FDA Advisory Committee Briefing Document for BLA 125387/S-075

Application Number	BLA 125387 Supplement 75
Established/Proper Name	Aflibercept
Trademark	EYLEA
Applicant	Regeneron Pharmaceuticals, Inc.
Date of Meeting	January 9, 2023
Advisory Committee	Dermatologic and Ophthalmic Advisory Committee Meeting
Division/Office	Division of Ophthalmology/Office of Specialty Medicine
Dosage Form	Intravitreal Injection
Dosing Regimen	Single injection, 0.4 mg (0.01 mL), may be repeated twice
Proposed Indication	Retinopathy of Prematurity

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought a discussion of the labeling of aflibercept for the treatment of retinopathy of prematurity to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
CA	Chronological age
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FD&C	Food, Drug and Cosmetic
IND	Investigational New Drug Application
ITT	intent to treat
mITT	modified intent to treat
PD	pharmacodynamics
PK	pharmacokinetics
PP	per protocol
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
ROP	Retinopathy of Prematurity
SGE	special government employee
TEAE	treatment emergent adverse event
VEGF	vascular endothelial growth factor

1. Product Introduction

Aflibercept is an inhibitor of vascular endothelial growth factor (VEGF). VEGF is overexpressed in several retinal diseases characterized by neovascularization, including in preterm infants with (ROP).

2. Analysis of Condition

Retinopathy of Prematurity (ROP) is a vision-threatening, vasoproliferative disease of the incompletely vascularized, immature retina of preterm infants (born <37 weeks of gestational age [GA]). The disease is characterized by incomplete vascularization and pathological neovascularization. ROP is a leading cause for childhood blindness worldwide. The condition was first described in the 1940s and linked to the use of oxygen in preterm infants by the 1950s.

3. Analysis of Current Treatment Options

Laser photocoagulation and cryotherapy (freezing) treatments have been used to destroy ischemic peripheral retina where physiological vascularization has not yet developed, reducing metabolic demand and production of factors such as vascular endothelial growth factor VEGF, preventing progression of ROP lesions. Laser and cryotherapies are effective; however, due to their destruction of peripheral retina, they lead to permanently reduced peripheral vision. Reduction in the use of oxygen is associated with increased mortality.

4. Product Quality

For this supplement, there has been no change in the drug substance, drug product or route of administration. The dosing has been changed from the standard adult dose of 2 mg to give a smaller dose in these infants. The recommended dose for ROP of EYLEA is 0.4 mg (0.01 mL or 10 microliters) administered by intravitreal injection. The dose is recommended to be drawn from a vial. Treatment is initiated with a single injection per eligible eye and may be given bilaterally on the same day. It may be repeated in each eye up to two times if there are signs of disease activity, but the treatment interval between doses injected into the same eye should be at least 4 weeks (at least 25 days). The maximum number of doses given to an individual child is three in each eye.

5. Regulatory Background

5.1 U.S. Regulatory Actions and Marketing History

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

Original: Treatment of neovascular (wet) AMD	11/18/2011
S004: Treatment of macular edema secondary to CRVO	9/21/2012
S037: Treatment of diabetic macular edema DME	7/29/2014
S043: Treatment of macular edema secondary to BRVO	10/6/2014
S048: Treatment of diabetic retinopathy in patients with DME	3/25/2015
S061: Treatment of diabetic retinopathy	5/13/2019

5.2 Summary of Pre-submission/Submission Regulatory Activity

On June 4, 2019, to obtain needed pediatric information on aflibercept, the Food and Drug Administration (FDA) issued a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Food and Drug Administration Amendments Act of 2007, and pursuant to section 351(m) of the Public Health Service Act (the PHS Act), as amended by the Biologics Price Competition and Innovation Act of 2009, that studies be submitted to investigate the potential use of aflibercept in the treatment of ROP.

On July 23, 2019, pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), the FDA granted Regeneron Pharmaceutical's orphan designation request of aflibercept for the treatment of retinopathy of prematurity.

5.3 Study Size and Power

Two studies were conducted (Firefleye and Butterfleye) to evaluate the effect of aflibercept for the treatment of retinopathy of prematurity. The sample size for these studies was based on the results from studies previously conducted and published in the medical literature for other anti-VEGF products. From the RAINBOW[1] study, the response rate was 66% for the laser group and 88% for the 0.2 mg ranibizumab group in Zone II disease. Based on investigator-initiated studies reported by Regeneron, the response rates for aflibercept ranged up to 100% (with at least 2 studies demonstrating a 100% response rate in terms of favorable anatomic structural outcomes/prevention of unfavorable anatomic structural outcomes) with

[1] Stahl A, Lepore D, Fielder A, *et al.* Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. Lancet. 2019. 394:1551-1559. http://dx.doi.org/10.1016/ S0140-6736(19)31344-3

intravitreal aflibercept doses ranging from 0.4 mg to 1 mg. An estimated 90% response rate for the aflibercept group and 66.1% response rate for the laser group was considered a reasonable assumption. It was assumed that the proportion of patients without active ROP were in line with this assumption. A sample size of 68 patients in the aflibercept group and 34 patients in the laser group (randomized in a 2:1 ratio) would provide 90% power for rejecting the null hypothesis at a 1-sided 2.5% significance level.

6. Sources of Clinical Data

Listing of Clinical Studies for the Aflibercept Pediatric Clinical Development Program

Study Identifier	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Randomized Number of Subjects	Diagnosis of Patients
Clinical Study BAY 86-5321 / 20090 & 20275 (FIREFLEYE)	Phase 3, multicenter, open-label, randomized, two-arm study (20090) and a 5-year follow-up study with no treatment (only data through week 52 CA) (20275)	**Study 20090**: 0.4 mg/0.01 mL IAI: single IVT injection of aflibercept 0.4 mg/0.01 mL per eligible eye at baseline. Up to 2 additional IVT injections of aflibercept 0.4 mg/0.01 mL could have been administered in each treatment requiring eye if prespecified retreatment criteria were met. Laser Photocoagulation: Laser treatment in each eligible eye at baseline. If multiple sessions were necessary within 1 week from baseline, they were counted as single treatment. **Study 20275**: No study treatment was administered. Retreatment with laser was allowed if prespecified criteria were met.	Total N=118 0.4 mg 0.01 mL IAI: 75 Laser Photo-coagulation: 43	Treatment-naïve participants with ROP (gestational age at birth ≤32 weeks or birth weight ≤1500 g).
VGFTe-ROP-1920 (BUTTERFLEYE)	Phase 3, multicenter, randomized, 2-arm, open-label study	0.4 mg/0.01 mL IAI: single intravitreal (IVT) injection of aflibercept 0.4 mg/0.01 mL per eligible eye at baseline. Up to 2 additional IVT injections of aflibercept 0.4 mg/0.01 mL could have been administered. Rescue treatment with laser was performed if prespecified conditions were met. Laser Photocoagulation: Laser treatment in each eligible eye at baseline. Supplementary laser treatments were allowed during the study. Retreatment with laser was allowed if prespecified criteria were met. Rescue treatment with aflibercept 0.4 mg/0.01 mL was allowed if the laser treatment was judged complete by the investigator and prespecified criteria were met.	Total N=127 0.4 mg 0.01 mL IAI: 94 Laser Photo-coagulation: 33	Treatment-naïve participants with ROP at 52 weeks of chronological age. Participants must have been of ≤32 weeks gestational age at birth or birth weight ≤1500 g.

7. Review of Individual Trials Used to Support Efficacy

Study Design

FIREFLEYE Trial Design
Open-Label, Randomized, Two-Arm, Controlled Study to assess efficacy, safety, and tolerability of Intravitreal (IVT) Aflibercept Compared to Laser Photocoagulation in Patients with Retinopathy of Prematurity (Study 20090), and Extension Study to Evaluate the Long-Term Outcomes of Subjects Who Received Treatment for Retinopathy of Prematurity in Study 20090 (Study 20275).

FIREFLEYE Key Inclusion Criteria
1. Gestational age at birth ≤32 weeks or birth weight ≤1500 g
2. Treatment-naïve ROP classified according to the International Classification for ROP (ICROP 2005) in at least one eye as:
   a. Zone I Stage 1 plus, or 2 plus, or 3 non-plus or 3 plus, or
   b. Zone II Stage 2 plus or 3 plus, or
   c. AP-ROP
3. Weight at baseline (day of treatment) ≥800 g

FIREFLEYE Key Exclusion Criteria
1. Known or suspected chromosomal abnormality, genetic disorder, or syndrome
2. Previous exposure to any IVT or systemic anti-VEGF agent, including maternal exposure during pregnancy and/or during breastfeeding
3. Clinically significant neurological disease (e.g., intraventricular hemorrhage grade 3 or higher, periventricular leukomalacia, congenital brain lesions significantly impairing optic nerve function, severe hydrocephalus with significantly increased intracranial pressure)
4. Pediatric conditions rendering the infant ineligible for study intervention at baseline or for repeated blood draws as evaluated by a neonatal intensive care unit specialist and a study ophthalmologist
5. Presence of active ocular infection within 5 days of the first treatment
6. Advanced stages of ROP with partial or complete retinal detachment (ROP Stages 4 and 5)
7. ROP involving only Zone III
8. Ocular abnormalities that may interfere with the administration of study intervention or assessment of the study primary endpoint
9. Postnatal treatment with oral or intravenous corticosteroids at an equivalent dose of prednisone ≥1 mg/kg/day for >2 weeks within 14 days of the first study intervention
10. Previous surgical or nonsurgical treatment for ROP (IVT anti-VEGF injection, ablative laser therapy, cryotherapy, and vitrectomy)
11. Participation of the subject or the mother in other clinical trials requiring administration of investigational treatments (other than vitamins and minerals) at the time of screening, or

within 30 days or 5 half-lives of administration of the previous study intervention, whichever was longer.

BUTTERFLEYE Trial Design
52 week, Open-Label, Randomized, Two-Arm, Controlled Study to assess efficacy, safety, and tolerability of Intravitreal (IVT) Aflibercept Compared to Laser Photocoagulation in Patients with Retinopathy of Prematurity

BUTTERFLEYE Key Inclusion and Exclusion Criteria
Same as FIREFLEYE

7.2 Study Endpoints

In both BUTTERFLEYE and FIREFLEYE with its extension, the primary efficacy endpoint was the proportion of participants with absence of both active ROP and unfavorable structural outcomes at 52 weeks chronological age (CA) based on the investigator's assessment. Active ROP was ROP (according to the inclusion criterion) requiring treatment and unfavorable structural outcome was defined as retinal detachment, macular dragging, macular fold, or retrolental opacity.

Statistical Analysis Plan
The primary analysis was a statistical evaluation of non-inferiority of aflibercept versus laser at week 52 CA, with respect to the primary efficacy variable. In both treatment groups, a vast majority of participants met the primary endpoint. The primary efficacy variable analyses were conducted on the full analysis set (FAS) which included all randomized patients who received any study intervention. The analysis on the FAS was performed according to the intervention assigned at baseline (as randomized). The non-inferiority margin was set at 5% based on the belief that differences greater than 5% would not be considered equivalent.

If the non-inferiority of the primary endpoint was declared significant, a hierarchical procedure for testing superiority was to be used for the analysis of the secondary endpoints to control the overall alpha error rate at the 0.05 level based on the following order:

- Proportion of patients requiring intervention with a second treatment modality from baseline to week 52 CA.
- Proportion of patients with recurrence of ROP through week 52 CA.

However, the primary endpoint (non-inferiority to the control) was not met in either study, and therefore no secondary endpoints were evaluated. Eyes were considered to be non-responders if rescue treatment was given. The primary analysis for this endpoint was based on the investigator assessment.

Compliance with Good Clinical Practices: Studies were conducted in compliance with good clinical practice guidelines.

