EYLEA® (aflibercept) Injection Reduced Risk of Developing Vision-Threatening Events by 75% After Two Years in Patients with Diabetic Retinopathy

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New data highlight importance of proactive EYLEA treatment as more than half of untreated patients in PANORAMA developed vision-threatening events over two years

High-dose aflibercept development program underway with Phase 3 trials planned for 2020

Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) announced positive two-year results from the Phase 3 PANORAMA trial evaluating EYLEA® (aflibercept) Injection 2 mg (0.05 mL) in patients with moderately severe to severe non-proliferative diabetic retinopathy (NPDR). The data were presented today for the first time at the Angiogenesis, Exudation, and Degeneration 2020 meeting in Miami, Florida.

The two-year pre-specified exploratory data demonstrate that untreated moderately severe and severe NPDR can lead to vision-threatening events, which includes vision-threatening complications (VTCs; proliferative diabetic retinopathy or anterior segment neovascularization) and center-involved diabetic macular edema (CI-DME). Based on a Kaplan-Meier analysis, more than half (58%) of patients in the untreated sham arm developed a VTC or CI-DME within two years of entering the trial, while EYLEA treatment was shown to reduce the likelihood of these vision-threatening events by at least 75% (nominal p<0.0001).

"These data reinforce that regular EYLEA treatment can be highly effective at reducing the risk of new vision-threatening events among patients with moderately severe to severe non-proliferative diabetic retinopathy," said Charles C. Wykoff, M.D., Ph.D., PANORAMA investigator, retina surgeon and ophthalmologist with Retina Consultants of Houston. "The PANORAMA trial shows that more than half of all untreated patients developed vision-threatening events over two years, underscoring the value of treating patients proactively and regularly."

The two-year results also showed a greater benefit for EYLEA patients treated at regular intervals compared to patients who received EYLEA treatment less frequently. Per the protocol, the group of trial patients who received EYLEA every 8 weeks in the first year were switched to receive it when their doctor determined they needed it (called pro re nata, or PRN) in the second year (i.e., the 8-week/PRN group). The proportion of these patients with a ≥2-step improvement from baseline in Diabetic Retinopathy Severity Scale (DRSS) scores decreased in the second year (80% improvement at 52 weeks and 50% at 100 weeks).* By comparison, in patients who continued to receive EYLEA every 16 weeks (i.e., the 16-week group), the ≥2-step DRSS scores remained consistent (65% at 52 weeks vs. 62% at 100 weeks).* In the second year, patients received an average of 1.8 injections in the 8-week/PRN group (out of a possible 6); a review of data from the independent reading center of investigator PRN decisions suggests that some of these patients may have been under-dosed based on the protocol rules of the trial. Patients in the 16-week group received 2.6 injections (out of a possible 3) in the second year.

During the 2-year PANORAMA trial, adverse events were consistent with the known profile of EYLEA. Serious ocular adverse events in the study eye occurred in 2% and 0% of the EYLEA 8-week/PRN and 16-week groups, respectively, and 2% of patients in the sham group. Ocular inflammation occurred in 2% and 1% of patients in the EYLEA treatment groups, respectively, and 1% of patients in the sham group. Anti-platelet trialists' collaboration (APTC)-defined arterial thromboembolic treatment emergent events occurred in 3% and 6% of patients in the EYLEA treatment groups, respectively, and 5% of patients in the sham group.

*p<0.0001 at 52 weeks; nominal p<0.0001 at 100 weeks, as all prespecified endpoints at 100 weeks are considered exploratory.

High-Dose Aflibercept Update
Also presented today was the rationale for high-dose (8 mg) aflibercept clinical trials. A Phase 2 trial (CANDELA) evaluating high-dose aflibercept in wet age-related macular degeneration (wet AMD) is currently enrolling. Phase 3 trials planned to start in 2020 in wet AMD (PULSAR, sponsored by Bayer) and DME (PHOTON, sponsored by Regeneron) will evaluate dosing intervals of 12 weeks and longer.

