TREATMENT OF PROLIFERATIVE DIABETIC RETINOPATHY

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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Disclosure: The author is a paid consultant to and has an ongoing relationship with Regeneron and/or its affiliates.

INDICATIONS

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

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

Please see additional Important Safety Information throughout and Brief Summary of full Prescribing Information at the end of this article.

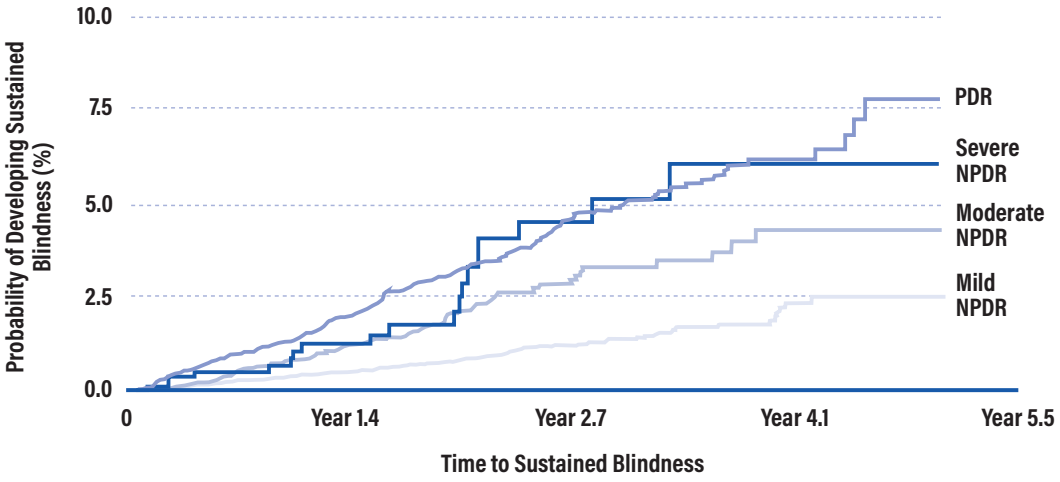
Introduction

The toll of proliferative diabetic retinopathy (PDR): severe vision loss

Diabetic retinopathy (DR) is the leading cause of new cases of blindness among adults aged 20 to 74 years in the United States.[1] DR may progress from nonproliferative diabetic retinopathy (NPDR), an often asymptomatic stage characterized by retinal microvascular damage, to a serious vision-threatening stage known as PDR. The hallmark of PDR is the proliferation of new blood vessels (neovascularization) in an attempt to supply oxygenated blood to the hypoxic retina.[2] About 52% of eyes with severe NPDR progress to PDR within 1 year and about 80% progress within 5 years.[3] The process of neovascularization in PDR is mediated in large part by vascular endothelial growth factor (VEGF), particularly VEGF-A,[4] and can lead to vitreous hemorrhage, retinal detachment, neovascular glaucoma, and severe vision loss.[2] Based on data from the National Health and Nutrition Examination Survey (NHANES) 2005–2008, approximately 1.5% of adults with diabetes had PDR.[1,5] Extrapolation to the overall population of 34.1 million adults with diabetes in the United States in 2018 suggests that more than 510,000 individuals in the United States may have PDR.[6]

PDR is more associated with sustained blindness than milder forms of NPDR. A retrospective cohort analysis of a large national registry included 53,535 eyes of adults with good vision at baseline who were newly diagnosed with DR. Of these 53,535 eyes, only 10.5% had PDR, but they accounted for 26.5% of eyes that developed sustained blindness within 2 years of diagnosis. Eyes with PDR at first diagnosis were 4.0 times more likely to develop sustained blindness 2 years after DR diagnosis compared with eyes with mild NPDR at diagnosis **(Figure 1)**.[7] In the aforementioned registry study, 12.0% of eyes in the analysis population had severe NPDR or PDR at first DR diagnosis,[7] underscoring the need for annual eye examinations in individuals with diabetes even in the absence of ocular symptoms or vision deficits.[8]

Figure 1. Probability of developing sustained blindness by DR severity at index[7]



American Academy of Ophthalmology (AAO) IRIS® (Intelligent Research in Sight) Registry records from January 1, 2013, through December 31, 2017; N=53,535 patients newly diagnosed with DR (n=678 evaluated for risk of sustained blindness). Risk of sustained blindness increased with development of glaucoma, age-related macular degeneration (AMD), retinal vein occlusion (RVO), diabetic macular edema (DME), vitreous hemorrhage, or retinal detachment. Sustained blindness defined as ≥2 visual acuity readings of 20/200 or worse ≥3 months apart; no improvement beyond 20/100 after first 20/200 reading.