FIREFLEYE Patient Disposition by Treatment Group (All Randomized Patients)

	Laser (N=43)		Aflibercept (N=75)	
All treated patients	38	88%	75	100%
Number of patients who discontinued early in Study 20090	7	16%	7	9%
Adverse Event	1	2%	1	1%
Death	0		3	4%
Other	0		1	1%
Physician Decision	1	2%	1	1%
Withdrawal by Parent/Guardian	5	12%	1	1%
Number of patients who completed Study 20090	36	84%	68	91%
Number of patients who entered Study 20275	34	79%	66	88%
Completed week 52 chronological age visit Number of patients ongoing in Study 20275	34	79%	66	88%

Three patients discontinued early from the main study (20090) but enrolled in the extension study (20275) and had data at week 52 of chronological age and were not considered as discontinued in the analyses.

BUTTERFLEYE Patient Disposition by Treatment Group (All Randomized Patients)

	Laser (N=33)		Aflibercept (N=94)	
All treated patients	27	82%	93	99%
Number of patients who completed study	26	79%	87	93%
Number of patients who discontinued from the study	7	21%	7	7%
Death	0		1	1%
Lost To Follow-Up	0		3	2%
Physician Decision	1	3%	0	
Withdrawal By Parent/Guardian	6	18%	3	3%

The percentage was based on the number of patients in each treatment group as denominator. PTT 14.1.1.3

FIREFLEYE Important Protocol Violations/Deviations

Two participants in the aflibercept group had treatment deviations resulting in either incorrect dose or deviation from protocol-specified treatment:

- 1 participant did not receive correct dose of aflibercept for the right eye;
- 1 participant was treated with laser in the right eye although retreatment criteria with aflibercept was met.

BUTTERFLEYE Protocol Violations/Deviations

Patients with Any Important Protocol Deviation	Laser		Aflibercept	
	(N=33)		(N=94)	
Any Important Protocol Deviation	7	15%	38	40%
Missed visits if impacting efficacy, patient safety, or patient rights. (All visits)	2	6%	10	11%
ROP and Posterior Segment Assessment not done	2	6%	8	9%
Hematology not done	1	3%	6	6%
Chemistry not done	1	3%	5	5%
Subject or mother (if breastfeeding) received IVT or systemic anti-VEGF agent impacting safety or efficacy	0		4	4%
Body weight not done (Baseline)	1	3%	2	2%
Subject received incorrect study treatment that may impact efficacy	0		3	3%

FIREFLEYE Table of Demographic Characteristics

	Laser (N=38)		Aflibercept (N=75)	
Chronological Age at Randomization (weeks) Mean (SD)	10.17	2.29	10.35	2.781
Median (Min; Max)	10.00	5.9:16.1	10.30	4.0:18.9
Gestational Age at Birth (weeks) Mean (SD)	25.97	1.618	26.48	2.071
Median (Min; Max)	26.00	23.6:31.0	26.00	23.1:31.0
Post-Menstrual Age at Randomization (weeks), Mean (SD)	36.14	2.15	36.82	2.73
Median (Min; Max)	36.00	32.6:43.3	36.60	32.1:44.6
Gestational Age at Birth group, n (%) <=26 weeks	22	58%	38	51%
>26 weeks	16	42%	37	49%
Race, n(%)				
White	28	74%	55	73%
Black or African American	0		2	2.7%
Asian	9	23.7%	17	22.7%
American Indian or Alaska Native	1	2.6%	0	
Native Hawaiian or Other Pacific Islander	0		0	
Multiple	0		1	1.3%
Gender Female	19	50%	34	45%
Gender Male	19	50%	41	55%
Weight at Birth (g) Mean (SD)	824.6	230.8	881.1	305.63
Median (Min; Max)	790.0	467:1500	820.0	410:1780
Baseline weight (g) Mean (SD)	1850.9	546.13	2026.7	678.93
Median (Min; Max)	1735.5	898:3608	1851.0	800:3800
APGAR score category 1 min after birth, 0 – 4	22	58%	36	48%
5 – 7	12	32%	27	36%
8 – 10	3	8%	8	11%
APGAR score category 5 min after birth, n (%) 0 - 4	6	16%	11	15%
5 – 7	19	50%	32	43%
8 – 10	9	24%	27	36%
O_2 supplementation at baseline, n (%) Yes	23	60.5%	45	60%
No	15	39.5%	30	40%
History of sepsis?, n (%) Yes	15	39.5%	32	42.7%
No	23	60.5%	43	57.3%
History of necrotizing enterocolitis?, n (%) Yes	5	13%	15	20%
No	33	87%	60	80%
History of intraventricular hemorrhage?, n (%) Yes	16	42%	19	25%
No	22	58%	56	75%
One Eye Treated at Baseline	5	13%	6	8%
Two Eyes Treated at Baseline	33	87%	69	92%

Post-menstrual age at randomization = Gestational age at birth + Chronological age at randomization.
Source: PTT 14.1.2.1

BUTTERFLEYE Table of Demographic Characteristics

	Laser (N=27)		Aflibercept (N=93)	
Chronological Age at Randomization (weeks) Mean (SD)	11.1	4.3	9.8	3.1
Median (Min; Max)	11.0	5.0:22.9	9.9	4.1:19.4
Gestational Age at Birth (weeks) Mean (SD)	27.1	2.7	27.3	2.8
Median (Min; Max)	26.9	23.1-31.9	27.0	23.0:33.0
Post-Menstrual Age at Randomization (weeks), Mean (SD)	38.1	3.6	37.1	2.4
Median (Min; Max)	38.3	32.9:50.6	36.9	32.6:43.6
Gestational Age at Birth group, n (%) <=26 weeks	11	41%	38	41%
>26 weeks	16	59%	55	59%
Race, n (%)				
White	11	41%	26	28%
Black or African American	2	7%	6	7%
Asian	13	48%	44	47%
American Indian or Alaska Native	0		0	
Native Hawaiian or Other Pacific Islander	0		0	
Other	1	4%	12	13%
Not Reported	0		5	5%
Gender Female	10	37%	52	56%
Gender Male	17	63%	41	44%
Weight at Birth (g) Mean (SD)	934.1	406.6	991.2	407.0
Median (Min; Max)	798	430:1990	900	476:2230
Baseline weight (g) Mean (SD)	2248.1	725	2058.3	548
Median (Min; Max)	2050.0	1090:4000	1948	1245:3930
APGAR score category 1 min after birth, 0 – 4	15	56%	35	38%
5 – 7	9	33%	40	43%
8 – 10	3	11%	11	12%
APGAR score category 5 min after birth, n (%) 0 - 4	6	22%	8	9%
5 – 7	9	33%	35	38%
8 – 10	7	26%	30	32%
O_2 supplementation at baseline, n (%) Yes	8	30%	35	38%
No	19	70%	58	62%
History of sepsis?, n (%) Yes	15	56%	51	55%
No	12	44%	42	45%
History of necrotizing enterocolitis?, n (%) Yes	3	11%	16	17%
No	24	89%	77	83%
History of intraventricular hemorrhage?, n (%) Yes	8	30%	35	38%
No	19	70%	58	62%
One Eye Treated at Baseline	4	15%	10	11%
Two Eyes Treated at Baseline	23	85%	83	89%

Post-menstrual age at randomization = Gestational age at birth + Chronological age at randomization.
Source: PTT 14.1.2.1

FIREFLEYE Baseline ROP

	Laser		Aflibercept	
	(N=72 eyes)		(N=146 eyes)	
Zone I	21	29%	51	35%
Stage 1, plus disease	0		2	1%
Stage 2, plus disease	7	10%	6	4%
Stage 3, no plus disease	1	1%	6	4%
Stage 3, plus disease	9	12.5%	27	18.5%
AP-ROP	8	11%	23	16%
Zone II	51	71%	95	65%
Stage 2, no plus disease	1	1%	0	
Stage 2, plus disease	11	15%	17	12%
Stage 3, plus disease	37	51%	75	51%
AP-ROP	2	3%	5	3%

BUTTERFLEYE Baseline ROP

	Laser		Aflibercept	
	(N=50 eyes)		(N=179)	
Zone I	13	26%	47	26%
Stage 2, plus disease	1	2%	16	9%
Stage 3, no plus disease	0		2	1%
State 3, plus disease	12	24%	21	12%
AP-ROP	3	6%	20	11%
Zone II	37	74%	132	74%
Stage 2, plus disease	5	10%	32	18%
Stage 3, plus disease	30	60%	100	56%
AP-ROP	3	6%	8	5%

8. Assessment of Efficacy Across Trials

Primary Endpoint

Proportion Analysis of Patients with Absence of Active ROP and Unfavorable Structural Outcomes at Week 52 of Chronological Age (FAS)

FIREFLEYE BAY 86-5321/ 20090 & 20275			**Difference (95% CI)**
Aflibercept	(N=75)	59/75 (79%)	-1.9% (-17%, 13%)
Laser	(N=38)	31/38 (82%)	

BUTTERFLEYE VGFTe-ROP-1920			**Difference (95% CI)**
Aflibercept	(N=93)	74/93 (80%)	1.8% (-16%, 19%)
Laser	(N=27)	21/27 (78%)	

The 95% Confidence Interval (CI) for non-inferiority margin was set at 5%. Each study exceeds the 5% limit, and therefore aflibercept fails to demonstrate non-inferiority to Laser Treatment. While it can be speculated that each study was underpowered to demonstrate non-inferiority, a definitive answer would require an additional clinical trial(s).

Proportion Analysis of Patients with Absence of Active ROP and Unfavorable Structural Outcomes at Week 52 of Chronological Age by ROP Status Subgroup (FAS)

FIREFLEYE

Baseline ROP Status	Treatment	Patients with absence of active ROP and unfavorable structural outcomes at Week 52	Difference (%) (95.1% CI)
Zone I	Aflibercept (N=15)	10/15 (67%)	9.5 (-34.4, 53.5%)
Zone I	Laser (N=7)	4/7 (57%)	
Zone II	Aflibercept (N=46)	39/46 (85%)	-3.7 (-19.8, 12.5)
Zone II	Laser (N=26)	23/26 (89%)	
AP-ROP	Aflibercept (N=14)	10/14 (71%)	-8.6% (-51.1, 33.9)
AP-ROP	Laser (N=5)	4/5 (80%)	

BUTTERFLEYE

Baseline ROP Status	Treatment	Patients with absence of active ROP and unfavorable structural outcomes at Week 52	Difference (%) (95.1% CI)
Zone I	Aflibercept (N=16)	11/16 (69%)	8.8 (-40.0, 57.5)
Zone I	Laser (N=5)	3/5 (60%)	
Zone II	Aflibercept (N=68)	56/68 (82%)	-2.7 (-20.8, 15.5)
Zone II	Laser (N=20)	17/20 (85%)	
AP-ROP	Aflibercept (N=9)	7/9 (78%)	27.8 (-47.0, 100.0)
AP-ROP	Laser (N=2)	1/2 (50%)	

Analysis is based on investigator assessment.

Secondary and Other Endpoints
Failure of the Primary Endpoint precludes testing of the secondary or other endpoints.

Non-inferiority vs Effectiveness
Failure of aflibercept administration to demonstrate non-inferiority to laser treatment does not necessarily mean that treatment with aflibercept is not effective. The natural history of ROP in this population has been studied in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (Arch Ophthalmol. 1990;106:1408-1416). The randomized, untreated control arm resulted in an unfavorable structural outcome in 50% of eyes.

