CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125387Orig1s048

Trade Name:	EYLEA
Generic or Proper Name:	aflibercept injection
Sponsor:	Regeneron Pharmaceuticals, Inc.
Approval Date:	March 25, 2015
Indication:	EYLEA is indicated for the treatment of patients with: ● Neovascular (Wet) Age-Related Macular Degeneration (AMD) ● Macular Edema Following Retinal Vein Occlusion (RVO) ● Diabetic Macular Edema (DME) ● Diabetic Retinopathy (DR) in Patients with DME

CENTER FOR DRUG EVALUATION AND RESEARCH

125387Orig1s048

CONTENTS

Reviews / Information Included in this NDA Review.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s048

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125387/48

SUPPLEMENT APPROVAL

Regeneron Pharmaceuticals, Inc.
Attention: Jennifer Woo, Ph.D., PPM, RAC
Associate Manager, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Dr. Woo:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received September 30, 2014, submitted under section 351(a) of the Public Health Service Act for Eylea (aflibercept) Injection. We acknowledge receipt of your amendments dated October 20, 2014, January 29, February 10, and March 4, 19, and 23, 2015.

This Prior Approval supplemental biologics application provides for the use of Eylea (aflibercept) Injection, for the treatment of Diabetic Retinopathy (DR) in patients with Diabetic Macular Edema (DME).

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 March 23, 2015.

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 package insert labeling 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 includes 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, 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for this application since studies are impossible or highly impracticable because Diabetic Macular Edema rarely occurs in the pediatric population.

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 package insert(s) to:

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

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), 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 Antimicrobial 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 and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
03/25/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s048

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 Injection
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

- Indications and Usage, Macular Edema Following Retinal Vein Occlusion (RVO) (1.2) 10/2014
- Indications and Usage, Diabetic Macular Edema (DME) (1.3) 7/2014
- Indications and Usage, Diabetic Retinopathy (DR) in Patients with DME (1.4) 3/2015
- Dosage and Administration, Macular Edema Following Retinal Vein Occlusion (RVO) (2.3) 10/2014
- Dosage and Administration, Diabetic Macular Edema (DME) (2.4) 7/2014
- Dosage and Administration, Diabetic Retinopathy (DR) in Patients with DME (2.5) 3/2015
- Warnings and Precautions, Thromboembolic Events (5.3) 10/2014

INDICATIONS AND USAGE

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

Macular Edema Following Retinal Vein Occlusion (RVO)
- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly). (2.3)

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 (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 (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks. (2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment. (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: 3/2015

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) in Patients with DME

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions

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

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

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

2.3 Macular Edema Following 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 (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 (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 (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.4)*].

2.5 Diabetic Retinopathy (DR) in Patients with DME

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 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 (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.5)*].

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.

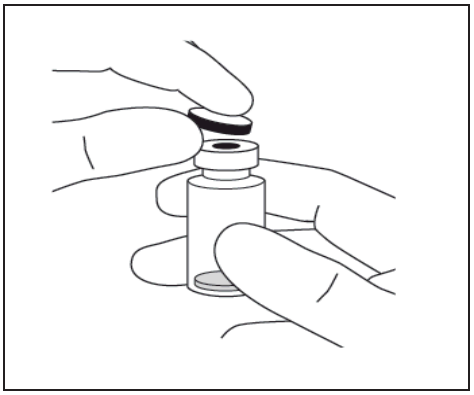
Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle.

Vial

The glass vial is for single use only.

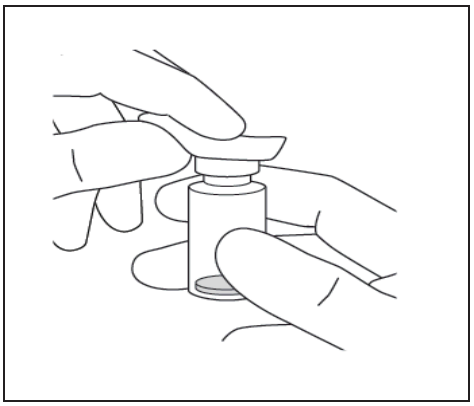
1. Remove the protective plastic cap from the vial (see Figure 1).

Figure 1:



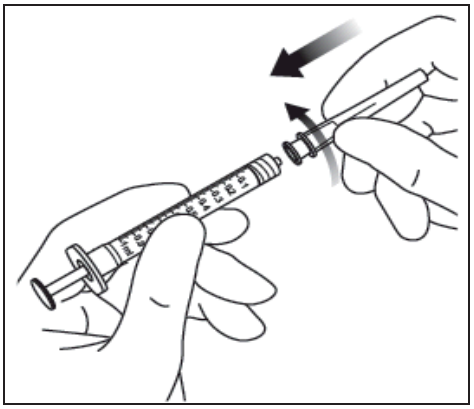
2. Clean the top of the vial with an alcohol wipe (see Figure 2).

Figure 2:



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

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:

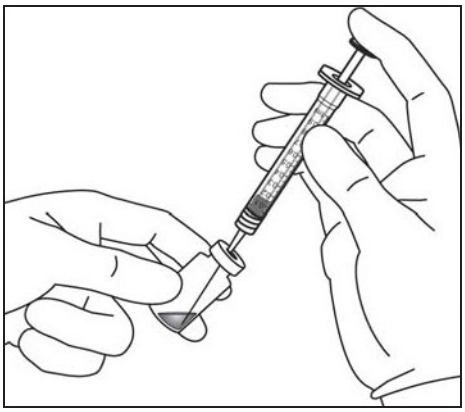
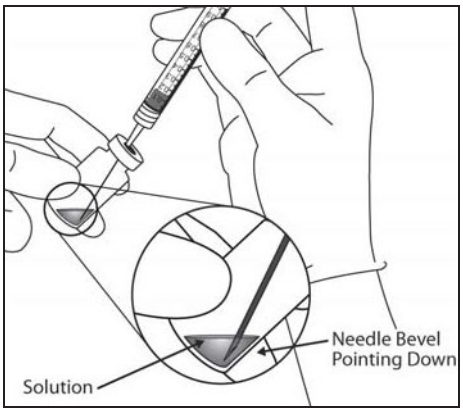


Figure 4b:

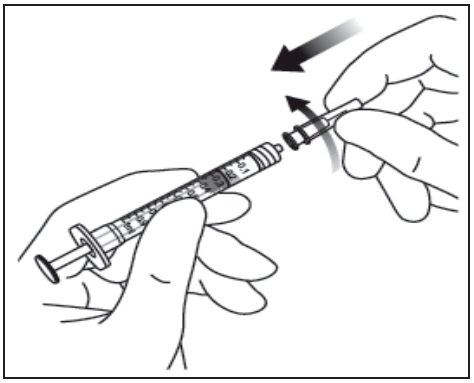


6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.

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 the plastic pouch and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 5).

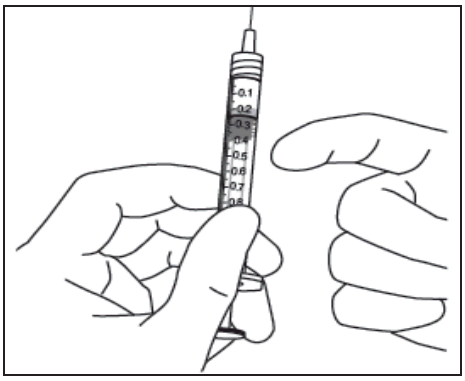
Figure 5:



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

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

Figure 6:



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

Figure 7a:

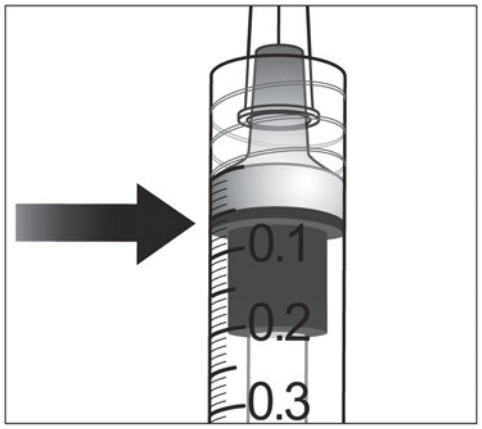
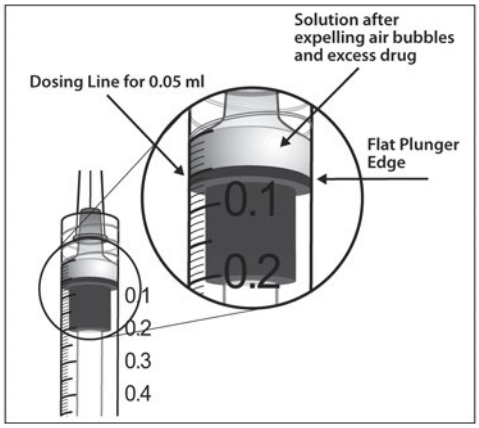


Figure 7b:



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

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) 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 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. 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 adverse reactions are discussed in greater detail in the *Warnings and Precautions (5)* section of the labeling:

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

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 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 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 floaters, intraocular pressure increased, and vitreous detachment.

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

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

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

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

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, 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 CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following 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)

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.

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

Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal 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 less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

In the clinical studies, approximately 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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

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

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

Macular Edema Following 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) 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, 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). Patient ages ranged from 49 to 99 years with a mean of 76 years.

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

Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in Table 4 and Figure 8 below.

Table 4: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies

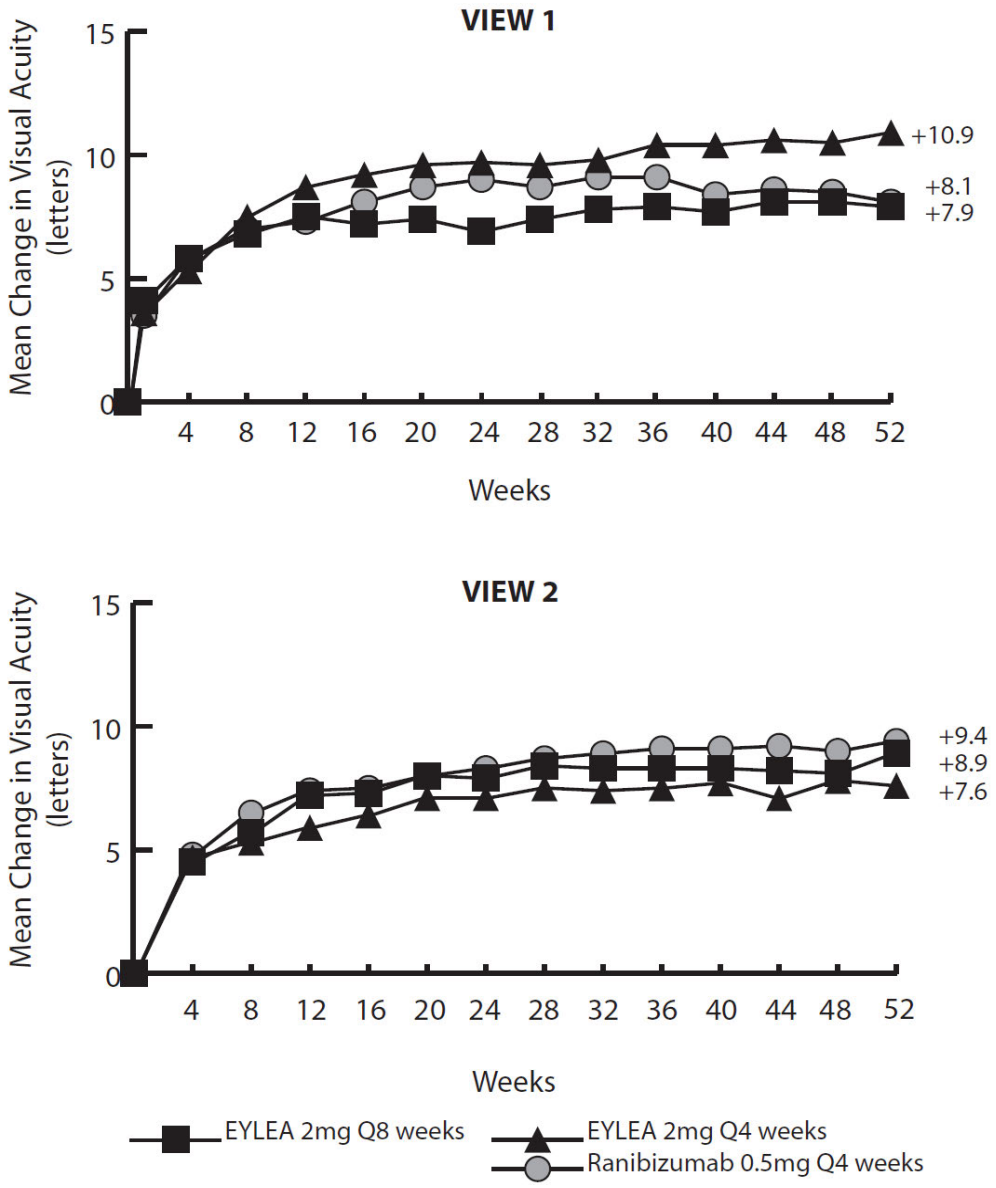
	VIEW1			VIEW2		
	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks	EYLEA 2 mg Q8 weeks [a]	EYLEA 2 mg Q4 weeks	ranibizumab 0.5 mg Q4 weeks
Full Analysis Set	N=301	N=304	N=304	N=306	N=309	N=291
Efficacy Outcomes						
Proportion of patients who maintained visual acuity (%) (<15 letters 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

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



14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

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

(COPERNICUS and GALILEO). In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4), or sham injections (control group) administered every 4 weeks for a total of 6 injections. Patient ages ranged from 22 to 89 years with a mean of 64 years.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the EYLEA 2 mg Q4 group was superior to the control group for the primary endpoint.

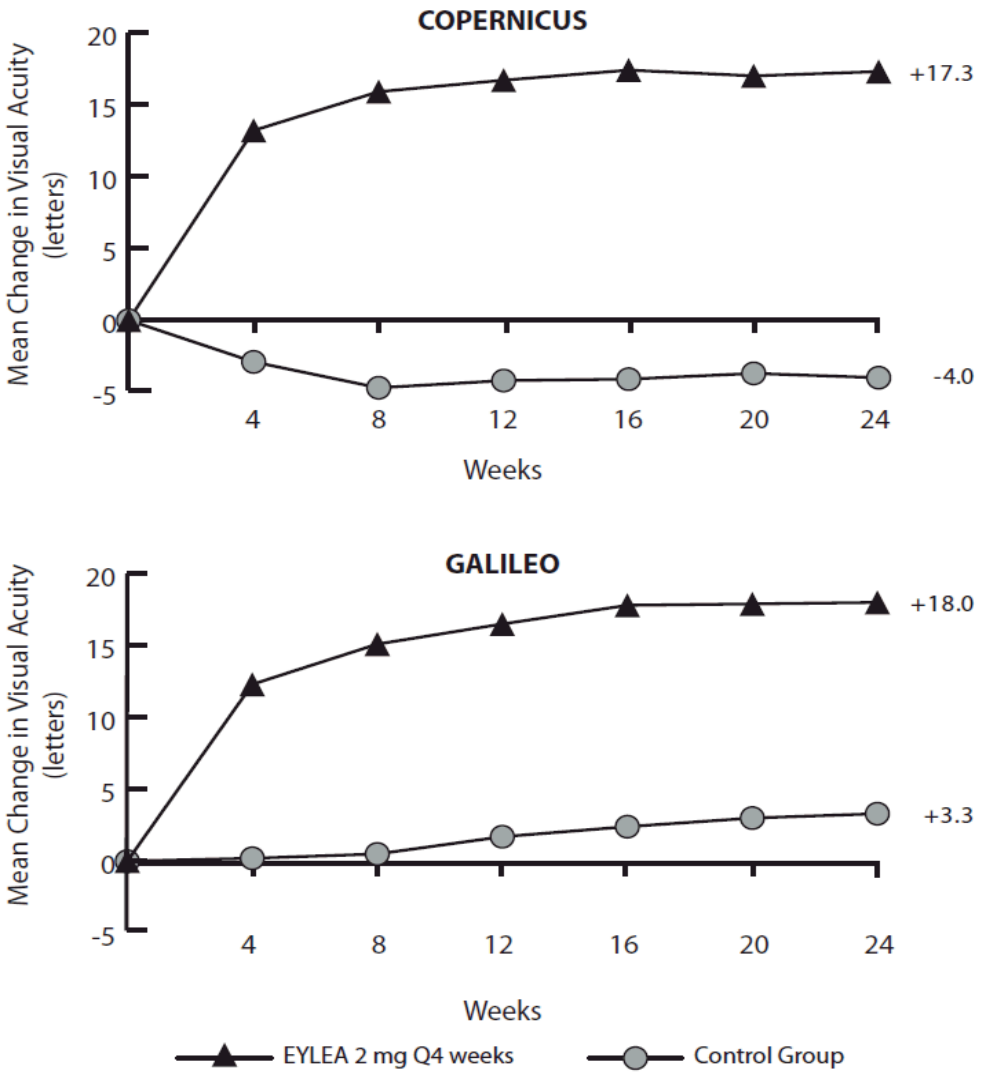
Results from the analysis of the COPERNICUS and GALILEO studies are shown in Table 5 and Figure 9 below.

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). 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.

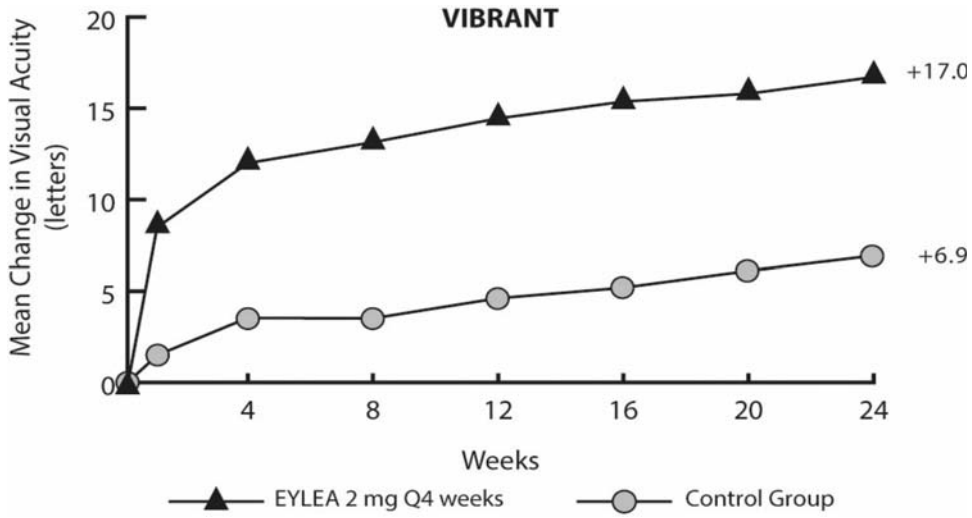
Detailed results from the analysis of the VIBRANT study are shown in Table 6 and Figure 10 below.

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. 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.

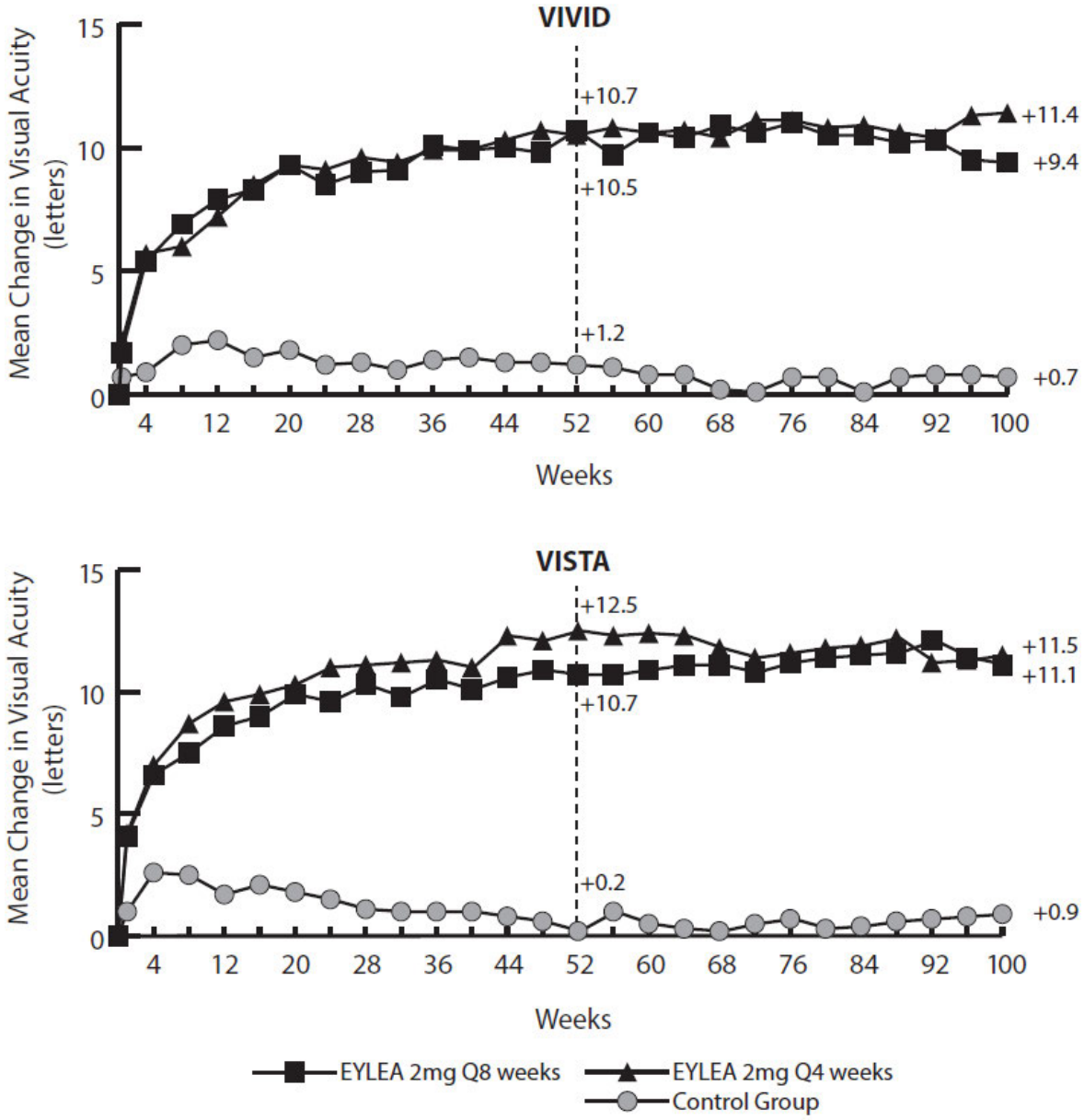
Results from the analysis of the VIVID and VISTA studies are shown in Table 7 and Figure 11 below.

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) in Patients with DME

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 (LOCF[a]) in VIVID and VISTA Studies

	VIVID			VISTA		
	EYLEA 2 mg Q8 weeks[b]	EYLEA 2 mg Q4 weeks	Control	EYLEA 2 mg Q8 weeks[b]	EYLEA 2 mg Q4 weeks	Control
Evaluable Patients[c]	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[d,e](%) (97.5% CI)	24%[f] (12, 36)	21%[f] (9, 33)		22%[f] (11, 33)	22%[f] (11, 33)	

[a] 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)
[b] After treatment initiation with 5 monthly injections
[c] The number of evaluable patients included all patients who had valid ETDRS-DRSS data at baseline
[d] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors
[e] Difference is EYLEA minus Control group
[f] $p<0.01$ 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.

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	one single-use, sterile, 3-mL, glass vial designed to deliver 0.05 mL of 40 mg/mL EYLEA 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

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

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, 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.

Issue Date: March 2015

Initial U.S. Approval: 2011

Regeneron U.S. Patents 7,070,959; 7,303,746; 7,303,747; 7,306,799; 7,374,757; 7,374,758; 7,531,173; 7,608,261; 7,972,598; 8,029,791; 8,092,803; 8,647,842; and other pending patents.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s048

SUMMARY REVIEW

Summary Review for BLA 125387/ S-048

Date	March 25, 2015
From	Wiley A. Chambers, M.D.
BLA #	BLA 125387/ S-048
Applicant	Regeneron Pharmaceuticals, Inc.
Date of Submission	September 30, 2014
Type of Application	BLA efficacy supplement
Name	Eylea (aflibercept) Injection
Dosage forms / Strength	40 mg/mL solution for intravitreal injection
Proposed Indication(s)	Treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME)
Action:	Approval

1. Introduction/Background

Aflibercept is a recombinant protein consisting of specific domains of the human VEGF receptors, VEGF-R1 and VEGF-R2, fused to a human IgG1 Fc. Manufacture of aflibercept involves (b) (4) (b) (4) recombinant Chinese Hamster Ovary cells and (b) (4) (b) (4) Aflibercept was approved in November 2011 for the treatment of neovascular (wet) AMD, in September 2012 for the treatment of macular edema secondary to central retinal vein occlusion (S-004), in July 2014 for the treatment of Diabetic Macular Edema (S-037), and in October 2014 for the treatment of macular edema secondary to BRVO (S-043).

This submission contains additional analyses of data from Studies VGFT-OD-1009 (Vista) and Study 91745 (Vivid) originally submitted in S-037. The two randomized, double-masked, sham-controlled Phase 3 studies [Study VGFT-09-1009 (VISTA, conducted in United States) and Study 91475 (VIVID, conducted in Europe, Japan, and Australia)] assessed the benefit of aflibercept compared with sham treatment in subjects with DME. Sham treatment received focal laser treatment at the start of the study.

In this efficacy supplement (S-048), Eylea (aflibercept) Injection is proposed for the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME). There are no proposed Chemistry/Manufacturing changes for this product or to the carton and container labeling in this supplemental application.

2. CMC

There are no proposed Chemistry/Manufacturing changes for this product or to the carton and container labeling in this supplemental application.

3. Nonclinical Pharmacology/Toxicology

No new Pharm/Tox studies were performed for this efficacy supplement. The Pharmacology/Toxicology aspects of aflibercept were reviewed as part of the initial approved marketing application for treatment of subjects with neovascular (wet) AMD.

4. Clinical/Statistical - Efficacy

For studies VGFT-OD-1009/VISTA and Study 91745/VIVID: The primary endpoint in the studies was the change in BCVA by ETDRS letter score from baseline to week 52 (visit 15). These 52 week results were reported previously. There was both a United States Statistical Analysis Plan (SAP) and a Global SAP. To evaluate persistence of effect, change from baseline in BCVA at week 100 was analyzed in the same method as for week 52 and was considered a secondary endpoint under the United States SAP at week 100. Under the global SAP, all secondary endpoints defined for week 52 were considered exploratory at week 100. Of these endpoints, all were considered secondary at week 100 under the United States SAP.

The following endpoints were hierchical secondary endpoints only in US SAP and exploratory in Global SAP:
2. Change in BCVA by ETDRS letter score from baseline to week 100
3. Proportion of subjects who gained ≥10 ETDRS letters from baseline to week 100
4. Proportion of subjects who gained ≥15 ETDRS letters from baseline to week 100
5. Proportion of subjects who achieved a ≥2-step improvement on the ETDRS DRSS from baseline to week 100
6. Change in CRT from baseline to week 100, as assessed on OCT
7. NEI VFQ-25 near activities subscale change from baseline to week 100
8. NEI VFQ-25 distance activities subscale change from baseline to week 100

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

Secondary Endpoints(s)

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

	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 the 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, as assessed by OCT	-105 (-140, -70)	<0.0001	-111 (-143, -79)	<0.0001
NEI VFQ-25 near activities subscale from baseline to week 100	4.59 (-0.73, 9.90)	0.0529	5.05 (0.12, 9.98)	0.0218
NEI VFQ-25 distance activities subscale change from baseline to week 100	5.80 (0.97, 10.64)	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. Sham

	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	33.1 (20.3, 45.9)	<0.0001	24.6 (11.9, 37.3)	<0.0001
Proportion of subjects (%) who gained >= 15 ETDRS letter from baseline to week 100	26.1 (14.8, 37.5)	<0.0001	19.0 (8.0, 29.9)	0.0001
Proportion of subjects (%)who achieved a >=2 step improvement on the ETDRS DRSS from 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, as assessed by OCT	-154 (-189, -120)	<0.0001	-127 (-165, -89)	<0.0001
NEI VFQ-25 near activities subscale from baseline to week 100	3.64 (-0.70, 7.98)	0.0596	-0.74 (-5.25, 3.78)	0.7144
NEI VFQ-25 distance activities subscale change from baseline to week 100	2.57 (-1.73, 6.86)	0.1792	-1.30 (-6.00, 3.39)	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* (16.0%)	58/153* (37.9%)	56/148* (37.8%)
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* (7.1%)	27/97* (27.8%)	32/101* (31.7%)
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 (9.7%)	43/108 (39.8%)	40/99 (40.4%)
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.

A two-step change on the DRSS in one eye was considered a clinically meaningful endpoint. Both aflibercept studies (Vista and Vivid) achieved this two-step change with statistical significance.

Vista: Proportion of Patients with a 3 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 >=3 step improvement from baseline	8 (5.2%)	35 (22.7%)	30 (19.9)
Difference (%) vs. Laser		17.8	14.6
97.5% CI for difference		(9.2, 26.4)	(6.3, 23.0)
P-value		<0.0001	0.0001

Vivid: Proportion of Patients with a 3 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 >=3 step improvement from baseline	0	6(7.3%)	2 (2.3%)
Difference (%) vs. Laser		7.3	2.3
97.5% CI for difference		(0.8, 13.9)	(-1.4, 6.0)
P-value		0.0118	0.1573

Only the 2Q4 dosing regimen demonstrated a 3 step improvement in the DRSS in both trials.

Summary Statement
There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Eylea (aflibercept) Injection is statistically superior to sham injection in the in the mean change in BCVA (as measured by ETDRS score) at week 52. At week 100, the proportion of patients improving by at least 2 steps on the ETDRS Retinopathy Score was significantly greater in both Eylea treatment groups (2Q4 and 2Q8) when compared to the control group.

5. Safety

The main support for safety comes from studies supporting the approval of the AMD and CRVO indications and the two clinical studies (VISTA and VIVID). Two year follow-up data was supplied in this supplement. There were no significant new safety findings between year 1 and year 2.

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

6. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

7. Pediatrics

This drug was not tested on a pediatric population. DME does not occur in pediatric patients except in very rare circumstances. This supplemental application and its BPCA/Pediatric Study Plan (IND 100083) were presented at PeRC on December 11, 2013. PeRC concurred with a full waiver of pediatric studies (PREA). The safety and effectiveness of Eylea (aflibercept) Injection in pediatric patients have not been established.

PeRC concurred with the full waiver of pediatric studies on February 4, 2015, for the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME) indication.

8. Other Relevant Regulatory Issues

OSI

An Office of Scientific Investigations (OSI) audit was requested; OSI completed their review on 5/7/14 for the diabetic macular edema indication. No new inspections were requested for this new supplemental application.

FINANCIAL DISCLOSURE

Financial disclosure has not been updated since the DME supplement S-037. Regeneron provided adequate financial disclosure information for Studies VISTA and VIVID during the review of S-037.

BIOSTATISTICS

The Statistical Review was completed for this submission. The Statistical Reviewer recommended approval of the indication for the treatment of Diabetic Retinopathy in patients with Diabetic Macular Edema. The Review recommends inclusion in the labeling of the Proportion of Patients who Achieved Improvement or Worsening in the DRSS Score at Week 100 (Full Analysis Set, LOCF). The labeling will not include tables describing the proportion of patients who did not have a worsening of their retinopathy because the prevention of worsening of diabetic retinopathy is considered a different claim than the improvement or treatment of diabetic retinopathy. A prevention claim was not requested by the applicant and is not supported by the application. The potential inclusion of a table of three line improvement was discussed with the applicant. The applicant has chosen not to include a table of three line improvement because a three line improvement was not a prespecified secondary endpoint.

OPDP

A review of the substantially complete labeling was completed by the Office of Prescription Drug Promotion (OPDP) on 3/13/15. OPDP has reviewed the proposed PI and has no comments at this time.

Regulatory Briefing

This supplemental application was presented at a CDER Regulatory Briefing on January 23, 2015. The group was asked their opinion of the evidence of efficacy for the treatment of DR in patients with DME; they were specifically asked if they recommended including a new indication in the Indications and Usage section of the label, “treatment of DR in patients with DME” and describing the efficacy results in the Clinical Studies section of the labeling. There was a unanimous recommendatoin that the new indication be included. The group did not agree with expanding the indication to all patients with diabetic retinopathy.

9. Labeling

BLA 125387/ S-048 Eylea (aflibercept) Injection with the labeling submitted by Regeneron Pharmaceuticals and attached at the end of this review on March 23, 2015 is recommended for approval.

10. Recommendations/Risk Benefit Assessment

REGULATORY ACTION:
BLA 125387/S-048 Eylea (aflibercept) Injection will be approved for the treatment treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME).

RISK BENEFIT ASSESSMENT:
There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Eylea (aflibercept) Injection is statistically superior to sham injection in the proportion of patients improving by at least 2 steps on the ETDRS-RSS. Both Eylea treatment groups (2Q4 and 2Q8) when compared to the control group were superior.

There is substantial evidence consisting of adequate and well controlled studies which demonstrate that Eylea (aflibercept) Injection is safe when administered 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 4 weeks (1 month) or every 8 weeks (2 months).

The benefits of using this drug product outweigh the risks for the above indication.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

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

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
03/25/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s048

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: BLA 125387/48

The following officers or employees of FDA participated in the decision to approve this supplemental application and consented to be identified on this list:

Boyd, William
Wadhwa, Sonal
Puglisi, Michael
Chefo, Solomon
Wang, Yan
Zhang, Yongheng

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s048

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review for BLA 125387/ S-048

Date	March 23, 2015
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #	BLA 125387/ S-048
Applicant	Regeneron Pharmaceuticals, Inc.
Date of Submission	September 30, 2014
PDUFA Goal Date	March 30, 2015
Type of Application	BLA efficacy supplement
Name	Eylea (aflibercept) Injection
Dosage forms / Strength	40 mg/mL solution for intravitreal injection
Proposed Indication(s)	Treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME)
Recommended:	Recommended for Approval

1. Introduction

Throughout the review, Eylea Injection may also be referred to as Eylea, aflibercept, VEGF Trap, or VEGF Trap-Eye.

Aflibercept is a recombinant protein consisting of specific domains of the human VEGF receptors, VEGF-R1 and VEGF-R2, fused to a human IgG1 Fc. Manufacture of VEGF Trap involves (b) (4) (b) (4) recombinant Chinese Hamster Ovary cells and (b) (4) (b) (4)

Aflibercept is an approved product in the US. It was approved in November 2011 for the treatment of neovascular (wet) AMD. It was also approved in September 2012 for the treatment of macular edema secondary to central retinal vein occlusion (S-004), in July 2014 for the treatment of Diabetic Macular Edema (S-037), and in October 2014 for the treatment of macular edema secondary to BRVO (S-043)

This submission contains additional analyses of data from Studies VGFT-OD-1009 (Vista) and Study 91745 (Vivid) originally submitted in S-037. Two randomized, double-masked, sham-controlled Phase 3 studies [Study VGFT-09-1009 (VISTA, conducted in United States) and Study 91475 (VIVID, conducted in Europe, Japan, and Australia)] assessed the benefit of VEGF Trap-Eye treatment administered by intravitreal injection compared with sham treatment in subjects with DME. Sham treatment received focal laser treatment at the start of the study.

2. Background

This is a BLA supplemental application.

In this efficacy supplement (S-048), Eylea (aflibercept) Injection is proposed for the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME). There are no proposed Chemistry/Manufacturing changes for this product or to the carton and container labeling in this supplemental application.

The following meetings were held regarding this supplemental application and the DME indication:

7/14/14	Submission to IND 100,083 to request breakthrough therapy
8/21/14	T-con to discuss breakthrough therapy request
9/5/14	Breakthrough therapy granted
9/5/14-9/9/14	Email correspondence regarding table of contents, waiver to update the financial disclosure, and updated summary level clinical site data set not required

3. CMC

There are no proposed Chemistry/Manufacturing changes for this product or to the carton and container labeling in this supplemental application.

Eylea (aflibercept) Injection was supplied by Regeneron and was administered by intravitreal injection using standard ophthalmic techniques. It was supplied in sealed, sterile 3 mL single-use vials with a "withdrawable" volume of approximately 0.5 mL. Sham injections using a syringe without a needle, were performed with no active drug and without intraocular penetration.

4. Nonclinical Pharmacology/Toxicology

No new Pharm/Tox studies were performed for this efficacy supplement. The Pharmacology/Toxicology aspects of aflibercept were reviewed as part of the initial approved marketing application for treatment of subjects with neovascular (wet) AMD.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 5/13/2014:

In this efficacy supplement (S-037), the Applicant submitted the following clinical study reports to support a new indication for the treatment of DME:

- Two exploratory studies (a Phase 1 safety study [VGFT-OD-0512] and a Phase 2 dose finding study [VGFT-OD-0706/Study 13336]).
- Two 3-year, randomized, double-masked, active-controlled, multi-center, Phase 3 studies (VGFT-OD-1009/VISTA DME and Study 91745/VIVID DME). In VIVID DME, a total of 404 subjects were enrolled and treated in European countries, Australia, and Japan. In VISTA DME, a total of 461 subjects were enrolled and treated in the US. Both Phase 3 studies are ongoing (to week 148).The primary efficacy endpoint in both studies was the change in ETDRS letter score from baseline to week 52.
- PK information was obtained in Phase 1 Study VGFT-OD-0307 (IV administration; sparse sampling), Phase 1 Study VGFT-OD-0512 (sparse sampling), Phase 2 PK substudy VEGF-OD-0706. PK (dense sampling), and Phase 3 Study VIVID DME (sparse sampling), which provided PK data up to Week 52.

A comparison of free and bound aflibercept systemic exposure following a 2 mg IVT administration of aflibercept in patients with DME with that reported in patients with neovascular AMD and CRVO is shown in Table 1 below. The numerical differences in the mean Cmax and AUC estimates between these different groups of patients are not deemed to be of any significant clinical relevance following IVT administration of aflibercept in patients with DME.

Table 1: Summary of PK parameters for free aflibercept (i.e., free VEGF Trap) and bound aflibercept:VEGF (i.e., Adjusted bound VEGF Trap) in DME patients (VGFT-OD-0706.PK), CRVO patients (GALILEO Study 14130) and AMD patients (Study VGFT-OD-0702.PK). *Source: Section 2.7.2 (BLA 125387/037)*

			Arithmetic[a] Mean[b]		Geometric[c] Mean		Median	
Study	N	IVT Dose (mg)	C_{max} µg/mL (CV%) (range)	AUC_{0-last}[d] µg•day/mL (CV%) (range)	C_{max} µg/mL (CV%) (range)	AUC_{0-last} µg•day/mL (CV%) (range)	t_{max} day (range)	t_{last} day (range)
Free VEGF Trap								
VGFT-OD-0706.PK DME	6-8	2	0.0320 (79.7) (0-0.0760)	0.0733 (85.0) (0-0.165)	ND	ND	0.625 (0.326-2.06)	3.55 (0.974-7.03)
VGFT-OD-0702.PK AMD	6	2	0.0193 (118) (0-0.0540)	0.119 (159) (0-0.474)	ND	ND	0.964 (0.253-3.07)	7.03 (1.95-14.1)
GALILEO (14130)[e] CRVO	7	2	0.049 (39.25) (0.024-0.081)	0.133 (51.25) (0.071-0.227)	0.046 (42.5) (0.024-0.081)	0.119 (54.3) (0.071-0.227)	0.95 (0.33-3.0)	4.01 (2.95-6.95)
Adjusted Bound VEGF Trap								
VGFT-OD-0706.PK DME	7-8	2	0.0850 (59.3) (0-0.182)	1.96 (65.1) (0-4.61)	ND	ND	13.9 (7.04-28.0)	28.0 (27.9-28.1)
VGFT-OD-0702.PK AMD	6	2	0.186 (40.3) (0.100-0.286)	4.43 (42.3) (2.12-6.71)	ND	ND	14.5 (14.0-28.0)	28.0 (28.0-29.0)
GALILEO (14130)[e] CRVO	8	2	0.0862 (25.61) (0.0427-0.108)	1.82 (30.0) (0.700-2.34)	0.083 (31.46) (0.043-0.108)	1.72 (41.59) (0.700-2.34)	14.0 (7-14)	28.5 (23.9-31.0)

NOTE: The free VEGF Trap concentrations were determined using the PPS in GALILEO (14130)

AUC_{0-last} = area under the concentration-time curve from time zero to the last validated measurable plasma concentration, BLQ = Below the limit of quantitation; C_{max} = maximal observed concentration, CV = coefficient of variation, IVT = Intravitreal; LLOQ = Lower limit of quantitation; t_{last} = time of last concentration; N=number; ND = not determined; t_{max} = time of maximal concentration.

[a] Arithmetic means (N ranging between 6 and 8) were calculated using zero for concentrations that were BLQ (i.e. <LLOQ; LLOQ=0.00156 µg/mL). All valid concentration values were used for the arithmetic means calculation.

[b] Values presented were not corrected for preexisting baseline levels of adjusted bound VEGF Trap that resulted from previous study-related administration of VEGF Trap-Eye (VGFT-OD-0702.PK, VGFT-OD-0706.PK).

[c] Geometric means (N = 7 of 9 subjects the PK sub-study analysis) were calculated in the GALILEO (14130) study by using ½ LLOQ values (LLOQ/2) for concentration values that were BLQ. Geometric mean values were only calculated if at least two-thirds of all concentration values for the respective time point were valid and ≥LLOQ.

[d] AUC0-last values presented as ng•hour/mL in GALILEO (14130) study report. The values converted to mg•day/L are presented in this table.

[e] PK parameters after the 1st dose (week 0) are presented.

6. Sterility Assurance

The product is sterile. There are no proposed Chemistry/Manufacturing changes for this product or to the carton and container labeling in this supplemental application.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 3/9/15:

Regarding VGFT-OD-1009/VISTA DME and Study 91745/VIVID DME:

The full analysis set (FAS) included all randomized subjects who received any investigational product, had a baseline efficacy assessment and at least 1 post-baseline assessment; it was based on the treatment allocated (as randomized). The FAS was the primary efficacy analysis set.

The per protocol set (PPS) included all subjects in the FAS who received at least 5 injections of study drug or sham, with the exception of subjects excluded due to major protocol violations, where a major protocol violation was one that could have affected the interpretation of study results. Major protocol violations were defined by Regeneron prior to database lock. The PPS was used for the efficacy analysis.

The safety analysis set (SAF) included all randomized subjects who received any investigational product; it was based on the treatment received (as treated). For the safety analysis set, a maximum of 1 incorrect injection was allowed.

The primary endpoint in the studies was the change in BCVA by ETDRS letter score from baseline to week 52 (visit 15). These 52 week results were reported previously.

There was both a United States Statistical Analysis Plan (SAP) and a Global SAP. To evaluate persistence of effect, change from baseline in BCVA at week 100 was analyzed in the same method as for week 52 and was considered a secondary endpoint under the United States SAP at week 100. Under the global SAP, all secondary endpoints defined for week 52 were considered exploratory at week 100. Of these endpoints, all were considered secondary at week 100 under the United States SAP.

