EYLEA® (aflibercept) Injection sBLA for Treatment of Retinopathy of Prematurity (ROP) Accepted for FDA Priority Review

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ROP is a leading cause of childhood blindness worldwide

TARRYTOWN, N.Y., Oct. 12, 2022 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced the U.S. Food and Drug Administration (FDA) has accepted for Priority Review the supplemental Biologics License Application (sBLA) for EYLEA® (aflibercept) Injection to treat Retinopathy of Prematurity (ROP) in preterm infants. The target action date for the FDA decision is February 11, 2023.

ROP is a leading cause of childhood blindness worldwide. Each year in the U.S., between 1,100 to 1,500 infants develop disease severe enough to require medical treatment. The rare eye disease often impacts infants who are born before 31 weeks of pregnancy have been completed or who weigh less than 1,500 grams (3.3 lbs) pounds at birth. As retinal blood vessels are often only fully developed when an infant is full-term (~9 months of pregnancy), these infants are at risk of developing retinal blood vessels that are abnormal (retinal neovascularization) potentially leading to retinal detachment and irreversible vision loss. Mild cases of ROP may get better without treatment, but some cases require treatment (for which the current standard of care is laser photocoagulation) to keep ROP from causing significant visual impairment and even blindness.

The sBLA is supported by data from two randomized global Phase 3 trials – FIREFLEYE (N=113) and BUTTERFLEYE (N=120) – investigating EYLEA 0.4 mg versus laser photocoagulation (laser) in infants with ROP. In both trials, approximately 80% of EYLEA-treated infants achieved an absence of both active ROP and unfavorable structural outcomes at 52 weeks of age, although their primary endpoint of non-inferiority was not met due to laser demonstrating comparable levels of efficacy that were higher than what have been historically observed in similar ROP trials. Notably, per an exploratory analysis, the time required to complete treatment administration per patient was considerably less for EYLEA than for laser (FIREFLEYE: 4 minutes versus 122 minutes; BUTTERFLEYE: 11 minutes versus 129 minutes).

No new EYLEA safety signals were observed in either trial. Comparing EYLEA to laser, ocular adverse events (AEs) among patients occurred in 39% versus 37% in FIREFLEYE and 18% versus 26% in BUTTERFLEYE, with serious ocular AEs occurring in 8% for both groups in FIREFLEYE and 6.5% versus 11% in BUTTERFLEYE. AEs in both trials were consistent with infant prematurity or to the injection procedure, and with the AEs in similar ROP trials.

The results of FIREFLEYE were published in Journal of the American Medical Association, and data from BUTTERFLEYE were recently presented at ROP Update 2022 meeting in the U.S. Both trials were conducted pursuant to FDA Pediatric Written Request, and a Pediatric Exclusivity Determination is under review by FDA with a response expected by early 2023. A Pediatric Exclusivity Determination is granted if the specifications of the Pediatric Written Request are met, regardless of whether a pediatric indication is approved.

EYLEA was granted orphan drug designation by the FDA for the treatment of ROP in July 2019. The safety and efficacy of EYLEA for the treatment of ROP have not been fully evaluated by the FDA and other regulatory authorities.

The lead sponsors of the trials were Regeneron for BUTTERFLEYE and Bayer for FIREFLEYE. Bayer and Regeneron are collaborating on the global development of EYLEA. Regeneron maintains exclusive rights of EYLEA in the United States. Bayer has licensed the exclusive marketing rights outside the United States, where the companies share equally the profits from sales of EYLEA.

About EYLEA
EYLEA 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. The EYLEA safety and efficacy profile is supported by a robust body of research that includes eight pivotal Phase 3 trials, 10 years of real-world experience and more than 50 million EYLEA injections globally.

IMPORTANT EYLEA SAFETY INFORMATION AND INDICATIONS

INDICATIONS
EYLEAâ (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).

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.

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.
- 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.

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.
- 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.
- 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.

For more information, please see full Prescribing Information.

About Regeneron
Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents, develops and commercializes life-transforming medicines for people with serious diseases. Founded and led for nearly 35 years by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to nine FDA-approved treatments and numerous product candidates in development, almost 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, hematologic conditions, 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 more information, 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 impact of SARS-CoV-2 (the virus that has caused the COVID-19 pandemic) on Regeneron's business and its employees, collaborators, and suppliers and other third parties on which Regeneron relies, Regeneron's and its collaborators' ability to continue to conduct research and clinical programs, Regeneron's ability to manage its supply chain, net product sales of products marketed or otherwise commercialized by Regeneron and/or its collaborators or licensees (collectively, "Regeneron's Products"), and the global economy; the nature, timing, and possible success and therapeutic applications of Regeneron's Products and product candidates being developed by Regeneron and/or its collaborators or licensees (collectively, "Regeneron's Product Candidates") and research and clinical programs now underway or planned, including without limitation EYLEA® (aflibercept) Injection for the treatment of Retinopathy of Prematurity in preterm infants ("ROP"); the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's Product Candidates and new indications for Regeneron's Products, such as EYLEA for the treatment of ROP (including potential regulatory approval by the U.S. Food and

Drug Administration based on the supplemental Biologics License Application discussed in this press release); the extent to which the results from the research and development programs conducted by Regeneron and/or its collaborators or licensees (including the studies evaluating EYLEA for the treatment of ROP discussed in this press release) may be replicated in other studies and/or lead to advancement of product candidates to clinical trials, therapeutic applications, or regulatory approval; uncertainty of the utilization, market acceptance, and commercial success of Regeneron's Products and Regeneron's Product Candidates and the impact of studies (whether conducted by Regeneron or others and whether mandated or voluntary), including the studies discussed or referenced in this press release, on any of the foregoing or any potential regulatory approval of Regeneron's Products and Regeneron's Product Candidates; the ability of Regeneron's collaborators, licensees, suppliers, or other third parties (as applicable) to perform manufacturing, filling, finishing, packaging, labeling, distribution, and other steps related to Regeneron's Products and Regeneron's Product Candidates; the ability of Regeneron to manage supply chains for multiple products and product candidates; safety issues resulting from the administration of Regeneron's Products and Regeneron's Product Candidates in patients, including serious complications or side effects in connection with the use of Regeneron's Products and Regeneron's Product Candidates in clinical trials; 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 Regeneron's Product Candidates; ongoing regulatory obligations and oversight impacting Regeneron's Products, research and clinical programs, and business, including those relating to patient privacy; the availability and extent of reimbursement of Regeneron's Products 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, or more cost effective than, Regeneron's Products and Regeneron's 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; 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), Praluent® (alirocumab), and REGEN-COV® (casirivimab and imdevimab)), 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 year ended December 31, 2021 and its Form 10-Q for the quarterly period ended June 30, 2022. 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 or otherwise) 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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