REGENERON

One-Year Results from Positive Phase 3 EYLEA Trial in Diabetic Retinopathy Presented at Angiogenesis Symposium

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TARRYTOWN, N.Y., Feb. 9, 2019 /PRNewswire/ --

Trial showed that early intervention with EYLEA improved diabetic retinopathy severity and prevented serious vision-threatening complications

EYLEA diabetic retinopathy sBLA target action date of May 13, 2019

Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced that positive detailed one-year results from the Phase 3 PANORAMA trial evaluating EYLEA® (aflibercept) Injection in patients with moderately severe to severe non-proliferative diabetic retinopathy (NPDR) were presented for the first time at the Angiogenesis, Exudation, and Degeneration 2019 symposium.

The trial confirmed that moderately severe and severe non-proliferative diabetic retinopathy is not a benign condition, with patients at high risk of rapidly progressing to vision-threatening events. In untreated patients with severe NPDR, 53% developed these events at one year. Most importantly, EYLEA treatment prevented approximately 74% of these complications.

Key one-year data presented at the meeting are summarized below:

	Sham Control (N=133)	EYLEA Every 16 Weeks (N=135)	EYLEA Every 8 Weeks (N=134)
Primary Endpoint			
% of patients with ≥2-step improvement on DRSS score from baseline[a]	15%	65%[a]	80%[a]
Impact on Vision-Threatening Events			
Patients who developed a vision-threatening event[b]	41%	10%[a]	11%[a]
Subgroup with severe NPDR at baseline (n=100)	53%	15%[c]	15%[c]
Subgroup with moderately severe NPDR at baseline (n=302)	36%	8%[d]	10%[d]

DRSS=Diabetic Retinopathy Severity Scale
[a] p<0.0001 versus sham
[b] Vision-threatening events defined as vision-threatening complications (VTC; proliferative diabetic retinopathy or anterior segment neovascularization) or central-involved diabetic macular edema (CI-DME)
[c] Nominal p=0.0019 versus sham
[d] Nominal p<0.0001 versus sham

Topline one-year results from PANORAMA were previously reported in October 2018.

"PANORAMA provides high-quality data to inform treatment of NPDR without DME, as it is the first prospective trial involving these high-risk patients since the landmark ETDRS trial of the 1980s when laser was the only treatment option," said Charles C. Wykoff, M.D., Ph.D., PANORAMA investigator, retina surgeon and ophthalmologist with Retina Consultants of Houston. "Without treatment, a large percentage of patients in the trial developed proliferative disease and CI-DME in the first year. EYLEA treatment reduced the risk of these events by approximately 74% compared to sham injection, underscoring the potential importance of early EYLEA anti-VEGF therapy. This efficacy was seen even with an every 16-week treatment regimen after loading doses, a management approach that may realistically be achieved in the real world."

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.

A supplemental Biologics License Application (sBLA) for EYLEA in diabetic retinopathy has been accepted for review by the U.S. FDA with a target action date of May 13, 2019.

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

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 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 (defined as 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.

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 proliferative diabetic retinopathy (PDR), a stage of the disease in which abnormal blood vessels grow onto the surface of the retina and into the vitreous cavity potentially causing 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 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 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 recent and any potential future U.S. government shutdowns on the anticipated timing of the decision by the U.S. Food and Drug Administration regarding the supplemental Biologics License Application for EYLEA in diabetic retinopathy referenced in this press release; 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 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-K for the year ended December 31, 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).

Contacts Regeneron:

Media Relations
Daren Kwok
Tel: +1 (914) 847-1328
daren.kwok@regeneron.com

Investor Relations
Mark Hudson
Tel: +1 (914) 847-3482
mark.hudson@regeneron.com