CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125387Orig1s061

Trade Name:	EYLEA
Generic or Proper Name:	aflibercept
Sponsor:	Regeneron Pharmaceuticals, Inc.
Approval Date:	May 13, 2019
Indication:	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

125387Orig1s061

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	**X**
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	**X**
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125387/S-061

SUPPLEMENT APPROVAL

Regeneron Pharmaceuticals, Inc.
Attention: Amanda Cook, Bsc. (Hons), Dip.Reg.Aff.
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Ms. Cook:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received July 13, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for EYLEA (aflibercept) Injection. This supplemental biologics application provides for the use of EYLEA (aflibercept) Injection for the treatment of diabetic retinopathy.

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 which is identical to the labeling submitted on May 3, 2019.

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 package insert 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.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new

active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for this application because diabetic retinopathy rarely occurs in the pediatric population and therefore studies are impossible or highly impracticable.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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/

WILEY A CHAMBERS
05/13/2019 12:54:34 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s061

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)	5/2019
• 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 for intravitreal injection 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 (≥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: 5/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

***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.

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:

- 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

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.

EYLEA is available packaged as follows:

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

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

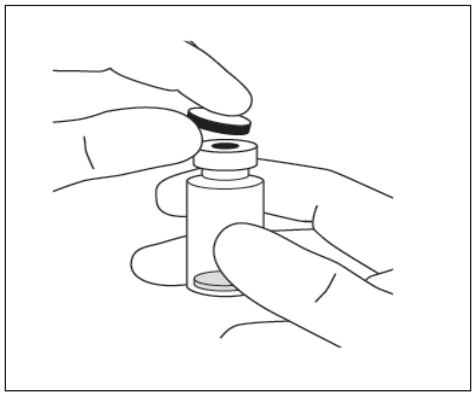
Use aseptic technique to carry out the following preparation steps:

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)

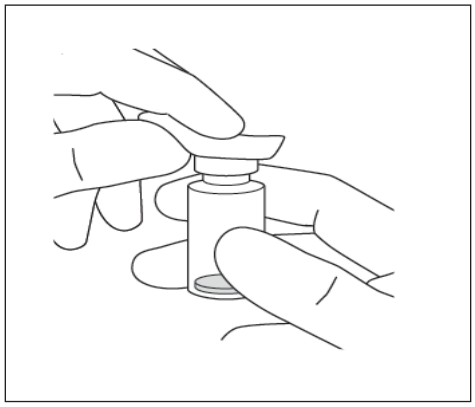
1. Remove the protective plastic cap from the vial (see Figure 1).

Figure 1:



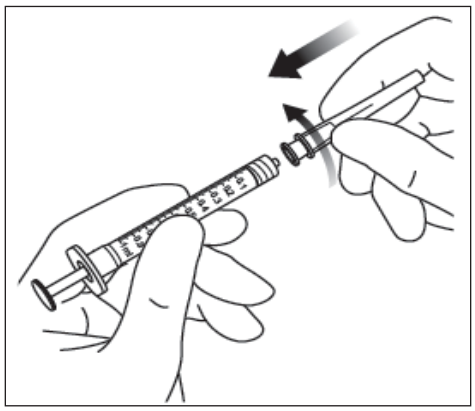
2. Clean the top of the vial with an alcohol wipe (see Figure 2).

Figure 2:



3. Remove the 19-gauge x 1½-inch, 5-micron, filter needle 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 3).

Figure 3:



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

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

Figure 4a:

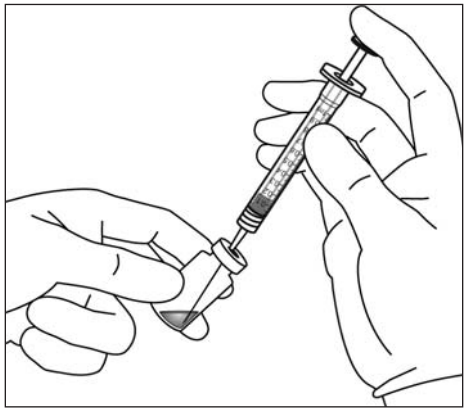
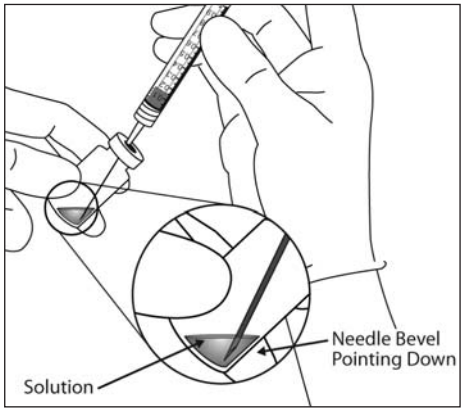
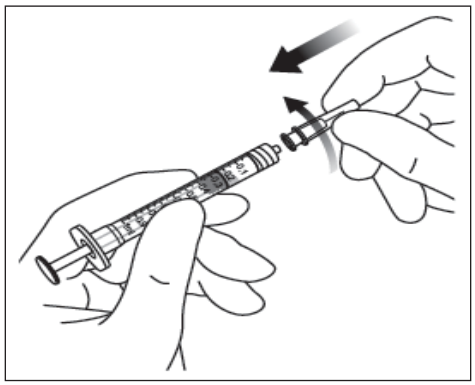


Figure 4b:



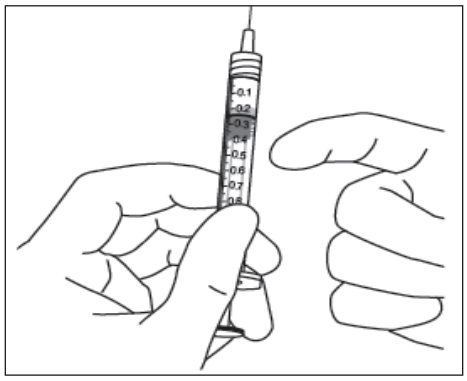
6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
7. Remove the filter needle from the syringe and properly dispose of the filter needle.
Note: Filter needle is **not** to be used for intravitreal injection.
8. Remove the 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 5).

Figure 5:



9. When ready to administer EYLEA, remove the plastic needle shield from the needle.
10. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).

Figure 6:



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

Figure 7a:

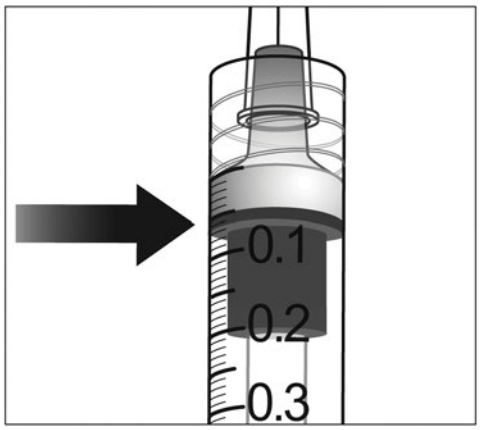
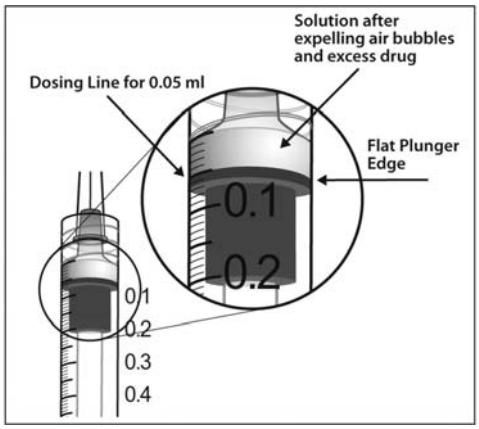


Figure 7b:



2.7 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 vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid

speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Injection: 2 mg/0.05 mL clear, colorless to pale yellow solution in a single-dose, glass vial for intravitreal injection.

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 (2.7) 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 (2.7)*].

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 (≥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, glass vial designed to deliver 0.05 mL (50 microliters) of solution containing 2 mg of EYLEA (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, pH 6.2).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability.

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

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 (t1/2) of free aflibercept in plasma was approximately 5 to 6 days after I.V. administration of doses of 2 to 4 mg/kg aflibercept.

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 8 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	ranibizumab 0.5 mg Q4 weeks	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 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)	

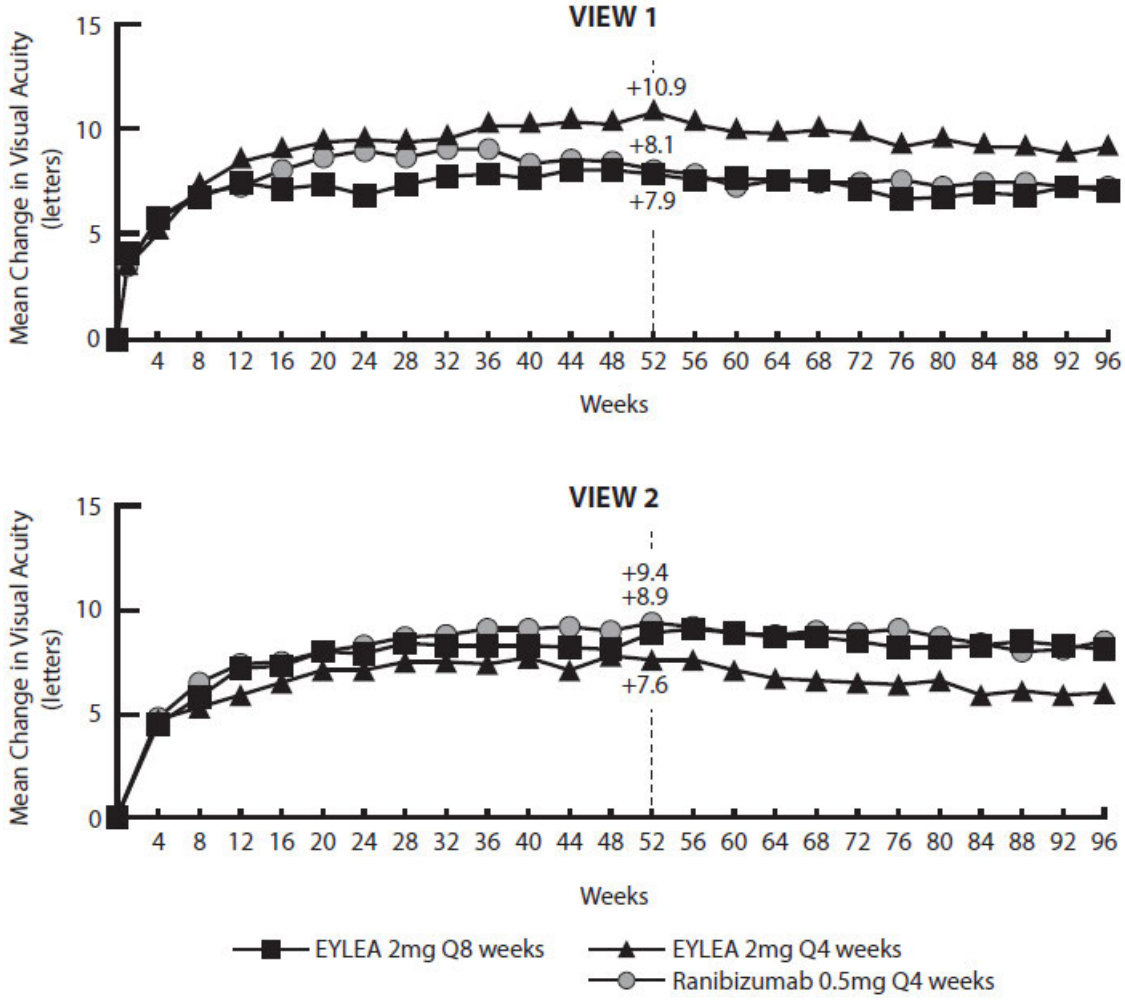
BCVA = Best Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCF = Last Observation Carried Forward (baseline values are not carried forward); 95.1% confidence intervals were presented to adjust for safety assessment conducted during the study

[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 8: 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.

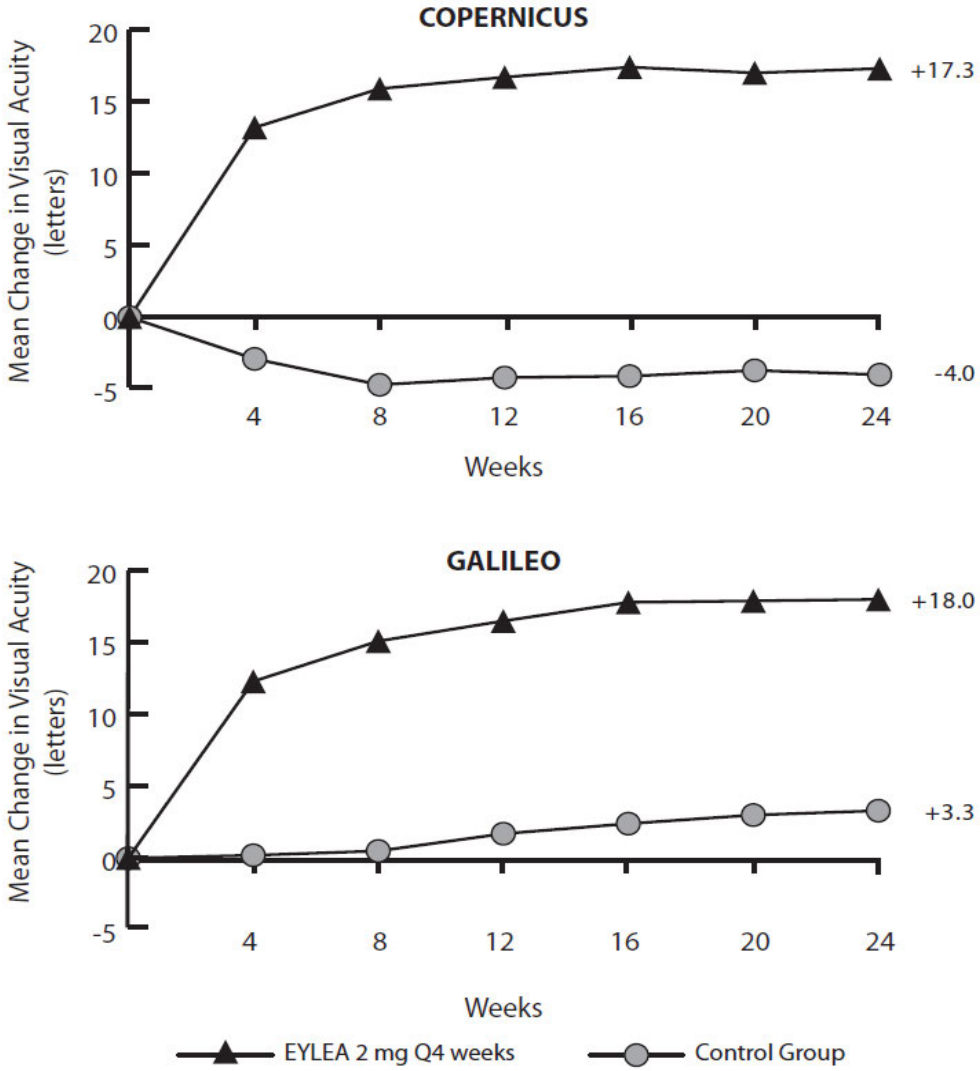
Results from the analysis of the COPERNICUS and GALILEO studies are shown in Table 5 and Figure 9 below.

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



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

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.

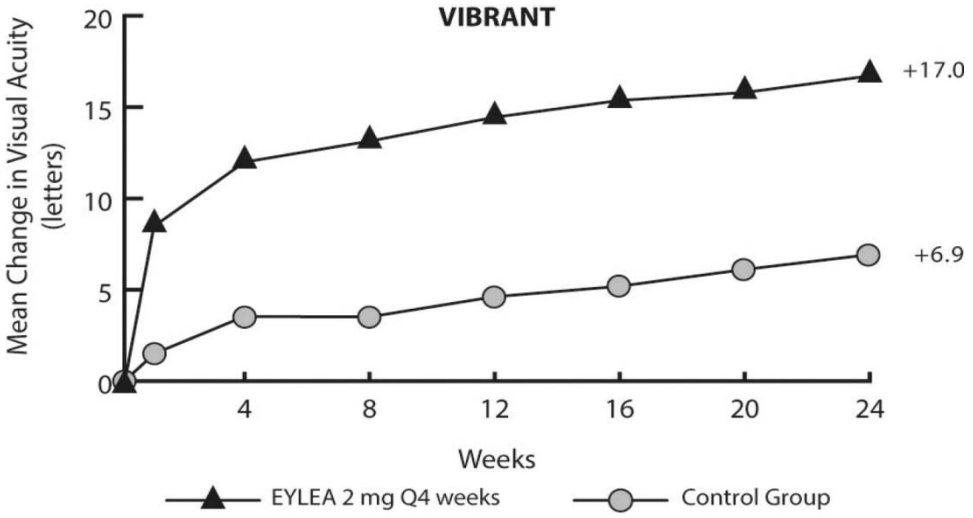
Detailed results from the analysis of the VIBRANT study are shown in Table 6 and Figure 10 below.

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 10: 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.

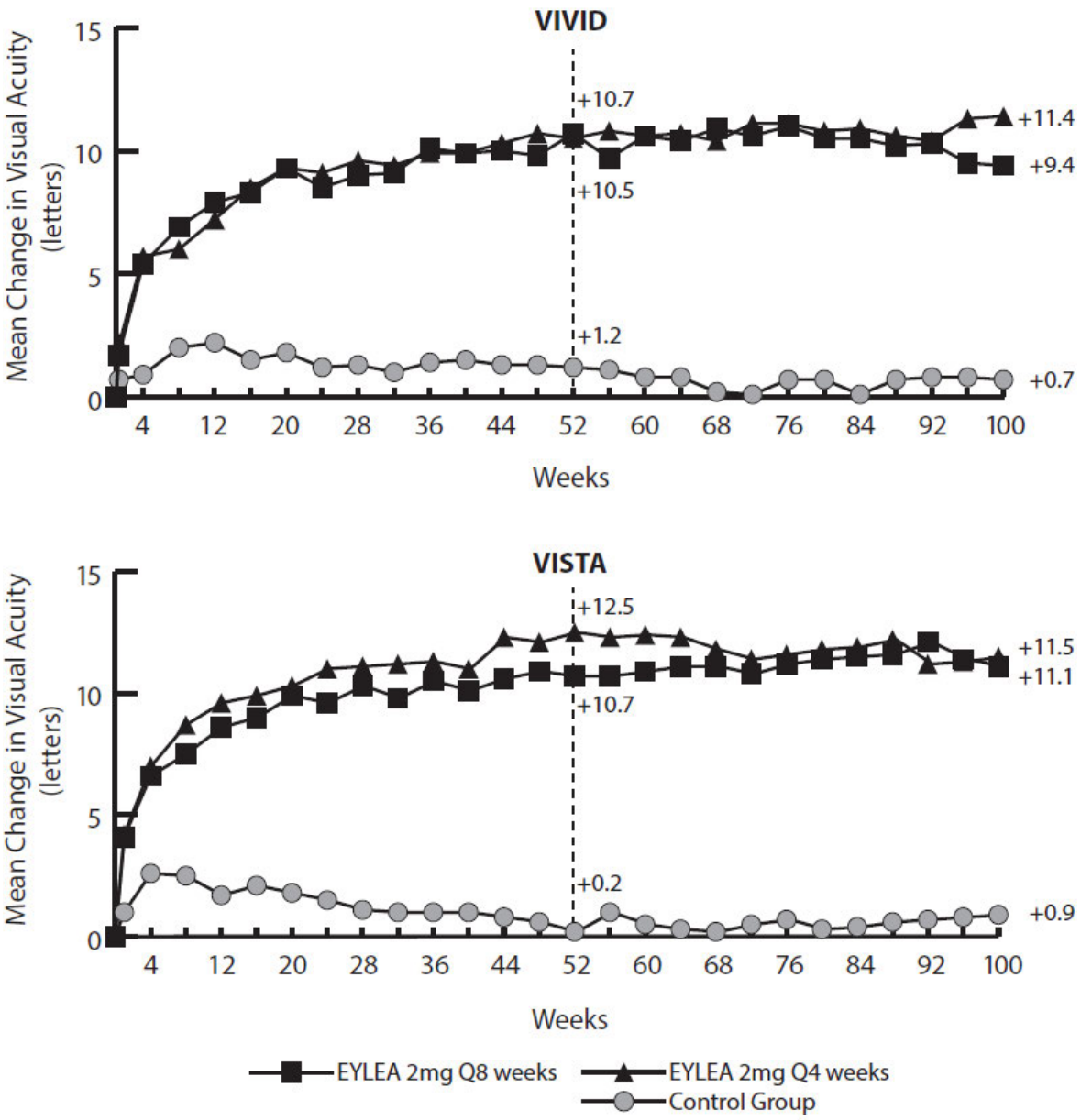
Results from the analysis of the VIVID and VISTA studies are shown in Table 7 and Figure 11 below.

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 11: 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%[e] (12, 36)	21%[e] (9, 33)		22%[e] (11, 33)	22%[e] (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). The proportion of patients with a ≥2-step improvement over time is shown in Figure 12.

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

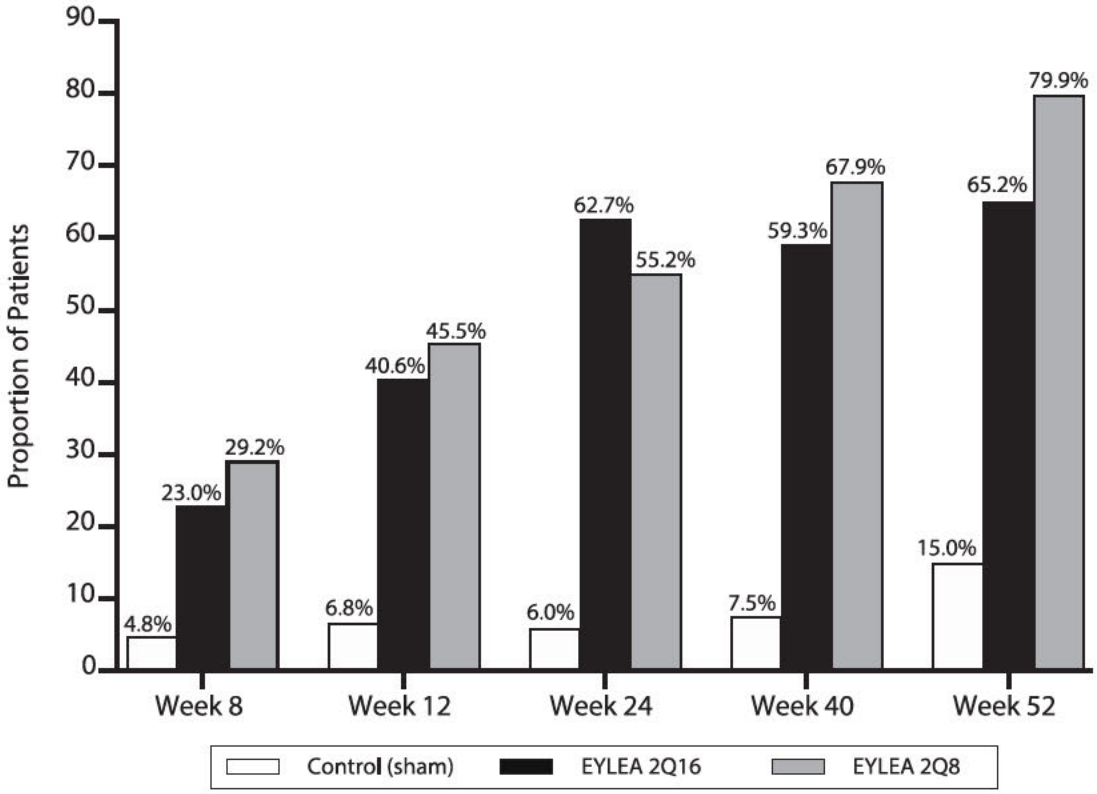


Table 10: Effect of EYLEA on Worsening of Diabetic Retinopathy in PANORAMA through Week 52

	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 Vial is for single eye use only. EYLEA is supplied in the following presentation [*see Dosage and Administration (2.6) and (2.7)*].

NDC NUMBER	CARTON TYPE	CARTON CONTENTS
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 8ºC (36°F to 46ºF). 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.

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.

Revised Date: May 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s061

SUMMARY REVIEW

Cross-Discipline Team Leader and Deputy Division Director Review of BLA 125386/S-061

Date	May 13, 2019
From	William M. Boyd, M.D.; Wiley A. Chambers, M.D.
Subject	Cross-Discipline Team Leader and Division Deputy Director Summary Review
BLA # and Supplement#	BLA 125387/S-061
Applicant	Regeneron Pharmaceuticals, Inc.
Date of Submission	July 13, 2018
PDUFA Goal Date	May 13, 2019
Proprietary Name	Eylea Injection
Established or Proper Name	aflibercept
Dosage Form(s)	intravitreal injection
Regulatory Action	Approval
Indication(s)/Population(s)	Treatment of diabetic retinopathy
Dosing Regimen(s)	The recommended dose for diabetic retinopathy is 2 mg (50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (50 microliters) via intravitreal injection once every 8 weeks (2 months).

1. Benefit-Risk Assessment

Eylea (aflibercept) Injection is an anti-VEGF recombinant antibody. It is an antagonist that binds vascular endothelial growth factor (VEGF) and placental growth factor (PlGF).

Eylea is currently approved for the treatment of diabetic retinopathy in patients with diabetic macular edema. The clinical studies contained in this submission support the use of Eylea for the treatment of diabetic retinopathy (DR) with or without macular edema. When this supplement is approved, Eylea would additionally be approved for the treatment of diabetic retinopathy in patients without diabetic macular edema.

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment
Eylea is currently approved for the treatment of diabetic retinopathy in patients with diabetic macular edema. Submitted studies demonstrated that the benefit-risk for the treatment of diabetic retinopathy is not altered by the presence of diabetic macular edema.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Diabetic retinopathy (DR) is a complication of both Type 1 and Type 2 diabetes mellitus. It is a pathology includes microvascular leakage followed by proliferation of abnormal vessels (PDR).	Diabetic retinopathy (DR) leads to loss of visual function.
Current Treatment Options	• Nonpharmacological treatment of diabetic retinopathy includes retinal photocoagulation, a destructive procedure. Efficacy in the treatment of diabetic retinopathy in patients with diabetic macular edema has been demonstrated previously. • Ranibizumab injection is approved for the treatment of diabetic retinopathy, with or without diabetic macular edema.	There is a need for additional treatment options for the treatment of diabetic retinopathy in patients without diabetic macular edema.
Benefit	• In Study VGFTe-OD-1411, the proportion of treated patients who improved by ≥2 steps from baseline in the DRSS score was superior to sham at weeks 24 and 52. • In Studies VGFT-09-1009 and Study 91475, the proportion of subjects who achieved a ≥2-step improvement on the ETDRS DRSS from baseline to week 100 was statistically significant.	Treatment with Eylea improved diabetic retinopathy in patients with or without diabetic macular edema.
Risk and Risk Management	• 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.	The clinical trials contained in this application demonstrated that the potential adverse events associated with use of Eylea for the DR indication are consistent with the other labeled indications and could be monitored.

2. Background

Diabetic retinopathy (DR) is a complication of both Type 1 and Type 2 diabetes mellitus. The earliest manifestation of the disease, non-proliferative diabetic retinopathy (NPDR), is characterized by microaneurysms, intraretinal hemorrhages, exudates, retinal nerve fiber layer infarcts (cotton wool spots), and, in more severe cases, venous beading and intraretinal microvascular abnormalities. These changes can be visualized on ophthalmoscopic examination or retinal photography. NPDR may progress to proliferative diabetic retinopathy (PDR) usually over a period of years and is characterized by growth of new, abnormal blood vessels (neovascularization) in the retina, optic disc, iris, and anterior chamber angle. The progression of diabetic retinopathy is serious and represents clinically significant progression of the disease.

Progression of DR is measured in discrete steps as described by the ETDRS DR Severity Scale (DRSS). This scale is well established for objective quantification of retinopathy severity and a validated method for quantification of DR change. The DR anatomic worsening measured on the ETDRS scale has been shown to be associated with a clinically significant increase in the risk of visual loss.

Table 11. ETDRS Final Retinopathy Severity Scale (for Individual Eyes)

Level	Severity	Definition
10	DR absent	Microaneurysms and other characteristics absent
14*	DR questionable	HE, SE, or IRMA definite; microaneurysms absent
15*	DR questionable	Hemorrhage(s) definite; microaneurysms absent
20	Microaneurysms only	Microaneurysms definite, other characteristics absent
35†	Mild NPDR	One or more of the following: Venous loops ≥ D/1; SE, IRMA, or VB = Q; Retinal hemorrhages present; HE ≥ D/1; SE ≥ D/1
43	Moderate NPDR	H/Ma = M/4–5 − S/1 *or* IRMA = D/1–3 (not both)
47	Moderately severe NPDR	Both L43 characteristics and/or one (only) of the following: IRMA = D4–5; H/Ma = S/2–3; VB = D/1
53	Severe NPDR†	One or more of the following: ≥2 of the 3 L47 characteristics; H/Ma ≥ S/4–5; IRMA ≥ M/1; VB ≥ D/2–3
61	Mild PDR	FPD or FPE present with NVD and NVE absent; or NVE = D
65	Moderate PDR	Either of the following: (1) NVE ≥M/1 or NVD = D; and VH and PRH = A or Q; (2) VH or PRH = D and NVE < M/1 and NVD absent
71	High-risk PDR	Any of the following: (1) VH or PRH ≥ M/1; (2) NVE ≥ M/1 and VH or PRH ≥ D/1; (3) NVD = 2 and VH or PRH ≥ D/1; (4) NVD ≥ M
75	High-risk PDR	NVD ≥ M and VH or PRH ≥ D/1
81	Advanced PDR: fundus partially obscured, center of macula attached	NVD = cannot grade, or NVD < D and NVE = cannot grade in ≥ 1 field and absent in all others; and retinal detachment at center of macula < D
85	Advanced PDR: posterior fundus obscured, or center of macula detached	VH = VS in fields 1 and 2; or retinal detachment at center of macula = D
90	Cannot grade, even sufficiently for level 81 or 85	

DR = diabetic retinopathy, HE = hard exudates, SE = soft exudates, IRMA = intraretinal microvascular abnormalities, NPDR = nonproliferative DR, VB = venous beading, H/Ma = hemorrhages/microaneurysms, PDR = proliferative DR, NVE = new vessels elsewhere (>1 DD from disc), NVD = new vessels disc (within 1 DD of disc margin), FPD = fibrous proliferations disc, FPE = fibrous proliferations elsewhere, VH = vitreous hemorrhage, PRH = preretinal hemorrhage. For definitions of severity grades, see footnote of Table 2.

