2018

INDICATIONS AND USAGE

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
- Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
- Diabetic Macular Edema (DME) (1.3)
- Diabetic Retinopathy (DR) (1.4)

DOSAGE AND ADMINISTRATION

- **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 (approximately every 28 days, 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 (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). (2.2)
 - Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly. (2.2)
- **Macular Edema Following Retinal Vein Occlusion (RVO)**
 - The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly). (2.3)

- **Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)**

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.4, 2.5)
- Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months). (2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

- Injection: 2 mg/0.05 mL solution in a single-dose pre-filled syringe (3)
- Injection: 2 mg/0.05 mL solution in a single-dose 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 ($\geq 5\%$) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased. (6.1)

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: X/201X

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- 1.2 Macular Edema Following Retinal Vein Occlusion (RVO)
- 1.3 Diabetic Macular Edema (DME)
- 1.4 Diabetic Retinopathy (DR)

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- 2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD)
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- 2.4 Diabetic Macular Edema (DME)
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- 14.4 Diabetic Macular Edema (DME)

- 14.5 Diabetic Retinopathy (DR)

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*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:

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

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions

For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

Pre-filled Syringe: A 30-gauge × ½-inch sterile injection needle is needed but not provided.

Vial: A 5-micron sterile filter needle (19-gauge × 1½-inch), a 1-mL Luer lock syringe and a 30-gauge × ½-inch sterile injection needle are needed.

EYLEA is available packaged as follows:

- Pre-filled Syringe
- Vial Kit with Injection Components (filter needle, syringe, injection needle)

[see *How Supplied/Storage and Handling (16)*].

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 (approximately every 28 days, 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 (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [see *Clinical Studies (14.1)*]. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.

2.3 Macular Edema Following Retinal Vein Occlusion (RVO)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly) [*see Clinical Studies (14.2), (14.3)*].

2.4 Diabetic Macular Edema (DME)

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, 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 (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.4)*]. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.5 Diabetic Retinopathy (DR)

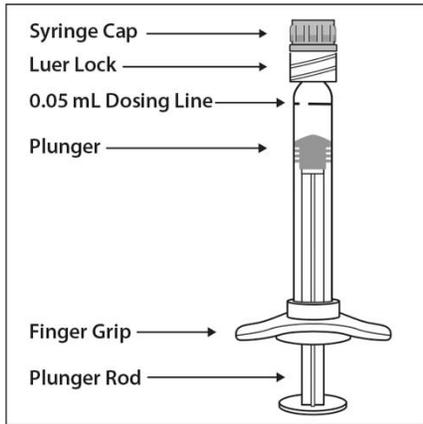
The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.5)*]. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.6 Preparation for Administration - Pre-filled Syringe

The EYLEA pre-filled glass syringe is sterile and for single use only. It should be inspected visually prior to administration. **Do not** use if particulates, cloudiness, or discoloration are visible, or if the package is open or damaged.

The intravitreal injection should be performed with a 30-gauge x ½-inch injection needle (not provided).

PRE-FILLED SYRINGE DESCRIPTION – Figure 1:



Use aseptic technique to carry out the following steps:

1. PREPARE

When ready to administer EYLEA, open the carton and remove sterilized blister pack. Carefully peel open the sterilized blister pack ensuring the sterility of its contents. Keep the syringe in the sterile tray until you are ready for assembly.

2. REMOVE SYRINGE

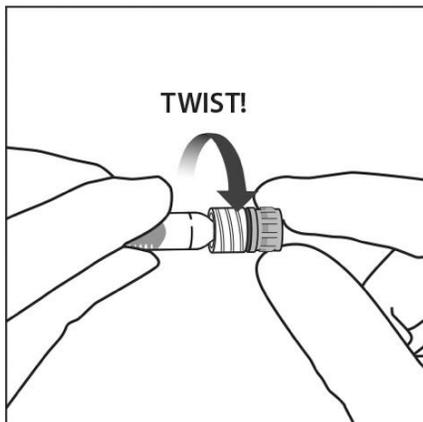
Using aseptic technique, remove the syringe from the sterilized blister pack.

3. TWIST OFF SYRINGE CAP

Twist off the syringe cap by holding the syringe in one hand and the syringe cap with the thumb and forefinger of the other hand (see [Figure 2](#)).

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

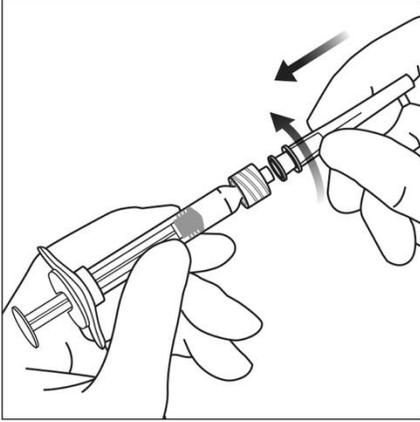
Figure 2:



4. ATTACH NEEDLE

Using aseptic technique, firmly twist a 30-gauge x ½-inch injection needle onto the Luer lock syringe tip (see [Figure 3](#)).

Figure 3:

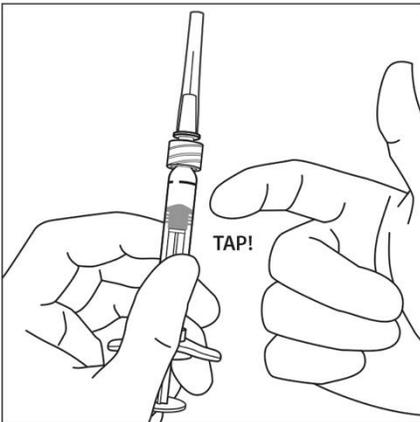


Note: When ready to administer EYLEA, remove the plastic needle shield from the needle.

5. DISLODGE AIR BUBBLES

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 4](#)).

Figure 4:



6. EXPEL AIR AND SET THE DOSE

To eliminate all bubbles and to expel excess drug, slowly depress the plunger rod to align the plunger dome edge (see [Figure 5a](#)) with the black dosing line on the syringe (equivalent to 50 microliters) (see [Figure 5b](#)).

Figure 5a:

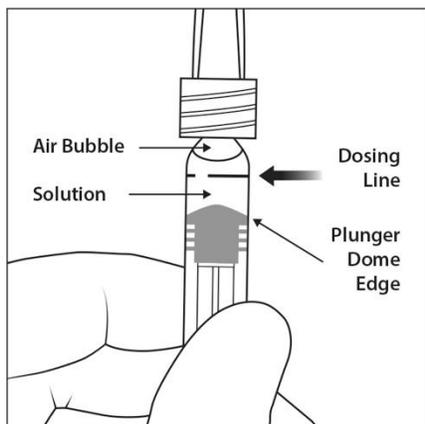
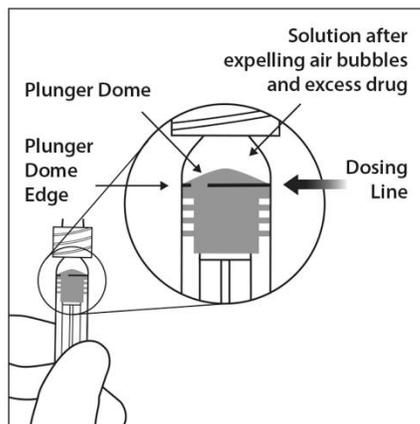


Figure 5b:



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

2.7 Preparation for Administration - Vial

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

The glass vial is for single use only.

Use aseptic technique to carry out the following preparation steps:

Prepare for intravitreal injection with the following medical devices for single use:

- a 5-micron sterile filter needle (19-gauge × 1½-inch)
- a 1-mL sterile Luer lock syringe (with marking to measure 0.05 mL)
- a sterile injection needle (30-gauge × ½-inch)

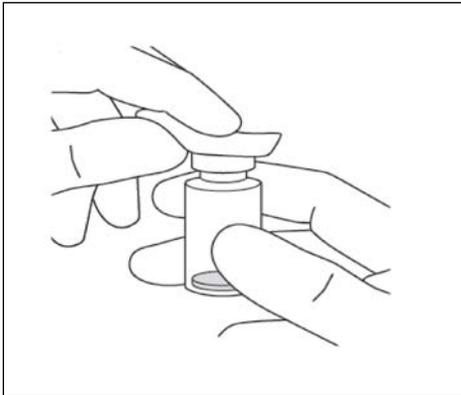
1. Remove the protective plastic cap from the vial (see [Figure 6](#)).