Adapted from Wykoff et al. *Diabetes Care.* 2021;44:748-756.[7]

Socioeconomic, emotional toll, and increased mortality risk

Blindness due to PDR imposes a significant socioeconomic and emotional toll on patients and/or their caregivers. Estimated direct, indirect, and intangible (i.e., lost monetized quality-adjusted life-years) costs were $2 billion in 2020 and are projected to increase to approximately $6 billion by 2050.[9] The emotional toll is significant as well, affecting patients' independence, mobility, risk of fall, quality of life, and mental health.[2,10-13]

PDR can also increase mortality risk. In a retrospective comparative study of patients with diabetes undergoing vitrectomy surgery for tractional retinal detachments (N=316), the long-term all-cause mortality rate over 10 years was 48.7% (mean survival of 2.7 years) compared with a mean 2.0% in historical controls.[14,15]

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Treatment of PDR: The role of anti-VEGF therapy

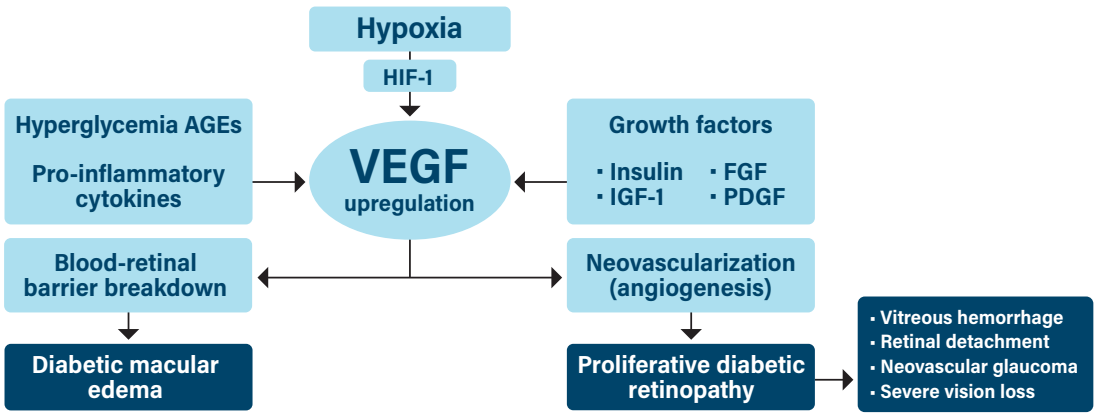
Current treatment options for PDR include panretinal photocoagulation (PRP) and intravitreal anti-VEGF therapy.[8,16,17] PRP has been the mainstay of PDR treatment for several decades since the Diabetic Retinopathy Study (1981) demonstrated a 50% reduction in the risk of severe vision loss in patients with high-risk PDR[17,18]; however, recent studies have elucidated the important role of VEGF in PDR and demonstrated the noninferiority and/or superiority of anti-VEGF agents compared with PRP in PDR.[19,20] As a result, anti-VEGF therapy, alone or in combination with PRP, is increasingly being used in PDR, and the use of PRP as monotherapy has correspondingly decreased.[21]

The increasing trend in anti-VEGF use in PDR is largely driven by treatment of patients with PDR and DME. Among patients with PDR included in the AAO IRIS Registry, use of anti-VEGF monotherapy increased from 25.0% in 2013 to 65.7% in 2017 in patients with DME but only increased from 21.1% to 32.9% in those without DME.[21] A large claims database analysis from 2020, including more than 280,000 patients with PDR without DME, suggested that 72% of these patients may be left untreated.[22] This can be of concern since patients with PDR are at higher risk for developing sustained blindness compared with patients with mild NPDR.[7]

Guidelines from the Diabetic Retinopathy Clinical Research (DRCR) Retina Network and the American Society of Retina Specialists (ASRS) support the use of anti-VEGF therapy as a first-line treatment option in PDR with or without DME.[16,17] In the DRCR Retina Network guidelines, anti-VEGF therapy is recommended first-line for PDR with center-involved diabetic macular edema (CI-DME) and may be considered first-line for PDR with non–CI-DME. In patients with PDR without DME, anti-VEGF and PRP can both be used as first-line treatment options.[16] According to the ASRS guidelines for the treatment of PDR without DME, anti-VEGF therapy and PRP may be used as first-line monotherapy or combination therapy.[17]

VEGF-A plays a key role in the neovascularization characteristic of PDR **(Figure 2)**.[4,23] Serum VEGF levels increase with increasing severity of DR. In a study by Ahuja and colleagues, serum VEGF levels were found to be a reliable biomarker of DR severity, with mean serum VEGF levels increasing with progression from mild NPDR to severe NPDR and PDR.[24] In another study, VEGF levels were found to be significantly higher in the aqueous humor of eyes with PDR than eyes with NPDR.[25]

Figure 2. Potential role of VEGF in the development of PDR[2,23]



AGE, advanced glycation end products; FGF, fibroblast growth factor; HIF-1, hypoxia inducible factor-1; IGF-1, insulin-like growth factor-1; PDGF, platelet-derived growth factor.