FIREFLEYE Time to Recurrence of ROP (FAS)		
Kaplan-Meier estimated time (days)	Laser (N=38)	Aflibercept (N=75)
Number of Events	10	23
Number Censored	28	52
Mean (SE)	60.3 (3.8)	100.4 (4.0)
Median (95.1% CI)	NE (NE-NE)	NE (NE - NE)
25% - 75%	72-NE	(93 - NE)

BUTTERFLEYE Time to Recurrence of ROP (FAS)		
Kaplan-Meier estimated time (days)	Laser (N=27)	Aflibercept (N=93)
Number of Events	8	37
Number Censored	19	56
Mean (SE)	123.9 (13.30)	154.9 (8.73)
Median (95.1% CI)	NE (162.00 - NE)	NE (119.00 - NE)
25% - 75%	(34 - NE)	(81 - NE)

Patients will be counted as "event" if at least one eye satisfies the criteria. Recurrence of disease is defined as the reappearance of the disease requiring further treatment (including retreatment or rescue), where both "presence of ROP" and "presence of active ROP requiring treatment" are marked as "Yes", after initial regression. Here, the initial regression is defined as, at a particular visit, absence of ROP or ROP treatment not required for active ROP, i.e., presence of ROP is marked as "No" or the presence of active ROP requiring treatment is marked as "No". Patients who did not have an event were censored at their last visit at or before the Week 52 visit. Analysis is based on investigator assessment.

9. Review of Safety

Deaths

FIREFLEYE: There were 3 deaths reported, all in the aflibercept group. All 3 deaths were considered unrelated to the study intervention and assessed as related to pulmonary complications of preterm birth. The first participant experienced Bronchopulmonary dysplasia and Pneumothorax and died 60 days after receiving the last administration of study intervention (144 days from first treatment). The second participant experienced Bronchiolitis and died 57 days after the first and only administration of study intervention. The third participant experienced a TEAE of Bronchopulmonary dysplasia and died 29 days after receiving the last administration of the study intervention (61 days from the first drug administration).

BUTTERFLEYE: There was 1 death during the course of the study, reported in the aflibercept group. The death was considered secondary to multiple organ dysfunction syndrome. The dysfunction was reported on day 29 after the first and last (bilateral) administration of aflibercept, and the participant passed away 59 days after the first and last (bilateral) aflibercept administration

Summary of Ocular Treatment-Emergent Adverse Events in the Study Eye(s) per Participant

	FIREFLEYE	BUTTERFLEYE	FIREFLEYE	BUTTERFLEYE
	Laser	Laser	Aflibercept	Aflibercept
	(N=38)	(N=27)	(N=75)	(N=93)
Atrophy of globe				1 (1%)
Conjunctival hemorrhage			4 (5%)	5 (5%)
Conjunctival oedema			2 (3%)	
Conjunctivitis	4 (10.5%)		3 (4%)	
Corneal epithelial defect				1 (1%)
Corneal infiltrate		1 (4%)		
Corneal oedema	1 (3%)		1 (1%)	
Corneal opacity		1 (4%)		
Epiretinal membrane			1 (1%)	
Eye hemorrhage				2 (2%)
Eyelid oedema	3 (8%)	1 (4%)	2 (3%)	
Hyphema		1 (4%)		
Injection site hemorrhage			3 (4%)	
Intraocular pressure increased			3 (4%)	
Iris adhesions	1 (3%)			
Iris vascular disorder		1 (4%)		
Keratitis			1 (1%)	
Lenticular opacities			1 (1%)	
Nystagmus				1 (1%)
Retinal artery occlusion			1 (1%)	

Retinal detachment	2 (5%)	2 (7%)	4 (5%)	6 (6.5%)
Retinal hemorrhage	5 (13%)	1 (4%)	5 (7%)	3 (3%)
Retinal neovascularization			1 (1%)	
Retinal vascular disorder			1 (1%)	
Subretinal fluid		1 (4%)		
Swelling of eyelid		1 (4%)	1 (1%)	
Vitreoretinal traction syndrome			1 (1%)	
Vitreous hemorrhage	1 (3%)		1 (1%)	3 (3%)
Vitreous opacities			1 (1%)	

Summary of Non-ocular Treatment-Emergent Adverse Events in Participants (limited to events which occurred in 2 or more subjects in one of the clinical trials

	FIREFLEYE	**BUTTERFLEYE**	**FIREFLEYE**	**BUTTERFLEYE**
	Laser	**Laser**	**Aflibercept**	**Aflibercept**
	(N=38)	**(N=27)**	**(N=75)**	**(N=93)**
Anemia	2		1	3
Apnea	3	4	2	2
Bacterial disease carrier	2			
Bradycardia			2	3
Brain stem auditory evoked response abnormal			2	
Bronchiolitis	1		2	
Bronchopulmonary dysplasia			2	6
Chronic respiratory disease			1	2
Dermatitis diaper	1		2	
Gastrooesophageal reflux disease	1	2	1	3
Generalized edema		1		2
Hemorrhage subcutaneous	3			
Hypoxic-ischemic encephalopathy			2	
Infantile apnea	2			
Inguinal hernia	1	2	2	6
Oral fungal infection	1		1	2
Osteopenia			2	
Otoacoustic emissions test abnormal			2	
Oxygen saturation decreased			3	
Pyrexia			3	2
Rash				3
Rhinitis	1		2	
Seizure				2
Tachypnoea			1	2
Umbilical hernia	3		2	5

Immunogenicity

In BUTTERFLEYE, immunogenicity samples were collected at baseline and Week 12 to determine the presence of anti-aflibercept antibodies in serum. No treatment-emergent/treatment-boosted ADA responses were observed through Week 12.

In FIREFLEYE, immunogenicity samples were collected at baseline and Week 12 to determine the presence of anti-aflibercept antibodies. Treatment-emergent ADA was reported in one patient (1%) in the aflibercept group at Week 12, and the ADA titer was low (1:30). No neutralizing antibody response was observed in this patient.

Adverse Events reported with Pediatric Use excluding submitted clinical trials

While aflibercept has not been approved for the treatment of retinopathy of prematurity, the availability of aflibercept for variety of other indications has led to its use in treating retinopathy of prematurity. The post-market reporting of adverse events for all indications has led to a cumulative total database of 4017 cases. Of these 4017 cases, 3861 cases were confirmed to describe patients 18 years of age or older or included patients with no reported age in an indication not specific to pediatric patients. Thus, these cases are excluded from this analysis. The remaining 156 cases either included a pediatric patient or were cases with a patient of unknown age using aflibercept for a pediatric indication, specifically retinopathy of prematurity (ROP).

Pediatric Cases
For the 156 pediatric cases, 61 were from spontaneous sources, 51 cases were from literature, and 44 cases were listed as being from observational study sources. The indications for these 156 cases were typically retinal and choroidal neovascularization and conditions seen in ROP. On review of the reported Preferred Terms (PT) and narratives, retinopathy of prematurity was the reported indication in 67 cases. Six cases included events with a fatal outcome. All 6 cases had the indication of ROP.

Retinopathy of Prematurity
Out of the 67 cases in patients with ROP, 29 cases were reported from spontaneous sources and 38 cases were reported from literature or as published reports [Turkey (27), Taiwan (8) Iran (2) & Portugal (1)]. Age range for these cases included premature infants from 5 weeks to 38 weeks. The dose per injection, (information provided in 12 cases), ranged from 0.4 mg to 2 mg per injection. The most frequently reported PTs in these ROP cases were those indicative of off-label use (71) (including the PTs off-label use, product use in an unapproved indication (29), and product administered to patient of unapproved indication (19) and product use issue (13)). Most cases included only events reflective of the off-label use with no other adverse events reported.

The most frequent adverse event PTs where an AE occurred in more than one patient (outside

of product use events described above) were iris vascular disorder (n=4), pupil fixed (n=4), retinal neovascularization (n=4), bronchopulmonary dysplasia (n=4), patent ductus arteriosus (n=3), fetal exposure during pregnancy (3), brain injury (2), central nervous system hemorrhage (n=2), intraocular pressure increased (n=2), intraventricular hemorrhage (n=2) neonatal candida infection (n=2), necrotizing colitis (2), pneumonia (2), and posthemorrhagic hydrocephalus (2). Of the 14 serious cases, 6 cases included events with a fatal outcome. The 8 remaining serious cases included:

- 2 cases of cataract (1 cataract subcapsular and 1 lenticular opacities in infants of unstated age)
- 2 cases of ROP (1 where there was a recurrence of ROP in an infant of 46 weeks of age and 1 where the seriousness criterion was hospitalization in an infant of unstated age)
- 1 case of retinal hemorrhage after needle insertion into the eye of an infant of unknown age
- 1 case of a 14-week-old premature infant who experienced hypertension at birth due to renal artery stenosis and was treated with intravitreal injection of aflibercept for aggressive posterior ROP.
- 1 case of eye disorder described as a calcification on the ridge (eye) in an infant of unstated age
- 1 case of endophthalmitis occurred in an infant of unstated age 4 days after receiving aflibercept for ROP. The case of endophthalmitis was culture negative.

Fatal Cases

There was a total of 6 pediatric cases associated with fatal outcome. All 6 cases were spontaneous reports from Russia and included infants with ROP treated with intravitreal injection of aflibercept. The adverse events where fatal outcome was reported in these 6 cases were bronchopulmonary dysplasia (4), patent ductus arteriosus (3), central nervous system hemorrhage (2), intraventricular hemorrhage (2), neonatal candida infection (2), posthemorrhagic hydrocephalus (2), necrotizing colitis (2), brain injury (2), pneumonia (2) general physical health deterioration, hydrocephalus, congenital pneumonia, ventricular septal defect, anemia neonatal, sepsis neonatal, pneumonia, CNS ventriculitis, encephalitis, pulmonary artery stenosis, trisomy 21, foot deformity, cerebral ischemia, somatic symptom disorder, meningitis, ascites, hepatitis, thrombocytopenia, gastrointestinal disorder, inguinal hernia, and neonatal disorder (1 each). These fatal events are consistent with the systemic complications of the comorbidities associated with ROP.

Two cases were literature reports from Turkey in patients receiving bilateral injections of 1 mg/0.025 mL of aflibercept in each eye for ROP. Events of increased IOP resolved in all 3 cases.

10.Systemic Blood Levels

Pharmacokinetics Assessment from FDA's Clinical Pharmacology Group

The systemic PK of aflibercept in pediatric patients with ROP who received IVT dose of 0.4 mg aflibercept per eye either unilaterally or bilaterally were assessed in BUTTERFLEYE and FIREFLEYE. In BUTTERFLEYE, the mean concentrations of free aflibercept in plasma declined from a maximum of 583 ng/mL at day 1 to 40.6 ng/mL at day 28 in bilaterally-treated patients. In unilaterally-treated patients, the mean concentrations of free aflibercept were approximately 78% lower on day 1 and similar on day 28 when compared to bilaterally-treated patients. In FIREFLEYE, the mean concentrations of free aflibercept, for all patients who were either bilaterally or unilaterally treated, declined from a maximum of 481 ng/mL at day 1 to concentrations below or close to the lower limit of quantification (LLOQ; 15.6 ng/mL) within approximately 8 weeks. In comparison to adult patients with wet AMD who received a 2 mg IVT dose in one eye, the mean concentrations of aflibercept in pediatric patients were higher.