Figure 6:



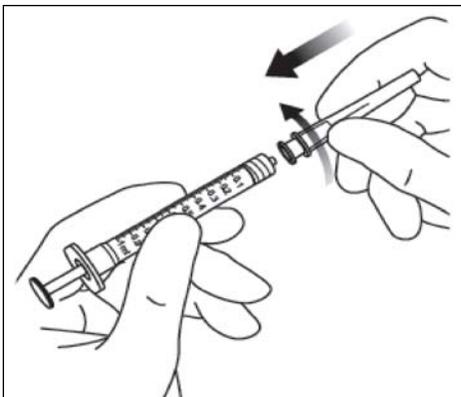
2. Clean the top of the vial with an alcohol wipe (see [Figure 7](#)).

Figure 7:



3. Remove the 19-gauge x 1½-inch, 5-micron, filter needle and the 1-mL syringe from their packaging. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip (see [Figure 8](#)).

Figure 8:



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 [Figure 9a](#) and [Figure 9b](#)).

Figure 9a:

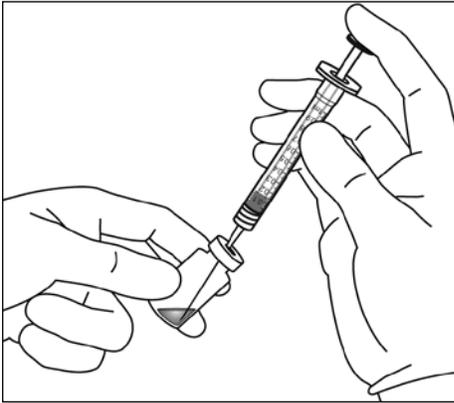
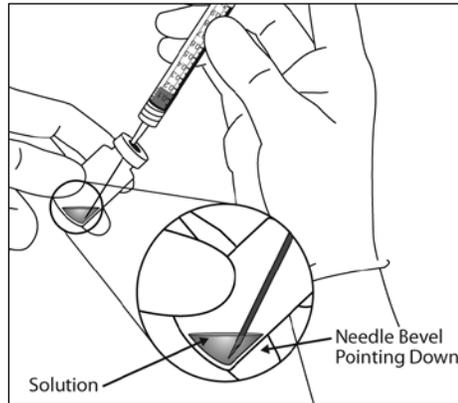
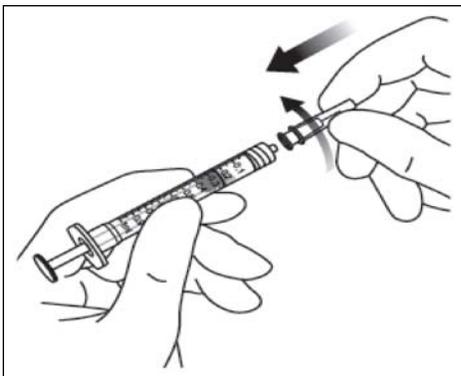


Figure 9b:



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.
8. Remove the 30-gauge x ½-inch injection needle from its packaging and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see [Figure 10](#)).

Figure 10:



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 11](#)).

Figure 11:



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 [Figure 12a](#) and [Figure 12b](#)).

Figure 12a:

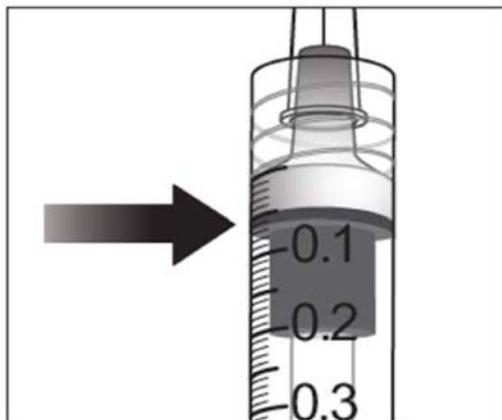
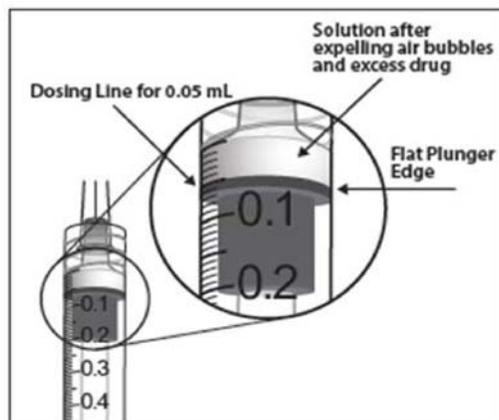


Figure 12b:



2.8 Injection Procedure

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 sterile, pre-filled syringe or vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new sterile, pre-filled syringe or 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.

3 DOSAGE FORMS AND STRENGTHS

EYLEA is a clear, colorless to pale yellow solution available as:

- Injection: 2 mg/0.05 mL in a single-dose pre-filled glass syringe
- Injection: 2 mg/0.05 mL in a single-dose glass vial

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 rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or 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 (2.8)* 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 vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [see *Dosage and Administration (2.8)*].

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 of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [see *Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [see *Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [see *Warnings and Precautions (5.2)*]
- Thromboembolic events [see *Warnings and Precautions (5.3)*]

6.1 Clinical Trials 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 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions ($\geq 5\%$) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

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, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1) [see *Clinical Studies (14.1)*].

Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

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

Adverse Reactions	Baseline to Week 52		Baseline to Week 96	
	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

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

Macular Edema Following Retinal Vein Occlusion (RVO)

The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT) [see *Clinical Studies (14.2), (14.3)*].

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

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

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

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)

The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100 [see *Clinical Studies (14.4)*].

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see [Table 3](#) above).

6.2 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, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [see *Animal Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [see *Clinical Pharmacology (12.1)*], treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥ 3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥ 0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic

exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation

Risk Summary

There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility

There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [*see Nonclinical Toxicology (13.1)*].

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 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥ 65 years of age and approximately 46% (1250/2701) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

11 DESCRIPTION

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 (aflibercept) Injection is a sterile, clear, and colorless to pale yellow solution. EYLEA is supplied as a preservative-free, sterile, aqueous solution for intravitreal injection in a single-dose pre-filled glass syringe or a single-dose glass vial designed to deliver 0.05 mL (50 microliters) of solution containing 2 mg of aflibercept in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, with a pH of 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.

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 during the first year.

Macular Edema Following Retinal Vein Occlusion (RVO)

Reductions in mean retinal thickness were observed in COPERNICUS, GALILEO, and VIBRANT at week 24 compared to baseline. Anatomic data were not used to influence treatment decisions [see *Clinical Studies (14.2), (14.3)*].

Diabetic Macular Edema (DME)

Reductions in mean retinal thickness were observed in VIVID and VISTA at weeks 52 and 100 compared to baseline. Anatomic data were not used to influence EYLEA treatment decisions [see *Clinical Studies (14.4)*].

12.3 Pharmacokinetics

EYLEA is administered intravitreally to exert local effects in the eye. In patients with wet AMD, RVO, or DME, 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, RVO, and DME, the mean C_{max} of free aflibercept in the plasma was 0.02 mcg/mL (range: 0 to 0.054 mcg/mL), 0.05 mcg/mL (range: 0 to 0.081 mcg/mL), and 0.03 mcg/mL (range: 0 to 0.076 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 ($t_{1/2}$) of free aflibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.

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 RVO study and in patients in a DME study. No dose adjustment based on renal impairment status is needed for either wet AMD, RVO, or DME patients.

Other

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

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 weekly doses ranging from 3 to 30 mg per 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. Intravenous administration of

the lowest dose of aflibercept assessed in monkeys (3 mg per kg) resulted in systemic exposure (AUC) for free aflibercept that was approximately 1500 times higher than the systemic exposure observed in humans after an intravitreal dose of 2 mg. All changes were reversible within 20 weeks after cessation of treatment.

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 per eye. At the NOAEL of 0.5 mg per eye in monkeys, the systemic exposure (AUC) was 56 times higher 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, up to week 52, 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); 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). Protocol-specified visits occurred every 28 ± 3 days. 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. Both EYLEA 2Q8 and EYLEA 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1.

Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in [Table 4](#) and [Figure 13](#) below.