Treatment with anti-VEGF therapy

Intravitreal injections of anti-VEGF agents are designed to block the action of VEGF in the eye, helping to improve the severity of DR.[23,26-30] In patients with PDR, including those who do not have DME, anti-VEGF inhibitors may improve visual outcomes and DR severity.[19,20]

Anti-VEGF treatment may also influence patient behavior, as revealed in a retrospective review of IQVIA claims data from patients with PDR. Importantly, 70% of patients (n=2632) treated with anti-VEGF therapy and/or laser treatment for PDR followed up with their retina specialist or injecting ophthalmologist. In contrast, 63% of patients (n=1345) receiving only laser and 39% (n=4415) receiving no treatment returned for follow-up visits during the same time period (January 2020-December 2020).[22]

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

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EYLEA: Proven anti-VEGF therapy

EYLEA is an anti-VEGF therapy indicated for the treatment of DR.[31] EYLEA is a recombinant fusion protein of key domains from VEGF receptors 1 and 2. These key domains are fused to the fragment crystallizable (Fc) portion of human immunoglobulin G1 (IgG1), which acts as a decoy for the natural receptor necessary for binding VEGF-A and placental growth factor (PlGF) dimers.[31,32] EYLEA binds multiple isoforms of VEGF-A and PlGF to prevent their interaction with native VEGF receptors.[31,33]

The key goal in the treatment of DR, particularly PDR, is to stop or even reverse the progression of disease to help prevent vision loss. The efficacy of EYLEA in improving Diabetic Retinopathy Severity Scale (DRSS) scores at various stages of DR has been demonstrated in multiple clinical trials.[20,27-30] In the VISTA and VIVID trials, EYLEA was shown to reduce the severity of retinopathy and improve visual acuity in patients with DR with DME.[27] In the PANORAMA trial, EYLEA reduced the risk of progression to PDR in patients with moderately severe to severe NPDR without DME.[30,31] In patients with PDR without DME, intravitreal anti-VEGF therapy with aflibercept was studied in the CLARITY trial.[20,34] The results of these trials are discussed below.

Proven to improve best-corrected visual acuity (BCVA) in patients with DR and DME

VISTA and VIVID were phase 3 multicenter, randomized, double-masked, controlled studies in which all enrolled patients had DR with CI-DME at baseline. The majority of patients (77%) had moderate to severe NPDR based on the Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale (ETDRS-DRSS), and 4% had PDR.[27,31] The remainder either had retinopathy that was mild or could not be graded.[27] Patients were randomly assigned (1:1:1) to receive EYLEA 2 mg every 4 weeks (Q4), EYLEA 2 mg every 8 weeks (Q8) following 5 initial monthly doses, or macular laser photocoagulation (control).[27,31] The primary efficacy endpoint was the mean change from baseline in BCVA at Year 1, as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.[27] In VISTA, the mean gains were 10.7, 12.5, and 0.2 letters in patients treated with EYLEA Q8, EYLEA Q4, and the control group, respectively. In VIVID, the mean change in BCVA was 10.7 letters and 10.5 letters in the EYLEA Q8 and Q4 groups, respectively, vs 1.2 letters in the control group.[27,31] In patients treated with EYLEA at either dose, vision gains were maintained through Years 2 and 3.[28,29]

The change from baseline in ETDRS-DRSS score at Year 2 was evaluated as an exploratory secondary endpoint in the VISTA and VIVID studies.[27] At Year 2, the proportion of patients improving by ≥2 steps on the ETDRS-DRSS was significantly greater in both EYLEA treatment groups compared with the control group **(Table 1)**,[27,31] demonstrating the efficacy of EYLEA in reducing the severity of DR in patients with DME.

Table 1. Proportion of patients who achieved a ≥2-step improvement from baseline in ETDRS-DRSS score in the VISTA and VIVID trials[31]

Secondary Endpoint					
VISTA			VIVID		
EYLEA Q8* (n=148)	EYLEA Q4 (n=153)	Control (n=150)	EYLEA Q8* (n=101)	EYLEA Q4 (n=97)	Control (n=99)
38%†	38%†	16%	32%†	28%†	7%

*After treatment initiation with 5 monthly injections.
†$P<0.01$ vs control.

SELECT IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT'D)

- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- 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.

