Two-Year Results From Phase 3 VIVID-DME Trial of EYLEA® (aflibercept) Injection for the Treatment of Diabetic Macular Edema Show Sustained Improvement in Vision

July 18, 2014

TARRYTOWN, N.Y., July 18, 2014 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced that in the Phase 3 VIVID-DME trial of EYLEA® (aflibercept) Injection for the treatment of diabetic macular edema (DME), EYLEA 2 milligrams (mg) dosed monthly (2Q4) and EYLEA 2 mg dosed every two months (after 5 initial monthly injections, 2Q8) showed a sustained improvement from baseline in best corrected visual acuity (BCVA) at week 100 (2 years), compared to laser photocoagulation. The 52-week results (primary analyses) from this study have been previously reported.

Patients in the VIVID-DME trial were randomized to receive either EYLEA 2Q4 (n=136), EYLEA 2Q8 (n=135), or the comparator treatment of laser photocoagulation (n=132). After two years, patients receiving EYLEA 2Q4 had a mean change from baseline in BCVA of 11.4 letters (10.5 letters at 52 weeks, *P less than 0.0001 vs. laser*). Patients receiving EYLEA 2Q8 had a mean change from baseline in BCVA of 9.4 letters (10.7 letters at 52 weeks, *P less than 0.0001 vs. laser*). Patients in the laser photocoagulation treatment group had a mean change from baseline in BCVA of 0.7 letters (1.2 letters at 52 weeks). Additionally, 31.1 percent of patients receiving EYLEA 2Q8 achieved an increase of greater than or equal to 15 letters, or approximately 3 lines of vision, from baseline (*P = 0.0001),* and 38.2 percent receiving EYLEA 2Q4 achieved an increase of greater than or equal to 15 letters from baseline *(P less than 0.0001 vs. laser),* compared with 12.1 percent of patients in the laser control arm achieving similar vision gains.

"These data showed that treatment with EYLEA in this trial improved vision and maintained the improvement over two years in patients with diabetic macular edema," said George D. Yancopoulos, M.D., Ph. D., Chief Scientific Officer of Regeneron and President of Regeneron Laboratories.

In this trial, EYLEA had a similar overall incidence of adverse events (AEs), ocular serious AEs, and non-ocular serious AEs across the EYLEA treatment groups and the laser control group. The most frequent ocular AEs observed in the VIVID-DME trial included conjunctival hemorrhage, cataract, and increased intraocular pressure. The most frequent non-ocular AEs included nasopharyngitis and hypertension. Arterial thromboembolic events as defined by the Anti-Platelet Trialists' Collaboration (non-fatal stroke, non-fatal myocardial infarction, and vascular death) were similar across the treatment groups and the laser control group with events occurring in 8 out of 136 patients in the EYLEA 2Q4 group, 5 out of 135 patients in the EYLEA 2Q8 group, and 3 out of 133 patients in the laser group. Four out of 136 patients died in the EYLEA 2Q4 group, 6 out of 135 patients in the EYLEA 2Q8 group, and 1 out of 133 patients in the laser treatment group.

Full two-year data from the VIVID-DME trial will be presented at upcoming medical conferences. Both the VIVID-DME and VISTA-DME trials will continue as planned up to 148 weeks.

EYLEA was approved in the United States for the treatment of neovascular (wet) Age-related Macular Degeneration (AMD) in November 2011 and for Macular Edema following Central Retinal Vein Occlusion (CRVO) in September 2012. EYLEA has also been approved in the EU and other countries for use in wet AMD and Macular Edema following CRVO. In Europe, the CHMP has given a positive opinion recommending approval for EYLEA in the treatment of DME. Regulatory submissions have also been made in Japan, Asia Pacific, Latin America, and the U.S., for the treatment of DME. In Japan, EYLEA has been additionally submitted for approval to regulators for the treatment of choroidal neovascularization secondary to pathologic myopia (mCNV). A regulatory submission has been made in the U.S. and Europe for EYLEA for the treatment of macular edema following Branch Retinal Vein Occlusion (BRVO).

Bayer HealthCare and Regeneron are collaborating on the global development of EYLEA. Regeneron maintains exclusive rights to EYLEA in the United States. Bayer HealthCare licensed the exclusive marketing rights outside the United States, where the companies share equally the profits from sales of EYLEA, except for Japan where Regeneron receives a percentage on net sales.

About the EYLEA® (aflibercept) Injection Phase 3 DME Program
The global Phase 3 DME program consists of three double-masked trials: VIVID-DME, VISTA-DME, and VIVID-EAST-DME, and one open-label, single-arm safety trial in Japanese patients (VIVID-Japan). All three double-masked studies have three treatment arms, where patients are randomized to receive either EYLEA 2 mg monthly, EYLEA 2 mg every two months (after 5 initial monthly injections), or the comparator treatment of laser photocoagulation. Based on protocol specified criteria, patients were eligible to receive rescue treatment from week 24 onwards. Rescue treatment in the EYLEA groups was adjunct laser treatment, and in the laser control group it was EYLEA 2 mg. The primary endpoint of all three studies is the mean change in best-corrected visual acuity from baseline, as measured on the Early Treatment Diabetic Retinopathy Scale (ETDRS) eye chart, a standard chart used in research to measure visual acuity. The VIVID-DME, VISTA-DME, and VIVID-EAST-DME studies are ongoing.