* Levels 14 and 15 are not considered separate steps in the scale, but are pooled with level 10 or 20.

† NPDR levels 35 and above all require presence of microaneurysms.

Aflibercept is an approved product in the US for the following indications:

Original: Treatment of neovascular (wet) AMD	11/18/11
S004: Treatment of macular edema secondary to CRVO	9/21/12
S037: Treatment of diabetic macular edema DME	7/29/14
S043: Treatment of macular edema secondary to BRVO	10/6/14
S048: Treatment of diabetic retinopathy in patients with DME	3/25/15

3. Product Quality

The Office of Biotechnology Products completed a review dated 3/28/2019. The review recommended that this supplement be approved from the product quality perspective. Regeneron requested a categorical exclusion from the requirements to prepare an environmental assessment (EA) under 21 CFR 25.3 l(c) and provided justifications. The claim of categorial exclusion from an EA is acceptable.

Regarding immunogenicity, the samples for anti-drug antibody (ADA) assessment were be collected at Visit 11 (week 52) and at Visit 18 (Week 100) in VGFTe-OD-1411. The trial is ongoing. The original supplement submission covered up to trial Week 24. Samples at Week 52 and Week 100 were not collected in time for the 120-day safety update. Clinical will review the final study report when available, but the lack of the ADA assessment now will not delay review of the supplement. Immunogenicity is not a concern for this product for the intended clinical population.

4. Nonclinical Pharmacology/Toxicology

There was no new Pharmacology/Toxicology information submitted. See the Pharmacology/Toxicology original review in DARRTS.

5. Clinical Pharmacology

There was no new Clinical Pharmacology information submitted. See the Clinical Pharmacology original application review in DARRTS/

6. Clinical/Statistical- Efficacy

This Supplemental BLA is submitted for the treatment of diabetic retinopathy following analysis of the 52-week safety and efficacy data (study is ongoing to 100 weeks) from the Regeneron-sponsored clinical study VGFTe-OD-1411 (PANORAMA). Supporting data are provided from the VIVID and VISTA clinical studies. Data from VIVID and VISTA were previously submitted for the indication for the treatment of patients with diabetic macula edema (DME) and in support of the treatment of diabetic retinopathy in patients with DME.

Efficacy Results – Panorama Primary Endpoint

Panorama: Proportion of Patients With a >=2 Step Improvement at Week 24 in the DRSS From Baseline (Full Analysis Set with LOCF)

	Sham N=133	2Q16 N=135	2Q8 N=134
Week 24			
Patients who gained >=2 steps in the DRSS at Week 24	8/133 (6%)	83/135 (61%)	74/134 (55%)
Adjusted difference (%) versus sham		55%	49%
95% CI for difference		(46, 64)	(40, 59)
P-value		<0.0001	<0.0001

The difference with CI was calculated using the Mantel-Haenszel weighting scheme adjusted by baseline DRSS stratification variable from IVRS (interactive voice response system). The p-value was calculated using a 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS stratification variable from IVRS.

Panorama: Sensitivity Analysis of the Proportion of Patients with a >=2 Step Improvement at Week 24 in the DRSS From Baseline (Full Analysis Set)

	Sham N=133	2Q16 N=135	2Q8 N=134
OC			
Patients who gained >=2 steps in the DRSS at Week 24	7/93 (7.5%)	77/117 (66%)	71/125 (57%)
Adjusted difference (%) versus sham		44%*	60%*
95% CI for difference		(31, 57)	(48, 72)
aLOCF			
Patients who gained >=2 steps in the DRSS at Week 24	17/133 (13%)	83/135 (61%)	74/134 (55%)
Adjusted difference (%) versus sham		49%*	42%*
95% CI for difference		(38.7, 58.6)	(32.3, 52.6)
aOC			
Patients who gained >=2 steps in the DRSS at Week 24	16/133 (14%)	78/119 (65%)	71/125 (57%)
Adjusted difference (%) versus sham		51%*	43%*
95% CI for difference		(41, 62)	(38, 53)

* p<0.0001, OC: Only observed, non-censored values were used for analysis; measurements taken after rescue were censored. aLOCF: The LOCF method was used to impute missing or non-gradable post-baseline data regardless of rescue. Baseline was carried forward if all post-baseline observations were missing or non-gradable. aOC: All observed values were used for analysis regardless of rescue treatment.

For the primary endpoint, a greater percentage of patients had a ≥2-step improvement in the DRSS in the intravitreal aflibercept injection 2 mg combined group (58%) compared with sham (6%). The robustness of the primary analysis was confirmed with sensitivity analyses using the OC, aLOCF, and aOC methods.

Panorama: Proportion of Patients With a >=2 Step Improvement at Week 52 in the DRSS From Baseline (Full Analysis Set with LOCF)

	Sham N=133	2Q16 N=135	2Q8 N=134
Week 52			
Patients who gained >=2 steps in the DRSS at Week 24	20/133 (15%)	88/135 (65%)	107/134 (80%)
Adjusted difference (%) versus sham		50%	65%
95% CI for difference		(40, 60)	(56, 74)
P-value		<0.0001	<0.0001

The difference with CI was calculated using the Mantel-Haenszel weighting scheme adjusted by baseline DRSS stratification variable from IVRS (interactive voice response system). The p-value was calculated using a 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS stratification variable from IVRS.

Panorama: Sensitivity Analysis of the Proportion of Patients with a >=2 Step Improvement at Week 52 in the DRSS From Baseline (Full Analysis Set)

	Sham N=133	2Q16 N=135	2Q8 N=134
OC			
Patients who gained >=2 steps in the DRSS at Week 24	17/75 (23%)	69/102 (68%)	95/113 (84%)
Adjusted difference (%) versus sham		44%*	60%*
95% CI for difference		(31, 57)	(48, 72)
aLOCF			
Patients who gained >=2 steps in the DRSS at Week 24	32/133 (24%)	89/135 (66%)	107/134 (80%)
Adjusted difference (%) versus sham		42%*	56%*
95% CI for difference		(31, 53)	(46, 66)
aOC			
Patients who gained >=2 steps in the DRSS at Week 24	27/106 (25%)	72/108 (67%)	96/116 (83%)
Adjusted difference (%) versus sham		41%*	56%*
95% CI for difference		(28, 53)	(46, 67)

*p-value <0.001. OC: Only observed, non-censored values were used for analysis; measurements taken after rescue were censored. The difference with CI was calculated using the Mantel-Haenszel weighting scheme adjusted by baseline DRSS stratification variable from IVRS. aLOCF: The LOCF method was used to impute missing or non-gradable post-baseline data regardless of whether or not rescue treatment was given. Baseline was carried forward if all post-baseline observations were missing or non-gradable. aOC: All observed values were used for analysis regardless of whether or not rescue treatment was given.

The additional primary endpoint at Week 52 was the proportion of patients who improved by ≥ 2 steps from baseline in the DRSS score in each of the individual 2Q16 and 2Q8 groups. The improvements in 2Q8 intravitreal aflibercept injection group was greater than in the sham group and the 2Q16 group. The robustness of the primary analysis was also confirmed with sensitivity analyses using the OC, aLOCF, and aOC methods.

Efficacy Results – Vista and Vivid Primary Endpoint

Since all 3 primary efficacy endpoints (at week 24 and week 52) were statistically significant, the statistical significance of the secondary efficacy endpoints for each dose group was determined by comparing the p-values vs. significance level of 0.025 using a hierarchical testing procedure, as prespecified in the SAP.

The following endpoints were hierarchical secondary endpoints only in US SAP and exploratory in Global SAP:

- Change in BCVA by ETDRS letter score from baseline to week 100
- Proportion of subjects who gained ≥10 ETDRS letters from baseline to week 100
- Proportion of subjects who gained ≥15 ETDRS letters from baseline to week 100
- Proportion of subjects who achieved a ≥2-step improvement on the ETDRS DRSS from baseline to week 100
- Change in CRT from baseline to week 100, as assessed on OCT
- NEI VFQ-25 near activities subscale change from baseline to week 100
- NEI VFQ-25 distance activities subscale change from baseline to week 100.

Vista: Overview of Secondary Efficacy Results at Week 100 (Full analysis set) LOCF Adjusted Group Difference vs. Laser

	VTE 2Q4 Estimate (97.5% CI)	P-value	VTE 2Q8 Estimate (97.5% CI)	P-value
Change in BCVA in ETDRS letter score from baseline at week 100	10.6 (7.1, 14.2)	<0.0001	10.1 (7.0, 13.3)	<0.0001
Proportion of subjects (%) who gained >= 10 ETDRS letter from baseline to week 100	36.2 (24.3, 48.1)	<0.0001	31.6 (19.5, 43.7)	<0.0001
Proportion of subjects (%) who gained >= 15 ETDRS letter from baseline to week 100	25.8 (15.1, 36.6)	<0.0001	20.1 (9.6, 30.6)	<0.0001
Proportion of subjects (%) who achieved a >=2 step improvement on ETDRS DRSS from baseline to week 100	22.1 (11.1, 33.2)	<0.0001	21.7 (10.5, 33.0)	<0.0001
Change in CRT from baseline at week 100, assessed by OCT	-105 (-140, -70)	<0.0001	-111 (-143, -79)	<0.0001
NEI VFQ-25 near activities subscale, baseline to week 100	4.6 (-0.73, 9.9)	0.0529	5.05 (0.12, 9.98)	0.0218
NEI VFQ-25 distance activities subscale change from baseline to week 100	5.8 (1.0, 10.6)	0.0072	3.57 (-0.96, 8.11)	0.0772

Vivid: Overview of Secondary Efficacy Results at Week 100 (Full analysis set) LOCF Adjusted Group Difference vs. Laser

	VTE 2Q4 Estimate (97.5% CI)	P-value	VTE 2Q8 Estimate (97.5% CI)	P-value
Change in BCVA in ETDRS letter score from baseline at week 100	10.7 (7.6, 13.8)	<0.0001	8.2 (5.2, 11.3)	<0.0001
Proportion of subjects (%) who gained >= 10 ETDRS letter from baseline to week 100	33 (20, 46)	<0.0001	24.6 (12, 37)	<0.0001
Proportion of subjects (%) who gained >= 15 ETDRS letter from baseline to week 100	26 (15, 37)	<0.0001	19 (8, 30)	0.0001
Proportion of subjects (%) who achieved a >=2 step improvement on the ETDRS DRSS, baseline to week 100	20.7 (8.8, 32.5)	0.0001	24.2 (12.4, 35.9)	<0.0001
Change in CRT from baseline at week 100, assessed by OCT	-154 (-189, -120)	<0.0001	-127 (-165, -89)	<0.0001
NEI VFQ-25 near activities subscale, baseline to week 100	3.6 (-0.7, 8.0)	0.0596	-0.7 (-5.3, 3.8)	0.7144
NEI VFQ-25 distance activities subscale change from baseline to week 100	2.6 (-1.7, 6.9)	0.1792	-1.3 (-6.0, 3.4)	0.5325

Vista: Proportion of Patients with A 2 Step Improvement from Baseline in the DRSS Score at Week 100 (Full Analysis Set) LOCF

	Laser N=154	VTE 2Q4 N=154	VTE 2Q8 N=151
Proportion of subjects with a >=2 step improvement from baseline	24/150* (16%)	58/153* (38%)	56/148* (38%)
Difference (%) vs. Laser		22.1	21.7
97.5% CI for difference		(11.1, 33.2)	(10.5, 33.0)
P-value		<0.0001	<0.0001

*Number with baseline evaluable photographs

Vivid: Proportion of Patients with a 2 Step Improvement from Baseline in the DRSS Score at Week 100 (Full Analysis Set) LOCF

	Laser N=132	VTE 2Q4 N=136	VTE 2Q8 N=135
Proportion of subjects with a 2 step improvement from baseline	7/99* (7%)	27/97* (28%)	32/101* (32%)
Difference (%) vs. Laser		20.7	24.2
97.5% CI for difference		(8.8, 32.5)	(12.4, 35.9)
P-value		0.0001	<0.0001

Both Vista and Vivid showed a two-step change on the DRSS in the study eye, and this change was statistically significant compared to laser treatment group.

7. Safety

The main support for safety is from studies which supported the original approval of this application. The safety is also supported by the 3 clinical studies (Panorama, Vista, and Vivid) identified in this review. Studies Vista and Vivid Week 52 results were reviewed as part of Supplement S-037 for the DME indication. Week 100 data from Vista and Vivid was reviewed as part of Supplement S-048 for the DR with DME indication. Refer to Medical Officer reviews for S-037 and S-048 for safety review of Vista and Vivid.

Panorama Treatment Exposure Not Including Rescue Treatment in the Study Eye in the First 52 Weeks (Safety Analysis Set)

	Sham N=133	**2Q16 N=135**	**2Q8 N=134**
Total number of active injections	0	749	1158
Number of active injections per patient			
1	0	2	0
2	0	1	1
3	0	6	1
4	0	9	0
5	0	11	3
6	0	106	3
7	0	0	2
8	0	0	10
9	0	0	114
Summary of active injections			
N	0	135	134
Mean (sd)		5.5 (1.0)	8.6 (1.1)
Min, Max		1, 6	2, 9

Panorama Deaths (Source: Week 52 VGFTe-OD-1411 Study Report)

Patient	**Group**	**Description**
From Baseline to Week 24		
Patient (b) (6)	Sham	Acute Respiratory Failure and Pulmonary Hypertension
Patient (b) (6)	Sham	Acute MI
Patient (b) (6)	Sham	MI
Between Week 24 and Week 52		
Patient (b) (6)	Sham	Did not have an event (PT) associated with the death
Patient (b) (6)	Sham	Pulseless Electrical Activity
Patient (b) (6)	Sham	MI
Patient (b) (6)	2Q8	Cardiac arrest

.Seven deaths (6 in the sham group and 1 in the 2Q8 group) were reported through Week 52.

Non-Ocular Treatment Emergent SAEs >=1% Through Week 52 (Safety Analysis Set)
(Source: Week 52 VGFTe-OD-1411 Study Report)

	Sham N=133	2Q16 N=135	2Q8 N=134
Number of subjects with at least 1 non-ocular TEAE	26 (19.5%)	25 (18.5%)	25 (18.7%)
Infections			
Cellulitis	1	1	5
Pneumonia	1	1	3
Diabetic foot infection	0	2	0
Cardiac disorders			
CHF	1	2	2
CAD	1	2	1
Metabolism disorders			
Dehydration	1	0	2
DKA	0	2	0
Nervous system disorders			
CVA	0	2	1
Skin disorders			
Diabetic foot	0	0	2

Non-ocular SAEs were reported by similar proportions of patients in the sham group (20%) and the intravitreal aflibercept injection groups (19% in the 2Q16 group and 19% in the 2Q8 group).

Ocular Treatment Emergent AEs in the Study Eye Occurring in >= 2% of Patients in Either Treatment Group Through Week 52 (Safety Analysis Set)
(Source: Week 52 VGFTe-OD-1411 Study Report)

	Sham N=133	2Q16 N=135	Q8 N=134
Eye disorders			
Conjunctival hemorrhage	7	16	23
Diabetic retinal edema	32	8	12
Vitreous floaters	3	6	12
Eye pain	4	10	5
Retinal exudates	5	5	7
Blepharitis	1	2	6
Vitreous detachment	1	4	4
Cataract	1	3	4
Dry eye	4	3	4
Cataract subcapsular	1	3	2
Diabetic retinopathy	13	2	3
Lacrimation increased	0	2	3
Punctate keratitis	2	2	3
Visual impairment	0	1	4
Eye irritation	0	1	3
Vision blurred	1	1	3
Macular edema	3	2	0
Injury			
Corneal abrasion	1	2	3

8. Advisory Committee Meeting

There were no issues identified in the review that were thought to benefit from an advisory committee discussion.

9. Pediatrics

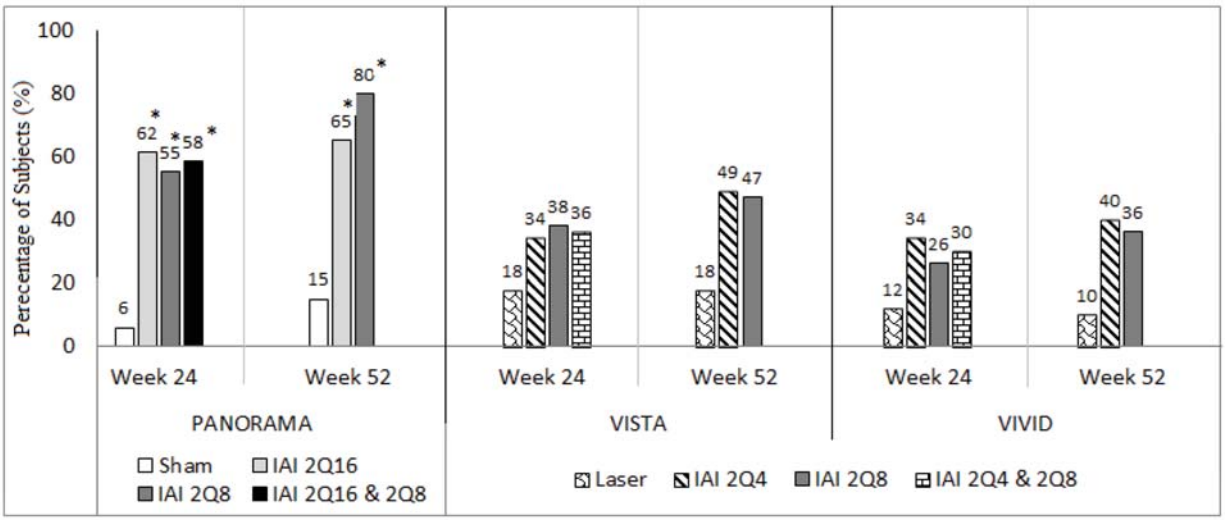
Proliferative diabetic retinopathy does not occur in pediatric patients except in very rare circumstances. The safety and effectiveness of Eylea (aflibercept) Injection in pediatric patients have not been established. Eylea was presented at the Pediatric Regulatory Committee (PeRC) on March 6, 2019, for the diabetic retinopathy indication. PeRC concurred with the plan for a full pediatric waiver as necessary studies would be impossible or highly impractical

10. Other Relevant Regulatory Issues

Biostatistics

Per the Biostatistics review dated 2/8/2019: In the PANORAMA study, the intravitreal aflibercept injection groups yielded substantial improvement in DRSS and were statistically superior to the sham group in the primary efficacy variable of the proportion of subjects who achieved ≥2-step improvement in DRSS from baseline at Week 24 and at Week 52. As shown in **Figure 1 below**, at Week 24, 58% of subjects in the combined intravitreal aflibercept injection group (61% in 2Q16 and 55% in 2Q8) achieved ≥2-step improvement in DRSS compared to 6% of subjects in the sham group. The treatment difference was 52% (98.3% CI; 44% to 61%). At Week 52, 65% of subjects in the intravitreal aflibercept injection 2Q16 group and 80% of subjects in the intravitreal aflibercept injection 2Q8 group achieved ≥2-step improvement compared to 15% of subjects in the sham group. The treatment difference was 50% (98.3% CI; 38% to 62%) for intravitreal aflibercept injection 2Q16 versus sham and 65% (98.3% CI; 54% to 76%) for intravitreal aflibercept injection 2Q8 versus sham.

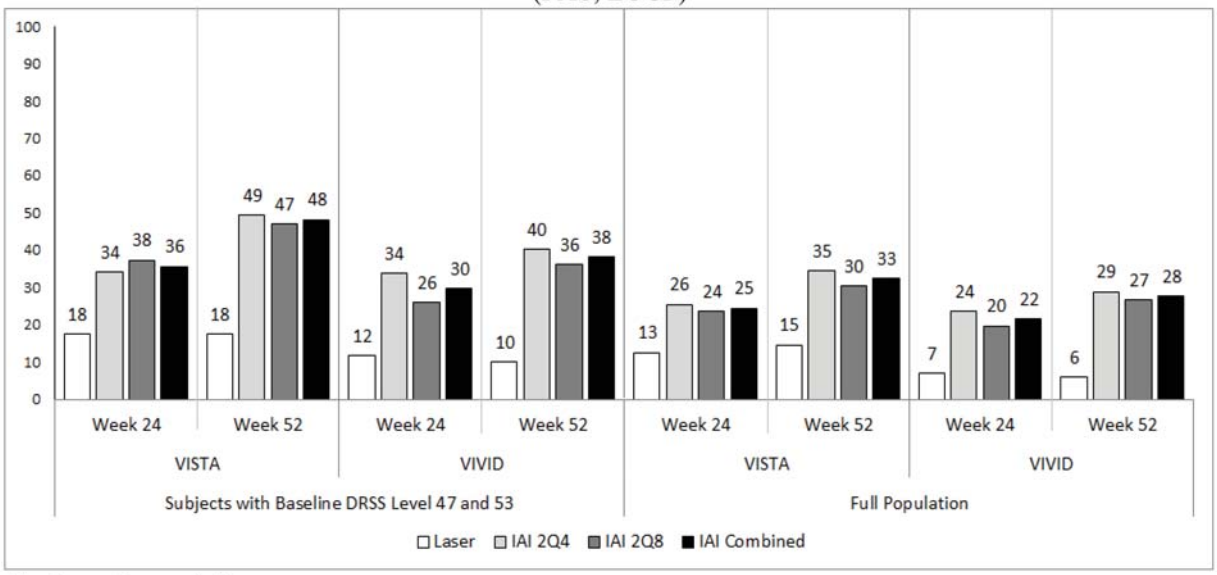
Figure 1: Proportion of subjects who achieved ≥2-step improvement in DRSS at Week 24 and Week 52 (Full Analysis Set)



* P-value<0.0001 versus sham– based on Cochran-Mantel-Haenszel (CMH) test, stratified by baseline DRSS level (level 47 versus level 53)
Note 1: The full analysis set included all randomized subjects who received any study drug.
Note 2: Missing DRSS data were imputed using the last observation carried forward (LOCF) method (see detail in Section 3.2.2).
Note 3: IAI 2Q4: Intravitreal aflibercept 2.0 mg injection administered every 4-week.

A 24-week and a 52-week analysis of VISTA and VIVID studies assessed in DME subjects with moderately severe or severe NPDR at baseline (analogous to the PANORAMA population) provided supporting evidence for IAI for the indication sought. As shown in **Figure 1 above** and in **Figure 2 below,** in these studies, IAI demonstrated greater improvement than laser treatment.

Figure 2: Proportion of subjects who achieved ≥ 2-step improvement in DRSS at Week 24 and Week 52
(VISTA and VIVID Studies)
(FAS; LOCF)



Based on reviewer analysis

Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators.

The following study design elements and operational practices were put in place to reduce the potential for an investigator to unduly influence the outcome of the VGFTe-OD-1411 (PANORAMA) clinical study:

- PANORAMA was designed as a double-masked, randomized trial to ensure objective assessments related to safety and efficacy (refer to the VGFTe-OD-1411 [PANORAMA] protocol, section 5.5.1 Masking)

- The primary efficacy endpoint at Week 24 of a ≥ 2-step improvement in diabetic retinopathy severity scale (DRSS) score was determined by independent, masked readers at a centralized reading center. The reading center also evaluated the baseline DRSS score to confirm eligibility.

OSI

A routine Office of Scientific Investigations (OSI) audit was requested. Per the OSI review dated 1/12/2019:

The clinical site of Dr. Emanuelli was inspected in support of this NDA. Based on the results of this inspection, the study (Protocol VGFTe-OD-1411) appears to have been conducted adequately. The primary efficacy endpoints were not verified on site as the derived primary endpoint data, the Diabetic Retinopathy Severity Score (DRSS), was calculated by an outside firm which then transmitted the DRSS score to the sponsor. The audit did not indicate deviations/findings that would impact the validity or reliability of the rest of the submitted data. The data generated by this site and submitted by the sponsor appear acceptable in support of the respective indication. The

final classification of the inspection of Dr. Emanuelli was No Action Indicated (NAI).

Site # Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
Site #840407 **Andres Emanuelli, M.D.** Emanuelli Research and Development Center, LLC 452 Ave Rivera Aulet Arecibo, Puerto Rico, 00613	VGFTe-OD-1411 Subjects: 35	9-11 Oct 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of the proposed labeling on 12/27/2018. Their evaluation of the proposed prescribing information did not identify areas of vulnerability that may lead to medication errors. They had no recommendations at this time.

11. Postmarketing Recommendations

A risk management plan is not necessary given the known risks of these classes of products.

12. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

	The patient experience data that was submitted as part of the application include:		Section where discussed, if applicable
☒	☒	Clinical outcome assessment (COA) data, such as	Sec 6.1 Study endpoints
	☐	Patient reported outcome (PRO)	
	☐	Observer reported outcome (ObsRO)	
	☒	Clinician reported outcome (ClinRO)	
	☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	

☒	**The patient experience data that was submitted as part of the application include:**			**Section where discussed, if applicable**
	☒	Other: Patient reported outcome using unqualified instrument		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

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13. Labeling

Eylea (aflibercept) Injection will be approved for the for the treatment of diabetic retinopathy based on adequate and well controlled clinical trials with the labeling below (submitted May 3, 2019).

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

WILLIAM M BOYD
05/13/2019 06:51:03 AM

WILEY A CHAMBERS
05/13/2019 08:12:02 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s061

CLINICAL REVIEW(S)

CLINICAL REVIEW BLA 125-387

Application Type	BLA
Application Number(s)	125387
Priority or Standard	Standard
Submit Date(s)	7/13/18
Received Date(s)	7/13/18
PDUFA Goal Date	5/13/19
Division/Office	DTOP/OND
Reviewer Name(s)	Sonal D. Wadhwa, MD
Review Completion Date	3/4/19
Established/Proper Name	aflibercept
Trade Name	Eylea
Applicant	Regeneron
Dosage Form(s)	Intravitreal injection
Dosing Regimen(s)	The recommended dose for diabetic retinopathy 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).
Indication(s)/Population(s)	Treatment of diabetic retinopathy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Indicated for the treatment of diabetic retinopathy

Table of Contents

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics

PMC	post-marketing commitment
PMR	post-marketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Aflibercept is an anti-VEGF recombinant antibody. It is an antagonist that binds VEGF and PlGF.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The clinical studies contained in this submission support the use of Eylea for the treatment of diabetic retinopathy (DR). BLA 125387/S-061 is recommended for approval with the revised labeling identified in this review.

1.3. Benefit-Risk Integrated Assessment

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Diabetic retinopathy (DR) is a complication of both Type 1 and Type 2 diabetes mellitus. It is a pathology includes microvascular leakage followed by proliferation of abnormal vessels (PDR).	Diabetic retinopathy (DR) leads to loss of visual function.
Current Treatment Options	• Nonpharmacological treatment of PDR includes retinal photocoagulation, a destructive procedure. • Ranibizumab injection is approved for the treatment of diabetic retinopathy.	There is a need for additional treatment options.
Benefit	• In Study VGFTe-OD-1411, the proportion of treated patients who improved by ≥2 steps from baseline in the DRSS score was superior to sham at weeks 24 and 52. • In Studies VGFT-09-1009 and Study 91475, the proportion of subjects who achieved a ≥2-step improvement on the ETDRS DRSS from baseline to week 100 was statistically significant.	Eylea, if approved, would provide an alternative treatment option for DR.
Risk and Risk Management	• 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.	The clinical trials contained in this application demonstrated that the potential adverse events associated with use of Eylea for the DR indication are consistent with the other labeled indications and could be monitored.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		Sec 6.1 Study endpoints
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Diabetic retinopathy (DR) is a complication of both Type 1 and Type 2 diabetes mellitus. The earliest manifestation of the disease, non-proliferative diabetic retinopathy (NPDR), is

characterized by microaneurysms, intraretinal hemorrhages, exudates, retinal nerve fiber layer infarcts (cotton wool spots), and, in more severe cases, venous beading and intraretinal microvascular abnormalities which can be visualized on ophthalmoscopic examination or retinal photography. NPDR may progress to proliferative diabetic retinopathy (PDR) usually over a period of years and is characterized by growth of new, abnormal blood vessels (neovascularization) in the retina, optic disc, iris, and anterior chamber angle as a result of retinal ocular ischemia and the resultant increase in VEGF levels. The progression through NPDR and PDR is serious and represents clinically significant progression of the disease pathology to the advanced stages of the disease. PDR traditionally has been treated with panretinal photocoagulation (PRP) or surgical intervention with vitrectomy.

Progression of DR is measured in discrete steps as described by the ETDRS DR Severity Scale (DRSS). This scale is well established for objective quantification of retinopathy severity and a validated method for quantification of DR change. The DR anatomic worsening measured on the ETDRS scale has been shown to be associated with a clinically significant increase in the risk of visual loss.