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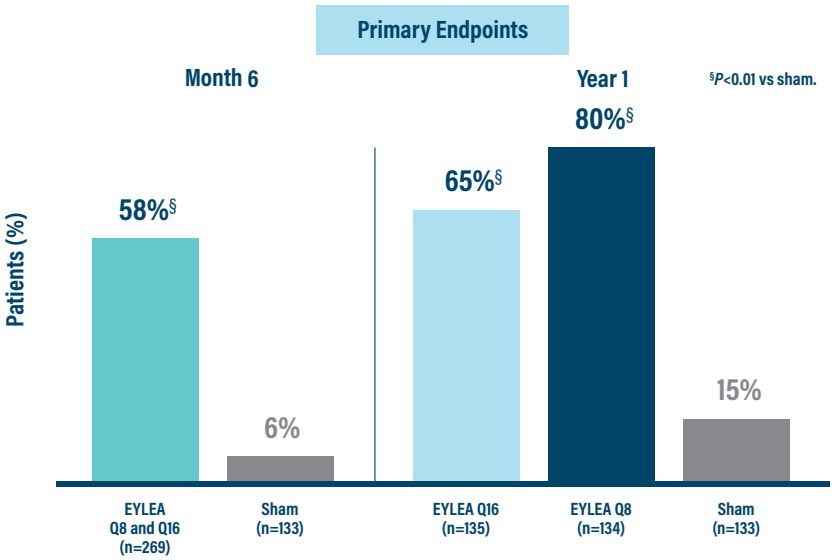
Proven to reduce DRSS scores in patients with NPDR without DME

In the PANORAMA trial, EYLEA was proven to reduce DRSS scores and significantly reduce the risk of progression to PDR in patients with untreated moderately severe to severe NPDR (DRSS level 47 or 53) without DME and prior to visual impairment.[30,31] This phase 3, randomized, multicenter, double-masked, controlled study (N=402) compared EYLEA with sham treatment. Patients were randomly assigned (1:1:1) to receive either EYLEA 2 mg every 16 weeks (Q16)—3 initial monthly injections, followed by 1 injection after 8 weeks, and then 1 injection Q16; EYLEA 2 mg Q8—5 initial monthly injections, followed by 1 injection Q8 through Year 1 (after Year 1, patients were switched to a different dosing regimen through Year 2); or sham treatment. The primary endpoint was the percentage of patients who improved by ≥2 steps on the DRSS from baseline to Month 6 (EYLEA combined vs sham) and Year 1 (Q16 and Q8 individually vs sham).[30,31]

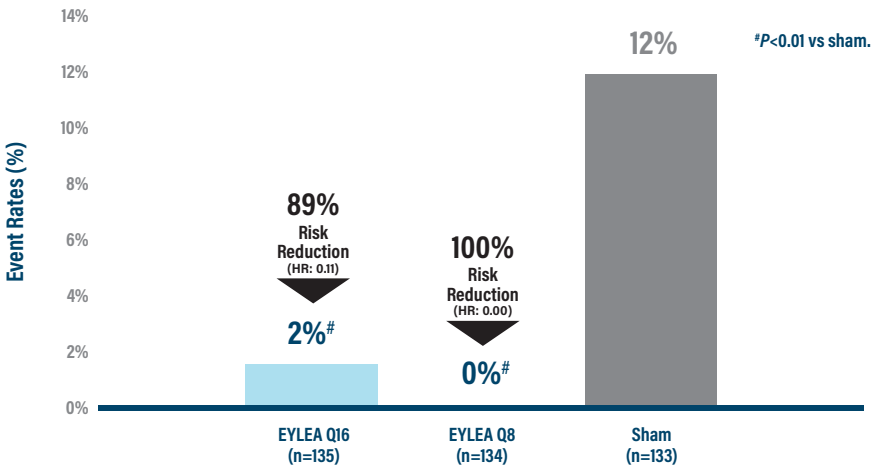
Significantly more patients receiving EYLEA vs sham treatment met the primary endpoint **(Figure 3)**, and these improvements were sustained at Year 2 (exploratory endpoint).[30,31] Among patients treated with EYLEA Q16, 62% had a ≥2-step improvement in ETDRS-DRSS at Year 2 vs 13% of patients treated with sham (nominal *P*<0.001).[30] Significantly less patients receiving EYLEA vs sham treatment progressed to PDR (defined as a ≥2-step worsening on the ETDRS-DRSS score through Year 1). The event rates were 1.6% in the EYLEA Q16 group, 0% in the EYLEA Q8 group, and 11.9% with sham treatment (*P*<0.01 for both EYLEA groups vs sham). This translates to an 89% reduction in the risk of progression to PDR with EYLEA Q16 (hazard ratio [HR]=0.11) and a 100% reduction with EYLEA Q8 (HR=0.00) at Year 1 **(Figure 4)**.[31]

Figure 3. Patients achieving a ≥2-step improvement from baseline in ETDRS-DRSS score at Month 6 and Year 1[30,31,‡]



‡Full analysis set.

