Wet AMD

EYLEA®
(afiblercept) Injection
For Intravitreal Injection

Help change the way your eyes see the world

Wet Age-related Macular Degeneration (Wet AMD) may try to slow your eyes down. EYLEA may be able to help.

EYLEA is the #1 prescribed treatment in its class FDA approved for Wet AMD.*

*IBM Truven MarketScan Data: Number of injections administered from October 2017 through September 2018; Data on File.

SELECT IMPORTANT SAFETY INFORMATION

EYLEA is a prescription medicine administered by injection into the eye. You should not use EYLEA if you have an infection in or around the eye, eye pain or redness, or known allergies to any of the ingredients in EYLEA, including aflibercept.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
WHAT IS WET AMD?
Wet AMD is the leading cause of vision loss among people 50 years of age and older in the United States.

How can Wet AMD affect my eyes?
Wet AMD affects your macula, located at the back of the eye. Abnormal blood vessels grow under the macula while also leaking blood and fluid. This damages and scars the macula.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
What can Wet AMD do to my vision?

Wet AMD may cause:
- Blurriness in the center of your vision
- Straight lines to look wavy
- Colors to look dull and washed out
- Blind spots or patches
- Objects to seem farther away than they really are

SELECT IMPORTANT SAFETY INFORMATION

Injection into the eye with EYLEA can result in an infection in the eye and retinal detachment (separation of retina from back of the eye). Inflammation in the eye has been reported with the use of EYLEA.
Your eyes can fight back against Wet AMD, because there’s more they want to see—and they have EYLEA on their side.

EYLEA® (aflibercept) Injection is a prescription medicine given by injection into the eye

EYLEA has been studied in more than 3,000 people with certain diseases of the retina. You should not use EYLEA if you have an infection in or around the eye, eye pain or redness, or known allergies to any of the ingredients in EYLEA, including aflibercept.

Download the Amsler Grid at EYLEA.com to routinely check your vision at home.

SELECT IMPORTANT SAFETY INFORMATION

In some patients, injections with EYLEA may cause a temporary increase in eye pressure within 1 hour of the injection. Sustained increases in eye pressure have been reported with repeated injections, and your doctor may monitor this after each injection.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.
EYLEA® (aflibercept) Injection is a prescription medicine given by injection into the eye. EYLEA has been studied in more than 3,000 people with certain diseases of the retina. You should not use EYLEA if you have an infection in or around the eye, eye pain or redness, or known allergies to any of the ingredients in EYLEA, including aflibercept.

**SELECT IMPORTANT SAFETY INFORMATION**

In some patients, injections with EYLEA may cause a temporary increase in eye pressure within 1 hour of the injection. Sustained increases in eye pressure have been reported with repeated injections, and your doctor may monitor this after each injection.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

**Vision improvements seen with EYLEA**

In 2 clinical studies, 1,815 people with Wet AMD received injections of EYLEA (2 mg) either once every 8 weeks after 3 initial monthly doses or once every 4 weeks.

Both studies measured the percentage of people whose vision was maintained (not losing 15 or more letters, or 3 lines, on the eye chart) at 1 year.

**In 2 clinical studies 94% of Wet AMD patients treated with EYLEA maintained their vision at 1 year**
On average, after treatment in the studies

People treated with EYLEA for Wet AMD saw at least
7 more letters on the eye chart at 1 year in 2 clinical studies.

Visit EYLEA.com to learn more.

These results are from 2 clinical studies; your individual results may vary.
Discuss with your eye care team what treatment schedule with EYLEA may be right for you.
IMPORTANT SAFETY INFORMATION AND INDICATIONS

- EYLEA® (aflibercept) Injection is a prescription medicine administered by injection into the eye. You should not use EYLEA if you have an infection in or around the eye, eye pain or redness, or known allergies to any of the ingredients in EYLEA, including aflibercept.

- Injection into the eye with EYLEA can result in an infection in the eye and retinal detachment (separation of retina from back of the eye). Inflammation in the eye has been reported with the use of EYLEA.

- In some patients, injections with EYLEA may cause a temporary increase in eye pressure within 1 hour of the injection. Sustained increases in eye pressure have been reported with repeated injections, and your doctor may monitor this after each injection.

- There is a potential risk of serious and sometimes fatal side effects related to blood clots, leading to heart attack or stroke in patients receiving EYLEA.