Table 11. ETDRS Final Retinopathy Severity Scale (for Individual Eyes)

Level	Severity	Definition
10	DR absent	Microaneurysms and other characteristics absent
14*	DR questionable	HE, SE, or IRMA definite; microaneurysms absent
15*	DR questionable	Hemorrhage(s) definite; microaneurysms absent
20	Microaneurysms only	Microaneurysms definite, other characteristics absent
35†	Mild NPDR	One or more of the following: Venous loops ≥ D/1; SE, IRMA, or VB = Q; Retinal hemorrhages present; HE ≥ D/1; SE ≥ D/1
43	Moderate NPDR	H/Ma = M/4–5 − S/1 *or* IRMA = D/1–3 (not both)
47	Moderately severe NPDR	Both L43 characteristics and/or one (only) of the following: IRMA = D4–5; H/Ma = S/2–3; VB = D/1
53	Severe NPDR†	One or more of the following: ≥2 of the 3 L47 characteristics; H/Ma ≥ S/4–5; IRMA ≥ M/1; VB ≥ D/2–3
61	Mild PDR	FPD or FPE present with NVD and NVE absent; or NVE = D
65	Moderate PDR	Either of the following: (1) NVE ≥M/1 or NVD = D; and VH and PRH = A or Q; (2) VH or PRH = D and NVE < M/1 and NVD absent
71	High-risk PDR	Any of the following: (1) VH or PRH ≥ M/1; (2) NVE ≥ M/1 and VH or PRH ≥ D/1; (3) NVD = 2 and VH or PRH ≥ D/1; (4) NVD ≥ M
75	High-risk PDR	NVD ≥ M and VH or PRH ≥ D/1
81	Advanced PDR: fundus partially obscured, center of macula attached	NVD = cannot grade, or NVD < D and NVE = cannot grade in ≥ 1 field and absent in all others; and retinal detachment at center of macula < D
85	Advanced PDR: posterior fundus obscured, or center of macula detached	VH = VS in fields 1 and 2; or retinal detachment at center of macula = D
90	Cannot grade, even sufficiently for level 81 or 85	

DR = diabetic retinopathy, HE = hard exudates, SE = soft exudates, IRMA = intraretinal microvascular abnormalities, NPDR = nonproliferative DR, VB = venous beading, H/Ma = hemorrhages/microaneurysms, PDR = proliferative DR, NVE = new vessels elsewhere (>1 DD from disc), NVD = new vessels disc (within 1 DD of disc margin), FPD = fibrous proliferations disc, FPE = fibrous proliferations elsewhere, VH = vitreous hemorrhage, PRH = preretinal hemorrhage. For definitions of severity grades, see footnote of Table 2.

* Levels 14 and 15 are not considered separate steps in the scale, but are pooled with level 10 or 20.

† NPDR levels 35 and above all require presence of microaneurysms.

2.2. Analysis of Current Treatment Options

Lucentis is approved for the treatment of diabetic retinopathy. Eylea is currently approved for the treatment of diabetic retinopathy in patients with diabetic macular edema. If this supplement is approved, Eylea would additionally be approved for the treatment of diabetic retinopathy in patients without diabetic macular edema.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Aflibercept is an approved product in the US for the following indications:

Original: Treatment of neovascular (wet) AMD	11/18/11
S004: Treatment of macular edema secondary to CRVO	9/21/12
S037: Treatment of diabetic macular edema DME	7/29/14
S043: Treatment of macular edema secondary to BRVO	10/6/14
S048: Treatment of diabetic retinopathy in patients with DME	3/25/15

3.2. Summary of Pre-submission/Submission Regulatory Activity

7/13/18 (SDN-697)	Submission of efficacy supplement
8/24/18 (SDN-722)	Submission of updated label
11/7/18 (SDN-752)	4-month safety update
12/17/18 (SDN-765)	CSR for Panorama study for 52-week data (original submission included only 24-week data)

3.3. Foreign Regulatory Actions and Marketing History

As of June 2018, Eylea has been approved for the treatment of neovascular AMD by health authorities in 107 countries, including in the European Union, Japan, Canada and Australia; for macular edema following central retinal vein occlusion in the US and 102 countries; for macular edema following branch retinal vein occlusion in the US and 98 countries; and for diabetic macular edema (DME) in the US and 102 countries. Eylea is also approved for the treatment of myopic choroidal neovascularization in 95 countries.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No issues were identified in the review of the clinical portion of the BLA to suggest a problem with data integrity. Routine clinical inspections were requested from OSI.

The clinical site Dr. Emanuelli was inspected in support of this BLA. The clinical site of Dr. Emanuelli was selected for inspection as it was the largest enrolling site in the Panorama study and had not been previously inspected. Based on the results of this inspection, Panorama appears to have been conducted adequately, and the data generated appear acceptable in support of the respective indication. The final compliance classification of the inspection of Dr. Emanuelli was No Action Indicated (NAI).

4.2. Product Quality

There were no changes in the product. See Product Quality original review.

4.3. Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.4. Nonclinical Pharmacology/Toxicology

There was no new Pharmacology/Toxicology information submitted. See Pharmacology/Toxicology original review.

4.5. Clinical Pharmacology

There was no new Clinical Pharmacology information submitted. See Clinical Pharmacology original review.

4.6. Devices and Companion Diagnostic Issues

Not applicable. There is not a companion device or diagnostic.

4.7. Consumer Study Reviews

Not applicable. No consumer studies were conducted.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Title	Objective	Study Design	Test Product and Dosing Regimen	Duration of Treatment	Study Status
Panorama (VGFTe-OD-1411)	Efficacy and Safety	Randomized, double-masked, sham controlled	Intravitreal aflibercept injection (IAI) 2Q8 group: 2 mg Q8 to week 48 (after 5 initial monthly doses), followed by a flexible treatment regimen with aflibercept 2 mg to week 96: 134 patients IAI 2Q16 group: IVT aflibercept 2 mg Q16 to week 96 (after 3 initial monthly doses and 1 Q8 interval): 135 patients Sham group: sham injections at every treatment visit through week 96: 133 patients TOTAL: 402 patients	24 weeks (one of two primary endpoints, other at 52 weeks) continuing to 100 weeks	Ongoing
Vista (VGFT-09-1009)	Efficacy and Safety	Randomized, double-masked, laser controlled	IAI 2 mg every 4 weeks (2Q4): 156 patients; IAI 2 mg every 8 weeks after 5 initial monthly injections (2Q8): 154 patients Laser Photocoagulation (no more than once every 12 weeks): 156 patients TOTAL: 466 patients	52 week (primary endpoint) continuing to 148 weeks	Completed
Vivid (Study 91475)	Efficacy and Safety	Randomized, double-masked, laser controlled	IAI 2 mg every 4 weeks (2Q4): 136 patients; IAI 2 mg every 8 weeks after 5 initial monthly injections (2Q8): 135 patients Laser Photocoagulation (no more than once every 12 weeks): 135 patients TOTAL: 406 patients	52 week (primary endpoint) continuing to 148 weeks	Completed

5.2. Review Strategy

This Supplemental BLA is being submitted for the indication for the treatment of diabetic retinopathy following analysis of the 52-week safety and efficacy data (study is ongoing to 100 weeks) from the Regeneron-sponsored clinical study VGFTe-OD-1411 (PANORAMA). Supporting data are provided from a the VIVID and VISTA clinical studies. Data from VIVID and VISTA were submitted for the indication for the treatment of patients with diabetic macula edema (DME) and in support of diabetic retinopathy in patients with DME.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study VGFT-09-1009 (VISTA) and Study 91475 (VIVID)

Vista and Vivid
The primary efficacy variable for both these studies was the change from baseline in BCVA in ETDRS letter score at week 52. Both studies achieved statistical significance for this endpoint. See Clinical Review for DME indication (Supplement-037) in DARRTS.

Secondary analyses of Vista and Vivid supported the treatment of diabetic retinopathy in patients with diabetic macular edema.

6.2. Panorama (VGFTe-OD-1411): A Phase 3 Double-Masked, Randomized Study of the Efficacy and Safety of Intravitreal Aflibercept Injection in Patients with Moderately Severe to Severe NPDR

6.2.1. Study Design

Primary Objective
The primary objective of the study was to assess the efficacy of IAI (intravitreal aflibercept injection) compared to sham treatment in the improvement of moderately severe to severe NPDR.

Secondary Objectives
- To characterize the safety of IAI in patients with moderately severe to severe NPDR
- To determine if IAI prevented the worsening of DR and reduced the incidence of DME
- To determine the anatomic effects of IAI in patients with moderately severe to severe NPDR

Trial Design
This is an ongoing phase 3, double-masked, randomized study of the efficacy and safety of IAI for the improvement of moderately severe to severe NPDR. At the day 1/baseline visit, patients underwent safety and ocular assessments prior to receiving the first dose of study drug. Eligible patients were enrolled into 1 of 3 treatment groups in a 1:1:1 randomization scheme and were

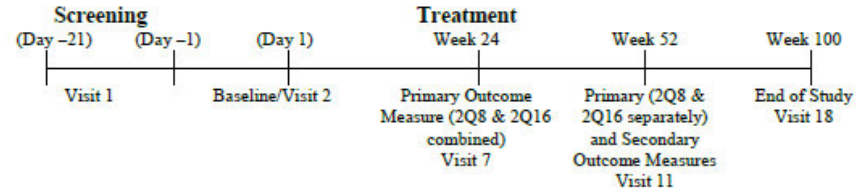
stratified based on their DRSS score (level 47 vs. level 53). Only 1 eye was selected as the study eye. The 3 treatment groups had the following dosing regimens from day 1 to week 48:

- IAI 2Q8 after 5 initial monthly doses
- IAI 2Q16 after 3 initial monthly doses and one 8-week interval
- sham treatment

In year 2 (beginning at week 56), the 2Q8 group will be treated with a flexible treatment regimen. The flexible dosing regimen is based on the masked investigator's assessment of DRSS score. An injection will be given at each visit unless a patient has reached level 35 or better (mild NPDR) on the DRSS, at which point treatment will be deferred (and a sham injection given).

The primary outcome measure of the study is the proportion of patients who improved by ≥2 steps from baseline on the DRSS in the combined 2Q8 and 2Q16 groups at week 24, and in each group separately at week 52. Patients were evaluated for efficacy (BCVA using the 4-meter ETDRS protocol, SD-OCT, and fluorescein angiography [FA]/fundus photography [FP]) and for ocular and systemic safety (including ophthalmic exams, visual field testing, and laboratory assessments) through week 100. Masking will be maintained to the end of the study (week 100).

Figure 1: Study Flow Diagram



Number of Patients Planned

Approximately 360 patients were planned to be enrolled in approximately 70 sites in the US, Japan, Germany, the UK, and Hungary, with a target enrollment of approximately 120 patients in each treatment group.

Inclusion Criteria

- Men or women ≥18 years of age with type 1 or 2 diabetes mellitus who had moderately severe to severe NPDR (DRSS levels 47 or 53), confirmed by the central reading center, in whom PRP could be safely deferred for at least 6 months per the investigator
- BCVA ETDRS letter score in the study eye of ≥69 letters (approximate Snellen equivalent of 20/40 or better)
- Willing and able to comply with clinic visits and study-related procedures
- Provide signed informed consent

Exclusion Criteria

- Presence of DME threatening the center of the macula (within 1,000 μm of the foveal center) in the study eye

- Evidence of retinal neovascularization on clinical examination or FA
- Any prior focal or grid laser photocoagulation (within 1,000 μm of the foveal center) or any prior PRP in the study eye
- Any prior systemic anti-VEGF treatment or IVT anti-VEGF treatment in the study eye
- Any prior intraocular steroid injection in the study eye (Note: For Japan only, this also included periocular steroid in the study eye within 120 days of day 1)
- History of vitreoretinal surgery in the study eye
- IOP ≥25 mm Hg in the study eye
- Evidence of active infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye
- Any intraocular inflammation or infection in either eye within 3 months of the screening visit
- Current ASNV, vitreous hemorrhage, or tractional retinal detachment visible at the screening assessments in the study eye
- Ocular media of insufficient quality to obtain fundus and OCT images in the study eye
- Hemoglobin A1c >12%, or if HbA1c was ≤12%, diabetes mellitus was uncontrolled in the opinion of the investigator
- Uncontrolled blood pressure (defined as systolic >160 mm Hg or diastolic >95 mm Hg while patient was sitting)
- History of cerebrovascular accident or myocardial infarction within 180 days of day 1
- Renal failure, dialysis, or history of renal transplant
- Women who were breastfeeding or who had a positive serum human chorionic gonadotropin/urine pregnancy test at the screening or baseline visit
- 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 could have interfered with the injection procedure or with evaluation of efficacy or safety
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicated the use of an investigational drug or that could have affected interpretation of the results of the study or rendered the patient at high risk for treatment complications
- Participation as a patient in any interventional clinical study within the 12 weeks prior to day 1 of the study
- Sexually active men or women of childbearing potential who were unwilling to practice adequate contraception prior to the initial dose/start of the first treatment, during the study, and for at least 3 months after the last dose. Adequate contraceptive measures included stable use of oral contraceptives or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device; bilateral tubal ligation; vasectomy; condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly.

Table 3: Schedule of Events – Year 1

Study Procedure	Screening Visit 1	Baseline Visit 2	Year 1 Treatment Period								
			Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11[1]
Week	--	0	4	8	12	16	24	32	40	48	52
Day (visit window)	-21 to -1	1	29 ±7 days	57 ±7 days	85 ±7 days	113 ±7 days	169 ±7 days	225 ±7 days	281 ±7 days	337 ±7 days	365 ±10 days
Screening/Baseline:											
Informed consent	X										
Genomics sub-study informed consent (optional)	X										
Inclusion/exclusion	X	X									
Medical and ophthalmic history	X										
Demographics	X										
Randomization		X									
Treatment:											
Review of concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Administer IVT aflibercept (IAI) or sham[2]		X	X	X	X	X	X	X	X	X	
Ocular Assessments:											
BCVA (ETDRS) and refraction	X	X	X	X	X	X	X	X	X	X	X
Slit lamp examination	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy[3]	X				X		X		X		X
Intraocular pressure[4]	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[5]	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	Screening Visit 1	Baseline Visit 2	Year 1 Treatment Period								
			Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11[1]
Week	--	0	4	8	12	16	24	32	40	48	52
Day (visit window)	-21 to -1	1	29 ±7 days	57 ±7 days	85 ±7 days	113 ±7 days	169 ±7 days	225 ±7 days	281 ±7 days	337 ±7 days	365 ±10 days
Visual field testing (study eye)[8]	X[9]										X
Non-Ocular Assessments:											
Physical examination	X[10]										
Vital signs[11]	X	X	X	X	X	X	X	X	X	X	X
ECG	X										X
Adverse events[12]	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing:[13]											
Hematology, blood chemistry, urinalysis, Vitamin D and HbA1c[14]	X						X[15]				X
Pregnancy test, women of childbearing potential[16]	serum	urine	urine	urine	urine	urine	urine	urine	urine	urine	
Anti-aflibercept antibody samples[17]		X									X
Genomic DNA sample (optional)		X[18]									

Table 4: Schedule of Events – Year 2

Study Procedure	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18/End of Study[1]
Week	56	64	72	80	88	96	100
Day (visit window)	393 ±7 days	449 ±7 days	505 ±7 days	561 ±7 days	617 ±7 days	673 ±7 days	701 ±10 days
Treatment:							
Review of concomitant medications	X	X	X	X	X	X	X
Administer IVT aflibercept (IAI) or sham[2]	X	X	X	X	X	X	
Ocular Assessments:							
BCVA (ETDRS) and refraction	X	X	X	X	X	X	X
Slit lamp examination	X	X	X	X	X	X	X
Gonioscopy[3]		X		X			X
Intraocular pressure[4]	X	X	X	X	X	X	X
Indirect ophthalmoscopy[5]	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X
FP[6]	X	X	X	X	X	X	X
FA[7]		X		X			X
Visual field testing (study eye)[8]							X
Non-Ocular Assessments:							
Vital signs[9]	X	X	X	X	X	X	X
ECG							X
Adverse events[10]	X	X	X	X	X	X	X
Laboratory Testing:[11]							
Hematology, blood chemistry, urinalysis, Vitamin D, and HbA1c[12]							X

Study Procedure	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	Visit 18/End of Study[1]
Week	56	64	72	80	88	96	100
Day (visit window)	393 ±7 days	449 ±7 days	505 ±7 days	561 ±7 days	617 ±7 days	673 ±7 days	701 ±10 days
Pregnancy test, women of childbearing potential[13]	urine	urine	urine	urine	urine	urine	urine
Anti-aflibercept antibody samples[14]							X
Genomic DNA sample (optional)[15]							

Primary Endpoint

The primary efficacy endpoint in the study was both the proportion of patients who improved by ≥2 steps from baseline in the DRSS score at week 24 in the combined 2Q8 and 2Q16 groups and at week 52 for the separate groups.

Secondary Endpoints

The secondary endpoints at Week 52 were as follows:

- Proportion of patients developing a VTC (Vision-threatening complications) due to DR. Vision-threatening complications are defined as the composite outcome of PDR (inclusive of patients who have vitreous hemorrhage or tractional retinal detachment believed to be due to PDR) and ASNV. Note: ASNV is defined as neovascularization of

the iris (at least 2 cumulative clock hours), and/or definitive neovascularization of the iridocorneal angle
- Proportion of patients developing CI-DME (Centrally involved diabetic macular edema)
- Time to development of a VTC
- Time to development of CI-DME
- Proportion of patients who received PRP, inclusive of patients undergoing vitrectomy with endolaser
- Area under the curve (AUC) for change in BCVA from baseline

Additional Efficacy Endpoints
The following additional endpoints were also evaluated in an exploratory manner at Week 52:
- Time to first improvement of ≥2 steps from baseline in the DRSS score through week 52
- Proportion of patients with ≥2-step worsening from baseline in the DRSS score at week 52
- Proportion of patients with ≥3-step improvement from baseline in the DRSS score at week 52
- Proportion of patients with ≥3-step worsening from baseline in the DRSS score at week 52
- Proportion of patients who received vitrectomy through week 52
- Change in CRT from baseline at week 52
- Change in mean deviation on visual field testing from baseline at week 52
- Change in BCVA from baseline at week 52
- Proportion of patients who gained ≥5, ≥10, or ≥15 letters from baseline at week 52
- Proportion of patients who lost ≥5, ≥10, or ≥15 letters from baseline at week 52
- Proportion of patients who were equal to or better than 20/20 or equal to or better than 20/40 at week 52

Investigational and Reference Treatment
The investigational product is IAI, which was supplied in sterile, sealed, 3 mL, single-use vials, each with a "withdrawable" volume of approximately 50 µL (0.05 mL) at a concentration of 40 mg/mL. The injection volume was 50 µL (0.05 mL) and it was administered to the patients by IVT injection. Only 1 eye was selected as the study eye.

Study eye
Patients were randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio:
- 2Q8: IAI 2Q8 to week 48 (after 5 initial monthly doses), followed by a flexible treatment regimen with IAI 2 mg to week 96
- 2Q16: IAI 2Q16 to week 96 (after 3 initial monthly doses and one 8-week (Q8) interval)
- Sham: sham injections Q4 to week 16, followed by sham injections Q8 to week 96

It should be noted that, at week 24, there was only a 1-dose difference between the 2Q8 and 2Q16 groups. The 2Q8 group had 5 initial monthly doses (baseline and weeks 4, 8, 12, and 16) followed by one 8-week interval before the week 24 assessment point, while the 2Q16 group had 3 initial monthly doses (baseline and weeks 4 and 8) followed by a dose at week 16, creating two 8-week intervals before the week 24 assessment point. By week 52, the 2Q16 group had

2 complete 16-week intervals.

Rescue Treatment in the Study Eye
Patients who developed PDR/ASNV or CI-DME in the study eye were treated, if deemed appropriate by the masked physician. For any of these complications, an FP was performed before rescue treatment was given. Patients who developed CI-DME could receive IAI or laser photocoagulation at the discretion of the investigator, and then no longer received their randomized treatment. Rescue treatment was given by the masked or unmasked physician. Patients who developed PDR and/or ASNV could receive PRP or vitrectomy with endolaser, if necessary, but remained on their randomized treatment schedule. PRP or surgical intervention was performed by either the masked or unmasked physician. In addition, 1 injection of IAI could be given, which must have been administered by the unmasked physician. If treatment for CI-DME or PDR/ASNV was given, patient data was censored from the time of treatment for the primary analysis.

Statistical Analysis Plan
This study examined the following hypotheses for the primary efficacy variable regarding the proportion of patients with a ≥2-step improvement from baseline in DRSS score in the study eye at week 24 in the combined 2Q8 and 2Q16 groups, and at week 52 for the 2Q8 and 2Q16 groups individually. Statistical testing of week 24 and week 52 was conducted to demonstrate the superiority of the IAI groups (combined, 2Q8 and 2Q16) to the sham group, respectively.

To control the family-wise type I error rate of 5%, the primary efficacy endpoint for the combined group (week 24), and the individual 2Q8 and 2Q16 groups (week 52) will be tested separately at the significance level of $\alpha = 1.67\%$. Secondary efficacy endpoints at week 52 were tested for the 2Q8 and 2Q16 groups by the hierarchical testing procedure at a significance level based on values below for different scenarios with the predefined testing order.

Table 5: Significance Levels for Testing Secondary Efficacy Endpoints

Scenario	1	2	3	4
Combined IAI group at week 24 positive?	Met	Met	Met	Met
2Q8 group at w 52 positive	X	X		
2Q16 group at week 52 positive	X		X	
Significance level for secondary endpoints	0.05	0.033	0.033	
Significance level for testing for 2Q8 group at week 52	0.025	0.033		
Significance level for testing for 2Q16 at week 52	0.025		0.033	

Efficacy analyses of all efficacy variables were conducted using the FAS population. The primary endpoint analysis was conducted at 2 time points (week 24 for the combined 2Q8 and 2Q16 groups, and week 52 for the 2Q8 and 2Q16 groups individually). Each of the 3 primary efficacy analyses were tested at the 1.67% (5%/3) significance level to control for multiplicity.

The primary analysis was a statistical evaluation of superiority of 3 comparisons (combined IAI vs. sham at week 24, IAI 2Q8 vs sham at week 52, and IAI 2Q16 vs sham at week 52) with respect to the primary efficacy variable. The statistical analysis was performed using the Cochran-Mantel-Haenszel (CMH) method, stratified by baseline DRSS level (level 47 vs level 53). Missing or non-gradable post-baseline values were imputed using the LOCF procedure. For any patient who received rescue treatment, measurements after rescue was given were imputed using the last observation prior to rescue treatment. Baseline was carried forward if all post-baseline observations were missing or non-gradable. Patients were considered to be non-responders if baseline observations were also missing or non-gradable. The IAI treatment was considered to be superior to sham if the estimated IAI group (combined, IAI 2Q8, or IAI 2Q16) was greater than the sham group, and the p-value was ≤0.0167.

Sensitivity Analyses for the Primary Efficacy Variable

The following sensitivity analyses were used for the primary efficacy variable:

- Observed case (OC) analysis: Measurements taken after the initiation of rescue treatment were censored; only observed, gradable, and non-censored values were used for analysis, (i.e., missing or non-gradable data were not imputed).
- Patients who received rescue treatment: In these analyses, the value at the given time point was used regardless of whether the patient received rescue treatment or not. Two different analyses were conducted:
- Ancillary LOCF (aLOCF): Data obtained after the initiation of rescue treatment were included; missing or non-gradable data were imputed by LOCF. Baseline was carried forward if all post-baseline observations were missing or non-gradable.
- Ancillary observed case (aOC): All observed values were used for analysis, including measurements taken after the initiation of rescue treatment, if given. Missing or non-gradable data were not imputed.
- Multiple imputation: The primary efficacy variable was also analyzed by multiple imputation (MI) in the FAS. The MI method was conducted using the following 3 steps:
    - Imputation - Missing or non-gradable DRSS data were imputed using the MI procedure based on the OC data. First, missing data were imputed to achieve a monotone missing pattern using the Markov Chain Monte Carlo method with number of imputations = 100. Subsequently missing data were imputed by a regression model with number of imputation = 1.
    - Analysis - The responder variable, which was improvement of ≥2 steps in the DRSS, was determined from the complete DRSS data sets. The proportion of responders was analyzed using Cochran-Mantel-Haenszel test with stratification adjustment for baseline DRSS level (level 47 vs level 53).
    - Pooling – The CMH statistic under the null hypothesis, had an asymptotic chi-square distribution. It was transformed to standard normal distribution by Wilson-Hilferty transformation. After normalization, the analysis results from multiple imputed data sets were combined into 1 overall result based on Rubin's rules using the MIANALYZE procedure.

Secondary Efficacy Analyses
If at least 1 of the IAI groups was shown to be superior to sham in the primary efficacy variable, additional comparisons were made for that IAI group with respect to the secondary efficacy variables at week 52. A hierarchical testing procedure was performed for each dose group to compare the secondary variables between the respective IAI group and the sham group in the following order:

2Q8 secondary endpoints at week 52:
- Proportion of patients developing a VTC (Vision threatening complication)
- Proportion of patients who develop CI-DME
- Time to development of a VTC
- Time to development of CI-DME
- Proportion of patients who receive PRP, inclusive of patients undergoing vitrectomy with endolaser
- AUC for change in BCVA from baseline

2Q16 secondary endpoints at week 52:
- Proportion of patients developing a VTC
- Proportion of patients who develop CI-DME
- Time to development of a VTC
- Time to development of CI-DME
- Proportion of patients who receive PRP, inclusive of patients undergoing vitrectomy with endolaser
- AUC for change in BCVA from baseline

The p-values at week 52 for the secondary endpoints were reported for all comparisons between the IAI groups and the sham group; however, a superiority claim could be made for a given endpoint only if all preceding endpoint comparisons in the hierarchy were shown to be statistically significant at the significance level specified in the protocol. The hierarchical method ensured the overall type I error rate of 5%, with multiplicity adjustment for primary and secondary endpoint analyses. All endpoints will also be analyzed descriptively at week 100 in an exploratory manner.

Efficacy Analysis Set
The full analysis set (FAS) included all randomized patients who received any study treatment. Analysis of the FAS was performed according to the treatment assigned at baseline (as randomized). The efficacy analysis on the FAS was considered to be the primary one (statistical evaluation of superiority). The FAS was used to evaluate all efficacy endpoints at week 52.

Safety Analysis Set
The safety analysis set (SAF) included all randomized patients who received at least 1 study treatment (IAI or sham). Patients were summarized according to the treatment actually received

(as treated). The 'as-treated' assignment only differed from the "as randomized" if the patient was systematically receiving treatment from an alternative treatment group. However, isolated incorrect treatments did not constitute a change in the "as treated" assignment. Patients whose "as treated" assignment differed from their "as randomized" assignment were listed. Treatment administration/compliance, all clinical safety, and tolerability assessments were analyzed using the SAF for the week 52 data. The safety analysis was performed on the observed safety data.

