CLINICAL SUMMARY REVIEW of BLA 125387/S-075

Application Type	Efficacy Supplement
Application Number	BLA 125387
Priority or Standard	Priority
Submit Date	August 11, 2022
Received Date	August 11, 2022
PDUFA Goal Date	February 11, 2022
Division/Office	Division of Ophthalmology/Office of Specialty Medicine
Reviewer Name	Wiley A. Chambers, MD
Review Completion Date	February 7, 2023
Established/Proper Name	Aflibercept
(Proposed) Trade Name	Eylea
Applicant	Regeneron Pharmaceuticals, Inc.
Dosage Form	Intravitreal Injection
Dosing Regimen	Single injection, 0.4 mg (0.01 mL), may be repeated
Proposed Indication	Retinopathy of Prematurity
Regulatory Action	Approval

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
eCTD	electronic common technical document

FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	post-marketing commitment
PMR	post-marketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

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

1.2. Conclusions on the Substantial Evidence of Effectiveness

In two adequate and well controlled trials, subjects treated initially with 0.4 mg of aflibercept administered intravitreally demonstrated reduced development of ROP compared to the expected natural history.

1.3. Benefit-Risk Integrated Assessment

Untreated Retinopathy of Prematurity (ROP) causes blindness. Current treatment modalities, (i.e., laser photocoagulation and cryo treatments) 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. The destruction of the peripheral retina leads to permanently reduced peripheral vision and increased myopia. Aflibercept inhibits VEGF resulting in a temporary prevention of ROP lesions. If the ROP lesions can be prevented long enough for physiological vascularization to be completed, vision loss due to ROP can be prevented. Because aflibercept only temporarily prevents ROP lesions, the necessary time for retinal monitoring is extended when aflibercept is administered.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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.
Current Treatment Options	Laser photocoagulation and cryo 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, slowing progression of ROP lesions.	Laser and cryo therapies are effective, but due to their destruction of peripheral retina, they lead to permanently reduced peripheral vision and increased myopia.
Benefit	Aflibercept inhibits VEGF, temporarily preventing the progression of ROP lesions.	Effective treatment requires prevention of the progression of ROP lesions until normal retinal vasculature has been completed.
Risk and Risk Management	Intravitreal injections introduce a risk for endophthalmitis. Delayed progression of ROP lesions require continued monitoring of the retina.	Use of aflibercept can avoid the need to destroy peripheral retina, but requires prolonged monitoring.

1.4. Patient Experience Data

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

☒	The patient experience data that was submitted as part of the application include:			Section where discussed
	☒	Clinical outcome assessment (COA) data, such as		
✓		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	7
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

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.

2.2. Analysis of Current Treatment Options

Laser photocoagulation and cryo 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 cryo therapies are effective, but due to their destruction of peripheral retina, they lead to permanently reduced peripheral vision and an increased incidence of myopia. Reduction in the use of oxygen is associated with increased mortality.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

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

Original: Treatment of neovascular (wet) AMD	11/18/2011
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

3.2. 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.

3.3. Foreign Regulatory Actions and Marketing History

EYLEA 0.4 mg dosing was approved for the treatment of retinopathy of prematurity (ROP) in Japan (2022). On November 10, 2022, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorization for the medicinal product Eylea. The marketing authorization holder for this medicinal product is Bayer AG. The CHMP adopted a new indication for the treatment of preterm infants with retinopathy of prematurity (ROP).

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

4.1. Office of Scientific Investigations (OSI)

From the Clinical Inspection Summary: The clinical sites of Drs. Ghorayeb and Cleland were inspected in support of this sBLA. Based on the results of these inspections, Protocol VGFTe-ROP-1920 appears to have been conducted adequately and the data generated by these sites appear acceptable in support of the respective indication.