Table 4: 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)	

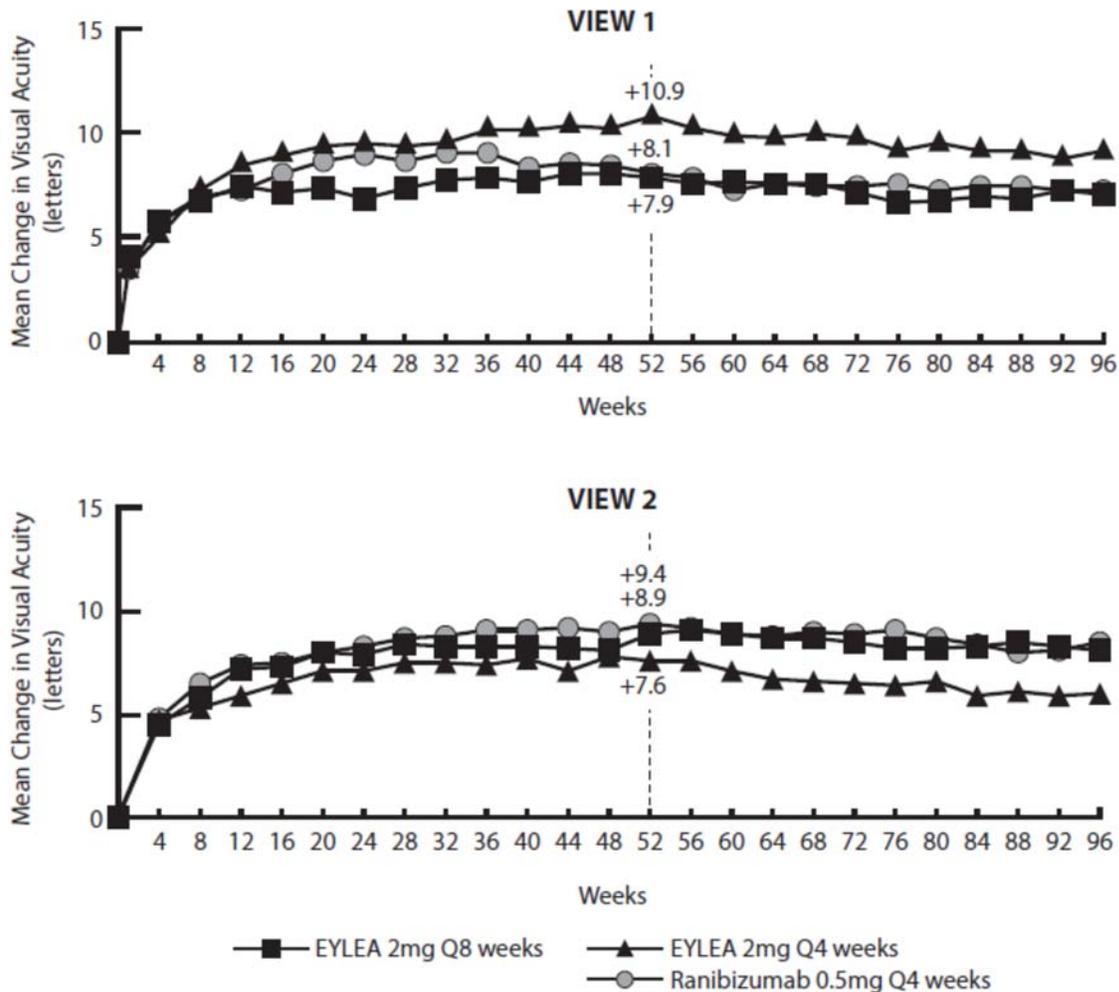
BCVA = Best Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCF = Last Observation Carried Forward (baseline values are not carried forward); 95.1% confidence intervals were presented to adjust for safety assessment conducted during the study

^a After treatment initiation with 3 monthly doses

^b EYLEA group minus the ranibizumab group

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

Figure 13: Mean Change in Visual Acuity from Baseline to Week 96* in VIEW1 and VIEW2 Studies



*Patient dosing schedules were individualized from weeks 52 to 96 using a modified 12-week dosing regimen.

VIEW1 and VIEW2 studies were both 96 weeks in duration. However after 52 weeks patients no longer followed a fixed dosing schedule. Between week 52 and week 96, patients continued to receive the drug and dosage strength to which they were initially randomized on a modified 12 week dosing schedule (doses at least every 12 weeks and additional doses as needed). Therefore, during the second year of these studies there was no active control comparison arm.

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 (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. Protocol-specified visits occurred every 28±7 days. 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 5](#) and [Figure 14](#) below.

Table 5: 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)

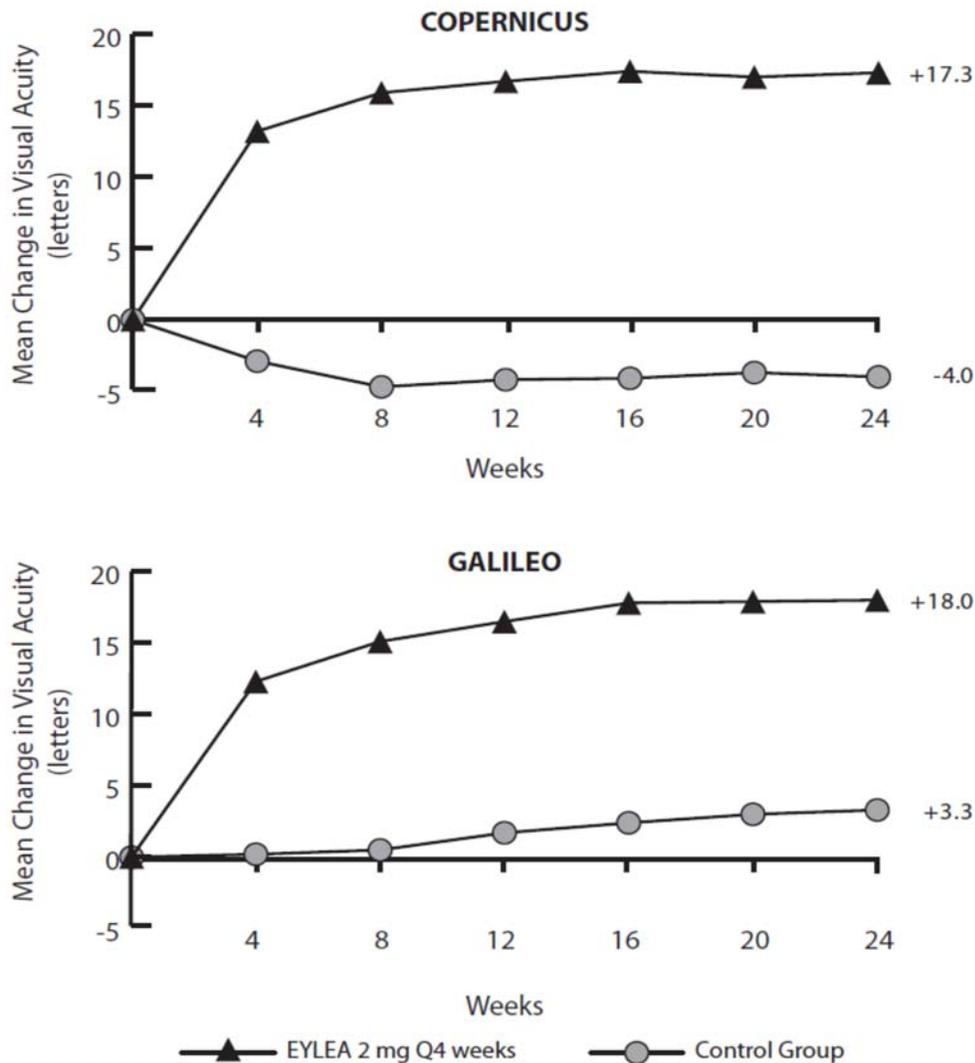
^a Difference is EYLEA 2 mg Q4 weeks minus Control

^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

Figure 14: 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.

14.3 Macular Edema Following Branch Retinal Vein Occlusion (BRVO)

The safety and efficacy of EYLEA were assessed in a 24-week, randomized, multi-center, double-masked, controlled study in patients with macular edema following BRVO. 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) or laser photocoagulation administered at baseline and subsequently as needed (control group). Protocol-specified visits occurred every 28±7 days. 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 2 mg Q4 group was superior to the control group for the primary endpoint.

Detailed results from the analysis of the VIBRANT study are shown in [Table 6](#) and [Figure 15](#) below.