Panorama: List of Investigators

Study Center Number	Investigator	Address	Number of Patients
840407	Emanuelli, Andres	Emanuelli Research and Development Center, 452 Ave Rivera Aulet Arecibo, Puerto Rico, 00613	35
840384	Hu, Allen	Cumberland Valley Retina Consultants 1150 Opal Court Hagerstown, MD 21740	25
840320	Jackson, Kurt	Retina Center of New Jersey 1255 Broad Street, Suite 104 Bloomfield, NJ 07003	19
840332	Berger, Adam	Center for Retina and Macular Disease 250 Avenue K Southwest, Suite 200 Winter Haven, FL 33880	16
840306	Brown, David M.	Retina Consultants of Houston 6560 Fannin Street, Suite 750 Houston, TX 77030	12
840313	Lee, Seong	Strategic Clinical Research Group 101 Chuck Wagon Trail Willow Park, TX 76087	10
840315	Sheth, Veeral	University Retina and Macula Associates 6320 West 159th Street, Suite A Oak Forest, IL 60452	10
840321	Gonzalez, Victor	Valley Retina Institute 1205 North Ed Carey Drive Harlingen, TX 78550	10
840326	Hershberger, Vrinda	Florida Eye Associates 502 East New Haven Avenue Melbourne, FL 32901	10
840362	Danzig, Carl	Rand Eye Institute 5 West Sample Road Deerfield Beach, FL 33064	9
840367	Calzada, Jorge	Charles Retina Institute 1432 Kimbrough Rd. Germantown, TN 38138	9
840360	Singer, Michael	Medical Center Ophthalmology Associates 9157 Huebner Road San Antonio, TX 78240	8
840370	Williams, Jonathan	Retina Consultants of Southern Colorado 2770 North Union Blvd., Suite 140 Colorado Springs, CO 80909	8

Study Center Number	Investigator	Address	Number of Patients
840308	Patel, Sunil	Retina Research Institute of Texas 5441 Health Center Drive Abilene, TX 79606	7
840386	Segal, Zachary	Medeye Associates 5858 SW 68 Street Miami, FL 33143	7
840392	Pirouz, Ashkan	Retina Consultants of Orange County 301 W Bastanchury Road, Suite 285 Fullerton, CA 92835	7
840301	Liao, David	Retina Vitreous Associates Medical Group 9001 Wilshire Blvd., Suite 301 Beverly Hills, CA 90211	6
840305	Wykoff, Charles	Retina Consultants of Houston 17350 St. Luke's Way, Suite 120 The Woodlands, TX 77384	6
840324	Kruger, Erik	Eye Care Specialists 703 Rutter Ave. Kingston, PA 18704	6
840355	Chiang, Allen	Mid Atlantic Retina 840 Walnut St., Suite 1020 Philadelphia, PA 19107	6
840381	Alfaro, Daniel	Charleston Neuroscience Institute 9565 Hwy 78, Building 300 Ladson, SC 29456	6
840389	Friedman, Scott	Florida Retina Consultants 2202 Lakeland Hills Blvd. Lakeland, FL33805	6
840398	Wirthlin, Robert	Spokane Eye Clinical Research 427 South Bernard Street Spokane, WA 99204	6
348308	Kiss, Katalin	Hungary	5
840309	Clark, W. Lloyd	Palmetto Retina Center 124 Sunset Court West Columbia, SC 29169	5
840311	Payne, John	Palmetto Retina Center 400 North Cashua Drive Florence, SC 29501	5
840322	Chiu, Mark	Eye Associates of New Mexico Retina Center, 4411 The 25 Way NE, Suite 325 Albuquerque, NM 87109	5
840330	Rofagha, Soraya	East Bay Retina Consultants 3300 Telegraph Avenue Oakland, CA 94609	5
840340	Kingsley, Ronald	Dean McGee Eye Institute 608 Stanton L. Young Blvd. Oklahoma City, OK 73104	5
840345	Dooner, James	Austin Retina Associates 801 West 38th Street, Suite 200 Austin, TX 78705	5

Study Center Number	Investigator	Address	Number of Patients
840371	Haak, Logan	Ophthalmic Clinical Trials San Diego 3231 Waring Court, Suite S Oceanside, CA 92056	5
840372	Hagedorn, Curtis	Colorado Retina Associates 400 Indiana Street, Suite 310 Golden, CO 80401	5
840401	Wang, Yujen	Oregon Retina Institute 1518 E. Barnett Road Medford, OR 97504	5
840405	Brooks, Jr., Harold	Southern Vitreoretinal Associates 2439 Care Dr. Tallahassee, FL 32308	5
840307	Heier, Jeffrey	Ophthalmic Consultants of Boston 50 Staniford Street, Suite 600 Boston, MA 02114	4
840319	Browning, David	Charlotte Eye Ear Nose & Throat Associates 6035 Fairview Road Charlotte, NC 28210	4
840346	Pavan, Peter	University of South Florida Eye Institute 12901 Bruce B. Downs Blvd. Tampa, FL 33612	4
840358	Lazarus, Howard	John Kenyon American Eye Institute 519 State Street New Albany, IN 47150	4
840364	DeCroos, Francis	Southeastern Retina Associates, PC 1606 Gunbarrel Road, Suite 101 Chattanooga, TN 37421	4
840373	Olson, John	Central Florida Retina 44 Lake Beauty Drive, Suite 300 Orlando, FL 32806	4
840375	Chang, Margaret	Retinal Consultants Medical Group 5775 Greenback Lane Sacramento, CA 95841	4
840388	Meleth, Annal	Marietta Eye Clinic 895 Canton Rd., Building 200 Marietta, Georgia 30060	4
276302	Spital, Georg	Germany	3
392305	Sakamoto, Taiji	Japan	3
392311	Shimouchi, Akito	Japan	3
840341	Ohr, Matthew	The Ohio State University 915 Olentangy River Rd., Suite 5000 Columbus, OH 43212	3
840343	Kitchens, John	Retina and Vitreous Associates of Kentucky 120 North Eagle Creek Drive, Suite 500 Lexington, KY 40509	3
840391	Shah, Milan	Midwest Eye Institute 10300 N. Illinois Street, Suite 1080	3

Study Center Number	Investigator	Address	Number of Patients
		Indianapolis, IN 46290	
348303	Vajas, Attila	Hungary	2
392308	Murata, Toshinori	Japan	2
840337	Abbey, Ashkan	Texas Retina Associates 9600 N. Central Expressway, Suite 100 Dallas, TX 75231	2
840339	Freeman, William	UCSD Shiley Eye Institute, Jacobs Retina Center, 9415 Campus Point Drive La Jolla, CA 92093	2
840342	Burgess, Stuart	Ft. Lauderdale Eye Institute 850 S. Pine Island Rd., Ste. A-100 Plantation, FL 33324	2
840348	Lim, Jennifer	Illinois Ear and Eye Infirmary 1905 West Taylor Street Chicago, IL 60612	2
840359	Kim, Brian	University of Vermont Medical Center 111 Colchester Avenue Burlington, VT 05401	2
840376	Chaudhry, Nauman	Retina Group of New England 400 Bayonet Street, Suite 206 New London, CT 06320	2
840377	Suan, Eric	The Retina Care Center 6115 Falls Road, Suite 300 Baltimore, MD 21209	2
840396	Guerami, Amir	The Retina Partners 16500 Ventura Blvd., Suite 250 Encino, CA 91436	2
840400	Berger, Brian	Retina Research Center 3705 Medical Parkway, Suite 420 Austin, TX 78705	2
840402	Fein, Jordana	The Retina Group of Washington 8505 Arlington Blvd., Suite 300 Fairfax, VA 22031	2
840404	Hairston, Richard	The Eye Institute of West Florida 148 13th Street SW Largo, FL 33770	2
276310	Sekundo, Walter	Germany	1
276313	Wiedemann, Peter	Germany	1
348302	Kerenyi, Ágnes	Hungary	1
348305	Facsko, Andrea	Hungary	1
348307	Vogt, Gábor	Hungary	1
392306	Oh, Hideyasu	Japan	1
392307	Kitaoka, Takashi	Japan	1
392312	Nakashizuka, Hiroyuki	Japan	1
826301	Menon, Geeta	UK	1
826302	Sivaprasad, Sobha	UK	1
840302	Samuel, Michael	Retina Institute of California 301 W. Huntington Dr., Suite 107 Arcadia, CA 91007	1

Study Center Number	Investigator	Address	Number of Patients
840304	Abraham, Prema	Black Hills Regional Eye Institute 2800 Third Street Rapid City, SD 57701	1
840316	Thach, Allen	Retina Consultants of Nevada 710 Coronado Center Dr., Suite 201 Henderson, NV 89052	1
840325	Novalis, George	Retina Centers 6585 North Oracle Road Tucson, AZ 85704	1
840327	Jacoby, Rachel	University of Utah John A. Moran Eye Center, 65 Mario Capecchi Drive Salt Lake City, UT 84132	1
840353	Campochiaro, Peter	Johns Hopkins Hospital School of Medicine, Wilmer Eye Institute 600 North Wolfe St. 717 Maumenee Baltimore, MD 21287	1
840368	Palmer, James	Northern California Retina Vitreous Associates, 2485 Hospital Drive, Suite 200 Mountain View, CA 94040	1
840369	Busbee, Brandon	Tennessee Retina, PC 345 23rd Avenue North, Suite 350 Nashville, TN 37203	1
840374	Stone, Cameron	Western Carolina Retinal Associates 21 Medical Park Drive Asheville, NC 28803	1
840383	Kwong, Jr, Henry	Associated Retina Consultants 1750 E. Glendale Ave. Phoenix, AZ 85020	1
840387	Walker, Joseph	National Ophthalmic Research Institute 6901 International Center Blvd. Fort Myers, FL 33912	1
840395	Jacobson, Michael	Georgia Retina 1462 Montreal Road West, Suite 412 Tucker, GA 30084	1
840399	Xavier, Samantha	Florida Eye Clinic 160 Boston Ave. Altamonte Springs, FL 32701	1
840408	Patel, Shriji	Vanderbilt University Medical Center 2311 Pierce Ave Nashville, TN 37232	1
840409	Lara, Wilfredo	Retina Macula Specialists of Miami 351 NW 42nd, Suite 501 Miami, FL 33126	1
840410	Berrocal, Maria	Berrocal and Associates 150 Diego Avenue, Suite 404 San Juan, Puerto Rico, 00907	1
840416	Ghorayeb, Ghassan	West Virginia University Eye Institute 1 Medical Center Drive Morgantown, WV 26506	1

6.2.2. Study Results

Panorama: Patient Disposition at Week 52 (All Randomized Patients)

	Sham N=133	2Q16 N=135	2Q8 N=134
Number of patients who completed Week 52	109 (82.0%)	122 (90.4%)	124 (92.5%)
Number of patients who discontinued before Week 52	24 (18.0%)	13 (9.6%)	10 (7.5%)
AE	2	4	0
Death	6	0	1
Withdrawal by patient	2	5	4
Lost to f/u	12	4	5
Protocol deviation	1	0	0
Pregnancy	1	0	0

Panorama: Analysis Sets

	Sham	2Q16	2Q8
Safety analysis set (SAF)	133	135	134
Full analysis set (FAS)	133	135	134

Panorama: Demographics

	Sham N=133	2Q16 N=135	2Q8 N=134
Gender			
Male	69	75	81
Female	64	60	53
Ethnicity			
Hispanic or Latino	58	37	41
Not Hispanic or Latino	74	97	93
Not reported	1	1	0
Race			
White	107	99	104
Black	13	16	12
Asian	4	12	7
American Indian or Alaska Native	1	1	4
Native Hawaiian or Other Pacific Islander	0	1	1
Multiple	0	1	1
Not reported	8	5	5
Age			
Mean (sd)	55.8 (10.3)	55.4 (11.1)	55.8 (10.2)
Min, Max	25, 76	25, 85	31, 79
Duration of diabetes			
Mean (sd)	15.5 (9.3)	13.7 (8.6)	14.0 (9.7)
Min, Max	1, 42	0, 41	0, 65
Diabetes type			
Type 1	10	14	10
Type 2	123	121	124

Panorama: Treatment Compliance in the Study Eye Through Week 52 (Full Analysis Set)

	Sham N=133	**2Q16 N=135**	**2Q8 N=134**
Number of patients receiving 100% of injections	111 (83.5%)	112 (83.0%)	122 (91.0%)
Compliance <50%	0	0	0
Compliance ≥=50%	133	135	134

Compliance was calculated as: number of active or sham injections received divided by total number of planned treatments prior to rescue treatment for CI-DME and during the period of participation in the study.

Compliance with Good Clinical Practices

This study was conducted in compliance with the study protocol and in accordance with Good Clinical Practices (GCPs).

Financial Disclosure

See financial disclosure template in Section 13.2 of this review.

Efficacy Results – Primary Endpoint

Panorama: Proportion of Patients With a >=2 Step Improvement at Week 24 in the DRSS From Baseline (Full Analysis Set with LOCF)

	Sham N=133	2Q16 N=135	2Q8 N=134	2mg Combined N=269
Week 24				
Patients who gained >=2 steps in the DRSS at Week 24	8/133 (6%)	83/135 (61%)	74/134 (55%)	157/269 (58%)
Adjusted difference (%) versus sham		55%	49%	52%
95% CI for difference		(46, 64)	(40, 59)	(45, 59)
P-value		<0.0001	<0.0001	<0.0001

The difference with CI was calculated using the Mantel-Haenszel weighting scheme adjusted by baseline DRSS stratification variable from IVRS (interactive voice response system).
The p-value was calculated using a 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS stratification variable from IVRS.

Panorama: Sensitivity Analysis of the Proportion of Patients with a >=2 Step Improvement at Week 24 in the DRSS From Baseline (Full Analysis Set)

	Sham N=133	2Q16 N=135	2Q8 N=134	2mg Combined N=269
OC				
Patients who gained >=2 steps in the DRSS at Week 24	7/93 (7.5%)	77/117 (66%)	71/125 (57%)	148/242 (61%)
Adjusted difference (%) versus sham		44%*	60%*	53%*
95% CI for difference		(31, 57)	(48, 72)	(45, 61)
aLOCF				
Patients who gained >=2 steps in the DRSS at Week 24	17/133 (13%)	83/135 (61%)	74/134 (55%)	157/269 (58%)
Adjusted difference (%) versus sham		49%*	42%*	46%*
95% CI for difference		(38.7, 58.6)	(32.3, 52.6)	(37.4, 53.7)
aOC				
Patients who gained >=2 steps in the DRSS at Week 24	16/133 (14%)	78/119 (65%)	71/125 (57%)	149/244 (61%)
Adjusted difference (%) versus sham		51%*	43%*	47%*
95% CI for difference		(41, 62)	(38, 53)	(38, 56)

* p<0.0001
OC: Only observed, non-censored values were used for analysis; measurements taken after rescue were censored.
aLOCF: The LOCF method was used to impute missing or non-gradable post-baseline data regardless of rescue. Baseline was carried forward if all post-baseline observations were missing or non-gradable.
aOC: All observed values were used for analysis regardless of rescue treatment.

Reviewer's Comment:

For the primary endpoint, a greater percentage of patients had a ≥2-step improvement in the DRSS in the IAI 2 mg combined group (58%) compared with sham (6%). The robustness of the primary analysis was confirmed with sensitivity analyses using the OC, aLOCF, and aOC methods.

Panorama: Proportion of Patients With a >=2 Step Improvement at Week 52 in the DRSS From Baseline (Full Analysis Set with LOCF)

	Sham N=133	2Q16 N=135	2Q8 N=134
Week 52			
Patients who gained >=2 steps in the DRSS at Week 24	20/133 (15%)	88/135 (65%)	107/134 (80%)
Adjusted difference (%) versus sham		50%	65%
95% CI for difference		(40, 60)	(56, 74)
P-value		<0.0001	<0.0001

The difference with CI was calculated using the Mantel-Haenszel weighting scheme adjusted by baseline DRSS stratification variable from IVRS (interactive voice response system).
The p-value was calculated using a 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS stratification variable from IVRS.

Panorama: Sensitivity Analysis of the Proportion of Patients with a >=2 Step Improvement at Week 52 in the DRSS From Baseline (Full Analysis Set)

	Sham N=133	2Q16 N=135	2Q8 N=134
OC			
Patients who gained >=2 steps in the DRSS at Week 24	17/75 (23%)	69/102 (68%)	95/113 (84%)
Adjusted difference (%) versus sham		44%*	60%*
95% CI for difference		(31, 57)	(48, 72)
aLOCF			
Patients who gained >=2 steps in the DRSS at Week 24	32/133 (24%)	89/135 (66%)	107/134 (80%)
Adjusted difference (%) versus sham		42%*	56%*
95% CI for difference		(31, 53)	(46, 66)
aOC			
Patients who gained >=2 steps in the DRSS at Week 24	27/106 (25.5%)	72/108 (66.7%)	96/116 (82.8%)
Adjusted difference (%) versus sham		41%*	56%*
95% CI for difference		(28, 53)	(46, 67)

*p-value <0.001
OC: Only observed, non-censored values were used for analysis; measurements taken after rescue were censored. The difference with CI was calculated using the Mantel-Haenszel weighting scheme adjusted by baseline DRSS stratification variable from IVRS.
aLOCF: The LOCF method was used to impute missing or non-gradable post-baseline data regardless of whether or not rescue treatment was given. Baseline was carried forward if all post-baseline observations were missing or non-gradable.
aOC: All observed values were used for analysis regardless of whether or not rescue treatment was given.

Reviewer's Comment:

The additional primary endpoint at Week 52 was the proportion of patients who improved by ≥2 steps from baseline in the DRSS score in each of the individual 2Q16 and 2Q8 groups. The improvements in both IAI groups were greater than in the sham group. The robustness of the primary analysis was also confirmed with sensitivity analyses using the OC, aLOCF, and aOC methods.

Secondary Endpoints

Panorama: Proportion of Patients Who Developed VTC and/or CI-DME Through Week 52 (Full Analysis Set)

	Sham N=133	2Q16 N=135	2Q8 N=134
Patients who developed any VTC	27/133 (20%)	5/135 (4%)	4/134 (3%)
Adjusted difference %		-17	-17
95% CI		(-24, -9)	(-25, -10)
P value		<0.0001	<0.0001
Patients who developed CI-DME	34/133 (25%)	9/135 (7%)	11/134 (8%)
Adjusted difference %		-19	-17
95% CI		(-27, -10)	(-26, -8)
P value		<0.0001	0.0002
Patients who developed any VTC and/or CI-DME	54/133 (41%)	13/135 (10%)	15/134 (11%)
Adjusted difference %		-31	-29
95% CI		(-41, -21)	(-39, -19)
P value		<0.0001	<0.0001

Reviewer's Comment:

Analyses of the secondary endpoints demonstrated statistically superior efficacy in the IAI groups compared to the sham group in the prevention of VTCs and CI-DME in patients with moderately severe to severe NPDR. The prevention of VTCs would be expected from a product which treats diabetic retinopathy. The prevention of CI-DME is expected from a product which treats diabetic macular edema. These endpoints are consistent with previous findings.

Panorama: Proportion of Patients With Panretinal Photocoagulation or Vitrectomy for PDR Through Week 52 (Full Analysis Set)

	Sham N=133	2Q16 N=135	2Q8 N=134
Patients who received PRP or vitrectomy	9/133 (7%)	1/135 (0.7%)	1/134 (0.7%)
Adjusted difference %		-6	-6
95% CI		(-10, -2)	(-10, -2)
P value		0.0089	0.0096

Reviewer's Comment:

The decision to perform PRP or vitrectomy involves multiple factors including financial resources. It is not a reliable endpoint.

Panorama: Proportions of Patients With a ≥3-Step Improvement, or ≥2-Step or ≥3-Step Worsening from Baseline at Week 52 in the DRSS (Full Analysis Set with LOCF)

	Sham N=133	2Q16 N=135	2Q8 N=134
Improvement in the DRSS			
Patients with a >=3 step improvement in DRSS score at week 52	1/133 (1%)	12/135 (9%)	20/134 (15%)
Adjusted difference %		8	14
95% CI		(4, 12)	(9, 20)
P value		0.0009	<0.0001
Worsening in the DRSS			
Patients with a >=2 step worsening in DRSS score at week 52	11/133 (8%)	1/135 (1%)	0/134 (0%)
Adjusted difference %		-7	-8
95% CI		(-12, -3)	(-13, -4)
P value		0.0030	0.0007
Patients with a >=3 step worsening in DRSS score at week 52	7/133 (5%)	1/135 (1%)	0/134 (0%)
Adjusted difference %		-4	-5
95% CI		(-9, -1)	(-9, -1)
P value		0.0302	0.0072

Reviewer's Comment:
The IAI groups demonstrated numerically superior effects compared to sham in all the additional analyses involving the DRSS assessments (proportions of patients with ≥3-step improvement and with ≥2-step or ≥3-step worsening in the DRSS).

Vista and Vivid
Since all 3 primary efficacy endpoints (at week 24 and week 52) were statistically significant, the statistical significance of the secondary efficacy endpoints for each dose group was determined by comparing the p-values vs. significance level of 0.025 using a hierarchical testing procedure, as prespecified in the SAP.

The following endpoints were hierarchical secondary endpoints only in US SAP and exploratory in Global SAP:

- Change in BCVA by ETDRS letter score from baseline to week 100
- Proportion of subjects who gained ≥10 ETDRS letters from baseline to week 100
- Proportion of subjects who gained ≥15 ETDRS letters from baseline to week 100
- Proportion of subjects who achieved a ≥2-step improvement on the ETDRS DRSS from baseline to week 100
- Change in CRT from baseline to week 100, as assessed on OCT
- NEI VFQ-25 near activities subscale change from baseline to week 100
- NEI VFQ-25 distance activities subscale change from baseline to week 100

Vista: Overview of Secondary Efficacy Results at Week 100 (Full analysis set) LOCF Adjusted Group Difference vs. Laser

	VTE 2Q4 Estimate (97.5% CI)	P-value	VTE 2Q8 Estimate (97.5% CI)	P-value
Change in BCVA in ETDRS letter score from baseline at week 100	10.6 (7.1, 14.2)	<0.0001	10.1 (7.0, 13.3)	<0.0001
Proportion of subjects (%) who gained >= 10 ETDRS letter from baseline to week 100	36.2 (24.3, 48.1)	<0.0001	31.6 (19.5, 43.7)	<0.0001
Proportion of subjects (%) who gained >= 15 ETDRS letter from baseline to week 100	25.8 (15.1, 36.6)	<0.0001	20.1 (9.6, 30.6)	<0.0001
Proportion of subjects (%)who achieved a >=2 step improvement on ETDRS DRSS from baseline to week 100	22.1 (11.1, 33.2)	<0.0001	21.7 (10.5, 33.0)	<0.0001
Change in CRT from baseline at week 100, assessed by OCT	-105 (-140, -70)	<0.0001	-111 (-143, -79)	<0.0001
NEI VFQ-25 near activities subscale, baseline to week 100	4.6 (-0.73, 9.9)	0.0529	5.05 (0.12, 9.98)	0.0218
NEI VFQ-25 distance activities subscale change from baseline to week 100	5.8 (1.0, 10.6)	0.0072	3.57 (-0.96, 8.11)	0.0772

Vivid: Overview of Secondary Efficacy Results at Week 100 (Full analysis set) LOCF Adjusted Group Difference vs. Laser

	VTE 2Q4 Estimate (97.5% CI)	P-value	VTE 2Q8 Estimate (97.5% CI)	P-value
Change in BCVA in ETDRS letter score from baseline at week 100	10.7 (7.6, 13.8)	<0.0001	8.2 (5.2, 11.3)	<0.0001
Proportion of subjects (%) who gained >= 10 ETDRS letter from baseline to week 100	33 (20, 46)	<0.0001	24.6 (12, 37)	<0.0001
Proportion of subjects (%) who gained >= 15 ETDRS letter from baseline to week 100	26 (15, 37)	<0.0001	19 (8, 30)	0.0001
Proportion of subjects (%)who achieved a >=2 step improvement on the ETDRS DRSS, baseline to week 100	20.7 (8.8, 32.5)	0.0001	24.2 (12.4, 35.9)	<0.0001
Change in CRT from baseline at week 100, assessed by OCT	-154 (-189, -120)	<0.0001	-127 (-165, -89)	<0.0001
NEI VFQ-25 near activities subscale, baseline to week 100	3.6 (-0.7, 8.0)	0.0596	-0.7 (-5.3, 3.8)	0.7144
NEI VFQ-25 distance activities subscale change from baseline to week 100	2.6 (-1.7, 6.9)	0.1792	-1.3 (-6.0, 3.4)	0.5325

Vista: Proportion of Patients with A 2 Step Improvement from Baseline in the DRSS Score at Week 100 (Full Analysis Set) LOCF

	Laser N=154	VTE 2Q4 N=154	VTE 2Q8 N=151
Proportion of subjects with a >=2 step improvement from baseline	24/150* (16%)	58/153* (38%)	56/148* (38%)
Difference (%) vs. Laser		22.1	21.7
97.5% CI for difference		(11.1, 33.2)	(10.5, 33.0)
P-value		<0.0001	<0.0001

*Number with baseline evaluable photographs

Vivid: Proportion of Patients with a 2 Step Improvement from Baseline in the DRSS Score at Week 100 (Full Analysis Set) LOCF

	Laser N=132	VTE 2Q4 N=136	VTE 2Q8 N=135
Proportion of subjects with a >=2 step improvement from baseline	7/99* (7%)	27/97* (28%)	32/101* (32%)
Difference (%) vs. Laser		20.7	24.2
97.5% CI for difference		(8.8, 32.5)	(12.4, 35.9)
P-value		0.0001	<0.0001

Vista: Proportion of Patients with a 2 Step Improvement from Baseline in the DRSS Score at Week 100 (Full Analysis Set) Observed Cases*

	Laser N=73	VTE 2Q4 N=110	VTE 2Q8 N=103
Proportion of subjects with a >=2 step improvement from baseline	7/72 (10%)	43/108 (40%)	40/99 (40%)
Difference (%) vs. Laser		30.0	30.7
97.5% CI for difference		(16.7, 43.2)	(17.0, 44.4)

Vivid: Proportion of Patients with a 2 Step Improvement from Baseline in the DRSS Score at Week 100 (Full Analysis Set) Observed Cases*

	Laser N=46	VTE 2Q4 N=62	VTE 2Q8 N=62
Proportion of subjects with a >=2 step improvement from baseline	5/46 (10.9%)	16/62 (25.8%)	22/62 (35.5%)
Difference (%) vs. Laser		14.9	24.5
97.5% CI for difference		(-1.5, 31.3)	(7.4, 41.5)

*Observed case method will used values observed at Week 100, excluding values after additional treatment is given.

Reviewer's Comment:

Both Vista and Vivid showed a two-step change on the DRSS in the study eye, and this change was statistically significant compared to laser treatment group.

Rescue Treatment

All patients in the study were eligible for rescue treatment if diagnosed with VTC or CI-DME in the study eye, at the discretion of the investigator. Patients who developed a VTC could receive PRP and/or vitrectomy with endolaser, if necessary, and 1 injection of IAI could be given. Patients who developed CI-DME could receive laser photocoagulation or IAI as needed.

Rescue Medications for VTC and CI-DME Through Week 52 (Safety Analysis Set)

	Sham N=133	2Q16 N=135	2Q8 N=134
Rescue for VTC:			
Total number of patients receiving 1 injection of IAI	7	2	2
Total number of patients receiving PRP	9	1	0
Total number of patients undergoing vitrectomy	0	0	1
Rescue for CI-DME:			
Total number of patients receiving IAI	29	5	2
Mean number of IAI injections (sd)	3.8 (2.1)	3.2 (2.9)	4.0 (1.4)
Total number of patients receiving macular laser	1	0	0

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Endpoints

An increase in the proportion of patients who improved by ≥2 steps from baseline in the DRSS score is demonstrated in Panorama, Vista and Vivid.

7.1.2. Subpopulations

Subgroups considered for efficacy and/or safety analyses included gender, Age: <40y, ≥40 - <65y, ≥65y, Race: White, Black or African American, Other, Ethnicity: Hispanic or Latino (no/yes), HbA1c: ≤8%, >8%, Baseline DRSS score: 47 vs 53, medical history of hypertension, medical history of cerebrovascular disease (ie. cardiovascular accident/stroke), medical history of ischemic heart disease (ie. MI), and renal impairment. In general, the results of the subgroup analyses for the percentages of patients who had ≥2-step improvements in the DRSS from baseline to Week 52 were consistent with those in the overall population. However, the following differences were observed:

- The percentages were lower in females than in males, within the subgroups
- The percentages were lower in the Black or African American subgroup compared with the other subgroups and with the overall population, although N was only 13 in the sham group, 16 in the 2Q16 group and 12 in the 2Q8 group, so no conclusions can be drawn The percentages were higher in patients with DRSS score level 53 compared with level 47, and with the overall population

7.2. Integrated Assessment of Effectiveness

The data contained in this submission supports the efficacy of Eylea in the treatment of diabetic retinopathy.

8. Review of Safety

8.1. Safety Review Approach

The main support for safety is from studies which supported the original approval of this application and is supplemented with the 3 clinical studies (Panorama, Vista, and Vivid) identified in this review. Studies Vista and Vivid Week 52 results were reviewed as part of Supplement #37 for the DME indication. Then Week 100 data from Vista and Vivid was reviewed as part of Supplement #48 for the DR with DME indication. Refer to medical officer reviews for S-037 and S-048 for safety review of Vista and Vivid.

8.2. Review of the Safety Database

8.2.1. Panorama

Treatment Exposure (Not Including Rescue Treatment) in the Study Eye in the First 52 Weeks (Safety Analysis Set)

	Sham N=133	**2Q16 N=135**	**2Q8 N=134**
Total number of active injections	0	749	1158
Number of active injections per patient			
1	0	2	0
2	0	1	1
3	0	6	1
4	0	9	0
5	0	11	3
6	0	106	3
7	0	0	2
8	0	0	10
9	0	0	114
Summary of active injections			
N	0	135	134
Mean (sd)		5.5 (1.0)	8.6 (1.1)
Min, Max		1, 6	2, 9

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

8.3.2. Categorization of Adverse Events

Adverse events were summarized by the number and percentage of subjects with TEAEs by treatment group, SOC, and PT using version 19.0 of the MedDRA coding dictionary.

8.3.3. Routine Clinical Tests

See Section 8.4.6

8.4. Safety Results

8.4.1. Deaths

Seven deaths (6 in the sham group and 1 in the 2Q8 group) were reported through Week 52.

Deaths

Patient	Group	Description
From Baseline to Week 24		
Patient (b) (6)	Sham	Acute Respiratory Failure and Pulmonary Hypertension
Patient (b) (6)	Sham	Acute MI
Patient (b) (6)	Sham	MI
Between Week 24 and Week 52		
Patient (b) (6)	Sham	Did not have an event (PT) associated with the death
Patient (b) (6)	Sham	Pulseless Electrical Activity
Patient (b) (6)	Sham	MI
patient (b) (6)	2Q8	Cardiac arrest

8.4.2. Serious Adverse Events

Ocular SAEs in the Study Eye
Ocular SAEs in the study eye were reported by 1 patient in the sham group (Iris Neovascularization) and 1 patient in the 2Q8 group (Visual Acuity Reduced and Vitreous Hemorrhage.

Non-Ocular Treatment Emergent SAEs >=1% Through Week 52 (Safety Analysis Set)

	Sham N=133	**2Q16 N=135**	**2Q8 N=134**
Number of subjects with at least 1 non-ocular TEAE	26 (19.5%)	25 (18.5%)	25 (18.7%)
Infections			
Cellulitis	1	1	5
Pneumonia	1	1	3
Diabetic foot infection	0	2	0
Cardiac disorders			
CHF	1	2	2
CAD	1	2	1
Metabolism disorders			
Dehydration	1	0	2
DKA	0	2	0
Nervous system disorders			
CVA	0	2	1
Skin disorders			
Diabetic foot	0	0	2

Reviewer's Comment:
Non-ocular SAEs were reported by similar proportions of patients in the sham group (19.5%) and the IAI groups (18.5% in the 2Q16 group and 18.7% in the 2Q8 group).

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

See Section 6.1.2 regarding patient's discontinuation and reasons for discontinuations.