The following endpoints were hierchical secondary endpoints only in US SAP and exploratory in Global SAP:
2. Change in BCVA by ETDRS letter score from baseline to week 100
3. Proportion of subjects who gained ≥10 ETDRS letters from baseline to week 100
4. Proportion of subjects who gained ≥15 ETDRS letters from baseline to week 100
5. Proportion of subjects who achieved a ≥2-step improvement on the ETDRS DRSS from baseline to week 100
6. Change in CRT from baseline to week 100, as assessed on OCT
7. NEI VFQ-25 near activities subscale change from baseline to week 100
8. NEI VFQ-25 distance activities subscale change from baseline to week 100

The following additional endpoints were analyzed at week 100 as exploratory in both the global and United States SAPs:

- Proportion of subjects who gained ≥0 and ≥5 ETDRS letters from baseline
- Proportion of subjects who lost ≥5, ≥10, and ≥15 ETDRS letters from baseline
- Time to first gain of ≥15 ETDRS letters from baseline
- Time to first confirmed gain of ≥15 ETDRS letters from baseline
- Proportion of subjects with a ≥2-step worsening from baseline in the DRSS score as assessed on FP

- Proportion of subjects with a ≥3-step improvement from baseline in the DRSS score as assessed on FP
- Proportion of subjects with a ≥3-step worsening from baseline in the DRSS score as assessed on FP
- Change from baseline in the NEI VFQ-25 total score and subscales over time

According to the global SAP, statistical hypotheses were not formally tested for the efficacy endpoints at week 100. According to the United States SAP, statistical comparisons between each of the VEGF Trap-Eye groups and the laser group were made for the secondary efficacy as listed above.

Description of the EDTRS-DRSS scale:

Only one eye was assessed for a 2 step improvement on the DRSS scale. A 2 step improvement in one eye is considered clinically significant.

Table 2: Steps for EDTRS diabetic retinopathy severity score

Severity Level (used to determine step change in DRSS)	Combined DR severity levels	Combined DR severity levels (as text)
1	10 and 12	DR absent
2	14, 15, 20	DR questionable, microaneurysms only
3	35	Mild NPDR
4	43	Moderate NPDR
5	47	Moderately severe NPDR
6	53	Severe NPDR
7	60, 61	Mild PDR
8	65	Moderate PDR
9	71	High-risk PDR
10	75	High-risk PDR
90	90	Cannot grade

DR: Diabetic Retinopathy; NPDR: Nonproliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy;
Note: Subjects with active PDR were not included in both studies

Analyses of Primary Endpoints

Study VISTA (VGFT-OD-1009) and Study Vivid (91475)

Analysis of Primary Endpoint(s)

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

Analysis of Secondary Endpoints(s)

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 the 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, as assessed by OCT	-105 (-140, -70)	<0.0001	-111 (-143, -79)	<0.0001
NEI VFQ-25 near activities subscale from baseline to week 100	4.59 (-0.73, 9.90)	0.0529	5.05 (0.12, 9.98)	0.0218
NEI VFQ-25 distance activities subscale change from baseline to week 100	5.80 (0.97, 10.64)	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	33.1 (20.3, 45.9)	<0.0001	24.6 (11.9, 37.3)	<0.0001
Proportion of subjects (%) who gained >= 15 ETDRS letter from baseline to week 100	26.1 (14.8, 37.5)	<0.0001	19.0 (8.0, 29.9)	0.0001
Proportion of subjects (%)who achieved a >=2 step improvement on the ETDRS DRSS from 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, as assessed by OCT	-154 (-189, -120)	<0.0001	-127 (-165, -89)	<0.0001
NEI VFQ-25 near activities subscale from baseline to week 100	3.64 (-0.70, 7.98)	0.0596	-0.74 (-5.25, 3.78)	0.7144
NEI VFQ-25 distance activities subscale change from baseline to week 100	2.57 (-1.73, 6.86)	0.1792	-1.30 (-6.00, 3.39)	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* (16.0%)	58/153* (37.9%)	56/148* (37.8%)
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* (7.1%)	27/97* (27.8%)	32/101* (31.7%)
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 (9.7%)	43/108 (39.8%)	40/99 (40.4%)
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.

A two-step change on the DRSS in one eye is considered a clinically meaningful endpoint. Both aflibercept studies (Vista and Vivid) achieved this two-step change with statistical significance.

Vista: Proportion of Patients with a 3 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 >=3 step improvement from baseline	8 (5.2%)	35 (22.7%)	30 (19.9)
Difference (%) vs. Laser		17.8	14.6
97.5% CI for difference		(9.2, 26.4)	(6.3, 23.0)
P-value		<0.0001	0.0001

Vivid: Proportion of Patients with a 3 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 >=3 step improvement from baseline	0	6(7.3%)	2 (2.3%)
Difference (%) vs. Laser		7.3	2.3
97.5% CI for difference		(0.8, 13.9)	(-1.4, 6.0)
P-value		0.0118	0.1573

Only the 2Q4 dosing regimen demonstrated a 3 step improvement in the DRSS in both trials.

Efficacy Summary Statement

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Eylea (aflibercept) Injection is statistically superior to laser photocoagulation and sham injection in the in the mean change in BCVA (as measured by ETDRS score) at week 52. At week 100, the proportion of patients improving by at least 2 steps on the ETDRS-RSS was significantly greater in both Eylea treatment groups (2Q4 and 2Q8) when compared to the control group.

8. Safety

From the original Medical Officer Review dated 3/9/15:

The main support for safety comes from studies supporting the approval of the AMD and CRVO indications and the two clinical studies (VISTA and VIVID).

Overall Exposure at Appropriate Doses/Durations

Study Vista (VGFT-OD-1009): Treatment Exposure (Not Including Additional Treatment) in the Study Eye in the First 100 Weeks (Safety Analysis Set)

	Laser N=154	**VTE 2Q4 N=155**	**VTE 2Q8 N=152**
Total number of active laser treatments	544	0	0
Total number of sham laser treatments	0	370	425
Number of active laser treatments during the first 100 weeks			
1	25	0	0
2	30	0	0
3	30	0	0
4	25	0	0
5	19	0	0
6	8	0	0
7	10	0	0
8	7	0	0
Summary of active laser treatments			
N	154	0	0
Mean (sd)	3.5 (2.0)		
Min, Max	1, 8		
Total number of active VTE injections	0	3308	2053
Total number of sham injections	2899	0	1315
Number of active VTE injections during the first 100 weeks			
1	0	4	2
2	0	1	0
3	0	0	0
4	0	1	2
5	0	0	3
6	0	3	2
7	0	1	0
8	0	1	3
9	0	0	2
10	0	2	2
11	0	0	7
12	0	1	6
13	0	1	8
14	0	2	25
15	0	1	89
16	0	4	1
17	0	4	0
18	0	4	0
19	0	1	0
20	0	4	0
21	0	9	0
22	0	11	0
23	0	15	0
24	0	27	0

	Laser N=154	VTE 2Q4 N=155	VTE 2Q8 N=152
25	0	58	0
Summary of active injections			
N	0	155	152
Mean (sd)	0	21.3 (5.8)	13.5 (2.9)
Min, Max	0	1, 25	1, 16

Study Vivid: Treatment Exposure (Not Including Additional Treatment) in the Study Eye in the First 100 Weeks (Safety Analysis Set)

	Laser N=133	VTE 2Q4 N=136	VTE 2Q8 N=135
Total number of active laser treatments	317	0	0
Total number of sham laser treatments	2	233	307
Number of active laser treatments during the first 100 weeks			
1	52	0	0
2	30	0	0
3	22	0	0
4	12	0	0
5	8	0	0
6	5	0	0
7	3	0	0
Summary of active laser treatments			
N	132	0	0
Mean (sd)	2.4 (1.6)		
Min, Max	1, 7		
Total number of active VTE injections	0	3077	1838
Total number of sham injections	2488	0	1205
Number of active VTE injections during the first 100 weeks			
1	0	2	2
2	0	2	0
3	0	2	0
4	0	2	0
5	0	0	0
6	0	0	3
7	0	1	5
8	0	1	2
9	0	0	4
10	0	0	5
11	0	0	1
12	0	1	1
13	0	1	6
14	0	0	11
15	0	0	94
16	0	1	1
17	0	0	0

	Laser N=133	VTE 2Q4 N=136	VTE 2Q8 N=135
18	0	3	0
19	0	1	0
20	0	2	0
21	0	1	0
22	0	4	0
23	0	4	0
24	0	13	0
25	0	95	0
Summary of active injections			
N	0	136	135
Mean (sd)	0	22.6 (5.8)	13.6 (2.9)
Min, Max	0	1, 25	1, 16

Additional Treatment in the VEGF Group

Subjects in the VEGF Trap-Eye groups received active laser beginning at week 24, if the criteria for additional treatment were met. The maximum number of possible additional laser treatments was 3.

Study Vista (VGFT-OD-1009): Exposure to Additional Treatment (Laser) in the Study Eye in the VEGF Trap-Eye Groups During Weeks 24 to 100 (Safety Analysis Set)

	VTE 2Q4 N=154	VTE 2Q8 N=151
Total number of subjects who received additional treatment (laser treatment)	5 (3.2%)	13 (8.6%)
Total number of additional treatments (laser) received	8	16
Summary of additional treatments received		
Mean (sd)	1.6 (0.9)	1.2 (0.6)
Min, Max	1, 3	1, 3

Study Vivid (91475): Exposure to Additional Treatment (Laser) in the Study Eye in the VEGF Trap-Eye Groups (Safety Analysis Set)

	VTE 2Q4 N=136	VTE 2Q8 N=135
Total number of subjects who received additional treatment (laser treatment)	10 (7.4%)	15 (11.1%)
Total number of additional treatments (laser) received	19	25
Summary of additional treatments received		
N	10	15
Mean (sd)	1.9 (1.1)	1.7 (0.8)
Min, Max	1, 4	1, 3

Additional Treatment in the Laser Group

Subjects in the laser group received VEGF Trap-Eye injections beginning at week 24, if the criteria for additional treatment were met. The maximum number of possible additional laser treatments from week 24 through week 100 was 7.

Study Vista and Vivid: Exposure to Additional Treatment (VEGF Trap-Eye) in the Laser Groups (Safety Analysis Set)

	Vista Laser N=154	**Vivid Laser N=133**
Total number of subjects who received additional treatment	63	46
Total number of additional treatments (VTE) received	559	403
Number of additional treatments received (VTE injections)		
1	1	2
2	0	0
3	2	0
4	1	0
5	5	4
6	5	7
7	5	0
8	4	6
9	8	3
10	10	9
11	10	6
12	12	9
Summary of additional treatments received		
Mean (sd)	8.9 (2.7)	8.8 (2.9)
Min, Max	1, 12	1, 12
Duration of additional treatment received		
Mean (sd)	377.5 (138.7)	51.8 (21.2)
Min, Max	28, 539	4, 77

Subject Disposition

Vista: Disposition

	Laser N=156	**VTE 2Q4 N=156**	**VTE 2Q8 N=154**
Randomized	156	156	154
Received study medication	154	155	152
Randomized but not treated	2	1	2
Completed week 100			
Yes	133 (85.3%)	125 (80.1%)	127 (82.5%)
No	23 (14.7%)	31 (19.9%)	27 (17.5%)

Primary reason for premature discontinuation			
AE	5	4	4
Death	3	7	5
Withdrawal by subject	9	11	11
Lost to f/u	2	4	5
Other	4	5	2

Vivid: Disposition

	Laser N=132	**VTE 2Q4 N=136**	**VTE 2Q8 N=135**
Randomized	135	136	135
Received study medication	133	136	135
Randomized but not treated	2	0	0
Completed week 100			
Yes	105 (79.5%)	115 (84.6%)	110 (81.5%)
No	27 (20.5%)	21 (15.4%)	25 (18.5%)
Primary reason for premature discontinuation			
AE	10	7	8
Death	0	3	6
Lack of efficacy	1	0	1
Withdrawal of consent by subject	14	7	5
Protocol deviation	2	0	1
Lost to f/u	1	2	4
Physician decision	2	1	0
Therapeutic procedure required	0	1	0

Listing of Deaths Through Week 100 (Safety Analysis Set)

Study Vista (VGFT-OD-1009): Listing of Deaths through Week 100 (Safety Analysis Set)

Treatment group	**Subject number**	**Study day**	**Number of days after last dose**	**Cause**
VTE 2Q4	(b) (6)	10	10	Cause of death is unknown. This 67-year old female subject had a medical history of CAD, DM, hypertension, and dyslipidemia. The subject died in her sleep. The subject received only 1 dose of VEGF Trap-Eye.
		88	4	MI
		633	40	Pulseless electrical activity
		479	82	Pneumonia
		657	14	Cardiac arrest
		514	61	Chronic renal failure
		494	2	CVA
		433	40	Acute cardiac failure

VTE 2Q8	(b) (6)	639	13	Cardiac arrest
		737	68	Cardiac failure
		672	175	Cardiac arrest
		494	15	CVA
		511	28	Arteriosclerosis
Laser		77	17	Sudden cardiac death
		587	52	Cardiac arrest
		510	4	Multi-organ failure

Study Vivid (91745): Listing of Deaths through Week 10 (Safety Analysis Set)

Treatment group	Subject number	Study day	Number of days after last dose	Cause
VTE 2Q4	(b) (6)	530	24	MI
		671	52	Colon CA
		504	24	MI
		549	19	Brain herniation
VTE 2Q8		346	17	Hypertensive heart disease
		321	32	Lung CA
		289	37	B cell lymphoma Pneumonia
		331	23	Cardiac failure
		406	77	MI
		605	17	Ventricular arrythmia
Laser		313	89	Acute MI

Adverse Events

I. Nonfatal Serious Adverse Events

Study Vista (VGFT-OD-1009): All Ocular SAEs in the Study Eye during First 100 Weeks (Safety Analysis Set)

	Laser N=154	VTE 2Q4 N=155	VTE 2Q8 N=152
No. of subjects with any ocular SAE in the study eye	7	9	4
Vitreous hemorrhage	3	2	1
Cataract	1	4	0
Visual acuity reduced	0	1	1
Hyphema	0	1	0
Lens dislocation	0	1	0
Punctate keratitis	0	1	0
Retinal artery occlusion	0	0	1
Retinal detachment	0	1	0
Retinal ischemia	0	1	0

IOP increased	0	0	1
Visual acuity test abnormal	0	0	1
Visual field defect	0	0	1
Diabetic retinopathy	2	0	0
Corneal epithelium defect	1	0	0
Retinal hemorrhage	1	0	0

Study Vista (VGFT-OD-1009): Non-Ocular SAEs through Week 100 Occurring in >= 1% of Any One Treatment (Safety Analysis Set)

	Laser N=154	**VTE 2Q4 N=155**	**VTE 2Q8 N=152**
No. of subjects with any non-ocular SAE in the study eye	67	67	56
Infections	19	20	21
Cellulitis	4	7	8
Osteomyelitis	3	5	2
Pneumonia	4	4	3
Abscess limb	2	2	2
Gangrene	0	2	1
Gastroenteritis	1	1	2
Urosepsis	1	2	1
Sepsis	2	2	0
UTI	2	0	0
Cardiac disorders	20	19	12
CHF	5	9	5
Coronary artery stenosis	3	4	5
MI	3	5	3
CAD	2	4	2
Acute MI	3	2	2
Atrial fibrillation	0	1	3
Cardiac arrest	2	1	1
Coronary artery occlusion	0	0	2
Cardiac failure acute	4	1	0
Renal disorders	15	18	11
Renal failure acute	7	6	6
Renal failure	4	5	1
Renal failure chronic	2	4	3
Metabolism	8	16	8
Diabetes mellitus inadequate control	0	3	2
Hypoglycemia	1	5	0
Dehydration	1	2	2
DKA	1	2	2
Hyperkalemia	4	3	1
Neoplasms	2	13	7
Prostate CA	0	3	0
Invasive ductal breast CA	0	1	3
Breast CA	0	3	0
Squamous cell CA of skin	0	1	2

	Laser N=154	**VTE 2Q4 N=155**	**VTE 2Q8 N=152**
Injury	7	9	7
Fall	2	3	5
Road traffic accident	1	2	1
Laceration	0	2	0
Blood disorders	1	11	5
Anemia	1	9	5
Nervous system disorders	9	13	12
CVA	2	5	5
Carotid artery stenosis	0	2	0
Syncope	2	2	0
TIA	3	0	1
Vascular disorders	7	11	6
HTN	3	5	1
Hypertensive crisis	2	2	0
Orthostatic hypotension	2	1	0
General disorders	7	5	9
Chest pain	3	1	4
Asthenia	0	0	2
Peripheral edema	2	0	1
GI disorders	11	4	5
GI hemorrhage	2	3	1
Diabetic gastroparesis	2	0	0
Small intestinal obstruction	2	0	0
Skin disorders	0	3	3
Diabetic foot	0	2	2
Musculoskeletal disorders	7	9	2
Osteoarthritis	3	4	0
Intervertebral disc protrusion	0	1	2
Neuropathic arthropathy	0	2	0
Psychiatric disorders	4	3	3
Mental status changes	0	2	1
Depression	2	1	0
Respiratory disorders	7	8	1
Hypoxia	0	2	0
COPD	2	0	0

Study Vivid (91475): All Ocular SAEs in the Study Eye during First 100 Weeks (Safety Analysis Set)

	Laser N=133	**VTE 2Q4 N=136**	**VTE 2Q8 N=135**
No. of subjects with any ocular SAE in the study eye	10	6	7

	Laser N=133	VTE 2Q4 N=136	VTE 2Q8 N=135
Cataract	0	3	3
Cataract operation	2	1	1
Cataract subcapsular	0	0	1
Diabetic retinopathy	2	0	0
Macular degeneration	1	0	0
Retinal artery occlusion	0	1	0
Retinal detachment	0	0	1
Retinal exudates	1	0	0
Retinal neovascularization	3	0	0
Retinal vascular disorder	1	0	0
Vitreous hemorrhage	2	1	1
Injection site injury	0	1	0

Study Vivid (91475): Treatment Emergent Non-Ocular SAEs through Week 100 Occurring in >=1% of Subjects (Safety Analysis Set)

	Laser N=133	VTE 2Q4 N=136	VTE 2Q8 N=135
No. of subjects with at least 1 non-ocular SAE in the study eye	30	36	38
Cardiac disorders	7	10	6
Acute MI	3	1	0
Cardiac failure	2	1	2
Coronary artery stenosis	0	2	0
MI	0	4	0
Infections	4	1	4
Cellulitis	2	0	0
Injury	5	5	6
Humerus fracture	0	2	1
Metabolism disorders	3	2	6
Diabetes mellitus	1	1	2
Hyperglycemia	1	0	2
Muscular disorders	4	4	4
Osteoarthritis	0	2	0
Nervous system disorders	1	7	3
CVA	0	2	1
Skin disorders	3	1	0
Psoriasis	2	0	0
Vascular disorders	5	3	4
Peripheral arterial occlusive disease	2	0	2

II. Common Adverse Events

Study Vista (VGFT-OD-1009): Ocular Treatment Emergent AEs in the Study Eye Through Week 100 Occurring in At Least 1% (Safety Analysis Set)

	Laser N=154	**2Q4 N=155**	**2Q8 N=152**
Number of patients with at least one ocular treatment emergent AE in study eye	120	113	108
Conjunctival hemorrhage	53	63	48
Eye pain	20	23	21
Vitreous floaters	14	21	17
Vitreous detachment	15	14	22
Cataract	17	21	13
Eye irritation	12	15	11
Macular fibrosis	15	11	15
Dry eye	10	14	7
Visual acuity reduced	11	8	11
Vision blurred	10	11	6
Retinal exudates	13	12	4
Posterior capsular opacification	12	7	8
Retinal hemorrhage	16	10	5
Cataract subcapsular	7	6	8
FBS in eyes	8	8	5
Lacrimation increased	6	7	6
Retinal pigment epitheliopathy	3	5	8
Vitreous hemorrhage	14	10	3
Ocular hyperemia	12	6	6
Punctate keratitis	1	5	7
Blepharitis	4	2	7
Cataract cortical	8	2	7
Cataract nuclear	6	5	2
Eye pruritis	3	3	4
Retinal vascular disorder	2	3	4
Retinal neovascularization	12	3	3
Vitreous adhesions	4	4	2
Optic atrophy	2	4	1
Retinal aneurysm	4	2	3
Abnormal sensation in eye	0	3	1
Conjunctival hyperemia	1	3	1
Conjunctivitis allergic	1	2	2
Diabetic retinopathy	8	2	2
Diplopia	1	4	0
Keratitis	2	1	3
Photophobia	3	2	2
Pinguecula	1	1	3
Visual impairment	7	1	3
Blindness transient	0	0	3
Chalazion	1	2	1
Diabetic retinal edema	5	1	2
Eye discharge	1	3	0
Eyelid edema	1	0	3

	Laser N=154	2Q4 N=155	2Q8 N=152
Narrow anterior chamber angle	0	1	2
Ocular hypertension	0	3	0
Optic disc vascular disorder	1	2	1
Photopsia	7	2	1
Retinal artery embolism	1	3	0
Blepharochalasis	0	2	0
Blindness unilateral	0	2	0
Corneal epithelial defect	1	0	2
Eyelid irritation	2	2	0
Glaucoma	4	1	1
Iridocyclitis	0	2	0
Retinopathy	0	0	2
CME	3	0	1
Macular edema	3	0	0
Ocular discomfort	3	0	0
Optic disc hemorrhage	5	0	0
IOP increased	2	12	10
Optic nerve c/d ratio increased	4	4	2
Visual acuity tests abnormal	5	2	3
Corneal abrasion	6	4	6
Procedural complication	2	0	0
Injection site pain	1	4	2
Injection site irritation	3	1	0
Drug hypersensitivity	2	1	0

Study Vivid (91475): Ocular Treatment Emergent AEs in the Study Eye Through Week 100 Occurring in At Least 1% (Safety Analysis Set)

	Laser N=133	2Q4 N=136	2Q8 N=135
Number of patients with at least one ocular treatment emergent AE in study eye	95	99	98
Conjunctival hemorrhage	7	36	33
Cataract	8	15	18
Visual acuity reduced	21	10	17
Retinal exudates	12	11	13
Eye pain	6	11	7
Retinal hemorrhage	16	6	11
Retinal aneurysm	6	6	8
Punctate keratitis	4	6	7
Ocular hypertension	0	8	4
Cataract cortical	0	6	5
Vitreous floaters	2	9	2
Cataract subcapsular	1	7	3
CME	12	1	9
Vitreous detachment	3	4	6
Lacrimation increased	0	6	3

	Laser N=133	**2Q4 N=136**	**2Q8 N=135**
Ocular hyperemia	2	3	6
Corneal erosion	4	3	5
Diabetic retinal edema	4	2	6
Dry eye	4	5	3
Macular fibrosis	4	2	6
Posterior capsular opacification	5	2	6
Vitreous hemorrhage	6	4	4
Retinal vascular disorder	2	4	3
Cataract nuclear	4	2	4
Conjunctival hyperemia	5	5	1
Conjunctivitis allergic	2	2	4
Eye pruritus	2	4	2
Eyelid edema	3	3	3
FBS	2	2	4
Keratitis	2	4	2
Blepharitis	4	1	4
Macular edema	7	1	4
Eyelid irritation	1	1	3
Phtophobia	0	2	2
Chalazion	0	2	1
Corneal opacity	2	1	2
Keratopathy	1	1	2
Lenticular opacities	2	2	1
Macular hole	1	2	1
Optic disc hemorrhage	0	0	3
Vision blurred	2	1	2
Visual impairment	2	0	3
Vitreous opacities	0	2	1
Abnormal sensation in eye	2	0	2
Corneal edema	2	1	1
Eye inflammation	0	2	0
Retinal artery occlusion	0	2	0
Retinal detachment	1	0	2
Retinal neovascularization	6	2	0
Retinal pigment epitheliopathy	2	1	1
Diabetic retinopathy	5	0	1
Macular cyst	3	1	0
Maculopathy	5	1	0
Conjunctival edema	2	0	0
Eye discharge	2	0	0
Eyelids pruritus	2	0	0
Iris neovascularization	2	0	0
Retinopathy	3	0	0
IOP increased	11	21	10
Visual acuity tests abnormal	25	5	13
Conjunctivitis	5	4	6
Injection site pain	1	2	3
Procedural pain	0	2	0
Cataract operation	2	1	1
Drug hypersensitivity	0	2	0

	Laser N=133	**2Q4 N=136**	**2Q8 N=135**
Sjogren's syndrome	3	0	0

Study Vista (VGFT-OD-1009): Non-Ocular Treatment Emergent AEs Occurring in >=3% of Subjects (Safety Analysis Set)

	Laser N=154	**VTE 2Q4 N=155**	**VTE 2Q8 N=152**
Any non-ocular AE	143	142	142
Infections	84	94	98
UTI	14	17	26
Nasophayrngitis	17	17	19
Upper respiratory tract	13	11	15
Sinusitis	12	13	12
Influenza	10	7	16
Cellulitis	7	10	12
Bronchitis	12	13	5
Localized infection	6	10	5
Pneumonia	7	8	7
Ear infection	4	3	6
Cystitis	1	6	2
Gastroenteritis viral	2	2	6
Osteomyelitis	4	6	2
Gastroenteritis	5	3	2
Vascular disorders	63	52	49
HTN	50	45	42
Metabolism disorders	56	63	50
DM	20	13	19
Hyperkalemia	12	10	6
Hypoglycemia	4	11	5
Type 2 diabetes mellitis	6	9	5
Dehydration	5	7	5
Vitamin D deficiency	7	6	5
Hypercholesterolemia	10	5	3
Hyperglycemia	7	6	2
Hyperlipidemia	5	6	2
Hypokalemia	3	5	2
Hyponatremia	1	0	5
GI disorders	53	48	42
Nausea	15	19	11
Diarrhea	14	14	6
Vomiting	7	14	3
Constipation	9	11	5
GERD	9	10	5
Investigations	53	42	47
Blood glucose increased	6	9	11
Glycosylated hemoglobin	7	7	13

	Laser N=154	**VTE 2Q4 N=155**	**VTE 2Q8 N=152**
increased			
Blood pressure increased	10	9	7
Blood CPK increased	12	7	4
Blood urea increased	4	6	3
Blood creatinine increased	5	5	3
Hematocrit decreased	4	5	3
Blood pressure systolic increased	2	2	5
Hemoglobin decreased	5	5	2
Urine protein/creatinine ratio increased	8	5	2
Blood potassium increased	5	4	2
Musculoskeletal disorders	53	49	38
Back pain	8	20	6
Arthralgia	9	9	8
Arthritis	7	5	10
Pain in extremity	10	8	5
Osteoarthritis	7	7	5
Muscle spasms	8	5	2
Musculoskeletal pain	5	3	3
Exostosis	1	5	0
Nervous system disorders	54	42	43
HA	19	19	7
Dizziness	8	8	9
Neuropathy peripheral	5	5	7
CVA	2	5	5
Diabetic neuropathy	3	2	5
Syncope	6	3	2
Hypaesthesia	5	2	1
Respiratory disorders	37	43	42
Cough	13	18	17
Dyspnea	6	12	11
Respiratory tract congestion	3	2	5
Pulmonary edema	4	5	0
Injury	40	41	40
Fall	9	9	14
Procedural pain	1	8	2
Laceration	3	3	5
Ligament sprain	5	1	7
General Disorders	35	39	34
Edema peripheral	9	15	16
Chest pain	12	4	9
Pyrexia	2	7	6
Fatigue	4	8	3
Asthenia	4	3	5
Pain	4	5	3
Renal	42	35	32

	Laser N=154	**VTE 2Q4 N=155**	**VTE 2Q8 N=152**
Renal failure acute	11	10	9
Renal failure	9	10	7
Renal failure chronic	4	9	8
Hematuria	5	1	2
Blood disorders	22	35	19
Anemia	13	29	16
Iron deficiency anemia	0	6	0
Cardiac Disorders	33	29	23
CHF	6	12	9
Coronary artery stenosis	3	5	5
CAD	3	5	4
MI	3	6	3
Psychiatric disorders	18	23	12
Anxiety	7	12	4
Depression	7	7	4
Insomnia	5	4	4
Immune system disorders	10	15	14
Seasonal allergy	8	6	9
Drug hypersensitivity	2	5	3
Endocrine disorders	9	8	7
Hypothyroidism	7	4	5

Study Vivid (91745): Non-Ocular Treatment Emergent AEs in the Study Eye Through Week 100 Occurring in >=3% (Safety Analysis Set)

	Laser N=133	**VTE 2Q4 N=136**	**VTE 2Q8 N=135**
Any non-ocular AE	102	113	112
Infections	53	49	59
Nasophayrngitis	29	32	32
UTI	4	6	10
Influenza	9	4	10
Bronchitis	8	9	2
Investigations	26	35	31
Glycosylated hemoglobin increased	9	10	7
Blood glucose increased	5	6	5
Blood urea increased	5	5	5
Blood creatinine increased	3	5	4
Vascular disorders	28	26	26
HTN	20	22	21
Musculoskeletal disorders	17	22	26
Musculoskeletal pain	1	1	6

	Laser N=133	**VTE 2Q4 N=136**	**VTE 2Q8 N=135**
Pain in extremity	4	4	2
Back pain	4	3	2
Intervertebral disc protrusion	4	2	0
GI disorders	23	22	24
Gastritis	1	5	2
Nervous system disorders	7	18	18
HA	3	4	5
Renal	15	14	16
Diabetic nephropathy	4	4	4
Respiratory disorders	14	12	13
Cough	4	4	6
Orophyrngeal pain	5	2	1
Blood disorders	11	9	11
Anemia	6	6	3
General disorders	13	6	10
Peripheral edema	3	5	2
Skin disorders	11	2	10
Skin ulcer	6	0	0

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

Safety Summary Statement

There is substantial evidence consisting of adequate and well controlled studies which demonstrate that Eylea (aflibercept) Injection is safe when administered 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 4 weeks (1 month) or every 8 weeks (2 months).

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

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

This drug was not tested on a pediatric population. DME does not occur in pediatric patients except in very rare circumstances. This supplemental application and its BPCA/Pediatric Study Plan (IND 100083) were presented at PeRC on December 11, 2013. PeRC concurred with a full waiver of pediatric studies (PREA). The safety and effectiveness of Eylea (aflibercept) Injection in pediatric patients have not been established.

Ths supplement was re-presented at PeRC on 2/4/15 for a full pediatric waiver for the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME) indication.

11. Other Relevant Regulatory Issues

OSI

An Office of Scientific Investigations (OSI) audit was requested; OSI completed their review on 5/7/14 for the diabetic macular edema indication. No new inspections were requested for this new supplemental application.

FINANCIAL DISCLOSURE

Financial disclosure has not been updated since the DME supplement S-037. Regeneron provided adequate financial disclosure information for Studies VISTA and VIVID during the review of S-037.

BIOSTATISTICS

Per the Biostatistics consultative review finalized 3/5/15:

In this efficacy supplemental BLA, the applicant seeks approval of Eylea (aflibercept) Injection for the treatment of diabetic retinopathy (DR) in patients with Diabetic Macular Edema (DME) based on 2 years data. The recommended Eylea dose for the indication sought is 2 mg injection administered once every 4 weeks for the first five injections followed by once every 8 weeks. The same Eylea dose was approved for the treatment of DME on July 2014 based on 1 year data. In this supplemental BLA, the applicant also seeks to update the label for the DME indication using the 2 years data.

Support for the efficacy and safety of Eylea for the treatment of DR in patients with DME was based on two ongoing phase 3 trials initially submitted for the DME application; Study VGFTOD- 1009 (VISTA) conducted in the US and Study 91745 (VIVID) conducted in the European Union, Japan, and Australia. Both studies were a randomized, double-masked, active-controlled, and multi-center clinical studies designed to evaluate the safety and efficacy of repeated doses of Eylea injection compared to laser in improving best corrected visual acuity (BCVA). Eligible patients in both studies were randomized to one of the following three treatment groups: (i) Eylea 2 mg injections administered once every four weeks (VTE 2Q4), (ii) Eylea 2 mg injections administered once every 4 weeks for the first five injections followed by once every 8 weeks (VTE 2Q8), and (iii) laser administered at baseline and as needed starting at week 12 based on protocol defined criteria (Laser).

The efficacy results for the four ordered secondary endpoints including the results for the exploratory endpoints relevant to the DR indication are shown in Table 1.

Table 1: Overview of secondary efficacy results at week 100
(Full Analysis Set; LOCF)

		VISTA		VIVID	
		Difference (97.5% CI) [1] versus Laser		Difference (97.5% CI) [1] versus Laser	
Secondary Endpoints	Test order	VTE 2Q4	VTE 2Q8	VTE 2Q4	VTE 2Q8
Change in BCVA in BCVA letter score from baseline at week 100	1	10.6 (7.1, 14.2)	10.1 (7.0, 13.3)	10.7 (7.6, 13.8)	8.2 (5.2, 11.3)
Proportion of patients (%) who gained >= 10 letter from baseline to week 100	2	36.2 (24.3, 48.1)	31.6 (19.5, 43.7)	33.1 (20.3, 45.9)	24.6 (11.9, 37.3)
Proportion of patients (%) who gained >= 15 letter from baseline to week 100	3	25.8 (15.1, 36.6)	20.1 (9.6, 30.6)	26.1 (14.8, 37.5)	19.0 (8.0, 29.9)
Proportion of patients who improved by ≥ 2-steps	4	22.1 (11.1, 33.2)	21.7 (10.5, 33.0)	20.7 (8.8, 32.5)	24.2 (12.4, 35.9)
Proportion of patients who improved by ≥ 3-steps	E	18.4 (9.7, 27.2)	14.9 (6.4, 23.4)	6.2 (0.7, 11.8)	2.9 (-0.8, 6.5)
Proportion of patients who worsened by ≥ 2-steps	E	-12.4 (-21.1, -3.7)	-12.5 (-21.0, -4.0)	-5.0 (-10.9, 0.9)	-5.1 (-10.9, 0.7)
Proportion of patients who worsened by ≥ 3-steps	E	-4.1 (-9.2, 1.1)	-3.3 (-8.6, 2.0)	-2.1 (-5.4, 1.2)	-1.1 (-5.0, 2.7)

E: Supporting exploratory endpoints for the indication of treatment of DR in patients with DME. LOCF: Last observation carried forward
[1] Difference (97.5% CI) for the first test in the order was based on ANCOVA model with baseline BCVA as covariate and stratification factors and treatment as fixed effects and for all other tests in the order was based on using CMH weighting scheme adjusted by study specific stratification factor.

In both studies, statistical significance for the key secondary efficacy endpoint of the proportion of patients who improved by ≥2- steps in DRSS from baseline at week 100 was achieved for each of the Eylea dose group versus laser.

OPDP
A review of the substantially complete labeling was completed by the Office of Prescription Drug Promotion (OPDP) on 3/13/15. OPDP has reviewed the proposed PI and has no comments at this time.

Regulatory Briefing
This supplemental application was presented at a CDER Regulatory Briefing on January 23, 2015. The group was asked their opinion of the evidence of efficacy for the treatment of DR in patients with DME; they were specifically asked if they recommended including a new indication in the Indications and Usage section of the label, "treatment of DR in patients with DME" and describing the efficacy results in the Clinical Studies section of the labeling. There was a unanimous conclusion that the new indication be included. The group did not agree with expanding the indication to all patients with diabetic retinopathy.

12. Labeling

BLA 125387/ S-048 Eylea (aflibercept) Injection is recommended for approval for the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME) with the labeling found in the Appendix at the end of this CDTL review (submitted by Regeneron Pharmaceuticals, Inc. on 3/23/15).

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
BLA 125387/S-048 Eylea (aflibercept) Injection is recommended for approval for the treatment treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME).

RISK BENEFIT ASSESSMENT:
There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that Eylea (aflibercept) Injection is statistically superior to sham injection in the proportion of patients improving by at least 2 steps on the ETDRS-RSS. Both Eylea treatment groups (2Q4 and 2Q8) when compared to the control group were superior.

There is substantial evidence consisting of adequate and well controlled studies which demonstrate that Eylea (aflibercept) Injection is safe when administered 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 4 weeks (1 month) or every 8 weeks (2 months).

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

In the absence of a clinically relevant difference between aflibercept treatment groups, the recommended dose for Eylea is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).

The benefits of using this drug product outweigh the risks for the above indication.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

Appendix

BLA 125387/ S-048 Eylea (aflibercept) Injection is recommended for approval for the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME) with the labeling found in the Appendix at the end of this CDTL review (submitted by Regeneron Pharmaceuticals, Inc. on 3/23/15).

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

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
03/24/2015

WILEY A CHAMBERS
03/25/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s048

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA 125387
Submission Number	S-048
Submission Code	Supplement
Letter Date	9/30/14
Stamp Date	9/30/14
PDUFA Goal Date	3/30/15
Reviewer Name	Sonal D. Wadhwa
Review Completion Date	2/20/15
Established Name	aflibercept
(Proposed) Trade Name	Eylea
Therapeutic Class	Anti-VEGF
Applicant	Regeneron
Priority Designation	P
Formulation	Intravitreal injection
Dosing Regimen	Intravitreal injection
Indication	Treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME)
Intended Population	Patients with DR and DME

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

BLA 125-387/S-048 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of Eylea for the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME).

1.2 Risk Benefit Assessment

The benefits of using this drug product outweigh the risks for the above indication.

1.3 Recommendations for Post-Marketing Risk Management Activities

There are no proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of drug product.

1.4 Recommendations for other Post-Marketing Study Commitments

There are no recommended Phase 4 clinical study commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Aflibercept (also called VEGF Trap) is a recombinant protein consisting of specific domains of the human VEGF receptors, VEGF-R1 and VEGF-R2, fused to an IgG1 Fc.

2.2 Tables of Currently Available Treatments for Proposed Indications

BLA 125156 Lucentis was approved in February 2015 for the treatment of diabetic retinopathy in patients with DR.

2.3 Availability of Proposed Active Ingredient in the United States

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

2.4 Important Safety Issues With Consideration to Related Drugs

There have been no additional safety concerns raised with this class of therapeutic products other than those listed in the current Eylea (aflibercept) injection package insert and those discussed within this review.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

7/14/14	Submission to IND 100,083 to request breakthrough therapy
8/21/14	T-con to discuss breakthrough therapy request
9/5/14	Breakthrough therapy granted
9/5/14-9/9/14	Email correspondence regarding table of contents, waiver to update the financial disclosure, and updated summary level clinical site data set is not required

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission contains additional analyses of data from Studies VGFT-OD-1009 (Vista) and Study 91745 (Vivid) originally submitted in S-037 which was approved July 29, 2014. Clinical site inspections were performed during the review of S-037.

3.2 Compliance with Good Clinical Practices

There is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

3.3 Financial Disclosures

Financial disclosure was not updated since the DME supplement S-037.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See original review.

4.2 Clinical Microbiology

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

4.3 Preclinical Pharmacology/Toxicology

The pharmacology/toxicology aspects of aflibercept were discussed as part of the initial approved marketing application for treatment of subjects with neovascular (wet) AMD. No new pharm/tox studies were performed for this efficacy supplement.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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

4.4.2 Pharmacodynamics

See original review. No new PK/PD information provided in this supplement.

4.4.3 Pharmacokinetics

See original review. No new PK/PD information provided in this supplement.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Title	Objective	Study Design	Test Product and Dosing Regimen	Duration of Treatment	Study Status
Vista (VGFT-09-1009)	Efficacy and Safety	Randomized, double-masked, laser controlled	VEGF Trap-Eye IVT 2 mg every 4 weeks (2Q4): 156 patients VEGF Trap-Eye IVT 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	Ongoing
Vivid (Study 91475)	Efficacy and Safety	Randomized, double-masked, laser controlled	VEGF Trap-Eye IVT 2 mg every 4 weeks (2Q4): 136 patients VEGF Trap-Eye IVT 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	Ongoing

5.2 Review Strategy

The sources of clinical data utilized in this review include the studies listed in section 5.1.

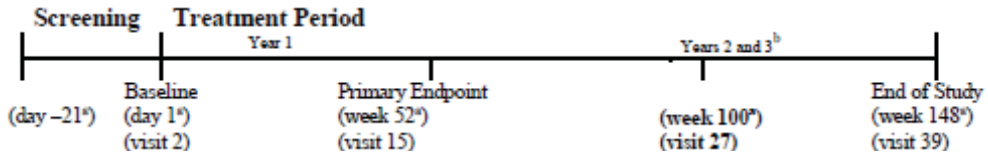
5.3 Discussion of Individual Studies

Vista: Study VGFT-OD-1009

VGFT-OD-1009 is an ongoing phase 3, randomized, double-masked, multicenter, clinical study to assess the potential benefit of VEGF Trap-Eye treatment administered IVT compared with standard of care laser treatment over 148 weeks in subjects with DME secondary to diabetes mellitus. VEGF Trap–Eye is delivered IVT at a dosage of 2 mg using 2 different regimens. Subjects had a screening visit (day -21 to day -1), were randomized (day 1), received active or sham treatment at baseline visit (day 1) and at study visits every 4 weeks from week 4 to week 144, and were evaluated for safety and efficacy. Randomization was stratified according to history of MI and/or CVA. Subjects were assessed for additional treatment criteria starting at week 24 and were treated if 1 of the following criteria were met:

- Loss at any single visit of ≥15 letters from the best previous VA score due to DME and the subject's current VA score is not better than the baseline score
- Loss at 2 consecutive visits at least 7 days apart (second visit may be an unscheduled visit) of ≥10 letters from the best previous VA score due to DME, and the subject's current VA score is not better than the baseline score

This report presents the results of the study obtained between start of screening and the data cut-off point for each individual subject at the 2-year (week 100) visit. The period covered is 5/26/11(first subject's first dose) to 12/18/13 (last subject's last visit week 100) for year 2. The primary, secondary, and additional endpoints were analyzed at week 52, and reported in CSR VGFT-OD-1009 (week 52). The study continues to week 148 and every effort is being made to preserve masking of subjects, investigators and their staffs, and sponsor personnel. All analyses have been performed by statisticians and statistical programmers that were no longer involved in the conduct of the study, and individuals involved in the continuing conduct of the study remained masked. Year 3 results (through week 148) will be reported separately.



