FDA Approves EYLEA® (aflibercept) Injection for Diabetic Retinopathy

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- **EYLEA improves diabetic retinopathy and prevents worsening disease that can lead to blindness**
- **Diabetic retinopathy is the leading cause of blindness among working-aged American adults**

Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced that the U.S. Food and Drug Administration (FDA) has approved EYLEA® (aflibercept) Injection to treat all stages of diabetic retinopathy (DR), and thereby reduce the risk of blindness.

"Millions of people have been robbed of their vision due to the progression of diabetic retinopathy," said David Brown, M.D., F.A.C.S., an investigator for the PANORAMA trial and Director of Research at Retina Consultants of Houston. "The prevention of worsening diabetic retinopathy with EYLEA provides a compelling rationale for early treatment of patients with this disease, particularly since eyes dosed with EYLEA as infrequently as every 16 weeks showed significant improvements in the pivotal PANORAMA trial."

Approximately eight million people live with DR, a complication of diabetes characterized by damage to the blood vessels in the retina. The disease generally starts as non-proliferative diabetic retinopathy (NPDR) and often has no warning signs or symptoms. Over time, NPDR often progresses to proliferative diabetic retinopathy (PDR), a stage in which abnormal blood vessels grow on the surface of the retina and into the vitreous cavity, potentially causing severe vision loss.

"With today's FDA approval, EYLEA has once again set a high bar for the treatment of diabetic eye diseases. The PANORAMA trial showed that by one year 20% of untreated patients developed proliferative diabetic eye disease, and EYLEA reduced this risk by 85% to 88% when administered using an every 16-week or eight-week dosing regimen, respectively," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer at Regeneron. "In fact, 80% of patients who received the EYLEA eight-week dosing regimen had significant improvement in their diabetic retinopathy."

EYLEA is the only vascular endothelial growth factor (VEGF) inhibitor approved with two dosing options for DR, allowing doctors to customize treatment to their patients' needs. In DR, EYLEA may be dosed every eight weeks following five initial monthly injections, or every four weeks.

About the PANORAMA trial
The FDA approval of EYLEA as a treatment for DR was based on six-month and one-year results from PANORAMA, a randomized, multi-center, controlled Phase 3 trial that enrolled 402 patients and was designed to investigate EYLEA for the improvement of moderately severe to severe NPDR without diabetic macular edema (DME), compared to sham injection. PANORAMA is the first prospective trial to study whether an anti-VEGF can also help prevent worsening disease in patients with NPDR without DME.

Details on trial design included:

- **Three treatment arms** – An observational sham injection group and two EYLEA treatment groups. EYLEA was dosed every eight weeks (following five initial monthly doses) or every 16 weeks (following three initial monthly doses and one eight-week interval).
- **Primary endpoint** – The primary endpoint was the proportion of patients who experienced a two-step or greater improvement in the diabetic retinopathy severity scale (DRSS) from baseline for the combined EYLEA treatment groups at week 24, and for each EYLEA treatment group separately (every eight-week group and every 16-week group) at week 52. The DRSS is a systematic grading scale to assess DR severity based on photographs of the retina.
- **Secondary endpoints** – These included assessment of whether EYLEA reduced the risk of worsening disease – specifically progression to PDR (including anterior segment neovascularization [ASNV]) or the development of center-involved DME – as well as change in visual acuity.

Key one-year results included:

	EYLEA Every 16-Week Regimen (N=135)	EYLEA Every 8-Week Regimen (N=134)	Sham Control (N=133)
Primary Endpoint			
Patients with ≥2-step improvement on DRSS score from baseline	65%	80%	15%

Composite Endpoint of Developing PDR or ASNV[a]			
Event Rate[b]	4%[d]	2%[d]	20%[d]
Hazard Ratio	0.15	0.12	
Development of PDR[c]			
Event Rate[b]	2%[d]	0%[d]	12%[d]
Hazard Ratio	0.11	0.00	

[a] As diagnosed by either the Reading Center or Investigator through week 52

[b] Estimated using Kaplan-Meier method

[c] Defined as ≥2-step worsening on the ETDRS-DRSS score through week 52

[d] $p<0.01$ compared with Control

Safety data observed in 269 patients with NPDR through the first year were consistent with those seen in the Phase 3 VIVID and VISTA trials.

About EYLEA® (aflibercept) Injection

EYLEA® (aflibercept) Injection is a VEGF inhibitor formulated as an injection for the eye. It is designed to block the growth of new blood vessels and decrease the ability of fluid to pass through blood vessels (vascular permeability) in the eye by blocking VEGF-A and placental growth factor (PLGF), two growth factors involved in angiogenesis. In the U.S., EYLEA is the market-leading, FDA-approved anti-VEGF treatment for its approved indications and is supported by a robust body of research that includes eight pivotal Phase 3 trials.