8.4.4. Significant Adverse Events

See Section 8.4.2.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Ocular Treatment Emergent AEs in the Study Eye Occurring in >= 2% of Patients in Either Treatment Group Through Week 52 (Safety Analysis Set)

	Sham N=133	2Q16 N=135	Q8 N=134
Eye disorders			
Conjunctival hemorrhage	7	16	23
Diabetic retinal edema	32	8	12
Vitreous floaters	3	6	12
Eye pain	4	10	5
Retinal exudates	5	5	7
Blepharitis	1	2	6
Vitreous detachment	1	4	4
Cataract	1	3	4
Dry eye	4	3	4
Cataract subcapsular	1	3	2
Diabetic retinopathy	13	2	3
Lacrimation increased	0	2	3
Punctate keratitis	2	2	3
Visual impairment	0	1	4
Eye irritation	0	1	3
Vision blurred	1	1	3
Macular edema	3	2	0
Injury			
Corneal abrasion	1	2	3

Non-Ocular Treatment Emergent AEs Occurring in >=2% of patients in Either Treatment Group Through Week 52 (Safety Analysis Set)

	Sham N=133	2Q16 N=135	2Q8 N=134
Infections			
Cellulitis	3	6	10
Nasopharyngitis	12	9	6
UTI	10	4	6
Influenza	7	5	4
Bronchitis	4	4	4
Pneumonia	3	2	4
Upper respiratory tract infection	3	2	2
Localized infection	3	1	1
Investigations			
Glycosylated hemoglobin increased	5	7	5
Blood pressure increased	1	5	4
Blood glucose increased	4	1	7
Blood cholesterol increased	0	3	1
Protein urine present	1	0	3
Vascular disorders			
HTN	19	20	16

	Sham N=133	2Q16 N=135	2Q8 N=134
Metabolism disorders			
DM	7	6	4
Hypercholesterolemia	2	3	4
Type 2 diabetes mellitus	0	1	4
Dehydration	2	1	3
Hyperkalemia	2	3	0
Diabetes mellitus inadequate control	3	1	1
Injury			
Fall	2	6	2
Contusion	2	2	3
Arthropod bite	0	1	3
Laceration	3	0	2
Meniscus injury	3	0	0
Muscle strain	3	0	0
Nervous system			
HA	1	6	5
Dizziness	1	2	3
Musculoskeletal disorders			
Back pain	6	5	2
Arthritis	2	1	4
Intervertebral disc protrusion	0	3	1
Pain in extremity	1	1	3
Musculoskeletal pain	3	2	1
Osteoarthritis	4	0	0
Respiratory disorders			
Cough	4	2	4
Nasal congestion	0	3	2
Cardiac disorders			
CAD	1	3	2
GI disorders			
Nausea	4	4	4
Vomiting	3	0	2
General Disorders			
Chest pain	0	3	1
Edema peripheral	3	2	2
Pyrexia	1	3	1
Blood disorders			
Anemia	3	6	1
Renal			
Chronic kidney disease	2	3	2

	Sham N=133	2Q16 N=135	2Q8 N=134
Ear disorders			
Vertigo	1	4	0
Hepatobiliary disorders			
Cholelithiasis	1	0	3
Reproductive disorders			
Prostatomegaly	3	0	0

8.4.6. Laboratory Findings

There were no clinically meaningful trends in mean or median changes from baseline in the hematology, chemistry, or urinalysis hematology parameters in any treatment group. There was little change in HbA1c between baseline and Week 52 in any of the treatment groups, and the majority of patients who entered the study with elevated HbA1c remained high at Week 52 in all of the treatment groups.

8.4.7. Vital Signs

Mean systolic and diastolic blood pressure, heart rate, and temperature were similar between treatment groups at baseline. There were no clinically meaningful changes over time in either treatment group for any of these parameters.

8.4.8. Electrocardiograms (ECGs)

Electrocardiograms were recorded at baseline and Week 52. No clinically meaningful changes were noted between baseline and week 52 in ventricular rate, PR duration, RR duration, QRS duration, QT duration, QTc (Bazett), or QTc (Fridericia) in any treatment group.

8.5. Integrated Assessment of Safety

The safety database contained in this submission establishes the relative safety of aflibercept for the treatment of diabetic retinopathy.

9. Advisory Committee Meeting and Other External Consultations

There were no issues identified in the review that were thought to benefit from an advisory committee discussion.

10. Labeling Recommendations

See labeling recommendations in Appendix 13.2.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

12. Postmarketing Requirements and Commitments

There are no recommended Post-marketing Requirements or Phase 4 Commitments.

13. Appendices

13.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): Panorama

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 88		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 13		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 12 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: 1 Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 12		
Is an attachment provided with the reason:	Yes☒	No ☐ (Request explanation from Applicant)

The following study design elements and operational practices were put in place to reduce the potential for an investigator to unduly influence the outcome of the VGFTe-OD-1411 (PANORAMA) clinical study:

1) PANORAMA was designed as a double-masked, randomized trial to ensure objective assessments related to safety and efficacy (refer to the VGFTe-OD-1411 [PANORAMA] protocol, section 5.5.1 Masking)

2) The primary efficacy endpoint at Week 24 of a ≥ 2-step improvement in diabetic retinopathy severity scale (DRSS) score was determined by independent, masked readers at a centralized reading center. The reading center also evaluated the baseline DRSS score to confirm eligibility.

3) Visual acuity examiners assessing Best Corrected Visual Acuity (BCVA) are masked throughout the duration of the study.

4) During interim reviews of masked data, data from investigators who disclosed financial interest that exceeded ≥5% of the total study enrollment were reviewed for any patterns related to AE reporting or efficacy bias, resulting in queries and/or additional monitoring.

13.2. Labeling

Following is the draft package insert submitted by the applicant on 12/17/2018 which has been revised with the inclusion of recommended Agency edits.

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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
04/29/2019 10:19:53 AM

WILLIAM M BOYD
04/29/2019 10:22:17 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s061

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial #:	125387/S-061
Drug Name:	Eylea® (aflibercept injection)
Indication(s):	Treatment of Diabetic Retinopathy
Applicant:	Regeneron Pharmaceuticals, Inc.
Date(s):	Stamp Date: July 13, 2018 PDUFA Date: May 13, 2019 Review Date: March 25, 2019
Review Priority:	Standard
Biometrics Division:	IV
Statistical Reviewer:	Solomon Chefo, Ph.D.
Concurring Reviewers:	Yan Wang, Ph.D., Team Leader
Medical Division:	Division of Transplant and Ophthalmology Products (DTOP)
Clinical Team:	Sonal Wadhwa, MD, Medical Officer William Boyd, MD, Team Leader
Project Manager:	Michael Puglisi

Keywords: Cochran–Mantel–Haenszel, Diabetic Retinopathy Severity Score

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

Diabetic Retinopathy (DR) is a complication of diabetes resulting from damage to the blood vessels of the retina, and Diabetic Macular Edema (DME), a consequence of DR, is the most common cause of vision loss among patients with DR. Eylea® (aflibercept 2.0 mg intravitreal injection) administered every 8-week after **five** initial monthly injections was first approved for the treatment of DME based on visual-acuity results in two Phase 3 studies (referred to as VISTA and VIVID) and was later approved for the *treatment of DR in patients with DME* based on additional DR-related analyses in the same studies.

In this supplemental Biologics License Application (sBLA), the applicant seeks approval of Eylea® for a new (broad) indication of treatment of DR (regardless of DME) based on a 24-week and a 52-week data from a new Phase 3 study (PANORAMA) and supporting data from VISTA and VIVID studies. The recommended dose for the new indication is: *Intravitreal aflibercept 2.0 mg injection administered every 8-week after* (b) (4) *initial monthly injections*. (b) (4) .

PANORAMA is an ongoing, randomized, double-masked, 2-year superiority study deigned to evaluate the efficacy and safety of aflibercept compared to sham in subjects with moderately severe non-proliferative diabetic retinopathy (NPDR) or severe NPDR without DME. Subjects were randomized in a 1:1:1 ratio to one of the three treatment groups: (i) Intravitreal Aflibercept Injection (IAI) administered every 8-week up to Week 48 after five initial monthly injections (IAI 2Q8), (ii) IAI administered every 16-week up to Week 96 after three initial monthly injection followed by one 8-week injection (IAI 2Q16), and (iii) Sham treatment. During year 2, subjects in IAI 2Q8 group were to receive a flexible dosing regimen based on investigator's assessment of DR severity.

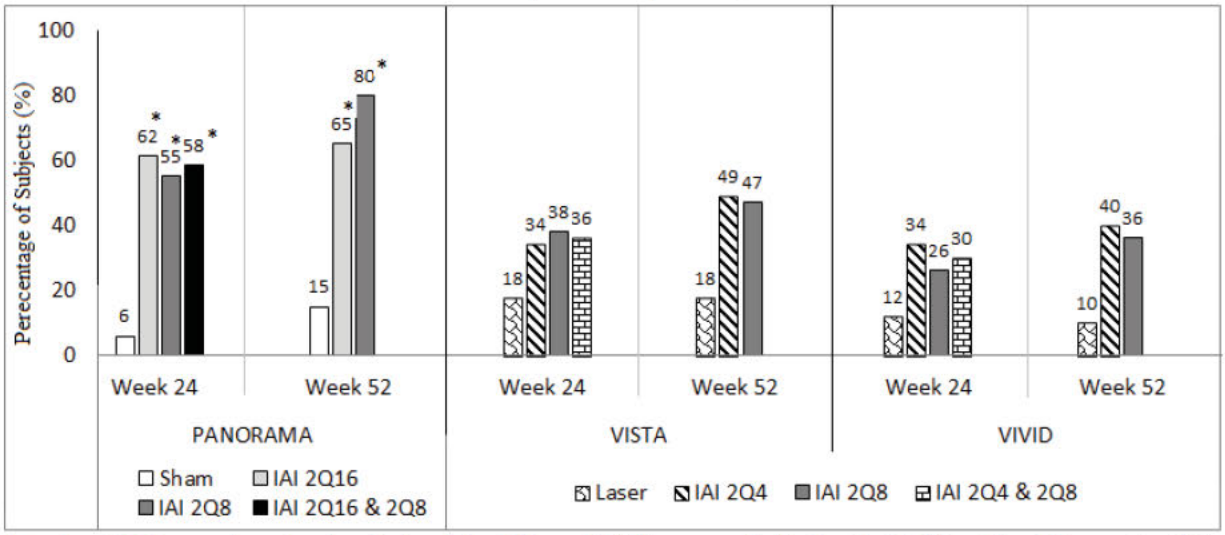
In the PANORAMA study, a total of 402 subjects received at least one dose of the study drug and were evaluable for efficacy. Most subjects (75%) had moderately severe NPDR at baseline. Subjects had a mean age of 56 years, a mean best corrected visual acuity (BCVA) of 82 letters, and a median diabetic duration of 14 years at baseline. Most subjects completed the treatment duration through Week 24 (95%) and through Week 52 (88%). Subjects in IAI 2Q8 and 2Q16 groups, respectively, received an average of five and four injections prior to Week 24 and nine and six injections prior to Week 52. All subjects were eligible to receive rescue treatment if they met the protocol-defined criteria during the study: 23 subjects in the sham group and 3 subjects in the combined IAI group (2 in 2Q16 and 1 in 2Q8) received rescue prior to Week 24 and 38 subjects in the sham group, 8 subjects in IAI 2Q16, and 5 subjects in IAI 2Q8 received rescue prior to Week 52.

The main efficacy evaluation was based on DR severity score (DRSS) assessed through Week 100; however, only data through Week 52 was available in this sBLA submission. During the 52-week period, DRSS data were collected at Baseline and Weeks 8, 12, 24, 40, and 52. The DRSS is a validated method for measuring DR severity based on a fundus photograph reading; it is graded in a 12-step severity score (see detail in Table 1).

In the PANORAMA study, the IAI groups yielded substantial improvement in DRSS and were statistically superior to the sham group in the primary efficacy variable of the proportion of subjects who achieved ≥2-step improvement in DRSS from baseline at Week 24 and at Week 52. As shown in Figure 1 below and in Table 5, at Week 24, 58% of subjects in the combined IAI group (61% in 2Q16

and 55% in 2Q8) achieved ≥2-step improvement in DRSS compared to 6% of subjects in the sham group. The treatment difference was 52% (98.3% CI; 44% to 61%). At Week 52, 65% of subjects in the IAI 2Q16 group and 80% of subjects in the IAI 2Q8 group achieved ≥2-step improvement compared to 15% of subjects in the sham group. The treatment difference was 50% (98.3% CI; 38% to 62%) for IAI 2Q16 versus sham and 65% (98.3% CI; 54% to 76%) for IAI 2Q8 versus sham. Additionally, as shown in Table 7, more subjects in the IAI groups achieved ≥3-step improvement in DRSS from baseline at Week 24 and at Week 52 compared to subjects in the sham group.

Figure 1: Proportion of subjects who achieved ≥2-step improvement in DRSS at Week 24 and Week 52 (Full Analysis Set)



* P-value<0.0001 versus sham– based on Cochran-Mantel-Haenszel (CMH) test, stratified by baseline DRSS level (level 47 versus level 53)
Note 1: The full analysis set included all randomized subjects who received any study drug.
Note 2: Missing DRSS data were imputed using the last observation carried forward (LOCF) method (see detail in Section 3.2.2).
Note 3: IAI 2Q4: Intravitreal aflibercept 2.0 mg injection administered every 4-week.

A 24-week and a 52-week analysis of VISTA and VIVID studies assessed in DME subjects with moderately severe or severe NPDR at baseline (analogous to the PANORAMA population) provided supporting evidence for IAI for the indication sought. As shown in Figure 1 above and in Figure 2, in these studies, IAI demonstrated greater improvement than laser treatment.

In summary, based on the totality of evidence from the PANORAMA study and supporting data from a 24-week and a 52-week analysis of VISTA and VIVID studies, the reviewer concludes that this application provided substantial evidence of efficacy of *intravitreal aflibercept 2.0 mg injection administered every 8-week after **five** initial monthly injections (IAI 2Q8)* for a new (broad) indication of treatment of DR (regardless of DME).

The applicant, however, requested the following aflibercept dosing regimen in the DOSAGE AND ADMINISTRATION Section of the label for the indication sought: *Intravitreal aflibercept 2.0 mg injection administered every 8-week after* (b) (4) *initial monthly injections*. The reviewer has no objection regarding the applicant proposed dosing regimen mainly because the proposed dosing regimen differs from the IAI 2Q8 dosing regimen by (b) (4)

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2 INTRODUCTION

2.1 Overview

Diabetic retinopathy (DR) is a serious sight-threatening complication of diabetes resulting from damage to the blood vessels of retina. It is a leading cause of blindness in adults.

DR is classified into two types:

i) **Nonproliferative Diabetic Retinopathy (NPDR):** is the early stage of the disease where blood vessels in the retina are weakened and begin to leak fluid into the retina. In this stage of the disease, new blood vessels are not growing.

ii) **Proliferative Diabetic Retinopathy (PDR):** is the more advanced form of the disease where damaged blood vessels close off, causing the growth of new, abnormal blood vessels in the retina. PDR may cause more severe vision loss than NPDR.

Recently, two drug products in the class of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapies were approved: (i) Eylea® (aflibercept 2 mg) administered every 8-week after five initial monthly injections for the treatment of DR in DME patients and (ii) Lucentis® (ranibizumab 0.3 mg) monthly injection for the treatment of DR regardless of DME.

Lucentis was approved for the treatment of DR in DME patients in February 2015 based on 2-year data from the pivotal RIDE and RISE Phase 3 studies, and it was later approved for a broad indication of treatment of DR (regardless of DME) based on NIH-funded Protocol S study. In Protocol S study, Lucentis was compared to panretinal laser in DR patients with and without DME. Most patients enrolled in the Protocol S study had at least mild PDR at baseline (87%).

The approval of Eylea for the treatment of DR in DME patients was based on 2-year data from two pivotal Phase 3 studies (VISTA and VIVID). Two aflibercept 2.0 mg dosing regimens, monthly dosing and dosing every two months after five initial monthly injections, were compared against laser (dosed at baseline and as needed) based on DR-related endpoints.

In this sBLA, the applicant seeks to extend the use of Eylea for a broad indication of treatment of DR (regardless of DME) based on a 24-week and 52-week data from an ongoing Phase 3 study (PANORAMA). In the PANORAMA study, the applicant enrolled subjects **with moderately severe or severe NPDR without DME** to provide more evidence on the effectiveness of anti-VEGF therapies in this subpopulation. It should be noted that very few subjects with moderately severe or severe NPDR without DME (<11%) were enrolled in the Protocol S study.

The PANORMA study is being conducted under a special protocol assessment (IND012462). The initial protocol submitted on September 29, 2015 (\\CDSESUB1\evsprod\IND012462\0613) received a no agreement letter on November 10, 2015 because the design and planned analysis of the study was determined inadequate to support a regulatory submission. The revised protocol re-submitted on February 18, 2016 (\\CDSESUB1\evsprod\IND012462\0641) was agreed by the Agency on March 23, 2016. The following key changes were made during the protocol revisions:

i) On December 24, 2015, the applicant submitted protocol amendment 1 (\\CDSESUB1\evsprod\IND012462\0629\). In this amendment, the initial primary outcome measure of "*The proportion of subjects who have improved by ≥ 2-steps from baseline in DRSS at Week 24 in the 2Q8 group, and at Week 52 in the 2Q16 group*" was changed to the

current primary efficacy measure of "*The proportion of subjects who have improved by ≥2 steps from baseline in the DRSS score at Week 24 in the combined 2Q8 and 2Q16 groups and at Week 52 for each group separately*." The Agency agreed to the changes in the primary efficacy measure but disagreed to the significance levels for testing the secondary efficacy endpoints proposed in the amendment.

ii) On February 12, 2016, the applicant submitted protocol amendment 2 (\\CDSESUB1\evsprod\IND012462\0629\) and revised the significance levels for testing the secondary efficacy endpoints. The Agency agreed to the proposed changes.

iii) On July 26, 2018, the applicant submitted a special protocol assessment amendment (\\CDSESUB1\evsprod\IND012462\0797). In this amendment, the evaluation time point of the secondary endpoints were changed from Week 100 to Week 52 and the Agency agreed to the modification.

According to the applicant, there was an informal teleconference between the applicant and the Agency on March 7, 2017 (\\CDSESUB1\evsprod\BLA125387\0400\m1\us\16-meetings). In this teleconference, the Agency agreed that "*the VGFTe-OD-1411 (PANORAMA) study will support the indication of treatment of diabetic retinopathy (inclusive of proliferative diabetic retinopathy [PDR]) based on this single study, supported by the VIVID and VISTA DME studies, at 6 months.*" Accordingly, the initial submission for this sBLA included only 6 months (24-week) efficacy and safety data; however, on December 17, 2018, the applicant submitted the 1-year (52-week) data and a separate clinical study report after the Mid-cycle meeting of the initial submission.

2.2 Data Sources

The primary data source for this review were the clinical study report and the analyses and tabulation datasets through Week 24 and through Week 52 of the PANORAMA study. These were provided in an electronic submission and are located at \\CDSESUB1\evsprod\BLA125387\0400\ for data through Week 24 and at \\CDSESUB1\evsprod\BLA125387\0467\ for data through Week 52. The primary analysis datasets are located at \\CDSESUB1\evsprod\BLA125387\0400\m5\datasets\ for data through Week 24 and at \\CDSESUB1\evsprod\BLA125387\0467\m5\datasets\ for data through Week 52.

The analysis datasets through Week 24 and Week 52 of the VISTA and VIVID studies were also additional data source for this review. These are located at \\CDSESUB1\evsprod\BLA125387\0138\.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer found the quality and integrity of the submitted data and analysis acceptable.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

i) Study Design:

PANORAM is an on-going Phase 3, double-masked, randomized, 2-year superiority study deigned to evaluate the efficacy and safety of IAI compared to sham in subjects with moderately severe or severe NPDR at baseline without DME.

In the study, a total of 402 eligible subjects at least 18 years of age with Type 1 or 2 diabetes who had BCVA score of ≥69 letters on the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart were enrolled in approximately 70 sites in the United States (N=374), Japan (N=11), Germany (N=5), the United Kingdom (N=2), and Hungary (N=10).

Eligible subjects were randomly assigned to one of the three treatment groups in a 1:1:1 ratio:

a) IAI 2Q8 (N = 133): aflibercept 2 mg injection administered every 8-week up to Week 48 after five initial monthly injections.

   Per the applicant, subjects in this group were to receive a flexible dosing regimen during year 2 (starting Week 56) based on masked investigator's assessment of DR severity– subjects received injection at each visit until they reach mild NPDR or better on the DR severity score.

b) IAI 2Q16 (N = 135): aflibercept 2.0 mg injection administered every 16-week up to Week 96 after three initial monthly injections followed by one 8-week injection.

c) Sham (N = 134)

Randomization was stratified by baseline diabetic retinopathy severity score (moderately severe NPDR (level 47) versus severe NPDR (level 53)).

The diabetic retinopathy severity score (DRSS) is a validated method for measuring DR severity based on a fundus photograph reading. As shown in Table 1 below, it is graded in a 12-step severity score ranging from 10 – 85. A DRSS level of 90 is designated for non-gradable images.

The total duration of the PANORAMA study is 2-years. In this submission, the applicant submitted the 52-week efficacy and safety data to support IAI for the indication sought. The study is still on-going.

Table 1: Steps for EDTRS-Diabetic Retinopathy Severity Score

DRSS Level	Description
10	DR absent
20	Microaneurysms only
35	Mild NPDR
43	Moderate NPDR
47	Moderately severe NPDR
53	Severe NPDR
60, 61	Mild PDR
65	Moderate PDR
71	High Risk PDR
75	High Risk PDR
81	Advanced PDR, fundus partially obscured, center of macula attached
85	Advanced PDR, posterior fundus obscured or center of macula detached
90	Cannot grade, even sufficiently for level 81 or 85

Source: Table 2 of Applicant Clinical Overview Report.

Key efficacy evaluation was based on the rate of improvement or worsening in DRSS from baseline through Week 52. During the 52-week treatment period, DRSS data were collected at Baseline (Screening visit), and at Weeks 8, 12, 24, 40, and 52.

Study Eye:

Only one eye per subject was selected as the study eye. For subjects who met the eligibility criteria in both eyes, the eye with the most severe DRSS score was selected as the study eye. For eyes with the same DRSS score, the applicant determined the study eye based on factors such as ocular dominance and patient preference.

Rescue Treatment:

In the study, subjects who developed PDR, anterior segment neovascularization (ASNV) or center-involved diabetic macular edema (CI-DME) during the study received rescue treatment in the study eye. Subjects who developed CI-DME received IAI or laser at the discretion of the investigator and no longer received their randomized treatment. Subjects who developed PDR and/or ASNV received panretinal photocoagulation or vitrectomy with endolaser but remained on their randomized treatment.

ii) Study Endpoints:

The following are the primary efficacy variables of the study. Of note, only data up to Week 52 was included in this submission.

- The proportion of subjects who achieved ≥ 2-step improvement in DRSS from baseline at Week 24 in the combined IAI 2Q8 and IAI 2Q16 group versus sham
- The proportion of subjects who achieved ≥ 2-step improvement in DRSS from baseline at Week 52 in the IAI 2Q8 group versus sham and
- The proportion of subjects who achieved ≥ 2-step improvement in DRSS from baseline at Week 52 in the IAI 2Q16 group versus sham.

Reviewer's Remark:

The same primary efficacy outcome measure of the proportion of subjects who achieved ≥ 2-step improvement in DRSS evaluated at Week 100 was used for the approval of aflibercept 2 mg for the treatment of DR in patients with DME.

The following are the secondary efficacy outcomes that were to be evaluated at Week 100.

- Proportion of patients developing a vision-threatening complications (VTCs) through Week 100. VTCs are defined as composite outcome of PDR and ASNV
- Proportion of patients who develop CI-DME and Week 100
- Time to development of a vision-threatening complication through Week 100
- Time to development of CI-DME through Week 100
- Proportion of patients who receive PRP through Week 100, inclusive of patients undergoing vitrectomy with endolaser
- Area under the curve (AUC) for change in BCVA from baseline at Week 100

Reviewer's Remark:

The secondary endpoints defined above were initially intended to be analyzed at Week 100; however, on July 26, 2018, the applicant submitted a protocol amendment and changed the evaluation time point of these endpoints from Week 100 to Week 52. Accordingly, the applicant proposed a hierarchical testing procedure to evaluate these endpoints at Week 52 in the order listed above if the primary efficacy variables at Week 24 and at Week 52 were met. If the primary efficacy variables were met, these secondary endpoints were to be tested hierarchically between the IAI 2Q16 group versus sham and the IAI 2Q8 group versus sham each at a two-sided significance level of 2.5%.

The applicant also defined the following additional efficacy outcomes that were to be evaluated at Week 52 and Week 100:

- Time to first improvement of ≥2 steps from baseline in the DRSS score through Week 52 and Week 100
- Proportion of patients with ≥2-step improvement from baseline in the DRSS score at Week 100
- Proportion of patients with ≥2-step worsening from baseline in the DRSS score at Week 52 and at Week 100
- Proportion of patients with ≥3-step worsening from baseline in the DRSS score at Week 52 and at Week 100
- Proportion of patients with ≥3-step improvement from baseline in the DRSS score at Week 52 and at Week 100
- Proportion of patients who receive vitrectomy through Week 52 and through week 100
- Change in central retinal thickness from baseline at Week 52 and at Week 100
- Change in mean deviation on visual field testing from baseline at Week 52 and at Week 100
- Change in BCVA from baseline at Week 24, Week 52 and Week 100

The following efficacy outcomes were also defined and summarized at Week 24 in an exploratory fashion in the clinical study report:

- The proportion of patients with ≥3-step improvement from baseline in the DRSS score
- The proportion of patients with ≥2-step worsening from baseline in the DRSS score
- The proportion of patients with ≥3-step worsening from baseline in the DRSS score
- The proportion of patients developing a VTCs
- The proportion of patients developing CI-DME
- The proportion of patients developing either a VTCs or CI-DME
- Time to development of a VTCs
- Time to development of CI-DME
- Time to development of either a VTCs or CI-DME
- Change in CRT from baseline

Subgroup Analysis:

The applicant defined the following subgroups for efficacy analyses: Sex, Age (<40; ≥40-<65; ≥65), Race (White; Black or African American; Other), Ethnicity - Hispanic or Latino (Yes/No), HbA1C (≤8%; >8%), and baseline DRSS score (level 47 versus level 53). Subgroup analysis by region (USA versus Non-USA) was also performed by the reviewer.

3.2.2 Statistical Methodology

In this section, the statistical methodology the applicant used for analysis of the efficacy data are summarized.

Analysis Populations:

Two analysis populations were defined:

Full analysis set (FAS): included all randomized subjects who received any study treatment. The primary efficacy analysis was performed on the FAS population; subjects in the FAS population were summarized according to the treatment assigned at baseline (as randomized).

Safety analysis set (SAF): included all randomized subject who received at least 1 study treatment (aflibercept or sham). Subjects in the SAF population were summarized according to the treatment received (as treated).

Primary Efficacy Analysis:

The primary efficacy analysis evaluated the superiority of the combined IAI group (IAI 2Q8 and 2Q16) versus sham at Week 24 and the individual IAI groups versus sham at Week 52 in the primary efficacy variable of the proportion of subjects who achieved ≥ 2-step improvement in DRSS from baseline. The statistical analysis to test for superiority was performed in the FAS population using the Cochran-Mantel-Haenszel (CMH) method, stratified by baseline DRSS level (level 47 versus level 53). To test for the three superiority comparisons, the applicant implemented appropriate multiplicity adjustments controlling the study Type I error rate at 5%.

Multiplicity Adjustment:

Bonferroni multiple comparison procedure was used to test for the three superiority comparisons: the combined IAI group against sham at Weet 24 and the individual IAI groups against sham at Week 52. As such, the combined IAI group (the individual IAI groups) was (were) considered superior to the sham group if the proportion of subjects who achieved ≥ 2-step improvement in DRSS from baseline at Week 24 (at Week 52) was (were) greater in the combined IAI group (in the individual IAI groups) than in the sham group and the p-value(s) was (were) < 0.0167 (0.05/3).

In addition to the p-values, the applicant also presented a weighted point estimates and two-sided 95% confidence interval (CI) estimates for the difference in the proportion of subjects who achieved ≥2-step improvement using the CMH weights and normal approximation of the weighted estimates.

Reviewer's Remark: *In the clinical study report, the applicant presented weighted point estimates and two-sided 95% confidence interval (CI) estimates for the difference in the proportions, in addition to the p-values for the hypothesis testing. However, in accordance with the multiplicity adjustment, the reviewer reported all CIs at a two-sided significance level of 1.67%.*

Handling of missing DRSS data and data after rescue treatment in the primary analysis:

In the primary efficacy analysis, the applicant imputed missing or non-gradable post-baseline DRSS values (level 90) using the last observation carry forward (LOCF) procedure.

Baseline DRSS values were carried forward if all post-baseline observations were missing or non-gradable. If baseline observations were also missing or non-gradable, the applicant considered subjects as non-responders. Regarding subjects who received rescue treatment during the study, the applicant censored data collected post-rescue treatment and used the last observation prior to rescue treatment in the primary analysis. **It should be noted that the same data handling approaches were adopted in the approval of aflibercept for the treatment of DR in DME patients.**

The applicant also performed the following sensitivity/supporting analyses to assess the impact of missing data due to dropouts or receipt of rescue treatment on the efficacy results: (i) Observed cases (no imputation) - excluding post-rescue data (OC), (ii) Observed cases - including post-rescue data (aOC), and (iii) Last observation carried forward - including post-rescue data (aLOCF).

The reviewer also performed additional sensitivity/supporting analysis considering subjects who received recue treatment during the study as non-responders. The efficacy results of the various sensitivity/supporting analyses are summarized in Section 3.2.4.4.