"Through millions of injections and eight pivotal Phase 3 trials, EYLEA has built a substantial body of evidence and safety profile. High-dose aflibercept will hopefully build on this standard-of-care therapy and represents our ongoing commitment to ophthalmologic research and development," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer at Regeneron. "We are eager to explore the potential of high-dose aflibercept to deliver sustained vision gains and extended duration of action in patients with wet AMD and DME."

The potential use of high-dose aflibercept is currently under clinical development and the safety and efficacy for this use have not been fully evaluated by any regulatory authority.

About the PANORAMA trial
The U.S. Food and Drug Administration (FDA) approval of EYLEA to treat diabetic retinopathy 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 DME, compared to sham injection. PANORAMA is the first prospective trial to study whether vascular endothelial growth factor (VEGF) inhibition 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 8-week interval). At week 52, the 8-week interval group switched to as needed (PRN) dosing determined by the investigator. All patients were followed to week 100.

- **Primary endpoint** – the primary endpoint was the proportion of patients who experienced a 2-step or greater improvement in the DRSS score 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 diabetic retinopathy severity based on photographs of the retina.
- **Secondary endpoints** – the secondary endpoints included assessment of whether EYLEA reduced the risk of worsening disease – specifically progression to PDR (including anterior segment neovascularization [ASNV]) or the development of CI-DME – as well as change in visual acuity, through week 52.
- **Exploratory endpoints** – all prespecified endpoints at week 100 (year two) are considered exploratory.

One-year results from PANORAMA were previously reported in October 2018 and February 2019. 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

Approximately eight million people live with diabetic retinopathy, 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 a stage of the disease in which abnormal blood vessels grow onto the surface of the retina and potentially cause severe, vision-threatening complications such as proliferative diabetic retinopathy and anterior segment neovascularization.

DME can occur at any stage of diabetic retinopathy 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 diabetic retinopathy 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 number one prescribed FDA-approved anti-VEGF treatment across 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 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
Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents life-transforming medicines for people with serious diseases. Founded and led for over 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 diseases, allergic and inflammatory diseases, cancer, cardiovascular and metabolic diseases, pain, infectious diseases and rare diseases.

Regeneron is accelerating and improving the traditional drug development process through our proprietary *VelociSuite*® technologies, such as *VelocImmune*® which uses unique genetically-humanized mice to produce optimized fully-human antibodies and bispecific antibodies, and through 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 products marketed by Regeneron and/or its collaborators (collectively, "Regeneron's Products") and Regeneron's product candidates and research and clinical programs now underway or planned, including without limitation EYLEA® (aflibercept) Injection and high-dose aflibercept; uncertainty of market acceptance and commercial success of Regeneron's Products and product candidates (such as EYLEA and high-dose aflibercept) and the impact of studies (whether conducted by Regeneron or others and whether mandated or voluntary), such as the Phase 3 PANORAMA trial discussed in this press release, on the commercial success of Regeneron's Products and product candidates; the availability and extent of reimbursement of Regeneron's Products (including 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; competing drugs and product candidates that may be superior to Regeneron's Products and product candidates, including EYLEA and high-dose aflibercept; unforeseen safety issues resulting from the administration of Regeneron's Products and product candidates (such as EYLEA and high-dose aflibercept) in patients, including serious complications or side effects in connection with the use of Regeneron's Products and product candidates in clinical trials; the likelihood and timing of possible regulatory approval and commercial launch of Regeneron's product candidates (including high-dose aflibercept) and new indications for Regeneron's 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 Products, 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 (such as high-dose aflibercept); 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 (as applicable) to perform manufacturing, filling, finishing, packaging, labeling, distribution, and other steps related to Regeneron's Products and product candidates; 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 Dupixent® (dupilumab) and Praluent® (alirocumab)), other litigation and other proceedings and government investigations relating to the Company and/or its operations, the ultimate outcome of any such proceedings and investigations, 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 fiscal year ended December 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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