Comparisons of systemic exposure (Cmax in ng/mL) in premature infants and adults

		Premature Infants			Adults	Adults
Study	FIREFLEYE		BUTTERFLEYE		VGFT-OD-0702	PDY6656
Dose	0.4 mg IVT/eye				2 mg IVT	1 mg/kg IV
	Bilaterally -treated	Unilaterally -treated	Bilaterally -treated	Unilaterally -treated	Unilaterally -treated	
N	69	6	81	10	6	12
Free aflibercept Median (range)	249 (0-4570)	181 (29-351)	258 (0-5760)	137 (36-837)	15.0 (0-54.0)	17600 (13000 - 24700)
Adj. Bound aflibercept Median (range)	1291 (0-5887)	810 (306-1090)	1047 (0-3370)	1133 (539-1513)	193 (100-286)	1190 (989 - 1540)

1. Concentrations below the LLOQ (0.0156 mg/L) are set to zero for mean calculation.
2. Source: Table 2, Module 2.5; reviewer's analysis from Tables 4 and 9 20090-BA-01V1; reviewer's analysis from adpcrs.xpt VGFTe-ROP-1920-CP-01V1; Tables 3.4.2.2 and 3.4.2.4 VGFT-OD-0702.PK; Tables 46 and 49 PDY6656

11.Ongoing Studies

In an effort to learn more about the longer term (i.e., >52 week) consequences of intravitreal treatment with aflibercept, FIREFLEYE and BUTTERFLEYE each have 4-year follow-up extensions.

FIREFLEYE NEXT study (Trial No. 20275); Sponsor Bayer AG
BUTTERFLEYE NEXT Study (VGFTe-ROP-2036), Sponsor: Regeneron Pharmaceuticals, Inc.
Multi-center studies to assess the long-term outcomes of patients previously diagnosed with ROP who were treated (with aflibercept and/or laser photocoagulation). No study treatments are defined to be administered or excluded from being prescribed. Any potential treatments are to be decided by the treating physician, according to local standards of care. Each patient is followed to 5 years of chronological age. Visits will be scheduled according to the patient's yearly birthday, with the last visit at the patient's 5th birthday (the visit window for visits 2-5 is -1 month / +3 months). Best corrected visual acuity (BCVA) and overall ophthalmological development will be evaluated. Safety will be assessed by monitoring and evaluation of adverse events (AEs), physical examinations, and vital signs. Neurodevelopment will be assessed by hearing tests and developmental scales.

12.Discussion of Treatment Options

The prevention and treatment of retinopathy of prematurity remains an unmet need. While the use of supplemental oxygen has been shown to be a contributing factor, it is not the only factor, and efforts to reduce its use has resulted in increases in premature infant mortality. The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) demonstrated an approximately 50% reduction in anatomically unfavorable outcomes with the use of cryotherapy. However, the anatomic outcomes frequently do not correlate with functional outcome and do account for loss of peripheral vision or increased high myopia. Peripheral retinal ablation by freezing was extensively replaced by transpupillary laser treatment in spite of very few head-to-head comparisons. Logistical considerations and reductions in pain, swelling and conjunctival incisions resulted in the shift to lasers. Laser treatment became the standard of care for the treatment of ROP until the introduction of intravitreal anti-VEGF treatments. Similar to cryotherapy, reductions in peripheral vision and increases in high myopia occur with laser treatment. Long term follow-up with either cryotherapy or laser reveals that functional vision at 5, 10 and 15 years has significant room for improvement.

Decreases in anatomic abnormalities as measured in the clinical trials described in this supplement are just one measure in the treatment of ROP. There are theoretical concerns of the systemic effect of anti-VEGF treatment in infants. Intravitreal administration of anti-VEFG treatments including aflibercept demonstrate that the biologic drug products reach the systemic circulation. While the levels are measurable, there has not been a definitive correlation with any adverse events in children. The trials submitted in this supplement did not demonstrate significant systemic adverse events through one

year, but it is not clear that all effects would be recognized with the complexities of medical conditions in these premature infants. The five-year follow-up may provide additional information.

Unlike peripheral ablation, intravitreal anti-VEGF treatment provides a change to the time course of ROP. Treatment with laser has less recurrence of signs of ROP and these recurrences occur within a shorter period of time. Treatment with anti-VEGF agents, therefore, necessitates more extended follow-up which must occur until there is full vascularization of the retina. Extended follow-up translates into additional examinations and examinations in older infants who are often more difficult to examine. The tradeoff for potentially maintaining peripheral vision and decreasing the incidence of high myopia is an extended period of clinical follow-up examinations under more difficult examination conditions and the risk of a late ROP recurrence with vision loss if the examinations are not regularly continued.

FIREFLEYE and BUTTERFLEYE failed to demonstrate the estimated rates of the primary endpoint. In some applications, this failure would be considered a fatal flaw. Such an application would not be considered for approval and the product would not include labeling for that indication. In the case of studies conducted in response to the FDA's written request, while the specific indication does not have to be approved, the labeling of the product must include information about the results of the studies.

The estimated rates used in planning FIREFLEYE and BUTTERFLEYE were based on previous studies with anti-VEGF treatments. These studies used to plan FIREFLEYE and BUTTERFLEYE were not necessarily as well controlled and structured as FIREFLEYE and BUTTERFLEYE. FIREFLEYE and BUTTERFLEYE failed to demonstrate that treatment with aflibercept was non-inferior to laser treatment in proportion of participants with absence of both active ROP and unfavorable structural outcomes at 52 weeks chronological age based on the investigator's assessment but did demonstrate that each treatment arm was superior to the known natural history of untreated ROP for that same endpoint. Compared to the expected natural history, there is a clear beneficial effect of using intravitreal treatment with aflibercept. In addition, ablation of the periphery such as laser or cryotherapy guarantees a loss of peripheral vision. A treatment which maintains peripheral vision such as aflibercept would be considered beneficial.

13.Advisory Committee Meeting

A meeting of the Dermatologic and Ophthalmic Advisory Committee is scheduled for January 9, 2023. The committee will discuss supplemental biologics license application (sBLA) 125387, aflibercept solution for intravitreal injection, submitted by Regeneron Pharmaceuticals, Inc. The supplement was submitted in response to FDA's pediatric written request. FDA's written request was for studies of aflibercept in the treatment of retinopathy of prematurity.

The Agency is interested in hearing from the committee their comments on how the studied use of aflibercept in the treatment of retinopathy of prematurity can best be communicated to physicians and the caregivers of these premature infants.

Use of aflibercept in the treatment of ROP requires adjustments in the monitoring frequency of premature infants compared to treatment with laser. Description of this alteration in monitoring frequency is considered essential to the potential safe use of aflibercept in the treatment of ROP. In these clinical trials, the median time to recurrence of ROP was longer in subjects treated with aflibercept.

14.Labeling

Based on 505A(j) of the FD&C Act,

> "If, on or after September 27, 2007, the Secretary determines that a pediatric study conducted under this section does or does not demonstrate that the drug that is the subject of the study is safe and effective, including whether such study results are inconclusive, in pediatric populations or subpopulations, the Secretary shall order the labeling of such product to include information about the results of the study and a statement of the Secretary's determination."

Regeneron has conducted two clinical studies in response to the FDA's written request and proposed labeling in accordance with 505A(j) of the Food Drug and Cosmetic Act. The results of those clinical studies have been submitted as a supplement to their biologic license.

The Physician's Package Insert that follows is based on a submission by Regeneron with modifications proposed by the FDA. Highlighted sections represent additions to the currently approved labeling for Eylea (aflibercept). The proposed labeling changes are the principal subject of the January 9, 2023, Advisory Committee Meeting.

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

EYLEA® (aflibercept) Injection, for Intravitreal Use
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

Indications and Usage (1.5)	x/202~~x~~3
Dosage and Administration (2)	x/202~~x~~3

INDICATIONS AND USAGE

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:
Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1.1)
Macular Edema Following Retinal Vein Occlusion (RVO) (1.2)
Diabetic Macular Edema (DME) (1.3)
Diabetic Retinopathy (DR) (1.4)
Retinopathy of Prematurity (ROP) (1.5)

DOSAGE AND ADMINISTRATION

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

Macular Edema Following Retinal Vein Occlusion (RVO)
The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly). (2.3)

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

Retinopathy of Prematurity (ROP)
The recommended dose for EYLEA is 0.4 mg (0.01 mL or 10 microliters) administered by intravitreal injection. Treatment ~~is initiated with a single injection per eligible eye and~~ may be given bilaterally on the same day. ~~In total, u~~Up to 3 injections per eye may be administered from treatment initiation ~~up to one year of chronological age, if there are signs of disease activity~~. The treatment interval between doses injected into the same eye should be at least ~~4 weeks (at least~~ 28~~5~~ days~~)~~. (2.6)

DOSAGE FORMS AND STRENGTHS

- Injection: 2 mg/0.05 mL solution in a single-dose pre-filled syringe (3)
- Injection: 2 mg/0.05 mL solution in a single-dose vial (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased. (6.1)

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: x/202~~x~~3

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)

1.5 Retinopathy of Prematurity (ROP)

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions

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

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

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

EYLEA is available packaged as follows:

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

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

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

The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks [*see Clinical Studies (14.1)*]. Some patients may need every 4 week

(monthly) dosing after the first 12 weeks (3 months). Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.

2.3 Macular Edema Following Retinal Vein Occlusion (RVO)

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

2.4 Diabetic Macular Edema (DME)

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

2.5 Diabetic Retinopathy (DR)

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

2.6 Retinopathy of Prematurity (ROP)

The recommended dose for EYLEA is 0.4 mg (0.01 mL or 10 microliters) administered by intravitreal injection. Treatment is initiated with a single injection per eligible eye and may be given bilaterally on the same day. In total, up to 3 injections per eye may be administered from treatment initiation ~~up to one year of chronological age, if there are signs of disease activity~~. The treatment interval between doses injected into the same eye should be at least ~~4 weeks (at least~~ 28<u>5</u> days~~)~~ ~~[*see Clinical Studies (14.6)*]~~.

2.7 Preparation for Administration - Pre-filled Syringe

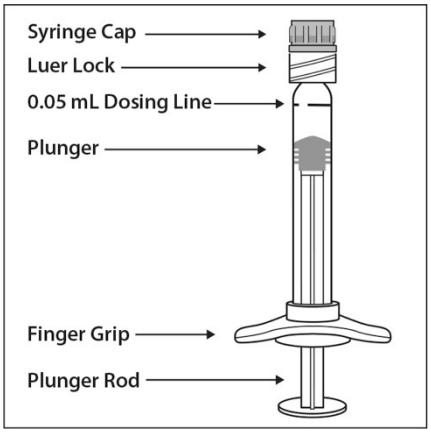
The EYLEA pre-filled glass syringe is sterile and for single use only. **Do not** use the EYLEA pre-filled syringe for the treatment of ROP.

The pre-filled syringe should be inspected visually prior to administration. **Do not** use if particulates, cloudiness, or discoloration are visible, or if the package is open or damaged. The appearance of the syringe cap on the pre-filled syringe may vary (for example, color and design). **Do not** use if any part of the pre-filled syringe is damaged or if the syringe cap is detached from the Luer lock.

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

The pre-filled syringe contains more than the recommended dose of 2 mg aflibercept (equivalent to 50 microliters). **The excess volume must be discarded prior to the administration.**

PRE-FILLED SYRINGE DESCRIPTION – Figure 1:



Use aseptic technique to carry out the following steps:

PREPARE

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

REMOVE SYRINGE

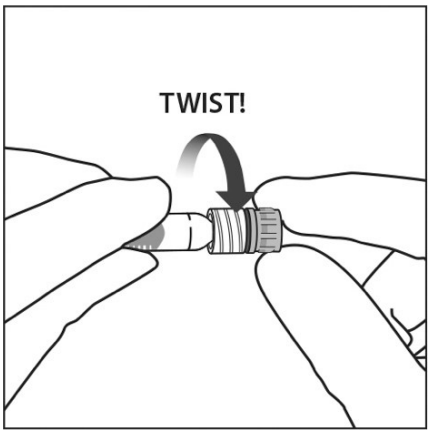
Using aseptic technique, remove the syringe from the sterilized blister pack.