Reviewer's Remark: *In the applicant missing date handling strategy, baseline DRSS values were carried forward if* ***all post-baseline observations were missing or non-gradable****. This definition, however, was applied separately in the 24-week and 52-week data submissions. For example, in the 24-week submission, a subject's baseline DRSS data was carried forward if the subject had gradable baseline DRSS data but had no post-baseline DRSS data at Weeks 8, 12, and 24. However, in the 52-week submission, the same subject's baseline DRSS data was not carried forward at Weeks 8, 12, and 24 if the same subject had post-baseline DRSS data at Weeks 40 or 52. This resulted in minor numerical differences for the Week 24 summary in the IAI 2Q16 group when the analysis was performed using the 24-week versus 52-week data submissions (See Table 5 for the Week 24 summary based on 24-week submission [61.5%] versus Figure 12 in Section 5.4 [proposed label] based on 52-week submission [62.7%]). Despite the minor numerical differences, the overall conclusion remains unchanged.*

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

Subject Disposition:

The summary of subject disposition and the primary reasons for study discontinuation prior to Week 24 and Week 52 are shown in Table 2. A total of 402 subjects were enrolled in the study, and 95% and 88% of subjects completed the Week 24 and Week 52 treatment period, respectively. More subjects in the sham group discontinued from the study prior to Week 24 (11%) and prior to Week 52 (18%) compared to in the IAI groups (<5% prior to Week 24 and <10% prior to Week 52). The main reason for discontinuation was due to lost to follow-up (7% at Week 24 and 9% at Week 52 in the sham group compared to <4% in the IAI groups). Six subjects in the sham group and one subject in IAI 2Q8 died prior to Week 52; three of the six subjects in the sham group died prior to Week 24.

Table 2: Summary of subject disposition
(FAS Population)

n (%)	Visit	Sham (N=133)	IAI 2Q16 (N=135)	IAI 2Q8 (N=134)	IAI Combined (N=269)	Total (N=402)
Completed	Week 24	119 (89.5)	129 (95.6)	132 (98.5)	261 (97.0)	380 (94.5)
	Week 52	109 (81.9)	122 (90.4)	124 (92.5)	246 (91.4)	355 (88.3)
Discontinued Prior to	Week 24	14 (10.5)	6 (4.4)	2 (1.5)	8 (3.0)	22 (5.5)
	Week 52	24 (18.1)	13 (9.6)	10 (7.5)	23 (8.6)	47 (11.7)
Reasons for Discontinuation:						
Adverse event	Week 24	0	2 (1.5)	0 (0.0)	2 (0.7)	2 (0.5)
	Week 52	2 (1.5)	4 (3.0)	0	4 (1.5)	6 (1.5)
Death	Week 24	3 (2.3)	0	0	0	3 (0.7)
	Week 52	6 (4.5)	0	1 (0.8)	1 (0.4)	7 (1.7)
Withdrawal by subject	Week 24	2 (1.5)	1 (0.7)	0 (0.0)	1 (0.4)	3 (0.7)
	Week 52	2 (1.5)	5 (3.7)	4 (3.0)	9 (3.3)	11 (2.7)
Lost to follow-up	Week 24	9 (6.8)	3 (2.2)	2 (1.5)	5 (1.9)	14 (3.5)
	Week 52	12 (9.0)	4 (3.0)	5 (3.7)	9 (3.3)	21 (5.2)
Investigator decision	Week 24	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
	Week 52	0	0	0	0	0
Protocol Deviation	Week 24	0	0	0	0	0
	Week 52	1 (0.8)	0	0	0	1 (0.3)
Pregnancy	Week 24	0	0	0	0	0
	Week 52	1 (0.8)	0	0	0	1

Source: Table 6 of Week 24 and Table 6 of Week 52 Clinical Study Reports

Demographic and Baseline Disease Characteristics:

The summaries of the demographic and baseline disease characteristics for subjects in the FAS population are shown in Table 3. Most subjects in the study were white (~77%), more than half were male (~56%), and about 34% were Hispanic or Latino. The average age of subjects was about 56 years with ~22% of subjects ≥65 years (range 25 to 85). The demographic characteristics were well balanced across the treatment groups.

In terms of baseline disease characteristics, most subjects (75%) had moderately severe NPDR at baseline and only 25% of subjects had severe NPDR. Subjects had a median duration of diabetes of about 14 years (range: 0 – 65 years). The mean HbA1C at baseline was about 9% and more than half of the subjects (56%) had HbA1C > 8% at baseline. Subjects enrolled in the study had relatively good vision - the average number of letters read at baseline was about 82 letters (range: 65 to 98 letters). As shown in Table 3, the baseline disease characteristics were well balanced across the treatment groups.

Table 3: Summary of demographic and baseline disease characteristics
(FAS Population)

Summary	Levels	Sham (N=133)	IAI 2Q16 (N=135)	IAI 2Q8 (N=134)	Combined IAI (N=269)	Total (N=402)
Sex, n (%)	Male	69 (51.9)	75 (55.6)	81 (60.4)	156 (58.0)	225 (56.0)
	Female	64 (48.1)	60 (44.4)	53 (39.6)	113 (42.0)	177 (44.0)
Age (in years)	Mean (SD)	55.8 (10.31)	55.4 (11.13)	55.8 (10.19)	55.6 (10.66)	55.7 (10.53)
	Median	57.0	56.0	55.0	55.0	56.0
	Range	25 - 76	25 - 85	31 - 79	25 - 85	25 - 85
Age Category: n (%)	<40y	11 (8.3)	14 (10.4)	10 (7.5)	24 (8.9)	35 (8.7)
	>=40 - <65y	94 (70.7)	92 (68.1)	91 (67.9)	183 (68.0)	277 (68.9)
	>=65y	28 (21.1)	29 (21.5)	33 (24.6)	62 (23.0)	90 (22.4)
Race, n (%)	White	107 (80.5)	99 (73.3)	104 (77.6)	203 (75.5)	310 (77.1)
	Black Or African American	13 (9.8)	16 (11.9)	12 (9.0)	28 (10.4)	41 (10.2)
	Asian	4 (3.0)	12 (8.9)	7 (5.2)	19 (7.1)	23 (5.7)
	American Indian Or Alaska Native	1 (0.8)	1 (0.7)	4 (3.0)	5 (1.9)	6 (1.5)
	Native Hawaiian Or Other Pacific	0	1 (0.7)	1 (0.7)	2 (0.7)	2 (0.5)
	Not Reported	8 (6.0)	5 (3.7)	5 (3.7)	10 (3.7)	18 (4.5)
	Multiple	0	1 (0.7)	1 (0.7)	2 (0.7)	2 (0.5)
Ethnicity, n (%)	Not Hispanic Or Latino	74 (55.6)	97 (71.9)	93 (69.4)	190 (70.6)	264 (65.7)
	Hispanic Or Latino	58 (43.6)	37 (27.4)	41 (30.6)	78 (29.0)	136 (33.8)
	Not Reported	1 (0.8)	1 (0.7)	0	1 (0.4)	2 (0.5)
HbA1c (%)	Mean (SD)	8.5 (1.54)	8.6 (1.69)	8.4 (1.64)	8.5 (1.66)	8.5 (1.62)
	Median	8.4	8.3	8.3	8.3	8.3
	Range	5 - 13	6 - 15	5 - 12	5 - 15	5 - 15
HbA1C Category: n (%)	<=8%	52 (39.1)	61 (45.2)	61 (45.5)	122 (45.4)	174 (43.3)
	>8%	81 (60.9)	72 (53.3)	73 (54.5)	145 (53.9)	226 (56.2)
	Missing	0	2 (1.5)	0	2 (0.7)	2 (0.5)
Baseline DRSS [1]	Moderately Severe NPDR (Level	99 (74.4)	102 (75.6)	101 (75.4)	203 (75.5)	302 (75.1)
	Severe NPDR (Level 53)	34 (25.6)	33 (24.4)	33 (24.6)	66 (24.5)	100 (24.9)
Diabetic Duration (years)	Mean (SD)	15.5 (9.34)	13.7 (8.61)	14.0 (9.69)	13.8 (9.15)	14.4 (9.24)
	Median	15.1	13.6	14.2	14.2	14.3
	Range	1 - 42	0 - 41	0 - 65	0 - 65	0 - 65
Baseline BCVA	Mean (SD)	82.7 (6.03)	82.2 (6.63)	82.3 (5.15)	82.3 (5.93)	82.4 (5.96)
	Median	84.0	83.0	83.0	83.0	84.0
	Range	68 - 98	65 - 96	69 - 95	65 - 96	65 - 98
Baseline CRT	Mean (SD)	249.4 (38.41)	246.0 (34.34)	246.8 (31.59)	246.4 (32.94)	247.4 (34.82)
	Median	243.0	245.0	245.0	245.0	244.5
	Range	188 - 410	174 - 400	176 - 336	174 - 400	174 - 410

Source: Table 8 of Week 24 and Table 9 of Week 52 Clinical Study Reports; CRT - Central Retinal Thickness; HbA1C – Hemoglobin A1C.
[1] One subject each in the sham and in the IAI 2Q16 group with baseline DRSS level = 47 were stratified as DRSS level = 53.

3.2.4 Efficacy Results and Conclusions

In this section, the results for the DR-related efficacy endpoints of the proportion of subjects who achieved ≥2-step and ≥3-step improvement, and who had ≥2-step and ≥3-step worsening in DRSS from baseline at Week 24 and at Week 52 are discussed. The summary of the change in DRSS and in BCVA from baseline at each visit are also presented by treatment group.

In the PANORAMA study, DR-related variables were assessed through Week 52 at Baseline, Week 8, Week 12, Week 24, Week 40, and Week 52. Table 4 below shows the summary of the number of subjects with observed DRSS data at these visits. Also included in the table are the number of subjects with ungradable DRSS level (level 90) and those with missed visit or discontinued early from the study (referred to as MV/ED).

Table 4: Number of subjects with observed DRSS data by visit

	Sham (N = 133)				IAI 2Q16 (N = 135)				IAI 2Q8 (N = 134)			
Visit	N_{OC}	N_{aOC}	$N_{DRSS=90}$	$N_{MV/ED}$	N_{OC}	N_{aOC}	$N_{DRSS=90}$	$N_{MV/ED}$	N_{OC}	N_{aOC}	$N_{DRSS=90}$	$N_{MV/ED}$
Baseline	133	133	0	0	135	135	0	0	134	134	0	0
Week 8	115	119	2	12	119	119	4	12	128	128	0	6
Week 12	108	118	1	14	123	123	4	8	122	122	4	8
Week 24	93	113	3	17	117	119	4	12	125	125	2	7
Week 40	84	107	1	25	109	115	4	16	122	125	3	6
Week 52	75	106	2	25	102	108	7	20	113	116	5	13

N_{OC}: Number of subjects with observed cases excluding post-rescue data; N_{aOC}: Number of subjects with observed cases including post rescue data; $N_{DRSS=90}$: Number of subject with DRSS = 90; and $N_{MV/ED}$: Number of subjects with missed visit or who discontinued early from the study.

As outlined in Section 3.2.2, the primary analysis was based on subjects with observed DRSS data (OC) where subjects with ungradable DRSS score or those who missed visit or dropout early from the study were imputed with the last gradable DRSS score (including with baseline data if all post-baseline observations were missing or non-gradable). For subjects who received rescue, the last gradable DRSS data prior to receiving rescue was used in the primary analysis. Regarding rescue, 23, 2, and 1 subjects through Week 24 and 38, 8, and 5 subjects through Week 52 had received rescue treatment in the sham, IAI 2Q16, and IAI 2Q8 groups, respectively.

3.2.4.1 Proportion of Subjects Who Achieved ≥2-Step Improvement in DRSS

The summary of the number and proportion of subjects who achieved ≥2-step improvement in DRSS from baseline at Week 24 and at Week 52 are shown in Table 5.

Overall, the IAI groups demonstrated substantial improvement in DRSS and were statistically superior to the sham group in the proportion of subjects who achieved ≥2-step improvement in DRSS from baseline at Week 24 and at Week 52 ($p<0.0001$). As shown in Table 5, at Week 24, 58% of subjects in the combined IAI group (61% in 2Q16 and 55% in 2Q8) achieved ≥2-step improvement in DRSS compared to 6% of subjects in the sham group. The treatment difference was 52.3% (98.3% CI; 43.6% to 61%). At Week 52, 65% and 80% of subjects in the IAI 2Q16 and IAI 2Q8 groups, respectively, achieved ≥2-step improvement in DRSS compared to 15% of subjects in the sham group. The treatment differences were 50% (98.3% CI; 38% to 62%) for IAI 2Q16 versus sham and 65% (98.3% CI; 54% to 76%) for IAI 2Q8 versus sham.

It is worth noting that more subjects with severe NPDR at baseline (level 53) achieved ≥2-step improvement in DRSS compared to subjects with moderately severe NPDR (level 47).

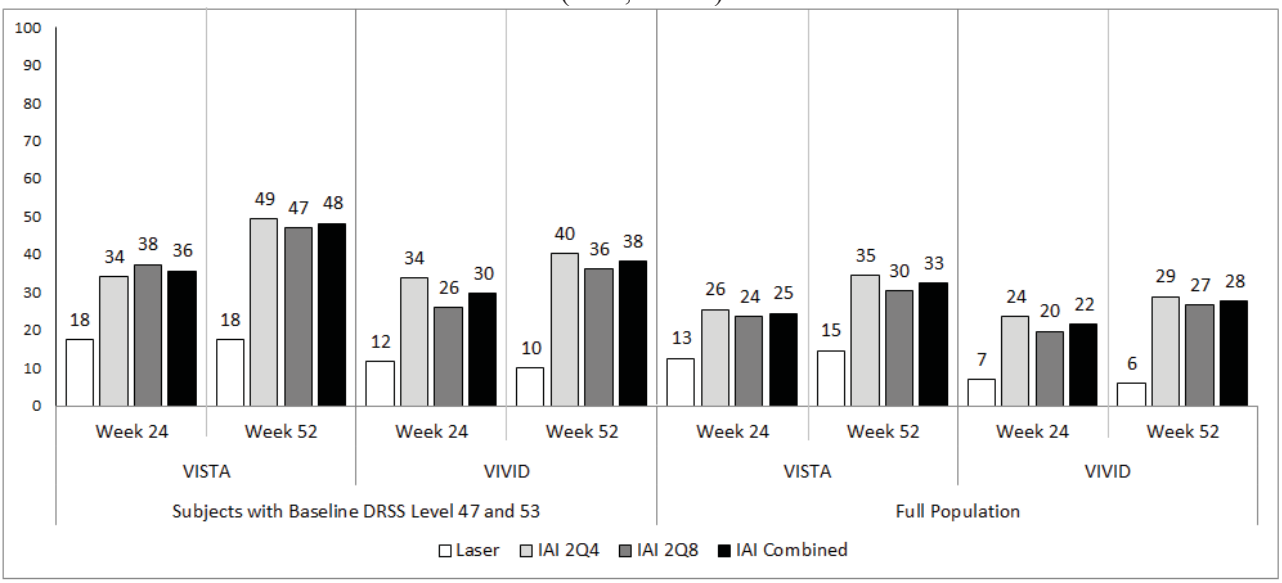
Table 5: Proportion of subjects who achieved ≥ 2-step improvement in DRSS at Week 24 and Week 52 (FAS; LOCF)

Treatment Group	Baseline DRSS: Level 47 n / N (%)	Baseline DRSS: Level 53 n / N (%)	Total n / N (%)	Difference vs Sham (%) (98.3% CI)	p-value [1]
Week 24					
Sham	5/100 (5.0)	3/ 33 (9.1)	8/133 (6.0)	--	--
IAI 2Q16	57/101 (56.4)	26/34 (76.5)	83/135 (61.5)	55.4 (44.3, 66.5)	<0.001
IAI 2Q8	53/101 (52.5)	21/ 33 (63.6)	74/134 (55.2)	49.2 (37.8, 60.7)	<0.001
IAI Combined	110/202 (54.5)	47/67 (70.2)	157/269 (58.4)	52.3 (43.6, 61.0)	<0.001
Week 52					
Sham	14/100 (14.0)	6/33 (18.2)	20/133 (15.0)	--	--
IAI 2Q16	60/101 (59.4)	28/34 (82.4)	88/135 (65.2)	50.1 (37.9, 62.3)	<0.001
IAI 2Q8	76/101 (75.3)	31/33 (93.9)	107/134 (80.0)	64.8 (53.8, 75.9)	<0.001
IAI Combined	136/202 (67.3)	59/67 (88.1)	195/269 (72.5)	57.4 (47.6, 67.3)	<0.001

FAS: Full Analysis Set - included all randomized subjects who received any study drug.
[1] Based on Cochran-Mantel-Haenszel (CMH) test, stratified by baseline DRSS level (level 47 versus level 53)
Note: Missing DRSS data were imputed using the last observation carried forward (LOCF) method (see detail in Section 3.2.2).

The efficacy findings observed in the PANORAMA study were supported by the 24-week and 52-week data of VISTA and VIVID. For these studies, Figure 2 shows the summary of the proportions of subjects who achieved ≥ 2-step improvement in DRSS at Week 24 and Week 52 in subjects with baseline DRSS level of 47 or 53 (analogous to the PANORAMA population) and in the full population.

Figure 2: Proportion of subjects who achieved ≥ 2-step improvement in DRSS at Week 24 and Week 52 (VISTA and VIVID Studies)
(FAS; LOCF)



Based on reviewer analysis

In the VISTA and VIVID studies, greater percentages of subjects in the full population as well as in subjects with baseline DRSS level of 47 and 53 had achieved ≥2-step improvement in DRSS in the IAI groups compared to in the laser group at Week 24 and at Week 52.

3.2.4.2 Analyses of Secondary Efficacy Variables

In this section, the analyses of the secondary efficacy variables evaluated at Week 52 are summarized. Note that the secondary efficacy variables defined at Week 52 were defined as exploratory at Week 24, and as such, p-values and confidence intervals presented for the Week 24 results are intended for descriptive use only.

i) Proportion of subjects who developed vision-threatening complications (PDR/ASNV) and/or CI-DME through Week 24 and through Week 52

In the PANORAMA study, subjects who developed PDR, anterior segment neovascularization (ASNV) or center-involved diabetic macular edema (CI-DME) during the study received rescue treatment in the study eye. In the clinical study reports, the applicant provided a summary of the proportion of subjects who developed vision-threatening complications (PDR/ASNV) and/or CI-DME through Week 24 and through Week 52. The results are shown in Table 6.

Table 6: Proportion of subjects who developed PDR/ASNV and/or CI-DME through Week 24 and through Week 52

Treatment Group	PDR/ASNV	Difference vs Sham (98.3% CI)	p-value	CI-DME	Difference vs Sham (98.3% CI)	p-value
Week 24						
Sham	18/133 (13.5)	--	--	23/133 (17.3)	--	--
IAI 2Q16	2/135 (1.5)	-12.1 (-19.6, -4.5)	0.0002	4/135 (3.0)	-14.4 (-23.0, -5.7)	<0.0001
IAI 2Q8	1/134 (0.7)	-12.8 (-20.1, -5.4)	<0.0001	7/134 (5.2)	-12.1 (-21.2, -2.9)	0.0019
IAI Combined	3/269 (1.1)	-12.4 (-19.7, -5.1)	<0.0001	11/269 (4.1)	-13.2 (-21.6, -4.8)	<0.0001
Week 52						
Sham	27/133 (20.3)			34/133 (25.6)		
IAI 2Q16	5/135 (3.7)	-16.6 (-25.8, -7.4)	<0.0001	9/135 (6.7)	-18.9 (-29.4, -8.5)	<0.0001
IAI 2Q8	4/134 (3.0)	-17.3 (-26.4, -8.2)	<0.0001	11/134 (8.2)	-17.3 (-28.1, -6.6)	0.0002
IAI Combined	9/269 (3.3)	-17.0 (-25.7, -8.2)	<0.0001	20/269 (7.4)	-18.1 (-28.0, -8.3)	<0.0001

Source: Table 26 of Week 24 and Table 13 of Week 52 Clinical Study Reports.

As shown in the table, more subjects in the sham group developed PDR/ASNV (14% through Week 24 and 20% through Week 52) and/or CI-DME (17% through Week 24 and 26% through Week 52) compared to subjects in the IAI groups (1% for PDR/ASNV and 4% for CI-DME in the combined IAI groups and <2% for PDR/ASNV and 3-5% for CI-DME in the individual IAI groups at Week 24, and 3% for PDR/ASNV and 7% for CI-DME in the combined IAI groups and 3-4% for PDR/ASNV and 7-8% for CI-DME in the individual IAI groups at Week 52).

Note that these two variables were defined as the first and the second secondary efficacy variables at Week 52 in the hierarchy (See Section 3.2.1 (ii)). As such, at Week 52, both the IAI 2Q16 and the IAI 2Q8 treatment groups were superior to sham in the proportion of subjects who developed PDR/ASNV or CI-DME through Week 52 ($p<0.025$). The applicant results for the other secondary efficacy variables in the hierarchy are shown in the Appendix Table 16.

Reviewer's Remark: *The applicant proposed to include* [redacted] (b) (4) *in the label (See detail in Section 5.4). This proposal was discussed during the internal filing and mid-cycle meetings. During these meetings, Dr. Chambers determined the applicant proposal unacceptable and instead suggested that* [redacted] (b) (4) *could be presented in the label (See Section 3.2.4.3 (iii) or Table 15 in the Appendix).*

3.2.4.3 Analyses of Exploratory Efficacy Variables

In this section, analyses of the exploratory efficacy variables at Week 24 and Week 52 are summarized. As such, p-values and confidence intervals presented in this section are intended for descriptive use only.

i) Proportion of subjects who achieved ≥3-step improvement in DRSS

In the PANORAMA study, the percentage of subjects who achieved ≥3-step improvement in DRSS from baseline at Week 24 and at Week 52 were evaluated as an exploratory variable and the results are presented Table 7.

As shown in the table, at Week 24, 9% of subjects in the combined IAI group (10% in IAI 2Q16 and 9% in IAI 2Q8) and <1% of subjects in the sham group achieved ≥3-step improvement in DRSS from baseline. The treatment difference was 8.5% (98.3% CI; 4.5% to 12.5%). At Week 52, 9% and 12% of subjects in the 2Q16 and 2Q8 groups, respectively, achieved ≥3-step improvement in DRSS compared to <1% of subjects in the sham group. The treatment differences were 8% (98.3% CI; 3% to 13%) for IAI 2Q16 versus sham and 14% (98.3% CI; 8% to 21%) for IAI 2Q8 versus sham.

It is worth noting that only subjects with severe NPDR (level 53) at baseline achieved ≥3-step improvement at Week 24.

Table 7: Proportion of subjects who achieved ≥ 3-step improvement in DRSS at Week 24 and Week 52 (FAS; LOCF)

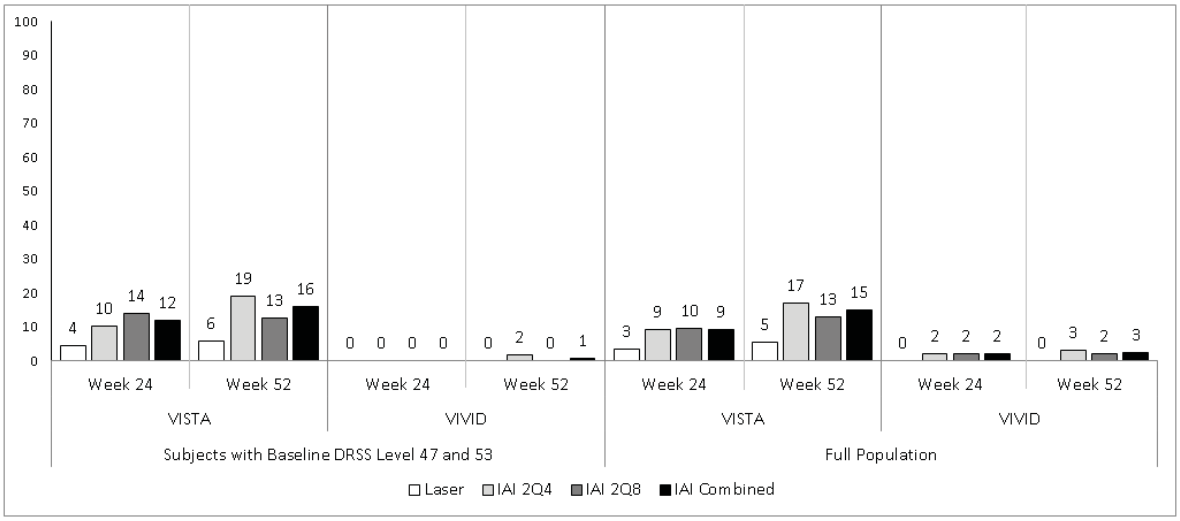
Treatment Group	Baseline DRSS		Total n / N (%)	Difference vs Sham (%) (98.3% CI)	p-value
	Level 47 n / N (%)	Level 53 n / N (%)			
Week 24					
Sham	0/100 (0.0)	1/ 33 (3.0)	1/133 (0.8)	--	--
IAI 2Q16	0/101 (0.0)	13/34 (38.2)	13/135 (9.6)	8.8 (3.4, 14.2)	<0.001
IAI 2Q8	0/101 (0.0)	12/ 33 (36.4)	12/134 (9.0)	8.2 (2.9, 13.6)	<0.001
IAI Combined	0/202 (0.0)	25/67 (37.3)	25/269 (9.3)	8.5 (4.5, 12.5)	<0.001
Week 52					
Sham	0/100 (0.0)	1/33 (3.0)	1/133 (0.8)		
IAI 2Q16	0/101 (0.0)	12/34 (35.3)	12/135 (8.9)	8.1 (2.8, 13.4)	<0.001
IAI 2Q8	5/101 (5.0)	15/33 (45.5)	20/134 (11.9)	14.2 (7.5, 21.0)	<0.001
IAI Combined	5/202 (2.5)	27/67 (40.3)	32/269 (11.9)	11.1 (6.6, 15.6)	<0.001

Source: Table 16 of Week 24 and Table 19 of Week 52 Clinical Study Reports.
Note: The footnotes in Table 5 are applicable here.

The efficacy findings of ≥3-step improvement in DRSS observed in the PANORAMA study was supported by the 24-week and 52-week data of VISTA and VIVID studies as shown in Figure 3.

Figure 3: Proportion of subjects who achieved ≥ 3-step improvement in DRSS at Week 24 and Week 52 (VISTA and VIVID Studies)

(FAS; LOCF)



Based on reviewer analysis

ii) Proportion of subjects who had ≥2-step or ≥3-step worsening in DRSS

The summary of the number and proportion of subjects who had ≥2-step or ≥3-step worsening in DRSS from baseline at Week 24 and at Week 52 are shown in Table 8.

As shown in the table, more subjects in the sham group had ≥2-step or ≥3-step worsening compared to subjects in the IAI groups. At Week 24, 6% and 2% of subjects in the sham group had ≥2-step and ≥3-step worsening, respectively, compared to <1% of subjects in the IAI groups. Similarly, at Week 52, 8% and 5% of subjects in the sham group had ≥2-step and ≥3-step worsening, respectively, compared to <1% of subjects in the IAI groups.

Table 8: Proportion of subjects who had ≥ 2- or ≥ 3-step worsening in DRSS at Week 24 and Week 52 (FAS; LOCF)

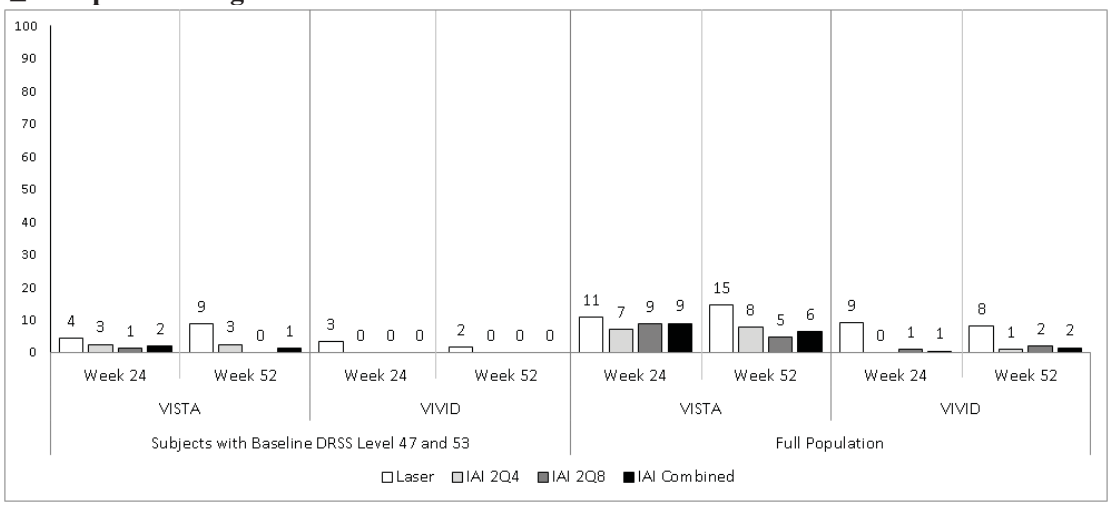
Treatment Group	**≥2-step worsening**	Difference vs Laser (98.3% CI) [1]	p-value	**≥3-step worsening**	Difference vs Sham (98.3% CI)	p-value
Week 24						
Sham	8/133 (6.0)	--	--	3/133 (2.3)	--	--
IAI 2Q16	1/135 (0.7)	-5.3 (-10.6, 0.0)	0.0170	1/135 (0.7)	-1.5 (-5.1, 2.0)	0.3089
IAI 2Q8	0/134 (0.0)	-6.0 (-11.0, -1.0)	0.0041	0/134 (0.0)	-2.3 (-5.3, 0.8)	0.0802
IAI Combined	1/269 (0.4)	-5.6 (-10.7, -0.6)	0.0003	1/269 (0.4)	-1.9 (-5.1, 1.3)	0.0736
Week 52						
Sham	11/133 (8.3)			7/133 (5.3)		
IAI 2Q16	1/135 (0.7)	-7.5 (-13.6, -1.5)	0.0030	1/135 (0.7)	-4.5 (-9.5, 0.5)	0.0302
IAI 2Q8	0/134 (0.0)	-8.3 (-14.0, -2.5)	0.0007	0/134 (0.0)	-5.3 (-9.9, -0.6)	0.0072
IAI Combined	1/269 (0.4)	-7.9 (-13.7, -2.1)	<0.0001	1/269 (0.4)	-4.9 (-9.6, -0.1)	0.0010

Source: Table 17 of Week 24 and Table 19 of Week 52 Clinical Study Reports.