Inclusion Criteria

- Adults ≥18 years with type 1 or 2 DM
- Subjects with DME involving the center of the macula (central subfield on OCT) in the study eye
- Decrease in vision determined to be primarily the result of DME in the study eye
- BCVA ETDRS letter score of 73 to 24 (20/40 to 20/320) in the study eye
- Willing and able to comply with clinic visits and study-related procedures
- US subjects were required to have a HIPAA authorization; in other countries, as applicable according to national laws
- Provide a signed ICF prior to any study procedures

Exclusion Criteria

- History of vitreoretinal surgery in the study eye
- Laser photocoagulation (panretinal or macular) in the study eye within 90 days of day 1
- Subject unlikely to benefit from additional macular laser photocoagulation
- Previous use of intraocular or periocular corticosteroids in the study eye within 120 days of day 1
- Previous treatment with anti-angiogenic drugs in the study eye (ie. pegaptanib sodium, bevacizumab, ranibizumab, etc.) within 90 days of day 1
- Active proliferative DR in the study eye
- History of idiopathic or autoimmune uveitis in the study eye
- Cataract surgery in the study eye within 90 days of day 1

- Aphakia in the study eye
- Yag capsulotomy in the study eye within 30 days of day 1
- Any intraocular surgery in the study eye within 90 days of day 1
- Vitreomacular traction or ERM in the study eye evident biomicroscopically or on OCT that is thought to affect central vision
- Current iris neovascularization, VH, or tractional retinal detachment in the study eye
- Pre-retinal fibrosis involving the macula in the study eye
- Structural damage to the center of the macula in the study eye that is likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia, or organized hard exudates
- Intraocular inflammation of trace or above in the study eye
- Evidence of infections in either eye
- Uncontrolled glaucoma in the study eye (subject who has had filtration surgery in the past, or likely to need filtration surgery in the future)
- IOP ≥25 mm Hg in the study eye
- Concurrent disease in the study eye, other than DME, that could compromise VA, require medical or surgical intervention during the study period, or confound interpretation of the results (including retinal vascular occlusion, retinal detachment, macular hole, or choroidal neovascularization of any cause)
- Ocular conditions with a poorer prognosis in the fellow eye than in the study eye
- Only 1 functional eye even if that eye is otherwise eligible for the study
- Ocular media of insufficient quality to obtain fundus and OCT images
- Current treatment for a serious systemic infection
- Administration of systemic anti-angiogenic agents within 180 days of day 1
- Uncontrolled DM in the opinion of the investigator
- Uncontrolled blood pressure (defined as systolic >160 mm Hg or diastolic >95 mm Hg while subject is sitting)
- History of CVA or MI within 180 days of day 1
- Renal failure, dialysis, or history of renal transplant
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, might affect interpretation of the results of the study, or renders the subject at high risk from treatment complications
- Known serious allergy to fluorescein
- Participation in an investigational study within 30 days prior to screening visit that involved treatment with any drug (excluding vitamins and minerals) or device
- Subjects with hypersensitivity to study drug or excipients
- Pregnant or breastfeeding women
- Sexually active men or women of childbearing potential who were unwilling to practice adequate contraception during the study (adequate contraceptive measures include 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)

- Women of childbearing potential with either a positive pregnancy test result or no pregnancy test at baseline. Post-menopausal women must have been amenorrheic for at least 12 months in order not to be considered of childbearing potential.

Investigational and Reference Treatment
The investigational product was VEGF Trap-Eye, which was supplied in a single use, 1 mL, glass pre-filled syringe (PFS) with a snap-off syringe cap. The injection volume was 50 µL (0.05 mL), which was administered to the subjects by IVT injection. Pre-filled glass syringes are supplied at a concentration of 40 mg/mL. The investigational treatment was administered in 2 treatment groups (2Q4 and 2Q8).

Eligible subjects were administered 1 of the following 3 treatments in the study eye:

VEGF Trap–Eye IVT Injection (2Q4) with Sham Laser, as Appropriate
Subjects in this group were administered VEGF Trap-Eye 2 mg at baseline (day 1, visit 2) and 2Q4 from week 4 (visit 3) to week 144 (visit 38); sham laser at baseline and at visits at which subjects met the criteria for laser re-treatment (starting at week 12 and no more often than every 12 weeks). Subjects were assessed for additional treatment criteria starting at week 24.

VEGF Trap–Eye IVT Injection (2Q8 after 5 Initial Monthly Injections) with Sham Laser, as Appropriate
Subjects in this group were administered VEGF Trap-Eye 2 mg at baseline (day 1, visit 2), week 4, week 8, week 12, and week 16 (2 mg 2Q4 for 5 visits), followed by 2 mg 2Q8 from week 24 to week 144 (visit 38); sham injections, starting at week 20, on alternating visits when subjects were not scheduled to receive an active injection; sham laser at baseline and at visits at which subjects met the criteria for laser re-treatment (starting at week 12 and no more often than every 12 weeks). Subjects were assessed for additional treatment criteria starting at week 24. The reference treatment was laser therapy.

Macular Laser Photocoagulation Treatment with Sham IVT Injection
During the first 2 years, subjects continued to receive laser therapy using the modified ETDRS protocol at day 1 and at visits at which subjects met any of the criteria for laser re-treatment (but no more often than every 12 weeks); sham injection at baseline (day 1) and at every study visit from week 4 to week 96. Subjects were assessed for additional treatment criteria starting at week 24.

During year 3, subjects randomized to the laser group who did not meet the criteria for additional treatment previously could have received VEGF Trap-Eye as needed (PRN), according to the VEGF Trap-Eye re-treatment criteria from week 100 to week 144 (visit 27 to visit 38).

Table 1: Description of Treatment Groups

Treatment Group	Study Drug	Dose	Route of Administration	Dosing Interval
2Q4	VEGF Trap-Eye	2 mg	IVT injection	4-week intervals
			Sham laser	Baseline, and at visits at which laser re-treatment criteria were met (starting at week 12 and no more often than every 12 weeks)
	Active Laser Additional Treatment		Laser treatment	Assessments began at week 24
2Q8	VEGF Trap-Eye	2 mg	IVT injection	1 dose every 4 weeks for 5 visits, followed by 8-week intervals
			Sham injection	Alternating visits when an active injection was not administered (starting at week 20)
			Sham laser	Baseline, and at visits at which laser re-treatment criteria were met (starting at week 12 and no more often than every 12 weeks)
	Active Laser Additional Treatment		Laser treatment	Assessments began at week 24
Laser	Active laser		Laser treatment	Day 1, and at visits at which laser re-treatment criteria were met (but not more often than every 12 weeks)
			Sham injection	Baseline (day 1), and at every study visit
	VEGF Trap-Eye Additional Treatment	2 mg	IVT injection	Assessments began at week 24; 2 mg VEGF Trap-Eye at every scheduled visit for 5 visits, before starting a 2Q8 schedule

2Q4 = 2 mg VEGF Trap-Eye given every 4 weeks; 2Q8 = 2 mg VEGF Trap-Eye given every 4 weeks until week 16 and every 8 weeks, thereafter; IVT = intravitreal; VEGF = vascular endothelial growth factor.

All patients will be evaluated for laser re-treatment by a masked physician at each visit starting at visit 5 (week 12) to the end of the study. If the patient meets any of the criteria for re-treatment, and at least 12 weeks have passed since the last laser or sham laser, a fluorescein angiography (FA) must be performed. Patients randomized to the laser arm will receive an active laser treatment, and patients randomized to a VEGF Trap-Eye arm will receive sham laser treatment. Laser re-treatment (active or sham) will be administered no more than once every 12 weeks.

Laser re-treatment criteria (at least 1 criterion must be met):

- Thickening of the retina at or within 500 microns of the center of the macula, observed on clinical exam
- Hard exudates at or within 500 microns of the center of the macula, if associated with thickening of adjacent retina
- A zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula

Additional Treatment
Patients will be evaluated for additional treatment starting at week 24 by a masked physician. For masking purposes, all patients will be evaluated for additional treatment.

Criteria for additional treatment (at least 1 criterion must be met):

- Loss at any single visit of ≥15 letters from the best previous VA score due to DME and the patient's current VA score is not better than the baseline score
- Loss at 2 consecutive visits at least 7 days apart (second visit may be an unscheduled visit) of ≥10 letters from the best previous VA score due to DME and the patient's current VA score is not better than the baseline score

Laser patients who meet any of the additional treatment criteria will qualify for additional treatment. These patients will receive 2 mg VEGF Trap-Eye at every scheduled visit for 5 visits, before starting a 2q8 schedule to week 144. In addition, patients will continue to be monitored for laser re-treatment. If laser re-treatment criteria are met, patients may receive both laser (at the discretion of the investigator) and VEGF Trap-Eye at the same visit, when applicable.

Patients in the VEGF Trap-Eye Arm
VEGF Trap-Eye patients who meet any of the additional treatment criteria will qualify for additional treatment. These patients will receive an active laser treatment at the current visit, and will continue with their randomized treatment at the current and all future visits. They will be evaluated for laser re-treatment criteria as before, but will receive active laser, rather than sham laser, when they meet the laser re-treatment criteria to the end of the study. Patients may receive laser (at the discretion of the investigator) and VEGF Trap-Eye, when applicable, at the same visit.

VEGF Trap-Eye Re-Treatment
During year 3, patients randomized to the laser arm, and not receiving additional treatment, will receive VEGF Trap-Eye administered by IVT when any of the following criteria for VEGF Trap-Eye re-treatment are met. Assessments and treatment with VEGF Trap-Eye will begin at week 100 (visit 27). VEGF Trap-Eye re-treatment criteria:

- There is a >50μm increase in CRT on OCT compared to the lowest previous measurement
- There are new or persistent cystic retinal changes or sub-retinal fluid on OCT, or persistent diffuse edema in the central subfield on OCT
- A loss of 5 or more letters from the best previous measurement in conjunction with any increase in retinal thickness in the central subfield on OCT
- An increase of BCVA between the current and most recent visit of ≥5 letters

Table 3: Schedule of Assessments and Study Procedures

Study Procedure	Screen	Screen day 1[1]	Treatment Period: Year 1							Year 2				Year 3	EOS[15]
Visit	1	1 + 2	2	2A	3-4	5-7	8	9-14	15	16-19	20	21-26	27	28-38	39
Week				1	4-8	12-20	24	28-48	52	56-68	72	76-96	100	104-144	148
Day (± 7 days)	-21 to -1	1	1	7[17]	29-57	85-141	169	197-337	365	393-477	505	533-673	701	729-1009	1037
Informed consent	X	X													
Demographic information	X	X													
Medical/ophthalmic history	X	X													
Inclusion/exclusion	X	X	X												
Randomization[20]		X	X												
Concomitant meds check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VEGF Trap-Eye/sham inj.[2]		X	X		X	X	X	X	X	X	X	X	X	X	
Evaluation for laser re-treatment[3]						X	X	X	X	X	X	X	X	X	
Laser/sham (re)-treatment[3]		X	X			X	X	X	X	X	X	X	X	X	
Additional treatment[4]							X	X	X	X	X	X	X	X	
VEGF Trap re-treatment[5]													X	X	
BCVA (ETDRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intraocular pressure[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FP/FA[7]	X[18]	X	X[18]			X[19]	X	X[19]	X	X[19]	X	X[19]	X	X[16, 19]	X
NEI VFQ-25/EQ-5D	X	X					X		X		X		X	X[16]	X
Adverse events[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone safety[9]		X	X		X	X	X	X	X	X	X	X	X	X	
Physical examination[10]	X	X													X
Vital signs[11]	X	X	X		X	X	X	X	X	X	X	X	X	X	X
ECG	X	X							X				X	X[16]	X
Hematology, chemistry[12,13]	X	X					X		X			X[12]	X	X[12]	X
HbA1c[12,13]	X	X					X		X			X[12]	X	X[12]	X
Serum/urine pregnancy test[1]	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Serum antibody sampling[13]	X	X							X				X		X
Urinalysis[13,14]	X	X					X		X			X[12]	X	X[12]	X

1 Visits 1 and 2 could be combined, except for women of childbearing potential. Serum pregnancy results were required to determine eligibility. If a subject was not of childbearing potential and screening/baseline visit was to be combined, all procedures listed for both visits were performed, except for the serum pregnancy test. In addition, all women of childbearing potential had a urine pregnancy test at each visit starting at visit 2 (day 1). A negative urine pregnancy test was required before treatment was administered.
2 See study protocol, Appendix 1 (Appendix 1.1) for study drug and sham injection protocol. Following study drug/sham injection, subjects were observed for approximately 30 minutes.
3 All subjects received either active or sham laser treatment on day 1 (visit 2) and were evaluated for laser re-treatment at each study visit starting week 12 to the end of the study. If any criterion for re-treatment was met, the subject received an active laser re-treatment if the subject was in the laser group and sham laser if the subject was in the VEGF Trap-Eye group (study protocol, section 5.2 [Appendix 1.1]). See study protocol, Appendix 2 and Appendix 3 (Appendix 1.1) for laser/sham protocol. Laser or sham laser was required to be administered before VEGF Trap-Eye or sham injection.
4 Starting week 24, all subjects were evaluated for additional treatment (study protocol, section 5.3 [Appendix 1.1]).
5 Starting at week 100, subjects randomized to the laser group received VEGF Trap-Eye according to the VEGF re-treatment criteria (study protocol, section 5.3.1 [Appendix 1.1]). All subjects will be assessed for VEGF Trap-Eye re-treatment criteria during year 3 to maintain masking.
6 This procedure was done pre-dose (bilateral) and post-dose (study eye). For IOP, the post-dose measurements were to be done before the end of the approximately 30-minute observation period after injection. If the IOP was elevated, IOP was to be monitored until it normalized.
7 FP: Fundus photography; FA: Fluorescein angiography.
8 AEs were collected from the time informed consent was signed to early termination or end of study (study protocol, section 7.2.3 [Appendix 1.1]).
9 Safety telephone calls were made 3 days ± 1 day after each visit to ensure that no signs or symptoms of retinal detachment, endophthalmitis, or other AEs had occurred. Calls were made after each visit starting at visit 2.
10 Including height and weight at screening visit.
11 Subject's blood pressure and pulse were measured after the subject had been sitting for 5 minutes.
12 Laboratory samples were collected approximately every 6 months, including HbA1c, at the screening visit, visit 8 (week 24), visit 15 (week 52), visit 21 (week 76), visit 27 (week 100), visit 33 (week 124), and visit 39 (end of study visit or early termination visit). Fasting prior to sample collection was not required.
13 After screening visit, samples were required to be collected prior to study drug injection.
14 At visits at which FA was performed, urinalysis samples were collected before FA in order to avoid false elevations in urine protein values.
15 EOS: End of study. If a subject withdrew from the trial before the end of trial, the subject was to undergo all end of study (week 148) procedures and assessments.
16 Performed at visit 33 (week 124) only.
17 For visit 2A only, ± 3 days window.
18 FP/FA may have been performed at visit 1 or visit 2; images were required to be reviewed by the investigator to confirm eligibility prior to randomization.
19 FA was required to be done at any visit where any laser re-treatment criteria were met, and at least 12 weeks had passed since the last laser or sham laser procedure.
20 All ocular assessments were required to be reviewed by the investigator to confirm eligibility prior to randomization.

Abbreviations: AE = adverse event; BCVA = best corrected visual acuity; ECG = electrocardiogram; EQ-5D = EuroQoL 5 Dimensions Questionnaire; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = hemoglobin A1c; IOP = intraocular pressure; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; OCT = optical coherence tomography; VEGF = vascular endothelial growth factor.

The primary endpoint in the study was:
The change in BCVA by ETDRS letter score from baseline to week 52 (visit 15). These results were reported previously in CSR VGFT-OD-1009 (week 52). To evaluate persistence of effect,

change from baseline in BCVA at week 100 was analyzed in the same method as for week 52 and was considered a secondary endpoint under the United States SAP at week 100.

Under the global SAP, all secondary endpoints defined for week 52 were considered exploratory at week 100. Of these endpoints, all were considered secondary at week 100 under the United States SAP.

The following endpoints were hierchical secondary endpoints only in US SAP and exploratory in Global SAP:
2. Change in BCVA by ETDRS letter score from baseline to week 100
3. Proportion of subjects who gained ≥10 ETDRS letters from baseline to week 100
4. Proportion of subjects who gained ≥15 ETDRS letters from baseline to week 100
5. Proportion of subjects who achieved a ≥2-step improvement on the ETDRS DRSS from baseline to week 100
6. Change in CRT from baseline to week 100, as assessed on OCT
7. NEI VFQ-25 near activities subscale change from baseline to week 100
8. NEI VFQ-25 distance activities subscale change from baseline to week 100

The following additional endpoints were analyzed at week 100 as exploratory in both the global and United States SAPs:

- Proportion of subjects who gained ≥0 and ≥5 ETDRS letters from baseline
- Proportion of subjects who lost ≥5, ≥10, and ≥15 ETDRS letters from baseline
- Time to first gain of ≥15 ETDRS letters from baseline
- Time to first confirmed gain of ≥15 ETDRS letters from baseline
- Proportion of subjects with a ≥2-step worsening from baseline in the DRSS score as assessed on FP
- Proportion of subjects with a ≥3-step improvement from baseline in the DRSS score as assessed on FP
- Proportion of subjects with a ≥3-step worsening from baseline in the DRSS score as assessed on FP
- Change from baseline in the NEI VFQ-25 total score and subscales over time

According to the global SAP, statistical hypotheses were not formally tested for the efficacy endpoints at week 100. According to the United States SAP, statistical comparisons between each of the VEGF Trap-Eye groups and the laser group were made for the secondary efficacy as listed above.

Description of the DRSS scale:

- None (level 10)
- Mild to moderate nonproliferative DR (levels 14, 15, 20, 35, and 43)
- Moderately severe/severe nonproliferative DR (levels 47 and 53)
- Mild/moderate/high-risk/advanced proliferative DR (levels 61, 65, 71, 75, 81, and 85)
- Cannot grade cases appear as level 90 in the database

Only one eye was assessed for a 2 step improvement on the DRSS scale. A 2 step improvement in one eye is considered clinically significant.

Vivid: Study 91745

Study 91745 is an ongoing phase 3, randomized, double-masked, multicenter international clinical study to assess the potential benefit of VEGF Trap-Eye treatment administered IVT compared with standard of care laser treatment over 148 weeks in subjects with DME secondary to diabetes mellitus. The protocol was the same as Vista except:

Inclusion Criteria

- Retinal thickness as assessed by OCT of ≥300 μm in the study eye
- Provided a signed informed consent form (ICF). In Japan only, the ICF for a subject under the age of 20 years required the co-signature of the subject's legally authorized representative

Exclusion Criteria

- More than 2 previous macular laser treatments in the study eye or, in the opinion of the investigator, the subject had no potential to benefit from laser treatments (eg, if too many laser treatments were applied in the past)
- History of idiopathic or autoimmune uveitis in the study eye
- Ocular inflammation including trace or above in the study eye
- Filtration surgery for glaucoma in the past or likely to be needed in the future on the study eye
- Myopia of a spherical equivalent prior to any possible refractive or cataract surgery of ≥-8 diopters
- Uncontrolled DM, as defined by glycosylated hemoglobin (HbA1c) >12%.
- Allergy to fluorescein
- Participation in an investigational study within 30 days prior to Screening visit that involved treatment with any drug (excluding vitamins and minerals) or device

Laser Re-treatment and Additional treatment identical to Study Vista.

Table 3 Schedule of Assessments and Study Procedures

Study Procedure	Screen	Treatment																End of Study
		Year 1								Year 2				Year 3				
Visit	1	2	3	4-5	6	7-8	9	10-15	16 [a]	17-21	22	23-27	28	29-33	34	35-39	ET [b]	40
Week	- 3 - 0	0	0	4-8	12	16-20	24	28-48	52	56-72	76	80-96	100	104-120	124	128-144		148
Day (± 7 days), except visits 2 and 3 (± 1-3 days)	-21 to -1	1	2-4	29-57	85	113 – 141	169	197 - 337	365	393 - 505	533	561 - 673	701	729-841	869	897 - 1009		1037
Informed consent	●																	
Demographics	●																	
Medical/ophthalmic history	●																	
In/exclusion criteria (check/review)	●	●																
Randomization		●																
Record concomitant medication	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Study drug or sham injection [c]		●		●	●	●	●	●	●	●	●	●	●	●	●	●		
Laser or sham laser (re)treatment [d]		●			O	O	O	O	O	O	O	O	O	O	O	O		
Administer additional treatment [e]							O	O	O	O	O	O	O	O	O	O		
Administer VTE treatment [f]													O	O	O	O		
Visual acuity – ETDRS (bilateral)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Gonioscopy (bilateral)	●						●		●		●		●		●		●	●
Slit lamp (bilateral)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Indirect ophthalmoscopy (bilateral) [g]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Intraocular pressure (bilateral) [g]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
OCT (bilateral)	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Fundus photography/FA (bilateral)	●						●		●		●		●		●		●	●
EQ-5D and NEI VFQ-25 [h]		●					●		●		●		●		●		●	●
Adverse events	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Physical examination [i]	●								●				●				●	●
Vital signs	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Electrocardiogram	●						●		●		●		●		●		●	●

continued

Study Procedure	Screen	Treatment																End of Study
		Year 1								Year 2				Year 3				
Visit	1	2	3	4-5	6	7-8	9	10-15	16 [a]	17-21	22	23-27	28	29-33	34	35-39	ET [b]	40
Week	- 3 - 0	0	0	4-8	12	16-20	24	28-48	52	56-72	76	80-96	100	104-120	124	128-144		148
Day (± 7 days), except visits 2 and 3 (± 1-3 days)	-21 to -1	1	2-4	29-57	85	113 – 141	169	197 - 337	365	393 - 505	533	561 - 673	701	729-841	869	897 - 1009		1037
NYHA functional classification	●						●		●		●		●		●		●	●
Serum pregnancy test [j]	●																	
PT and aPTT	●																	
Hematology panel	●						●		●		●		●		●		●	●
Chemistry panel, hemoglobin A1c	●						●		●		●		●		●		●	●
Urinalysis	●						●		●		●		●		●		●	●
Pharmacokinetics		●[k]	●				●		●									
Antibody sampling		●							●				●				●	●
Pharmacogenetics [L]		●																
Safety follow-up [m]		●		●	●	●	●	●	●	●	●	●	●	●	●	●		

Notes: ● procedure was mandatory at this visit; O procedure was performed only if the appropriate criteria are fulfilled.
aPTT = activated partial thromboplastin time; ED-5D = Euro QOL-5 dimensions questionnaire; ET = early termination; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; NYHA = New York Heart Association; OCT = optical coherence tomography; PT = prothrombin time; VTE = VEGF Trap-Eye.

a Primary endpoint analysis
b If a subject withdrew early, ET procedures and assessments were performed. ET visit was 4 weeks after last dose of study drug (as of Amendment 2).
c The investigator may have scheduled an additional safety visit for the day after the injection.
d All subjects were assessed for laser retreatment at every visit beginning at week 12. If retreatment criteria were met, subjects in the laser group received an active laser treatment, and subjects in the VTE groups received sham laser. Laser/sham laser retreatment was administered on the same day as and prior to sham/VTE injection, and no more than once every 12 weeks.
e Subjects may have been considered for and received additional treatment from week 24 onwards if conditions were met. Subjects who received additional treatment continued with this treatment until the end of the study. Subjects continued with study visits and continued to receive their randomized treatment (as of Amendment 2).
f During year 3, to maintain masking, all subjects except those who have been assigned to receive additional treatment will be assessed using VTE treatment criteria. Subjects randomized to the laser group will receive VTE as needed (as of Amendment 1).
g If an injection (or sham) was part of the visit, procedure is done twice: 6 to 0 hours before on both eyes, and approximately 30 minutes after the injection/laser treatment on study eye only.
h The questionnaires were administered in a quiet room by a certified person.
i Abnormal physical examination findings were documented as AEs, if clinically significant, or in the medical history (as of Amendment 2).

j In women of childbearing potential, a pregnancy test was done as close as possible before the day of injection and repeated in accordance with local law before each study treatment. If local law required, pregnancy tests were performed monthly.
k Before study drug administration (baseline) and 1-4 hours after application.
L A separate informed consent was signed for pharmacogenetics. DNA blood sampling was taken prior to injection, preferably at visit 2; however, it could have also been taken at a later visit, but not later than visit 6.
m Safety follow-up phone call was made 16 to 36 hours after the visit to ensure no signs and symptoms of retinal detachment, endophthalmitis, or other AEs have occurred. Alternatively, the investigator may have scheduled an additional follow-up visit the day after treatment (as of Amendment 1). Safety follow-up for visit 2 could have been combined with visit 3 if visit 3 was on day 2 to day 4 (as of Amendment 1).

Under the global SAP, all secondary endpoints defined for week 52 were considered exploratory at week 100. Of these endpoints, all were considered secondary at week 100 under the US SAP. Under the US SAP, hypothesis testing at year 1 paused after a single secondary endpoint in order to reserve alpha for additional hypothesis testing in year 2. The list of endpoints and testing hierarchy defined in both the US and the global SAP are depicted below in Table 5.

Table 5 Efficacy Endpoints at Week 100 - Status and Statistical Analysis Plans Across Regions

Variable	Global SAP (exUS)		United States SAP	
	Status	Test order	Status	Test order [a]
Change in BCVA from baseline	Exploratory	-	Secondary	2 [b]
Proportion of subjects who gained ≥ 10 ETDRS letters from baseline	Exploratory	-	Secondary	3
Proportion of subjects who gained ≥ 15 ETDRS letters from baseline	Exploratory	-	Secondary	4
Proportion of subjects with a ≥ 2-step improvement from baseline in the ETDRS DRSS, assessed by FP	Exploratory	-	Secondary	5
Change in CRT from baseline, as assessed by OCT	Exploratory	-	Secondary	6
NEI VFQ-25 near activities subscale change from baseline	Exploratory	-	Secondary	7
NEI VFQ-25 distance activities subscale change from baseline	Exploratory	-	Secondary	8
Proportion of subjects who gained ≥0 and ≥5 ETDRS letters from baseline	Exploratory	-	Exploratory	-
Proportion of subjects who lost ≥5, ≥10, and ≥15 ETDRS letters from baseline	Exploratory	-	Exploratory	-
Time to first gain of ≥15 ETDRS letters from baseline	Exploratory	-	Exploratory	-
Time to first confirmed gain of ≥15 ETDRS letters from baseline	Exploratory	-	Exploratory	-
Proportions of subjects with a ≥2-step worsening from baseline in the DRSS score as assessed on FP	Exploratory	-	Exploratory	-
Proportions of subjects with a ≥3-step improvement from baseline in the DRSS score as assessed on FP	Exploratory	-	Exploratory	-
Proportions of subjects with a ≥3-step worsening from baseline in the DRSS score as assessed on FP	Exploratory	-	Exploratory	-
Change from baseline in the NEI VFQ-25 total score and subscales over time	Exploratory	-	Exploratory	-

BCVA = best corrected visual acuity; CRT = central retinal thickness; DRSS = diabetic retinopathy severity scale; ETDRS = Early Treatment Diabetic Retinopathy Study; FP = fundus photography; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; OCT = optical coherence tomography; SAP = Statistical Analysis Plan; US = United States.
a Hierarchical testing procedure for secondary endpoints to control for Type-I error.
b "Proportion of subjects who gained ≥ 15 ETDRS Letters from baseline to week 52" was analyzed at week 52 as the first secondary endpoint.

For all efficacy analyses, measurements obtained after the initiation of additional treatment were censored. Missing or censored values were imputed using the last non-censored value (LOCF). Baseline values were not carried forward.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is the treatment of diabetic retinopathy in patients with diabetic macular edema.

6.1.1 Methods

The support for efficacy is from two clinical studies [Studies Vista (VGFT-09-1009) and Vivid (91475)].

6.1.2 Demographics

For demographic data including age, sex, ethnicity, and race refer to Clinical Review for Supplement 037.

Vista: Baseline DRRS Score

	Laser N=154	**VTE 2Q4 N=154**	**VTE 2Q8 N=151**
Baseline DRRS score			
10	1	4	4
20	3	5	3
35	5	7	9
43	60	49	52
47	26	26	32
53	42	53	40
61	1	1	2
65	10	4	5
71	1	4	1
75	1	0	0
90	4	1	3

Vivid: Baseline DRRS Score

	Laser N=132	**VTE 2Q4 N=136**	**VTE 2Q8 N=135**
Baseline DRRS score			
10	0	0	0
20	1	0	0
35	2	0	1
43	36	31	28
47	24	18	27
53	35	44	42
61	1	2	2

	Laser N=132	VTE 2Q4 N=136	VTE 2Q8 N=135
65	0	2	1
71	0	0	0
75	0	0	0
90	33	39	34

6.1.3 Patient Disposition

Vista: Disposition

	Laser N=156	VTE 2Q4 N=156	VTE 2Q8 N=154
Randomized	156	156	154
Received study medication	154	155	152
Randomized but not treated	2	1	2
Completed week 100			
Yes	133 (85.3%)	125 (80.1%)	127 (82.5%)
No	23 (14.7%)	31 (19.9%)	27 (17.5%)
Primary reason for premature discontinuation			
AE	5	4	4
Death	3	7	5
Withdrawal by subject	9	11	11
Lost to f/u	2	4	5
Other	4	5	2

Vivid: Disposition

	Laser N=132	VTE 2Q4 N=136	VTE 2Q8 N=135
Randomized	135	136	135
Received study medication	133	136	135
Randomized but not treated	2	0	0
Completed week 100			
Yes	105 (79.5%)	115 (84.6%)	110 (81.5%)
No	27 (20.5%)	21 (15.4%)	25 (18.5%)
Primary reason for premature discontinuation			
AE	10	7	8
Death	0	3	6
Lack of efficacy	1	0	1
Withdrawal of consent by subject	14	7	5
Protocol deviation	2	0	1
Lost to f/u	1	2	4

	Laser N=132	VTE 2Q4 N=136	VTE 2Q8 N=135
Physician decision	2	1	0
Therapeutic procedure required	0	1	0

6.1.4 Analysis of Primary Endpoint(s)

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

6.1.5 Analysis of Secondary Endpoints(s)

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 the 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, as assessed by OCT	-105 (-140, -70)	<0.0001	-111 (-143, -79)	<0.0001
NEI VFQ-25 near activities subscale from baseline to week 100	4.59 (-0.73, 9.90)	0.0529	5.05 (0.12, 9.98)	0.0218
NEI VFQ-25 distance activities subscale change from baseline to week 100	5.80 (0.97, 10.64)	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	P-value	VTE 2Q8 Estimate	P-value

	(97.5% CI)		**(97.5% CI)**	
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	33.1 (20.3, 45.9)	<0.0001	24.6 (11.9, 37.3)	<0.0001
Proportion of subjects (%) who gained >= 15 ETDRS letter from baseline to week 100	26.1 (14.8, 37.5)	<0.0001	19.0 (8.0, 29.9)	0.0001
Proportion of subjects (%)who achieved a >=2 step improvement on the ETDRS DRSS from 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, as assessed by OCT	-154 (-189, -120)	<0.0001	-127 (-165, -89)	<0.0001
NEI VFQ-25 near activities subscale from baseline to week 100	3.64 (-0.70, 7.98)	0.0596	-0.74 (-5.25, 3.78)	0.7144
NEI VFQ-25 distance activities subscale change from baseline to week 100	2.57 (-1.73, 6.86)	0.1792	-1.30 (-6.00, 3.39)	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* (16.0%)	58/153* (37.9%)	56/148* (37.8%)
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* (7.1%)	27/97* (27.8%)	32/101* (31.7%)
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 (9.7%)	43/108 (39.8%)	40/99 (40.4%)
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:
A two-step change on the DRSS in one eye is considered a clinically meaningful endpoint. Both aflibercept studies (Vista and Vivid) achieved this two-step change with statistical significance.

6.1.6 Other Endpoints

Vista: Proportion of Patients with a 3 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 >=3 step improvement from baseline	8 (5.2%)	35 (22.7%)	30 (19.9)
Difference (%) vs. Laser		17.8	14.6
97.5% CI for difference		(9.2, 26.4)	(6.3, 23.0)
P-value		<0.0001	0.0001

Vivid: Proportion of Patients with a 3 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 >=3 step improvement from baseline	0	6(7.3%)	2 (2.3%)
Difference (%) vs. Laser		7.3	2.3
97.5% CI for difference		(0.8, 13.9)	(-1.4, 6.0)
P-value		0.0118	0.1573

Reviewer's Comment:
Only the 2Q4 dosing regimen demonstrated a 3 step improvement in the DRSS in both trials.

6.1.7 Subpopulations

Reviewer's Comment:
There was not a significant interaction between treatment effect and age, gender, race, or HBA1c in the two trials.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See Section 6.1.4.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The current analysis of Vista and Vivid examined the efficacy of aflibercept at Week 100. The studies are ongoing and further efficacy analyses will be available once the studies are completed.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Two clinical studies (Vista and Vivid) were used to evaluate safety.

7.1.2 Adequacy of Data

The main support for safety comes from the following 2 trials: Vista and Vivid.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Two studies are used to support the safety of Eylea.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Study Vista (VGFT-OD-1009): Treatment Exposure (Not Including Additional Treatment) in the Study Eye in the First 100 Weeks (Safety Analysis Set)

	Laser N=154	**VTE 2Q4 N=155**	**VTE 2Q8 N=152**
Total number of active laser treatments	544	0	0
Total number of sham laser treatments	0	370	425
Number of active laser treatments during the first 100 weeks			
1	25	0	0
2	30	0	0
3	30	0	0
4	25	0	0
5	19	0	0
6	8	0	0
7	10	0	0
8	7	0	0
Summary of active laser treatments			

	Laser N=154	**VTE 2Q4 N=155**	**VTE 2Q8 N=152**
N	154	0	0
Mean (sd)	3.5 (2.0)		
Min, Max	1, 8		
Total number of active VTE injections	0	3308	2053
Total number of sham injections	2899	0	1315
Number of active VTE injections during the first 100 weeks			
1	0	4	2
2	0	1	0
3	0	0	0
4	0	1	2
5	0	0	3
6	0	3	2
7	0	1	0
8	0	1	3
9	0	0	2
10	0	2	2
11	0	0	7
12	0	1	6
13	0	1	8
14	0	2	25
15	0	1	89
16	0	4	1
17	0	4	0
18	0	4	0
19	0	1	0
20	0	4	0
21	0	9	0
22	0	11	0
23	0	15	0
24	0	27	0
25	0	58	0
Summary of active injections			
N	0	155	152
Mean (sd)	0	21.3 (5.8)	13.5 (2.9)
Min, Max	0	1, 25	1, 16

Study Vivid: Treatment Exposure (Not Including Additional Treatment) in the Study Eye in the First 100 Weeks (Safety Analysis Set)

	Laser N=133	**VTE 2Q4 N=136**	**VTE 2Q8 N=135**
Total number of active laser treatments	317	0	0
Total number of sham laser treatments	2	233	307
Number of active laser treatments			

	Laser N=133	**VTE 2Q4 N=136**	**VTE 2Q8 N=135**
during the first 100 weeks			
1	52	0	0
2	30	0	0
3	22	0	0
4	12	0	0
5	8	0	0
6	5	0	0
7	3	0	0
Summary of active laser treatments			
N	132	0	0
Mean (sd)	2.4 (1.6)		
Min, Max	1, 7		
Total number of active VTE injections	0	3077	1838
Total number of sham injections	2488	0	1205
Number of active VTE injections during the first 100 weeks			
1	0	2	2
2	0	2	0
3	0	2	0
4	0	2	0
5	0	0	0
6	0	0	3
7	0	1	5
8	0	1	2
9	0	0	4
10	0	0	5
11	0	0	1
12	0	1	1
13	0	1	6
14	0	0	11
15	0	0	94
16	0	1	1
17	0	0	0
18	0	3	0
19	0	1	0
20	0	2	0
21	0	1	0
22	0	4	0
23	0	4	0
24	0	13	0
25	0	95	0
Summary of active injections			
N	0	136	135
Mean (sd)	0	22.6 (5.8)	13.6 (2.9)
Min, Max	0	1, 25	1, 16

Additional Treatment in the VEGF Group

Subjects in the VEGF Trap-Eye groups received active laser beginning at week 24, if the criteria for additional treatment were met. The maximum number of possible additional laser treatments was 3.

Study Vista (VGFT-OD-1009): Exposure to Additional Treatment (Laser) in the Study Eye in the VEGF Trap-Eye Groups During Weeks 24 to 100 (Safety Analysis Set)

	VTE 2Q4 N=154	**VTE 2Q8 N=151**
Total number of subjects who received additional treatment (laser treatment)	5 (3.2%)	13 (8.6%)
Total number of additional treatments (laser) received	8	16
Summary of additional treatments received		
Mean (sd)	1.6 (0.9)	1.2 (0.6)
Min, Max	1, 3	1, 3

Study Vivid (91475): Exposure to Additional Treatment (Laser) in the Study Eye in the VEGF Trap-Eye Groups (Safety Analysis Set)

	VTE 2Q4 N=136	**VTE 2Q8 N=135**
Total number of subjects who received additional treatment (laser treatment)	10 (7.4%)	15 (11.1%)
Total number of additional treatments (laser) received	19	25
Summary of additional treatments received		
N	10	15
Mean (sd)	1.9 (1.1)	1.7 (0.8)
Min, Max	1, 4	1, 3

Additional Treatment in the Laser Group

Subjects in the laser group received VEGF Trap-Eye injections beginning at week 24, if the criteria for additional treatment were met. The maximum number of possible additional laser treatments from week 24 through week 100 was 7.

Study Vista (VGFT-OD-1009): Exposure to Additional Treatment (VEGF Trap-Eye) in the Laser Groups (Safety Analysis Set)

	Laser N=154
Total number of subjects who received additional treatment	63 (40.9%)
Total number of lasers given before additional treatment received	
Mean	2.7 (1.4)

	Laser N=154
Min, Max	1, 7
Total number of additional treatments (VTE) received	559
Number of additional treatments received (VTE injections)	
1	1
2	0
3	2
4	1
5	5
6	5
7	5
8	4
9	8
10	10
11	10
12	12
Summary of additional treatments received	
Mean (sd)	8.9 (2.7)
Min, Max	1, 12
Duration of additional treatment received	
Mean (sd)	377.5 (138.7)
Min, Max	28, 539

Study Vivid (91475): Exposure to Additional Treatment (VEGF Trap-Eye) in the Laser Groups (Safety Analysis Set)

	Laser N=133
Total number of subjects who received additional treatment	46
Total number of lasers given before additional treatment received	46
Mean	2.3 (1.2)
Min, Max	1, 5
Total number of additional treatments (VTE) received	403
Number of additional treatments received (VTE injections)	
1	2
2	0
3	0
4	0
5	4
6	7
7	0
8	6
9	3

	Laser N=133
10	9
11	6
12	9
Summary of additional treatments received	
Mean (sd)	8.8 (2.9)
Min, Max	1, 12
Duration of additional treatment received	
Mean (sd)	51.8 (21.2)
Min, Max	4, 77

7.2.2 Explorations for Dose Response

Two dosing regimens were studied, i.e. 2Q4 and 2Q8.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

Vista:
The following parameters were monitored: hematology, chemistry, U/A, and HbA1c. The incidence of cholesterol levels and glucose levels above normal limits were lower at week 100 compared to baseline. No other trends toward an increase or decrease in the frequency of chemistry parameters above normal limits were seen.

Vivid:
No trends towards an increase or decrease in mean values over time were seen in the parameters tested in any of the treatment groups in hematology, chemistry, U/A, or HbA1c.

