Aflibercept 8 mg BLA for Treatment of Wet Age-Related Macular Degeneration and Diabetic Macular Edema Accepted for FDA Priority Review

February 23, 2023

BLA supported by two pivotal trials demonstrating non-inferior vision gains to EYLEA® (aflibercept) Injection, with vast majority of patients maintaining extended dosing regimens through 48 weeks

If approved, aflibercept 8 mg will be second ophthalmology medicine developed by Regeneron

TARRYTOWN, N.Y., Feb. 23, 2023 (GLOBE NEWSWIRE) -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced that the U.S. Food and Drug Administration (FDA) has accepted for Priority Review the Biologics License Application (BLA) for aflibercept 8 mg for treatment of patients with wet age-related macular degeneration (wAMD), diabetic macular edema (DME) and diabetic retinopathy. The FDA target action date is June 27, 2023 following the use of a priority review voucher.

The BLA is supported by positive data from two pivotal trials – PULSAR in wAMD and PHOTON in DME – that were previously presented at the 55th Annual Scientific Session of The Retina Society in November 2022. In both trials, patients treated with aflibercept 8 mg (PULSAR n=673; PHOTON n=491) met the primary endpoint of non-inferiority in vision gains for both the 12- and 16-week dosing regimens after initial monthly doses at 48 weeks compared to patients treated with an EYLEA® (aflibercept) Injection (PULSAR n=336; PHOTON n=167) 8-week dosing regimen. Additionally, the vast majority of patients randomized to aflibercept 8 mg in both trials were able to maintain the 12- and 16-week dosing regimens to which they were respectively initiated through 48 weeks (wAMD: 79% and 77%; DME: 91% and 89%). The safety profile for aflibercept 8 mg was similar to EYLEA in both trials, and consistent with the known safety profile of EYLEA from previous clinical trials. Comparing aflibercept 8 mg to EYLEA, ocular adverse events occurred in 31% (n=491) versus 28% (n=167) in PHOTON and 38% (n=673) versus 39% (n=336) in PULSAR, and there were no cases of retinal vasculitis, occlusive retinitis or endophthalmitis in either trial.

Aflibercept 8 mg is being jointly developed by Regeneron and Bayer AG. In the U.S., Regeneron maintains exclusive rights to EYLEA and aflibercept 8 mg. Bayer has licensed the exclusive marketing rights outside of the U.S., where the companies share equally the profits from sales of EYLEA and future sales of aflibercept 8 mg following any regulatory approvals.

Aflibercept 8 mg is investigational, and its safety and efficacy have not been evaluated by any regulatory authority.

About the Aflibercept 8 mg Trial Program
PHOTON in DME and PULSAR in wAMD are double-masked, active-controlled pivotal trials that are being conducted in multiple centers globally. In both trials, patients were randomized into 3 treatment groups to receive either: aflibercept 8 mg every 12 weeks, aflibercept 8 mg every 16 weeks, or EYLEA every 8 weeks.

Patients treated with aflibercept 8 mg in both trials had 3 initial monthly doses, and patients treated with EYLEA received 5 initial monthly doses in PHOTON and 3 in PULSAR. In the first year, patients in the aflibercept 8 mg groups could have their dosing intervals shortened down to an every 8-week interval if protocol-defined criteria for disease progression were observed. Intervals could not be extended until the second year of the study, with those results still to be assessed. Patients in all EYLEA groups maintained a fixed 8-week dosing regimen throughout their participation in the trials.

The lead sponsors of the trials were Regeneron for PHOTON and Bayer for PULSAR.

About DME and wAMD
DME is a common complication in eyes of people living with diabetes. DME occurs when high levels of blood sugar lead to damaged blood vessels in the eye that leak fluid into the macula. This can lead to vision loss and, in some cases, blindness. Of the nearly 28 million American adults living with diabetes, an estimated 1.2 million have DME.

wAMD is a retinal disease that may affect people as they age. It occurs when abnormal blood vessels grow and leak fluid under the macula, the part of the eye responsible for sharp central vision and seeing fine detail. This fluid can damage and scar the macula, which can cause vision loss. An estimated 1.1 million Americans have wAMD, and this number is expected to double by 2050.

IMPORTANT EYLEA SAFETY INFORMATION AND INDICATIONS

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), Diabetic Retinopathy (DR), and Retinopathy of Prematurity (ROP).

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 and/or caregivers should be instructed to report any signs and/or 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.
- In infants with ROP, reactivation of abnormal angiogenesis and tortuosity may occur following treatment with EYLEA. Infants should be monitored closely after injection with EYLEA until retinal vascularization has completed or until the examiner is assured that reactivation of ROP will not occur. Treatment with EYLEA will necessitate extended periods of ROP monitoring and additional EYLEA injections and/or laser treatments may be necessary.
- 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.
- In pre-term infants with ROP receiving EYLEA the most common adverse reactions (≥4%) reported were retinal detachment, conjunctival hemorrhage, and intraocular pressure increased. Adverse reactions established for adult indications are considered applicable to pre-term infants with ROP, though not all were observed in the clinical studies.
- 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 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 aflibercept 8 mg; 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 aflibercept 8 mg for the treatment of patients with wet age-related macular degeneration, diabetic macular edema, and diabetic retinopathy (including potential approval by the U.S. Food and Drug Administration based on the Biologics License Application discussed in this press release); 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 (such as aflibercept 8 mg); 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 (such as aflibercept 8 mg) 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, including without limitation aflibercept 8 mg; 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; the extent to which the results from the research and development programs conducted by Regeneron and/or its collaborators or licensees may be replicated in other studies and/or lead to advancement of product candidates to clinical trials, therapeutic applications, or regulatory approval; 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, collaboration, or supply agreement, including Regeneron's agreements with Sanofi and Bayer (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® (aflibercept) Injection, 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, 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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Source: Regeneron Pharmaceuticals, Inc.