Figure 4. Effect of EYLEA on development of PDR in patients with moderately severe to severe NPDR without DME[31,‖,¶]



‖Full analysis set.
¶Event rate was estimated using the Kaplan-Meier method.
Q16, 3 initial monthly injections followed by 1 injection after 8 weeks and then 1 injection every 16 weeks; Q8, 5 initial monthly injections, followed by 1 injection every 8 weeks at Year 1 and a different dosing regimen at Year 2.

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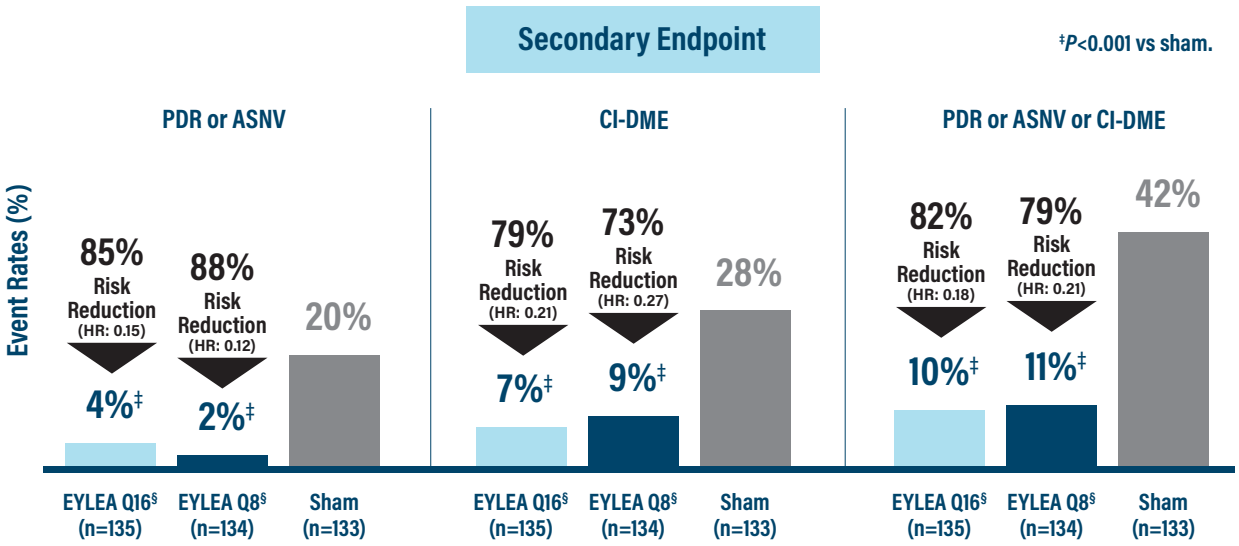
The event rates for the composite secondary endpoint of progression to PDR or anterior segment neovascularization (ASNV) were 4.0% and 2.4% in the EYLEA Q16 and Q8 groups, respectively, vs 20.1% in the sham group (*P*<0.01 for both EYLEA groups vs sham). In addition, EYLEA reduced the risk of progression to CI-DME, as well as the composite endpoint of progression to PDR or ASNV or CI-DME **(Figure 5)**.[30,31]

Figure 5: Cumulative incidence of progression to PDR, ASNV, or CI-DME at Year 1[30,31,*,†]



*Full analysis set.

†Event rate was estimated using the Kaplan-Meier method. Composite endpoint of developing PDR or ASNV was diagnosed by either the reading center or investigator through Year 2.

§Q16, 3 initial monthly injections followed by 1 injection after 8 weeks and then 1 injection Q16; Q8, 5 initial monthly injections, followed by 1 injection Q8 through Year 1 and a different dosing regimen at Year 2.

Safety profile consistent in DR with or without DME

Table 2. Most common adverse reactions (≥1%) in the VISTA and VIVID trials[31]

	Year 1		Year 2	
Adverse reaction	**EYLEA (n=578)**	**Control (n=287)**	**EYLEA (n=578)**	**Control (n=287)**
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Safety data observed in 269 patients with NPDR through Week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials.[31]

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CLARITY study results[20,31,34]

52-week results of a multicenter, randomized, phase 2b, non-inferiority study of aflibercept and PRP for previously untreated or post-laser treated active PDR.

Information provided by Regeneron Pharmaceuticals, Inc.