7.2.5 Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance, and interaction were not performed due to the negligible systemic absorption of aflibercept.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events for this class of drug (anti-VEGF) are known. AEs include: elevated IOP, intraocular inflammation, AEs at the injection site (i.e. subconjunctival hemorrhage, scleral pathology, etc.), non-infectious inflammatory eye reactions due to immunogenicity, arterial

thromboembolic events, systemic reactions related to immunogenicity, hypertension, problems with nasal mucosa, and RPE tears

7.3 Major Safety Results

7.3.1 Deaths

Study Vista (VGFT-OD-1009): Listing of Deaths through Week 100 (Safety Analysis Set)

Treatment group	Subject number	Study day	Number of days after last dose	Cause
VTE 2Q4	(b) (6)	10	10	Cause of death is unknown. This 67-year old female subject had a medical history of CAD, DM, hypertension, and dyslipidemia. The subject died in her sleep. The subject received only 1 dose of VEGF Trap-Eye.
		88	4	MI
		633	40	Pulseless electrical activity
		479	82	Pneumonia
		657	14	Cardiac arrest
		514	61	Chronic renal failure
		494	2	CVA
		433	40	Acute cardiac failure
VTE 2Q8		639	13	Cardiac arrest
		737	68	Cardiac failure
		672	175	Cardiac arrest
		494	15	CVA
		511	28	Arteriosclerosis
Laser		77	17	Sudden cardiac death
		587	52	Cardiac arrest
		510	4	Multi-organ failure

Study Vivid (91745): Listing of Deaths through Week 10 (Safety Analysis Set)

Treatment group	Subject number	Study day	Number of days after last dose	Cause
VTE 2Q4	(b) (6)	530	24	MI
		671	52	Colon CA
		504	24	MI
		549	19	Brain herniation
VTE 2Q8		346	17	Hypertensive heart disease
		321	32	Lung CA
		289	37	B cell lymphoma Pneumonia

Treatment group	Subject number	Study day	Number of days after last dose	Cause
	(b) (6)	331	23	Cardiac failure
		406	77	MI
		605	17	Ventricular arrythmia
Laser		313	89	Acute MI

7.3.2 Nonfatal Serious Adverse Events

Study Vista (VGFT-OD-1009): All Ocular SAEs in the Study Eye during First 100 Weeks (Safety Analysis Set)

	Laser N=154	VTE 2Q4 N=155	VTE 2Q8 N=152
No. of subjects with any ocular SAE in the study eye	7	9	4
Vitreous hemorrhage	3	2	1
Cataract	1	4	0
Visual acuity reduced	0	1	1
Hyphema	0	1	0
Lens dislocation	0	1	0
Punctate keratitis	0	1	0
Retinal artery occlusion	0	0	1
Retinal detachment	0	1	0
Retinal ischemia	0	1	0
IOP increased	0	0	1
Visual acuity test abnormal	0	0	1
Visual field defect	0	0	1
Diabetic retinopathy	2	0	0
Corneal epithelium defect	1	0	0
Retinal hemorrhage	1	0	0

Study Vista (VGFT-OD-1009): Non-Ocular SAEs through Week 100 Occurring in >= 1% of Any One Treatment (Safety Analysis Set)

	Laser N=154	VTE 2Q4 N=155	VTE 2Q8 N=152
No. of subjects with any non-ocular SAE in the study eye	67	67	56
Infections	19	20	21
Cellulitis	4	7	8
Osteomyelitis	3	5	2
Pneumonia	4	4	3
Abscess limb	2	2	2
Gangrene	0	2	1

	Laser N=154	**VTE 2Q4 N=155**	**VTE 2Q8 N=152**
Gastroenteritis	1	1	2
Urosepsis	1	2	1
Sepsis	2	2	0
UTI	2	0	0
Cardiac disorders	20	19	12
CHF	5	9	5
Coronary artery stenosis	3	4	5
MI	3	5	3
CAD	2	4	2
Acute MI	3	2	2
Atrial fibrillation	0	1	3
Cardiac arrest	2	1	1
Coronary artery occlusion	0	0	2
Cardiac failure acute	4	1	0
Renal disorders	15	18	11
Renal failure acute	7	6	6
Renal failure	4	5	1
Renal failure chronic	2	4	3
Metabolism	8	16	8
Diabetes mellitus inadequate control	0	3	2
Hypoglycemia	1	5	0
Dehydration	1	2	2
DKA	1	2	2
Hyperkalemia	4	3	1
Neoplasms	2	13	7
Prostate CA	0	3	0
Invasive ductal breast CA	0	1	3
Breast CA	0	3	0
Squamous cell CA of skin	0	1	2
Injury	7	9	7
Fall	2	3	5
Road traffic accident	1	2	1
Laceration	0	2	0
Blood disorders	1	11	5
Anemia	1	9	5
Nervous system disorders	9	13	12
CVA	2	5	5
Carotid artery stenosis	0	2	0
Syncope	2	2	0
TIA	3	0	1
Vascular disorders	7	11	6

	Laser N=154	VTE 2Q4 N=155	VTE 2Q8 N=152
HTN	3	5	1
Hypertensive crisis	2	2	0
Orthostatic hypotension	2	1	0
General disorders	7	5	9
Chest pain	3	1	4
Asthenia	0	0	2
Peripheral edema	2	0	1
GI disorders	11	4	5
GI hemorrhage	2	3	1
Diabetic gastroparesis	2	0	0
Small intestinal obstruction	2	0	0
Skin disorders	0	3	3
Diabetic foot	0	2	2
Musculoskeletal disorders	7	9	2
Osteoarthritis	3	4	0
Intervertebral disc protrusion	0	1	2
Neuropathic arthropathy	0	2	0
Psychiatric disorders	4	3	3
Mental status changes	0	2	1
Depression	2	1	0
Respiratory disorders	7	8	1
Hypoxia	0	2	0
COPD	2	0	0

Study Vivid (91475): All Ocular SAEs in the Study Eye during First 100 Weeks (Safety Analysis Set)

	Laser N=133	VTE 2Q4 N=136	VTE 2Q8 N=135
No. of subjects with any ocular SAE in the study eye	10	6	7
Cataract	0	3	3
Cataract operation	2	1	1
Cataract subcapsular	0	0	1
Diabetic retinopathy	2	0	0
Macular degeneration	1	0	0
Retinal artery occlusion	0	1	0
Retinal detachment	0	0	1
Retinal exudates	1	0	0
Retinal neovascularization	3	0	0
Retinal vascular disorder	1	0	0
Vitreous hemorrhage	2	1	1

	Laser N=133	VTE 2Q4 N=136	VTE 2Q8 N=135
Injection site injury	0	1	0

Study Vivid (91475): Treatment Emergent Non-Ocular SAEs through Week 100 Occurring in >=1% of Subjects (Safety Analysis Set)

	Laser N=133	VTE 2Q4 N=136	VTE 2Q8 N=135
No. of subjects with at least 1 non-ocular SAE in the study eye	30	36	38
Cardiac disorders	7	10	6
Acute MI	3	1	0
Cardiac failure	2	1	2
Coronary artery stenosis	0	2	0
MI	0	4	0
Infections	4	1	4
Cellulitis	2	0	0
Injury	5	5	6
Humerus fracture	0	2	1
Metabolism disorders	3	2	6
Diabetes mellitus	1	1	2
Hyperglycemia	1	0	2
Muscular disorders	4	4	4
Osteoarthritis	0	2	0
Nervous system disorders	1	7	3
CVA	0	2	1
Skin disorders	3	1	0
Psoriasis	2	0	0
Vascular disorders	5	3	4
Peripheral arterial occlusive disease	2	0	2

7.3.3 Dropouts and/or Discontinuations

Study Vista (VGFT-OD-1009): Treatment Emergent AEs Leading to Discontinuation of Study Drug through Week 100 (Safety Analysis Set)

	Laser N=154	**VTE 2Q4 N=155**	**VTE 2Q8 N=152**
Subjects with at least 1 TEAE leading to discontinuation of drug	2	4	2
Nervous system	0	2	1
Brain stem stroke	0	1	0
CVA	0	1	0
Multiple sclerosis	0	0	1
Eye disorders	1	2	0
Cataract	0	1	0
Retinal ischemia	0	1	0
Vitreous hemorrhage	1	0	0
General disorders	0	0	1
Asthenia	0	0	1
Metabolism disorders	0	0	1
Dehydration	0	0	1
Neoplasms	0	0	1
Diffuse large B-cell lymphoma	0	0	1
Investigations	1	0	0
Decreased hemoglobin	1	0	0

Study Vivid (91475): Treatment Emergent AEs Leading to Discontinuation of Study Drug through Week 100 (Safety Analysis Set)

	Laser N=133	**VTE 2Q4 N=136**	**VTE 2Q8 N=135**
Subjects with at least 1 TEAE leading to discontinuation of drug	8	6	5
Ocular disorders	5	1	0
Diabetic retinopathy	2	0	0
PCO	1	0	0
Retinal artery occlusion	0	1	0
Retinal exudates	1	0	0
Retinal neovascularization	1	0	0
Retinopathy	1	0	0
Sudden visual loss	1	0	0
Visual acuity reduced	1	0	0
Cardiac disorders	2	0	0

	Laser N=133	VTE 2Q4 N=136	VTE 2Q8 N=135
Acute MI	2	0	0
Gastrointestinal disorders	1	1	0
Enterocolitis	1	0	0
Intestinal obstruction	0	1	0
Injury	0	0	1
Subdural hematoma	0	0	1
Neoplasms	0	1	2
Adenocarcinoma of colon	0	0	1
Colon CA	0	1	0
Nervous system disorders	0	1	0
Ischemic stroke	0	1	0
Renal disorders	1	1	2
Renal failure	1	0	0
Renal failure chronic	0	1	1
Renal impairment	0	0	1
Vascular disorders	0	1	0
Hypertensive crisis	0	1	0

7.3.4 Significant Adverse Events

See section 7.3.2

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study Vista (VGFT-OD-1009): Ocular Treatment Emergent AEs in the Study Eye Through Week 100 Occurring in At Least 1% (Safety Analysis Set)

	Laser N=154	2Q4 N=155	2Q8 N=152
Number of patients with at least one ocular treatment emergent AE in study eye	120	113	108
Conjunctival hemorrhage	53	63	48

Eye pain	20	23	21
Vitreous floaters	14	21	17
Vitreous detachment	15	14	22
Cataract	17	21	13
Eye irritation	12	15	11
Macular fibrosis	15	11	15
Dry eye	10	14	7
Visual acuity reduced	11	8	11
Vision blurred	10	11	6
Retinal exudates	13	12	4
Posterior capsular opacification	12	7	8
Retinal hemorrhage	16	10	5
Cataract subcapsular	7	6	8
FBS in eyes	8	8	5
Lacrimation increased	6	7	6
Retinal pigment epitheliopathy	3	5	8
Vitreous hemorrhage	14	10	3
Ocular hyperemia	12	6	6
Punctate keratitis	1	5	7
Blepharitis	4	2	7
Cataract cortical	8	2	7
Cataract nuclear	6	5	2
Eye pruritis	3	3	4
Retinal vascular disorder	2	3	4
Retinal neovascularization	12	3	3
Vitreous adhesions	4	4	2
Optic atrophy	2	4	1
Retinal aneurysm	4	2	3
Abnormal sensation in eye	0	3	1
Conjunctival hyperemia	1	3	1
Conjunctivitis allergic	1	2	2
Diabetic retinopathy	8	2	2
Diplopia	1	4	0
Keratitis	2	1	3
Photophobia	3	2	2
Pinguecula	1	1	3
Visual impairment	7	1	3
Blindness transient	0	0	3
Chalazion	1	2	1
Diabetic retinal edema	5	1	2
Eye discharge	1	3	0
Eyelid edema	1	0	3
Narrow anterior chamber angle	0	1	2
Ocular hypertension	0	3	0
Optic disc vascular disorder	1	2	1
Photopsia	7	2	1
Retinal artery embolism	1	3	0
Blepharochalasis	0	2	0

Blindness unilateral	0	2	0
Corneal epithelial defect	1	0	2
Eyelid irritation	2	2	0
Glaucoma	4	1	1
Iridocyclitis	0	2	0
Retinopathy	0	0	2
CME	3	0	1
Macular edema	3	0	0
Ocular discomfort	3	0	0
Optic disc hemorrhage	5	0	0
IOP increased	2	12	10
Optic nerve c/d ratio increased	4	4	2
Visual acuity tests abnormal	5	2	3
Corneal abrasion	6	4	6
Procedural complication	2	0	0
Injection site pain	1	4	2
Injection site irritation	3	1	0
Drug hypersensitivity	2	1	0

Study Vivid (91475): Ocular Treatment Emergent AEs in the Study Eye Through Week 100 Occurring in At Least 1% (Safety Analysis Set)

	Laser N=133	**2Q4 N=136**	**2Q8 N=135**
Number of patients with at least one ocular treatment emergent AE in study eye	95	99	98
Conjunctival hemorrhage	7	36	33
Cataract	8	15	18
Visual acuity reduced	21	10	17
Retinal exudates	12	11	13
Eye pain	6	11	7
Retinal hemorrhage	16	6	11
Retinal aneurysm	6	6	8
Punctate keratitis	4	6	7
Ocular hypertension	0	8	4
Cataract cortical	0	6	5
Vitreous floaters	2	9	2
Cataract subcapsular	1	7	3
CME	12	1	9
Vitreous detachment	3	4	6
Lacrimation increased	0	6	3
Ocular hyperemia	2	3	6
Corneal erosion	4	3	5
Diabetic retinal edema	4	2	6
Dry eye	4	5	3
Macular fibrosis	4	2	6
Posterior capsular opacification	5	2	6

Vitreous hemorrhage	6	4	4
Retinal vascular disorder	2	4	3
Cataract nuclear	4	2	4
Conjunctival hyperemia	5	5	1
Conjunctivitis allergic	2	2	4
Eye pruritus	2	4	2
Eyelid edema	3	3	3
FBS	2	2	4
Keratitis	2	4	2
Blepharitis	4	1	4
Macular edema	7	1	4
Eyelid irritation	1	1	3
Phtophobia	0	2	2
Chalazion	0	2	1
Corneal opacity	2	1	2
Keratopathy	1	1	2
Lenticular opacities	2	2	1
Macular hole	1	2	1
Optic disc hemorrhage	0	0	3
Vision blurred	2	1	2
Visual impairment	2	0	3
Vitreous opacities	0	2	1
Abnormal sensation in eye	2	0	2
Corneal edema	2	1	1
Eye inflammation	0	2	0
Retinal artery occlusion	0	2	0
Retinal detachment	1	0	2
Retinal neovascularization	6	2	0
Retinal pigment epitheliopathy	2	1	1
Diabetic retinopathy	5	0	1
Macular cyst	3	1	0
Maculopathy	5	1	0
Conjunctival edema	2	0	0
Eye discharge	2	0	0
Eyelids pruritus	2	0	0
Iris neovascularization	2	0	0
Retinopathy	3	0	0
IOP increased	11	21	10
Visual acuity tests abnormal	25	5	13
Conjunctivitis	5	4	6
Injection site pain	1	2	3
Procedural pain	0	2	0
Cataract operation	2	1	1
Drug hypersensitivity	0	2	0
Sjogren's syndrome	3	0	0

Study Vista (VGFT-OD-1009): Non-Ocular Treatment Emergent AEs Occurring in >=3% of Subjects (Safety Analysis Set)

	Laser N=154	**VTE 2Q4 N=155**	**VTE 2Q8 N=152**
Any non-ocular AE	143	142	142
Infections	84	94	98
UTI	14	17	26
Nasophayrngitis	17	17	19
Upper respiratory tract	13	11	15
Sinusitis	12	13	12
Influenza	10	7	16
Cellulitis	7	10	12
Bronchitis	12	13	5
Localized infection	6	10	5
Pneumonia	7	8	7
Ear infection	4	3	6
Cystitis	1	6	2
Gastroenteritis viral	2	2	6
Osteomyelitis	4	6	2
Gastroenteritis	5	3	2
Vascular disorders	63	52	49
HTN	50	45	42
Metabolism disorders	56	63	50
DM	20	13	19
Hyperkalemia	12	10	6
Hypoglycemia	4	11	5
Type 2 diabetes mellitis	6	9	5
Dehydration	5	7	5
Vitamin D deficiency	7	6	5
Hypercholesterolemia	10	5	3
Hyperglycemia	7	6	2
Hyperlipidemia	5	6	2
Hypokalemia	3	5	2
Hyponatremia	1	0	5
GI disorders	53	48	42
Nausea	15	19	11
Diarrhea	14	14	6
Vomiting	7	14	3
Constipation	9	11	5
GERD	9	10	5
Investigations	53	42	47
Blood glucose increased	6	9	11
Glycosylated hemoglobin increased	7	7	13
Blood pressure increased	10	9	7
Blood CPK increased	12	7	4

	Laser N=154	**VTE 2Q4 N=155**	**VTE 2Q8 N=152**
Blood urea increased	4	6	3
Blood creatinine increased	5	5	3
Hematocrit decreased	4	5	3
Blood pressure systolic increased	2	2	5
Hemoglobin decreased	5	5	2
Urine protein/creatinine ratio increased	8	5	2
Blood potassium increased	5	4	2
Musculoskeletal disorders	53	49	38
Back pain	8	20	6
Arthralgia	9	9	8
Arthritis	7	5	10
Pain in extremity	10	8	5
Osteoarthritis	7	7	5
Muscle spasms	8	5	2
Musculoskeletal pain	5	3	3
Exostosis	1	5	0
Nervous system disorders	54	42	43
HA	19	19	7
Dizziness	8	8	9
Neuropathy peripheral	5	5	7
CVA	2	5	5
Diabetic neuropathy	3	2	5
Syncope	6	3	2
Hypaesthesia	5	2	1
Respiratory disorders	37	43	42
Cough	13	18	17
Dyspnea	6	12	11
Respiratory tract congestion	3	2	5
Pulmonary edema	4	5	0
Injury	40	41	40
Fall	9	9	14
Procedural pain	1	8	2
Laceration	3	3	5
Ligament sprain	5	1	7
General Disorders	35	39	34
Edema peripheral	9	15	16
Chest pain	12	4	9
Pyrexia	2	7	6
Fatigue	4	8	3
Asthenia	4	3	5
Pain	4	5	3
Renal	42	35	32

	Laser N=154	VTE 2Q4 N=155	VTE 2Q8 N=152
Renal failure acute	11	10	9
Renal failure	9	10	7
Renal failure chronic	4	9	8
Hematuria	5	1	2
Blood disorders	22	35	19
Anemia	13	29	16
Iron deficiency anemia	0	6	0
Cardiac Disorders	33	29	23
CHF	6	12	9
Coronary artery stenosis	3	5	5
CAD	3	5	4
MI	3	6	3
Psychiatric disorders	18	23	12
Anxiety	7	12	4
Depression	7	7	4
Insomnia	5	4	4
Immune system disorders	10	15	14
Seasonal allergy	8	6	9
Drug hypersensitivity	2	5	3
Endocrine disorders	9	8	7
Hypothyroidism	7	4	5

Study Vivid (91745): Non-Ocular Treatment Emergent AEs in the Study Eye Through Week 100 Occurring in >=3% (Safety Analysis Set)

	Laser N=133	VTE 2Q4 N=136	VTE 2Q8 N=135
Any non-ocular AE	102	113	112
Infections	53	49	59
Nasophayrngitis	29	32	32
UTI	4	6	10
Influenza	9	4	10
Bronchitis	8	9	2
Investigations	26	35	31
Glycosylated hemoglobin increased	9	10	7
Blood glucose increased	5	6	5
Blood urea increased	5	5	5
Blood creatinine increased	3	5	4
Vascular disorders	28	26	26
HTN	20	22	21

	Laser N=133	**VTE 2Q4 N=136**	**VTE 2Q8 N=135**
Musculoskeletal disorders	17	22	26
Musculoskeletal pain	1	1	6
Pain in extremity	4	4	2
Back pain	4	3	2
Intervertebral disc protrusion	4	2	0
GI disorders	23	22	24
Gastritis	1	5	2
Nervous system disorders	7	18	18
HA	3	4	5
Renal	15	14	16
Diabetic nephropathy	4	4	4
Respiratory disorders	14	12	13
Cough	4	4	6
Orophyrngeal pain	5	2	1
Blood disorders	11	9	11
Anemia	6	6	3
General disorders	13	6	10
Peripheral edema	3	5	2
Skin disorders	11	2	10
Skin ulcer	6	0	0

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

7.4.2 Laboratory Findings

See section 7.2.4.

7.4.3 Vital Signs

In both studies, mean systolic and diastolic blood pressure, heart rate, and body temperature were similar among treatment groups at baseline and varied slightly relative to the baseline values in all treatment groups throughout the study, with no obvious trends over time relative to treatment or dose.

7.4.4 Electrocardiograms (ECGs)

In both studies electrocardiograms were recorded at baseline and week 100. No clinically meaningful changes were noted between baseline and week 100 in ventricular rate, PR duration, RR duration, QRS duration, QT duration, QTc (Bazett), or QTc (Fridericia) in any treatment group

7.4.5 Special Safety Studies

Study Vista (VGFT-OD-1009): Proportion of Subject with Increases in IOP in the Study Eye through Week 100 (Safety Analysis Set)

	Laser N=154	**VTE 2Q4 N=155**	**VTE 2Q8 N=152**
Number of subjects with >=10 mmHg increase in pre-injection IOP from baseline	8	9	8
Number of subjects with a pre-injection IOP>21 mmHg	28	32	25
Number of subjects with a pre-injection IOP>25 mmHg	5	6	5
Number of subjects with IOP>=35 mmHg at any time	0	0	2

Study Vivid (91475): Proportion of Subject with Increases in IOP in the Study Eye through Week 100 (Safety Analysis Set)

	Laser N=133	**VTE 2Q4 N=136**	**VTE 2Q8 N=135**
Number of subjects with >=10 mmHg increase in pre-injection IOP from baseline	3	3	5
Number of subjects with a pre-injection IOP>21 mmHg	24	28	28
Number of subjects with a pre-injection IOP>25 mmHg	3	4	8
Number of subjects with IOP>=35 mmHg at any time	0	4	3

Reviewer's Comment:
There are no clinically relevant differences between treatment groups in IOP.

7.4.6 Immunogenicity

Study Vista (VGFT-OD-1009): Number of Subjects with Anti-VEGF Trap Antibodies by Treatment Group (Safety Analysis Set)

	Laser N=154	**VTE 2Q4 N=155**	**VTE 2Q8 N=152**
Negative	151	145	149
Positive	3	10	3
Treatment emergent positive	2	3	1
Not treatment emergent positive	1	7	2

Study Vivid (91475): Number of Subjects with Anti-VEGF Trap Antibodies by Treatment Group (Safety Analysis Set)

	Laser N=133	**VTE 2Q4 N=136**	**VTE 2Q8 N=135**
Negative	131	136	133
Positive	2	0	2
Treatment emergent positive	1	0	1
Not treatment emergent positive	1	0	1

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not performed.

7.5.2 Time Dependency for Adverse Events

Not performed.

7.5.3 Drug-Demographic Interactions

See section 6.1.7.

7.5.4 Drug-Disease Interactions

Eylea was evaluated for the treatment of DME and DR with no drug-disease interaction analysis.

7.5.5 Drug-Drug Interactions

No studies were conducted to evaluate a drug-drug interaction between Eylea and any of the concomitant medications allowed in those studies.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Because of the low absorption of aflibercept, no carcinogenicity studies were conducted.

7.6.2 Human Reproduction and Pregnancy Data

This drug has not been tested in pregnant women.

7.6.3 Pediatrics and Effect on Growth

This drug was not tested on a pediatric population. Height and weight data were not collected as part of this protocol. Regeneron has requested a waiver to perform pediatric studies because pediatric studies in DR and DME would be impossible or highly impracticable due to the very limited number of pediatric patients with DR and DME.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Eylea is a non-narcotic and does not have abuse potential.

7.7 Additional Submissions

On 1/29/15 the applicant submitted the 4 month safety update. During the period from week 100 to the cut-off date of 9/30/14, 3 additional deaths were reported in Vivid, and 8 additional deaths were reported in Vista.

The overall frequency and types of SAEs in the safety update for Vista and Vivid are similar to that through week 100.

8 Post-marketing Experience

9 Appendices

9.1 Literature Review/References

A pub med search conducted by the medical officer did not reveal any new information on aflibercept.

9.2 Labeling Recommendations

See Appendix (next page).

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SONAL D WADHWA
03/09/2015

WILLIAM M BOYD
03/09/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s048

PRODUCT QUALITY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies, NIH Bldg 29B, HFD-123
29B Lincoln Drive, Bethesda, MD 20892

STN 125387/48, Product Review

Date: October 14, 2014

Reviewer: Tura C. Camilli, Ph.D., DMA/OBP

Through: Michele Dougherty, PhD., Team Leader, DMA/OBP

Submission Type: Efficacy supplement

Product: Aflibercept (Eylea)

Sponsor: Regeneron Pharmaceuticals, Inc.

PDUFA date: March 30, 2015

Purpose of the supplement: Additional indication of treatment of Diabetic nephropathy in patients with Macular Edema (DME).

Comments/Recommendations: From a CMC perspective, no information would preclude the approval of this supplement.

Reviewer comment:

- *No product quality (CMC) –related changes were made to labeling.*
- *A request for Categorical Exclusion from Environment Assessment was submitted and is acceptable per 21 CFR.25.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TURA C CAMILLI
11/04/2014

MICHELE K DOUGHERTY
11/04/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s048

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	sBLA 125387
Supporting document/s:	Efficacy supplement-048
Applicant's letter date:	9-30-14
CDER stamp date:	9-30-14
Product:	Eylea® (aflibercept) Injection
Indication:	Treatment of diabetic retinopathy in patients with diabetic macular edema
Applicant:	Regeneron Pharmaceuticals, Inc
Review Division:	Transplant and Ophthalmology Product
Reviewer:	María I Rivera. PhD
Supervisor/Team Leader:	Lori E Kotch, PhD
Division Director:	Renata Albrecht, MD
Project Manager:	Michael Puglisi

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of sBLA 125387/48 are owned by Regeneron or are data for which Regeneron has obtained a written right of reference. Any information or data necessary for approval of sBLA 125387/48 that Regeneron does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of sBLA 125387/48.

This efficacy supplement proposes a new indication for EYLEA®, i.e., the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME). This application provides 100-week clinical data from two ongoing Phase 3 studies (VGFT-OD-1009 [VISTA DME] and 91745 [VIVID DME]) to support the safety and efficacy of EYLEA in the treatment of DR in patients with DME. The VISTA DME and VIVID DME studies are continuing to Week 148, and additional safety data will be provided in the 4-Month Safety Update Report.

The intended dose for EYLEA® in the treatment of DR is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks for the first 5 injections followed by 2 mg via intravitreal injection once every 8 weeks. The intended dosing regimen is identical to that previously approved by the FDA for the treatment of DME. No new nonclinical studies were submitted with this supplemental BLA. There are no revisions to the nonclinical sections of the previously approved label. As such, there are no new concerns/recommendations from the nonclinical perspective.

CC list:
M. Puglisi/PM
L. Lim/MO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARIA I RIVERA
01/13/2015

LORI E KOTCH
01/13/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s048

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-048
Drug Name:	EYLEA® (aflibercept) Injection
Indication(s):	For the Treatment of Diabetic Retinopathy (DR) in Patients with Diabetic Macular Edema (DME)
Applicant:	Regeneron Pharmaceuticals, Inc.
Date(s):	Stamp Date: September 29, 2014 PDUFA Date: March 30, 2015 Review Date: March 05, 2015
Review Priority:	Priority
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
Clinical Team:	Sonal Wadhwa, MD, Medical Officer William Boyd, MD, Team Leader
Project Manager:	Michael Puglisi

Keywords: Clinical Studies, ANCOVA, Diabetic Macular Edema, Best Corrected Visual Acuity, Diabetic Retinopathy

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

In this efficacy supplemental BLA, the applicant seeks approval of EYLEA® (aflibercept) injection for the treatment of diabetic retinopathy (DR) in patients with Diabetic Macular Edema (DME) based on 2 years data. The recommended Eylea dose for the indication sought is 2 mg injection administered once every 4 weeks for the first five injections followed by once every 8 weeks. The same Eylea dose was approved for the treatment of DME on July 2014 based on 1 year data. In this supplemental BLA, the applicant also seeks to update the label for the DME indication using the 2 years data.

Support for the efficacy and safety of Eylea for the treatment of DR in patients with DME was based on two ongoing phase 3 trials initially submitted for the DME application; Study VGFT-OD-1009 (VISTA) conducted in the US and Study 91745 (VIVID) conducted in the European Union, Japan, and Australia. Both studies were a randomized, double-masked, active-controlled, and multi-center clinical studies designed to evaluate the safety and efficacy of repeated doses of Eylea injection compared to laser in improving best corrected visual acuity (BCVA). Eligible patients in both studies were randomized to one of the following three treatment groups: (i) Eylea 2 mg injections administered once every four weeks (VTE 2Q4), (ii) Eylea 2 mg injections administered once every 4 weeks for the first five injections followed by once every 8 weeks (VTE 2Q8), and (iii) laser administered at baseline and as needed starting at week 12 based on protocol defined criteria (Laser).

The duration of each study was approximately 3 years, and the studies are currently ongoing. The one year (52 week) data was submitted to the Agency as a supplement (BLA125387 SN0101/S-037) for the treatment of DME. The primary endpoint for the DME indication was the mean change in BCVA at week 52 and the key secondary efficacy endpoint was the proportion of patients who gained ≥ 15 letters in BCVA from baseline at week 52. Statistical significance was achieved for these endpoints, and subsequently Eylea 2 mg injections administered once every 4 weeks for the first five injections followed by once every 8 weeks was approved on July 2014 for the treatment of DME.

Contingent upon statistical significance in the primary and the key secondary endpoints for a given Eylea dose group versus laser at week 52, several key secondary endpoints were planned to be compared at week 100 between each Eylea dose group and the laser group separately in a hierarchical manner. In the current submission, the two year (100 week) data was submitted to the Agency as a supplement for the treatment of DR in patients with DME.

The first four secondary endpoints in the hierarchy with visual acuity and DR relevance include: (i) the change in BCVA from baseline at week 100, (ii) the proportion of patients who gained ≥ 10 letters and (iii) ≥ 15 letters in BCVA from baseline at week 100, and (iv) the proportion of patients who improved by ≥2-steps in DR severity score (DRSS) from baseline at week 100.

The secondary endpoint of the proportion of patients who improved by ≥2-steps in DRSS from baseline at week 100 was the applicant defined main analysis in the DR submission. Furthermore, the proportions of patients who improved by ≥3-steps and worsened by ≥2- and ≥3-steps in DRSS at week 100 were protocol-defined exploratory endpoints relevant to the DR indication.

The efficacy results for the four ordered secondary endpoints including the results for the exploratory endpoints relevant to the DR indication are shown in Table 1.

During the first year treatment period, Eylea treated patients gained about 10 more letters on average compared to laser treated patients; the significant number of letters gained during the first year of treatment period was maintained during the second year of treatment period (See Figure 4). For example, at week 100, patients treated with VTE 2Q4 gained about 11 more letters and patient treated with VTE 2Q8 gained about 8 to 10 more letters on average compared to laser treated patients. Similarly, significantly more Eylea treated patients gained ≥10 and ≥15 letters from baseline at week 100 compared to laser treated patients. Thus, in all vision related efficacy measures, Eylea treated patients demonstrated superior efficacy benefit in improving vision compared to laser treated patients.

Table 1: Overview of secondary efficacy results at week 100
(Full Analysis Set; LOCF)

		VISTA		VIVID	
	Test order	Difference (97.5% CI) [1] versus Laser		Difference (97.5% CI) [1] versus Laser	
Secondary Endpoints		VTE 2Q4	VTE 2Q8	VTE 2Q4	VTE 2Q8
Change in BCVA in BCVA letter score from baseline at week 100	1	10.6 (7.1, 14.2)	10.1 (7.0, 13.3)	10.7 (7.6, 13.8)	8.2 (5.2, 11.3)
Proportion of patients (%) who gained >= 10 letter from baseline to week 100	2	36.2 (24.3, 48.1)	31.6 (19.5, 43.7)	33.1 (20.3, 45.9)	24.6 (11.9, 37.3)
Proportion of patients (%) who gained >= 15 letter from baseline to week 100	3	25.8 (15.1, 36.6)	20.1 (9.6, 30.6)	26.1 (14.8, 37.5)	19.0 (8.0, 29.9)
Proportion of patients who improved by ≥ 2-steps	4	22.1 (11.1, 33.2)	21.7 (10.5, 33.0)	20.7 (8.8, 32.5)	24.2 (12.4, 35.9)
Proportion of patients who improved by ≥ 3-steps	E	18.4 (9.7, 27.2)	14.9 (6.4, 23.4)	6.2 (0.7, 11.8)	2.9 (-0.8, 6.5)
Proportion of patients who worsened by ≥ 2-steps	E	-12.4 (-21.1, -3.7)	-12.5 (-21.0, -4.0)	-5.0 (-10.9, 0.9)	-5.1 (-10.9, 0.7)
Proportion of patients who worsened by ≥ 3-steps	E	-4.1 (-9.2, 1.1)	-3.3 (-8.6, 2.0)	-2.1 (-5.4, 1.2)	-1.1 (-5.0, 2.7)

E: Supporting exploratory endpoints for the indication of treatment of DR in patients with DME. LOCF: Last observation carried forward
[1] Difference (97.5% CI) for the first test in the order was based on ANCOVA model with baseline BCVA as covariate and stratification factors and treatment as fixed effects and for all other tests in the order was based on using CMH weighting scheme adjusted by study specific stratification factor.

In Table 1 above, the results for the proportion of patients who improved by ≥ 2-steps from baseline in DRSS at week 100 including the results for the exploratory endpoints relevant to the DR indication are presented; detailed results are shown in Figure 1 below. In both studies, more Eylea treated patients experienced significant improvement and fewer Eylea treated patients experienced worsening in DR severity at week 100 compared to laser treated patients.

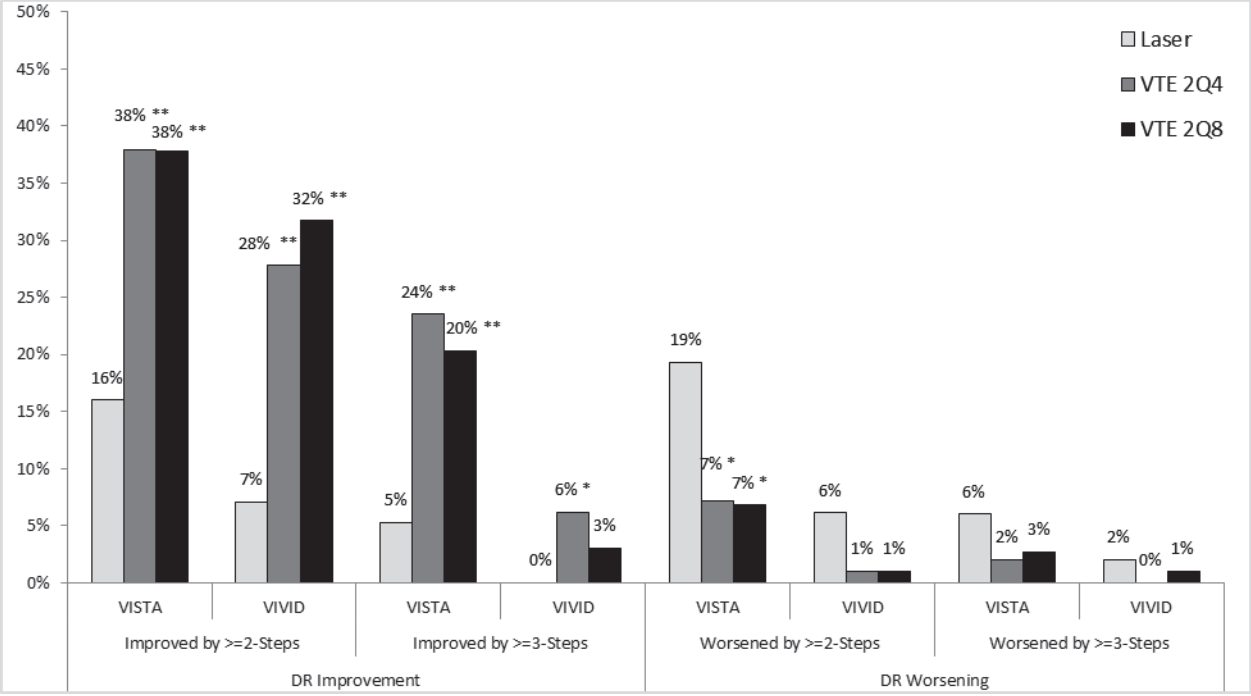
In the VISTA study, 38% and 24% of patients treated with VTE 2Q4, 39% and 20% of patients treated with VTE 2Q8, and 16% and 5% of patients treated with laser improved by ≥2- and ≥3-steps in DRSS, respectively; the treatment differences, respectively, were 22% [97.5% CI: (11%, 33%)] and 18% [97.5% CI: (10%, 27%)] for VTE 2Q4 versus laser and were 22% [97.5% CI: (11%, 33%)] and 15% [97.5% CI: (6%, 23%)] for VTE 2Q8 versus laser.

In the VIVID study, 28% and 6% of patients treated with VTE 2Q4, 32% and 3% of patients treated with VTE 2Q8, and 7% and 0% of patients treated with laser improved by ≥2- and ≥3-steps in DRSS, respectively; the treatment differences, respectively, were 21% [97.5% CI: (9%, 33%)] and 6% [97.5% CI: (1%, 12%)] for VTE 2Q4 versus laser and were 24% [97.5% CI: (12%, 36%)] and 3% [97.5% CI: (-1%, 7%)] for VTE 2Q8 versus laser.

In both studies, statistical significance for the key secondary efficacy endpoint of the proportion of patients who improved by ≥2- steps in DRSS from baseline at week 100 was achieved for each of the Eylea dose group versus laser.

The results of the exploratory endpoints based on DR worsening by ≥2- and ≥3-steps at week 100 further supported the effectiveness of Eylea over laser in the prevention of DR progression. For example, fewer Eylea-treated patients experienced worsening in DR severity at week 100 compared to laser-treated patients; about 12% and 4% fewer Eylea treated patients in the VISTA study and about 5% and 2% fewer Eylea treated patients in the VIVID study worsened by ≥2- and ≥3-steps at week 100, respectively, compared to laser treated patients.

Figure 1: Proportion of patients who improved or worsened in DRSS at week 100 (Full Analysis Set, LOCF)



Note: P-value: * < 0.025 and ** < 0.001 calculated using 2-sided Cochran-Mantel-Haenszel (CMH) test adjusted by study specific stratification factor

Based on collective efficacy evidence from the two years data, treatment with Eylea 2 mg injection administered once every 4 weeks or once every 8 weeks after 5 initial monthly injections demonstrated significant improvement in visual acuity. Furthermore, each Eylea dose group demonstrated superior efficacy benefit over laser in improving DR severity in patients with DME.

The efficacy benefit between the two Eylea dose groups in improving best corrected visual acuity as well as in improving DR severity in patients with DME was comparable. Thus, considering the significant efficacy benefits and the less injection burden to patients, the reviewer recommends approval of Eylea 2 mg injections administered every 4 weeks for the first 5 injections followed by every 8 weeks for the treatment of DR in patients with DME.

2. INTRODUCTION

2.1. OVERVIEW

In this supplemental BLA, the applicant seeks to add the indication of treatment of DR in patients with DME to the EYLEA® (aflibercept) U.S. Package Insert (USPI) and to update the BCVA data in the label for the DME indication. Support for the safety and efficacy of Eylea for the treatment of DR in patients with DME and to update the BCVA data for treatment of DME was based on 2 years clinical data from two ongoing pivotal phase 3 studies.

2.1.1. Class and Indication

Diabetic retinopathy (DR) is a slowly progressing disease that occurs as a complication of both Type 1 and Type 2 diabetes mellitus (DM) and it is a leading cause of blindness in adult. It is the result of damage to the blood vessels that nourish the retina; it occurs when blood vessels in the retina of patients with diabetes begin to leak into the macula, the part of the eye responsible for detailed central vision. These leaks cause the macula to thicken and swell, gradually distorting acute vision.

There are two types of diabetic retinopathy:

i) Nonproliferative diabetic retinopathy (NPDR): the earliest stage of DR where damaged blood vessels in the retina begin to leak extra fluid and small amounts of blood into the eye. This stage of the disease may be asymptomatic.

ii) Proliferative diabetic retinopathy (PDR): mainly occurs when many of the blood vessels in the retina close, preventing enough blood flow. To supply blood where the original vessels closed, the retina grows new blood vessels. However, the new blood vessels are abnormal and do not supply the retina with proper blood flow. PDR may cause more severe vision loss than NPDR.

Currently there is no FDA approved available therapy for the treatment of DR. Current management of DR that benefit in slowing the occurrence and worsening (but not for improvement and reversal) of the disease includes early detection of DR in patients with Type 1 and Type 2 DM, lifestyle changes, and control of hyperglycemia, hyperlipidemia, and hypertension. Treatment options for management of vision-threatening complications in patients with more advanced stages of DR include intravitreal anti-VEGF therapy (Eylea and Lucentis), macuar/focal grid laser, intravitreal steroid injection, panretinal photocoagulation (PRP) and vitrectomy.

Among the current treatment options for the management of DR is anti-VEGF therapy; VEGF was indicated to play a role in abnormal vessel growth and leakage in the eye, and recent clinical development programs have focused on VEGF inhibition as one way to improve vision in patients with DME and other ocular conditions. Eylea®, also known as VEGF Trap-Eye (VTE), is a member of the pharmacological class of VEGF inhibitors formulated for intravitreal use. The initial marketing application for Eylea has been approved for treatment of neovascular (wet) age-related macular degeneration (AMD). Later it was approved for the treatment of macular edema following central retinal vein occlusion (CRVO) and for the treatment of DME.

In this sBLA submission, Eylea® is indicated for the treatment of DR in patients with DME. Currently there are no intravitreal therapies specifically indicated for the treatment of DR.

2.1.2. History of Drug Development

In this sBLA submission, evidence to support the clinical efficacy of Eylea for the treatment of DR in patients with DME was based on 100-week data from two ongoing phase 3 studies: VISTA study conducted in the US and VIVID study conducted in the European Union, Japan, and Australia. The duration of each study was approximately 3 years, and the studies are currently ongoing. The primary endpoint in both studies was the mean change in BCVA at week 52 in patients with DME. The data from the 1 year primary endpoint were submitted to the Agency as a supplement (BLA125387 SN0101/S-037) for the treatment of DME and the drug was subsequently approved on 29 July 2014.

Although both studies were designed to evaluate the effects of Eylea on outcome measures associated with DME, the improvement or worsening of DR severity on the validated Early Treatment Diabetic Retinopathy Study (ETDRS) DR severity score (as assessed from fundus photographs) obtained at pre-specified time-points were also assessed in both studies. Based on analysis of the one year data, Eylea appeared to have shown clinical benefit over laser for the improvement of DR in patients with DME.

2.1.2.1. Meeting Correspondence

Based on promising results seen for the DR related endpoints from the one year data, on July 14, 2014, the applicant requested for a Breakthrough Designation for Eylea for the indication of prevention of vision-threatening events in patients with severe NPDR or mild/moderate PDR (IND 100083-0289). The Division and Regeneron discussed the Breakthrough Therapy request on August 21, 2014, and agreed that the designation be changed to '*Diabetic Retinopathy in Patients with DME*'. The breakthrough designation for Eylea for the indication of treatment of DR in patients with DME was granted on September 05, 2014.

A Type C meeting was held on January 25, 2013. During this meeting, the applicant inquired whether the Agency would consider improvement by ≥2-steps on the DR severity score as a clinically meaningful endpoint for the indication sought. The Division indicated the acceptability of the proposed endpoint if only one eye per patient was enrolled in the studies. The applicant confirmed that only one eye per patient was enrolled and assessed in both studies.

In this BLA supplement, the applicant submitted the 100-week data to the Agency and proposed improvement by ≥2-steps on the DR severity score from baseline at week 100 as the main efficacy claim for the proposed indication of treatment of DR in patients with DME.

2.1.3. Specific Studies Reviewed

The submission contains two ongoing pivotal phase 3 studies. Both studies share a common design and statistical methodology, and were a 3-year, randomized, double-masked, active-controlled and multi-center phase 3 ongoing clinical studies. These studies were initially submitted for the DME application based on 52 week data, and the specific detail of these studies were described in the primary statistical review for this application (see DARRTs entry on 07/08/2014).

In this supplement, the same studies including the two years data were submitted. Therefore, for detail of the specific studies reviewed in this supplement, we defer readers to the primary statistical review for the DME application.

2.2. Data Sources

The data source for this review included the clinical study reports and the analysis and tabulation datasets for both studies. These were provided in electronic submission and are located at \\CDSESUB1\evsprod\BLA125387\0138 and \\CDSESUB1\evsprod\BLA125387\0152.

The data analyzed in this review are based on the two year data from the two Phase 3 studies submitted as the pivotal evidence to support the safety and efficacy of Eylea.

3. STATISTICAL EVALUATION

3.1. Data and Analysis Quality

The sBLA was provided in an electronic submission. It included, among other documents, the clinical study reports, the analysis and tabulation datasets, and case report forms for few subjects. The SAS codes used to perform the analyses and to create the analysis datasets were also provided.

There were no issues identified with respect to the quality and integrity of the submitted data. Although the submitted datasets were not fully CDISC compliant, the submission included certain elements of the CDISC standards. In addition, the *Reviewer's Guide Document* and the *Define.pdf* files included with the sBLA submission document provided sufficient detail for the reviewer to access and to easily work with the datasets.

Therefore, minimal efforts were needed to process the data and hence no additional support was needed from other sources.

3.2. Evaluation of Efficacy

In this section, the efficacy assessment for the VISTA and VIVID studies including a description of the study design; the primary, secondary, and supportive efficacy endpoints; demographic and baseline characteristics; patient disposition; statistical methodology used; the applicant's results; and the reviewer's findings are provided.

3.2.1. Study Design and Endpoints

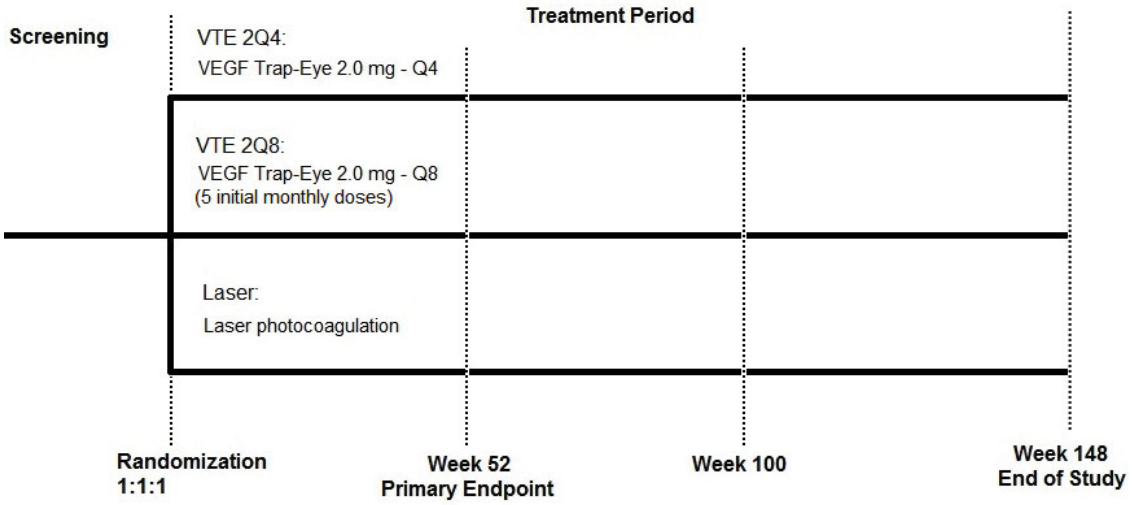
i) Study Design

The VISTA and VIVID studies were designed to evaluate the safety and efficacy of repeated doses of Eylea compared to laser in improving BCVA in patients at least 18 years of age who had a BCVA of 20/40 to 20/320 (letter score of 73 to 24) in the study eye and with DME secondary to diabetes.