- Serious side effects related to the injection procedure with EYLEA are rare but can occur including infection inside the eye and retinal detachment.

- The most common side effects reported in patients receiving EYLEA are increased redness in the eye, eye pain, cataract, vitreous (gel-like substance) detachment, vitreous floaters, moving spots in the field of vision, and increased pressure in the eye.

- It is important that you contact your doctor right away if you think you might be experiencing any side effects, including eye pain or redness, light sensitivity, or blurring of vision, after an injection.

- EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is a prescription medicine approved for the treatment of patients with Wet Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is a prescription medicine approved for the treatment of patients with Wet Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).
Help your eyes fight back

Financial Support

EYLEA has several programs available—depending on your insurance situation—to help eligible patients with the cost of EYLEA.

Either you or someone from your eye doctor’s office can call 1-855-EYLEA4U (1-855-395-3248) Monday through Friday 9 AM to 8 PM Eastern Time to get you started.

Sign up at EYLEA.com to get the latest materials and communications about EYLEA—and a complimentary pocket magnifier, too.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

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777 Old Saw Mill River Road, Tarrytown, NY 10591
EYLEA® (aflibercept) Injection, for Intravitreal Use
Initial U.S. Approval: 2011

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

RECENT MAJOR CHANGES
• Indications and Usage (1) 5/2019
• Dosage and Administration (2) 8/2019

INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for:
• Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
• 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 once 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)

CONTRAINDICATIONS
• 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)

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 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.

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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 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

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 × 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 × 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:
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 micробicide 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

### 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 monitored 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 1.1% (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 2.2% (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 (≥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

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

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 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), (14.5)].
Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>CRVO (N=578)</th>
<th>Control (N=287)</th>
<th>BRVO (N=91)</th>
<th>Control (N=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye pain</td>
<td>13%</td>
<td>5%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>12%</td>
<td>11%</td>
<td>20%</td>
<td>4%</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>8%</td>
<td>6%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Corneal epithelium defect</td>
<td>5%</td>
<td>4%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Vitreous floaters</td>
<td>5%</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Ocular hyperemia</td>
<td>5%</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>3%</td>
<td>5%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>3%</td>
<td>4%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Laceration increased</td>
<td>3%</td>
<td>4%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>3%</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>1%</td>
<td>&lt;1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Intraocular inflammation</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Cataract</td>
<td>&lt;1%</td>
<td>1%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>&lt;1%</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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 and Diabetic Retinopathy (DR) and endophthalmitis.

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 ≥5 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, ectodactyly, intestinal atresia, spina bifida, encephalomingingocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternabrach, 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
Afiblercept 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. Afiblercept 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. Afiblercept is produced in recombinant Chinese hamster ovary (CHO) cells. EYLEA (afiblercept) 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 afiblercept 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 (PIGF) 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. PIGF binds only to VEGFR-1, which is also present on the surface of leukocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability.

Afiblercept acts as a soluble decoy receptor that binds VEGF-A and PIGF, 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 EYLEA 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 afiblercept:VEGF complex. Once absorbed into the systemic circulation, afiblercept presents in the plasma as free afiblercept (unbound to VEGF) and a more predominant stable inactive form with circulating endogenous VEGF (i.e., afiblercept:VEGF complex).

Absorption/Distribution
Following intravitreal administration of 2 mg per eye of EYLEA to patients with wet AMD, RVO, and DME, the mean Cmax of free afiblercept 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 afiblercept plasma concentrations were undetectable two weeks post-dosing in all patients. Afiblercept 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 afiblercept is more than 100 fold lower than the concentration of afiblercept required to half-maximally bind systemic VEGF.

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

Metabolism/Excretion
Afiblercept is a therapeutic protein and no drug metabolism studies have been conducted. Afiblercept 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 afiblercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg afiblercept.
Table 4: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies

<table>
<thead>
<tr>
<th></th>
<th>VIEW1</th>
<th>VIEW2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EYLEA 2 mg Q8 weeks*</td>
<td>EYLEA 2 mg Q4 weeks</td>
</tr>
<tr>
<td></td>
<td>ranibizumab 0.5 mg Q4 weeks</td>
<td>ranibizumab 0.5 mg Q4 weeks</td>
</tr>
<tr>
<td>Full Analysis Set</td>
<td>N=301</td>
<td>N=304</td>
</tr>
<tr>
<td></td>
<td>N=304</td>
<td>N=306</td>
</tr>
<tr>
<td></td>
<td>N=309</td>
<td>N=291</td>
</tr>
<tr>
<td><strong>Efficacy Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients who maintained visual acuity (%) (&lt;15 letters of BCVA loss)</td>
<td>94%</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td><strong>Mean change in BCVA as measured by ETDRS letter score from Baseline</strong></td>
<td>7.9</td>
<td>10.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.6</td>
</tr>
<tr>
<td><strong>Difference (%)</strong></td>
<td>0.6</td>
<td>1.3</td>
</tr>
<tr>
<td>(95.1% CI)</td>
<td>(-3.2, 4.4)</td>
<td>(-2.4, 5.0)</td>
</tr>
<tr>
<td></td>
<td><strong>Mean change in BCVA as measured by ETDRS letter score from Baseline</strong></td>
<td>92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>91</td>
</tr>
<tr>
<td></td>
<td><strong>Number of patients who gained at least 15 letters of vision from Baseline (%)</strong></td>
<td>(31%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(31%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(29%)</td>
</tr>
<tr>
<td></td>
<td><strong>Difference (%)</strong></td>
<td>-0.4</td>
</tr>
<tr>
<td>(95.1% CI)</td>
<td>(-7.7, 7.0)</td>
<td>(-1.0, 14.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-10.2, 4.9)</td>
</tr>
</tbody>
</table>

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.

* After treatment initiation with 3 monthly doses

**EYLEA group minus the ranibizumab group

**Mean change in BCVA as measured by ETDRS letter score from Baseline

**Difference (%) = Difference in LS mean, CI = Confidence Interval based on an ANCOVA model.

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 (Q4), or sham injections (control group) administered every 4 weeks for a total of 26 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 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 below.

Table 5: Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in COPERNICUS and GALILEO Studies

<table>
<thead>
<tr>
<th>COPERNICUS</th>
<th>GALILEO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>EYLEA 2 mg Q4 weeks</td>
</tr>
<tr>
<td>Control</td>
<td>EYLEA 2 mg Q4 weeks</td>
</tr>
<tr>
<td>N=73</td>
<td>N=114</td>
</tr>
<tr>
<td>N=68</td>
<td>N=103</td>
</tr>
<tr>
<td><strong>Efficacy Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)</td>
<td>12%</td>
</tr>
<tr>
<td>22%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Weighted Difference</strong> (%)</td>
<td>-44.8%</td>
</tr>
<tr>
<td>(95.1% CI)</td>
<td>(32.9, 56.6)</td>
</tr>
<tr>
<td><strong>Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)</strong></td>
<td>-4.0 (18.0)</td>
</tr>
<tr>
<td>17.3 (12.8)</td>
<td></td>
</tr>
<tr>
<td>3.3 (14.1)</td>
<td></td>
</tr>
<tr>
<td>18.0 (12.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Difference in LS mean</strong> (%)</td>
<td>21.7 (17.3, 26.1)</td>
</tr>
<tr>
<td>(95.1% CI)</td>
<td>14.7 (10.7, 18.7)</td>
</tr>
</tbody>
</table>

* 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.

p<0.01 compared with Control

LS mean and CI based on an ANCOVA model.
### 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 evaluated 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 photoagulation 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**

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>EYLEA 2 mg Q4 weeks</th>
<th>Weighted Difference (95% CI)</th>
<th>Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)</th>
<th>Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)</th>
<th>Difference in LS mean (95% CI)</th>
<th>Adjusted Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIBRANT</td>
<td>N=90</td>
<td>N=91</td>
<td>26.7%</td>
<td>6.9 (12.9)</td>
<td>10.5 (7.1, 14.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VISTA</td>
<td>N=115</td>
<td>N=114</td>
<td>28.7%</td>
<td>7.1 (12.9)</td>
<td>12.5 (7.3, 17.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Difference is EYLEA 2 mg Q4 weeks versus Control
*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)
*p<0.01 compared with Control
*LS mean and CI based on an ANCOVA model

### 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 photoagulation (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**

<table>
<thead>
<tr>
<th>Study</th>
<th>EYLEA 2 mg Q4 weeks</th>
<th>EYLEA 2 mg Q8 weeks</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIVID</td>
<td>N=135</td>
<td>N=135</td>
<td>N=135</td>
</tr>
<tr>
<td>VISTA</td>
<td>N=151</td>
<td>N=154</td>
<td>N=154</td>
</tr>
</tbody>
</table>

*Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)
*Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)
Efficacy Outcomes at Week 100

<table>
<thead>
<tr>
<th>Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)</th>
<th>EYLEA 2 mg Q8 weeks</th>
<th>EYLEA 2 mg Q4 weeks</th>
<th>Control</th>
<th>EYLEA 2 mg Q8 weeks</th>
<th>EYLEA 2 mg Q4 weeks</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.4 (10.5)</td>
<td>11.4 (11.2)</td>
<td>11.1 (10.7)</td>
<td>11.5 (13.8)</td>
<td>0.9 (13.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Difference\(^a\) in LS mean (97.5% CI) (5.2, 11.3) (7.6, 13.8) (7.0, 13.3) (7.1, 14.2)

Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)

Baseline (76) 12 20 28 36 44 52 60 68 76 84 92 100

Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)

Mean Change in Visual Acuity (letters)

VIVID

<table>
<thead>
<tr>
<th>Evaluative Patients</th>
<th>N=101</th>
<th>N=97</th>
<th>N=148</th>
<th>N=150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients achieving a ≥2-step improvement on ETDRS-DRSS from Baseline (%)</td>
<td>32 (32%)</td>
<td>27 (28%)</td>
<td>7 (7%)</td>
<td>56 (38%)</td>
</tr>
<tr>
<td>Difference(^e) (97.5% CI)</td>
<td>(12, 36)</td>
<td>(9, 33)</td>
<td>(38%)</td>
<td>(38%)</td>
</tr>
</tbody>
</table>

VISTA

<table>
<thead>
<tr>
<th>Evaluative Patients</th>
<th>N=99</th>
<th>N=148</th>
<th>N=153</th>
<th>N=150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients achieving a ≥2-step improvement on ETDRS-DRSS from Baseline (%)</td>
<td>32 (32%)</td>
<td>27 (28%)</td>
<td>7 (7%)</td>
<td>56 (38%)</td>
</tr>
<tr>
<td>Difference(^e) (97.5% CI)</td>
<td>(12, 36)</td>
<td>(9, 33)</td>
<td>(38%)</td>
<td>(38%)</td>
</tr>
</tbody>
</table>

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

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

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
\(^b\) Comparison of groups at 5 months

\(^c\) Difference in EYLEA group minus Control group
\(^d\) Difference in EYLEA group minus Control group

\(^e\) After treatment initiation with 5 monthly injections
\(^f\) The number of evaluable patients included all patients who had valid ETDRS-DRSS data at baseline

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

\(^h\) Difference is EYLEA minus Control group

\(^i\) 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), with central-involved DME (C1-DME). A total of 402 randomized patients were evaluable for efficacy. Protocol-specific 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 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 2Q6 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 2Q6 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.

All enrolled patients had DR and DME at baseline. The majority of patients enrolled in these studies (77%) had mild- to moderate 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 9: Proportion of Patients Who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score at Weeks 24 and 52 in PANORAMA

<table>
<thead>
<tr>
<th>Week</th>
<th>EYLEA Combined</th>
<th>Control (sham)</th>
<th>EYLEA 2Q16</th>
<th>EYLEA 2Q8</th>
<th>Control (sham)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Analysis Set</td>
<td>N=269</td>
<td>N=133</td>
<td>N=135</td>
<td>N=134</td>
<td>N=133</td>
</tr>
<tr>
<td>Proportion of patients with a ≥2-step improvement on ETDRS-DRSS from Baseline (%)</td>
<td>58%</td>
<td>6%</td>
<td>65%</td>
<td>80%</td>
<td>15%</td>
</tr>
<tr>
<td>Adjusted Differencea (%) (95% CI)b</td>
<td>52%c (45, 60)</td>
<td>50%c (40, 60)</td>
<td>65%c (56, 74)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>EYLEA 2Q16</th>
<th>EYLEA 2Q8</th>
<th>Control (Sham)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Analysis Set</td>
<td>N=135</td>
<td>N=134</td>
<td>N=133</td>
</tr>
<tr>
<td>Composite Endpoint of Developing PDR or ASNVa</td>
<td>Event Rateb</td>
<td>4.0%c</td>
<td>2.4%d</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.15</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Development of Proliferative Diabetic Retinopathyb</td>
<td>Event Rateb</td>
<td>1.6%c</td>
<td>0.0%d</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.11</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

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

REGENERON

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