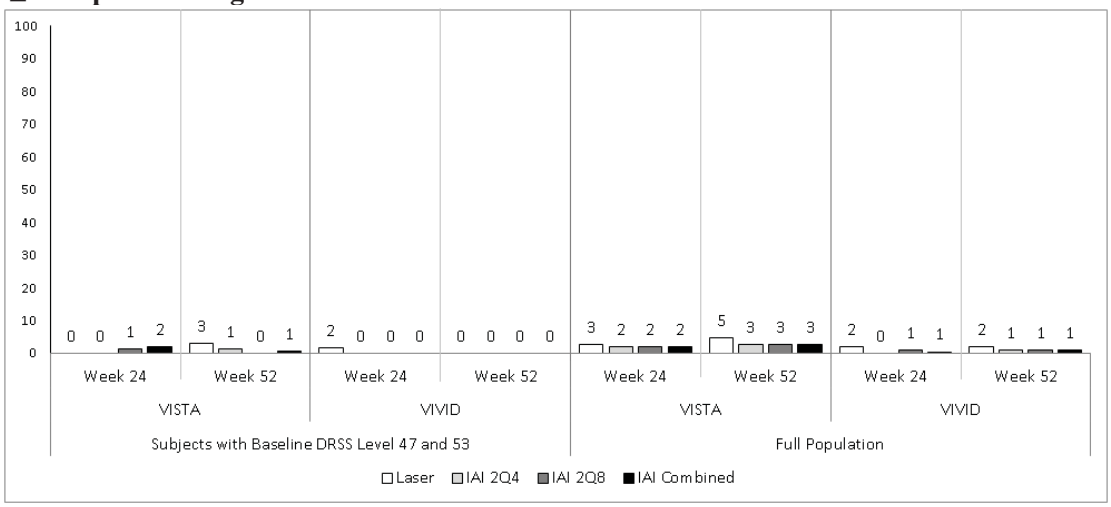
The efficacy findings observed in the PANORAMA study are supported by the 24-week and 52-week data of VISTA and VIVID studies as shown in Figure 4.

Figure 4: Proportion of subjects who had ≥ 2- or ≥ 3-step worsening in DRSS at Week 24 and Week 52 (VISTA and VIVID Studies)
(FAS; LOCF)

≥ 2-step worsening



≥ 3-step worsening



Based on reviewer analysis

iii) Proportion of subjects with incidence of new cases of PDR at Week 24 and Week 52

In the PANORAMA study, the incidence of new cases of PDR; that is, worsening of DRSS by ≥ 2-step for subjects with moderately severe NPDR (level 47) at baseline and by ≥ 1-step for subjects with severe NPDR (level 53) at baseline was also explored at Week 24 and Week 52. The results are shown in Table 9 below.

Clearly, the risk of experiencing new cases of PDR during the study was lower in the IAI treated subjects than in the sham treated subjects. As shown in the table, more sham treated subjects (6% at Week 24 and 10% at Week 52) experienced a new case of PDR compared to IAI treated subjects (<1%).

Table 9: Proportion of subjects with incidence of new cases of PDR at Week 24 and Week 52 (FAS; LOCF)

Treatment Group	Week 24 n/N (%)	Week 24 Difference vs Sham (98.3% CI) [1]	Week 24 p-value	Week 52 Total n/N (%)	Week 52 Difference vs Sham (98.3% CI) [1]	Week 52 p-value
Sham	8/133 (6.0)	--	--	13/133 (9.8)		
IAI 2Q8	1/135 (0.7)	-5.3 (-10.6, 0.0)	0.0170	1/135 (0.7)	-9.0 (-15.5, -2.6)	0.0009
IAI 2Q16	0/134 (0.0)	-6.0 (-11.0, -1.0)	0.0041	1/134 (0.7)	-9.0 (-15.5, -2.6)	0.0009
IAI Combined	1/269 (0.4)	-5.6 (-10.7, -0.6)	0.0003	2/269 (0.7)	-9.0 (-15.5, -2.7)	<0.0001

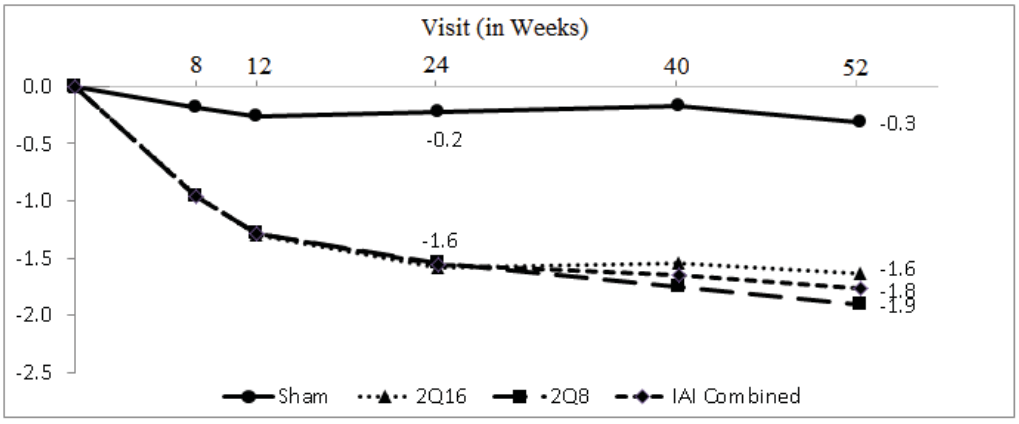
See Appendix Table 15 for the results at each visit and through Week 24 and through Week 52. The results through Week 24 was summarized based on any incidence of PDR at Weeks 8, 12, or 24 and the results through Week 52 was summarized based on any incidence of PDR at Weeks 8, 12, 24, 40, or 52.

iv) Summary of change in DRSS from baseline at each visit

The summary of the change in DRSS from baseline at each visit through Week 52 are shown in Figure 5 and in Table 10.

As shown, subjects in the IAI groups yielded greater improvement in DRSS over time from baseline compared to subjects in sham group. At Week 24 and Week 52, subjects in the IAI groups had a median improvement of about 2-units whereas subjects in the sham group showed a median improvement of 0 unit.

Figure 5: Mean change in DRSS (±SE) from baseline through Week 52 (FAS; LOCF)



Based on reviewer analysis

Table 10: Summary of change in DRSS from baseline at each visit (FAS; LOCF)

Visit	Summary	Sham	IAI 2Q16	IAI 2Q8	IAI Combined
Week 8	Mean (SE)	-0.2 (0.07)	-0.9 (0.07)	-1.0 (0.07)	-1.0 (0.05)
	Median	0	-1	-1	-1
	Percentile (2.5, 97.5)	(-2, 1)	(-3, 0)	(-2, 0)	(-2, 0)
Week 12	Mean (SE)	-0.3 (0.07)	-1.3 (0.08)	-1.3 (0.07)	-1.3 (0.05)
	Median	0	-1	-1	-1
	Percentile (2.5, 97.5)	(-2, 2)	(-3, 0)	(-2, 0)	(-3, 0)

Visit	Summary	Sham	IAI 2Q16	IAI 2Q8	IAI Combined
Week 24	Mean (SE)	-0.2 (0.09)	-1.6 (0.09)	-1.5 (0.07)	-1.6 (0.05)
	Median	0	-2	-2	-2
	Percentile (2.5, 97.5)	(-2, 2)	(-3, 0)	(-3, 0)	(-3, 0)
Week 40	Mean (SE)	-0.3 (0.13)	-1.6 (0.09)	-1.8 (0.07)	-1.7 (0.06)
	Median	-0.5	-2	-2	-2
	Percentile (2.5, 97.5)	(-2, 3)	(-3,0)	(-3, 0)	(-3, 0)
Week 52	Mean (SE)	-0.3 (0.11)	-1.6 (0.08)	-1.9 (0.06)	-1.8 (0.05)
	Median	0	-2	-2	-2
	Percentile (2.5, 97.5)	(-2, 3)	(-3, 0)	(-3, 0)	(-3, 0)

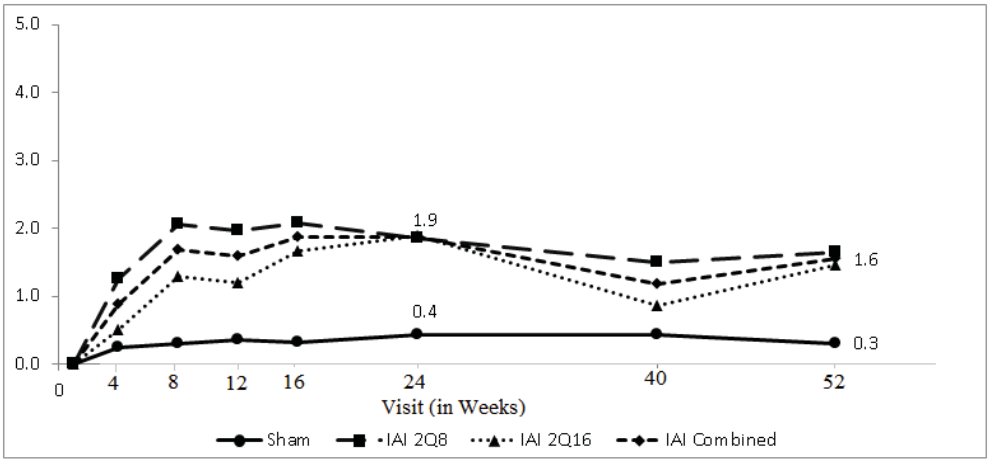
Based on reviewer analysis

v) Summary of change in BCVA from baseline at each visit

The summary of the change in BCVA from baseline at each visit through Week 52 are shown in Figure 6. Subjects enrolled in the PANORAMA study had relatively good vision - the mean baseline BCVA in the study was about 82 letters (range: 65 to 98 letters) and was comparable across the treatment groups.

As shown, subjects in the IAI groups displayed a slight improvement in the mean change in BCVA from baseline through Week 52. However, the mean change in BCVA was stable for subjects in the sham group. At Week 24 and Week 52, the IAI groups gained an average of about +2 letters from baseline whereas the sham group gained an average of about +0.4 letters.

Figure 6: Mean change in BCVA from baseline through Week 52
(FAS; LOCF)



Based on reviewer analysis.
Source: See Appendix Table 14.

The BCVA summary of VISTA and VIVID studies through Week 52 in subjects with moderately severe and severe NPDR at baseline (analogous to the PANORAMA population) are shown in Appendix Figure 7. Unlike in the PANORAMA study, subjects that received IAI in the VISTA and VIVID studies gained an average of 8-11 letters from baseline at Week 24 and 10-12 letters from baseline at Week 52 compared to about 2 letters in the PANORAMA study. This is likely due to the difference in the mean baseline BCVA (about 82 letters in PANORAMA study versus about 60 letters in VISTA and VIVID) and the fact that subjects enrolled in the PANORAMA study had **no DME at baseline** whereas subjects enrolled in VISTA and VIVID studies **had DME at baseline** which is known to affect central vision.

3.2.4.4 Sensitivity/Supporting Analyses

In the PANORAMA study, 30% (40/133) of subjects at Week 24 and 44% (58/133) of subjects at Week 52 in the sham group, and 10% (27/269) of subjects in the combined IAI group at Week 24 and 24% (33/135) and 17% (21/134) of subjects in IAI 2Q16 and 2Q8, respectively, at Week 52 were considered to have no DRSS data in the primary efficacy analysis. Subjects were considered to have no DRSS data for the primary efficacy analyses at Week 24 and Week 52 mainly due to early dropout, missed visit, or receipt of rescue therapy.

Regarding rescue, 23 (**or 38**) subjects in the sham group and 3 (**or 13**) subjects in the combined IAI group (2 [**or 8**] in 2Q16 and 1 [**or 5]** in 2Q8) had received rescue treatment through Week 24 (**or through Week 52**).

- At Week 24, 21 of the 23 subjects in the sham group had post-rescue data and 2 had no post-rescue data due to early dropout or missed visit. All three subjects in the combined IAI group had post-rescue data at Week 24; however, for one of the three subjects the applicant did not attribute the Week 24 DRSS data due to rescue treatment and hence was used in the primary analysis.

- At Week 52, 32 of the 38 subjects in the sham group and 10 of the 13 subjects in the combined IAI group had post-rescue data at Week 52. Six subjects in the sham group and three subjects in the combined IAI groups (2 of 8 in 2Q16 and 1 of 5 in 2Q8) had no post-rescue data at Week 52 due to early dropout or missed visit.

Overall, 40 (**or 58**) subjects in the sham group had no DRSS data at Week 24 (**or at Week 52**) because 23 (**or 38**) subjects had received rescue (post-rescue data excluded), 3 (**or 2**) subjects had ungradable DRSS (level 90), and 14 (**or 18**) subjects had missed visit or dropped out early. Similarly, at Week 24, 27 subjects in the combined IAI group had no DRSS data because 2 subjects received rescue (post-rescue data excluded), 6 subjects had ungradable DRSS, and 19 subjects missed visit or dropped out early. At Week 52, a total of 33 and 21 subjects in the IAI 2Q16 and IAI 2Q8 groups, respectively, had no DRSS data because 8 and 5 subjects, respectively, had received rescue, 7 and 5 subjects, respectively, had ungradable DRSS, and 18 and 11 subjects, respectively, had missed visit or dropped out early.

In the applicant primary efficacy analysis, subject with no DRSS data were imputed by the last available gradable DRSS value (including gradable baseline DRSS data). For subjects that received rescue therapy during the 24-week and 52-week treatment period, data collected post-rescue were censored and the last available data prior to rescue treatment was used in the analysis.

In the study, the applicant performed several sensitivity/supporting analyses to assess the robustness of the primary efficacy results: *(i) using observed cases (no imputation) - excluding post-rescue data (OC), (ii) using observed cases - including post-rescue data (aOC); and (iii) using LOCF methods - including post-rescue data (aLOCF)*. The reviewer also performed additional sensitivity/supporting analysis by considering subjects who received rescue therapy or those with no DRSS data at Week 24 (or Week 52) as non-responders (Responder Analysis).

Table 11 shows the efficacy results under the different data handling methods. As shown, except for small numerical differences, the overall conclusion from the various sensitivity analyses was consistent with the primary analysis method using LOCF.

Table 11: Sensitivity/Supporting analyses for the proportion of subjects who achieved ≥ 2-step improvement in DRSS at Week 24 and at Week 52

		Sham	IAI 2Q16	IAI 2Q8	IAI Combined
WEEK 24					
LOCF	N	133	135	134	269
	n (%)	8 (6.0)	83 (61.5)	74 (55.2)	157 (58.4)
	Diff. vs. Sham	--	55.4	49.2	52.3
	(98.3% CI)		(44.3, 66.5)	(37.8, 60.7)	(43.6, 61.0)
OC	N	93	117	125	242
	n (%)	7 (7.5)	77 (65.8)	71 (56.8)	148 (61.2)
	Diff. vs. Sham	--	57.8	48.8	53.1
	(98.3% CI)		(45.3, 70.3)	(36.2, 61.5)	(43.1, 63.2)
aOC	N	113	119	125	244
	n (%)	16 (14.2)	78 (65.5)	71 (56.8)	149 (61.1)
	Diff. vs. Sham	--	51.4	42.6	46.9
	(98.3% CI)		(38.4, 64.5)	(29.3, 55.8)	(36.1, 57.7)
aLOCF	N	133	135	134	269
	n (%)	17 (12.8)	83 (61.5)	74 (55.2)	157 (58.4)
	Diff. vs. Sham	--	48.6	42.5	45.6
	(98.3% CI)		(36.5, 60.8)	(30.0, 54.9)	(35.6, 55.5)
Responder Analysis [1]	N	133	135	134	269
	n (%)	7 (5.3)	77 (57.0)	71 (53.0)	148 (55.0)
	Diff. vs. Sham	--	51.7	47.7	49.7
	(98.3% CI)		(40.5, 63.0)	(36.4, 59.1)	(41.1, 58.4)
WEEK 52					
LOCF	N	133	135	134	269
	n (%)	20 (15.0)	88 (65.2)	107 (79.9)	195 (72.5)
	Diff. vs. Sham	--	50.1	64.8	57.4
	(98.3% CI)		(37.9, 62.3)	(53.8, 75.9)	(47.6, 67.3)
OC	N	75	102	113	215
	n (%)	17 (22.7)	69 (67.6)	95 (84.1)	164 (76.3)
	Diff. vs. Sham	--	44.0	59.7	52.3
	(98.3% CI)		(27.7, 60.3)	(45.1, 74.3)	(38.5, 66.0)
aOC	N	106	108	116	224
	n (%)	27 (25.5)	72 (66.7)	96 (82.8)	168 (75.0)
	Diff. vs. Sham	--	40.7	56.4	48.8
	(98.3% CI)		(25.7, 55.7)	(43.1, 69.8)	(36.4, 61.2)
aLOCF	N	133	135	134	269
	n (%)	32 (24.1)	89 (65.9)	107 (79.9)	196 (72.9)
	Diff. vs. Sham	--	41.8	55.8	48.8
	(98.3% CI)		(28.6, 55.0)	(43.7, 67.9)	(37.8, 59.8)
Responder Analysis [1]	N	133	135	134	269
	n (%)	17 (12.8)	69 (51.1)	95 (70.9)	164 (61.0)
	Diff. vs. Sham	--	38.3	58.1	48.2
	(98.3% CI)		(25.9, 50.8)	(46.4, 69.8)	(38.2, 58.1)

[1] Based on reviewer analysis: subjects who received rescue therapy or had no DRSS data at Week 24 were treated as non-responders in this analysis.

Reviewer's Remark: *It is worth noting that the response rate in the sham group were higher when post-rescue data were included in the analysis (see rows aOC and aLOCF versus OC and LOCF). This is likely because subjects in the sham group received aflibercept (IAI) as a rescue therapy during the study which further affirms the effectiveness of aflibercept in improving DR severity.*

3.2.5 Efficacy Conclusion

Based on our review of the 24-Week and 52-week data from the PANORAM study and supporting data from a 24-week and a 52-week analysis of the VISTA and VIVID studies, the following efficacy conclusions were made:

i) In the PANORAMA study, the IAI groups demonstrated substantial improvement in DRSS and were statistically superior to the sham group in the primary efficacy variable of the proportion of subjects who achieved ≥2-step improvement in DRSS from baseline at Week 24 and at Week 52 ($p<0.0001$).

   At Week 24, 58% of subjects in the IAI combined group (61% in 2Q16 and 55% in 2Q8) achieved ≥2-step improvement from baseline compared to 6% of subjects in the sham group. The treatment difference was 52.3% (98.3% CI; 43.6% to 61%). At Week 52, 65% of subjects in the IAI 2Q16 group and 80% of subjects in the IAI 2Q8 group achieved ≥2-step improvement compared to 15% of subjects in the sham group. The treatment difference was 50% (98.3% CI; 38% to 62%) for IAI 2Q16 versus sham and 65% (98.3% CI; 54% to 76%) for IAI 2Q8 versus sham.

ii) In the study, more IAI treated subjects showed ≥3-step improvement (Table 7) and fewer IAI treated subjects had worsening in DRSS (Table 8) and developed new of cases of PDR (Table 9) at Week 24 and at Week 52 from baseline compared to sham treated subjects.

iii) A 24-week and a 52-week data analysis of the VISTA and VIVID studies supported the efficacy findings of the PANORAMA study.

   - In subjects with moderately severe NPDR or severe NPDR at baseline (analogous to the PANAORAM population), 36% of subjects in VISTA and 30% of subjects in VIVID in the IAI combined group (IAI 2Q4 and 2Q8) achieved ≥2-step improvement at Week 24 compared to 18% and 12% of laser treated subjects in VISTA and VIVID, respectively. Similarly, at Week 52, 47% of subjects in VISIT and 36% of subjects in VIVID in IAI 2Q8 group achieved ≥2-step improvement compared 18% of subjects in VISTA and 10% of subjects in VIVID in the laser group.
   - In the full population, 25% of subject in VISTA and 22% of subjects in VIVID in the IAI combined group achieved ≥2-step improvement at Week 24 compared to 13% and 7% of laser treated subjects in VISTA and VIVID, respectively. Similarly, at Week 52, 30% of subjects in VISITA and 27% of subjects in VIVID in IAI 2Q8 achieved ≥2-step improvement compared 15% of subjects in VISTA and 6% of subjects in VIVID in the sham group.

In summary, the combined aflibercept 2.0 mg dosing regimen (IAI 2Q8 and 2Q16) as well as the individual IAI dosing regimens demonstrated substantial improvement in DRSS and were statistically superior to sham treatment.

3.3 Safety Evaluation

In the PANORAMA study, safety was assessed through exposure to study medication and summary of ocular and non-ocular adverse events (AEs), serious AEs, and deaths. Safety was summarized according to the safety analysis set.

A high-level safety summary is summarized in this section; see the FDA medical review for a comprehensive safety evaluation.

i) Summary of Exposure to Treatment Medication

The summary of aflibercept injections received prior to Week 24 and prior to Week 52 are shown in Table 12. Prior to Week 24, subjects in the IAI 2Q16 group received ~4 injections on average and subjects in IAI 2Q8 group received ~5 injections. Prior to Week 52, subjects in the IAI 2Q16 group received ~6 injections on average and subjects in IAI 2Q8 group received ~9 injections

Table 12: Summary of aflibercept injection received prior to Week 52

		Week 24			Week 52		
IAI Treatment Group	N	Mean (SD)	Median	Range	Mean (SD)	Median	Range
2Q16	135	3.9 (0.46)	4	1-4	5.5 (1.02)	6	1-6
2Q8	134	4.9 (0.39)	5	2-5	8.6 (1.10)	9	2-9
Combined	269	4.4 (0.68)	4	1-5	7.1 (1.88)	6	1-9

Source: Table 19 of Week 24 and Table 26 of Week 52 Clinical Study Reports.

ii) Adverse Events

Overall, similar percentage of subjects had treatment emergent adverse events (TEAEs) in the sham group (88%) and in the combined IAI group (87%) through Week 52.

Summary of Ocular Adverse Event

The frequency of ocular TEAEs in the sham group (50%) was slightly higher than in the combined IAI group (44%) through Week 52. A higher percentage of subjects in the combined IAI groups (20%) had injection-related ocular TEAEs in the study eye than in the sham group (9%) through Week 52. The most frequent ocular TEAEs (≥2%) reported through Week 52 are shown in Table below.

In the study, 3% of subject in the sham group and 2.6% of subjects in the combined IAI group experienced at least one serious ocular TEAEs through Week 52. One subject in the combined IAI group discontinued from the study due to ocular TEAE.

Primary System Organ Class Preferred Term MedDRA Version 21.0	Sham (N=133)	2Q16 (N=135)	2Q8 (N=134)	IAI 2 mg Combined (N=269)
Number of patients with at least 1 such TEAE, n (%)	**67 (50.4%)**	**58 (43.0%)**	**60 (44.8%)**	**118 (43.9%)**
Eye disorders	**64 (48.1%)**	**57 (42.2%)**	**59 (44.0%)**	**116 (43.1%)**
Conjunctival hemorrhage	7 (5.3%)	16 (11.9%)	23 (17.2%)	39 (14.5%)
Diabetic retinal edema	32 (24.1%)	8 (5.9%)	12 (9.0%)	20 (7.4%)
Vitreous floaters	3 (2.3%)	6 (4.4%)	12 (9.0%)	18 (6.7%)
Eye pain	4 (3.0%)	10 (7.4%)	5 (3.7%)	15 (5.6%)
Retinal exudates	5 (3.8%)	5 (3.7%)	7 (5.2%)	12 (4.5%)
Blepharitis	1 (0.8%)	2 (1.5%)	6 (4.5%)	8 (3.0%)
Vitreous detachment	1 (0.8%)	4 (3.0%)	4 (3.0%)	8 (3.0%)
Cataract	1 (0.8%)	3 (2.2%)	4 (3.0%)	7 (2.6%)
Dry eye	4 (3.0%)	3 (2.2%)	4 (3.0%)	7 (2.6%)
Cataract subcapsular	1 (0.8%)	3 (2.2%)	2 (1.5%)	5 (1.9%)
Diabetic retinopathy	13 (9.8%)	2 (1.5%)	3 (2.2%)	5 (1.9%)
Lacrimation increased	0	2 (1.5%)	3 (2.2%)	5 (1.9%)
Punctate keratitis	2 (1.5%)	2 (1.5%)	3 (2.2%)	5 (1.9%)
Visual impairment	0	1 (0.7%)	4 (3.0%)	5 (1.9%)
Eye irritation	0	1 (0.7%)	3 (2.2%)	4 (1.5%)
Vision blurred	1 (0.8%)	1 (0.7%)	3 (2.2%)	4 (1.5%)
Macular edema	3 (2.3%)	2 (1.5%)	0	2 (0.7%)
Injury, poisoning and procedural complications	**3 (2.3%)**	**2 (1.5%)**	**6 (4.5%)**	**8 (3.0%)**
Corneal abrasion	1 (0.8%)	2 (1.5%)	3 (2.2%)	5 (1.9%)

Source: Table 29 of Week 52 Clinical Study Report

Summary of Non-Ocular Adverse Event

The frequency of non-ocular TEAEs in the sham group (70%) and in the combined IAI group (73%) were comparable through Week 52.

In the PANORAMA study, a total of six subjects in the sham group and one subject in IAI 2Q8 group died during the 52-week treatment period. Three of the six subjects in the sham group died during the 24-week treatment period.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The primary efficacy variable of the proportion of subjects who achieved ≥2-step improvement in DRSS at Week 24 and at Week 52 were summarized in this section by the subgroups of gender, age group (<40 vs 40-65 vs ≥65), race (White vs Others), baseline DRSS category (47 vs 53), and region (US vs Non-US). We should note that all other race categories except for 'White' were pooled as 'Others' in this subgroup analysis due to small sample size.

Table 13 shows the results for the proportion of subjects who achieved ≥2-step improvement in DRSS at Week 24 and at Week 52 for each levels of the subgroup variables. As shown, in each levels of the subgroup variables, IAI treated subject yielded substantial improvement compared to sham treated subjects and the results were consistent with the overall population. We should note that in some subgroups there were only small number of subjects, and as such, the results for these subgroups may not be indicative of the overall treatment effects.

Table 13: Proportion of subjects with ≥2-step improvement in DRSS at Week 24 and Week 52 by Subgroup
(FAS; LOCF)

Subgroup	Levels	Sham	IAI 2.0 mg			Difference versus sham (%) (98.3% CI)		
			2Q16	2Q8	Combined	IAI 2Q16	IAI 2Q8	Combined
WEEK 24								
Overall		**8/133 (6.0%)**	**83/135 (61.5%)**	**74/134 (55.2%)**	**157/269 (58.4))**	**55.5 (44.4, 66.7)**	**49.2 (37.8, 60.7)**	**52.3 (43.6, 61.1)**
Sex	Male	4/ 69 (5.8%)	51/ 75 (68.0%)	42/ 81 (51.9%)	93/ 156 (59.6%)	62.2 (47.6, 76.9)	46.1 (31.1, 61.1)	53.8 (42.2, 65.4)
	Female	4/ 64 (6.3%)	32/ 60 (53.3%)	32/ 53 (60.4%)	64/ 113 (56.6%)	47.1 (29.9, 64.3)	54.1 (36.3, 71.9)	50.4 (37.0, 63.8)
Age Group (in years)	<40	0/ 11 (0.0%)	11/ 14 (78.6%)	6/ 10 (60.0%)	17/ 24 (70.8%)	78.6 (51.3, 105.8)	60.0 (20.9, 99.1)	70.8 (48.1, 93.5)
	40-65	4/ 94 (4.3%)	53/ 92 (57.6%)	47/ 91 (51.6%)	100/ 183 (54.6%)	53.4 (40.0, 66.7)	47.4 (33.8, 61.0)	50.4 (40.2, 60.5)
	>=65	4/ 28 (14.3%)	19/ 29 (65.5%)	21/ 33 (63.6%)	40/ 62 (64.5%)	51.2 (24.4, 78.1)	49.4 (23.4, 75.3)	50.2 (28.4, 72.0)
Race	White	5/ 107 (4.7%)	61/ 99 (61.6%)	60/ 104 (57.7%)	121/ 203 (59.6%)	56.9 (44.2, 69.7)	53.0 (40.4, 65.7)	54.9 (45.3, 64.5)
	Other	3/ 26 (11.5%)	22/ 36 (61.1%)	14/ 30 (46.7%)	36/ 66 (54.5%)	49.6 (24.6, 74.5)	35.1 (8.2, 62.1)	43.0 (21.7, 64.3)
Baseline DRSS	47	5/ 99 (5.1%)	58/ 102 (56.9%)	53/ 101 (52.5%)	111/ 203 (54.7%)	51.8 (38.9, 64.7)	47.4 (34.3, 60.5)	49.6 (39.7, 59.5)
	53	3/ 34 (8.8%)	25/ 33 (75.8%)	21/ 33 (63.6%)	46/ 66 (69.7%)	66.9 (45.3, 88.6)	54.8 (31.3, 78.4)	60.9 (42.8, 78.9)
Country	US	8/127 (6.3%)	74/121 (61.2%)	67/126 (53.2%)	141/247 (57.1%)	54.9 (45.2, 64.6)	46.9 (37.2, 56.6)	50.8 (43.3, 58.3)
	Non-US [1]	0/6	9/14 (64.3%)	7/8 (87.5%)	16/22 (72.7%)	64.3 (38.2, 90.3)	87.5 (63.0, NA)	72.7 (53.7, 91.8)

Subgroup	Levels	Sham	IAI 2.0 mg			Difference versus sham (%) (98.3% CI)		
			2Q16	2Q8	Combined	IAI 2Q16	IAI 2Q8	Combined
WEEK 52								
Overall		20/ 133 (15.0%)	88/ 135 (65.2%)	107/ 134 (79.9%)	195/ 269 (72.5%)	50.1 (37.8, 62.5)	64.8 (53.6, 76.0)	57.5 (47.5, 67.4)
Sex	Male	10/ 69 (14.5%)	51/ 75 (68.0%)	69/ 81 (85.2%)	120/ 156 (76.9%)	53.5 (37.0, 70.0)	70.7 (56.7, 84.7)	62.4 (49.4, 75.5)
	Female	10/ 64 (15.6%)	37/ 60 (61.7%)	38/ 53 (71.7%)	75/ 113 (66.4%)	46.0 (27.3, 64.7)	56.1 (37.5, 74.6)	50.7 (35.4, 66.0)
Age Group (in years)	<40	2/ 11 (18.2%)	11/ 14 (78.6%)	7/ 10 (70.0%)	18/ 24 (75.0%)	60.4 (20.5,100.3)	51.8 (5.0, 98.6)	56.8 (20.5, 93.1)
	40-65	15/ 94 (16.0%)	55/ 92 (59.8%)	76/ 91 (83.5%)	131/ 183 (71.6%)	43.8 (28.5, 59.1)	67.6 (54.5, 80.6)	55.6 (43.5, 67.7)
	>=65	3/ 28 (10.7%)	22/ 29 (75.9%)	24/ 33 (72.7%)	46/ 62 (74.2%)	65.1 (41.1, 89.2)	62.0 (38.4, 85.6)	63.5 (43.9, 83.0)
Race	White	18/ 107 (16.8%)	66/ 99 (66.7%)	86/ 104 (82.7%)	152/ 203 (74.9%)	49.8 (35.5, 64.2)	65.9 (53.4, 78.3)	58.1 (46.7, 69.4)
	Other	2/ 26 (7.7%)	22/ 36 (61.1%)	21/ 30 (70.0%)	43/ 66 (65.2%)	53.4 (29.9, 76.9)	62.3 (38.3, 86.3)	57.5 (38.4, 76.5)
Baseline DRSS	47	14/ 99 (14.1%)	61/ 102 (59.8%)	76/ 101 (75.2%)	137/ 203 (67.5%)	45.7 (31.3, 60.1)	61.1 (47.8, 74.4)	53.3 (41.8, 64.9)
	53	6/ 34 (17.6%)	27/ 33 (81.8%)	31/ 33 (93.9%)	58/ 66 (87.9%)	64.2 (41.4, 86.9)	76.3 (57.5, 95.1)	70.2 (51.6, 88.8)
Country	US	20/ 127 (15.7%)	78/ 121 (64.5%)	99/ 126 (78.6%)	177/ 247 (71.7%)	48.7 (35.7, 61.7)	62.8 (51.1, 74.6)	55.9 (45.5, 66.3)
	Non-US [1]	0/ 6 (0.0%)	10/ 14 (71.4%)	8/ 8 (100%)	18/ 22 (81.8%)	71.4 (41.4, NA)	100.0 (NA, NA)	81.8 (61.7, NA)

Based on reviewer analysis.
[1] Included Japan (N=11), Germany (N=5), the United Kingdom (N=2), and Hungary (N=10)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The reviewer identified no statistical issues in this review.