In both studies, eligible patients that underwent the screening criteria on Day -21 to Day -1 were randomized on Day 1 in a 1:1:1 ratio to receive one of the following three treatments: (i) Eylea 2 mg injection administered once every 4 weeks (VTE 2Q4), (ii) Eylea 2 mg injection administered once every 4 weeks for the first 5 injections followed by once every 8 weeks (VTE 2Q8), and (ii) laser administered at baseline and as needed starting at week 12 based on protocol defined criteria (Laser). Randomization was stratified according to history of myocardial infarction (MI) and/or Cerebrovascular Accident (CVA) in the VISTA study and according to geographic region (Europe and Australia versus Japan) in the VIVID study.

Figure 2 below shows the flow chart for both the VISTA and VIVID Phase 3 studies.

Figure 2: Study Flow Chart (VISTA and VIVID Studies)



In both studies, only one eye per patients was enrolled; for patients that met the eligibility criteria in both eyes, the eye with the worst visual acuity was considered as the study eye.

Efficacy outcomes in both studies was assessed at every visit by masked examiners using the ETDRS protocol to measure BCVA letter score at 4 meters. BCVA data were collected at baseline, day 3 (in the VIVID study), week 1 (in the VISTA study), and every 4 weeks. Furthermore, the efficacy outcome for the DR indication was based on the diabetic retinopathy severity scale (DRSS) derived from the ETDRS study; DRSS data in both studies were collected at baseline, week 24, week 52, week 72 (in VISTA study), week 75 (in VIVID study), and at week 100 visits. More detail on the DRSS data are covered in Section 3.2.2.2 item (ii).

For further description of the study designs, we defer readers to the primary statistical review for the DME application (see DARRTs entry on 07/08/2014).

ii) Study Endpoints

In both studies, the primary efficacy endpoint was the change in BCVA letter score from baseline at week 52. The following were the key secondary efficacy endpoints evaluated in the order listed:

Test order	Secondary Endpoints
1	Proportion of patients who gain ≥ 15 ETDRS letters from baseline to Week 52
2	Change from baseline in BCVA at Week 100
3	Proportion of patients who gain ≥ 10 ETDRS letters from baseline to Week 100
4	Proportion of patients who gain ≥ 15 ETDRS letters from baseline to Week 100
5	Proportion of patients with an improvement of ≥ 2-step from baseline in ETDRS DRSS at Week 100
6	Change in CRT from baseline to Week 100 as assessed by OCT
7	NEI VFQ-25 near activities subscale change from baseline to Week 100
8	NEI VFQ-25 distance activities subscale change from baseline to Week 100

The first secondary endpoint was evaluated at week 52 while the rest were evaluated at week 100. Based on the first three secondary endpoints evaluated at week 100 with visual acuity relevance, the applicant proposed to update the label for the DME indication.

The secondary efficacy endpoint of the proportion of patients who improved by ≥2-steps in DRSS from baseline at week 100 was the applicant defined main analysis in the DR submission. The proportions of patients who improved by ≥3-steps and worsened by ≥2- and ≥3-steps in DRSS at week 100 were protocol-defined exploratory endpoints relevant to the DR indication.

3.2.2. Statistical Methodologies

3.2.2.1. Analysis Population

Three analysis populations were defined in the study protocols and statistical analysis plans: (i) the full analysis set (FAS) which included all randomized patients who received any study treatment and have a baseline and at least one post-baseline assessment of BCVA, (ii) the per protocol analysis set (PPS) which included all patients in the FAS that did not have any major protocol deviations until week 100, and (iii) the safety analysis set (SAF) which included all randomized patients who received at least one study treatments for safety summary. The full and per protocol analysis sets were for efficacy summary and the safety analysis set was for safety summary.

3.2.2.2. Efficacy Analysis

i) Best Corrected Visual Acuity (BCVA) Data

The primary efficacy endpoint in both studies was the change in BCVA score from baseline at week 52. The primary efficacy analysis was a statistical evaluation of superiority of each of the VTE groups versus laser in the FAS population and was based on analysis of covariance (ANCOVA) model with treatment as the main effect, and the study specific stratification factors, and the baseline BCVA as covariates.

The key secondary efficacy endpoint evaluated at week 52 was the proportion of patients who gained ≥15 letters in BCVA score from baseline. The secondary efficacy analysis within each study was a statistical evaluation of superiority of each of the VTE groups versus laser in the FAS population and was based on a stratified Cochran-Mantel-Haenszel (CMH) test..

In the applicant efficacy analysis approach, missing BCVA data were imputed using the last-observation-carried-forward (LOCF) method; for subjects that received additional treatment during the study, the last measurement taken before the initiation of the additional treatment was used in the LOCF approach.

To assess the impact on the analyses result of missing data due to drop-outs or receipt of additional treatment, several sensitivity analyses were performed by the applicant under different analysis population, different methods of handling missing data, and by including data after additional treatments. For detailed description of the various sensitivity analysis methods used and implemented, we defer readers to the primary statistical review report for the DME application (see DARRTs entry on 07/08/2014).

ii) Diabetic Retinopathy Severity Score (DRSS) Data

In both the VISTA and VIVID studies, the effectiveness of Eylea in treating diabetic retinopathy in patients with DME was evaluated based on two years data from the DME application. Efficacy evaluation was based on improvement or worsening in diabetic retinopathy severity score (DRSS) derived from the ETDRS study. The DRSS, a validated method measuring changes in DR, characterizes retinopathy based on assessment of abnormalities in seven defined fields of fundus photographs (FP). According to the applicant, the fundus images were read by masked readers, and photographs at study sites were masked to treatment assignment.

The DRSS, graded according to a 10-step severity score, divides DR severity into levels ranging from absent to severe proliferative diabetic retinopathy (Table 2).

Table 2: Steps for EDTRS diabetic retinopathy severity score

Severity Level (used to determine step change in DRSS)	Combined DR severity levels	Combined DR severity levels (as text)
1	10 and 12	DR absent
2	14, 15, 20	DR questionable, microaneurysms only
3	35	Mild NPDR
4	43	Moderate NPDR
5	47	Moderately severe NPDR
6	53	Severe NPDR
7	60, 61	Mild PDR
8	65	Moderate PDR
9	71	High-risk PDR
10	75	High-risk PDR
90	90	Cannot grade

DR: Diabetic Retinopathy; NPDR: Nonproliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy;
Note: Subjects with active PDR were not included in both studies

In both studies, DRSS data was collected at baseline, week 24, week 52, week 72 (in the VISTA study), week 75 (in the VIVID study), and at week 100 visits.

The applicant primary efficacy claim for the treatment of DR in patients with DME was based on the secondary efficacy endpoint of the proportion of patients who improved by ≥2-steps in DRSS from baseline at week 100 (e.g. a shift from sever to moderate NPDR). A subject was considered to have improved (or worsened) by ≥2-steps if the change from baseline using the re-coded DR severity score data (column 1 of Table 2) was ≤ -2 (or ≥ +2). Additionally, the effect of each of the Eylea dose group on DR severity was also assessed using the exploratory endpoints of the proportion of patients who improved by ≥3-steps and worsened by ≥2- or ≥3-steps in DRSS at week 100.

All DR related efficacy endpoints were analyzed using the secondary efficacy analysis method outlined in Section 3.2.2.2 item (i). For the analysis of DR related efficacy endpoints, the applicant used LOCF method for missing data imputation. However, no detail was given in the study protocol as well as in the statistical analysis plan on how the LOCF method was carried out for patients with non-gradable DRSS data (i.e., DRSS = 90).

Upon investigation of the applicant derived DRSS dataset (**adxodr.sas7bdat**), we noted that different approaches were used for handling missing data as well as non-gradable DRSS data in producing the analysis results in the clinical study reports (CSR) and the analysis results in the proposed labeling for the two pivotal studies (VIVID and VISTA).

(a) Approach used to produce the analysis results in the CSR for VISTA study

In this study, only gradable post-baseline DRSS data were used to impute for missing DRSS data (See example below).

VISTA		Observed				LOCF			
Subjid	Baseline	Week 24	Week 52	Week 72	Week 100	Week 24	Week 52	Week 72	Week 100
(b) (6)	90	6	.	.	.	6	6	6	6
	5	5	4	5	90	5	4	5	90
	10	.	.	.	.	.	.	.	.
	5	90	.	.	.	90	.	.	.
	6	6	90	.	.	6	90	.	.
	6	6	4	4	.	6	4	4	4
	6	90	90	.	3	90	90	.	3

Imputed data using LOCF are shown in red font. Subjid: Subject identification number

All patients were included in the analysis in this study; patients with non-gradable DRSS data at the baseline visit (eg subjid = (b) (6)) or at the post-baseline visit after LOCF (eg subjid= (b) (6) (b) (6) or with missing DRSS data at the post-baseline visit after LOCF (eg subjid= (b) (6) (b) (6)) were considered to have shown no improvement or no worsening in DR severity.

(b) Approach used to produce the analysis results in the CSR for VIVID study:

In this study, both gradable and non- gradable DRSS data (DRSS=90) were used to impute for missing DRSS data (See example below).

VIVID		Observed				LOCF			
Subjid	Baseline	Week 24	Week 52	Week 75	Week 100	Week 24	Week 52	Week 75	Week 100
(b) (6)	90	6	.	.	.	6	6	6	6
	90	.	.	.	.	.	.	.	.
	2	4	90	.	.	4	90	90	90
	4	4	90	4	90	4	90	4	90
	4	90	.	.	.	90	90	90	90
	5	.	.	.	.	.	.	.	.
	7	4	4	4	.	4	4	4	4
	6	90	90	.	6	90	90	90	6

Imputed data using LOCF are shown in red font. Subjid: Subject identification number

In this study, patients with non-gradable DRSS data at the baseline visit (eg subjid = (b) (6) & (b) (6)) or at the post-baseline visit after LOCF (eg subjid = (b) (6), (b) (6), and (b) (6)), or patients with only baseline data (eg subjid = (b) (6)) were excluded from the analysis.

(c) Approach used to produce the analysis results in the proposed labeling

The approach used in the VIVID study was used to produce the analysis results in the proposed labeling.

Reviewer's Analysis Approach:

We conducted additional analysis in which non-gradable post-baseline DRSS values were treated as missing and were imputed using the last gradable DRSS values (including with baseline values if all post-baseline values were either missing or non-gradable). In our analysis, patients with non-gradable baseline DRSS values were excluded since the change from baseline data for these patients could not be evaluated.

The following tables provide the imputed values for the subjects listed in items (i) and (ii) using the reviewer imputation approach.

VIVID		Observed				LOCF			
Subjid	Baseline	Week 24	Week 52	Week 75	Week 100	Week 24	Week 52	Week 75	Week 100
(b) (6)	90	6	.	.	.	6	6	6	6
	90	.	.	.	.	.	.	.	.
	2	4	90	.	.	4	4	4	4
	4	4	90	4	90	4	4	4	4
	4	90	.	.	.	4	4	4	4
	5	.	.	.	.	5	5	5	5
	7	4	4	4	.	4	4	4	4
	6	90	90	.	6	6	6	6	6

Imputed data using LOCF are shown in red font. Subjid: Subject identification number

VISTA		Observed				LOCF			
Subjid	Baseline	Week 24	Week 52	Week 72	Week 100	Week 24	Week 52	Week 72	Week 100
(b) (6)	90	6	.	.	.	6	6	6	6
	5	5	4	5	90	5	4	5	5
	10	.	.	.	.	10	10	10	10
	5	90	.	.	.	5	5	5	5
	6	6	90	.	.	6	6	6	6
	6	6	4	4	.	6	4	4	4
	6	90	90	.	3	6	6	6	3

Imputed data using LOCF are shown in red font. Subjid: Subject identification number

Therefore, unless stated otherwise, all efficacy analyses results (on the DRSS data) presented in this review were based on the reviewer's data handling approach.

To assess the impact of missing data due to drop-outs or receipt of additional treatment on the efficacy results related to the DR endpoints, treatment comparison were performed: (i) using observed cases (OC) - excluding the DRSS data after additional treatment was given, (ii) using observed cases (aOC) - including DRSS data after additional treatment was given, and (iii) using last observation carried forward (aLOCF) - including DRSS data after additional treatment was given.

iii) Central Retinal Thickness (CRT) and Quality of Life Data (NEI VFQ-25)

All secondary efficacy endpoints based on continuous variables (the change from baseline in CRT at week 100, and the change from baseline in NEI VFQ-25 near and distance activities subscale at week 100) were analyzed using the primary efficacy analysis method outlined in Section 3.2.2.2 item (i) with the respective baseline values included in the model as covariates.

3.2.2.3. Analysis Testing Strategy

Two Eylea doses (each compared to laser) and multiple endpoints were tested. For comparison of the two Eylea dose group versus laser on the primary efficacy endpoint, Bonferroni multiple comparison correction was used, i.e., each comparison on the primary endpoint was tested at a significance level of 2.5%.

Once statistical significance was achieved for the primary endpoint for a given Eylea dose group versus laser, the key secondary endpoints were compared between each Eylea dose group and laser separately at an overall significance level of 2.5%. The testing of key secondary endpoints was based on a hierarchical testing strategy. In the hierarchical testing strategy, if one test in the hierarchy was not positive, then all the subsequent tests would not be considered positive regardless of the associated p-values.

Based on the analysis testing strategy, superiority of a given Eylea dose group versus laser in the primary endpoint was declared if the lower limit of the two-sided 97.5% confidence interval for the difference in mean change in BCVA was greater than zero.

Once statistical significance was achieved in the primary endpoint, superiority of a given Eylea dose group versus laser for a given binary secondary endpoints was declared if the p-value was < 0.025 and all the preceding tests in the hierarchy were positive. A weighted point and two-sided 97.5% confidence interval estimates for the treatment differences for the binary efficacy variables was provided using the CMH weights and normal approximation of the weighted estimates.

3.2.3. Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1. Patient Disposition

The summary of patient disposition and the primary reasons for study discontinuation during the 100-week treatment period for both studies are shown in Table 3. Overall, 466 and 406 patients were randomized in the VISTA and VIVID studies, respectively.

Of the 466 patients randomized in the VISTA study; 156 patients each were assigned in the laser and VTE 2Q4 treatment groups and 154 patients were assigned in the VTE 2Q8 treatment group. Five randomized patients did not receive study medication (two in laser, one in VTE 2Q4, and two in VTE 2Q8). According to the applicant, subjects (b) (6) (laser), (b) (6) (VTE 2Q4), and (b) (6) (VTE 2Q8) did not meet inclusion criteria and were inadvertently randomized and subject (b) (6) (laser) and (b) (6) (VTE 2Q8) withdrew consent. A total of 81 (17.4%) patients in the VISTA study discontinued before week 100; the discontinuation rates were slightly higher in each of the VTE groups. The most common reasons for discontinuation among all randomized patients were withdrawal of consent by a subject (laser: 6% versus combined VTE: 7%) followed by adverse event in the laser group (3%) and lost to follow up in the combined VTE group (3%). A total of 31 patients, 9 in the laser group and 22 in the combined VTE groups, discontinued the study due to death.

Of the 406 patients randomized in the VIVID study; 135 patients each were assigned in the laser and VTE 2Q8 groups, and 136 patients were assigned in the VTE 2Q4 group. Two patients randomized in the laser group did not receive study medication. A total of 76 (19%) patients in the VIVID study discontinued before week 100; the discontinuation rate in the laser group (22%)

was slightly higher than in the VTE 2Q4 (15%) and VTE 2Q8 (19%) groups. The most common reasons for discontinuation among all randomized patients were adverse events and withdrawal by patients. In the VIVID clinical database, a total of nine patients (all in the VTE group) discontinued the study due to death.

Table 3: Disposition of patients and reasons for study discontinuation
(All Randomized Subjects)

	VISTA			VIVID		
	Laser (N=156)	VTE 2Q4 (N= 156)	VTE 2Q8 (N=154)	Laser (N=135)	VTE 2Q4 (N=136)	VTE 2Q8 (N=135)
Subject who completed 10 weeks; n (%)	133 (85.3)	125 (80.1)	127 (82.5)	105 (77.8)	115 (84.6)	110 (81.5)
Subject who discontinued study before week 100, n (%)	23 (14.7)	31 (19.9)	27 (17.5)	30 (22.2)	21 (15.4)	25 (18.5)
Primary Reason for Premature Discontinuation, n (%)						
Adverse event	5 (3.2)	4 (2.6)	4 (2.6)	10 (7.4)	7 (5.1)	8 (5.9)
Death	3 (1.9)	7 (4.5)	5 (3.2)	0 (0.0)	3 (2.2)	6 (4.4)
Lack of efficacy	0	0	0	1 (0.7)	0 (0.0)	1 (0.7)
Withdrawal by subject	9 (5.8)	11 (7.1)	11 (7.1)	14 (10.4)	7 (5.1)	5 (3.7)
Protocol violation	0	0	0	2 (1.5)	0 (0.0)	1 (0.7)
Lost to follow-up	2 (1.3)	4 (2.6)	5 (3.2)	1 (0.7)	2 (1.5)	4 (3.0)
Physician decision	0	0	0	2 (1.5)	1 (0.7)	0 (0.0)
Therapeutic procedure required	0	0	0	0 (0.0)	1 (0.7)	0 (0.0)
Other	4 (2.6)	5 (3.2)	2 (1.3)	0	0	0

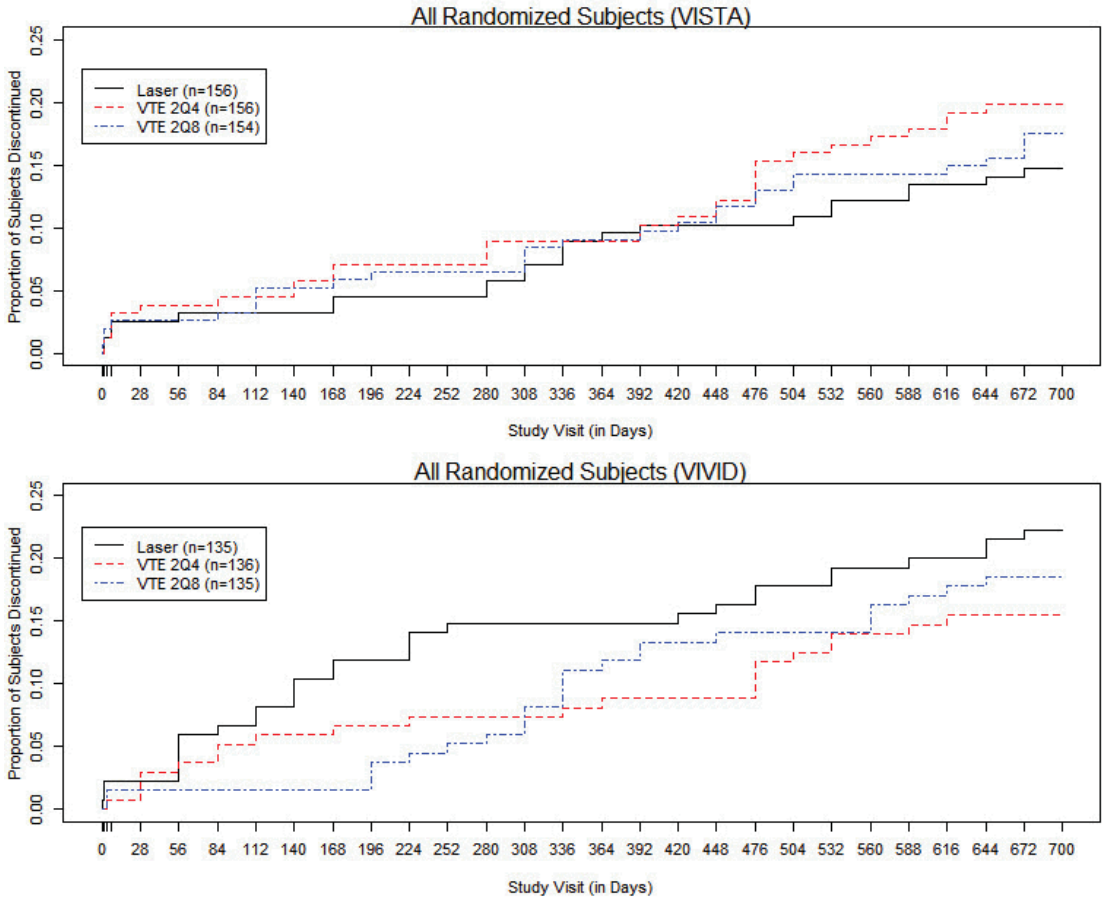
Source: Table 7 of VISTA and Table 6 of VIVID Clinical Study Reports

The proportion of patients discontinued during the 100-week period is shown in Figure 3.

In the VISTA study, the discontinuation rate over time was comparable among the treatment groups throughout the study.

In the VIVID study, the discontinuation rates at all visits were relatively higher in the laser group; in this group, discontinuation started early on in the study and continued till the end of the 100-week treatment period. In the VTE groups, discontinuation started early on in the VTE 2Q4 group but started after Day 196 in the VTE 2Q8 group.

Figure 3: Proportion of patients discontinued from study over time



3.2.3.2. Demographic and Baseline Characteristics

In both studies, the majority of patients were Caucasian, 65 years of age and older, and more than half were male. The average age of patients in the VISTA study was 62 years (range 23 to 87 years) and in the VIVID study was 64 years (range 32 to 84 years). The average duration of diabetes for patients in the VISTA study was about 17 years and for patients in the VIVID study was about 14 years. The mean HbA1C at baseline was about 8% in both studies.

The demographic and baseline characteristics within both studies, with the exception of HbA1c, were well balanced among the treatment groups. In the VISTA study, many patients in each of the VTE groups (about 37%) had baseline HbA1c > 8% compared to patients in the laser group (about 29%); in the VIVID study, many patients in the VTE 2Q4 group (about 40%) had baseline HbA1c > 8% compared to patients in the VTE 2Q8 group (about 33%) and patients in the laser group (about 32%). Nearly 70% of patients in the VISTA study had received prior treatment for DME; 43% had received prior anti-VEGF and 53% had received prior laser treatment; only 9% of patients in the VIVID study received prior anti-VEGF treatment.

Furthermore, the baseline disease characteristics in both studies were fairly well balanced among the treatment groups. The overall mean baseline BCVA in the VISTA study was about 59 letters and in the VIVID study was about 60 letters; over 70% of patients within both studies had a baseline BCVA of at least 55 letters. The overall mean baseline central retinal thickness (CRT)

for patients in the VISTA study was about 483 μm (range 231 to 1179 μm) and for patients in the VIVID study was about 520 μm (range 283 to 1183 μm). In both studies, vision-related quality of life was assessed using the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25); the mean NEI VFQ-25 near and distance activities subscale scores in the VISTA study were about 58 and 65 , respectively, and in the VIVID study were about 65 and 74, respectively.

For further detail on the summary of the demographic and baseline characteristics, we defer readers to Table 6 and Table 7 of the primary statistical review report for the DME application (see DARRTs entry on 07/08/2014).

Baseline DR Severity Score:

The summary of the number (%) of patients by the baseline DR severity score data are shown in Table 4 below. The majority of patients (about 83% in the VISTA study and about 70% in the VIVID study) had moderate to severe NPDR at baseline (DRSS = 43, 47, and 53), and about 7% of patients in the VISTA study and about 2% of patients in the VIVID study had mild to high risk PDR at baseline (DRSS = 61, 65, 71, and 75).

About 2% of patients in the VISTA study and a quarter of the patients in the VIVID study (about 26%) had baseline images that could not be graded (DRSS = 90). The applicant indicated that the higher proportion of patients with non-gradable baseline DRSS scores in the VIVID study as compared to in the VISTA study was due to the slight difference in the algorithms used between the two reading centers to determine if particular images were gradable or not.

Table 4: Summary of DR severity score at baseline
(Full Analysis Set)

	VISTA			VIVID		
Baseline DRSS, n (%)	Laser (N = 154)	VTE 2Q4 (N = 154)	VTE 2Q8 (N = 151)	Laser (N = 132)	VTE 2Q4 (N = 136)	VTE 2Q8 (N = 135)
DR Absent to Mild NPDR (DRSS<43)	**9 (5.8%)**	**16 (10.4%)**	**16 (10.6%)**	**3 (2.3%)**	**0 (0.0%)**	**1 (0.1%)**
10 (DR Absent)	1 (0.6%)	4 (2.6%)	4 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
20 (Microaneurysms only)	3 (1.9%)	5 (3.2%)	3 (2.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
35 (Mild NPDR)	5 (3.2%)	7 (4.5%)	9 (6.0%)	2 (1.5%)	0 (0.0%)	1 (0.7%)
Moderate to Sever NPDR (DRSS = 43, 47, and 53)	**128 (83.1%)**	**128 (83.1%)**	**124 (82.1%)**	**95 (72.0%)**	**93 (68.4%)**	**97 (71.9%)**
43 (Moderate NPDR)	60 (39.0%)	49 (31.8%)	52 (34.4%)	36 (27.3%)	31 (22.8%)	28 (20.7%)
47 (Moderately Severe NPDR)	26 (16.9%)	26 (16.9%)	32 (21.2%)	24 (18.2%)	18 (13.2%)	27 (20.0%)
53 (Severe NPDR)	42 (27.3%)	53 (34.4%)	40 (26.5%)	35 (26.5%)	44 (32.4%)	42 (31.1%)
Mild to High Risk PDR (DRSS = 61, 65, 71, and 75)	**13 (8.4%)**	**9 (5.8%)**	**8 (5.3%)**	**1 (0.1%)**	**4 (2.9%)**	**3 (2.2%)**
61 (Mild PDR)	1 (0.6%)	1 (0.6%)	2 (1.3%)	1 (0.8%)	2 (1.5%)	2 (1.5%)
65 (Moderate PDR)	10 (6.5%)	4 (2.6%)	5 (3.3%)	0 (0.0%)	2 (1.5%)	1 (0.7%)
71 (High Risk PDR)	1 (0.6%)	4 (2.6%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
75 (High Risk PDR)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
90 (could not grade)	4 (2.6%)	1 (0.6%)	3 (2.0%)	33 (25.0%)	39 (28.7%)	34 (25.2%)

Note: Percentage is based on the number of FAS patients in each treatment group as the denominator
DRSS: Diabetic Retinopathy Severity Score; FAS = Full Analysis Set; n = Number of patients; N = Total number of patients; NPDR = Non-proliferative Diabetic Retinopathy; PDR = Proliferative Diabetic Retinopathy

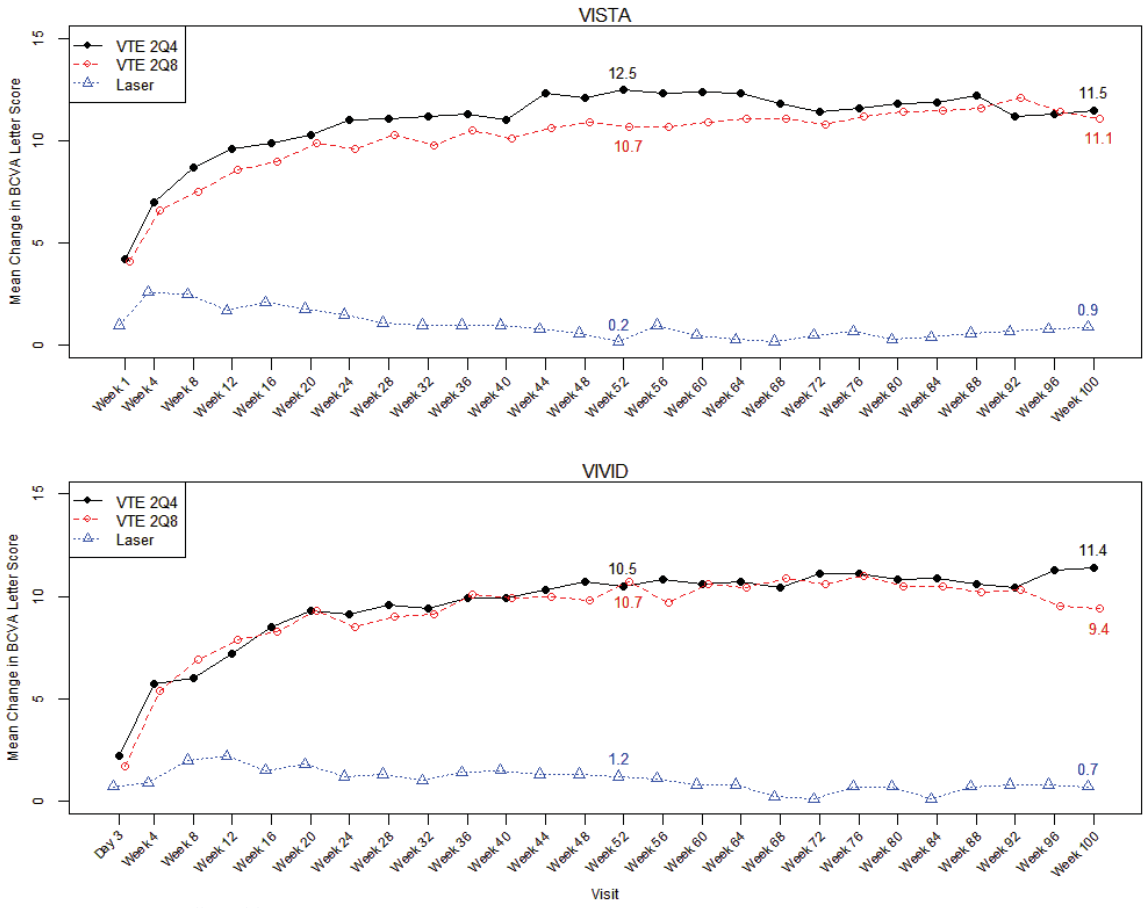
3.2.4. Results and Conclusions

The primary efficacy endpoint in both studies was the change in BCVA score from baseline at week 52 and the first secondary endpoint in the hierarchy was the proportion of patients who gained ≥15 letters in BCVA score from baseline at week 52. Statistical significances were achieved for these endpoints for each of the Eylea dose group versus laser. Therefore, the key secondary endpoints in the hierarchy evaluated at week 100 were compared between each of the VTE groups and the laser group separately at an overall significance level of 2.5%.

3.2.4.1. Mean change in BCVA score from baseline at week 100

The mean change in BCVA score from baseline at each visit is shown in Figure 4 below by treatment group. There was a clear separation between each of the VTE groups versus laser throughout the study, and the separation that was established during the first year treatment period was clearly maintained throughout the second year treatment period. Overall, the average number of letters gained from baseline at each visit was significantly higher in the Eylea treated patients compared to in the laser treated patients.

Figure 4: Mean change from baseline in BCVA letter scores over time
(Full Analysis Set, LOCF)



Source: Appendix Table 18

Treatment comparisons between each of the VTE groups versus laser for the average number of letters gained from baseline at week 100 were made using the analysis approach performed at

week 52. The summary of the letter scores at baseline, week 100, and the change from baseline at week 100 based on the FAS population using the LOCF method are shown in Table 5.

Table 5: Mean change from baseline to week 52 in BCVA letter score
(Full Analysis Set, LOCF)

Study	Visit	Summary	Laser (N=154)	VTE 2Q4 (N=154)	VTE 2Q8 (N=151)
VISTA	Baseline	Mean (SD)	59.7 (10.95)	58.9 (10.77)	59.4 (10.89)
		Median	63	61	62
		Range	25.0, 73.0	26.0, 73.0	24.0, 73.0
	Week 100	Mean (SD)	60.6 (17.70)	70.4 (16.15)	70.5 (13.37)
		Median	62	74	73
		Range	1.0, 92.0	0.0, 95.0	10.0, 90.0
	Change from Baseline at Week 100	Mean (SD)	0.9 (13.94)	11.5 (13.75)	11.1 (10.70)
		Median	1	13	11
		Range	-56.0, 41.0	-57.0, 45.0	-54.0, 46.0
		LS Means (SE)	0.6 (1.16)	11.2 (1.11)	10.7 (0.89)
		Diff. vs Laser (97.5% CI) [1]	--	10.6 (7.1, 14.2)	10.1 (7.0, 13.3)
			Laser (N=132)	VTE 2Q4 (N=136)	VTE 2Q8 (N=135)
VIVID	Baseline	Mean (SD)	60.8 (10.61)	60.8 (10.74)	58.8 (11.23)
		Median	63	63	61
		Range	26.0, 76.0	25.0, 75.0	25.0, 80.0
	Week 100	Mean (SD)	61.5 (15.15)	72.1 (13.14)	68.2 (13.66)
		Median	62	74	71
		Range	18.0, 94.0	15.0, 100.0	33.0, 98.0
	Change from Baseline at Week 100	Mean (SD)	0.7 (11.77)	11.4 (11.21)	9.4 (10.53)
		Median	1	12	9
		Range	-32.0, 27.0	-54.0, 43.0	-22.0, 43.0
		LS Means (SE)	0.1 (1.12)	10.8 (1.02)	8.4 (0.99)
		Diff. vs Laser (97.5% CI) [1]	--	10.7 (7.6, 13.8)	8.2 (5.2, 11.3)

[1] Based on ANCOVA model with baseline measurement as covariate and study specific stratification factors and treatment as fixed factors

In the VISTA study, VTE treated patients on average gained about 11 to 12 letters from baseline at week 100 while laser treated patients gained about one letter. The treatment difference for the average number of letters gained at week 100 was 11 [97.5% CI: (7, 14)] for VTE 2Q4 versus laser and was 10 [97.5% CI: (7, 13)] for VTE 2Q8 versus laser. Similarly, in the VIVID study, VTE treated patients on average gained about 9 to 11 letters from baseline at week 100 while laser treated patients gained about one letter. The treatment differences for the average number of letters gained at week 100 was 11 [97.5% CI: (8, 14)] for VTE 2Q4 versus laser and was 8 [97.5% CI: (5, 11)] for VTE 2Q8 versus laser. Statistical significance was achieved for the average number of letters gained for each of the Eylea dose group versus laser.

To assess the robustness of the primary efficacy results for the change in BCVA score from baseline at week 52, several sensitivity analyses were performed (see Section 3.2.4.1.2 of primary statistical review: DARRTs entry on 07/08/2014). All the sensitivity analyses methods performed at week 52 were also performed for the analysis of change in BCVA score from baseline at week 100, and the results were consistent with the LOCF method yielding the average number of letters gained at week 100 in each of the Eylea dose group was superior to the laser group.

3.2.4.2. Proportion of patients who gained ≥10 and ≥15 letters from baseline at week 100

The summary of the proportion of patients who gained ≥10 and ≥15 letters from baseline at week 100 for the overall population and by the levels of the study specific stratification factors are shown in Table 6. In both studies, the proportions patients who gained letters were significantly higher in the VTE treated patients compared to in the laser treated patients; the patterns within the levels of the stratification factors were consistent with those in the overall population.

Table 6: Proportion of patients who gained ≥10 and ≥15 letters in BCVA at week 100 (Full Analysis Set, LOCF)

VISTA

Treatment	Medical history of MI or CVA: Yes n / N (%)	Medical history of MI or CVA: No n / N (%)	Total n / N (%)	Difference vs Laser (%) (97.5% CI) [1]	p-value[2]
Gained ≥ 10 Letters					
Laser	10/ 46 (21.7)	33/108 (30.1)	43/154 (27.9)	--	
VTE 2Q4	33/ 56 (58.9)	65/ 98 (66.3)	98/154 (63.6)	36.2 (24.3, 48.1)	<0.001
VTE 2Q8	24/ 44 (54.6)	66/107 (61.7)	90/151 (59.6)	31.6 (19.5, 43.7)	<0.001
Gained ≥ 15 Letters					
Laser	5/ 46 (10.9)	15/108 (13.4)	20/154 (13.0)	--	
VTE 2Q4	17/ 56 (30.4)	42/ 98 (42.9)	59/154 (38.3)	25.8 (15.1, 36.6)	<0.001
VTE 2Q8	10/ 44 (22.7)	40/107 (37.4)	50/151 (33.1)	20.1 (9.6, 30.6)	<0.001

VIVID

Treatment	Geographic Region: Non-Japanese n / N (%)	Geographic Region: Japanese n / N (%)	Total n / N (%)	Difference vs Laser (%) (97.5% CI) [1]	p-value [2]
Gained ≥ 10 Letters					
Laser	25/107 (23.4)	8/ 25 (32.0)	33/132 (25.0)	--	
VTE 2Q4	64/110 (58.2)	15/ 26 (57.7)	79/136 (58.1)	33.1 (20.3, 45.9)	<0.001
VTE 2Q8	60/110 (54.6)	7/ 25 (28.0)	67/135 (49.6)	24.6 (11.9, 37.3)	<0.001
Gained ≥ 15 Letters					
Laser	13/107 (12.2)	3/ 25 (12.0)	16/132 (12.1)	--	
VTE 2Q4	44/110 (40.0)	8/ 26 (30.8)	52/136 (38.2)	26.1 (14.8, 37.5)	<0.001
VTE 2Q8	38/110 (34.6)	4/ 25 (16.0)	42/135 (31.1)	19.0 (8.0, 29.9)	<0.001

[1] Difference with confidence interval (CI) based on using CMH weighting scheme adjusted by study specific stratification factor.
[2] P-value calculated using 2-sided Cochran-Mantel-Haenszel (CMH) test adjusted by study specific stratification factor.

In the VISTA study, 64% and 38% of patients treated with VTE 2Q4, 60% and 33% of patients treated with VTE 2Q8, and 28% and 13% of patients treated with laser gained ≥10 and ≥15 letters from baseline at week 100, respectively; the treatment differences, respectively, were 36% [97.5% CI: (24%, 48%)] and 26% [97.5% CI: (15%, 37%)] for VTE 2Q4 versus laser and were 32% [97.5% CI: (20%, 44%)] and 20% [97.5% CI: (10%, 31%)] for VTE 2Q8 versus laser.

In the VIVID study, 58% and 38% of patients treated with VTE 2Q4, 50% and 31% of patients treated with VTE 2Q8, and 25% and 12% of patients treated with laser gained ≥10 and ≥15 letters from baseline at week 100, respectively; the treatment differences, respectively, were 33% [97.5% CI: (20%, 46%)] and 26% [97.5% CI: (15%, 38%)] for VTE 2Q4 versus laser and were 25% [97.5% CI: (12%, 37%)] and 19% [97.5% CI: (8%, 30%)] for VTE 2Q8 versus laser.

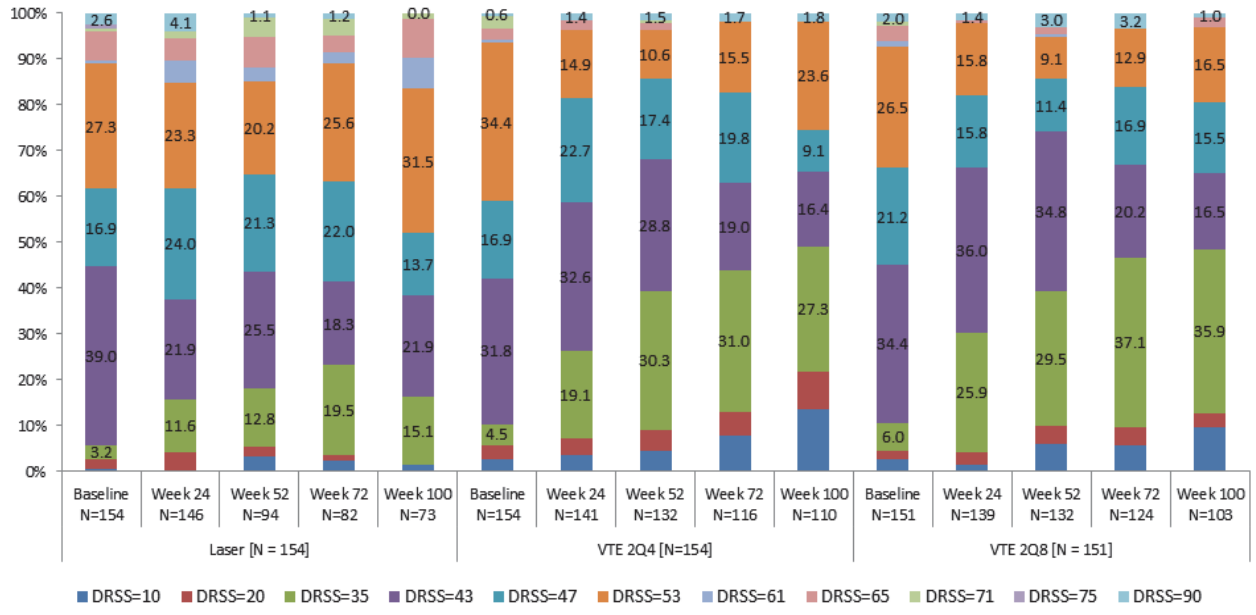
Statistical significance was achieved for the proportion of patients who gained ≥10 and ≥15 letters from baseline at week 100 for each of the Eylea dose group versus laser.

To assess the robustness of the efficacy results for the proportion of patients who gained ≥15 letters from baseline at week 52, several sensitivity analyses were performed (see Section 3.2.4.2.2 of primary statistical review: DARRTs entry on 07/08/2014). All the sensitivity analyses methods performed at week 52 were also performed for the analysis of the proportions of patients who gained ≥10 and ≥15 letters from baseline at week 100. The results were consistent with the LOCF method yielding the proportions of patients who gained ≥10 and ≥15 letters from baseline at week 100 in each of the Eylea dose group was superior to the laser group.

3.2.4.3. Analysis results of secondary endpoints for treatment of DR in patients with DME

The distributions of patients by change in DR severity score from baseline to week 100 are shown in Figure 5 for the VISTA study and in Figure 6 for VIVID study; numbers reported inside bars are the percentage of patients with the respective DR severity level at each visit. Overall, many Eylea treated patients appeared to have shown improvement in DR severity over time compared to laser treated patients.