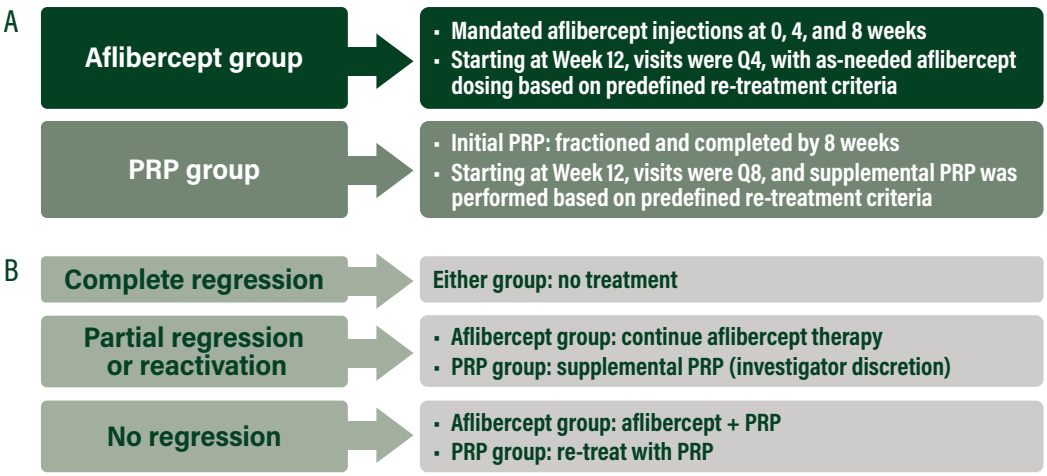
- EYLEA® (aflibercept) Injection is known in the scientific literature as VEGF Trap-Eye or Intravitreal Aflibercept Injection (IAI)
- This publication describes the 52-week results of CLARITY, a multicenter, randomized, phase 2b, noninferiority study evaluating the efficacy and safety of IAI 2 mg vs PRP in patients with previously untreated or post-laser treated active proliferative DR
- This is a single study. No confirmatory studies have been conducted. Definitive conclusions or comparisons about the relative efficacy and safety of EYLEA based on results of this study cannot be made
- This study was funded by the Efficacy and Mechanism Evaluation Programme, a Medical Research Council and National Institute for Health Research partnership. Bayer Plc (Reading, UK) supplied the aflibercept solution for injection in accordance with its marketing authorization
- This is a non-U.S. study and has not been evaluated by the U.S. FDA. This scientific information is being shared as additional, current, supportive, yet not conclusive data
- A dosing regimen of IAI different from that of the EYLEA U.S. Prescribing Information was utilized in this study
- The recommended dose of EYLEA for the treatment of DR 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 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. Some patients may need every-4-week (monthly) dosing after the first 20 weeks (5 months)
- Scientific information presented in this publication is not contained within the U.S. Prescribing Information for EYLEA and includes:
  - Patients were randomized to IAI or to PRP standard care
  - The IAI 2 mg (0.05 mL) dosing paradigm was 3 initial monthly doses, followed by as-needed dosing every 4 weeks based on predefined anatomic parameters
  - The primary efficacy endpoint was the mean change in visual acuity letter score with IAI vs PRP at 52 weeks. Please see Table S15 in the Supplementary Appendix of the primary publication of the CLARITY trial (Sivaprasad S, Prevost AT, Vasconcelos JC, et al. *Lancet*. 2017;389(10085): 2193-2203) for results from a comparison between groups of ETDRS Diabetic Retinopathy levels at 12 and 52 weeks
  - Intent-to-treat (ITT) and per-protocol (PP) patient populations were evaluated for efficacy and safety

Regeneron is providing the following truthful, nonmisleading clinical study data, which are not included in the EYLEA U.S. Prescribing Information.

Per the CLARITY study protocol, from Week 12, patients could be re-treated based on predefined criteria for neovascularization regression patterns. Patients in the aflibercept group who did not experience any regression of neovascularization by Week 12 received supplemental PRP in addition to aflibercept. In the PRP group, patients who had no regression, partial regression, or reactivation at the Week 12 assessment received supplemental PRP.[34] From Week 12, 65% of patients in the PRP group required supplemental PRP compared with 2% in the aflibercept group.[20]

Baseline characteristics were well balanced between treatment groups, with no significant differences. Of the 232 patients randomized to treatment, 123 (53%) were previously untreated. Approximately one-third of patients had a hemoglobin A_{1c} of <8%.[20] Patients with DME were excluded. Patients were randomized in a 1:1 ratio to receive 2 mg intravitreal aflibercept or PRP (single spot or multispot) per the following schedule **(Figure 6)**[20]:

Figure 6: CLARITY study design (A) and predefined re-treatment criteria (B) based on new vessel regression patterns[20,34]



SELECT IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.