Table 6: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in VIBRANT Study

	VIBRANT	
	Control	EYLEA 2 mg Q4 weeks
	N=90	N=91
Efficacy Outcomes		
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	26.7%	52.7%
Weighted Difference ^{a, b} (%) (95% CI)		26.6% ^c (13.0, 40.1)
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	6.9 (12.9)	17.0 (11.9)
Difference in LS mean ^{a, d} (95% CI)		10.5 ^c (7.1, 14.0)

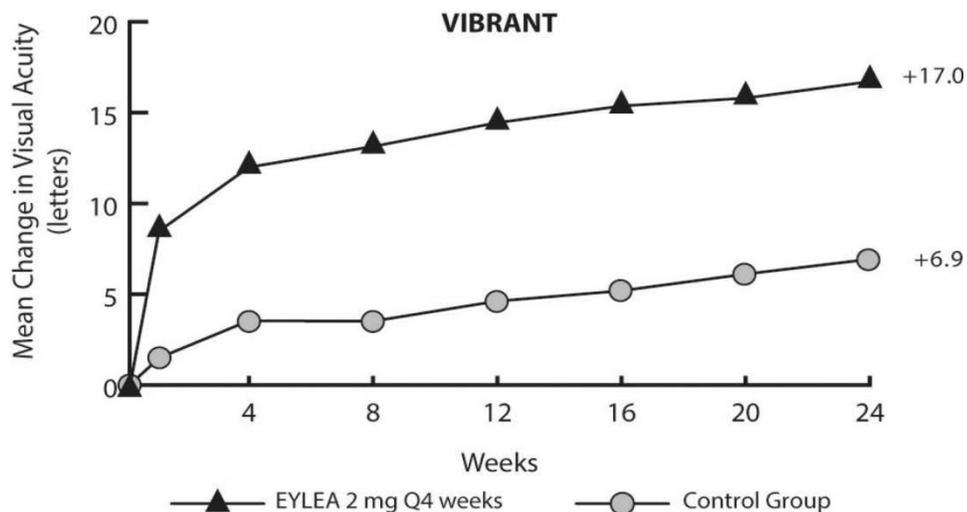
^a Difference is EYLEA 2 mg Q4 weeks minus Control

^b Difference and 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 p<0.01 compared with Control

^d LS mean and CI based on an ANCOVA model

Figure 15: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in VIBRANT Study



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.

14.4 Diabetic Macular Edema (DME)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28 ± 7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years.

Of those, 576 were randomized to EYLEA groups in the two studies (VIVID and VISTA). 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 (at baseline and then as needed). 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.

In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score. Efficacy of both EYLEA 2Q8 and EYLEA 2Q4 groups was statistically superior to the control group. This statistically superior improvement in BCVA was maintained at week 100 in both studies.

Results from the analysis of the VIVID and VISTA studies are shown in [Table 7](#) and [Figure 16](#) below.

Table 7: Efficacy Outcomes at Weeks 52 and 100 (Full Analysis Set with LOCF) in VIVID and VISTA Studies

	VIVID			VISTA		
	EYLEA 2 mg Q8 weeks ^a	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q8 weeks ^a	EYLEA 2 mg Q4 weeks	Control
Full Analysis Set	N=135	N=136	N=132	N=151	N=154	N=154
Efficacy Outcomes at Week 52						
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	10.7 (9.3)	10.5 (9.6)	1.2 (10.6)	10.7 (8.2)	12.5 (9.5)	0.2 (12.5)
Difference ^{b, c} in LS mean (97.5% CI)	9.1 ^d (6.3, 11.8)	9.3 ^d (6.5, 12.0)		10.5 ^d (7.7, 13.2)	12.2 ^d (9.4, 15.0)	
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	33.3%	32.4%	9.1%	31.1%	41.6%	7.8%
Adjusted Difference ^{c, e} (%) (97.5% CI)	24.2% ^d (13.5, 34.9)	23.3% ^d (12.6, 33.9)		23.3% ^d (13.5, 33.1)	34.2% ^d (24.1, 44.4)	
Efficacy Outcomes at Week 100						
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	9.4 (10.5)	11.4 (11.2)	0.7 (11.8)	11.1 (10.7)	11.5 (13.8)	0.9 (13.9)
Difference ^{b, c} in LS mean (97.5% CI)	8.2 ^d (5.2, 11.3)	10.7 ^d (7.6, 13.8)		10.1 ^d (7.0, 13.3)	10.6 ^d (7.1, 14.2)	
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	31.1%	38.2%	12.1%	33.1%	38.3%	13.0%
Adjusted Difference ^{c, e} (%) (97.5% CI)	19.0% ^d (8.0, 29.9)	26.1% ^d (14.8, 37.5)		20.1% ^d (9.6, 30.6)	25.8% ^d (15.1, 36.6)	

^a After treatment initiation with 5 monthly injections

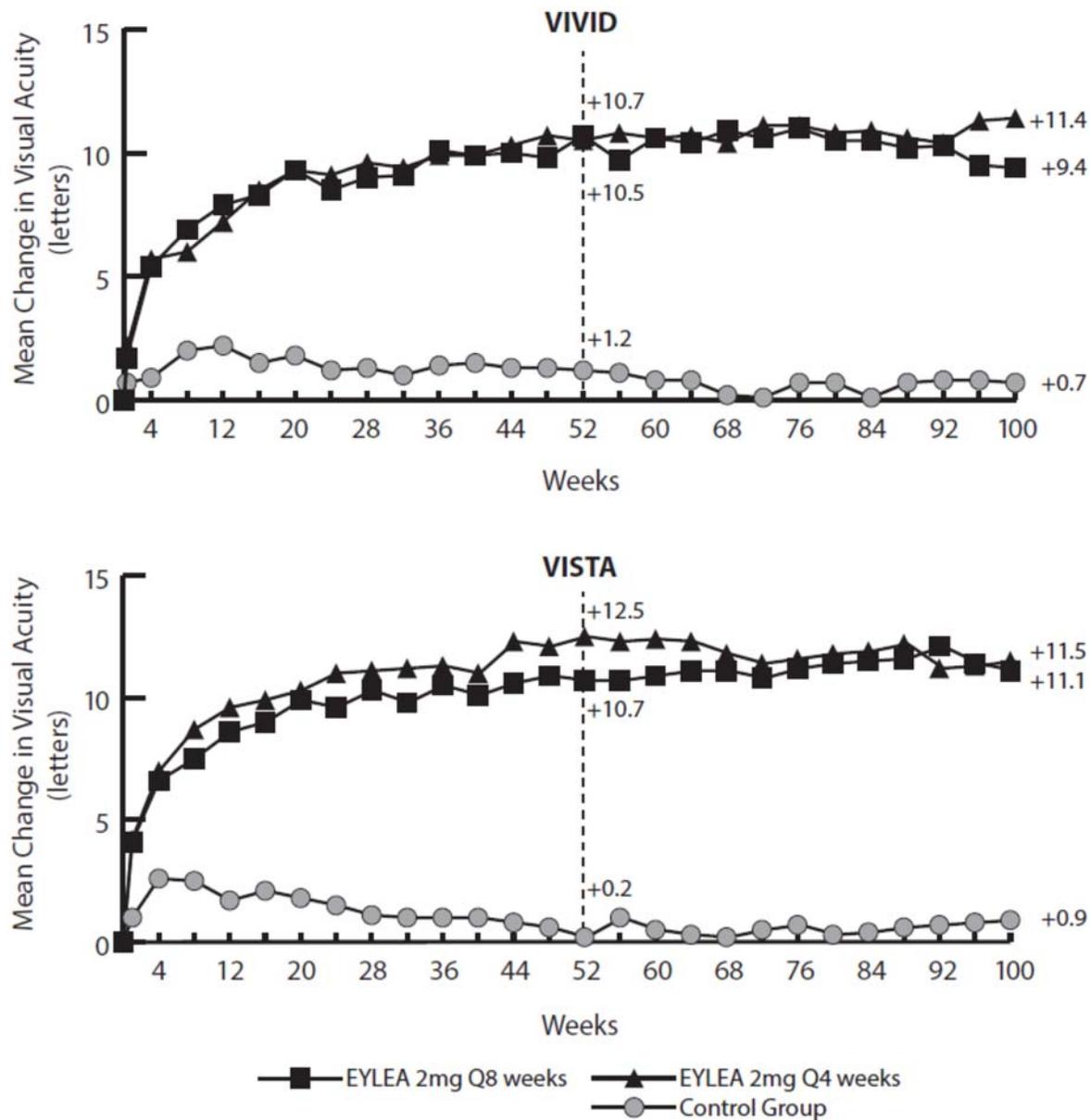
^b LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, protocol specified stratification factors were included in the model

^c Difference is EYLEA group minus Control group

^d p<0.01 compared with Control

^e Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors

Figure 16: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 100 in VIVID and VISTA Studies



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.