TWIST OFF SYRINGE CAP

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

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

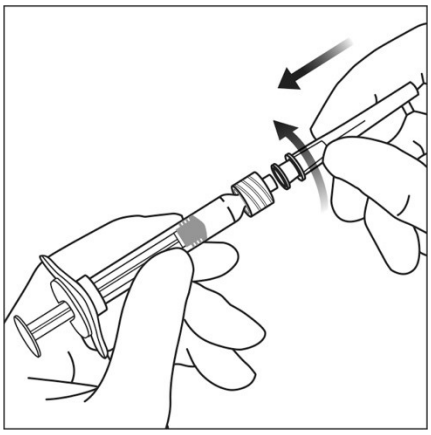
Figure 2:



ATTACH NEEDLE

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

Figure 3:

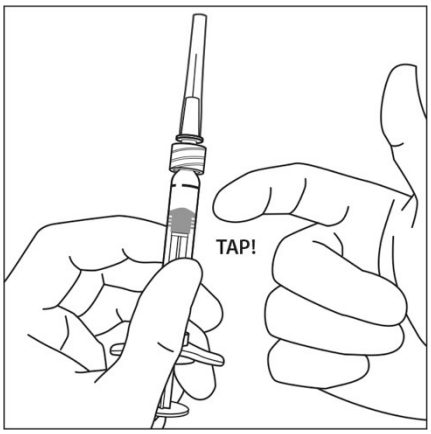


Note: When ready to administer EYLEA, remove the plastic needle shield from the needle.

DISLODGE AIR BUBBLES

Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 4).

Figure 4:



EXPEL AIR AND SET THE DOSE

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

Figure 5a:

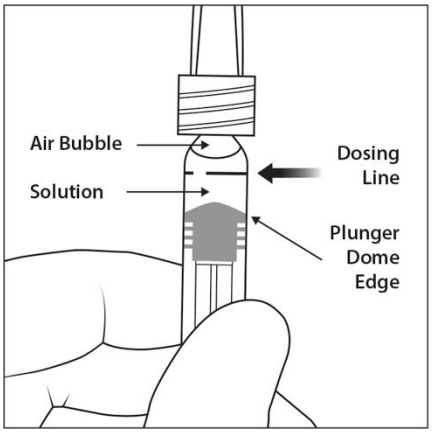
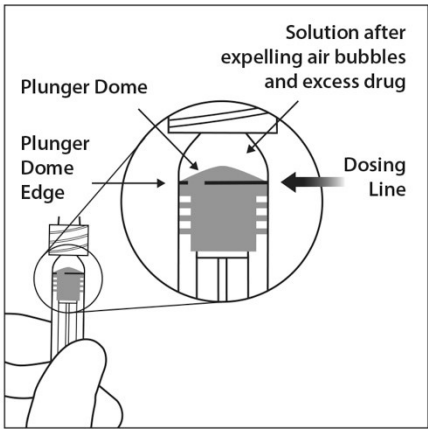


Figure 5b:



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

2.8 Preparation for Administration - Vial

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

The glass vial is for single use only.

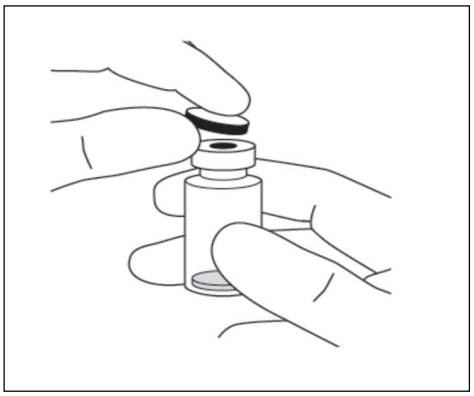
Use aseptic technique to carry out the following preparation steps:

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

- a 5-micron sterile filter needle (19-gauge × 1½-inch)
- a 1-mL sterile Luer lock syringe with marking to measure 0.05 mL for adults or 0.01 mL for pre-term infants with ROP
- a sterile injection needle (30-gauge × ½-inch)

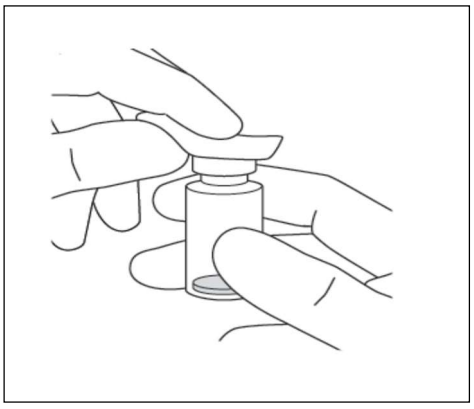
1. Remove the protective plastic cap from the vial (see Figure 6).

Figure 6:



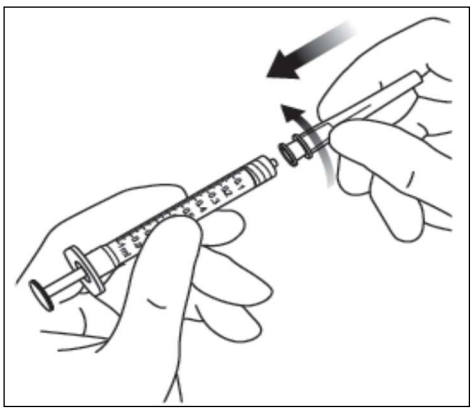
2. Clean the top of the vial with an alcohol wipe (see Figure 7).

Figure 7:



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

Figure 8:



4. Push the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.
5. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid (see Figure 9a and Figure 9b).

Figure 9a:

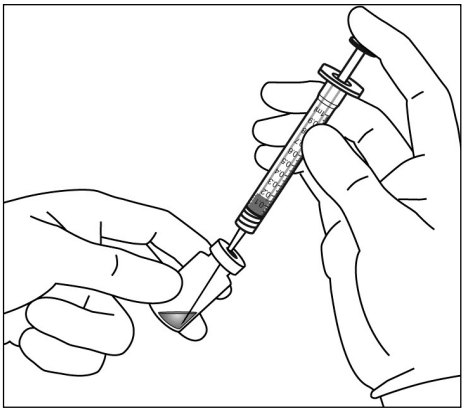
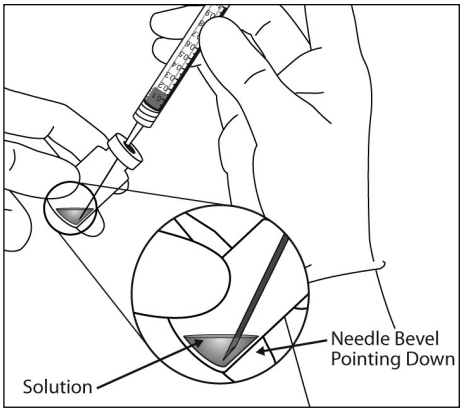
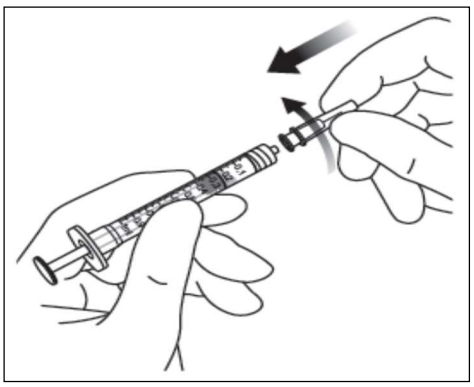


Figure 9b:



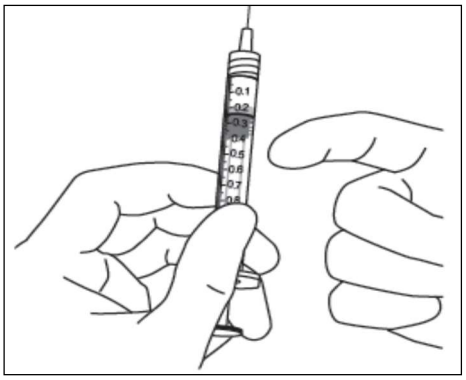
6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
7. Remove the filter needle from the syringe and properly dispose of the filter needle. **Note**: Filter needle is **not** to be used for intravitreal injection.
8. Remove the 30-gauge x ½-inch injection needle from its packaging and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip (see Figure 10).

Figure 10:



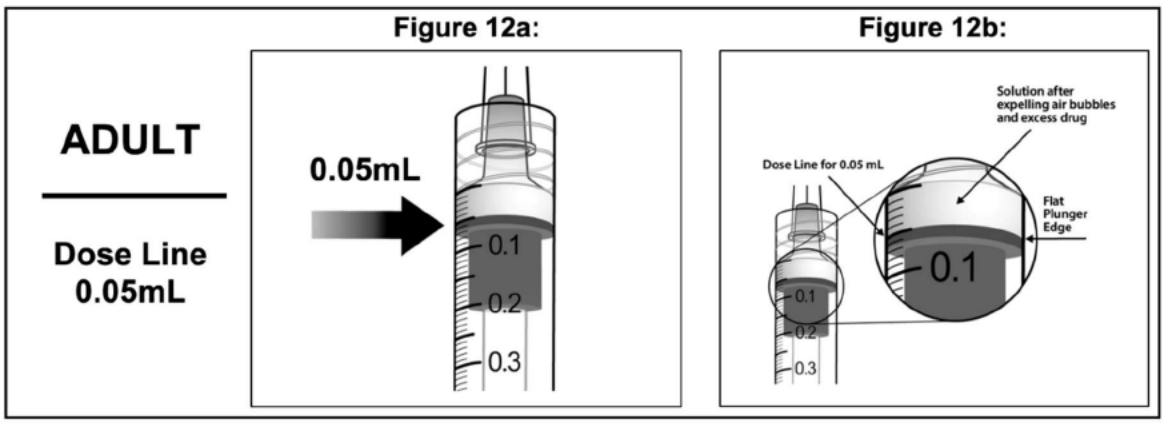
9. When ready to administer EYLEA, remove the plastic needle shield from the needle.
10. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 11).

Figure 11:



Administration in Adults:

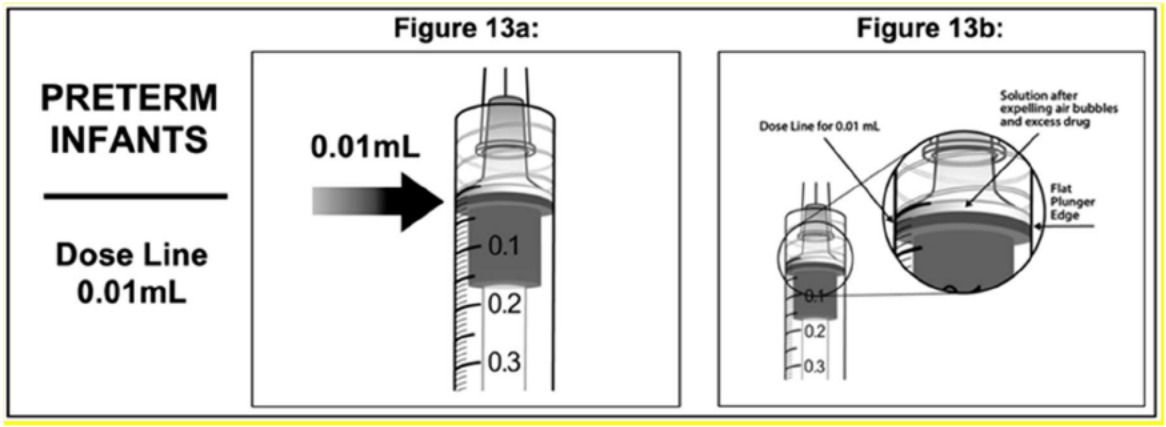
11. To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger rod so that the plunger edge aligns with the line that marks 0.05 mL on the syringe (see Figure 12a and Figure 12b).



Administration in pre-term infants with ROP:

Follow steps 1-10 listed above.

11.To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger rod so that the plunger edge aligns with the line that marks **0.01 mL** on the syringe (see Figure 13a and Figure 13b).