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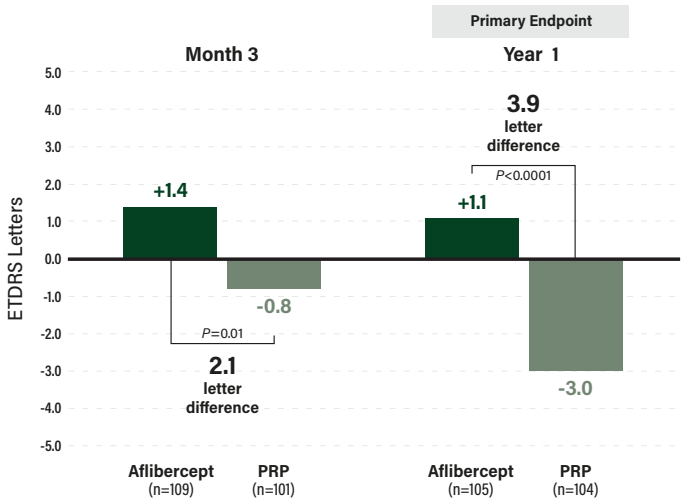
Changes in visual acuity

The primary efficacy outcome was the mean change in BCVA letter score (ETDRS letters) from baseline to Year 1 in the aflibercept group compared with the PRP group. Mean change in BCVA from baseline to Week 12 was evaluated as a secondary endpoint. Mean (SD) BCVA at baseline was 81.4 (8.1) letters. Month 3 and Year 1 results are presented in **Figure 7**.[20]

Figure 7: CLARITY: Mean change from baseline in BCVA (ETDRS letters) at Month 3 and Year 1[20,*]



- Aflibercept was noninferior and superior to PRP in mean change in BCVA at Year 1 in both the ITT and PP populations (mean BCVA difference of 3.9 letters for the modified ITT and difference of 4.0 letters for PP, both compared with PRP; *P*<0.0001 for both)[20]
- Adjusted difference between treatment groups was more than the prespecified acceptable margin of -5 letters for the 95% CI at both Month 3 and Year 1[20]
- Adjusted difference in visual acuity between treatment groups at Year 1 remained significant in 3 sensitivity analyses (adjusting for sites, excluding outliers, and assessing missing data assumptions)[20]

*Modified ITT population.

Reductions in disease severity

At Month 3 and Year 1, significantly more patients treated with aflibercept vs PRP saw improvements in their disease severity, as measured by changes in ETDRS-DRSS **(Table 3)**. At Month 3, 29% of patients in the aflibercept group vs 13% in the PRP group improved from PDR (DRSS ≥61) to NPDR (DRSS ≤53) (*P*=0.007). At Year 1, 22% of patients treated with aflibercept improved to NPDR or better from PDR vs 10% in the PRP group (*P*=0.016). Conversely, more patients in the PRP group remained at PDR than in the aflibercept group at Month 3 (87% vs 71%, respectively) and at Year 1 (90% vs 78%, respectively).[34]

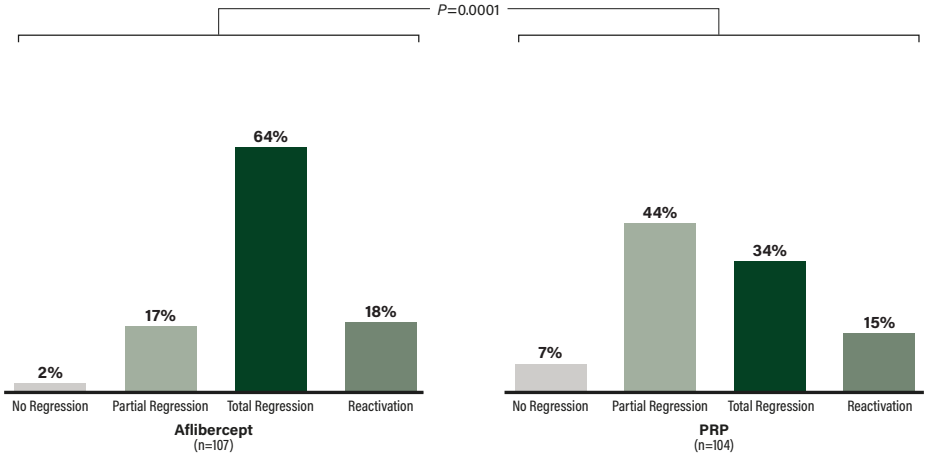
Table 3: Comparison of the change in DR severity at Month 3 and Year 1 between treatment groups[34]

	Month 3			Year 1		
	Aflibercept (n=97)	PRP (n=99)	*P* value	Aflibercept (n=104)	PRP (n=102)	*P* value
Patients who remained at PDR (≥61)	71%	87%	0.007	78%	90%	0.016
Patients who improved to NPDR (≤53) from PDR (≥61)	29%	13%	0.007	22%	10%	0.016

Regression of retinal neovascularization

Significantly more eyes in the aflibercept group vs the PRP group had total regression of new retinal vessels at Year 1, with a 30% difference between treatment groups (64% vs 34%, respectively; *P*<0.0001) **(Figure 8)**.[20,34]