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

14.5 Diabetic Retinopathy (DR)

Efficacy and safety data of EYLEA in diabetic retinopathy (DR) are derived from the VIVID, VISTA, and PANORAMA studies.

VIVID AND VISTA

In the VIVID and VISTA studies, an efficacy outcome was the change in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (ETDRS-DRSS). The ETDRS-DRSS score was assessed at baseline and approximately every 6 months thereafter for the duration of the studies [see *Clinical Studies (14.4)*].

All enrolled patients had DR and DME at baseline. The majority of patients enrolled in these studies (77%) had moderate-to-severe nonproliferative diabetic retinopathy (NPDR) based on the ETDRS-DRSS. At week 100, the proportion of patients improving by at least 2 steps on the ETDRS-DRSS was significantly greater in both EYLEA treatment groups (2Q4 and 2Q8) when compared to the control group.

Results from the analysis of ETDRS-DRSS at week 100 in the VIVID and VISTA studies are shown in [Table 8](#) below.

Table 8: Proportion of Patients Who Achieved a ≥ 2 -Step Improvement from Baseline in the ETDRS-DRSS Score at Week 100 in VIVID and VISTA Studies

	VIVID			VISTA		
	EYLEA 2 mg Q8 weeks ^a	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q8 weeks ^a	EYLEA 2 mg Q4 weeks	Control
Evaluable Patients ^b	N=101	N=97	N=99	N=148	N=153	N=150
Number of patients with a ≥ 2 -step improvement on ETDRS-DRSS from Baseline (%)	32 (32%)	27 (28%)	7 (7%)	56 (38%)	58 (38%)	24 (16%)
Difference ^{c, d} (%) (97.5% CI)	24% ^c (12, 36)	21% ^c (9, 33)		22% ^c (11, 33)	22% ^c (11, 33)	

Non-gradable post-baseline ETDRS-DRSS values were treated as missing and were imputed using the last gradable ETDRS-DRSS values (including baseline values if all post-baseline values were missing or non-gradable)

^a After treatment initiation with 5 monthly injections

^b The number of evaluable patients included all patients who had valid ETDRS-DRSS data at baseline

^c Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors

^d Difference is EYLEA minus Control group

^e $p < 0.01$ compared with Control

Results of the evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity) on the proportion of patients who achieved a ≥ 2 -step improvement on the ETDRS-DRSS from baseline to week 100 were, in general, consistent with those in the overall population.

PANORAMA

The PANORAMA study assessed the safety and efficacy of EYLEA in a randomized, multi-center, double-masked, controlled study in patients with moderately severe to severe

nonproliferative diabetic retinopathy (NPDR) (ETDRS-DRSS of 47 or 53), without central-involved DME (CI-DME). A total of 402 randomized patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days for the first 5 visits, then every 8 weeks (56±7 days). Patient ages ranged from 25 to 85 years with a mean of 55.7 years.

Patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) 3 initial monthly EYLEA 2 mg injections followed by one injection after 8 weeks and then one injection every 16 weeks (EYLEA 2Q16); 2) 5 monthly EYLEA 2 mg injections followed by one injection every 8 weeks (EYLEA 2Q8); and 3) sham treatment.

The primary efficacy endpoint was the proportion of patients who improved by ≥2 steps on the DRSS from baseline to week 24 in the combined EYLEA groups and at week 52 in the 2Q16 and 2Q8 groups individually versus sham. A key secondary endpoint was the proportion of patients developing the composite endpoint of proliferative diabetic retinopathy or anterior segment neovascularization through week 52.

At week 52, efficacy in the 2Q16 and 2Q8 groups was superior to the sham group (see [Table 9](#) and [Table 10](#)). The proportion of patients with a ≥2-step improvement over time is shown in [Figure 17](#).

Table 9: Proportion of Patients Who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score at Weeks 24 and 52 in PANORAMA

	PANORAMA				
	Week 24		Week 52		
	EYLEA Combined	Control (sham)	EYLEA 2Q16	EYLEA 2Q8	Control (sham)
Full Analysis Set	N=269	N=133	N=135	N=134	N=133
Proportion of patients with a ≥2-step improvement on ETDRS-DRSS from Baseline (%)	58%	6%	65%	80%	15%
Adjusted Difference ^a (%) (95% CI) ^b	52% ^c (45, 60)		50% ^c (40, 60)	65% ^c (56, 74)	

Non-gradable post-baseline ETDRS-DRSS values were treated as missing and were imputed using the last gradable ETDRS-DRSS values (including baseline values if all post-baseline values were missing or non-gradable)

^a Difference is EYLEA group minus sham

^b Difference with CI was calculated using the Mantel-Haenszel weighting scheme adjusted by baseline DRSS stratification variable

^c p<0.01 compared with Control. p-value was calculated using a 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS stratification variable.

Figure 17: Proportion of Patients Who Achieved a ≥ 2 -Step Improvement from Baseline in the ETDRS-DRSS Score Through Week 52 in PANORAMA

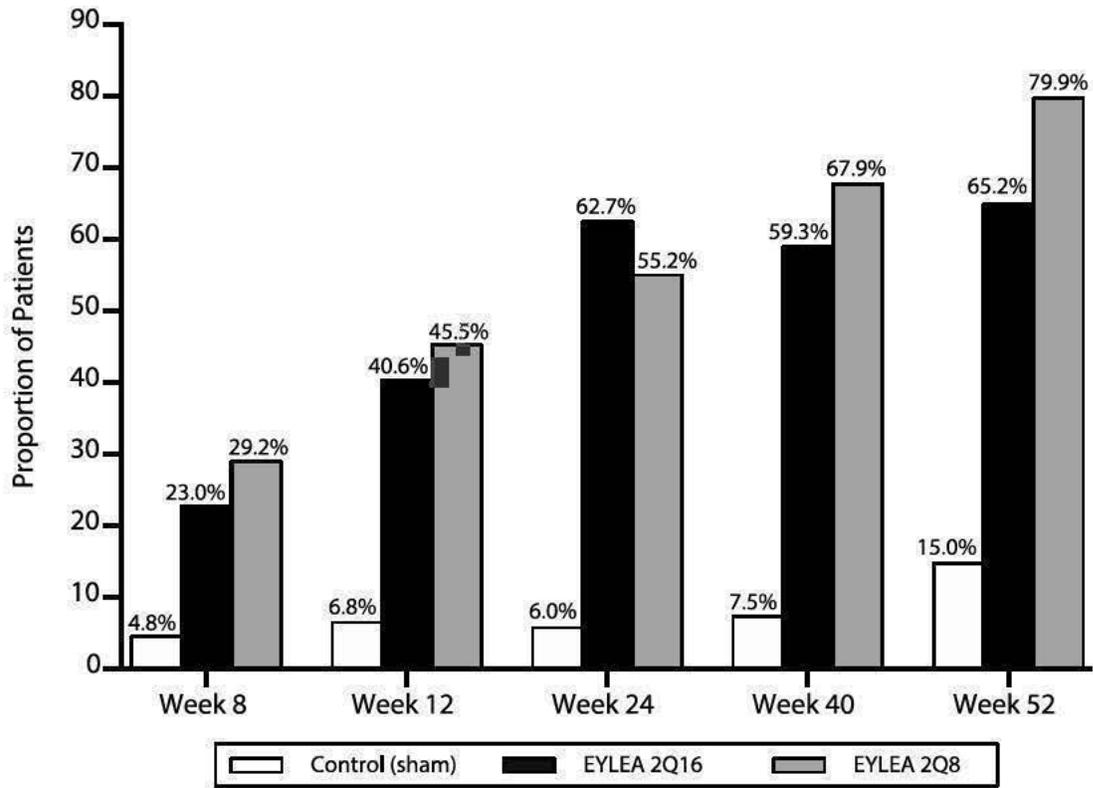


Table 10: Effect of EYLEA on Worsening of Diabetic Retinopathy in PANORAMA through Week 52

	EYLEA 2Q16	EYLEA 2Q8	Control (Sham)
Full Analysis Set	N=135	N=134	N=133
Composite Endpoint of Developing PDR or ASNV ^a			
Event Rate ^b	4.0% ^d	2.4% ^d	20.1%
Hazard Ratio	0.15	0.12	
Development of Proliferative Diabetic Retinopathy ^c			
Event Rate ^b	1.6% ^d	0.0% ^d	11.9%
Hazard Ratio	0.11	0.00	

PDR = Proliferative Diabetic Retinopathy; ASNV = Anterior Segment Neovascularization

^a As diagnosed by either the Reading Center or Investigator through week 52

^b Estimated using Kaplan-Meier method

^c Defined as ≥ 2 -step worsening on the ETDRS-DRSS score through week 52

^d $p < 0.01$ compared with Control

16 HOW SUPPLIED/STORAGE AND HANDLING

Each pre-filled syringe or vial is for single eye use only. EYLEA is supplied in the following presentations [*see Dosage and Administration (2.6), (2.7), and (2.8)*].