5.2 Collective Evidence

In the PANORAMA study, the IAI treatment groups had substantial improvement in DR severity score and were superior to the sham group in the primary efficacy variable of the proportion of subjects who achieved ≥2-step improvement in DRSS from baseline at Week 24 and at Week 52 ($p<0.0001$). Additionally, in this study, more IAI treated subjects showed ≥3-step improvement (Table 7) and fewer aflibercept treated subjects had worsening in DRSS (Table 8) and developed new of cases of PDR (Table 9) at Week 24 and Week 52 from baseline compared to sham treated subjects.

The efficacy findings in the PANORAMA study were also supported by the 24-week and 52-week data of the VISTA and VIVID studies.

In summary, aflibercept 2.0 mg administered every 16-week after three initial monthly and one 8-week injections (IAI 2Q16) or administered every 8-week after five initial monthly injections (IAI 2Q8) demonstrated substantial improvement in DR severity in DR patients without DME compared to sham treatment.

5.3 Conclusion and Recommendation

Based on the totality of evidence from the PANORAMA study and the supporting data from a 24-week and a 52-week analysis of the VISTA and VIVID studies, the reviewer concludes that this application provided substantial evidence of efficacy of *intravitreal aflibercept 2.0 mg injection administered every 8-week after **five** initial monthly injections (IAI 2Q8)* for a new (broad) indication of treatment of DR (regardless of DME).

The applicant, however, requested the following aflibercept dosing regimen in the DOSAGE AND ADMINISTRATION Section of the label for the indication sought: *Intravitreal aflibercept 2.0 mg injection administered every 8-week after* (b) (4) *initial monthly injections*. The reviewer has no objection regarding the applicant proposed dosing regimen mainly because the proposed dosing regimen differs from the IAI 2Q8 dosing regimen by (b) (4) .

5.4 Labeling Recommendation

In the current submission, the applicant requested to include the new indication of treatment of DR for Eylea in the DOSAGE AND ADMINISTRATION Section of the Eylea label and to add the [redacted] of PANORAMA study in Section 14.5 of the label.

Proposed update to the DOSAGE AND ADMINISTRATION Section:

In the DOSAGE AND ADMINISTRATION Section of the approved Eylea label, the indication of DME and DR in patients with DME were presented together under the heading "*Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with Diabetic Macular Edema*". In the current submission, the applicant presented the two indications separately and proposed the following texts for the new DR indication. The texts bolded in blue were the changes proposed by the applicant to the approved label.

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~~ [redacted] followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.5)*

- *Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (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)~~ [redacted]). (2.5)*

Reviewer's Remark:

The applicant proposal to include a new (broad) indication of DR for Eylea in the DOSAGE AND ADMINISTRATION Section appear acceptable.

Proposed update to Section 14.5 "*Diabetic Retinopathy (DR)* ~~*in Patients with Diabetic Macular Edema*~~":

The applicant also requested to update Section 14.5 of the label by including [redacted] data of the PANORAMA study.

Section 14.5 of the approved label included the Week 100 DR-related efficacy data of VISTA and VIVID studies. In the current submission, the applicant requested to include [redacted] data of the PANORAMA study in Section 14.5 of the label.

PANORAMA STUDY

In the current submission, the applicant proposed to include the texts below (in blue fonts), Table 9 and Figure 12 for the primary DR-related endpoints, and Table 10 and [redacted]. The reviewer's suggested edits are shown in green fonts.

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. Most patients enrolled in the study had moderately severe NPDR (75%).

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. (b) (4)

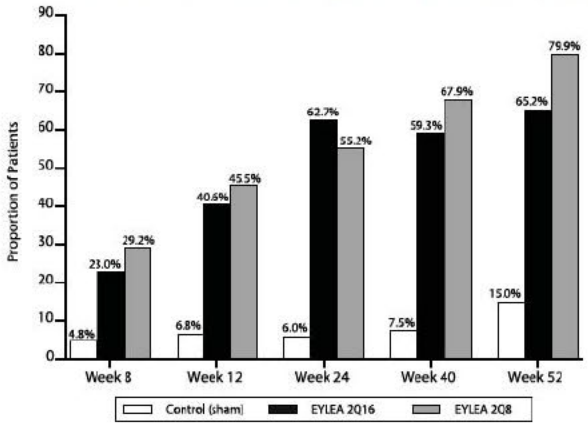
At week (b) (4), efficacy in the (b) (4) was superior to the sham group, (b) (4). The proportion of patients with a ≥2-step improvement over time is shown in Figure 12.

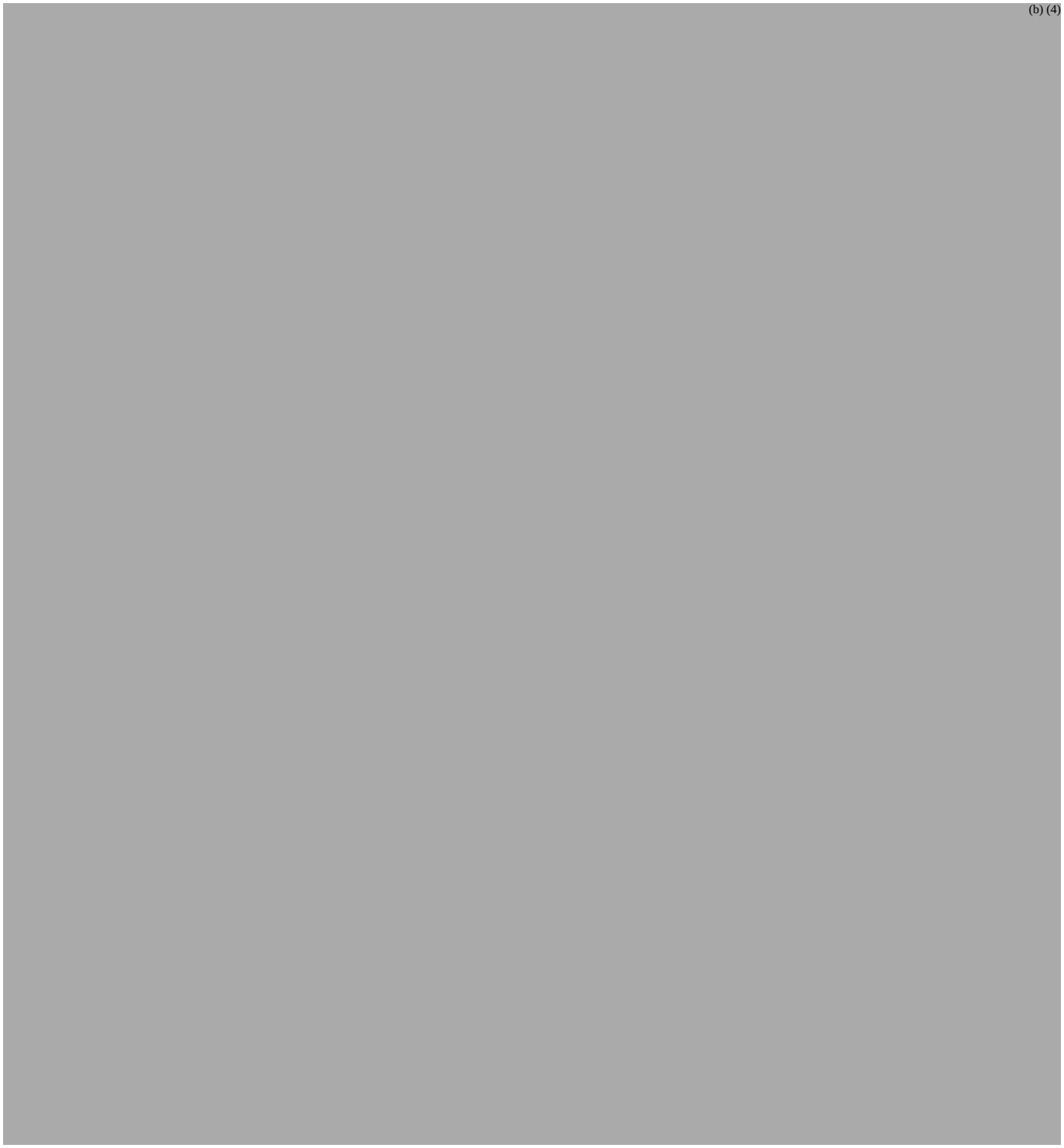
Table 9: Proportion of Patients Who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score at Weeks 24 and 52 (b) (4) in PANORAMA[24, 25]

	PANORAMA				
	Week 24		Week 52		
	EYLEA Combined	Control (sham)	EYLEA 2Q16	EYLEA 2Q8	Control (sham)
(b) (4)	N=269	N=133	N=135	N=134	N=133
Proportion of patients with a ≥2-step improvement on ETDRS-DRSS from Baseline (%)	(b) (4)				
Adjusted Difference[a] (%) (95% CI)[b]					

[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 12: Proportion of Patients Who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score Through Week 52 (b) (4) in PANORAMA[26]





Reviewer's Remark:

The reviewer agrees with the applicant's proposed texts above and the inclusion of Table 9 and Figure 12 in Section 14.5 of the label. Regarding the texts highlighted in yellow and the inclusion of Table 10 and (b) (4) *in the label, we defer to the medical review team for the relevance of the text and the table for the indication sought.*

APPENDIX:

Table 14: Summary of BCVA (letter scores) at each visit through Week 52 (FAS; LOCF)

	Sham (N = 133)			IAI 2Q16 (N = 135)			IAI 2Q8 (N = 134)			Combined IAI (N = 269)		
Visit	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range
Actual BCVA												
Baseline	82.7 (6.03)	84	68, 98	82.2 (6.63)	83	65, 96	82.3 (5.15)	83	69, 95	82.3 (5.93)	83	65, 96
Week 4	83.0 (5.46)	84	63, 96	83.5 (5.99)	84	68, 95	82.9 (5.50)	83	68, 98	83.2 (5.74)	84	68, 98
Week 8	83.0 (6.23)	84	57, 99	84.3 (6.19)	85	66, 96	83.6 (5.60)	84	67, 97	84.0 (5.90)	85	66, 97
Week 12	83.1 (5.94)	84	57, 98	84.2 (6.06)	85	65, 96	83.5 (5.76)	84	65, 96	83.9 (5.91)	85	65, 96
Week 16	83.1 (6.32)	84	57, 99	84.3 (6.26)	85	61, 97	84.0 (5.86)	84	67, 97	84.2 (6.05)	85	61, 97
Week 24	83.2 (6.26)	84	57, 98	84.1 (6.93)	85	58, 95	84.2 (5.86)	84.5	66, 97	84.2 (6.41)	85	58, 97
Week 40	83.2 (6.51)	84	57, 95	83.7 (6.72)	85	65, 98	83.2 (7.43)	84	50, 99	83.5 (7.08)	84	50, 99
Week 52	83.1 (6.66)	84	57, 98	83.9 (6.88)	85	56, 99	83.8 (7.07)	84	50, 99	83.8 (6.96)	84	50, 99
Change in BCVA from Baseline												
Week 4	0.3 (3.70)	0	-8, 15	1.3 (3.74)	1	-16, 20	0.5 (3.70)	1	-12, 14	0.9 (3.73)	1	-16, 20
Week 8	0.3 (4.80)	0	-21, 15	2.1 (3.95)	2	-6, 15	1.3 (3.97)	1	-9, 12	1.7 (3.97)	1	-9, 15
Week 12	0.4 (4.47)	0	-21, 14	2.0 (4.69)	2	-20, 19	1.2 (4.47)	1	-19, 12	1.6 (4.59)	1	-20, 19
Week 16	0.3 (4.22)	0	-21, 14	2.1 (4.78)	2	-20, 18	1.7 (4.74)	2	-13, 16	1.9 (4.76)	2	-20, 18
Week 24	0.4 (4.13)	0	-21, 15	1.9 (5.40)	2	-20, 16	1.9 (4.59)	1	-11, 16	1.9 (5.01)	2	-20, 16
Week 40	0.4 (4.51)	0	-21, 14	1.5 (4.95)	2	-20, 16	0.9 (5.82)	1	-32, 18	1.2 (5.40)	1	-32, 18
Week 52	0.3 (4.76)	1	-21, 14	1.6 (5.19)	1	-20, 17	1.5 (5.69)	2	-27, 18	1.6 (5.43)	2	-27, 18

Based on reviewer analysis.

Table 15: Proportion of subjects with incidence of new cases of PDR during the study (FAS; LOCF)

Visit	Sham	IAI 2Q16	IAI 2Q8	IAI Combined
Week 8	4/ 133 (3.0)	0/ 135 (0.0)	0/ 134 (0.0)	0/ 269 (0.0)
Difference vs Sham (98.3% CI)	--	-3.0 (-6.6, 0.6)	-3.0 (-6.6, 0.6)	-3.0 (-6.6, 0.6)
Week 12	4/ 133 (3.0)	1/ 135 (0.7)	0/ 134 (0.0)	1/ 269 (0.4)
Difference vs Sham (98.3% CI)	--	-2.3 (-6.3, 1.7)	-3.0 (-6.6, 0.6)	-2.6 (-6.3, 1.0)
Week 24	8/ 133 (6.0)	1/ 135 (0.7)	0/ 134 (0.0)	1/ 269 (0.4)
Difference vs Sham (98.3% CI)	--	-5.3 (-10.6, 0.0)	-6.0 (-11.0, -1.0)	-5.6 (-10.7, -0.6)
Week 40	15/133 (11.3)	2/135 (1.5)	1/134 (0.7)	3/269 (1.1)
Difference vs Sham (98.3% CI)		-9.8 (-16.9, -2.7)	-10.5 (-17.4, -3.7)	-10.2 (-16.9, -3.4)
Week 52	13/133 (9.8)	1/135 (0.7)	1/134 (0.7)	2/269 (0.7)
Difference vs Sham (98.3% CI)	--	-9.0 (-15.5, -2.6)	-9.0 (-15.5, -2.6)	-9.0 (-15.3, -2.7)
Through Week 24 [1]	10/ 133 (7.5)	1/ 135 (0.7)	0/ 134 (0.0)	1/ 269 (0.4)
Difference vs Sham (98.3% CI)	--	-6.8 (-12.6, -1.0)	-7.5 (-13.0, -2.0)	-7.1 (-12.7, -1.6)
Through Week 52 [2]	17/133 (12.8)	2/ 135 (1.5)	1/134 (0.7)	3/269 (1.1)
Difference vs Sham (98.3% CI)	--	-11.3 (-18.7, -3.9)	-12.0 (-19.2, -4.8)	-11.7 (-18.8, -4.5)

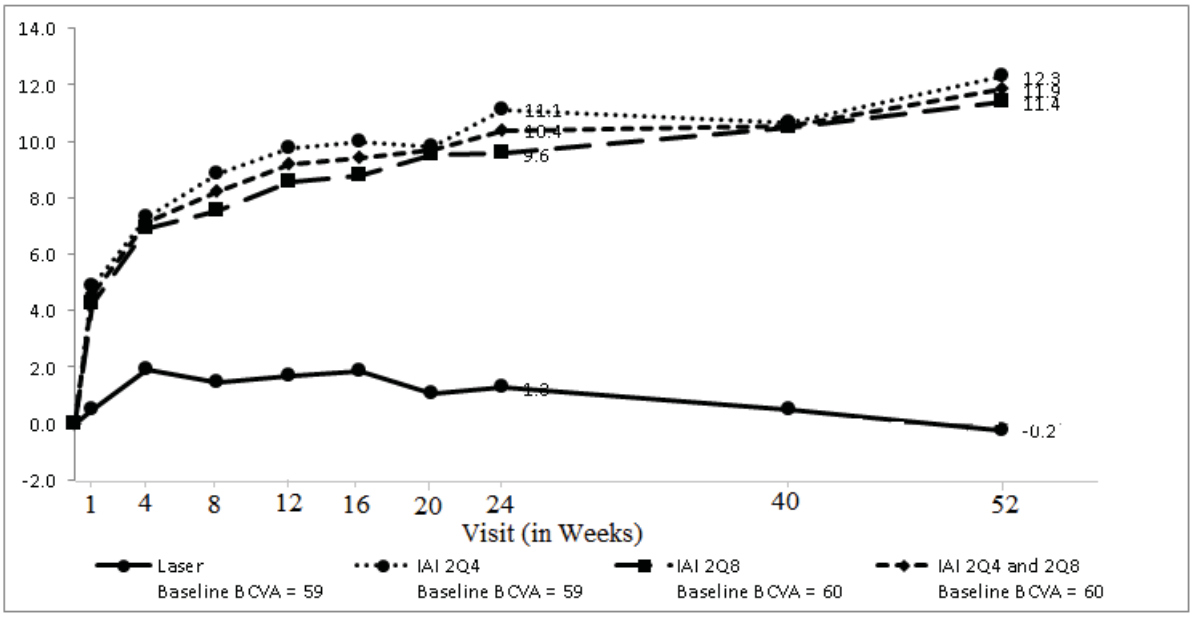
Based on reviewer analysis

[1] Summarized based on subjects who had new incidences of PDR through Week 24; that is, any new incidence at Week 8, Week 12, or Week 24.

[2] Summarized based on subjects who had new incidences of PDR through Week 52; that is, any new incidence at Week 8, 12, 24, 40, or 52.

Figure 7: Mean change in BCVA from baseline through Week 52 in VISTA and VIVID Studies (FAS; LOCF)

VISTA



VIVID

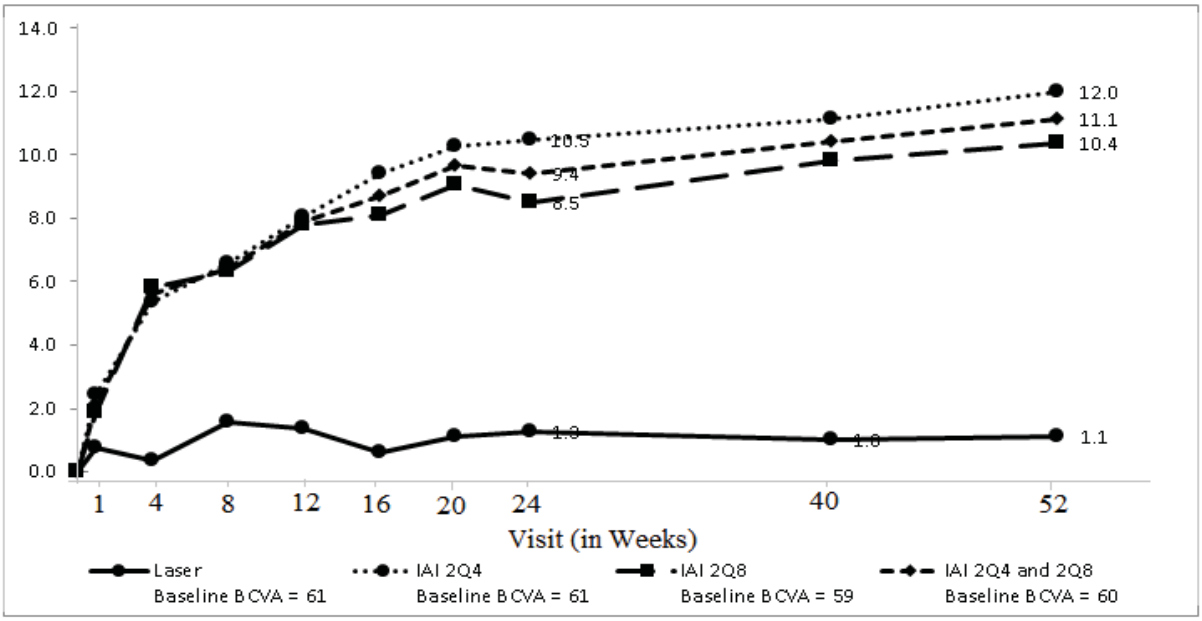


Table 16: Applicant's summary of other secondary efficacy variables at Week 52 (Extracted from the Week 52 Clinical Study report)

Table 15: Time to Development of Vision-Threatening Complications and/or Central-Involved DME Through Week 52 (Full Analysis Set)

Kaplan-Meier estimated time to develop vision-threatening complications and/or CI-DME through week 52*	Sham (N=133)	IAI 2Q16 (N=135)	IAI 2Q8 (N=134)
VTC			
Number of events	27	5	4
Number censored	106	130	130
Median	NE	NE	NE
Q1 – Q3	(371 - NE)	(NE - NE)	(NE - NE)
Estimated event rate at week 52	20.11%	4.00%	2.35
p-value[1]	-	<0.0001	<0.0001
CI-DME			
Number of events	34	9	11
Number censored	99	126	123
Median	NE	NE	NE
Q1 - Q3	(333 - NE)	(NE - NE)	(NE - NE)
Estimated event rate at week 52	27.63%	7.00%	8.46%
p-value[1]	-	<0.0001	<0.0001
Vision-threatening complications or CI-DME			
Number of events	54	13	15
Number censored	79	122	119
Median	373	NE	NE
Q1 – Q3	(169 - NE)	(NE - NE)	(NE - NE)
Estimated event rate at week 52	41.77%	10.10%	10.81%
p-value[1]	-	<0.0001	<0.0001

Abbreviations: IAI=intravitreal aflibercept injection, 2Q16=IAI 2 mg every 16 weeks after 3 initial monthly doses and one 8-week interval, 2Q8=IAI 2 mg every 8 weeks after 5 initial monthly doses, VTC=vision-threatening complication, CI-DME=central-involved diabetic macular edema, NE=not evaluable, Q1=first quartile, Q3=third quartile.

* Patients who did not have an event were censored at their last visit, at or before the week 52 visit.

1: P-values calculated using log-rank test

Source: Post-text Table 14.02.08/5a, Post-text Table 14.02.08/6a, and Post-text Table 14.02.08/4a

Table 16: Proportion of Patients with Panretinal Photocoagulation or Vitrectomy for PDR Through Week 52 (Full Analysis Set)

	Sham (N=133)	IAI 2Q16 (N=135)	IAI 2Q8 (N=134)
Patients who received PRP or vitrectomy, n (%)	9/133 (6.8%)	1/135 (0.7%)	1/134 (0.7%)
Adjusted difference (%) and 95% CI[1]	-	-6.0 (-10.5, -1.6)	-6.0 (-10.5, -1.5)
p-value[2]	-	0.0089	0.0096

Abbreviations: IAI=intravitreal aflibercept injection, 2Q16=IAI 2 mg every 16 weeks after 3 initial monthly doses and one 8-week interval, 2Q8=IAI 2 mg every 8 weeks after 5 initial monthly doses, VTC=vision-threatening complication, CI-DME=central-involved diabetic macular edema, CI=confidence interval, DRSS= Diabetic Retinopathy Severity Scale, IVRS= interactive voice response system.
The percentage was based on the number of patients with available measurements in each treatment group as denominator.
1: Difference with CI was calculated using Mantel-Haenszel weighting scheme adjusted by baseline DRSS stratification variable from IVRS.
2: P-value is calculated using 2-sided Cochran-Mantel-Haenszel (CMH) test adjusted by baseline DRSS stratification variable from IVRS.
Source: Post-text Table 14.02.08/10a

Table 17: Area Under Curve for Change from Baseline at Week 52 in BCVA, OC (Full Analysis Set)

	Sham (N=133)	IAI 2Q16 (N=135)	IAI 2Q8 (N=134)
n	133	135	134
Mean AUC (SD)	0.5 (3.01)	1.7 (3.50)	1.3 (3.49)
LS mean AUC[1] (SE)	0.5 (0.31)	1.6 (0.30)	1.2 (0.31)
Estimate for contrast and 95% CI (LS mean)[2]	-	1.14 (0.33, 1.94)	0.80 (-0.01, 1.60)
p-value[2]	-	0.0057	0.0529

Note: Only observed, non-censored values were used for analysis; measurements taken after rescue treatment was given were censored.
Abbreviations: IAI=intravitreal aflibercept injection, OC=observed case, AUC=area under the curve, CI=confidence interval, SD=standard deviation, SE=standard error, LS=least squares, ANOVA=analysis of variance, DRSS= Diabetic Retinopathy Severity Scale, IVRS= interactive voice response system.
1: AUC was calculated as a weighted average based on total AUC (using the trapezoidal rule) divided by total duration in days. For patients who did not have available measurement at week 52, AUC was calculated up to the last available measurements. AUC = 0 for patients who had no post-baseline measurements or changes from baseline were all 0 at all visits.
2: LS mean difference, CI, and p-value were based on ANOVA model with treatment group and baseline DRSS stratification variable from IVRS as fixed factors.
Source: Post-text Table 14.02.03/1a

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/s/

SOLOMON CHEFO
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YAN WANG
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I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s061

OTHER REVIEW(S)

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 27, 2018
Requesting Office or Division:	Division of Transplant and Ophthalmology (DTOP)
Application Type and Number:	BLA 125387/S-061
Product Name and Strength:	Eylea (Aflibercept) Injection, 2mg/0.05mL
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Regeneron Pharmaceuticals, Inc. (Regeneron)
FDA Received Date:	Supplement received August 24, 2018, updated PI received December 17, 2018
OSE RCM #:	2018-2596
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW

Regeneron submitted an efficacy supplement for Eylea (aflibercept) injection solution in order to add a new indication of diabetic retinopathy (DR). Subsequently, the Division of Transplant and Ophthalmology (DTOP) requested that we review the proposed prescribing information for areas that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION

Our evaluation of the proposed prescribing information did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Eylea that Regeneron submitted on December 17, 2018.

Table 4. Relevant Product Information for Eylea	
Initial Approval Date	11/18/2011
Active Ingredient	Aflibercept
Indication	EYLEA is a vascular endothelial growth factor (VEGF) inhibitor 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) in Patients with DME
Route of Administration	Intravitreal injection
Dosage Form	Injectable solution
Strength	2mg/0.05mL
Dose and Frequency	• **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. • **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)

<table>
<tr><td></td><td>

- **Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with Diabetic Macular Edema**
  - 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)

</td></tr>
<tr><td>How Supplied</td><td>

NDC NUMBER	CARTON TYPE	CARTON CONTENTS
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
61755-005-03	Vial Only	one EYLEA 2 mg/0.05 mL single-dose glass vial one package insert

</td></tr>
<tr><td>Storage</td><td>Refrigerate EYLEA at 2°C to 8ºC (36°F to 46ºF). Do Not Freeze. Do not use beyond the date stamped on the carton and container label. Store in the original carton until time of use to protect from light.</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On December 19, 2018, we searched the L:drive and AIMS using the terms, Eylea to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review[a], in which we identified concerns with the Prescribing Information (PI), container labels, and carton labeling that may lead to medication errors. We confirmed that our previous recommendations were implemented or considered.

[a] Fava, W. Label and Labeling Review for Eylea BLA 125387. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 AUG 05. RCM No.:2011-539.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Eylea labels and labeling submitted by Regeneron on December 17, 2018.

- Prescribing Information (Image not shown)

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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