Figure 8: Patterns of regression of retinal neovascularization at Year 1 in patients treated with aflibercept or PRP[20,34]



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Development of DME

DME may occur at any stage of DR.[2] Patients with clinical evidence of DME and a central subfield thickness (CST) of ≥300 µm due to macular edema at baseline were excluded.[20] At Year 1, the proportion of patients with no DME was 89% (n=93) in the aflibercept group and 71% (n=74) in the PRP group. Of these, 9% (n=9) and 21% (n=22), respectively, developed DME and 3% (n=3) and 8% (n=8), respectively, had CI-DME. Consistent with these findings, macular thickening was also greater in the PRP group. Mean CST increased in the PRP group but decreased in the aflibercept group at Year 1, a statistically significant difference (+24.0 µm vs -8.9 µm; *P*<0.0001).[34]

Safety outcomes

Adverse events were assessed in all study participants. Differences in ocular and systemic safety profiles between the aflibercept and PRP groups from baseline to Year 1 were assessed. Vascular events, as defined by the Antiplatelet Trialists' Collaboration (APTC) were also compared between groups.[20]

The most common ocular adverse event was new or increasing vitreous hemorrhage, occurring in 18% of patients in the PRP group vs 9% in the aflibercept group, a significant difference (*P*=0.034) **(Table 4)**. Other common ocular adverse events included visual disturbances, inflammation, ocular discomfort, and vitreous hemorrhage requiring vitrectomy. Inflammation, ocular discomfort, and cornea-related problems occurred at a higher incidence in the aflibercept group, but these differences were not significant.[20]

Table 4: Ocular adverse events through Year 1[20]

	Aflibercept (n=116)	PRP (n=116)	*P* value
Endophthalmitis	0%	0%	
Inflammation†	8%	3%	0.08
Visual disturbances‡	9%	9%	0.82
Ocular discomfort§	5%	3%	0.52
Cornea-related problems‖	4%	0%	0.06
Retinal tear	1%	0%	1.00
Progression of cataract	0%	1%	1.00
Elevation in intraocular pressure	1%	0%	1.00
Iris neovascularization	0%	0%	
Neovascular glaucoma	0%	0%	
Vitreoretinal interface abnormalities¶	2%	1%	1.00
Subconjunctival hemorrhage	1%	0%	1.00
Increasing severity of DR	1%	0%	1.00
Macular edema	0%	2%	0.50
Retinal detachment	0%	0%	
New or increasing vitreous hemorrhage	9%	18%	0.03
Vitreous hemorrhage requiring vitrectomy	1%	6%	0.07

†Inflammation included reported conjunctivitis, uveitis, hordeolum, keratitis, blepharitis, and dacryoadenitis.
‡Visual disturbance included floaters, flashing lights, nyctalopia, tunnel vision, decreased vision, nystagmus, and diplopia.
§Ocular discomfort included pain, twitching, and foreign body sensation.
‖Cornea-related adverse events included corneal abrasion, punctate epithelial erosion, and conjunctival laceration.
¶Vitreoretinal interface abnormalities included epiretinal membrane, posterior vitreous detachment, and lamellar hole.

There were no significant differences between treatment groups in the frequency of systemic adverse events or events predefined by the APTC **(Table 5)**.[20]

Table 5: Prespecified (APTC) adverse events through Year 1[20]

	Aflibercept (n=116)	PRP (n=116)	*P* value
Nonfatal myocardial infarction	3%	3%	1.00
Nonfatal stroke	3%	0%	0.25
Vascular death	2%	1%	1.00
Unknown death	0%	0%	
Any APTC event	7%	3%	0.24

SELECT IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS (CONT'D)

- 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.

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Conclusion

Patients with severe NPDR are at high risk for progression to PDR, with more than half of patients progressing to PDR within 1 year.[3] As DR progresses from severe NPDR to PDR, the risk of severe vision loss increases—patients with PDR have a 4 times higher risk of developing sustained blindness compared with patients with mild NPDR, underscoring the importance of prompt treatment to help reverse disease progression in this patient population.[7]

A legacy of clinical experience with EYLEA

- 8 phase 3 clinical trials enrolling >3000 patients across all approved indications[31]
- 10 years of extensive real-world experience[22]
- >16 million doses administered to over 1.3 million eyes since launch[22]

SELECT IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS (CONT'D)

- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Please see additional Important Safety Information throughout and Brief Summary of full Prescribing Information at the end of this article.

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EYLEA® (aflibercept) Injection
For Intravitreal Injection

01/2022 EYL.21.08.0064

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 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), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

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

5 WARNINGS AND PRECAUTIONS

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

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

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
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

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

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

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT).

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

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

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

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

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

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

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

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

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

8.5 Geriatric Use
In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
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Issue Date: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019
EYLEA® (aflibercept) Injection full Prescribing Information.

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