2.9 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.

Note for the pre-filled syringe: A small residual volume may remain in the syringe after a full dose has been injected. This is normal.

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

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

For the treatment of ROP, the injection needle should be inserted into the eye 1 mm from the limbus with the needle pointing towards the optic nerve.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.9) 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 (2.9)*].

5.3 Thromboembolic Events

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

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

Hypersensitivity [*see Contraindications (4.3)*]

Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]

Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]

Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

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

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

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

The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1) [*see Clinical Studies (14.1)*].

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

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

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

Adverse Reactions	Baseline to Week 52		Baseline to Week 96	
	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

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

- **Macular Edema Following Retinal Vein Occlusion (RVO)**

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

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

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

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

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

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

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

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

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

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

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

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

- **Retinopathy of Prematurity (ROP)**

The data described below reflect exposure to EYLEA in 168 pre-term infants with ROP randomized to EYLEA and treated with the 0.4 mg dose in 2 clinical studies (BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT) from time of first administration up to 52 weeks of chronological age [*see Clinical Studies (14.6)*]. Adverse reactions established for adult indications are considered applicable to pre-term infants with ROP, though not all were observed in the ~~Phase 3~~clinical studies.

Table 4: Adverse Reactions in ROP Studies

Adverse Reactions	Baseline to 52 weeks of chronological age BUTTERFLEYE		Baseline to 52 weeks of chronological age FIREFLEYE/FIREFLEYE NEXT	
	EYLEA (N=93)	Laser (N=27)	EYLEA (N=75)	Laser (N=28)
Retinal detachment	6~~.5~~%	7~~.4~~%	5~~.3~~%	5~~.3~~%
Conjunctival hemorrhage	5~~.4~~%	0%	5~~.3~~%	0%
Injection site hemorrhage	0%	0%	4~~.0~~%	0%
Intraocular pressure increased	0%	0%	4~~.0~~%	0%
Corneal epithelium defect	1~~.1~~%	0%	0%	0%
Eyelid edema	0%	~~3.74~~%	~~2.73~~%	~~7.98~~%

Adverse Reactions	Baseline to 52 weeks of chronological age BUTTERFLEYE		Baseline to 52 weeks of chronological age FIREFLEYE/FIREFLEYE NEXT	
	EYLEA (N=93)	Laser (N=27)	EYLEA (N=75)	Laser (N=28)
Corneal edema	0%	0%	1~~.~~3%	~~2.~~63%
Lenticular Opacities	0%	0%	1~~.~~3%	0%

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

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

Data

- *Animal Data*

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

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in adult patients after a single intravitreal dose of 2 mg.

8.2 Lactation

Risk Summary

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

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

8.3 Females and Males of Reproductive Potential

Contraception

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

Infertility

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

8.4 Pediatric Use

The safety and effectiveness of EYLEA have been demonstrated in pre-term infants with ROP.

Two ~~Phase 3~~, randomized, open-label, controlled studies while demonstrating a clinical course better than the expected natural history in untreated subjects, ~~were conducted to~~failed to demonstrate that ~~evaluate the safety and effectiveness of~~ EYLEA ~~compared to~~was non-inferior to laser photocoagulation in ~~245~~ the treatment of pre-term infants with ROP ~~until 52 weeks of chronological~~

~~age~~ *[see Dosage and Administration (2.6), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.6)]*.

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.

10 OVERDOSAGE

Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdosage, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

11 DESCRIPTION

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

EYLEA (aflibercept) Injection is a sterile, clear, and colorless to pale yellow solution. EYLEA is supplied as a preservative-free, sterile, aqueous solution for intravitreal injection in a single-dose pre-filled glass syringe or a single-dose glass vial designed to deliver 0.05 mL (50 microliters) of solution containing 2 mg of aflibercept in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, with a pH of 6.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

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

In the clinical studies anatomic measures of disease activity improved similarly in all treatment groups from baseline to week 52. Anatomic data were not used to influence treatment decisions during the first year.

- **Macular Edema Following Retinal Vein Occlusion (RVO)**

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

- **Diabetic Macular Edema (DME)**

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

~~**Retinopathy of Prematurity (ROP)**~~

~~An exploratory PK/PD analysis showed no relationship between systemic aflibercept concentrations and pharmacodynamic effects on blood pressure.~~

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

Pediatric Patients

Pharmacokinetics of aflibercept were evaluated in pre-term infants with ROP at a dose of 0.4 mg aflibercept (per eye) administered unilaterally or bilaterally. In the BUTTERFLEYE study, mean concentrations of free aflibercept in plasma declined from a maximum of 0.583 mcg/mL at Day 1 to 0.0406 mcg/mL at Day 28 in bilaterally treated patients.

In the FIREFLEYE~~/FIREFLEYE NEXT~~ study, mean concentrations of free aflibercept in plasma for all patients (bilateral and unilateral administration combined) declined from a maximum of 0.481 mcg/mL at Day 1 to 0.13 mcg/mL at Day 28. Concentrations of free aflibercept in plasma subsequently declined to values below or close to the lower limit of quantitation within approximately 8 weeks.

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 dosage modification is required based on gender or in the elderly.

12.6 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. Similarly, in pediatric ROP studies, after unilateral or bilateral dosing, antibodies to EYLEA were detected in less than 1% of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity. ~~In the pediatric ROP studies, after unilateral or bilateral dosing with EYLEA 0.4 mg, antibodies to EYLEA were detected in less than 1% of patients for up to 12 weeks. Because of the low occurrence of ADA, the effect of these antibodies on the pharmacokinetics, safety, or effectiveness of aflibercept 0.4 mg per eye is unknown.~~

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at weekly doses ranging from 3 to 30 mg per kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm morphology and motility were observed at all dose levels. In addition, females showed decreased ovarian and uterine weight accompanied by compromised luteal development and reduction of maturing follicles. These changes correlated with uterine and vaginal atrophy. A No Observed Adverse Effect Level (NOAEL) was not identified. Intravenous administration of the lowest dose of aflibercept assessed in monkeys (3 mg per kg) resulted in systemic exposure (AUC) for free aflibercept that was approximately 1500 times higher than the systemic exposure observed in adult patients 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 adult patients after an intravitreal dose of 2 mg and 2-fold higher based on C_{max} when compared to corresponding values observed in pre-term infants from FIREFLEYE/FIREFLEYE NEXT. Similar effects were not seen in other clinical studies [*see Clinical Studies (14)*].

14 CLINICAL STUDIES

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

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with EYLEA) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 3 initial monthly doses (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); 3) EYLEA 0.5 mg administered every 4 weeks (EYLEA 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). Protocol-specified visits occurred every 28±3 days. Patient ages ranged from 49 to 99 years with a mean of 76 years.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Both EYLEA 2Q8 and EYLEA 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1.

Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in Table 5 and Figure 14 below.

Table 5: Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies

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

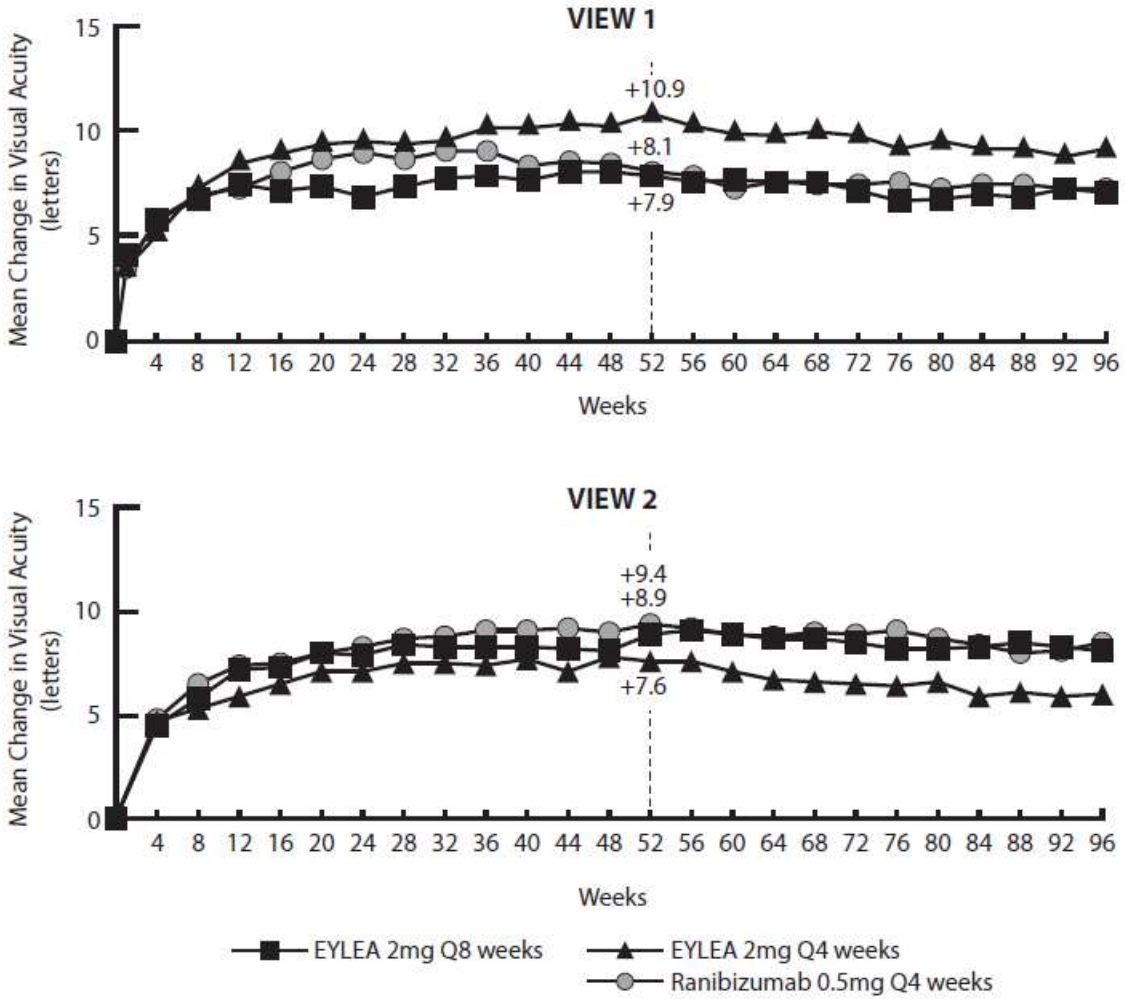
BCVA = Best Corrected Visual Acuity; CI = Confidence Interval; ETDRS = Early Treatment Diabetic Retinopathy Study; LOCF = Last Observation Carried Forward (baseline values are not carried forward); 95.1% confidence intervals were presented to adjust for safety assessment conducted during the study

[a] After treatment initiation with 3 monthly doses

[b] EYLEA group minus the ranibizumab group

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

Figure 14: Mean Change in Visual Acuity from Baseline to Week 96* in VIEW1 and VIEW2 Studies



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

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

14.2 Macular Edema Following Central Retinal Vein Occlusion (CRVO)

The safety and efficacy of EYLEA were assessed in two randomized, multi-center, double-masked, sham-controlled studies in patients with macular edema following CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with EYLEA) in the two studies (COPERNICUS and GALILEO). In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg EYLEA administered every 4 weeks (2Q4), or sham injections (control group) administered every 4 weeks for a total of 6 injections. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 22 to 89 years with a mean of 64 years.