NDC NUMBER	CARTON TYPE	CARTON CONTENTS
61755-005-01	Pre-filled Syringe	one blister pack containing one EYLEA 2 mg/0.05 mL sterile, single-dose pre-filled glass syringe one package insert
61755-005-02	Vial Kit with Injection Components	one EYLEA 2 mg/0.05 mL single-dose glass vial one 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents one 30-gauge x ½-inch injection needle for intravitreal injection one 1-mL syringe for administration one package insert

Storage

Refrigerate EYLEA at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not use beyond the date stamped on the carton and container label. Store in the original carton until time of use to protect from light. Do not open sealed blister tray 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, advise patients to 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)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:

Regeneron Pharmaceuticals, Inc.

777 Old Saw Mill River Road

Tarrytown, NY 10591-6707

U.S. License Number 1760

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

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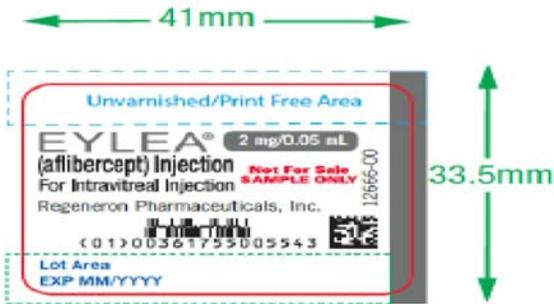
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Revised Date: Month 201X

Container Labels (submitted on October 9, 2018) Syringe Label -Trade



Container Labels (submitted on October 9, 2018) Syringe Label -Sample



Tray labeling (submitted on October 9, 2018) Tyvek Blister Tray Lid – Trade



Tray labeling (submitted on October 9, 2018) Tyvek Blister Tray Lid – Sample



Carton Labeling (submitted on July 24, 2019) Trade



Carton Labeling (submitted on October 9, 2018) Sample





Kathleen
Clouse Strebel

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125387Orig1s060

OTHER ACTION LETTERS



BLA 125387/S-060

COMPLETE RESPONSE – CMC

Regeneron Pharmaceuticals, Inc.
Attention: Candace Drumma, M.S., RAC
Senior Manager, CMC Regulatory Affairs
81 Columbia Turnpike, Building 85
Rensselaer, NY 12144

Dear Ms. Drumma:

Please refer to your supplemental biologics license application (sBLA) dated and received June 15, 2018, submitted under section 351(a) of the Public Health Service Act for EYLEA (afibercept) Injection.

Your resubmission dated and received April 12, 2019, constitutes a complete response to our October 15, 2019, action letter and the user fee goal date is August 12, 2019.

If you have any questions, please call me at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Michael Puglisi
Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MICHAEL J PUGLISI
05/31/2019 04:17:06 PM



BLA 125387/S-060

COMPLETE RESPONSE

Regeneron Pharmaceuticals, Inc.
Attention: Candace Drumma
Senior Manager of CMC Regulatory Affairs
81 Columbia Turnpike, Bldg 85
Rensselaer, NY 12144

Dear Ms. Drumma:

Please refer to your Supplemental Biologics License Application (sBLA) dated June 15, 2018, received June 15, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for Eylea (afibercept) injection.

This supplemental biologics license application proposes the introduction of a Pre-Filled Syringe (PFS) presentation for Eylea.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. On September 19, 2018, information was requested to address syringe verification data, risk analysis, syringe validation, release testing, and syringe / needle compatibility. The purpose of requesting this information is to confirm that the performance and quality of the released product is adequate to assure the labeled dose is reliably delivered to a patient. The response did not provide the requested information and therefore it is unclear if the product quality is adequate. Provide the following information:
 - a. Deliverable volume data are needed to confirm that the volume injected into the patient meets labeled dosing requirements. The data should show that when used with a 30G, ½ inch needle per the labeling, the product delivers the labeled dose. Provide test data confirming that the deliverable volume specification of the product is met in-use (i.e., syringe and needle). Confirm that the deliverable volume endpoints used in this study are equivalent to deliverable volume performance of the clinically studied product.
 - b. The control strategy for the syringe needs to assure that the essential performance requirements for the syringe are reliably met on released product. Essential performance requirements for syringes generally include deliverable volume and breakloose / glide force of the plunger. The product release specifications currently include breakloose / glide force; however, there is no release specification or other control strategy to assure deliverable volume specifications in its final, to-be-marketed packaging. Provide an updated control strategy that

describes how the deliverable volume specifications may fail to be met (e.g., risk analysis) and describe how you are controlling product quality to assure that deliverable volume specifications are reliably achieved for the final product.

2

(b) (4)

3. The information and data provided to support the commercial shipping of the (b) (4) blister packed PFS do not provide sufficient assurance that the quality of the DP will be maintained during commercial shipping and distribution. The mechanical performance studies,

b(4)

(b) (4)

(b) (4)

(b) (4) Include a detailed description of how the study was performed and, if performed using simulated studies, provide a justification for how the simulated studies are sufficiently representative of the commercial shipping conditions.

CLINICAL

4. There is no clinical data or human factors study data provided that utilizes the proposed commercial prefilled syringe. A clinical study in at least 30 subjects utilizing the proposed commercial Eylea (afibercept) Injection prefilled syringe configuration should be submitted.

ADDITIONAL COMMENTS (PRODUCT QUALITY)

5. The data provided from the leachables studies of the afibercept drug product in the container closure system did not extend to the product shelf life of 24 months. Only 18 months of data were provided for the (b) (4) syringe and only the initial time point was provided for the (b) (4) syringe. Upon resubmission, provide all available data from the leachable studies for the (b) (4) and (b) (4) syringes.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf>.

If you have any questions, call Andrew Shiber, Regulatory Business Process Manager, at (301) 796 - 4798.

Sincerely,

{See appended electronic signature page}

Kathleen A. Clouse, Ph.D.
Director
Division of Biotechnology Review and Research I
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Kathleen
Clouse Strebel

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Date: 10/15/2018 05:02:14PM
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125387Orig1s060

MEDICAL REVIEW(S)

**Clinical Review of BLA 125387/S-060
Supplemental Application**

BLA 125387/S-060
SDN-799

Submission Date: 6/15/2018
Receipt Date: 6/15/2018
Review Date: 8/5/18

Applicant:

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707
914-345-7926

**Applicant's
Representative:**

Candace Drumma, M.S., RAC
Senior Manager, CMC Regulatory Affairs

Drug:

Eylea (aflibercept) Injection

Pharmacologic Category:

anti-VEGF

Submitted:

Submitted is Complete Response to the letter issued October 15, 2018, for the Prior Approval Supplement (S-060) providing for the introduction of an EYLEA (aflibercept) Injection prefilled syringe (PFS) configuration.

EYLEA is currently supplied in the following approved presentations:

Vial Kit with Injection Components	one EYLEA 2 mg/0.05 mL single-dose glass vial one 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents one 30-gauge x ½-inch injection needle for intravitreal injection one 1-mL syringe for administration one package insert
Vial Only	one EYLEA 2 mg/0.05 mL single-dose glass vial one package insert

Background:

A Complete Response letter was issued on October 15, 2018. In addition to Product Quality deficiencies, Clinical had the following issue, per the letter:

This supplemental application providing for the introduction of an EYLEA (afibercept) Injection prefilled syringe configuration is not recommend for approval. There is no clinical data or human factors study data provided to support the proposed commercial prefilled syringe.