Figure 5: Distribution of patients by DR severity score from baseline to week 100 (VISTA) (Full Analysis Set; Observed Cases)

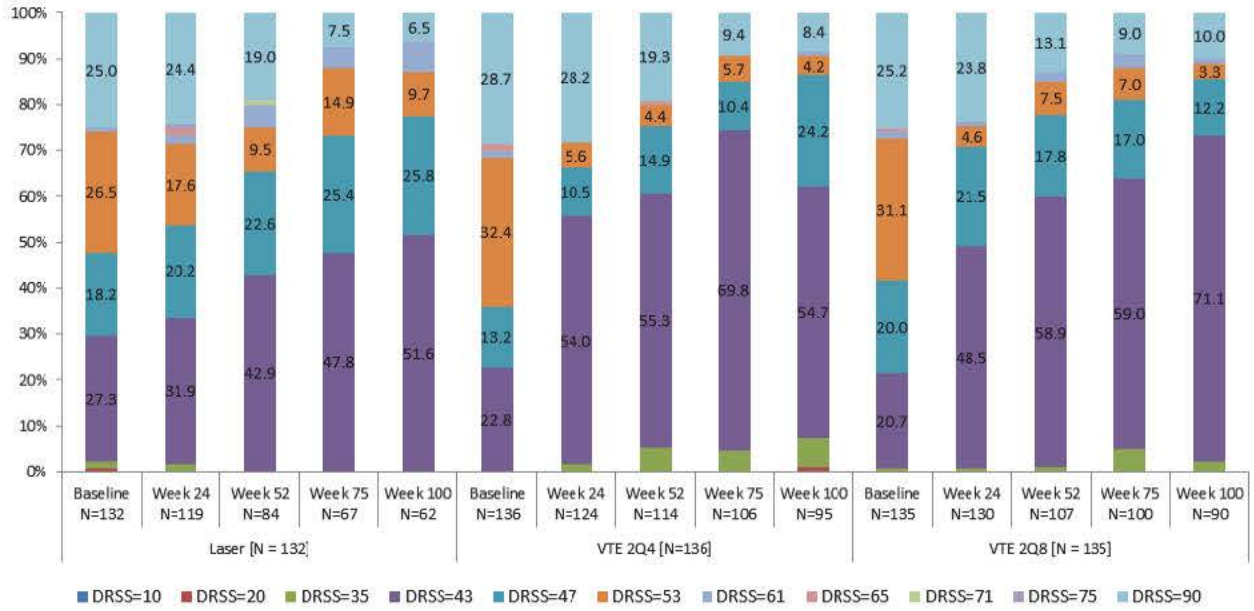


Note: Percentages reported inside bars were calculated based on the observed number of cases at each visit; note that DRSS data collected after reciept of additional treatment were not included in the observed case analysis.
Source: Appendix Table 17

In the VISTA study, the median DR severity score in the VTE treated patients shifted from moderately severe NPDR at the baseline visit to moderate NPDR over time while the median severity score in the laser treated patients was moderately severe NPDR throughout the study.

In the VIVID study, the median DR severity score in each treatment group was moderately severe NPDR at the baseline visit and was moderate NPDR at each of the post-baseline visits except at the week 24 visit in the laser treated patients where the median DR severity scale at this visit was moderately severe NPDR.

Figure 6: Distribution of patients by DR severity score from baseline to week 100 (VIVID)
(Full Analysis Set; Observed Cases)



Note: Percentages reported inside bars were calculated based on the observed number of cases at each visit; note that DRSS data collected after reciept of additional treatment were not included in the observed case analysis.
Source: Appendix Table 17

In Table 7, the number of patients with gradable, non-gradable (DRSS = 90), and missing DRSS data are shown by visit.

Table 7: Number of patients with gradable, non-gradable, and missing DRSS data by visit
(Full Analysis Set)

	Laser [N = 154]					VTE 2Q4 [N = 154]					VTE 2Q8 [N = 151]				
	Weeks					Weeks					Weeks				
	0	24	52	75	100	0	24	52	75	100	0	24	52	75	100
VISTA															
Available [1]	150	140	93	81	73	153	139	130	114	108	148	137	128	120	102
DRSS = 90 [2]	4	6	1	1	0	1	2	2	2	2	3	2	4	4	1
Missing [3]	0	8	60	72	**81**	0	13	22	38	**44**	0	12	19	27	**48**
LOCF [4]	-	150	150	150	150	-	153	153	153	153	-	148	148	148	148
LOCF [5]	-	136	140	139	141	-	139	143	144	144	-	136	140	140	141
VIVID															
	Laser [N = 132]					VTE 2Q4 [N = 136]					VTE 2Q8 [N = 135]				
Available [1]	99	90	68	62	58	97	89	92	96	87	101	99	93	91	81
DRSS = 90 [2]	33	29	16	5	4	39	35	22	10	8	34	31	14	9	9
Missing [3]	0	13	48	65	**70**	0	12	22	30	**41**	0	5	28	35	**45**
LOCF [4]	-	99	99	99	99	-	97	97	97	97	-	101	101	101	101
LOCF [5]	-	78	80	85	85	-	73	81	86	82	-	81	83	88	86

Note: Week 0 = Baseline
[1], [2], and [3] are, respectively, the number of patients with gradable, non-gradable (DRSS = 90), and missing DRSS data.
[4] and [5] are, respectively, the number of patients with change from baseline data at each visit using the reviewer and applicant LOCF approach.

In both studies, DRSS data were considered missing if patients were early dropout, missed visit, or received additional treatment for DME. The number of patients with missing DRSS data at week 100 by reasons for missing data is shown in Table 8.

Table 8: Number of patients with missing DRSS data at week 100 by reason for missing data

DRSS Data Missing at Week 100	Laser	VTE 2Q4	VTE 2Q8	Laser	VTE 2Q4	VTE 2Q8
Due to Receipt of Additional Treatment (A)	63	5	13	46	10	15
Completed Study (A1)	56	5	13	41	10	14
Early drop-out (A2)	7	0	0	5	0	1
Due to Other reasons (B)	18	39	35	24	31	30
Missing Visit (B1)	4	10	11	2	10	6
Early drop-out (B2)	14	29	24	22	21	24
Total Missing at Week 100 (C)	**81**	**44**	**48**	**70**	**41**	**45**

Total Number Missing at Week 100 (C) = A + B; A = A1 + A2; B = B1 + B2

In the applicant analysis approach, missing DRSS data were imputed using LOCF method. A description of the applicant LOCF approach for handling missing data and non-gradable DRSS data are discussed in Section 3.2.2.2 item (ii). The reviewer's proposed imputation approach and opinion on the applicant LOCF approach are also presented in the same section.

In Table 7, the number of patients with non-missing data for change from baseline in DRSS at each visit using the reviewer LOCF approach (see footnote [4]) and the applicant LOCF approach (See footnote [5]) are shown.

Therefore, unless stated otherwise, all efficacy analyses results (on the DRSS data) presented in the following sections were based on the reviewer's data handling approach. We should note that the overall conclusions between the two approaches were the same even though minor differences were noted in the number of patients that experienced DR improvement (or worsening) and the total number of patients included in the analyses. The results from the applicant's data handling approach are presented in Appendix Table 15.

Analysis Results of DR Severity Score

The primary efficacy claim for the treatment of DR in patients with DME was based on the proportion of patients who improved by ≥2-steps from baseline at week 100 (e.g. a shift from severe to moderate NPDR). To further explore the effect of each Eylea dose group for the treatment of DR, the proportion of patients who improved by ≥3-steps and worsened by ≥2- or ≥3-steps in DR severity score were evaluated in a similar manner at week 100. A subject was considered to have improved (or worsened) by ≥2-steps if the change from baseline using the re-coded severity scale data (column 1 of Table 2) was ≤ -2 (or ≥ +2).

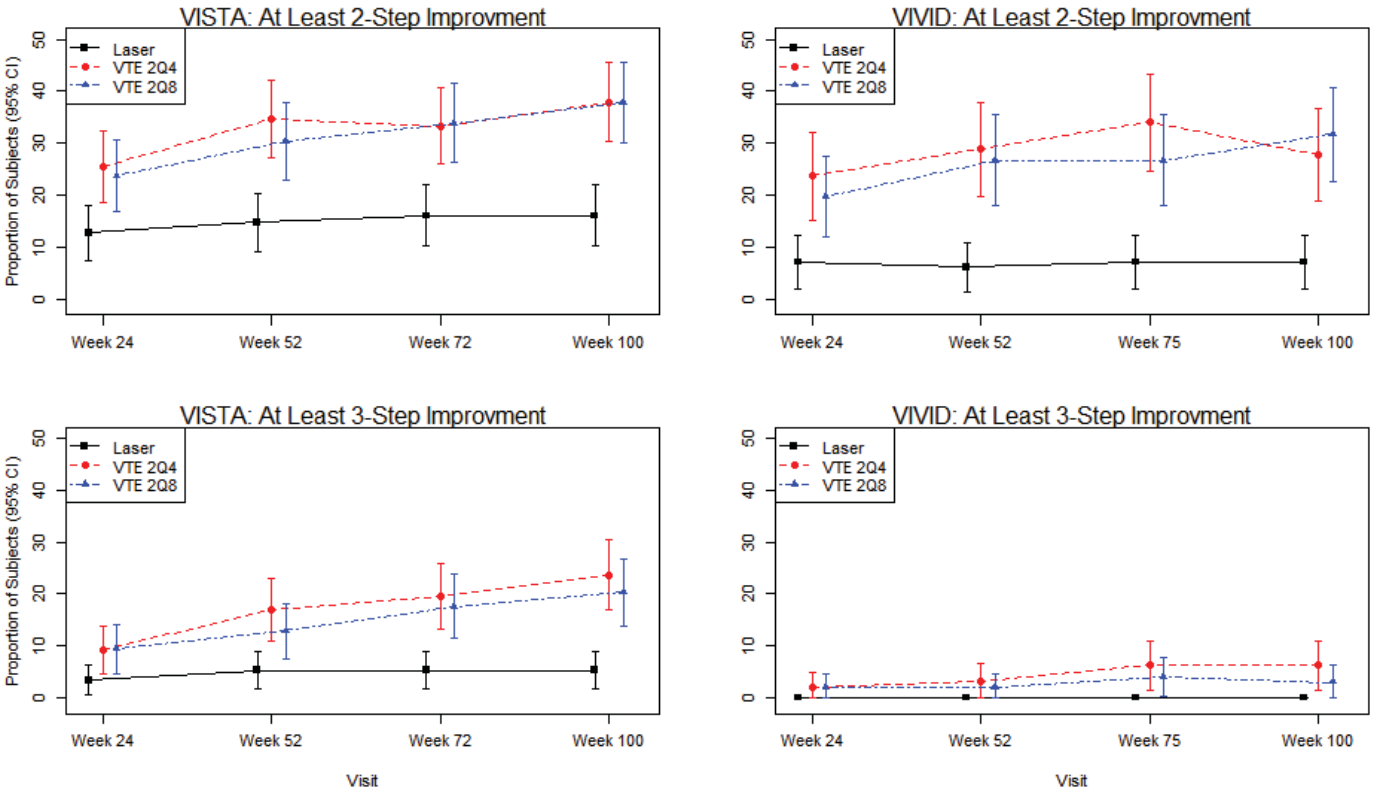
Note that the secondary efficacy analysis within each study was a statistical evaluation of superiority of the VTE groups versus laser in the FAS population based on the LOCF data. The proportion of patients who improved by ≥2-steps was compared between each of the VTE groups and the laser group separately at a significance level of 2.5%. Treatment comparison was made using a stratified Cochran-Mantel-Haenszel (CMH) test.

Superiority of each VTE group to laser was declared if the p-value for each comparison was < 0.025. A weighted point and two-sided 97.5% confidence interval estimates for the difference in the proportion of patients who improved by ≥2-steps (*VTE 2Q4 minus laser and VTE 2Q8 minus laser*) adjusted for the study specific strata was performed using the CMH weights and normal approximation of the weighted estimates.

3.2.4.3.1. Proportion of patients who improved by ≥2- or ≥3-steps in DRSS at week 100

In Figure 7 below the proportion of patients who improved by ≥2- and ≥3-steps from baseline throughout the study are shown.

Figure 7: Proportion of patients who improved by ≥2- and ≥3-steps from baseline over time (Full Analysis Set, LOCF)



There was a clear separation between each of the VTE groups versus the laser group over time; at each visit, many Eylea treated patients appeared to have experienced significant improvement in DR severity compared to laser treated patients.

The summary of the proportion of patients who improved by ≥2- and ≥3-steps from baseline at week 100 for the overall population and by the levels of the study specific stratification factors are shown in Table 9.

In both studies, many Eylea treated patients' experienced significant improvement in DR severity compared to laser treated patients. The overall patterns within the levels of the stratification factors were consistent with those in the overall population.

Table 9: Proportion of patients who improved by ≥2- and ≥3-step at week 100
(Full Analysis Set, LOCF)

VISTA

Treatment	Medical history of MI or CVA		Total	Difference vs Laser (%) (97.5% CI) [1]	p-value[2]
	Yes n / N (%)	No n / N (%)	n / N (%)		
≥ 2-Steps Improvement					
Laser	4/ 46 (8.7)	20/104 (19.2)	24/150 (16.0)	--	
VTE 2Q4	22/ 56 (39.3)	36/ 97 (37.1)	58/153 (37.9)	22.1 (11.1, 33.2)	<0.001
VTE 2Q8	16/ 43 (37.2)	40/105 (38.1)	56/148 (37.8)	21.7 (10.5, 33.0)	<0.001
≥ 3-Steps Improvement					
Laser	1/ 46 (2.2)	7/104 (6.7)	8/ 150 (5.3)	--	
VTE 2Q4	12/ 56 (21.4)	24/ 97 (24.7)	36/ 153 (23.5)	18.4 (9.7, 27.2)	<0.001
VTE 2Q8	8/ 43 (18.6)	22/105 (20.9)	30/ 148 (20.3)	14.9 (6.4, 23.4)	<0.001

VIVID

Treatment	Geographic Region		Total	Difference vs Laser (%) (97.5% CI) [1]	p-value [2]
	Non-Japanese n / N (%)	Japanese n / N (%)	n / N (%)		
≥ 2-Steps Improvement					
Laser	5/81 (6.2)	2/ 18 (11.1)	7/99 (7.1)	--	
VTE 2Q4	21/77 (27.3)	6/ 20 (30.0)	27/97 (27.8)	20.7 (8.8, 32.5)	<0.001
VTE 2Q8	21/80 (26.3)	11/ 21 (52.4)	32/101 (31.7)	24.2 (12.4, 35.9)	<0.001
≥ 3-Steps Improvement					
Laser	0/81 (0.0)	0/ 8 (0.0)	0/99 (0.0)	--	
VTE 2Q4	5/77 (6.5)	1/ 20 (5.0)	6/97 (6.2)	6.2 (0.7, 11.8)	0.012
VTE 2Q8	1/80 (1.3)	2/ 21 (9.5)	3/101 (3.0)	2.9 (-0.8, 6.5)	0.096

[1] Difference with confidence interval (CI) based on using CMH weighting scheme adjusted by study specific stratification factor.
[2] P-value calculated using 2-sided Cochran-Mantel-Haenszel (CMH) test adjusted by study specific stratification factor.
N: Total number of patients with gradable DRSS data at baseline

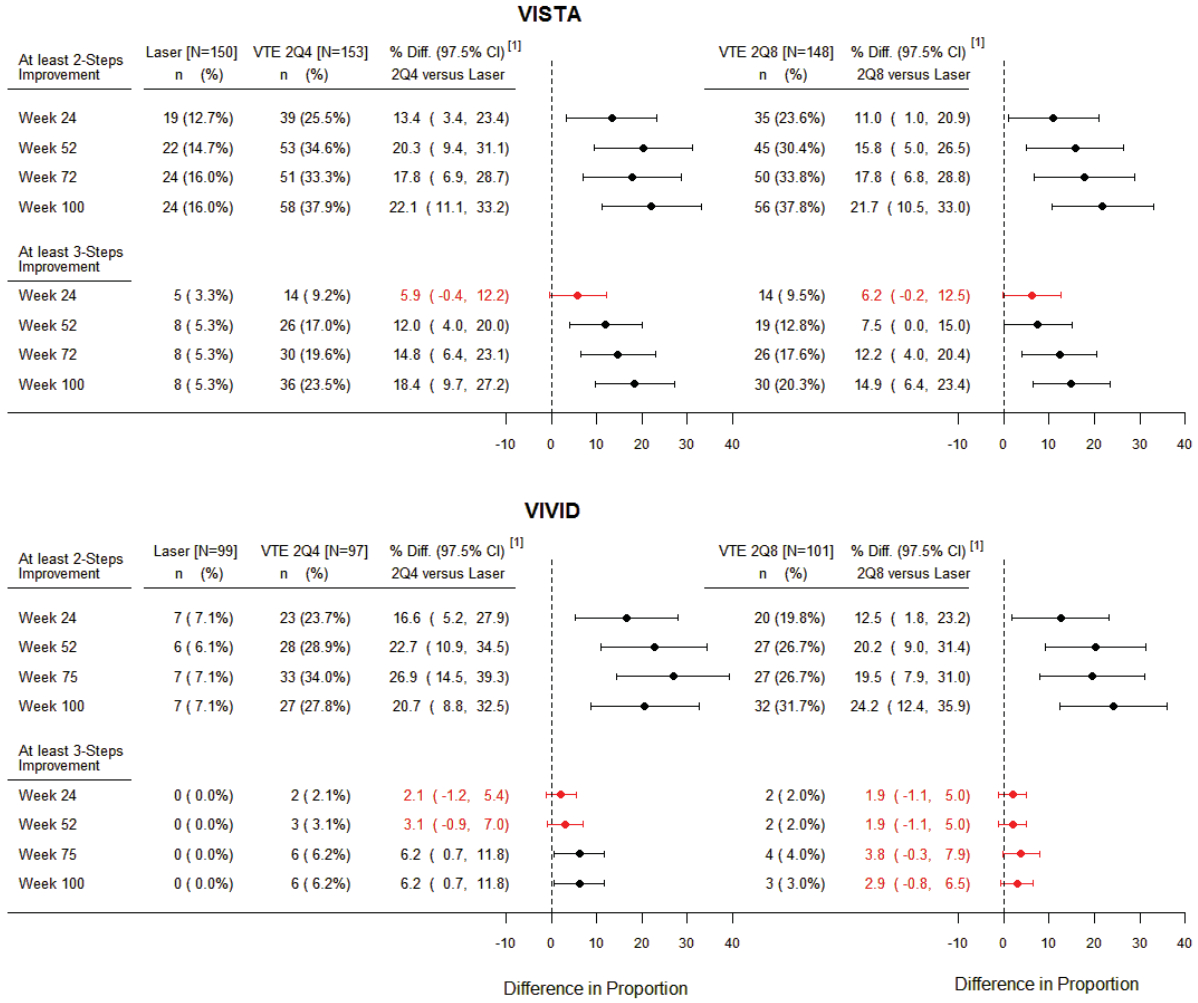
In the VISTA study, 38% and 24% of patients treated with VTE 2Q4, 38% and 20% of patients treated with VTE 2Q8, and 16% and 5% of patients treated with laser improved by ≥2- and ≥3-steps from baseline at week 100, respectively; the treatment differences, respectively, were 22% [97.5% CI: (11%, 33%)] and 18% [97.5% CI: (10%, 27%)] for VTE 2Q4 versus laser and were 22% [97.5% CI: (11%, 33%)] and 15% [97.5% CI: (6%, 23%)] for VTE 2Q8 versus laser. In this study, statistical significance for the secondary endpoint of ≥2- steps improvement and the exploratory endpoint of ≥3-steps improvement from baseline at week 100 was achieved for each of the Eylea dose group versus laser.

In the VIVID study, 28% and 6% of patients treated with VTE 2Q4, 32% and 3% of patients treated with VTE 2Q8, and 7% and 0% of patients treated with laser improved by ≥2- and ≥3-steps, respectively; the treatment differences, respectively, were 21% [97.5% CI: (9%, 33%)] and 6% [97.5% CI: (1%, 12%)] for VTE 2Q4 versus laser and were 24% [97.5% CI: (12%, 36%)] and 3% [97.5% CI: (-1%, 7%)] for VTE 2Q8 versus laser. In this study, statistical significance was achieved for the secondary endpoint of ≥ 2-steps improvement for each of the VTE groups versus laser and for the exploratory endpoint of ≥3-steps improvement for the VTE 2Q4 group versus laser. However, there was no sufficient evidence to support the superiority of the VTE

2Q8 group over laser for the exploratory endpoint of ≥3-steps improvement, and the differences from laser for this endpoint was not statistically significant (p=0.096).

The proportion of patients who improved by ≥2- and ≥3-steps from baseline at each visit is shown in Figure 8 below. The treatment differences for the proportion of patients who improved by ≥2- and ≥3-steps versus laser were slightly increasing over time with the largest treatment differences occurring at week 100 in most cases.

Figure 8: Proportion of patients who improved by ≥2- and ≥3-step by visit
(Full Analysis Set, LOCF)



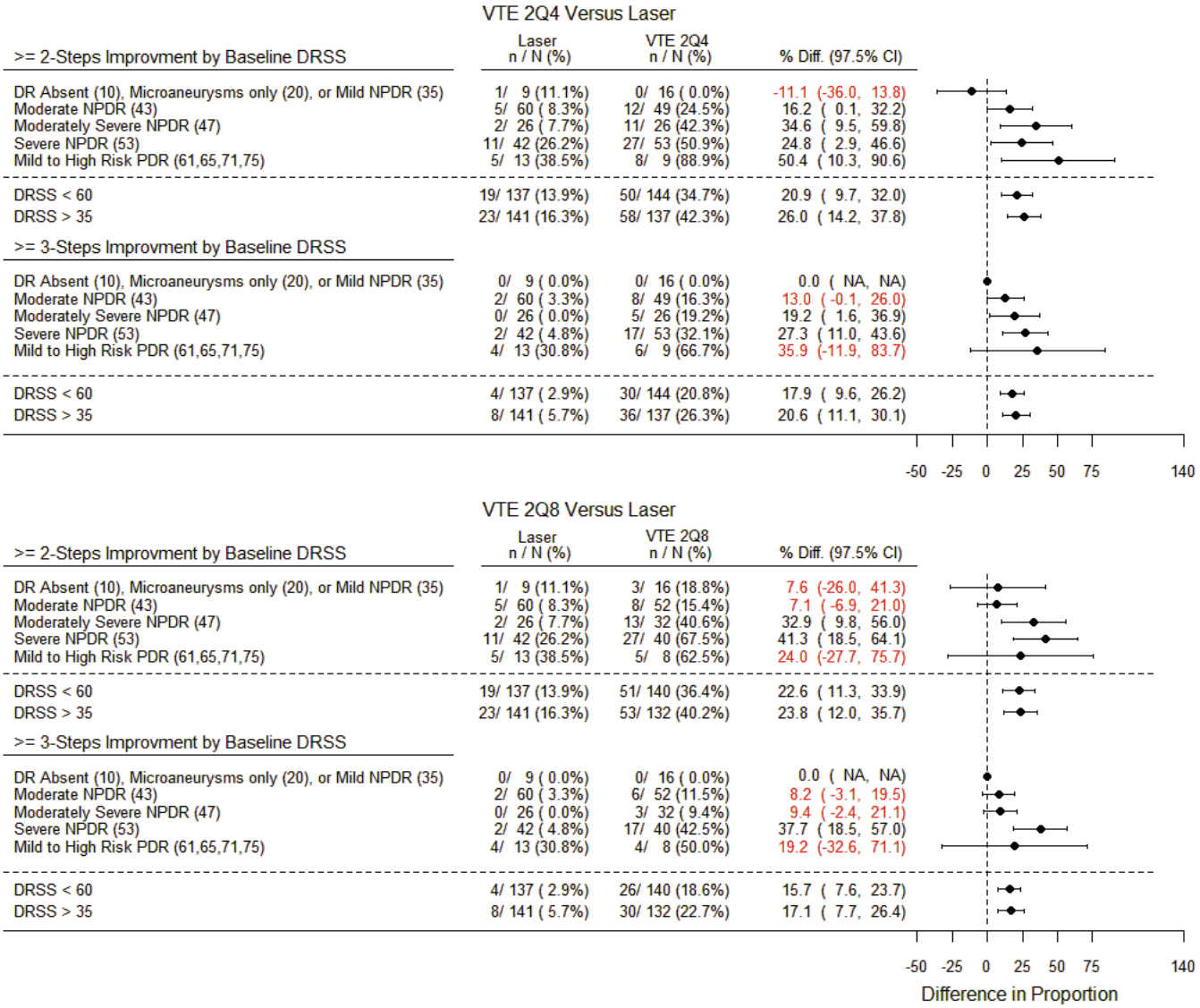
N: Total number of patients with gradable DRSS data at baseline; post-baseline missing DRSS data or non-gradable DRSS data was imputed using the last gradable DRSS value.
[1] Difference (VTE group minus laser group) with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors

Analysis of DR Improvement by ≥2-step and ≥3-step by baseline DR severity score

The rate of DR improvement by ≥2-steps and ≥3-steps from baseline at week 100 was investigated by baseline DR severity level.

The results for the VISTA study are shown in Figure 9 and for the VIVID study are shown in Figure 10.

Figure 9: Proportion of patients with DR improvement at week 100 by baseline DRSS (VISTA)
(Full Analysis Set, LOCF)

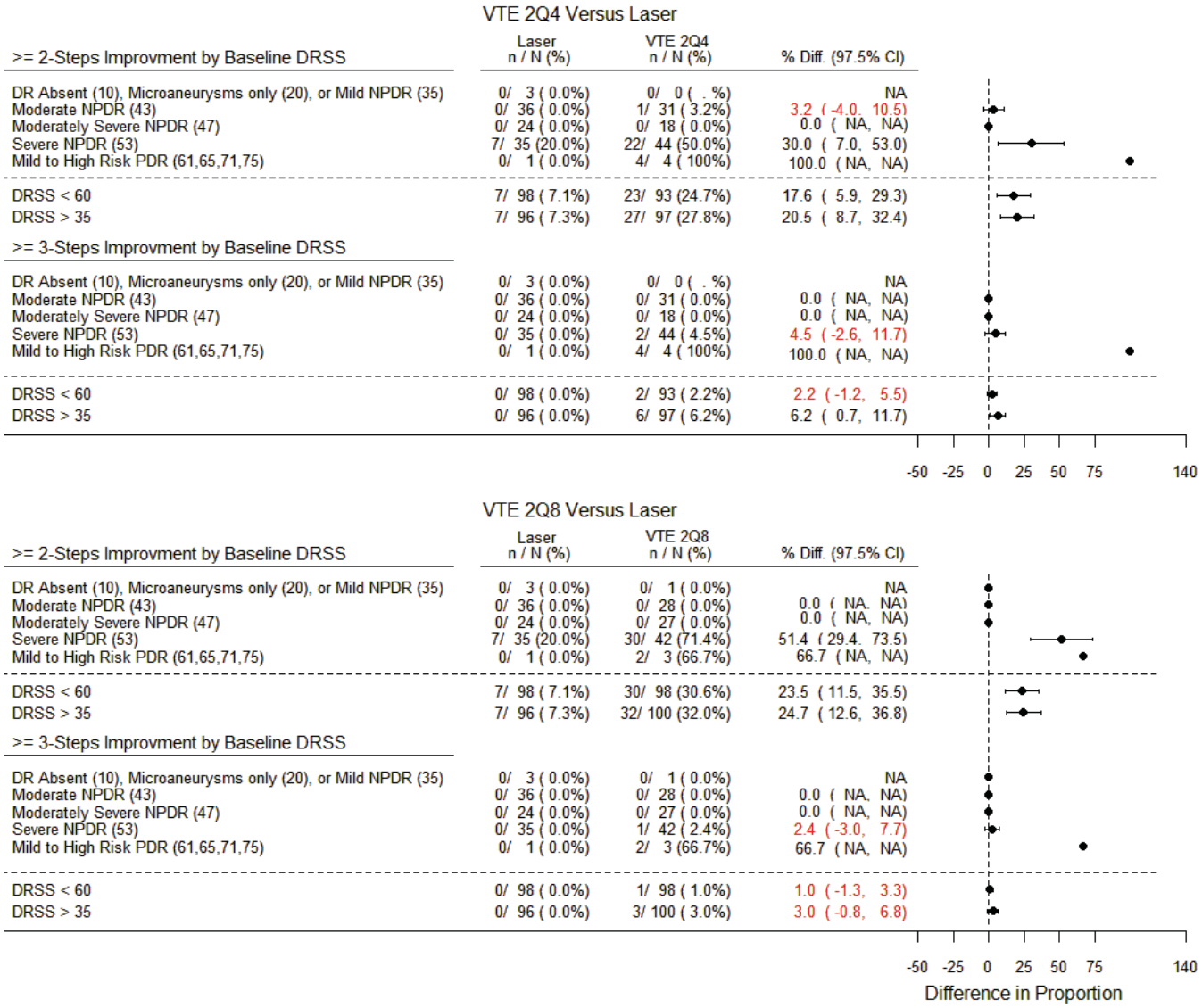


Among the groups with relatively more patients at baseline (i.e., DRSS=43, 47, 53), many patients with severe NPDR (DRSS=47) at baseline experienced ≥2-steps improvement at week 100. The improvement in this group was significantly higher in Eylea treated patients compared to laser treated patients; in the VISTA study, 25% more VTE 2Q4 treated patients and 42% more VTE 2Q8 treated patients improved by ≥2-steps compared to laser treated patients. Similarly, in the VIVID study, 30% more VTE 2Q4 treated patients and 51% more VTE 2Q8 treated patients improved by ≥2-steps compared to laser treated patients.

Even though the number of patients with at least mild PDR at baseline (DRSS >=60) was very small, in this group in the VISTA study, 5 and 4 out of 13 patients in the laser group; 8 and 6 out of 9 patients in the VTE 2Q4 group; and 5 and 4 out of 8 patients in the VTE 2Q8 group improved by ≥2- and ≥3-steps, respectively. In the VIVID study, 4 out of 4 patients in the VTE

2Q4 group and 2 out of 3 patients in the VTE 2Q8 group improved by ≥2- and ≥3-steps in this group while no subject in the laser group improved by ≥3-steps

Figure 10: Proportion of patients with DR improvement at week 100 by baseline DRSS (VIVID) (Full Analysis Set, LOCF)



The rates of DR improvement by ≥2- and ≥3-steps from baseline at week 100 were further explored in patients with at least moderate NPDR at baseline (DRSS > 35) and in patients with at most sever NPDR at baseline (DRSS < 60).

In both subpopulations, many Eylea treated patients' experienced significant improvement in DR severity compared to laser treated patients, and the rate of treatment differences between each of the VTE groups versus laser in these subpopulations was virtually the same.

In the VISTA study, about 21% and 17% more Eylea treated patients with baseline DRSS <60 and about 25% and 19% more Eylea treated patients with baseline DRSS >35 experienced ≥2- and ≥3-steps improvement compared to laser treated patients, respectively. Similarly, in the

VIVID study, about 22% and 2% more Eylea treated patients with baseline DRSS <60 and about 22% and 5% more Eylea treated patients with baseline DRSS >35 experienced ≥2- and ≥3-steps improvement, respectively, compared to laser treated patients.

3.2.4.3.2. Proportion of patients who worsened by ≥2- or ≥3-steps in DRSS at week 100

To further explore the effect of VTE treatment in the prevention of DR progression, the exploratory endpoints of the proportion of patients who worsened by ≥2- or ≥3-steps on the DR severity score from baseline at week 100 were explored in a similar manner. The results for these endpoints are shown in Table 10.

In both studies, fewer Eylea treated patients experienced progression in DR severity at week 100 compared to laser treated patients.

Table 10: Proportion of patients who worsened by ≥2- and ≥3-step from baseline at week 100 (Full Analysis Set, LOCF)

Visit	Laser (N = 154)	VTE 2Q4 (N = 154)	VTE 2Q8 (N = 151)	%Difference (97.5% CI) versus Laser (%) [1]	
				VTE 2Q4	VTE 2Q8
VISTA					
≥ 2-steps	29/ 150 (19.3%)	11/ 153 (7.2%)	10/ 148 (6.8%)	-12.4 (-21.1, -3.7)	-12.5 (-21.0, -4.0)
≥ 3-steps	9/ 150 (6.0%)	3/ 153 (2.0%)	4/ 148 (2.7%)	-4.1 (-9.2, 1.1)	-3.3 (-8.6, 2.0)
VIVID					
Visit	Laser (N = 132)	VTE 2Q4 (N = 136)	VTE 2Q8 (N = 135)	%Difference (97.5% CI) versus Laser (%) [1]	
				VTE 2Q4	VTE 2Q8
≥ 2-steps	6/ 99 (6.1%)	1/ 97 (1.0%)	1/ 101 (1.0%)	-5.0 (-10.9, 0.9)	-5.1 (-10.9, 0.7)
≥ 3-steps	2/ 99 (2.0%)	0/ 97 (0.0%)	1/ 101 (1.0%)	-2.1 (-5.4, 1.2)	-1.1 (-5.0, 2.7)

[1] Difference with confidence interval (CI) based on using CMH weighting scheme adjusted by study specific stratification factor
Percentages were calculated based on total number of patients with gradable DRSS data at baseline

In the VISTA study, 12% and 4% fewer VTE 2Q4 treated patients compared to laser treated patients and 13% and 3% fewer VTE 2Q8 treated patients compared to laser treated patients worsened by ≥2- and ≥3-steps from baseline at week 100, respectively. In this study, statistical significance was achieved for the proportion of patients who worsened by ≥2-steps from baseline at week 100 for each of the VTE groups versus laser: the treatment difference was -12% [97.5% CI: (-21%, -4%)] for VTE 2Q4 versus laser and was -13% [97.5% CI: (-21%, -4%)] for VTE 2Q8 versus laser.

In the VIVID study, 5% and 2% fewer VTE 2Q4 treated patients compared to laser treated patients and 5% and 1% fewer VTE 2Q8 treated patients compared to laser treated patients worsened by ≥2- and ≥3-steps from baseline at week 100, respectively. In each treatment group, the incidences of DR worsening by ≥3-steps in both studies and DR worsening by ≥2-steps in the VIVID study were very low, and no statistically significant difference was achieved among the treatment groups. Due to the low incidence rates for these endpoints, the DME studies may not have an adequate number of patients to show statistical difference.

The proportion of subjects who worsened by ≥2- and ≥3-steps from baseline at each visit is shown in Appendix Figure **14**. The rates of DR worsening at each visit were slightly higher in the laser treated patients compared to the Eylea treated patients.

3.2.4.3.3. Sensitivity analysis for DR related secondary efficacy endpoint

The secondary efficacy analysis for the DRSS data was performed based on the FAS population using LOCF method for missing data; DRSS data were considered missing if patients were early dropout, missed visit, or received additional treatment for DME. For patients that received additional treatment during the study, the DRSS data measured after receipt of additional were not used in the secondary efficacy analysis. Instead, the last available DRSS data measured before initiation of the additional treatment was used in the LOCF approach. To assess the impact on the secondary efficacy results of missing data due to drop-outs or receipt of additional treatment, treatment comparison for the secondary and exploratory endpoints with DR relevance were performed using: (i) observed cases (OC) - excluding the DRSS data after additional treatment was given, (ii) observed cases (aOC) - including DRSS data after additional treatment was given, and (iii) last observation carried forward (aLOCF) - including DRSS data after additional treatment was given.

The sensitivity analysis results are shown in Appendix Table 16. The results under the various data handling approaches were consistent with the secondary efficacy analysis results based on the LOCF method - yielding the same conclusion that more Eylea treated patients experienced significant improvement while fewer Eylea treated patients experienced worsening in DR severity at week 100 compared to laser treated patients.

3.2.4.3.4. Additional efficacy analysis with DR relevance

i) Incidence of new cases of PDR (DRSS ≥ 60) at each visit

The incidence of new cases of PDR (DRSS ≥ 60) – progression in DR severity level from at most sever NPDR level at baseline to at least mild PDR at each visit – was also explored by visit; the results are shown in Table 11 below.

Clearly, the risk of experiencing a new PDR event during the study was lower in the Eylea treated patients compared to the laser treated patients; in the VISTA and VIVID study, respectively, about 10% and 5% fewer Eylea treated patients developed new cases of PDR at week 100 compared to laser treated patients.

Table 11: Proportion of patients who progressed from NPDR at baseline to PDR at each visit (Full Analysis Set, LOCF)

Visit	Laser (N = 154)	VTE 2Q4 (N = 151)	VTE 2Q8 (N = 154)	%Difference (97.5% CI) versus Laser (%) [1]	
				VTE 2Q4	VTE 2Q8
VISTA					
Week 24	8/ 150 (5.3%)	3/ 153 (2.0%)	1/ 148 (0.7%)	-3.4 (-8.2, 1.5)	-4.7 (-9.1, -0.3)
Week 52	13/ 150 (8.7%)	3/ 153 (2.0%)	2/ 148 (1.4%)	-6.7 (-12.5, -1.0)	-7.3 (-12.9, -1.7)
Week 72	12/ 150 (8.0%)	1/ 153 (0.7%)	0/ 148 (0.0%)	-7.3 (-12.5, -2.2)	-8.0 (-13.0, -3.0)
Week 100	16/ 150 (10.7%)	1/ 153 (0.7%)	1/ 148 (0.7%)	-10.0 (-15.9, -4.2)	-10.0 (-15.9, -4.1)
VIVID					
Visit	Laser (N = 132)	VTE 2Q4 (N = 136)	VTE 2Q8 (N = 135)	%Difference (97.5% CI) versus Laser (%) [1]	
				VTE 2Q4	VTE 2Q8
Week 24	3/ 99 (3.0%)	0/ 97 (0.0%)	0/ 101 (0.0%)	-3.0 (-6.9, 0.9)	-3.0 (-6.9, 0.9)
Week 52	6/ 99 (6.1%)	1/ 97 (1.0%)	1/ 101 (1.0%)	-5.0 (-10.9, 0.8)	-5.1 (-10.9, 0.8)
Week 75	5/ 99 (5.1%)	0/ 97 (0.0%)	2/ 101 (2.0%)	-5.1 (-10.0, -0.1)	-3.1 (-8.9, 2.8)
Week 100	6/ 99 (6.1%)	1/ 97 (1.0%)	1/ 101 (1.0%)	-5.0 (-10.9, 0.8)	-5.1 (-10.9, 0.8)

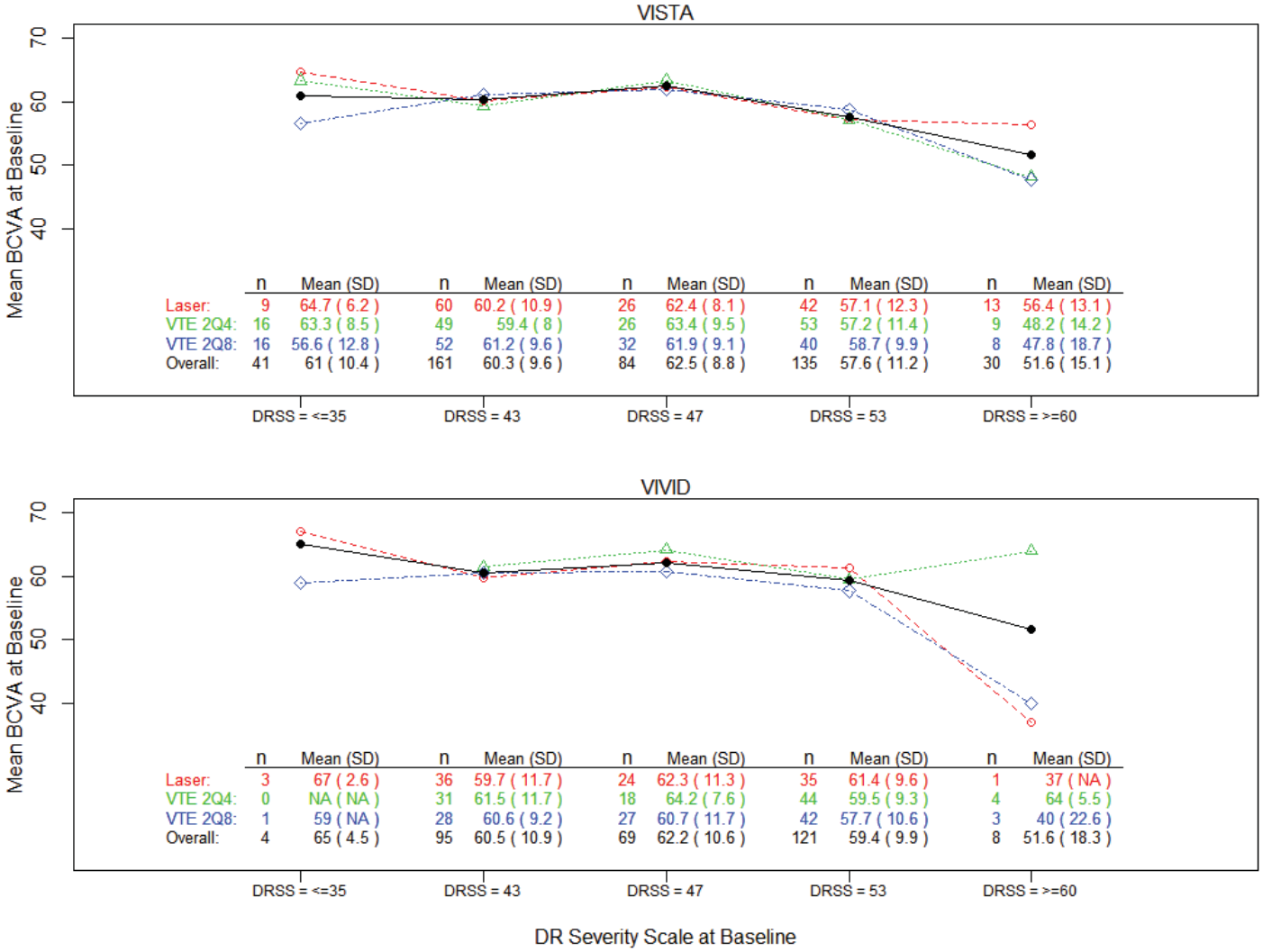
[1] Difference with confidence interval (CI) based on using CMH weighting scheme adjusted by study specific stratification factor

ii) Relationship between visual acuity and DR severity level

To assess the impact of DR severity improvement (or worsening) on visual acuity, we examined the relationship between the BCVA data and the DRSS data before treatment was received (at the baseline visit) and after treatment was received for two years (at week 100).