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

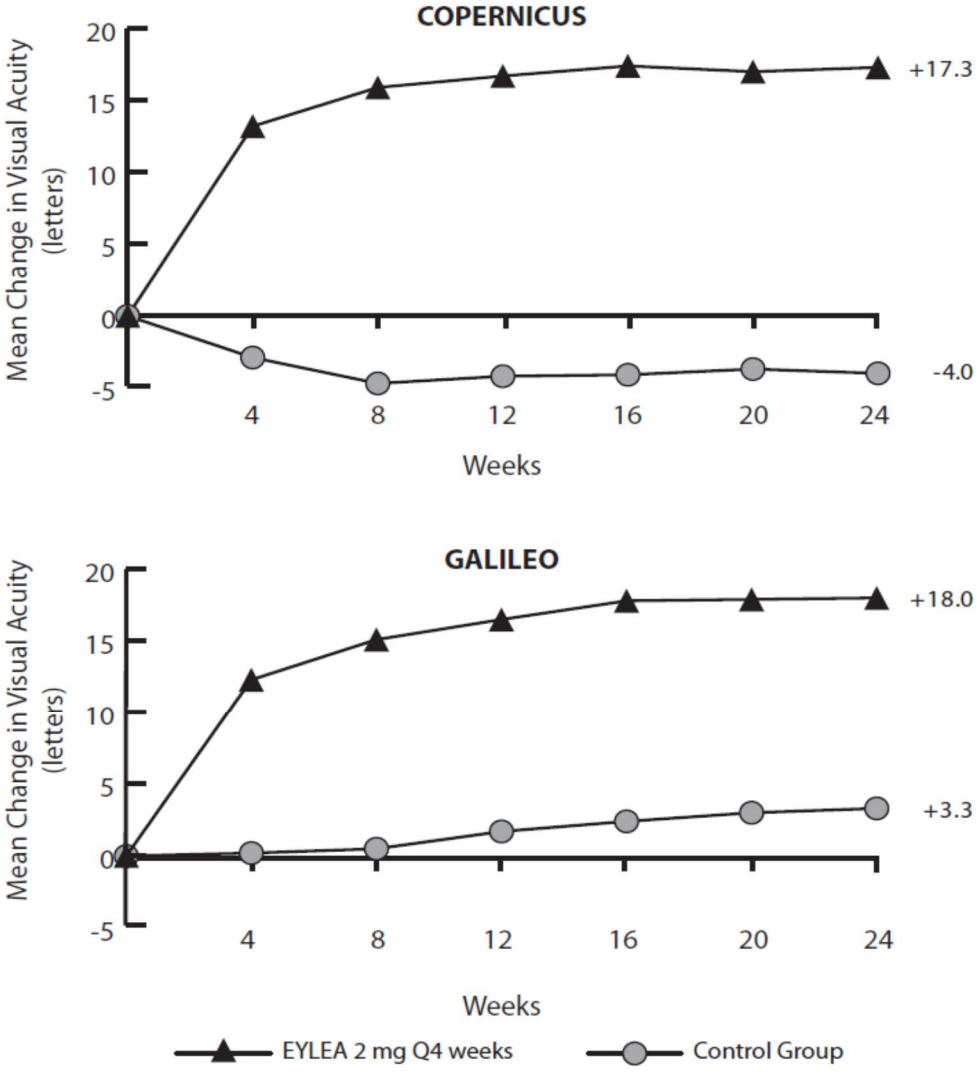
Results from the analysis of the COPERNICUS and GALILEO studies are shown in Table 6 and Figure 15 below.

Table 6: 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 15: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in COPERNICUS and GALILEO Studies



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

14.3 Macular Edema Following Branch Retinal Vein Occlusion (BRVO)

The safety and efficacy of EYLEA were assessed in a 24-week, randomized, multi-center, double-masked, controlled study in patients with macular edema following BRVO. A total of 181 patients were treated and evaluable for efficacy (91 with EYLEA) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg EYLEA administered every 4 weeks

(2Q4) or laser photocoagulation administered at baseline and subsequently as needed (control group). Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 42 to 94 years with a mean of 65 years.

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

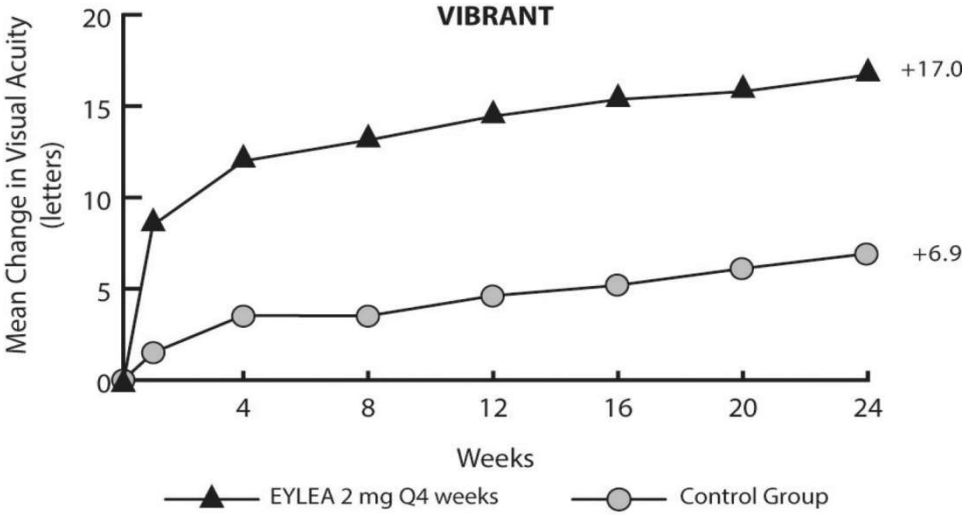
Detailed results from the analysis of the VIBRANT study are shown in Table 7 and Figure 16 below.

Table 7: 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 16: Mean Change in BCVA as Measured by ETDRS Letter Score from Baseline to Week 24 in VIBRANT Study



Treatment effects in evaluable subgroups (e.g., age, gender, and baseline retinal perfusion status) in the study were in general consistent with the results in the overall populations.

14.4 Diabetic Macular Edema (DME)

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

Of those, 576 were randomized to EYLEA groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) EYLEA administered 2 mg every 8 weeks following 5 initial monthly injections (EYLEA 2Q8); 2) EYLEA administered 2 mg every 4 weeks (EYLEA 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the EYLEA groups could receive laser and patients in the laser group could receive EYLEA.

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

Results from the analysis of the VIVID and VISTA studies are shown in Table 8 and Figure 17 below.

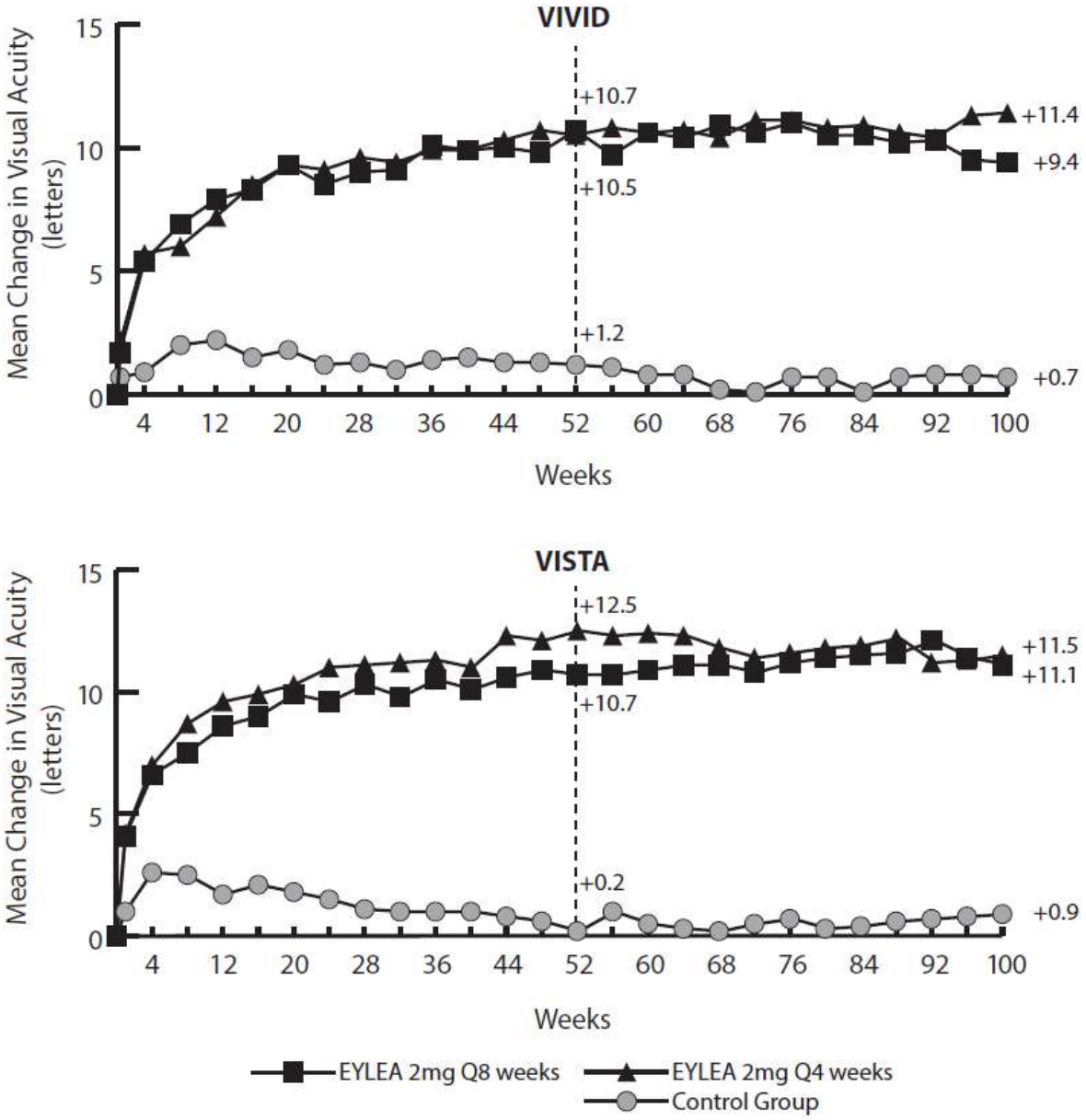
Table 8: Efficacy Outcomes at Weeks 52 and 100 (Full Analysis Set with LOCF) in VIVID and VISTA Studies

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



Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor prior to study participation were similar to those seen in patients who were VEGF inhibitor naïve prior to study participation.

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

14.5 Diabetic Retinopathy (DR)

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

VIVID AND VISTA

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

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

Results from the analysis of ETDRS-DRSS at week 100 in the VIVID and VISTA studies are shown in Table 9 below.

Table 9: Proportion of Patients Who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score at Week 100 in VIVID and VISTA Studies

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

Non-gradable post-baseline ETDRS-DRSS values were treated as missing and were imputed using the last gradable ETDRS-DRSS values (including baseline values if all post-baseline values were missing or non-gradable)
[a] After treatment initiation with 5 monthly injections
[b] The number of evaluable patients included all patients who had valid ETDRS-DRSS data at baseline
[c] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors
[d] Difference is EYLEA minus Control group

[e] p<0.01 compared with Control

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

PANORAMA

The PANORAMA study assessed the safety and efficacy of EYLEA in a randomized, multi-center, double-masked, controlled study in patients with moderately severe to severe nonproliferative diabetic retinopathy (NPDR) (ETDRS-DRSS of 47 or 53), without central-involved DME (CI-DME). A total of 402 randomized patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days for the first 5 visits, then every 8 weeks (56±7 days). Patient ages ranged from 25 to 85 years with a mean of 55.7 years.

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

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

At week 52, efficacy in the 2Q16 and 2Q8 groups was superior to the sham group (see Table 10 and Table 11). The proportion of patients with a ≥2-step improvement over time is shown in Figure 18.

