# EYLEA® (aflibercept) Injection Improves Diabetic Retinopathy and Reduces Vision-Threatening Complications in Phase 3 Trial

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**First trial in non-proliferative diabetic retinopathy to show both a reduction in vision-threatening complications and in development of diabetic macular edema**

**Both every 8-week and every 16-week dosing groups met primary and key secondary endpoints at one year**

**EYLEA supplemental application for treatment of diabetic retinopathy, based on previously announced 24-week results, currently under FDA review with an action date of May 13, 2019**

**Regeneron also provides update on EYLEA pre-filled syringe regulatory submission**

Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced that the Phase 3 PANORAMA trial evaluating EYLEA® (aflibercept) Injection in patients with moderately severe and severe non-proliferative diabetic retinopathy (NPDR) met its one-year (52-week) primary endpoint and key secondary endpoints. On the primary endpoint at one year, 80% and 65% of patients receiving EYLEA on an every 8- and every 16-week interval (after an initial monthly dosing period), respectively, experienced a two-step or greater improvement from baseline on the Diabetic Retinopathy Severity Scale, compared to 15% of patients receiving sham injection ($p<0.0001$). Regarding the two key secondary endpoints, which achieved statistical significance based on the pre-specified hierarchical analysis, treatment with EYLEA also reduced vision-threatening complications (VTCs) by 82%-85% and the development of center-involved diabetic macular edema (CI-DME) by 68%-74% compared with sham injection.

- The development of VTCs (proliferative diabetic retinopathy and anterior segment neovascularization) was 3% for the EYLEA every 8-week group, 4% for the EYLEA every 16-week group, and 20% for the sham injection group ($p<0.001$).
- CI-DME occurred in 8% of the EYLEA every 8-week group, 7% of the EYLEA every 16-week group, and 26% of the sham injection group ($p<0.001$).
- These events collectively occurred in 11% and 10% of patients receiving EYLEA every 8 weeks or every 16 weeks, respectively, compared to 41% of patients receiving sham injection ($p<0.001$).

"Blindness caused by diabetes is one of the most feared consequences of this disease," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer of Regeneron. "In this trial of patients with diabetic eye disease and normal vision, it is notable that without treatment more than one third of patients developed a vision-threatening complication or diabetic macular edema within one year. EYLEA was able to reduce these complications by 68%-85% even with every four-month dosing, and moreover was able to reverse the anatomic severity of the disease. These results point to the potential value of earlier intervention in diabetic retinopathy and may in the future change the way retina specialists treat this disease."

The average number of injections in the first year was 8.6 (of 9 planned) for the EYLEA every 8-week group and 5.5 (of 6 planned) for the EYLEA every 16-week group.

Adverse events were consistent with the known profile of EYLEA. Serious ocular treatment-emergent adverse events in the study eye occurred in 0 and 1 patients in the EYLEA treatment groups and 1 patient in the sham injection group. Ocular inflammation occurred in 1 patient in each EYLEA treatment group and 0 patients in the sham injection group. Anti-Platelet Trialists' Collaboration (APTC)-defined arterial thromboembolic treatment-emergent events occurred in 4 and 2 patients in the EYLEA treatment groups and 5 patients in the sham injection group.

**Regulatory Update on EYLEA Pre-filled Syringe**
Regeneron also announced today that the U.S. Food and Drug Administration (FDA) issued a complete response letter (CRL) regarding the Chemistry, Manufacturing and Controls (CMC) Prior-Approval Supplement (PAS) for the EYLEA pre-filled syringe. The CRL requested additional information regarding manufacturing and supply processes and the completion of a usability study evaluating a single injection of the EYLEA pre-filled syringe in approximately 30 patients. Regeneron expects to compile all the requested information and resubmit the PAS in early 2019 and continues to expect a 2019 launch of the EYLEA pre-filled syringe.

**About the PANORAMA trial**
PANORAMA is an ongoing, pivotal, double-masked, randomized, two-year trial that enrolled 402 patients and is designed to investigate EYLEA for the improvement of moderately severe to severe NPDR in patients without DME, compared to sham injections. Details on trial design include:

- **Three treatment arms** – An observational sham injection group and two EYLEA treatment groups. EYLEA was dosed every 8 weeks (following five initial monthly doses) or every 16 weeks (following three initial monthly doses and one 8-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 score (DRSS) from baseline for the combined EYLEA treatment groups at week 24, and for each EYLEA treatment group separately (every 8-week group and every 16-week group) at week 52. The DRSS is a systematic grading scale to assess the severity of diabetic retinopathy based on photographs of the retina

following a dilated eye exam.
- **Secondary endpoints** – These include assessment of whether EYLEA reduced VTCs (proliferative diabetic retinopathy and anterior segment neovascularization) or development of CI-DME, as well as its impact on other anatomic effects, visual acuity improvement, and safety.

One-year results from PANORAMA will be submitted for presentation at a future medical congress. Six-month PANORAMA results were previously reported in March 2018. A supplemental Biologics License Application (sBLA) for EYLEA in diabetic retinopathy based on 24-week results was accepted for review by the U.S. FDA with a target action date of May 13, 2019. Regeneron also plans to submit the 52-week results to the FDA.

The safety and efficacy of EYLEA in diabetic retinopathy in patients without diabetic macular edema (DME) have not been fully evaluated by any regulatory authority.

A separate ongoing trial sponsored by the Diabetic Retinopathy Clinical Research Network known as Protocol W is also evaluating EYLEA for the treatment of NPDR in patients without DME.

**About Diabetic Retinopathy (DR)**
Approximately eight million people live with DR, a disease characterized by microvascular damage to the blood vessels in the retina often caused by poor blood sugar control in people with diabetes. The disease generally starts as NPDR and often has no warning signs or symptoms. NPDR may progress to PDR, a stage of the disease in which abnormal blood vessels grow onto the surface of the retina and potentially cause severe vision loss.

DME can occur at any stage of DR as the blood vessels in the retina become increasingly fragile and leak fluid, potentially causing visual impairment. In the U.S., approximately 1.5 million adults are diagnosed with DME, while approximately 3.5 million people have DR without DME.

**About EYLEA® (aflibercept) Injection**
EYLEA® (aflibercept) Injection is a vascular endothelial growth factor (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 United States, 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 seven 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 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) in patients with DME.

Please visit www.EYLEA.us to see the full Prescribing Information for EYLEA.

**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, heart disease, allergic and inflammatory diseases, pain, cancer, 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.

**Regeneron 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, including without limitation any potential regulatory approval of EYLEA for patients withdiabetic retinopathy; the impact of the complete response letter issued by the U.S. Food and Drug Administration (the "FDA") and discussed in this press release on the Chemistry, Manufacturing and Controls Prior-Approval Supplement for the EYLEA pre-filled syringe (the "PAS"), whether the planned resubmission of the PAS with the FDA will be made timely or at all, and whether regulatory approval of the PAS will be obtained in the currently anticipated timeframe or at all; 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 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 proceedings relating to EYLEA, Dupixent® (dupilumab) Injection, and Praluent®(alirocumab) Injection, the ultimate outcome of any such litigation 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-Q for the quarterly period ended June 30, 2018. 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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