IMPORTANT SAFETY INFORMATION FOR EYLEA® (aflibercept) INJECTION

- EYLEA®(aflibercept) Injection 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.
- 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.
- 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.
- 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.

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).

DOSAGE AND ADMINISTRATION

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

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).

- 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).

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

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

Macular Edema Following Retinal Vein Occlusion (RVO)

- The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly).

For more information, please see full Prescribing Information.

About Regeneron Pharmaceuticals, Inc.
Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents life-transforming medicines for people with serious diseases. Founded and led for 30 years by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to seven FDA-approved treatments and numerous product candidates in development, all of which were homegrown in our laboratories. Our medicines and pipeline are designed to help patients with eye disease, allergic and inflammatory diseases, cancer, cardiovascular and metabolic diseases, neuromuscular diseases, infectious diseases and rare diseases.

Regeneron is accelerating and improving the traditional drug development process through our proprietary *VelociSuite*® technologies, such as *VelocImmune*® which produces optimized fully-human antibodies, and ambitious research initiatives such as the Regeneron Genetics Center, which is conducting one of the largest genetics sequencing efforts in the world.

For additional information about the company, please visit www.regeneron.com or follow @Regeneron on Twitter.

Forward-Looking Statements and Use of Digital Media
This press release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron Pharmaceuticals, Inc. ("Regeneron" or the "Company"), and actual events or results may differ materially from these forward-looking statements. Words such as "anticipate," "expect," "intend," "plan," "believe," "seek," "estimate," variations of such words, and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements concern, and these risks and uncertainties include, among others, the nature, timing, and possible success and therapeutic applications of Regeneron's products, product candidates, and research and clinical programs now underway or planned, including without limitation EYLEA® (aflibercept) Injection; unforeseen safety issues resulting from the administration of products and product candidates in patients, including serious complications or side effects in connection with the use of Regeneron's product candidates in clinical trials; the likelihood and timing of possible regulatory approval and commercial launch of Regeneron's late-stage product candidates and new indications for marketed products; the extent to which the results from the research and development programs conducted by Regeneron or its collaborators may be replicated in other studies and lead to therapeutic applications; ongoing regulatory obligations and oversight impacting Regeneron's marketed products (such as EYLEA), research and clinical programs, and business, including those relating to patient privacy; determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize Regeneron's products and product candidates; competing drugs and product candidates that may be superior to Regeneron's products and product candidates; uncertainty of market acceptance and commercial success of Regeneron's products and product candidates and the impact of studies (whether conducted by Regeneron or others and whether mandated or voluntary) on the commercial success of Regeneron's products and product candidates; the ability of Regeneron to manufacture and manage supply chains for multiple products and product candidates; the ability of Regeneron's collaborators, suppliers, or other third parties to perform (as applicable) manufacturing, filling, finishing, packaging, labeling, distribution, and other steps related to Regeneron's products and product candidates; the availability and extent of reimbursement of the Company's products (such as EYLEA) from third-party payers, including private payer healthcare and insurance programs, health maintenance organizations, pharmacy benefit management companies, and government programs such as Medicare and Medicaid; coverage and reimbursement determinations by such payers and new policies and procedures adopted by such payers; unanticipated expenses; the costs of developing, producing, and selling products; the ability of Regeneron to meet any of its financial projections or guidance and changes to the assumptions underlying those projections or guidance; the potential for any license or collaboration agreement, including Regeneron's agreements with Sanofi, Bayer, and Teva Pharmaceutical Industries Ltd. (or their respective affiliated companies, as

applicable), to be cancelled or terminated without any further product success; and risks associated with intellectual property of other parties and pending or future litigation relating thereto, including without limitation the patent litigation and other related proceedings relating to EYLEA, Dupixent® (dupilumab) Injection, and Praluent®(alirocumab) Injection, the ultimate outcome of any such proceedings, and the impact any of the foregoing may have on Regeneron's business, prospects, operating results, and financial condition. A more complete description of these and other material risks can be found in Regeneron's filings with the U.S. Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2018 and its Form 10-Q for the quarterly period ended March 31, 2019. Any forward-looking statements are made based on management's current beliefs and judgment, and the reader is cautioned not to rely on any forward-looking statements made by Regeneron. Regeneron does not undertake any obligation to update publicly any forward-looking statement, including without limitation any financial projection or guidance, whether as a result of new information, future events, or otherwise.

Regeneron uses its media and investor relations website and social media outlets to publish important information about the Company, including information that may be deemed material to investors. Financial and other information about Regeneron is routinely posted and is accessible on Regeneron's media and investor relations website (http://newsroom.regeneron.com) and its Twitter feed (http://twitter.com/regeneron).

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