4.2. Product Quality

For this supplement, there has been no change in the drug substance, drug product or route of administration. The dosing recommendation for ROP has been changed to give a smaller dose than the approved dose for the treatment of neovascular (wet) age-related macular degeneration. The recommended dose of EYLEA for the treatment of ROP is 0.4 mg (0.01 mL or 10 microliters) administered by intravitreal injection. The dose is recommended to be drawn from a vial. It is not recommended to be dosed from the pre-filled syringe to minimize the potential of giving a larger dose. Treatment is initiated with a single injection per eligible eye and may be given bilaterally on the same day. It may be repeated, if there are signs of disease activity, but the treatment interval between doses injected into the same eye should be at least 10 days.

4.3. Nonclinical Pharmacology/Toxicology

No significant new information.

4.4. Clinical Pharmacology

No significant new information.

4.5. Devices and Companion Diagnostic Issues

No changes from current approved product.

5. Sources of Clinical Data

Listing of Clinical Studies for the Aflibercept Pediatric Clinical Development Program

Study Identifier	Location of Study Report	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Randomized Number of Subjects	Diagnosis of Patients	Study Status and Type of Report
Clinical Study BAY 86-5321 / 20090 & 20275 (FIREFLEYE)	Module 5.3. 20090/20275 CSR	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).	Complete for final analysis. Final CSR This CSR includes pooled data from Study 20090 and from Study 20275 through 52 weeks CA.
VGFTe-ROP-1920 (BUTTERFLEYE)	Module 5.3.5.1 VGFTe-ROP-1920 CSR	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.	Complete for final analysis. Final CSR

6. Review of Relevant Individual Trials Used to Support Efficacy

Trial Design

Firefleye: Multicenter, Open-Label, Randomized, Two-Arm, Controlled, 24-week 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).

Butterfleye: Multicenter, Randomized, 2-arm, Open-label, 52-week, clinical study to assess the efficacy, safety, and tolerability of intravitreal (IVT) aflibercept versus laser in participants with retinopathy of prematurity (ROP).

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

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.

Study Endpoints
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.

Power and Sample Size

From the RAINBOW study [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). *Lancet* 2019; 394: 1551–59. Published Online September 12, 2019.http://dx.doi.org/10.1016/S0140-6736(19)31344-3] an open-label randomized controlled trial, the response rate was 66% for the laser group. The response rate was 80% for Zones I and II, and 88% in Zone II for the 0.2 mg ranibizumab group. Based on the clinical evidence for aflibercept investigator-initiated studies, the response rates 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 intravitreal aflibercept doses ranging from 0.4 mg to 1 mg. An estimated 90% response rate for the aflibercept group and 66% response rate for the laser group was used to power Butterfleye and Firefleye. 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. The protocol projected efficacy estimates turned out to be inaccurate.

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 majority of participants met the primary endpoint. The primary and secondary 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%.

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.

The primary endpoint (non-inferiority to the control) was not met in either study; 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		Aflibercept	
	(N=38)		(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		Aflibercept	
	(N=27)		(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 (N=72 eyes)		Aflibercept (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 (N=50 eyes)		Aflibercept (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%

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. 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% [68%, 87%])	-1.9% (-17%, 13%)
Laser	(N=38)	31/38 (82%)	

BUTTERFLEYE VGFTe-ROP-1920			**Difference (95% CI)**
Aflibercept	(N=93)	74/93 (80% [70%,87%])	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 exceeded the 5% limit, and therefore aflibercept failed 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.

7.2. Secondary and Other Endpoints

Primary Endpoint failed, precluding evaluation of the secondary endpoints.

7.3. 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 approximately 50% of eyes.

7.4 Time to Recurrence of ROP needing further treatment

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)

NE=Not able to be calculated. 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.

As noted above, compared to peripheral ablation, intravitreal anti-VEGF treatment provides a change (longer) 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.

8. Review of Safety

8.1. 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 treatment emergent adverse event (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

8.2. 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%)	

8.3. 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

8.4. 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.

8.5. Adverse Events reported with Pediatric Use excluding submitted clinical trials

While aflibercept had not been approved for the treatment of retinopathy of prematurity, the availability of aflibercept for a variety of other indications 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.