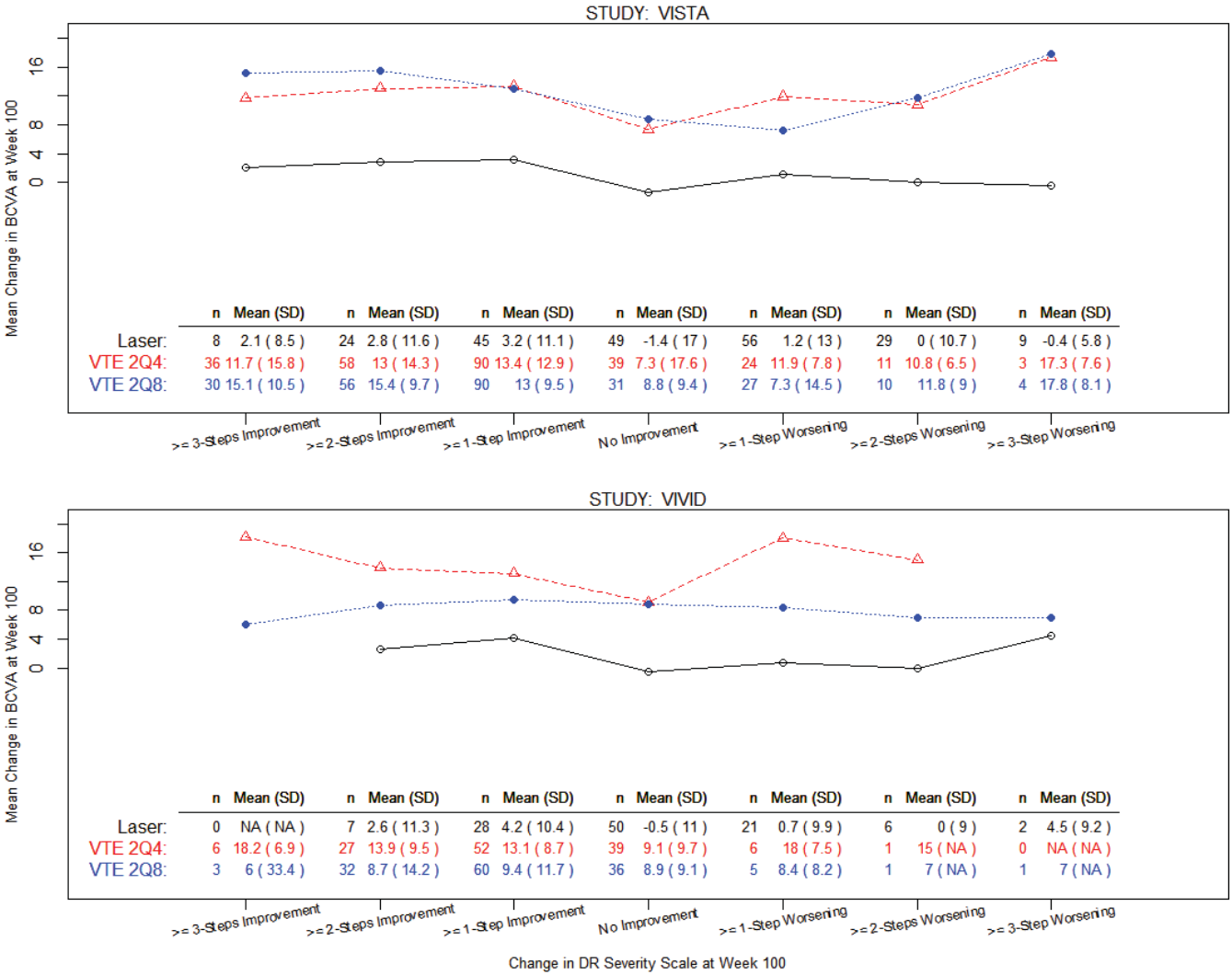
In Figure 11, the plot of mean baseline BCVA by baseline DR severity level are shown. Overall, patients with lower DR severity level at baseline have a slightly higher mean baseline BCVA score compared to patients with higher DR severity score.

Figure 11: Mean baseline BCVA by baseline DRSS for patients with gradable DRSS data (Full Analysis Set)



In Figure 12, the plot of mean change in BCVA score from baseline at week 100 is shown by the change in DR severity level from baseline at week 100. Patients that experienced ≥2- and ≥3-steps improvement in DR severity at week 100 demonstrated a slight gain in BCVA score on average compared to those who experienced no improvement or worsened by ≥1- or ≥2-steps. The number of patients who worsened by ≥3-steps is very small in both studies; thus, no sufficient data to describe the relationship.

Figure 12: Mean change in BCVA at week 100 by change in DR severity score at week 100
(Full Analysis Set; patients with gradable DRSS data)



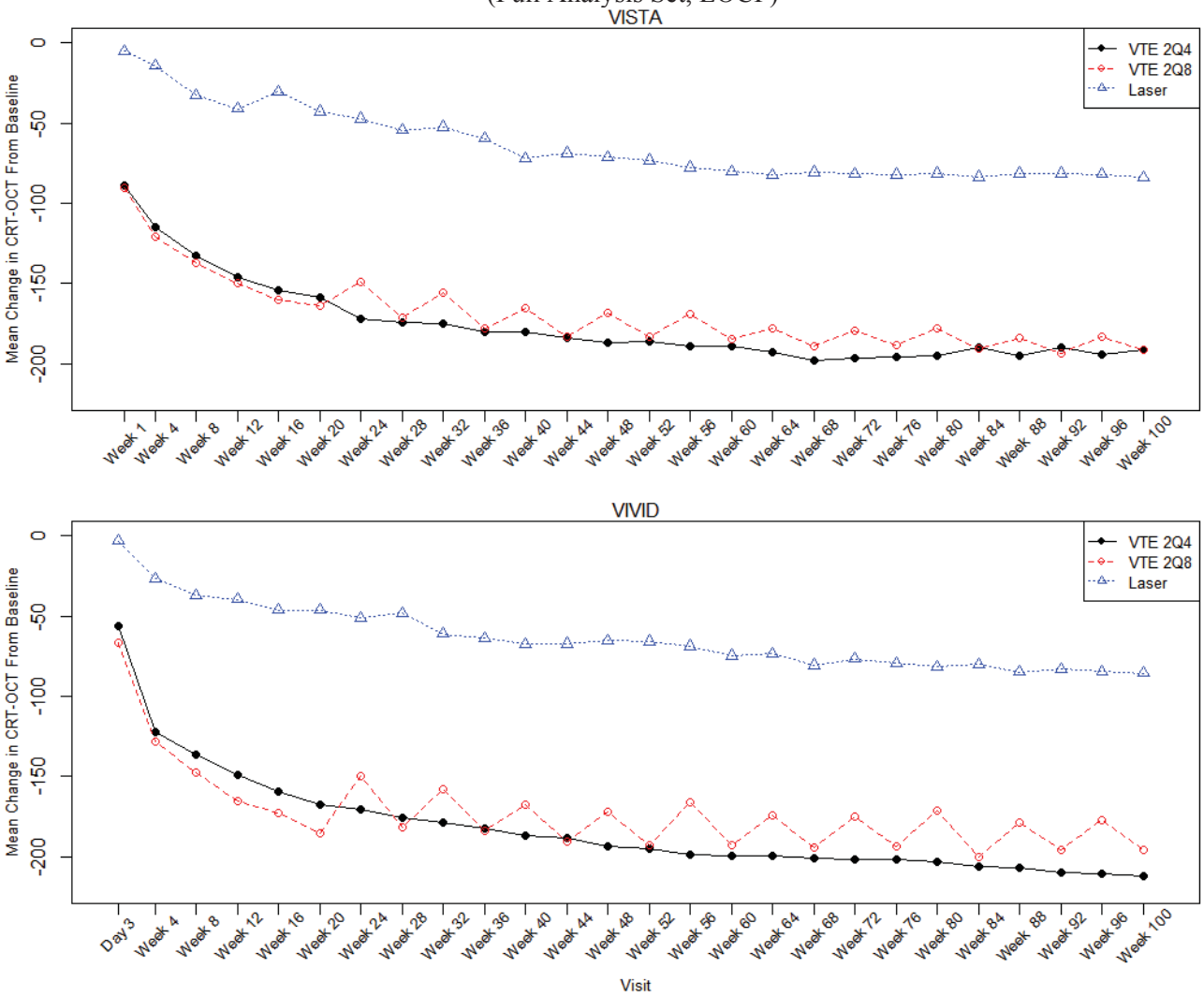
3.2.4.4. Change in central retinal thickness (CRT) from baseline at week 100

The central retinal thickness (CRT) was assessed by optical coherence tomography (OCT) to measure the extent and progression of macular swelling. Figure 13 below shows the mean change in CRT from baseline over time. At all study visits there was a clear separation between each of the VTE groups versus laser, and the separation that was established during the first year treatment period was maintained during the second year treatment period.

In the VISTA study, the mean change in CRT from baseline at week 100 in the VTE 2Q4 treated patients was -191, in the VTE 2Q8 treated patients was -197, and in the laser treated patients was -86. The treatment difference was -105 [97.5% CI: (-140, -70)] for VTE 2Q4 versus laser and was -111 [97.5% CI: (-143, -79)] for VTE 2Q8 versus laser. Similarly, in the VIVID study, the mean change in CRT from baseline at week 100 in the VTE 2Q4 treated patients was -225, in the VTE 2Q8 treated patients was -198, and in the laser treated patients was -71. The treatment difference was -154 [97.5% CI: (-189, -120)] for VTE 2Q4 versus laser and was -127 [97.5% CI:

(-165, -89)] for VTE 2Q8 versus laser. In both studies, statistical significance was achieved for the mean change in CRT from baseline at week 100 for each of the Eylea dose group versus laser.

Figure 13: Mean change from baseline in CRT over time
(Full Analysis Set, LOCF)



3.2.4.5. Assessment of vision-related quality of life

In both studies, vision-related quality of life (QoL) was assessed using the National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25). The NEI VFQ-25 subscales are scored from 0-100; a positive difference represents improved functioning.

In both studies, QoL was assessed by change in mean score from baseline to week 100 for the near and distance activities subscale based on the FAS population using the LOCF method. Near activities included reading ordinary prints in newspapers, see well up close, and finding something on a crowded shelf. Distance activities included reading street signs or the names of stores; going down steps, stairs, or curbs in dim light or at night; and going out to see movies, plays, or sports events.

3.2.4.5.1. Change in NEI VFQ-25 near activities subscale from baseline at week 100

In the VISTA study, the mean change in near activity subscale score from baseline at week 100 was 10 in the VTE 2Q4 group, 11 in the VTE 2Q8 group, and 6 in the laser group. The treatment difference was 5 [97.5% CI: (-1, 10)] for VTE 2Q4 versus laser and was 5 [97.5% CI: 0.1, 10)] for VTE 2Q8 versus laser. Similarly, in the VIVID study, it was 8 in the VTE 2Q4 group, 4 in the VTE 2Q8 group, and 5 in the laser group. The treatment difference was 4 [97.5% CI: (-1, 8)] for VTE 2Q4 versus laser and was -1 [97.5% CI: (-5, 4)] for VTE 2Q8 versus laser.

Statistical significance for comparison of near activity subscale QoL was achieved only between the VTE 2Q8 versus the laser group in the VISTA study. Therefore, only these two treatment groups were compared for the distance activities subscale QoL at week 100 since the hierarchical testing procedure for comparison of near activity subscale QoL between the VTE 2Q4 groups and the laser group in the VISTA study and between each of the VTE groups and the laser group in the VIVID study at week 100 was broken.

3.2.4.5.2. Change in NEI VFQ-25 distance activities subscale from baseline at week 100

In the VISTA study, the mean change in distance activity subscale score from baseline at week 100 in the VTE 2Q4, 2Q8, and laser treated patients were 10, 8, and 4, respectively. The treatment difference was 6 [97.5% CI: (1, 11)] for VTE 2Q4 versus laser and was 4 [97.5% CI: (-1, 8)] for VTE 2Q8 versus laser. Similarly, in the VIVID study, the mean change in distance activity subscale score from baseline at week 100 in the VTE 2Q4, 2Q8, and laser treated patients were about 5, 1, and 2, respectively. The treatment difference was 3 [97.5% CI: (-2, 7)] for VTE 2Q4 versus laser and was -1 [97.5% CI: (-6, 3)] for VTE 2Q8 versus laser. Thus, for the distance activity subscale, none of the treatment comparisons was considered positive.

3.2.5. Efficacy Conclusion

The primary and the first secondary efficacy endpoints both evaluated at week 52 were met in both studies for the DME indication. Furthermore, statistical significances were achieved for the secondary endpoints of change in BCVA at week 100 and for the proportion of patients who gained ≥10 and ≥15 letters from baseline at week 100 for each VTE group versus laser. That is, treatment with Eylea injection continued to provide significant improvement in visual acuity since the treatment benefit observed during the first year of treatment period was clearly maintained throughout the second year of treatment period.

One of the pre-specified secondary efficacy endpoints in the DME protocol was the proportion of patients who improved by ≥2-steps in DR severity from baseline at week 100; the applicant defined main analysis for the proposed indication of treatment of DR in patients with DME was based on this endpoint. Furthermore, the proportions of patients who improved by ≥3-steps and worsened by ≥2- and ≥3-steps were also defined in the DME protocols as exploratory endpoints relevant to the DR indication.

Overall, more Eylea treated patients experienced significant improvement in DR severity while fewer Eylea-treated patients experienced worsening in DR severity at week 100. In both studies, statistical significance was achieved for the pre-specified secondary endpoint relevant to the DR indication. Furthermore, the results of the exploratory endpoints with DR relevance also demonstrated treatment benefit with Eylea injection in improving DR severity in patients with DME.

3.3. SAFETY EVALUATION

In both the VISTA and VIVID studies, safety was evaluated based on all randomized subjects who received at least a single dose of double blind treatment. The safety parameters included extent of exposure to study drug, adverse events (AEs), clinical laboratory evaluation, and additional safety variables which included intraocular pressure, vital signs, electrocardiogram, and ophthalmic examinations.

In this review a high level safety summary is provided; a comprehensive safety evaluation is primarily covered in the FDA clinical review.

The integrated safety population included a total of 865 subjects; 287 subjects were included in the laser group, 291 subjects were included in the VTE 2Q4 group, and 287 subjects were included in the VTE 2Q8 group. Subjects included in the integrated safety population had mean age of 62.9 years at enrollment with ages ranging 23 to 87 years old, most subjects were white (82%), and there were more men (58%) than women (42%).

3.3.1. Study Exposure

During the 100 week treatment period, the planned exposure in the study eye for patients in the VTE 2Q4 group was 25 injections, for patients in the VTE 2Q8 group was 15 injections, and laser therapy at baseline (day 1) for subjects in the laser group and then as needed (but no more often than every 12 weeks).

Table 12 shows summary for the number of active injections in each of the VTE groups, the number of active laser in the laser group, and the duration of treatment. The majority of subjects in each of the VTE treatment groups received the planned treatment injections; the average number of injections in the VTE 2Q4 group was about 21 and in the VTE 2Q8 group was about 14. All subjects in the laser treatment group received laser therapy at baseline and the mean number of active laser treatments was about 2.4 and the maximum number about 8.

Table 12: Exposure to treatment (not including additional treatment) in the first 100 weeks (Safety Analysis Set)

	VISTA			VIVID		
	Laser (N = 154)	VTE 2Q4 (N = 155)	VTE 2Q8 (N = 152)	Laser (N = 136)	VTE 2Q4 (N = 135)	VTE 2Q8 (N = 133)
Summary of Active Treatments [1]						
Mean (SD)	3.5 (2.0)	21.3 (5.8)	13.5 (2.9)	2.4 (1.6)	22.6 (5.8)	13.6 (2.9)
Median	3.0	24.0	15.0	2.0	25.0	15.0
Range	1 - 8	1 – 25	1 – 16	1 - 7	1 - 25	1 - 16
Duration of Treatment (Weeks)						
Mean (SD)	93.9 (18.8)	90.1 (23.2)	92.7 (20.6)	88.1 (27.8)	91.9 (23.5)	91.6 (20.9)
Median	100.0	99.9	100.0	100.0	100.0	100.0
Range	4 – 102	4 – 102	4 – 102	4 - 106	4 - 105	4 - 107

[1] Active treatment refer active laser for subjects in the laser group and active injection for subjects in each of the VTE groups; VTE injections given in laser group for additional treatment are not included and laser given in VTE groups for additional treatment is not included

Source: Tables 36 of the VISTA study report and Table 41 of Applicant's Summary of Clinical Safety report

3.3.2. Adverse Events

In the combined VISTA and VIVID studies, a total of 865 subjects were exposed to the study drug. Table 13 presents overview of treatment emergent AEs (TEAEs) by treatment group for for each study. During the two years treatment period, at least 95% and 30% of patients in each treatment group experienced at least one treatment-emergent AE and SAE, respectively. The incidences of TEAEs considered by the investigator as drug-related were slightly higher for VTE treated patients compared to laser-treated patients; the rate of injection related TEAEs were also slightly higher in the VTE groups than in the laser group.

Table 13: Treatment emergent adverse events overview by treatment group
(Safety Analysis Set)

	VISTA			VIVID		
	Laser (N = 154)	VTE 2Q4 (N = 155)	VTE 2Q8 (N = 152)	Laser (N = 133)	VTE 2Q4 (N = 136)	VTE 2Q8 (N = 135)
Number (%) of subjects with any TEAE	150 (97.4)	152 (98.1)	148 (97.4)	128 (96.2)	132 (97.1)	126 (93.3)
Any ocular TEAE	131 (85.1)	128 (82.6)	122 (80.3)	105 (78.9)	112 (82.4)	111 (82.2)
Study Eye	120 (77.9)	113 (72.9)	108 (71.1)	95 (71.4)	99 (72.8)	98 (72.6)
Any non-ocular TEAE	143 (92.9)	142 (91.6)	142 (93.4)	102 (76.7)	113 (83.1)	112 (83.0)
Any drug-related TEAE	6 (3.9)	11 (7.1)	5 (3.3)	9 (6.8%)	28 (20.6)	23 (17.0)
Any drug-related ocular TEAE	3 (1.9)	7 (4.5)	3 (2.0)	6 (4.5)	26 (19.1)	16 (11.9)
Any drug-related non-ocular TEAE	3 (1.9	4 (2.6)	) 2 (1.3)	1 (0.8)	4 (2.9)	5 (3.7)
Any injection related TEAE	72 (46.8)	80 (51.6)	72 (47.4)	23 (17.3)	68 (50.0)	59 (43.7)
Any laser related TEAE	8 (5.2)	5 (3.2)	1 (0.7)	13 (9.8)	5 (3.7)	13 (9.6)
Any treatment emergent SAE	73 (47.4)	77 (49.7)	59 (38.8)	40 (30.1)	41 (30.1)	46 (34.1)
Any treatment emergent ocular SAE	12 (7.8)	18 (11.6)	9 (5.9)	11 (8.3)	10 (7.4)	9 (6.7)
Any treatment emergent non-ocular SAE	67 (43.5)	67 (43.2)	56 (36.8)	30 (22.6)	36 (26.5)	38 (28.1)
Any drug related treatment emergent SAE	1 (0.6)	2 (1.3)	2 (1.3)	1 (0.8)	5 (3.7)	5 (3.7)
Any drug-related ocular serious TEAE	0	0	1 (0.7)	0	1 (0.7)	0
Any drug-related non-ocular TE SAE	1 (0.6)	2 (1.3)	1 (0.7)	1 (0.8)	4 (2.9)	5 (3.7)
Any injection related Serious TEAE	0	1 (0.6)	1 (0.7)	0	3 (2.2)	2 (1.5)
Any laser related Serious TEAE	0	0	0	2 (1.5)	0	0
Any TEAEs leading to discontinuation from the study drug	5 (3.2)	4 (2.6)	4 (2.6)	10 (7.5)	7 (5.1)	9 (6.7)
Any Death due to TEAE	3 (1.9)	8 (5.2)	4 (2.6)	1 (0.8)	4 (2.9)	6 (4.4)
Any treatment emergent APTC-classified events	9 (5.8)	13 (8.4)	11 (7.2)	3 (2.3)	8 (5.9)	5 (3.7)

Source: Table 41 of VISTA and Table 45 of VIVID study reports

During the two years treatment period, at least 70% of patients in each treatment group experienced ocular TEAE in the study eye and the incidence rates were comparable across the treatment groups.

A total of 13 subjects in the VISTA study and 26 subjects in the VIVID study discontinued study drug due to treatment-emergent AEs; the discontinuation rates due to AE was comparable across the treatment groups. During the 100-week study period, a total of 13 and 26 deaths were reported in the VISTA and VIVID studies, respectively.

For a comprehensive safety evaluation, we defer readers to the medical review report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1. Analysis of ≥2-steps improvement in DR severity score by Subgroup

The secondary endpoint of the proportion of patients who improved by ≥ 2-steps in DRSS from baseline at week 100 was analyzed by the subgroup variables of gender, age, race, ethnicity, HbA1C level, and BCVA categories. The difference in proportion and 97.5% confidence interval estimates between each of the VTE groups versus laser by the levels of the subgroup variables are shown in Table 14. The secondary efficacy results in each of the subgroups were consistent with those in the overall population. In some subgroups there were only small number of subjects and the results for these subgroups may not be indicative of the overall treatment effects.

Table 14: Proportion of patients who improved by ≥2-step at week 100 by subgroup (Full Analysis Set, LOCF)

					Difference (97.5% CI) versus Laser[1]	
Subgroup	**Level**	**Laser**	**VTE 2Q4**	**VTE 2Q8**	**VTE 2Q4**	**VTE 2Q8**
VISTA						
Overall	Overall	24/150 (16.0)	58/153 (37.9)	56/148 (37.8)	21.9 (10.8, 33.0)	21.8 (10.6, 33.0)
Sex	Male	11/ 81 (13.6)	34/ 86 (39.5)	32/ 78 (41.0)	26.0 (11.3, 40.6)	27.4 (12.2, 42.7)
	Female	13/ 69 (18.8)	24/ 67 (35.8)	24/ 70 (34.3)	17.0 (0.0, 33.9)	15.4 (-1.2, 32.1)
Age	<55	7/ 26 (26.9)	13/ 29 (44.8)	10/ 26 (38.5)	17.9 (-11, 46.9)	11.5 (-18, 41.1)
	>=55 - <65	9/ 70 (12.9)	22/ 55 (40.0)	21/ 51 (41.2)	27.1 (9.7, 44.6)	28.3 (10.3, 46.3)
	>=65 - <75	6/ 42 (14.3)	19/ 54 (35.2)	19/ 58 (32.8)	20.9 (1.8, 40.0)	18.5 (-0.1, 37.0)
	>=75	2/ 12 (16.7)	4/ 15 (26.7)	6/ 13 (46.2)	10.0 (-27, 46.6)	29.5 (-11, 70.4)
Race	White	18/127 (14.2)	54/128 (42.2)	44/123 (35.8)	28.0 (16.0, 40.1)	21.6 (9.6, 33.6)
	Black or african american	5/ 16 (31.3)	2/ 16 (12.5)	9/ 18 (50.0)	-19 (-52, 14.2)	18.8 (-19, 56.9)
	Other	1/ 7 (14.3)	2/ 9 (22.2)	3/ 7 (42.9%)	7.9 (-38, 53.9)	28.6 (-27, 84.0)
Ethnicity	Not hispanic or latino	23/130 (17.7)	47/124 (37.9)	48/122 (39.3)	20.2 (7.8, 32.6)	21.7 (9.2, 34.1)
	Hispanic or latino	1/ 20 (5.0)	11/ 29 (37.9)	8/ 26 (30.8)	32.9 (9.5, 56.3)	25.8 (2.2, 49.3)
HbA1C	>8%	7/ 43 (16.3)	20/ 57 (35.1)	23/ 57 (40.4)	18.8 (-0.4, 38.0)	24.1 (4.6, 43.5)
	<=8%	17/106 (16.0)	38/ 93 (40.9)	33/ 91 (36.3)	24.8 (10.8, 38.8)	20.2 (6.3, 34.1)
BCVA	<40	2/ 13 (15.4)	6/ 10 (60.0)	7/ 12 (58.3)	44.6 (1.2, 88.0)	42.9 (2.3, 83.6)
	>=40 - <55	7/ 25 (28.0)	16/ 36 (44.4)	11/ 22 (50.0)	16.4 (-11, 44.3)	22.0 (-9.9, 53.9)
	>=55 - <65	6/ 51 (11.8)	18/ 49 (36.7)	17/ 60 (28.3)	25.0 (6.3, 43.6)	16.6 (-0.1, 33.2)
	>=65	9/ 61 (14.8)	18/ 58 (31.0)	21/ 54 (38.9)	16.3 (-0.9, 33.4)	24.1 (6.0, 42.3)
VIVID						
Overall	Overall	7/ 99 (7.1)	27/ 97 (27.8)	32/101 (31.7)	20.8 (9.0, 32.5)	24.6 (12.7, 36.5)
Sex	M	6/ 61 (9.8)	17/ 61 (27.9)	23/ 67 (34.3)	18.0 (2.5, 33.6)	24.5 (8.8, 40.2)
	F	1/ 38 (2.6)	10/ 36 (27.8)	9/ 34 (26.5)	25.1 (7.2, 43.1)	23.8 (5.6, 42.0)
Age	<55	0/ 11 (0.0)	6/ 16 (37.5)	4/ 8 (50.0)	37.5 (9.5, 65.5)	50.0 (7.6, 92.4)
	>=55 - <65	2/ 36 (5.6)	11/ 42 (26.2)	16/ 42 (38.1)	20.6 (3.0, 38.3)	32.5 (13.5, 51.6)
	>=65 - <75	5/ 41 (12.2)	10/ 34 (29.4)	9/ 41 (22.0)	17.2 (-4.0, 38.4)	9.8 (-8.9, 28.5)
	>=75	0/ 11 (0.0)	0/ 5 (0.0)	3/ 10 (30.0)	0.0 (0.0, 0.0)	30.0 (-4.2, 64.2)
Race	White	5/ 80 (6.3)	21/ 76 (27.6)	20/ 77 (26.0)	21.4 (8.3, 34.5)	19.7 (6.9, 32.5)
	Asian	2/ 18 (11.1)	6/ 21 (28.6)	12/ 24 (50.0)	17.5 (-11, 45.8)	38.9 (9.9, 67.8)
Ethnicity	Not hispanic or latino	7/ 96 (7.3)	26/ 94 (27.7)	31/ 99 (31.3)	20.4 (8.4, 32.4)	24.0 (11.9, 36.1)
	Hispanic or latino	0/ 1 (0.0)	1/ 3 (33.3)	1/ 2 (50.0)	33.3 (., .)	50.0 (., .)
HbA1C	>8%	2/ 32 (6.3)	7/ 38 (18.4)	8/ 31 (25.8)	12.2 (-5.1, 29.5)	19.6 (-0.8, 39.9)
	<=8%	5/ 67 (7.5)	20/ 58 (34.5)	24/ 70 (34.3)	27.0 (11.2, 42.9)	26.8 (12.1, 41.5)
BCVA	<40	0/ 7 (0.0)	0/ 4 (0.0)	3/ 9 (33.3)	0.0 (0.0, 0.0)	33.3 (-4.0, 70.7)
	>=40 - <55	1/ 15 (6.7)	7/ 16 (43.8)	8/ 19 (42.1)	37.1 (4.7, 69.4)	35.4 (5.4, 65.5)
	>=55 - <65	3/ 30 (10.0)	13/ 32 (40.6)	12/ 35 (34.3)	30.6 (7.2, 54.0)	24.3 (2.2, 46.4)
	>=65	3/ 47 (6.4)	7/ 45 (15.6)	9/ 38 (23.7)	9.2 (-5.5, 23.8)	17.3 (-0.3, 34.9)

[1] Difference with confidence interval (CI) based on using unadjusted CMH weighting scheme.

5. SUMMARY AND CONCLUSIONS

5.1. STATISTICAL ISSUES

There are no major statistical issues identified in this submission.

For analysis of the secondary efficacy endpoint relevant to the DR indication, the applicant used the LOCF method for missing data imputation. However, no detail was given in the study protocol as well as in the statistical analysis plan on how the LOCF method was carried out for patients with non-gradable DRSS data (i.e., DRSS = 90).

Upon investigation of the applicant derived DRSS dataset (**adxodr.sas7bdat**), we noted that different approaches were used for handling missing data as well as non-gradable DRSS data in producing the analysis results in the clinical study reports (CSR) and the analysis results in the proposed labeling for the two pivotal studies (VIVID and VISTA).

- In the approach used to produce the analysis results in the VISTA CSR, only gradable post-baseline DRSS data were used to impute for missing DRSS data. In this study, all patients were included in the analysis; patients with non-gradable DRSS data at the baseline visit or at the post-baseline visit after LOCF or with missing DRSS data at the post-baseline visit after LOCF were considered to have shown no improvement or no worsening in DR severity.
- In the approach used to produce the analysis results in the VIVID CSR, both gradable and non- gradable DRSS data (DRSS=90) were used to impute for missing DRSS data. In this study, patients with non-gradable DRSS data at the baseline visit or at the post-baseline visit after LOCF, or patients with only baseline data were excluded from the analysis.
- In the proposed labeling, the approach used in the VIVID study was used to produce the analysis results presented in the label.

The reviewer conducted additional analysis in which non-gradable post-baseline DRSS values were treated as missing and were imputed using the last gradable DRSS values (including with baseline values if all post-baseline values were either missing or non-gradable). In the reviewer analysis approach, only patients with non-gradable baseline DRSS values were excluded from analysis since the change from baseline data for these patients could not be evaluated.

On February 27, 2015, we submitted information request to the applicant to confirm our understanding of their data handling approach and to validate the reviewer's analysis results. On March 05, 2015, the applicant confirmed our understanding of their data handling method and submitted the validated results using the reviewer's data handling approach.

Therefore, all the efficacy analyses results on the DRSS data presented in this review were based on the reviewer's data handling approach.

5.2. COLLECTIVE EVIDENCE

The primary efficacy evidence to support the superiority of the VTE treatment groups administered once every 4 weeks (VTE 2Q4) or once every 8 weeks after 5 initial monthly doses (VTE 2Q8) to the laser treatment group was based on two pivotal phase 3 trials (the VISTA and VIVID studies). The duration of each study was approximately 3 years, and the studies are currently ongoing.

The first year (52 week) data was submitted to the Agency as a supplement (BLA125387 SN0101/S-037) for the treatment of DME. The primary endpoint for the DME indication was the mean change in BCVA at week 52 and the key secondary efficacy endpoint was the proportion of patients who gained ≥ 15 letters in BCVA from baseline at week 52. Statistical significance was achieved for these endpoints, and subsequently Eylea 2mg injection administered once every 8 weeks after 5 initial monthly injections was approved on 29 July 2014 for the treatment of DME.

Once statistical significance was achieved for the primary endpoint and the key secondary endpoint for a given Eylea dose group versus laser at week 52, several key secondary endpoints were compared at week 100 between each Eylea dose group and laser separately in a hierarchical manner. In the current submission, the second year (100 week) data was submitted to the Agency as a supplement for the indication of treatment of DR in patients with DME and to update the BCVA data in the label for the treatment of DME.

Statistical significances were achieved for the secondary efficacy endpoints of change in BCVA at week 100 and for the proportion of patients who gained ≥10 and ≥15 letters from baseline at week 100 for each VTE group versus laser in the hierarchy. That is, treatment with Eylea injection continued to provide significant improvement in visual acuity; furthermore, the treatment benefit observed during the first year of treatment period was clearly maintained throughout the second year of treatment period.

One of the pre-specified secondary efficacy endpoints in the hierarchy was the proportion of patients who improved by ≥2-steps in DR severity from baseline at week 100; the applicant defined main analysis for the proposed indication of treatment of DR in patients with DME was based on this endpoint; the proportions of patients who improved by ≥3-steps and worsened by ≥2- and ≥3-steps were also defined as exploratory endpoints with relevance to the DR indication.

Overall, more Eylea treated patients experienced significant improvement in DR severity while fewer Eylea-treated patients experienced worsening in DR severity at week 100 compared to laser-treated patients. In both studies, statistical significance was achieved for the pre-specified secondary endpoint relevant to the DR indication, and the results of the exploratory endpoints with DR relevance also provided supporting evidence for the treatment benefit with Eylea injection in improving DR severity in patients with DME.

5.3. Conclusion and Recommendation

Based on the collective efficacy evidences derived from the two years data, treatment with Eylea 2 mg injection administered once every 4 weeks or once every 8 weeks after 5 initial monthly injections demonstrated significant improvement in visual acuity. Furthermore, each Eylea dose group demonstrated superior efficacy benefit over laser in improving DR severity in patients with DME.

The efficacy benefit between the two Eylea dose groups in improving best corrected visual acuity as well as in improving DR severity in patients with DME was comparable. Thus, considering the significant efficacy benefits and the less injection burden to patients, the reviewer recommends approval of Eylea 2 mg injections administered every 4 weeks for the first 5 injections followed by every 8 weeks for the treatment of DR in patients with DME.

5.4. LABELING RECOMMENDATION

Based on the efficacy results derived from the two year data in the VISTA and VIVID studies, the applicant proposed:

i) To update the BCVA data in the label for the DME indication and

ii) To add the indication of treatment of DR in patients with DME to the EYLEA® U.S. Package Insert (USPI).

The applicant updated the BCVA results in the Clinical Studies Section 14.4 "Diabetic Macula Edema (DME)" based on efficacy results from the two years data. In the reviewer's opinion, the updated BCVA data in the label are acceptable and the reviewer has no concern with the information contained in the label for the updated BCVA results.

For the indication of treatment of DR in patients with DME, the applicant proposed to present the efficacy results for the proportion of patients who improved by ≥2 steps in DRSS from baseline at week 100 in the new Clinical Studies Section 14.5 "Diabetic Retinopathy (DR) in Patients with DME". For the analysis results proposed to be included in the label by the applicant, patients with non-gradable DRSS data at the baseline visit or at the post-baseline visit after LOCF, or patients with only baseline data were excluded in both studies. This analysis approach was the same as the analysis approach used in the VIVID study.

For the efficacy results presented in the clinical study reports and in the label, the applicant analysis approach used LOCF method for missing data; however, their approach did not impute non-gradable DRSS data regardless of whether gradable DRSS data existed in the preceding visits or not.

The reviewer conducted additional analysis in which non-gradable post-baseline DRSS values were treated as missing and were imputed using the last gradable DRSS values (including with gradable baseline values). In the reviewer analysis approach, only patients with non-gradable baseline DRSS values were excluded from analysis since the change from baseline data for these patients could not be evaluated.

Therefore, the reviewer recommends the efficacy results from the reviewer analysis be included in Section 14 Clinical Studies of the U.S. Package Insert (USPI). Furthermore, the reviewer recommends all the efficacy results from the key secondary endpoint as well as the exploratory endpoints results with DR relevance be included in the label. In the reviewer opinion, including all the DR related efficacy results in the label will provide patients as well as prescribing physicians a comprehensive picture regarding the efficacy benefit of Eyea in the treatment of DR in patients with DME.

Recommendation for the Clinical Studies section:

In the VIVID and VISTA studies, a pre-specified efficacy outcome measure for the treatment of DR in patients with DME was the change in the diabetic retinopathy severity scale (DRSS) from baseline at week 100. The DRSS score was assessed at baseline and approximately every 6 months thereafter for the duration of the studies.

In addition to the baseline characteristics previously described for the VIVID and VISTA studies [see Clinical Studies Section 14.4], the baseline DR severity scale in both studies ranged from

absent to sever proliferative diabetic retinopathy. The majority of patients enrolled in these studies (about 83% in the VISTA study and about 70% in the VIVID study) had moderate-to-severe non-proliferative diabetic retinopathy (NPDR), and about 7% of patients in the VISTA study and 2% of patients in the VIVID study had mild-to-high risk proliferative diabetic retinopathy (PDR) at baseline. The baseline DRSS valuest could not be graded for approximately 2% of patients in the VISTA study and for a quarter (about 26%) of patients in the VIVID study.

Results from the analysis of the DRSS data at week 100 in the VISTA and VIVID studies are shown in the Table below.

At week 100, more Eylea-treated patients experienced significant improvement in DR severity compared to laser-treated patients while fewer Eylea-treated patients experienced worsening in DR severity compared to laser-treated patients.

Proportion of Patients who Achieved Improvement or Worsening in the DRSS Score at Week 100 (Full Analysis Set, LOCF)

	VISTA			VIVID		
	Laser	VTE 2Q4	VTE 2Q8	Laser	VTE 2Q4	VTE 2Q8
Evaluable Patients [1]	150	153	148	99	97	101
Number of patients with a ≥2-step improvement on DRSS from Baseline (%)	24 (16.0)	58 (37.9)	56 (37.8)	7 (7.1)	27 (27.8)	32 (31.7)
Difference (%) [2] (97.5% CI)		22.1 (11.1, 33.2)	21.7 (10.5, 33.0)		20.7 (8.8, 32.5)	24.2 (12.4, 35.9)
Number of patients with a ≥3-step improvement on DRSS from Baseline (%)	8 (5.3)	36 (23.5)	30 (20.3)	0 (0.0)	6 (6.2)	3 (3.0)
Difference (%) [2] (97.5% CI)		18.4 (9.7, 27.2)	14.9 (6.4, 23.4)		6.2 (0.7, 11.8)	2.9 (-0.8, 6.5)
Number of patients with a ≥2-step worsening on DRSS from Baseline (%)	29 (19.3)	11 (7.2)	10 (6.8)	6 (6.1)	1 (1.0)	1 (1.0)
Difference (%) [2] (97.5% CI)		-12.4 (-21.1, -3.7)	-12.5 (-21.0,-4.0)		-5.0 (-10.9, 0.7)	-5.1 (-10.9, 0.7)
Number of patients with a ≥3-step worsening on DRSS from Baseline (%)	9 (6.0)	3 (2.0)	4 (2.7)	2 (2.0)	0 (0.0)	1 (1.0)
Difference (%)[2] (97.5% CI)		-4.1 (-9.2, 1.1)	-3.3 (-8.6,2.0)		-2.1 (-5.4, 1.2)	-1.1 (-5.0, 2.7)

[1] The number of evaluable patients comprised of all patients who had a gradable DRSS data at baseline; Post-baseline missing or non-gradable DRSS values were imputed using the last gradable DRSS value.

[2] Difference (Eylea minus Laser) with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors

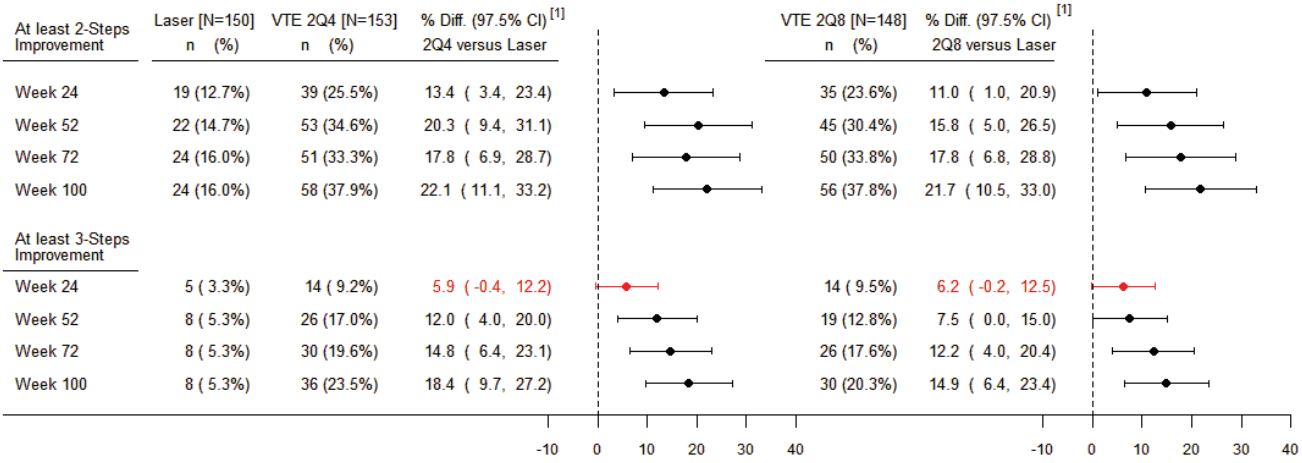
Results from the analysis of DRSS at each visit in the VIVID and VISTA studies are shown in Figure 12 below.

In both studies, treatment difference in the proportion of patients with DR improvement by at least 2-step was observed between each Eylea dose group and laser as early as week 24. Treatment difference in at least 3-step improvement was observed as early as week 52 in the VISTA study and as early as week 75 in the VIVID study for the Eylea 2Q4 group versus laser.

Proportion of Patients with ≥2-Step and ≥3-Step Improvement in DRSS from Baseline over Time in the VIVID and VISTA Studies (LOCF)

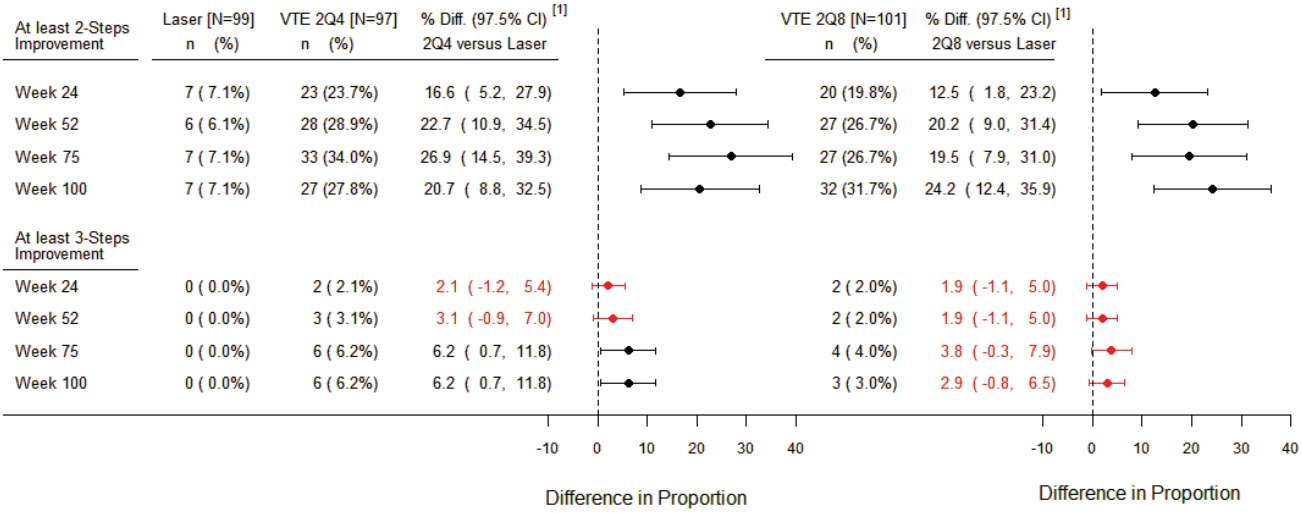
VISTA

At least 2-Steps Improvement	Laser [N=150] n (%)	VTE 2Q4 [N=153] n (%)	% Diff. (97.5% CI) [1] 2Q4 versus Laser	VTE 2Q8 [N=148] n (%)	% Diff. (97.5% CI) [1] 2Q8 versus Laser
Week 24	19 (12.7%)	39 (25.5%)	13.4 (3.4, 23.4)	35 (23.6%)	11.0 (1.0, 20.9)
Week 52	22 (14.7%)	53 (34.6%)	20.3 (9.4, 31.1)	45 (30.4%)	15.8 (5.0, 26.5)
Week 72	24 (16.0%)	51 (33.3%)	17.8 (6.9, 28.7)	50 (33.8%)	17.8 (6.8, 28.8)
Week 100	24 (16.0%)	58 (37.9%)	22.1 (11.1, 33.2)	56 (37.8%)	21.7 (10.5, 33.0)
At least 3-Steps Improvement					
Week 24	5 (3.3%)	14 (9.2%)	5.9 (-0.4, 12.2)	14 (9.5%)	6.2 (-0.2, 12.5)
Week 52	8 (5.3%)	26 (17.0%)	12.0 (4.0, 20.0)	19 (12.8%)	7.5 (0.0, 15.0)
Week 72	8 (5.3%)	30 (19.6%)	14.8 (6.4, 23.1)	26 (17.6%)	12.2 (4.0, 20.4)
Week 100	8 (5.3%)	36 (23.5%)	18.4 (9.7, 27.2)	30 (20.3%)	14.9 (6.4, 23.4)



VIVID

At least 2-Steps Improvement	Laser [N=99] n (%)	VTE 2Q4 [N=97] n (%)	% Diff. (97.5% CI) [1] 2Q4 versus Laser	VTE 2Q8 [N=101] n (%)	% Diff. (97.5% CI) [1] 2Q8 versus Laser
Week 24	7 (7.1%)	23 (23.7%)	16.6 (5.2, 27.9)	20 (19.8%)	12.5 (1.8, 23.2)
Week 52	6 (6.1%)	28 (28.9%)	22.7 (10.9, 34.5)	27 (26.7%)	20.2 (9.0, 31.4)
Week 75	7 (7.1%)	33 (34.0%)	26.9 (14.5, 39.3)	27 (26.7%)	19.5 (7.9, 31.0)
Week 100	7 (7.1%)	27 (27.8%)	20.7 (8.8, 32.5)	32 (31.7%)	24.2 (12.4, 35.9)
At least 3-Steps Improvement					
Week 24	0 (0.0%)	2 (2.1%)	2.1 (-1.2, 5.4)	2 (2.0%)	1.9 (-1.1, 5.0)
Week 52	0 (0.0%)	3 (3.1%)	3.1 (-0.9, 7.0)	2 (2.0%)	1.9 (-1.1, 5.0)
Week 75	0 (0.0%)	6 (6.2%)	6.2 (0.7, 11.8)	4 (4.0%)	3.8 (-0.3, 7.9)
Week 100	0 (0.0%)	6 (6.2%)	6.2 (0.7, 11.8)	3 (3.0%)	2.9 (-0.8, 6.5)



N: Total number of patients with gradable DRSS value at baseline; post-baseline missing or non-gradable DRSS values were imputed using the last gradable DRSS value.