About Diabetic Macular Edema (DME)
Diabetic Macular Edema (DME) is a common complication of Diabetic Retinopathy (DR), a disease affecting the blood vessels of the retina. Clinically significant DME occurs when fluid leaks into the center of the macula, the light-sensitive part of the retina responsible for sharp, direct vision. Fluid in the macula can cause severe vision loss or blindness.

DME is the most frequent cause of blindness in young and mid-aged adults. The treatable population for DME globally is estimated at about 6.2 million people. According to the American Diabetes Association, over 18 million Americans currently suffer from diabetes, and many more are at risk for developing diabetes. The incidence of diabetes is steadily climbing and it is projected that up to seven percent of all patients with diabetes will develop DME during their lifetime.

About EYLEA® (aflibercept) Injection for Intravitreal Injection
Vascular Endothelial Growth Factor (VEGF) is a naturally occurring protein in the body. In patients with diabetic macular edema (DME),

hyperglycemia-induced vascular dysfunction and hypoxia result in elevated intraocular VEGF levels in the eye and resultant blood vessel permeability that leads to macular edema, which can result in vision loss. EYLEA is a recombinant fusion protein, consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 and formulated as an iso-osmotic solution for intravitreal administration. EYLEA acts as a soluble decoy receptor that binds VEGF-A and placental growth factor (PlGF) and thereby can inhibit the binding and activation of their cognate VEGF receptors.

IMPORTANT PRESCRIBING INFORMATION FOR EYLEA® (aflibercept) INJECTION IN THE UNITED STATES

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with neovascular (Wet) Age-related Macular Degeneration (AMD). The recommended dose for EYLEA is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

EYLEA is indicated for the treatment of patients with Macular Edema following Central Retinal Vein Occlusion (CRVO). The recommended dose for EYLEA is 2 mg administered by intravitreal injection every 4 weeks (monthly).

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 use of intravitreal VEGF inhibitors, including EYLEA, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of ATEs in the VIEW 1 and VIEW 2 wet AMD studies in patients treated with EYLEA was 1.8 percent during the first year. The incidence of ATEs in the COPERNICUS and GALILEO CRVO studies was 0 percent in patients treated with EYLEA compared with 1.4 percent in patients receiving sham control during the first six months.

The most common adverse reactions (5 percent or more) noted in the U.S. prescribing information for the approved indications of EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

Serious adverse reactions related to the injection procedure have occurred in less than 0.1 percent of intravitreal injections with EYLEA including endophthalmitis, traumatic cataract, increased intraocular pressure, and vitreous detachment.

Please see the full U.S. Prescribing Information for EYLEA at www.EYLEA.com

About the EYLEA® (aflibercept) Injection Global Collaboration

Regeneron is collaborating with Bayer HealthCare on the global development of EYLEA. EYLEA is currently marketed for the treatment of wet AMD in over 50 countries outside the U.S., including Japan and Australia. Bayer HealthCare has received a positive recommendation for approval by the European Committee for Medicinal Products for Human Use (CHMP) for the treatment of visual impairment due to Macular Edema secondary to Central Retinal Vein Occlusion (CRVO).

Regeneron maintains exclusive rights to EYLEA in the United States.

About Regeneron Pharmaceuticals

Regeneron is a leading science-based biopharmaceutical company based in Tarrytown, New York that discovers, invents, develops, manufactures, and commercializes medicines for the treatment of serious medical conditions. Regeneron commercializes medicines for eye diseases, colorectal cancer, and a rare inflammatory condition and has product candidates in development in other areas of high unmet medical need, including hypercholesterolemia, oncology, rheumatoid arthritis, asthma, and atopic dermatitis. For additional information about the company, please visit www.regeneron.com.

About Bayer HealthCare

The Bayer Group is a global enterprise with core competencies in the fields of health care, agriculture and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of EUR 18.9 billion (2013), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover, develop, manufacture and market products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 56,000 employees (Dec 31, 2013) and is represented in more than 100 countries. More information at www.healthcare.bayer.com.

Regeneron Forward-Looking Statements

This news release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron, 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, such as the EYLEA® (aflibercept) Injection Phase 3 DME Program; the likelihood and timing of possible regulatory approval and commercial launch of Regeneron's late-stage product candidates and new indications for marketed products, such as the application of EYLEA® (aflibercept) Injection in the treatment of Diabetic Macular Edema, choroidal neovascularization secondary to pathologic myopia, and macular edema following Branch Retinal Vein Occlusion; ongoing regulatory obligations and oversight impacting Regeneron's 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; the ability of Regeneron to manufacture and manage supply chains for multiple products and product candidates; coverage and reimbursement determinations by third-party payers, including Medicare and Medicaid; unanticipated expenses; the costs of developing, producing, and selling products; the ability of Regeneron to meet any of its sales or other 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 and Bayer HealthCare LLC, 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. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2013 and its Form 10-Q for the quarterly period ended March 31, 2014. 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.

Bayer Forward-Looking Statements

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

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