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.

8.6. Off-label Use in Subjects with ROP

Concerning the off-label use of aflibercept in patients with ROP, as of 15 May 2022, a total of 67 cases reporting 53 non-serious and 14 serious events were reported. 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 preferred terms (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.

9. Financial Disclosure

Covered Clinical Study (Name and/or Number): VGFTe-ROP-1920 (BUTTERFLEYE)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 436		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in: 0		

Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided?	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason?	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 20090 and 20275 Firefleye/Firefleye Next

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 533		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided?	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason?	Yes ☒	No ☐ (Request explanation from Applicant)

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 area with unmet needs. While the use of supplemental oxygen has been shown to be a contributing factor, it is not the only factor, and efforts to reduce the use of oxygen 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.

There are a number of differences between laser treatment and pharmacologic treatment with respect to the time needed to administer each treatment and required ancillary treatments. Laser treatment commonly requires 1-2 hours to perform, often with the infant under general anesthesia. Infants needing treatment are not always sufficiently stable from a general medical condition to be placed under anesthesia. Injections of aflibercept are more commonly performed in 10-30 minutes and usually do not need general anesthesia.

Laser and pharmacologic treatments are not mutually exclusive. Pharmacologic treatments can be used to delay the development of ROP, allowing normal retina development to extend further into the periphery, decreasing the area of risk. If laser can be directed to a smaller peripheral area, the loss of peripheral vision decreases as does the chance of developing high myopia.

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 pre-study 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. The 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 the proportion of participants with absence of both active ROP (ROP needing additional treatment) and unfavorable structural outcomes at 52 weeks chronological age. This endpoint was based on the investigator's assessment. Considering the expected poor outcome of no treatment, there was not a direct comparison to the 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 (approximately 79% for aflibercept [95% Confidence interval of 72% to 85%] vs approximately 50% as the natural history). 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 was held on January 9, 2023. The committee discussed supplemental biologics license application (sBLA) 125387, aflibercept solution for intravitreal injection, submitted by Regeneron Pharmaceuticals, Inc. for the treatment of ROP. The Agency was interested in hearing from the committee their comments on how the studied use of aflibercept in the treatment of retinopathy of prematurity could best be communicated to physicians and the caregivers of these premature infants.

The discussion from the committee included suggestions for revisions to the draft labeling including:

1. describing benefits and warnings with the use of laser and aflibercept treatment,
2. how the use of aflibercept in the treatment of ROP requires adjustments in the monitoring frequency of premature infants compared to treatment with laser,
3. potential use of both aflibercept and laser in the same infant,
4. re-arrangement in the dosing instructions for ROP to be together in one section.

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 conducted two adequate and well controlled 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. The Office of Prescription Drug Promotion provided a consult review. The comments in the review have been considered but were not considered improvements in the understandability of the labeling. The highlights already include the most frequent adverse events. The majority of suggested additional events are due to the disease, not the treatment. There is no evidence that warnings suggested to be added in Section 2.4 would cause harm if not followed. Thrombotic events were not referenced as being associated with ROP because they were not observed. Immunogenicity was moved to 12.6 because it was not demonstrated to cause harm. The statement "Efficacy of each treatment is supported by the demonstration of a clinical course which was better than would have been expected without treatment" is not promotional, it is the reason that the product is considered to be efficacious. Anatomic endpoints are not discussed in the Pharmacokinetics section of the labeling because unlike the other endpoints, the anatomic endpoints are already discussed as the primary endpoint. There is no reference to DR studies in the Immunogenicity section because they were not separate studies. The indication is based on the DME studies.

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

15. Regulatory Conclusions

BLA 125387, Supplement 75, the additiona of an indication for the treatment of retinopathy of prematurity will be approved with the labeling submitted and included in this review.

Wiley A. Chambers, MD
Director, Division of Ophthalmology

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

/s/

WILEY A CHAMBERS
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