A Complete Response letter for this supplemental application should be prepared, requesting a clinical study in at least 30 subjects utilizing the proposed commercial EYLEA (afibercept) Injection prefilled syringe configuration. Labeling for the prefilled syringe configuration is deferred until the clinical data requested is provided in the Complete Response.

4/12/19 (SDN-799): Resubmission of the PFS Prior Approval Supplement.

4/17/19 (SDN-801): Supplement mistakenly referred to as device. This amendment to the PAS fixes those instances and correctly describes it as a drug.

The 4/12/19 (SDN-799) submission contains the following Tables, 2-4:

Table 2: Information Requests Received for the Afibercept Pre-filled Syringe Submission (125387/S-060)

Agency Question	Response	eCTD Module Reference	Details
1	24Aug2018	SN0427	(b) (4) Updated 356h form and information regarding products (b) (4) E-mail correspondence from (b) (4)
2	18Sep2018	SN0437	(b) (4) Response to questions related to syringe essential performance specifications and shipping validation, provided specifications for PFS components, clarified that the afibercept PFS is not packaged with a needle.
3	18Sep2018		E-mail correspondence from the Agency confirming the afibercept PFS is not considered a combination product
4	20Sep2018	SN0441	(b) (4) Response to microbiological questions (b) (4) (b) (4) sterilization validation data including associated reports, (b) (4) method). Provided shipping validation data and reports for plunger movement studies. (b) (4)
5	28Sep2018	SN0445	Labeling comments
6	03Oct2018	N/A	E-mail correspondence from the Sponsor Response to request from the Agency (M. Puglisi) for clinical or human factors data. A comparable safety profile was observed between vials and pre-filled syringes used in previously submitted clinical trials.
7	04Oct2018	SN0447	(b) (4) Labeling comments
8	04Oct2018	SN0446	Response to question regarding the classification of process controls and actions taken in case of excursions.
9	09Oct2018	N/A	E-mail correspondence from the Sponsor (b) (4)
10	10Oct2018	SN0448	(b) (4) Response to question regarding visual inspection of pre-filled syringes. Update to (b) (4) Bulk PFS to incorporate requested details for visual inspection Update to (b) (4) Bulk PFS and (b) (4) PFS to specify actions taken in case of excursions.

Table 3: Overview of Response to Issues raised with the Complete Response Letter

Agency Request		Response Reference	Details
1a	Deliverable volume data are needed to confirm that the volume injected into the patient meets labeled dosing requirements. The data should show that when used with a 30G, ½ inch needle per the labeling, the product delivers the labeled dose. Provide test data confirming that the deliverable volume specification of the product is met in-use (i.e., syringe and needle). Confirm that the deliverable volume endpoints used in this study are equivalent to deliverable volume performance of the clinically studied product.	(b) (4)	(b) (4)
1b	The control strategy for the syringe needs to assure that the essential performance requirements for the syringe are reliably met on released product. Essential performance requirements for syringes generally include deliverable volume and breakloose / glide force of the plunger. The product release specifications currently include breakloose / glide force; however, there is no release specification or other control strategy to assure deliverable volume specifications in its final, to-be-marketed packaging. Provide an updated control strategy that describes how the deliverable volume specifications may fail to be met (e.g., risk analysis) and describe how you are controlling product quality to assure that deliverable volume specifications are reliably achieved for the final product.		<p>Syringe essential performance requirements to reliably deliver the labelled dose include break loose/glide force and deliverable volume. Control of these attributes are controlled by the following:</p> <ul style="list-style-type: none"> • (b) (4) • • •
Agency Request			Details
2a	Provide complete qualification test reports for (b) (4)		<p>Results, protocols and reports for all validation studies (b) (4)</p> <p>A description of the testing and verification of results is included in the test reports and summarized in (b) (4)</p>
2b	Provide additional sterilization validation information which includes a clear description of the (b) (4)		A detailed description of (b) (4) is provided in the background for question 2 in (b) (4)
	Provide additional sterilization validation information which includes (b) (4)		(b) (4)
	Provide additional sterilization validation (b) (4)		(b) (4)
	(b) (4)		(b) (4)
2c	(b) (4)		(b) (4)

Agency Request	Response Reference	Details
(b) (4)	(b) (4)	(b) (4)
<p>3 The information and data provided to support the commercial shipping of the (b) (4) blister packed PFS do not provide sufficient assurance that the quality of the DP will be maintained during commercial shipping and distribution. The mechanical performance studies, which (b) (4)</p> <p>(b) (4) Include a detailed description of how</p>		<p>Simulated and actual shipping validation studies were completed for the (b) (4) PFS (b) (4) as well as for the bulk PFS and the bulk blistered PFS (b) (4)</p> <p>The objective of the simulated shipping validation was to demonstrate the non-impact of transport stress encountered during simulated shipping on the DP quality. Actual shipping validation (b) (4)</p> <p>A summary of all shipping validation studies, including description of how the studies were performed, results and conclusions are included in (b) (4) response to question 3 and in (b) (4) Shipping Validation. Full details for all shipping studies are presented in the shipping validation study reports included as attachment to (b) (4)</p>
Agency Request		Details
<p>the study was performed and, if performed using simulated studies, provide a justification for how the simulated studies are sufficiently representative of the commercial shipping conditions.</p>		
<p>4 There is no clinical data or human factors study data provided that utilizes the proposed commercial prefilled syringe. A clinical study in at least 30 subjects utilizing the proposed commercial Eylea (afibercept) Injection prefilled syringe configuration should be submitted.</p>		<p>Clinical data for the afibercept PFS using the (b) (4) PFS is provided for study VGETe-OD-1881 in (b) (4) The study established that the (b) (4) pre-filled syringe (b) (4) allows for successful preparation and administration of a 2 mg dose of afibercept by retina specialists.</p> <p>Clinical data to support the (b) (4) PFS will be included for commercialization in a subsequent submission to the Agency.</p>
<p>5 The data provided from the leachables studies of the afibercept drug product in the container closure system did not extend to the product shelf life of 24 months. Only 18 months of data were provided for the (b) (4) syringe and only the initial time point was provided for the (b) (4) syringe. Upon resubmission, provide all available data from the leachable studies for the (b) (4) and (b) (4) syringes.</p>		<p>All available data from leachable assessment of afibercept DP in the (b) (4) syringe through 18 months are summarized in (b) (4) Container Closure- Primary. No leachable impurities above the dose specific analytical evaluation threshold (AET) of (b) (4) µg/mL were detected for any of the (b) (4) samples tested. Full details of the study are provided (b) (4)</p> <p>Twenty-four months of leachable data for the (b) (4) syringe will be included for commercialization in a subsequent submission to the Agency.</p>

Table 4: Changes in the resubmission as compared to the PAS submitted in June

Change	Reason
Market (b) (4) syringe only.	Agency requirement to include PFS representative of commercial presentation in clinical study. (b) (4)
(b) (4)	Sterilization validation activities completed successfully at (b) (4)
	Associated validation activities completed successfully at (b) (4)
Update control strategy for sterility assurance of the external PFS and blister tray	(b) (4)
(b) (4)	(b) (4)
Provide updated stability data	Stability data was updated with all available time points tested.
Updates sections based on IR and CRL responses	Based on Agency feedback.

Reviewer’s Comments:

Item #4, Table #3, from the Complete Response letter is addressed with Clinical data for the aflibercept prefilled syringe using the primary container closure sourced from (b) (4) which was manufactured following the commercial pathway. The responses for the remaining items in Table 3 from the Complete Response letter are deferred to OBP.

The proposed EYLEA (aflibercept) Injection prefilled syringe configuration does not constitute a drug-device combination product under regulation. Per 21 CFR 200.50, the prefilled syringe and aflibercept are regulated as a drug product. The syringe will be packaged with the product with which it will be used (i.e. aflibercept). Reviews for this supplemental application which refer to this prefilled syringe configuration as a combination are incorrect; this prefilled syringe configuration is regulated as a drug.

Study VGFTe-OD-1881: A Study in Patients with Choriorretinal Vascular Disease to Evaluate an Aflibercept Pre-filled Syringe

Primary Study Objectives

This study was intended to confirm that the single-dose PFS pack supports successful preparation and administration of an aflibercept injection by retina specialists. Per regulatory agency feedback, a clinical study of at least 30 patients utilizing the proposed commercial aflibercept PFS configuration was conducted.