Table 10: Proportion of Patients Who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score at Weeks 24 and 52 in PANORAMA

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

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

[a] Difference is EYLEA group minus sham

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

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

Figure 18: Proportion of Patients Who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score Through Week 52 in PANORAMA

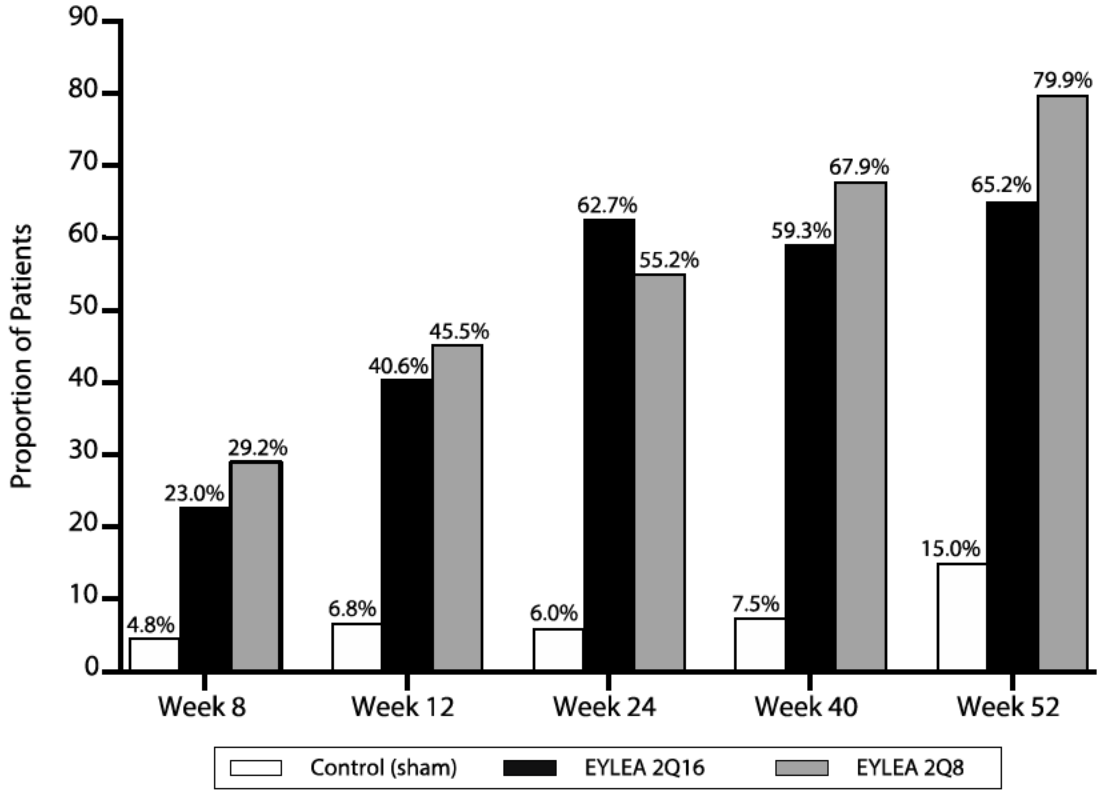


Table 11: Effect of EYLEA on Worsening of Diabetic Retinopathy in PANORAMA through Week 52

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

PDR = Proliferative Diabetic Retinopathy; ASNV = Anterior Segment Neovascularization
[a] As diagnosed by either the Reading Center or Investigator through week 52
[b] Estimated using Kaplan-Meier method
[c] Defined as ≥2-step worsening on the ETDRS-DRSS score through week 52
[d] p<0.01 compared with Control

14.6 Retinopathy of Prematurity (ROP)

Efficacy and safety data of EYLEA in ROP are derived from the BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT studies.

~~BUTTERFLEYE~~

~~The~~Both BUTTERFLEYE and FIREFLEYE stud~~y~~ies assessed the efficacy, safety and~~,~~ tolerability of EYLEA in ~~a~~ randomized, 2-arm, open-label, parallel-group stud~~y~~ies in pre-term infants with ROP in comparison to laser photocoagulation therapy (laser). Patients received study treatment at baseline per eligible eye. Additional treatment (re-treatment) and/or rescue treatment, if needed, was administered based on pre-specified criteria. ~~The FIREFLEYE study assessed the efficacy, safety and, tolerability of EYLEA in a randomized, 2-arm, open-label, parallel-group study in pre-term infants with ROP in comparison to laser photocoagulation therapy (laser) through 24 weeks of study duration.~~ FIREFLEYE NEXT was an observational follow-up Phase 3~~b~~, multi-center study which evaluated the ~~long term~~ Week 52 safety outcomes and visual function of patients included and treated in the FIREFLEYE study~~; data from patients from both FIREFLEYE/FIREFLEYE NEXT studies through week 52 of chronological age is presented. No study treatment was administered during FIREFLEYE NEXT.~~.

Eligible patients had a maximum gestational age at birth of 32 weeks or a maximum birth weight of 1500 g, ~~and~~ had to weigh >800 g on the day of treatment. ~~A total of 127 pre-term infants were randomized. Eligible patients~~ and had treatment-naïve ROP classified according to the International Classification for Retinopathy of Prematurity (IC-ROP 2005) in at least one eye with one of the following retinal findings:

ROP Zone 1 Stage 1+, 2+, 3 or 3+, or

ROP Zone II Stage 2+ or 3+, or

AP-ROP (aggressive posterior ROP)

The primary efficacy endpoint of each study was the proportion of patients with absence of active ROP and unfavorable structural outcomes (retinal detachment, macular dragging, macular fold, retrolental opacity) at week 52 of chronological age. ~~A key secondary endpoint included patients requiring intervention with a second treatment modality from baseline to week 52 of chronological age.~~

In BUTTERFLEYE, ~~P~~patients were randomized in a 3:1 ratio to receive 1 of 2 treatment regimens: 1) EYLEA 0.4 mg at baseline and if required, up to 2 additional injections ~~in each eye in case retreatment criteria were met~~and 2) laser photocoagulation in each eye at baseline and if required, retreatment ~~permitted, if criteria were met~~. In FIREFLEYE, patients were randomized to the same two treatments, but in a 2:1 ratio. Rescue treatment was administered if required, per pre-~~-~~specified criteria. In both studies, greater than ~~Eligible patients had a maximum gestational age at birth of 32 weeks or a maximum birth weight of 1500 g and had to weigh >800 g on the day of treatment.~~ 92~~.5~~% of all treated patients in the aflibercept group received bilateral injections during the study.

~~The primary efficacy endpoint was the proportion of patients with absence of active ROP and unfavorable structural outcomes (retinal detachment, macular dragging, macular fold, retrolental opacity) at week 52 of chronological age. A key secondary endpoint included patients requiring intervention with a second treatment modality from baseline to week 52 of chronological age.~~

~~FIREFLEYE/FIREFLEYE NEXT~~

~~The FIREFLEYE study assessed the efficacy, safety and, tolerability of EYLEA in a randomized, 2-arm, open-label, parallel-group study in pre-term infants with ROP in comparison to laser photocoagulation therapy (laser) through 24 weeks of study duration. FIREFLEYE NEXT was an observational follow-up Phase 3b, multi-center study which evaluated the long-term safety outcomes and visual function of patients included and treated in the FIREFLEYE study; data from patients from both FIREFLEYE/FIREFLEYE NEXT studies through week 52 of chronological age is presented. No study treatment was administered during FIREFLEYE NEXT.~~

~~A total of 118 pre-term infants were randomized in FIREFLEYE. Eligible patients had treatment naïve ROP classified according to the IC-ROP 2005 in at least one eye with one of the following retinal findings:~~

- ~~ROP Zone 1 Stage 1+, 2+, 3 or 3+, or~~
- ~~ROP Zone II Stage 2+ or 3+, or~~
- ~~AP-ROP (aggressive posterior ROP)~~

~~Patients enrolled in FIREFLEYE study were randomized in a 2:1 to receive 1 of 2 treatment regimens: 1) EYLEA 0.4 mg at baseline and if required, up to 2 additional injections in each eye in case retreatment criteria were met 2) laser photocoagulation in each eye at baseline and if required, retreatment permitted, if criteria were met. Eligible patients had a maximum gestational age at birth of 32 weeks or a maximum birth weight of 1500 g and had to weigh >800 g on the day of treatment. 94.7% of all treated patients in the aflibercept group received bilateral injections during the study.~~

~~The primary efficacy endpoint for the FIREFLEYE/FIREFLEYE NEXT study was the proportion of patients with absence of active ROP and unfavorable structural outcomes (retinal detachment, macular dragging, macular fold, retrolental opacity) at week 52 of chronological age. A key secondary endpoint included proportion of patients requiring intervention with a second treatment modality from baseline to week 52 of chronological age.~~

Results

Results from week 52 of chronological age in the BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT studies are shown in Table 12 below. EYLEA was not demonstrated to be non-inferior to Laser treatment.

Table 12: Efficacy Outcomes at Week 52 Chronological Age in BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT Studies

	BUTTERFLEYE[a]		FIREFLEYE/FIREFLEYE NEXT[a]	
	EYLEA 0.4 mg	**Laser**	**EYLEA 0.4 mg**	**Laser**
~~**All Randomized/ITT**~~[b]				
	~~N=94~~	~~N=33~~	~~N=75~~	~~N=43~~
~~**Efficacy Outcomes**~~				
~~Proportion of patients with absence of active ROP and unfavorable structural outcomes (%)~~	~~78.7%~~	~~63.6%~~	~~78.7%~~	~~72.1%~~
~~Adjusted Difference[e] (%) (95.1% CI)~~	~~14.90% (3.5, 33.3)~~		~~7.51% (8.50, 23.5)~~	
Full Analysis ~~Set~~[d]~~Set~~[c]				
	N=93	N=27	N=75	N=38
Efficacy Outcomes				

Proportion of patients with absence of active ROP and unfavorable structural outcomes (%)	79.6%	77.8%	78.7%	81.6%
Adjusted Difference[cb] (%) (95.1% CI)	1.81% (-15.7, 19.3)		-1.88% (-17.0, 13.2)	
~~Proportion of patients requiring intervention with second treatment modality from Baseline to Week 52 of Chronological Age (%)~~	~~15.1%~~	~~18.5%~~	~~13.3%~~	~~13.2%~~
~~Adjusted Difference[e](%) (95.1% CI)~~	~~3.66% (19.9, 12.5)~~		~~0.37% (13.6, 12.8)~~	

[a] In case of bilateral treatment, success was achieved only if both eyes met the primary endpoint. Treatment interval between 2 doses injected into the same eye had to be at least 28 days

~~[b] Included 6 patients in the laser group and 1 patient in the EYLEA group in the BUTTERFLEYE study and 5 patients from the laser group in FIREFLEYE/FIREFLEYE NEXT study that were randomized to their respective open label groups, but were withdrawn from the trial before study treatment~~

[cb] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by baseline ROP status. Success criterion: Lower limit of 95.1% CI above -5%

[dc] Included patients who were both randomized and treated from the BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT studies. This was the primary analysis population as defined in the Statistical Analysis Plans.

~~[e] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by baseline ROP status. Success criterion: Lower limit of 95.1% CI above 0%~~

16 HOW SUPPLIED/STORAGE AND HANDLING

Each pre-filled syringe or vial is for single eye use only. EYLEA is supplied in the following presentations [*see Dosage and Administration (2.7), (2.8), and (2.9)*].

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

– **Storage**

Refrigerate EYLEA at 2°C to 8ºC (36°F to 46ºF). Do not freeze. Do not use beyond the date stamped on the carton and container label. Store in the original carton until time of use to protect from light. Do not open sealed blister tray until time of use.

17 PATIENT COUNSELING INFORMATION

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

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U.S. License Number 1760

For patent information: https://www.regeneron.com/downloads/us-patent-products.pdf

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