[1] Difference (Eylea minus Control [laser] group) with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors

APPENDIX

Table 15: Proportion of patients who improved or worsened at week 100 – Applicant Analysis (Full Analysis Set, LOCF)

VISTA [1]

DR Severity		Laser	VTE 2Q4	VTE 2Q8	%Difference (97.5% CI) versus Laser (%) [5]	
					VTE 2Q4	VTE 2Q8
	N	**154**	**154**	**151**	**--**	**--**
Improvement	≥ 2-steps	24 (15.6%)	57 (37.0%)	56 (37.1%)	21.7 (10.8, 32.6)	21.5 (10.4, 32.5)
	≥ 3-steps	8 (5.2%)	35 (22.7%)	30 (19.9%)	17.8 (9.2, 26.4)	14.6 (6.3, 23.0)
Worsening	≥ 2-steps	29 (18.8%)	11 (7.1%)	10 (6.6%)	-12.0 (-20.6, -3.4)	-12.2 (-20.5, -3.8)
	≥ 3-steps	9 (5.8%)	3 (1.9%)	4 (2.6%)	-3.9 (-9.0, 1.2)	-3.2 (-8.3, 2.0)

VISTA [2]

DR Severity		Laser	VTE 2Q4	VTE 2Q8	%Difference (97.5% CI) versus Laser (%) [5]	
					VTE 2Q4	VTE 2Q8
	N	**141**	**144**	**141**	**--**	**--**
Improvement	≥ 2-steps	24 (17.0%)	57 (39.6%)	56 (39.7%)	22.7 (11.1, 34.2)	22.6 (10.9, 34.3)
	≥ 3-steps	8 (5.7%)	35 (24.3%)	30 (21.3%)	18.8 (9.7, 28.0)	15.6 (6.6, 24.5)
Worsening	≥ 2-steps	29 (20.6%)	11 (7.6%)	10 (7.1%)	-13.2 (-22.4, -4.1)	-13.4 (-22.3, -4.4)
	≥ 3-steps	9 (6.4%)	3 (2.1%)	4 (2.8%)	-4.3 (-9.8, 1.1)	-3.5 (-9.1, 2.1)

VIVID [3]

DR Severity		Laser	VTE 2Q4	VTE 2Q8	%Difference (97.5% CI) versus Laser (%) [5]	
					VTE 2Q4	VTE 2Q8
	N	**132**	**136**	**135**	**--**	**--**
Improvement	≥ 2-steps	7 (5.3%)	24 (17.6%)	28 (20.7%)	12.3 (3.8, 20.9)	15.5 (6.6, 24.4)
	≥ 3-steps	0 (0.0%)	6 (4.4%)	2 (1.5%)	4.4 (0.4, 8.4)	1.5 (-0.9, 3.8)
Worsening	≥ 2-steps	5 (3.8%)	1 (0.7%)	1 (0.7%)	-3.1 (-7.2, 1.0)	-3.0 (-7.1, 1.1)
	≥ 3-steps	2 (1.5%)	0 (0.0%)	1 (0.7%)	-1.5 (-3.9, 0.9)	-0.8 (-3.7, 2.2)

VIVID [4]

DR Severity		Laser	VTE 2Q4	VTE 2Q8	%Difference (97.5% CI) versus Laser (%) [5]	
					VTE 2Q4	VTE 2Q8
	N	**85**	**82**	**86**	**--**	**--**
Improvement	≥ 2-steps	7 (8.2%)	24 (29.3%)	28 (32.6%)	20.9 (7.7, 34.2)	24.4 (11.3, 37.4)
	≥ 3-steps	0 (0.0%)	6 (7.3%)	2 (2.3%)	7.3 (0.8, 13.9)	2.3 (-1.4, 6.0)
Worsening	≥ 2-steps	5 (5.9%)	1 (1.2%)	1 (1.2%)	-4.7 (-11.1, 1.8)	-4.7 (-11.1, 1.6)
	≥ 3-steps	2 (2.4%)	0 (0.0%)	1 (1.2%)	-2.4 (-6.2, 1.4)	-1.2 (-5.7, 3.4)

[1] and [3]: Patients with missing change in DRSS from baseline at week 100 were considered to have shown no improvement or no worsening. Change in DRSS from baseline at week 100 was missing if baseline DRSS was non-gradable or week 100 DRSS after LOCF was non-gradable or missing.

[2] and [4]: Patients with missing change in DRSS from baseline at week 100 were excluded from analysis.

[1] and [4]: The VISTA and VIVID clinical study reports were based on these analysis results, respectively.

[2] and [4]: The applicant proposed label was based on these analysis results.

[5]: Difference with confidence interval (CI) based on using CMH weighting scheme adjusted by study specific stratification factor

Figure 14: Proportion of patients who worsened by ≥2- and ≥3-step by visit
(Full Analysis Set, LOCF)

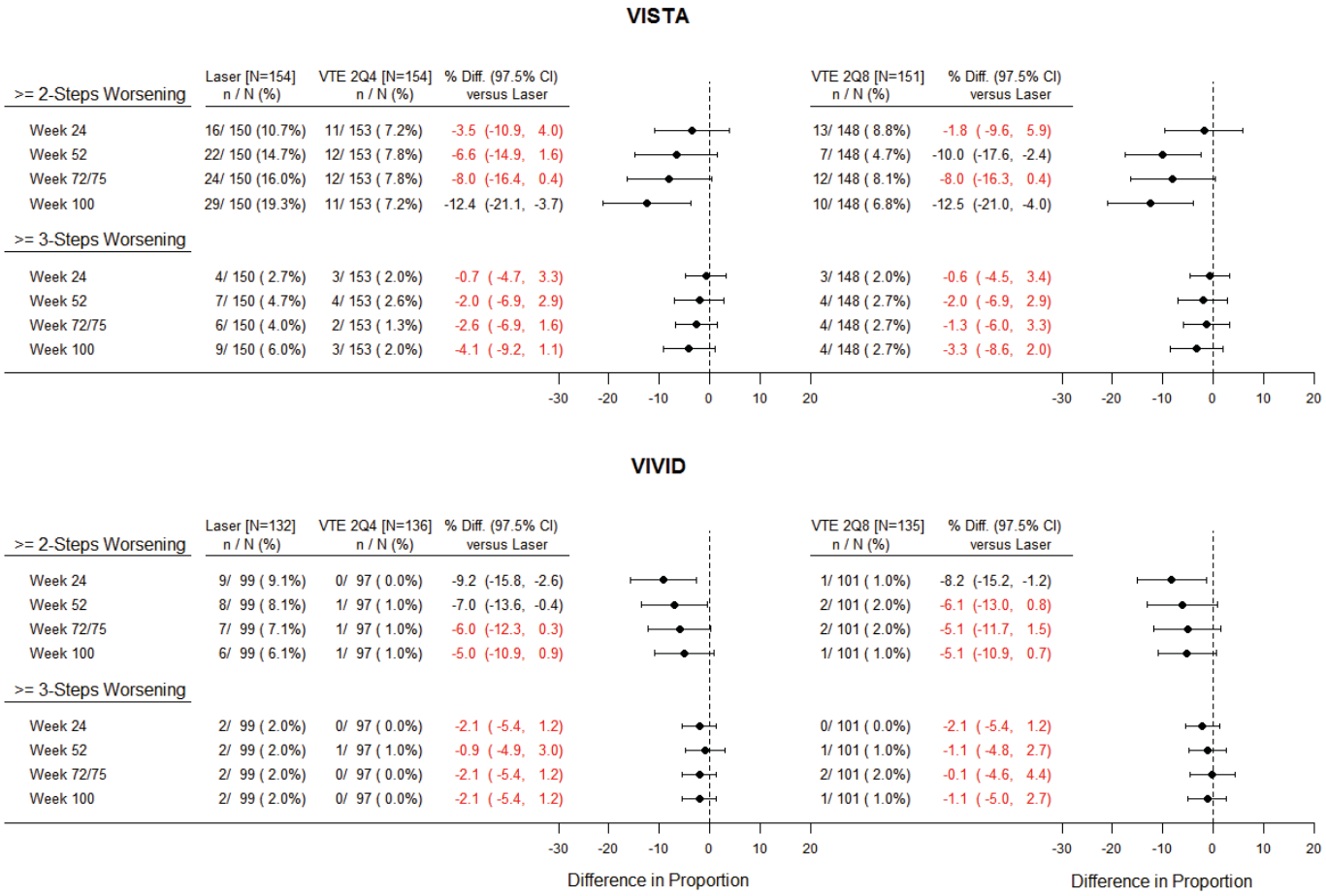


Table 16: Proportion of patients with DR improvement and worsening at week 100 (Sensitivity Analysis)

VISTA

	Laser (N = 154)	VTE 2Q4 (N = 154)	VTE 2Q8 (N = 151)	%Difference (97.5% CI) versus Laser (%) [1]	
				VTE 2Q4	VTE 2Q8
≥2-steps improvement					
OC	7/ 72 (9.7%)	43/ 108 (39.8%)	40/ 99 (40.4%)	30.0 (16.7, 43.2)	30.7 (17.0, 44.4)
aOC	25/ 119 (21.0%)	43/ 112 (38.4%)	46/ 112 (41.1%)	17.3 (3.9, 30.6)	20.0 (6.5, 33.5)
aLOCF	35/ 150 (23.3%)	58/ 153 (37.9%)	58/ 148 (39.2%)	14.7 (2.9, 26.4)	15.8 (3.8, 27.7)
≥3-steps improvement					
OC	3/ 72 (4.2%)	28/ 108 (25.9%)	21/ 99 (21.2%)	21.6 (10.7, 32.6)	17.0 (6.3, 27.7)
aOC	10/ 119 (8.4%)	28/ 112 (25.0%)	23/ 112 (20.5%)	16.6 (5.7, 27.4)	11.9 (1.6, 22.3)
aLOCF	14/ 150 (9.3%)	36/ 153 (23.5%)	30/ 148 (20.3%)	14.4 (5.0, 23.8)	10.9 (1.7, 20.1)
≥2-steps worsening					
OC	18/ 72 (25.0%)	10/ 108 (9.3%)	9/ 99 (9.1%)	-16.0 (-28.9, -3.2)	-15.8 (-28.6, -3.0)
aOC	20/ 119 (16.8%)	10/ 112 (8.9%)	10/ 112 (8.9%)	-8.1 (-17.9, 1.7)	-7.6 (-17.2, 1.9)
aLOCF	23/ 150 (15.3%)	10/ 153 (6.5%)	11/ 148 (7.4%)	-9.1 (-17.2, -1.0)	-7.9 (-15.9, 0.2)
≥3-steps worsening					
OC	5/ 72 (6.9%)	2/ 108 (1.9%)	4/ 99 (4.0%)	-5.2 (-12.6, 2.3)	-2.8 (-10.8, 5.2)
aOC	5/ 119 (4.2%)	2/ 112 (1.8%)	5/ 112 (4.5%)	-2.5 (-7.6, 2.6)	0.4 (-5.6, 6.3)
aLOCF	6/ 150 (4.0%)	2/ 153 (1.3%)	5/ 148 (3.4%)	-2.7 (-7.0, 1.6)	-0.6 (-5.5, 4.3)

VIVID

	Laser (N = 132)	VTE 2Q4 (N = 136)	VTE 2Q8 (N = 135)	%Difference (97.5% CI) versus Laser (%) [1]	
				VTE 2Q4	VTE 2Q8
≥2-steps improvement					
OC	5/ 46 (10.9%)	16/ 62 (25.8%)	22/ 62 (35.5%)	14.9 (-1.5, 31.3)	24.5 (7.4, 41.5)
aOC	11/ 72 (15.3%)	20/ 70 (28.6%)	24/ 72 (33.3%)	13.2 (-2.4, 28.8)	17.7 (2.0, 33.3)
aLOCF	12/ 99 (12.1%)	29/ 97 (29.9%)	31/ 101 (30.7%)	17.8 (4.9, 30.7)	18.3 (5.7, 30.9)
≥3-steps improvement					
OC	0/ 46 (0.0%)	5/ 62 (8.1%)	2/ 62 (3.2%)	8.1 (0.2, 15.9)	3.2 (-1.9, 8.3)
aOC	0/ 72 (0.0%)	5/ 70 (7.1%)	2/ 72 (2.8%)	7.2 (0.1, 14.2)	2.7 (-1.6, 7.0)
aLOCF	0/ 99 (0.0%)	6/ 97 (6.2%)	3/ 101 (3.0%)	6.2 (0.7, 11.8)	2.9 (-0.8, 6.5)
≥2-steps worsening					
OC	2/ 46 (4.3%)	1/ 62 (1.6%)	1/ 62 (1.6%)	-2.8 (-10.6, 5.1)	-2.8 (-10.6, 5.0)
aOC	2/ 72 (2.8%)	1/ 70 (1.4%)	1/ 72 (1.4%)	-1.4 (-7.1, 4.3)	-1.6 (-6.9, 3.8)
aLOCF	3/ 99 (3.0%)	1/ 97 (1.0%)	2/ 101 (2.0%)	-2.0 (-6.6, 2.6)	-1.1 (-6.1, 3.9)
≥3-steps worsening					
OC	1/ 46 (2.2%)	0/ 62 (0.0%)	1/ 62 (1.6%)	-2.2 (-7.2, 2.7)	-0.6 (-6.7, 5.5)
aOC	1/ 72 (1.4%)	0/ 70 (0.0%)	1/ 72 (1.4%)	-1.6 (-5.1, 1.9)	-0.2 (-4.6, 4.2)
aLOCF	1/ 99 (1.0%)	0/ 97 (0.0%)	1/ 101 (1.0%)	-1.1 (-3.5, 1.3)	-0.2 (-3.3, 3.0)

[1] Difference with confidence interval (CI) based on using CMH weighting scheme adjusted by study specific stratification factor
OC: Observed cases - excluded DRSS data after additional treatment was given; aOC: Observed cases - included DRSS data after additional treatment was given; and aLOCF: last observation carried forward - included DRSS data after additional treatment was given.

Table 17: Distribution of patients by DR severity scale from baseline to week 100
(Full Analysis Set; Observed Cases)

VISTA

			DRSS Levels										
		N	**10 and 12**	**14, 15, 20**	**35**	**43**	**47**	**53**	**60, 61**	**65**	**71**	**75**	**90**
Laser (N = 154)	Baseline	154	1 (0.6%)	3 (1.9%)	5 (3.2%)	60 (39.0%)	26 (16.9%)	42 (27.3%)	1 (0.6%)	10 (6.5%)	1 (0.6%)	1 (0.6%)	4 (2.6%)
	Week 24	146	0 (0.0%)	6 (4.1%)	17 (11.6%)	32 (21.9%)	35 (24.0%)	34 (23.3%)	7 (4.8%)	7 (4.8%)	2 (1.4%)	0 (0.0%)	6 (4.1%)
	Week 52	94	3 (3.2%)	2 (2.1%)	12 (12.8%)	24 (25.5%)	20 (21.3%)	19 (20.2%)	3 (3.2%)	6 (6.4%)	4 (4.3%)	0 (0.0%)	1 (1.1%)
	Week 72	82	2 (2.4%)	1 (1.2%)	16 (19.5%)	15 (18.3%)	18 (22.0%)	21 (25.6%)	2 (2.4%)	3 (3.7%)	3 (3.7%)	0 (0.0%)	1 (1.2%)
	Week 100	73	1 (1.4%)	0 (0.0%)	11 (15.1%)	16 (21.9%)	10 (13.7%)	23 (31.5%)	5 (6.8%)	6 (8.2%)	1 (1.4%)	0 (0.0%)	0 (0.0%)
VTE 2Q4 (N = 154)	Baseline	154	4 (2.6%)	5 (3.2%)	7 (4.5%)	49 (31.8%)	26 (16.9%)	53 (34.4%)	1 (0.6%)	4 (2.6%)	4 (2.6%)	0 (0.0%)	1 (0.6%)
	Week 24	141	5 (3.5%)	5 (3.5%)	27 (19.1%)	46 (32.6%)	32 (22.7%)	21 (14.9%)	0 (0.0%)	3 (2.1%)	0 (0.0%)	0 (0.0%)	2 (1.4%)
	Week 52	132	6 (4.5%)	6 (4.5%)	40 (30.3%)	38 (28.8%)	23 (17.4%)	14 (10.6%)	0 (0.0%)	2 (1.5%)	1 (0.8%)	0 (0.0%)	2 (1.5%)
	Week 72	116	9 (7.8%)	6 (5.2%)	36 (31.0%)	22 (19.0%)	23 (19.8%)	18 (15.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)
	Week 100	110	15 (13.6%)	9 (8.2%)	30 (27.3%)	18 (16.4%)	10 (9.1%)	26 (23.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)
VTE 2Q8 (N = 151)	Baseline	151	4 (2.6%)	3 (2.0%)	9 (6.0%)	52 (34.4%)	32 (21.2%)	40 (26.5%)	2 (1.3%)	5 (3.3%)	1 (0.7%)	0 (0.0%)	3 (2.0%)
	Week 24	139	2 (1.4%)	4 (2.9%)	36 (25.9%)	50 (36.0%)	22 (15.8%)	22 (15.8%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	2 (1.4%)
	Week 52	132	8 (6.1%)	5 (3.8%)	39 (29.5%)	46 (34.8%)	15 (11.4%)	12 (9.1%)	1 (0.8%)	2 (1.5%)	0 (0.0%)	0 (0.0%)	4 (3.0%)
	Week 72	124	7 (5.6%)	5 (4.0%)	46 (37.1%)	25 (20.2%)	21 (16.9%)	16 (12.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.2%)
	Week 100	103	10 (9.7%)	3 (2.9%)	37 (35.9%)	17 (16.5%)	16 (15.5%)	17 (16.5%)	0 (0.0%)	2 (1.9%)	0 (0.0%)	0 (0.0%)	1 (1.0%)

VIVID

		N	**10 and 12**	**14, 15, 20**	**35**	**43**	**47**	**53**	**60, 61**	**65**	**71**	**75**	**90**
Laser (N = 132)	Baseline	132	0 (0.0%)	1 (0.8%)	2 (1.5%)	36 (27.3%)	24 (18.2%)	35 (26.5%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	33 (25.0%)
	Week 24	119	0 (0.0%)	0 (0.0%)	2 (1.7%)	38 (31.9%)	24 (20.2%)	21 (17.6%)	2 (1.7%)	2 (1.7%)	0 (0.0%)	1 (0.8%)	29 (24.4%)
	Week 52	84	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (42.9%)	19 (22.6%)	8 (9.5%)	4 (4.8%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	16 (19.0%)
	Week 75	67	0 (0.0%)	0 (0.0%)	0 (0.0%)	32 (47.8%)	17 (25.4%)	10 (14.9%)	3 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (7.5%)
	Week 100	62	0 (0.0%)	0 (0.0%)	0 (0.0%)	32 (51.6%)	16 (25.8%)	6 (9.7%)	4 (6.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (6.5%)
VTE 2Q4 (N = 136)	Baseline	136	0 (0.0%)	0 (0.0%)	0 (0.0%)	31 (22.8%)	18 (13.2%)	44 (32.4%)	2 (1.5%)	2 (1.5%)	0 (0.0%)	0 (0.0%)	39 (28.7%)
	Week 24	124	0 (0.0%)	0 (0.0%)	2 (1.6%)	67 (54.0%)	13 (10.5%)	7 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	35 (28.2%)
	Week 52	114	0 (0.0%)	0 (0.0%)	6 (5.3%)	63 (55.3%)	17 (14.9%)	5 (4.4%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	22 (19.3%)
	Week 75	106	0 (0.0%)	0 (0.0%)	5 (4.7%)	74 (69.8%)	11 (10.4%)	6 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (9.4%)
	Week 100	95	0 (0.0%)	1 (1.1%)	6 (6.3%)	52 (54.7%)	23 (24.2%)	4 (4.2%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (8.4%)
VTE 2Q8 (N = 135)	Baseline	135	0 (0.0%)	0 (0.0%)	1 (0.7%)	28 (20.7%)	27 (20.0%)	42 (31.1%)	2 (1.5%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	34 (25.2%)
	Week 24	130	0 (0.0%)	0 (0.0%)	1 (0.8%)	63 (48.5%)	28 (21.5%)	6 (4.6%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	31 (23.8%)
	Week 52	107	0 (0.0%)	0 (0.0%)	1 (0.9%)	63 (58.9%)	19 (17.8%)	8 (7.5%)	2 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (13.1%)
	Week 75	100	0 (0.0%)	0 (0.0%)	5 (5.0%)	59 (59.0%)	17 (17.0%)	7 (7.0%)	3 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (9.0%)
	Week 100	90	0 (0.0%)	0 (0.0%)	2 (2.2%)	64 (71.1%)	11 (12.2%)	3 (3.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (10.0%)

DRSS: Diabetic Retinopathy Severity Score
10 (DR Absent); 20 (Microaneurysms only) ; 35 (Mild NPDR); 43 (Moderate NPDR); 47 (Moderately Severe NPDR); 53 (Severe NPDR); 61 (Mild PDR); 65 (Moderate PDR); 71 (High Risk PDR); 75 (High Risk PDR); 90 (could not grade).

Table 18: Mean change (SE) in BCVA letter score from baseline over time
(Full Analysis Set, LOCF)

Visit	VISTA					VIVID				
	Laser (N = 154)	VTE 2Q4 (N = 154)	VTE 2Q8 (N = 151)	Difference (97.5% CI) vs Laser [1]		Laser (N = 132)	VTE 2Q4 (N = 136)	VTE 2Q8 (N = 135)	Difference (97.5% CI) vs Laser [1]	
				VTE 2Q4	VTE 2Q8				VTE 2Q4	VTE 2Q8
Week 1	0.9 (0.43)	4.0 (0.54)	3.9 (0.43)	3.1 (1.6, 4.6)	3.0 (1.7, 4.3)	0.5 (0.54)	1.9 (0.47)	1.3 (0.49)	1.4 (-0.1, 2.9)	0.8 (-0.7, 2.3)
Week 4	2.5 (0.50)	6.8 (0.55)	6.5 (0.46)	4.4 (2.7, 6.0)	4.0 (2.6, 5.5)	0.6 (0.61)	5.4 (0.51)	4.9 (0.57)	4.7 (3.1, 6.4)	4.3 (2.6, 6.0)
Week 8	2.5 (0.73)	8.6 (0.59)	7.5 (0.52)	6.1 (4.0, 8.1)	4.9 (3.0, 6.9)	1.8 (0.65)	5.8 (0.74)	6.4 (0.57)	4.0 (1.9, 6.0)	4.6 (2.8, 6.4)
Week 12	1.5 (0.83)	9.4 (0.59)	8.4 (0.58)	7.9 (5.6, 10.1)	6.8 (4.6, 9.0)	1.7 (0.74)	6.7 (0.75)	7.2 (0.62)	5.1 (2.9, 7.2)	5.5 (3.5, 7.5)
Week 16	1.9 (0.86)	9.8 (0.64)	8.7 (0.64)	7.8 (5.5, 10.2)	6.8 (4.5, 9.1)	1.0 (0.84)	8.1 (0.77)	7.5 (0.64)	7.0 (4.6, 9.4)	6.5 (4.3, 8.6)
Week 20	1.7 (0.90)	10.1 (0.72)	9.8 (0.55)	8.4 (5.8, 10.9)	8.1 (5.7, 10.4)	1.6 (0.81)	9.2 (0.78)	8.8 (0.70)	7.6 (5.2, 9.9)	7.2 (5.0, 9.4)
Week 24	1.4 (0.94)	10.9 (0.69)	9.5 (0.58)	9.5 (6.9, 12.0)	8.0 (5.6, 10.5)	0.7 (0.88)	8.6 (0.79)	7.7 (0.72)	7.9 (5.4, 10.3)	7.0 (4.7, 9.3)
Week 28	1.0 (0.96)	11.0 (0.71)	10.2 (0.59)	10.0 (7.3, 12.7)	9.2 (6.7, 11.6)	0.8 (0.89)	9.1 (0.81)	8.2 (0.75)	8.3 (5.8, 10.8)	7.4 (5.0, 9.8)
Week 32	0.9 (0.99)	11.1 (0.77)	9.7 (0.64)	10.2 (7.4, 13.0)	8.8 (6.2, 11.4)	0.5 (0.91)	9.0 (0.81)	8.4 (0.78)	8.5 (6.0, 11.0)	7.8 (5.4, 10.3)
Week 36	1.0 (1.01)	11.2 (0.81)	10.5 (0.63)	10.2 (7.3, 13.1)	9.4 (6.8, 12.0)	1.0 (0.97)	9.5 (0.83)	9.3 (0.82)	8.4 (5.8, 11.1)	8.3 (5.7, 10.9)
Week 40	0.9 (1.02)	10.8 (0.83)	10.0 (0.65)	9.9 (7.0, 12.8)	9.1 (6.4, 11.7)	1.3 (0.98)	9.7 (0.85)	9.3 (0.83)	8.4 (5.7, 11.1)	8.0 (5.4, 10.7)
Week 44	0.6 (1.04)	12.1 (0.79)	10.4 (0.67)	11.5 (8.6, 14.4)	9.8 (7.1, 12.5)	1.0 (0.98)	10.0 (0.88)	9.3 (0.82)	9.1 (6.3, 11.8)	8.3 (5.7, 10.9)
Week 48	0.4 (1.04)	11.9 (0.80)	10.6 (0.67)	11.5 (8.6, 14.4)	10.3 (7.6, 13.0)	1.0 (1.00)	10.3 (0.86)	9.1 (0.85)	9.4 (6.7, 12.1)	8.2 (5.5, 10.9)
Week 52	0.1 (1.03)	12.3 (0.76)	10.6 (0.69)	12.2 (9.4, 15.0)	10.5 (7.7, 13.2)	0.9 (1.00)	10.2 (0.89)	10.0 (0.85)	9.3 (6.5, 12.0)	9.1 (6.3, 11.8)
Week 56	0.9 (1.07)	12.2 (0.77)	10.6 (0.69)	11.2 (8.3, 14.1)	9.7 (6.9, 12.4)	0.7 (1.03)	10.5 (0.89)	8.9 (0.84)	9.7 (6.9, 12.6)	8.2 (5.5, 11.0)
Week 60	0.4 (1.09)	12.3 (0.77)	10.8 (0.71)	11.8 (8.9, 14.8)	10.4 (7.5, 13.2)	0.7 (1.02)	10.4 (0.91)	10.1 (0.87)	9.7 (6.9, 12.5)	9.4 (6.7, 12.2)
Week 64	0.1 (1.06)	12.1 (0.87)	10.9 (0.63)	12.0 (9.0, 15.1)	10.8 (8.1, 13.5)	0.8 (1.03)	10.7 (0.94)	9.9 (0.91)	9.9 (7.0, 12.8)	9.1 (6.3, 11.9)
Week 68	0.1 (1.08)	11.6 (1.01)	10.9 (0.67)	11.5 (8.2, 14.8)	10.8 (8.0, 13.6)	-0.1 (1.11)	10.1 (0.94)	10.1 (0.90)	10.2 (7.1, 13.2)	10.1 (7.2, 13.1)
Week 72	0.3 (1.10)	11.2 (0.99)	10.6 (0.74)	10.9 (7.6, 14.2)	10.3 (7.4, 13.2)	-0.2 (1.14)	10.8 (0.94)	9.9 (0.90)	10.9 (7.9, 14.0)	10.0 (7.0, 13.0)
Week 76	0.6 (1.10)	11.5 (0.99)	11.1 (0.79)	10.9 (7.6, 14.2)	10.5 (7.6, 13.5)	0.3 (1.10)	10.7 (0.95)	10.1 (0.91)	10.4 (7.4, 13.4)	9.8 (6.9, 12.7)
Week 80	0.2 (1.10)	11.6 (0.99)	11.2 (0.71)	11.4 (8.1, 14.7)	11.0 (8.1, 13.9)	0.4 (1.12)	10.4 (1.00)	9.7 (0.89)	10.1 (7.0, 13.2)	9.4 (6.4, 12.3)
Week 84	0.3 (1.11)	11.7 (1.02)	11.4 (0.74)	11.4 (8.1, 14.8)	11.1 (8.2, 14.0)	-0.4 (1.14)	10.3 (1.01)	9.4 (0.94)	10.7 (7.5, 13.9)	9.9 (6.8, 12.9)
Week 88	0.5 (1.10)	12.0 (1.06)	11.4 (0.74)	11.6 (8.2, 15.0)	11.0 (8.1, 13.9)	0.2 (1.11)	10.1 (0.99)	9.3 (0.91)	9.9 (6.8, 13.0)	9.1 (6.1, 12.0)
Week 92	0.5 (1.12)	11.0 (1.15)	11.8 (0.72)	10.4 (6.9, 14.0)	11.3 (8.4, 14.2)	0.1 (1.11)	9.7 (1.00)	9.2 (0.92)	9.6 (6.5, 12.7)	9.1 (6.1, 12.0)
Week 96	0.6 (1.15)	11.0 (1.17)	11.1 (0.84)	10.5 (6.8, 14.1)	10.5 (7.4, 13.6)	0.2 (1.12)	10.7 (1.00)	8.4 (0.92)	10.5 (7.4, 13.6)	8.3 (5.3, 11.3)
Week 100	0.6 (1.16)	11.2 (1.11)	10.7 (0.89)	10.6 (7.1, 14.2)	10.1 (7.0, 13.3)	0.1 (1.12)	10.8 (1.02)	8.4 (0.99)	10.7 (7.6, 13.8)	8.2 (5.2, 11.3)

[1] Based on ANCOVA model with baseline measurement as covariate and study specific stratification factors and treatment as as fixed factors

Table 19: Proportion of patients who gained ≥15 letters in BCVA from baseline over time
(Full Analysis Set, LOCF)

Visit	VISTA					VIVID				
	Laser (N = 154)	VTE 2Q4 (N = 154)	VTE 2Q8 (N = 151)	Difference (97.5% CI) vs Laser [1]		Laser (N = 132)	VTE 2Q4 (N = 136)	VTE 2Q8 (N = 135)	Difference (97.5% CI) vs Laser [1]	
				VTE 2Q4	VTE 2Q8				VTE 2Q4	VTE 2Q8
Week 1	1 (0.7%)	9 (5.9%)	3 (2.0%)	5.4 (0.8, 10.0)	1.4 (-1.6, 4.4)	1 (0.8%)	1 (0.7%)	0 (0.0%)	-0.0 (-2.4, 2.3)	-0.8 (-2.4, 0.9)
Week 4	4 (2.6%)	23 (14.9%)	10 (6.7%)	12.7 (5.5, 19.8)	4.1 (-1.4, 9.5)	3 (2.3%)	6 (4.4%)	12 (8.9%)	2.1 (-2.8, 7.1)	6.6 (0.4, 12.8)
Week 8	5 (3.2%)	26 (16.9%)	17 (11.3%)	14.3 (6.8, 21.8)	8.1 (1.4, 14.8)	4 (3.0%)	13 (9.6%)	16 (11.9%)	6.5 (-0.1, 13.1)	8.8 (1.7, 15.9)
Week 12	7 (4.5%)	42 (27.3%)	24 (15.9%)	23.0 (14.1, 32.0)	11.3 (3.6, 19.1)	6 (4.5%)	19 (14.0%)	21 (15.6%)	9.4 (1.6, 17.3)	11.0 (2.9, 19.0)
Week 16	6 (3.9%)	39 (25.3%)	28 (18.5%)	21.9 (13.2, 30.6)	14.6 (6.7, 22.6)	8 (6.1%)	26 (19.1%)	23 (17.0%)	13.1 (4.1, 22.0)	10.9 (2.3, 19.6)
Week 20	7 (4.5%)	46 (29.9%)	35 (23.2%)	25.8 (16.7, 34.9)	18.6 (10.0, 27.2)	6 (4.5%)	29 (21.3%)	28 (20.7%)	16.8 (7.9, 25.7)	16.2 (7.3, 25.0)
Week 24	10 (6.5%)	49 (31.8%)	31 (20.5%)	25.8 (16.2, 35.4)	14.0 (5.4, 22.7)	2 (1.5%)	31 (22.8%)	26 (19.3%)	21.3 (12.8, 29.7)	17.7 (9.8, 25.6)
Week 28	12 (7.8%)	45 (29.2%)	36 (23.8%)	21.9 (12.3, 31.5)	16.0 (6.8, 25.3)	3 (2.3%)	33 (24.3%)	29 (21.5%)	22.0 (13.2, 30.8)	19.2 (10.8, 27.6)
Week 32	12 (7.8%)	49 (31.8%)	40 (26.5%)	24.3 (14.5, 34.0)	18.7 (9.3, 28.2)	3 (2.3%)	34 (25.0%)	28 (20.7%)	22.7 (13.9, 31.6)	18.4 (10.2, 26.6)
Week 36	11 (7.1%)	49 (31.8%)	43 (28.5%)	24.8 (15.1, 34.4)	21.3 (11.8, 30.8)	7 (5.3%)	33 (24.3%)	39 (28.9%)	19.0 (9.6, 28.3)	23.6 (13.8, 33.3)
Week 40	9 (5.8%)	54 (35.1%)	42 (27.8%)	29.9 (20.3, 39.5)	21.9 (12.7, 31.2)	7 (5.3%)	39 (28.7%)	36 (26.7%)	23.4 (13.6, 33.2)	21.3 (11.8, 30.8)
Week 44	14 (9.1%)	61 (39.6%)	47 (31.1%)	31.1 (20.9, 41.4)	22.0 (12.0, 32.0)	7 (5.3%)	45 (33.1%)	39 (28.9%)	27.8 (17.7, 37.9)	23.5 (13.8, 33.3)
Week 48	14 (9.1%)	59 (38.3%)	48 (31.8%)	29.8 (19.5, 40.0)	22.7 (12.7, 32.7)	8 (6.1%)	39 (28.7%)	34 (25.2%)	22.6 (12.7, 32.5)	19.1 (9.5, 28.7)
Week 52	12 (7.8%)	64 (41.6%)	47 (31.1%)	34.2 (24.1, 44.4)	23.3 (13.5, 33.1)	12 (9.1%)	44 (32.4%)	45 (33.3%)	23.3 (12.6, 33.9)	24.2 (13.5, 34.9)
Week 56	14 (9.1%)	62 (40.3%)	48 (31.8%)	31.5 (21.2, 41.8)	22.7 (12.7, 32.7)	8 (6.1%)	42 (30.9%)	40 (29.6%)	24.8 (14.8, 34.9)	23.5 (13.6, 33.5)
Week 60	16 (10.4%)	67 (43.5%)	50 (33.1%)	33.4 (22.8, 44.0)	22.7 (12.4, 33.0)	10 (7.6%)	43 (31.6%)	45 (33.3%)	24.0 (13.7, 34.4)	25.7 (15.2, 36.3)
Week 64	13 (8.4%)	65 (42.2%)	48 (31.8%)	34.4 (24.1, 44.6)	23.3 (13.4, 33.2)	14 (10.6%)	47 (34.6%)	46 (34.1%)	24.0 (13.0, 35.0)	23.5 (12.4, 34.5)
Week 68	14 (9.1%)	69 (44.8%)	55 (36.4%)	36.2 (25.8, 46.6)	27.3 (17.0, 37.5)	11 (8.3%)	46 (33.8%)	46 (34.1%)	25.5 (14.9, 36.1)	25.7 (15.1, 36.3)
Week 72	13 (8.4%)	61 (39.6%)	56 (37.1%)	31.7 (21.5, 41.9)	28.6 (18.4, 38.8)	9 (6.8%)	49 (36.0%)	44 (32.6%)	29.2 (18.8, 39.7)	25.7 (15.4, 36.1)
Week 76	16 (10.4%)	60 (39.0%)	62 (41.1%)	29.0 (18.6, 39.5)	30.7 (20.1, 41.3)	12 (9.1%)	55 (40.4%)	44 (32.6%)	31.4 (20.4, 42.3)	23.5 (12.8, 34.1)
Week 80	19 (12.3%)	65 (42.2%)	58 (38.4%)	30.3 (19.5, 41.1)	26.1 (15.3, 36.8)	14 (10.6%)	53 (39.0%)	46 (34.1%)	28.4 (17.2, 39.6)	23.4 (12.4, 34.4)
Week 84	17 (11.0%)	69 (44.8%)	56 (37.1%)	34.0 (23.3, 44.7)	26.1 (15.5, 36.6)	15 (11.4%)	49 (36.0%)	47 (34.8%)	24.7 (13.5, 35.8)	23.4 (12.3, 34.5)
Week 88	16 (10.4%)	69 (44.8%)	56 (37.1%)	34.8 (24.2, 45.4)	26.7 (16.2, 37.1)	17 (12.9%)	49 (36.0%)	46 (34.1%)	23.2 (11.8, 34.5)	21.2 (9.9, 32.4)
Week 92	16 (10.4%)	68 (44.2%)	56 (37.1%)	34.1 (23.5, 44.7)	26.7 (16.2, 37.1)	14 (10.6%)	45 (33.1%)	45 (33.3%)	22.5 (11.6, 33.4)	22.7 (11.8, 33.5)
Week 96	16 (10.4%)	69 (44.8%)	54 (35.8%)	34.8 (24.2, 45.4)	25.3 (14.9, 35.7)	16 (12.1%)	53 (39.0%)	42 (31.1%)	26.9 (15.5, 38.2)	19.0 (8.0, 30.0)
Week 100	20 (13.0%)	59 (38.3%)	50 (33.1%)	25.8 (15.1, 36.6)	20.1 (9.6, 30.6)	16 (12.1%)	52 (38.2%)	42 (31.1%)	26.1 (14.8, 37.5)	19.0 (8.0, 29.9)

[1] Difference for letters gained with confidence interval (CI) based on using CMH weighting scheme adjusted by study specific stratification factor.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SOLOMON CHEFO
03/05/2015

YAN WANG
03/05/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s048

CLINICAL PHARMACOLOGY REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA:	125-387/Efficacy Supplement 048
Submission Date(s):	September 30, 2014
Proposed Brand Name	EYLEA®
Generic Name	Aflibercept Injection
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND Division	DTOP
Applicant	Regeneron Pharmaceuticals, Inc.
Relevant IND(s)	12462, 100083
Submission Type; Code	New indication ; 6P
Formulation; Strength(s)	Aflibercept Ophthalmic Solution for Intravitreal Injection; 40 mg/mL (2 mg/50 μL)
Indication	For the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME)

1. SUMMARY

Aflibercept (EYLEA) is a fully human, water-soluble recombinant decoy VEGF receptor. It is biologically engineered to contain key extracellular VEGF-binding domains of VEGF receptor-1 and VEGF receptor-2 fused to the constant Fc region of IgG1. The initial marketing application for aflibercept, administered as an intravitreal (IVT) injection, was for the treatment of neovascular (wet) age-related macular degeneration (AMD). The application was submitted on February 17, 2011, and approved by the Agency on November 18, 2011. Subsequently, three additional efficacy supplements were submitted and approved by FDA:

- The efficacy supplements (S-004) for the treatment of macular edema secondary to central retinal vein occlusion (CRVO) was approved on September 21, 2012.
- The efficacy supplement (S-037) for the treatment of diabetic macular edema (DME) was approved on July 29, 2014.
- The efficacy supplement (S-043) for the treatment of macular edema following branch retinal vein occlusion (BRVO) was approved on October 6, 2014.

This efficacy supplement (S-048) provides the100-week clinical data (Statistical analysis plan prespecified) from two ongoing Phase 3 studies (VGFT-OD-1009 [VISTA DME] and 91745 [VIVID DME]) to support the safety and efficacy of EYLEA in the treatment of DR in patients with DME. It should be noted that the data from the 52-week primary endpoints in the same two Phase 3 studies were the basis for the approval of the previous efficacy supplement (S-037). Both the VISTA DME and VIVID DME studies are continuing to Week 148, and additional safety data will be provided in the 4-Month Safety Update Report.

The intended dose for EYLEA® in the treatment of DR in patients with DME is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks for the first 5 injections followed by 2 mg via intravitreal injection once every 8 weeks, which is identical to that previously approved by the

FDA for the treatment of DME (S-037). No new clinical pharmacology studies were submitted with this supplemental BLA and no new clinical pharmacology related revisons have been made to the labeling for EYLEA®. Thus, no further review is warranted from a clinical pharmacology perspective.

1.1. Recommendation

This efficacy supplement for EYLEA® for the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME) is acceptable from a clincial pharmacology perspective, and we recommend approval of this indication. There are no clinical pharmacology related labeling revisons / comments for the sponsor.

Yongheng Zhang, Ph.D.
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

Concurrence:

Philip Colangelo, Pharm.D., Ph. D.
Team Leader
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

cc: Division File: BLA 125387/043; HFD-520 (CSO/ Puglisi); HFD-520 (MO/Boyd); HFD-520 (Chambers); HFD-880 (Lazor)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YONGHENG ZHANG
01/22/2015

PHILIP M COLANGELO
01/23/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125387Orig1s048

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: March 13, 2015

To: Mike Puglisi, Regulatory Project Manager
Division of Transplant and Ophthalmic Products (DTOP)

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: BLA 125387/ S-48
EYLEA™ (aflibercet injection) intravitreal injection

As requested in your consult dated October 7, 2014, the Office of Prescription Drug Promotion (OPDP) has reviewed the proposed labeling for EYLEA™ (aflibercet injection) intravitreal injection. OPDP notes that this supplement (S-48) involves changes to the PI as a result of an additional indication of Diabetic Retinopathy in patients with Diabetic Macular Edema.

OPDP's comments are based on the substantially complete version of the labeling (PI) titled, "Eyelea_Label.doc" which was received via email from DTOP on March 11, 2015.

OPDP has reviewed the attached proposed PI and has no comments at this time.

Thank you for the opportunity to review the proposed PI. If you have any questions, please contact Zarna Patel at zarna.patel@fda.hhs.gov.

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

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZARNA PATEL
03/13/2015