The primary objective of the study was to determine if the PFS can be used effectively and safely by retina specialists to administer the 2 mg dose of aflibercept.

Secondary Study Objectives

The secondary objective of the study was to assess ocular safety in the study eye.

Number of Subjects

Approximately 35 patients were planned to be enrolled at approximately 2 sites in the US.

Description of Study

This was a phase 4, single-arm, open-label study in patients with chorioretinal vascular disease (nAMD, DME, RVO, and DR in patients with DME) to evaluate use of the aflibercept PFS. The study consisted of a screening period, a single aflibercept injection, and a follow-up period through day 29.

After providing informed consent, patients were assessed for study eligibility at the screening visit, up to 2 weeks before the day 1/baseline visit. Screening and the day 1/baseline visit may have occurred on the same day. Only 1 eye was selected as the study eye. At the day 1/baseline visit, patients underwent safety assessments, and then received a single injection of study drug, prepared (by retina specialist and/or technician) and administered with the PFS by a retina specialist. There was a follow-up period of 28 days with a window of -7 days to +14 days, during which patients were evaluated for safety (ocular AEs and all [ocular and non-ocular] SAEs).

Inclusion Criteria

- Men or women ≥ 18 years of age who had nAMD, DME, RVO, or DR with DME in the study eye
- Study eye considered by the retina specialist to be indicated for treatment with aflibercept
- Willing and able to comply with clinic visits and study-related procedures
- Provide informed consent signed by study patient or legally acceptable representative
- Able to understand and complete study-related questionnaires

Exclusion criteria

- Evidence of active infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye
- Any active intraocular inflammation or infection in either eye or history of intraocular inflammation or infection after past IVT injections with any agent in either eye
- History of or any current indication of excessive bleeding and recurrent hemorrhages, including any prior excessive intraocular (including subconjunctival) bleeding or hemorrhages after IVT injection or intraocular procedures in either eye
- Treatment with any IVT injection in the study eye within the 28 days prior to day 1
- IOP > 25 mm Hg in the study eye at screening
- Count fingers or worse vision in one or both eyes
- Use of therapies that were known to be toxic to any ocular tissues (ie. radiation) in either eye

- Any intraocular surgery in the study eye at any time during the past 3 months
- Any prior extended-release therapeutic agent, or ocular drug-release device implantation (approved or investigational including steroids) in the study eye
- Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could have either increased the risk to the patient beyond what was to be expected from standard procedures of IVT injections, or which otherwise may have interfered with the injection procedure or with evaluation of safety
- Participation as a patient in any interventional clinical study within the 12 weeks prior to day 1 of the study
- Current systemic infectious disease or a therapy for active infectious disease
- Pregnant or breastfeeding women
- Women of childbearing potential. Post-menopausal women must have been amenorrheic for at least 12 months in order not to be considered of childbearing potential.

Formulation, Dosage, and Storage of Medication

The drug product was supplied as a sterile aqueous solution for injection in a PFS. The PFSs were single-dose 1 mL glass syringes (b) (4) and were provided in sealed blister packs. Each single-dose PFS provided a usable amount to deliver a single dose of 2 mg aflibercept in a volume of 50 µL, via IVT injection. The PFS, enclosed in a sealed blister pack (b) (4) utilized in this study was fully representative of the presentation intended for commercialization. The PFS utilized the primary container closure sourced from (b) (4) which was manufactured following the commercial pathway. Only 1 eye was selected as the study eye. Instructions on dose preparation were provided in the pharmacy manual. A single batch of study drug (lot 8281800001A) was used for all 35 patients.

Study Flow Chart

Table 1: Schedule of Events

Study Procedure	Screening ¹ Visit 1	Combined Screening/Baseline Visit ¹ Visit 1/2	Baseline ¹ Visit 2	End of Study Visit 3
Day	-14 to -1	1	1	29 (-7 to +14 days)
Screening/Baseline:				
Inclusion/exclusion	X	X ²		
Informed consent	X	X ²		
Medical history	X	X ²		
Demographics	X	X ²		
Treatment:				
Review of concomitant meds	X	X ²	X ²	X
Administer intravitreal aflibercept		X ²	X ³	
Safety:				
Slit lamp examination	X	X ²	X ²	X
Indirect ophthalmoscopy	X	X ⁴	X ⁴	X
SD-OCT	X	X ²	X ²	X
ETDRS 4M BCVA	X	X ²	X ²	X
Intraocular pressure	X	X ³	X ³	X
Adverse events (ocular study eye and all serious adverse events)	X	X	X	X

SD-OCT=spectral domain optical coherence tomography, ETDRS= Early Treatment Diabetic Retinopathy Study, BCVA= Best Corrected Visual Acuity.

Statistical Analysis

There was no statistical hypothesis in this study. All safety variables were summarized descriptively with appropriate statistics: categorical variables by frequency (absolute and relative frequencies) and continuous variables by sample statistics (ie. mean, standard deviation, minimum, median, quartiles, and maximum). Continuous variables were described by visit and as change from baseline, if applicable.

Primary Endpoint

The primary endpoint in the study was the number of aflibercept injections successfully administered utilizing the PFS.

Secondary Endpoints

The secondary endpoint was the ocular safety of aflibercept delivered in the PFS. Safety was measured by the incidence of ocular adverse events (AEs) and serious adverse events (SAEs) in the study eye, through day 29.

Interim Analysis

None.

Results of Study

Patient Disposition

A total of 35 patients were enrolled into the study and received a single injection of aflibercept with the PFS. All 35 patients completed the study (end of study was Day 29).

Ocular Treatment-Emergent Adverse Events in the Study Eye

Overall, 6 (17%) patients reported ocular TEAEs in the study eye. Three (9%) patients each reported Conjunctival Hemorrhage and Eye Irritation, and 1 (3%) patient reported Corneal Abrasion.

Table 5: Ocular Treatment-Emergent Adverse Events in the Study Eye Through Day 29 (Safety Analysis Set)

Primary System Organ Class	
Preferred Term	2 mg Aflibercept in PFS
MedDRA Version 21.1	(N=35)
Number of patients with at least 1 such TEAE, n (%)	6 (17.1%)
Eye disorders	6 (17.1%)
Conjunctival hemorrhage	3 (8.6%)
Eye irritation	3 (8.6%)
Injury, poisoning, and procedural complications	1 (2.9%)
Corneal abrasion	1 (2.9%)

Abbreviations: PFS=prefilled syringe, TEAE=treatment-emergent adverse event.

The percentage was based on the number of patients in the treatment group as denominator.

Source: [Post-text Table 14.03.01/2-1](#).

Deaths

There were no deaths in the study.

Serious AEs – Ocular and Non-Ocular

There were no ocular SAEs in the study eye.

One (3%) patient had a non-ocular SAE of Iron Deficiency Anemia. This 68-year old white male was enrolled into the study and started treatment in the right eye on study day 1. He had a relevant medical history of colon cancer and colectomy. On study day 14, he experienced an SAE of Iron Deficiency Anemia, which was moderate in intensity.

Reviewer's Comments:

A total of 35 patients were enrolled in the study, and each patient received a single administration of 2 mg aflibercept in the PFS. There were no new safety signals identified in this study, and the safety profile is consistent with that from other studies with aflibercept in patients with chorioretinal vascular disease. Overall, 6 (17%) patients reported ocular TEAEs in the study eye. Three (9%) patients each reported conjunctival hemorrhage and eye irritation, and 1 of those patients also reported corneal abrasion. There were no ocular SAEs and no deaths.

The submitted study report, "Study VGFTe-OD-1881: A Study in Patients with Chorioretinal Vascular Disease to Evaluate an Aflibercept Pre-filled Syringe," is adequate to address Clinical's concerns regarding item #4 in the Complete Response letter:

There is no clinical data or human factors study data provided that utilizes the proposed commercial prefilled syringe. A clinical study in at least 30 subjects utilizing the proposed commercial Eylea (aflibercept) Injection prefilled syringe configuration should be submitted.

Recommendation:

This supplemental biologic license application which proposes the introduction of a Pre-Filled Syringe (PFS) presentation for Eylea is recommended for approval.

Sonal Wadhwa, M.D.
Medical Officer

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SONAL D WADHWA
08/07/2019 01:18:30 PM

WILLIAM M BOYD
08/07/2019 01:23:15 PM