NIH-Sponsored Comparative Effectiveness Trial in Diabetic Macular Edema Shows EYLEA® (aflibercept) Injection Demonstrated Significantly Greater Gains in Visual Acuity than Both Bevacizumab and Ranibizumab

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TARRYTOWN, N.Y., Feb. 18, 2015 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced that results from the National Institutes of Health (NIH)-sponsored, Diabetic Retinopathy Clinical Research Network comparative effectiveness study in patients with Diabetic Macular Edema (Protocol T) were published in the *New England Journal of Medicine* and a corresponding slide set was posted online at DRCR.net. EYLEA® (aflibercept) Injection demonstrated significantly greater improvement on the primary endpoint of mean visual acuity letter score change at one year [EYLEA +13 letters; bevacizumab (Avastin®) +10; ranibizumab (Lucentis®) +11]. These differences were driven by patients with moderate or worse vision loss at the start of the trial (worse than 20/40); in these patients, EYLEA showed a statistically significant 7-letter (approximately 1.5 lines on an eye chart) improvement over bevacizumab and a 5-letter (1 line on an eye chart) improvement over ranibizumab (EYLEA +19 letters; bevacizumab +12; ranibizumab +14).

"In this independent, government-sponsored diabetic macular edema study, EYLEA provided significantly greater efficacy, despite one fewer injection and fewer laser treatments than comparators," said George D. Yancopoulos, M.D., Ph.D., Chief Scientific Officer of Regeneron and President of Regeneron Laboratories. "The improvements with EYLEA relative to alternative anti-VEGF therapies were particularly apparent in the group with moderate or worse vision loss at the start of the trial, where there was a greater opportunity to demonstrate gains in vision."

Key efficacy results at 52 weeks included:

- In the overall population (n=660), for the primary endpoint of mean change from baseline in best corrected visual acuity (BCVA), patients receiving EYLEA had a mean change from baseline of +13 letters. Patients treated with bevacizumab had a mean change from baseline of +10 letters (p less than 0.001, EYLEA vs. bevacizumab) and patients treated with ranibizumab had a mean change from baseline of +11 letters (p=0.03, EYLEA vs. ranibizumab).
- In the pre-specified group of approximately 50 percent of patients (n=305) with baseline visual acuity worse than 20/40, patients receiving EYLEA had a mean change from baseline in BCVA of +19 letters (almost 4 lines). Patients treated with bevacizumab had a mean change from baseline of +12 letters (almost 2.5 lines) (p less than 0.001, EYLEA vs. bevacizumab) and patients treated with ranibizumab had a mean change from baseline of +14 letters (almost 3 lines) (p equals 0.003, EYLEA vs. ranibizumab). There were no differences in visual acuity changes in those patients with baseline vision of 20/40 or better, with all groups gaining approximately 8 letters. However, even in these patients, both EYLEA and ranibizumab showed a statistically significant improvement in retinal edema, as measured by Optical Coherence Tomography (OCT) compared to bevacizumab (p less than 0.001).
- In the overall population, 42 percent of patients receiving EYLEA gained at least 15 letters (3 lines on an eye chart) in BCVA from baseline compared to 29 percent of patients treated with bevacizumab (p=0.03) and 32 percent of patients treated with ranibizumab (p=0.07).
- In the patients with baseline visual acuity worse than 20/40, 67 percent of patients receiving EYLEA gained at least 15 letters in BCVA from baseline, compared to 41 percent of patients treated with bevacizumab (p less than 0.001) and 50 percent of patients treated with ranibizumab (p=0.01). In patients with baseline visual acuity of 20/40 or better, there were no significant differences among groups.
- The median number of injections using the protocol-specified retreatment regimen was one fewer in patients treated with EYLEA (9 injections) compared to bevacizumab (10 injections) and ranibizumab (10 injections).
- Macular laser treatments could be initiated at or after the 24-week visit and repeated as often as every 13 weeks based on protocol specified criteria. Macular laser treatment was performed at least once in 36 percent of the patients in the EYLEA group, 56 percent of patients in the bevacizumab group (p less than 0.001; EYLEA vs. bevacizumab) and 46 percent of patients in the ranibizumab group (p = 0.058 EYLEA vs. ranibizumab).

In this study, the rates of most ocular and systemic adverse events (AEs) were similar across the three study groups. Additional safety findings included:

- The rates of arterial thromboembolic events as defined by the Anti-Platelet Trialists' Collaboration (non-fatal stroke, non-fatal myocardial infarction, and vascular death) in the trial were 3 percent in the EYLEA group, 4 percent in the bevacizumab group and 5 percent in the ranibizumab group.
- There were no differences in intraocular inflammation among the three treatment groups.
- There were no significant differences in overall rates of major cardiovascular events among the groups. In a post hoc analysis of combined cardiac and vascular events, there were more events in the ranibizumab group (17 percent), compared to the EYLEA group (8 percent) and the bevacizumab group (9 percent) (nominal p equals 0.012); this included

more cardiac events (11 percent ranibizumab; 6 percent EYLEA; 6 percent bevacizumab) and cerebrovascular events (5 percent ranibizumab; 0 percent EYLEA; 2 percent bevacizumab).
- The rate of death was 1 percent in the EYLEA group, 2 percent in the bevacizumab group, and 2 percent in the ranibizumab group.

The investigators plan to present the results at the Annual Macula Society Meeting, February 25-28, 2015 in Scottsdale, Arizona.

The independent, government-sponsored study was designed to compare three different anti-VEGF therapies, EYLEA, bevacizumab and ranibizumab, for the treatment of diabetic macular edema (DME). In the study, 660 patients were randomized to receive either EYLEA 2 milligrams (mg), bevacizumab 1.25 mg, or ranibizumab 0.3 mg dosed according to a protocol-specified algorithm. Patients were treated with focal/grid laser at or after the 24 week visit if: 1) the OCT central subfield thickness was greater than or equal to 250 microns or there was edema that was threatening the fovea and 2) the eye did not improve on OCT or visual acuity from the last two consecutive injections. The full publication is available at www.nejm.org.

About Diabetic Macular Edema (DME)
Diabetic Macular Edema (DME) or "swelling of the macula" is a common complication in the eyes of patients with diabetes. It is the most frequent cause of vision loss in patients with diabetes and eventually can lead to blindness. It is estimated that of the 29.1 million American adults living with diabetes, 1.5 million have been diagnosed with DME, and approximately another million cases are undiagnosed.

DME occurs when blood vessels in the retina are damaged by chronic high blood sugar levels caused by diabetes. This allows fluid from blood vessels to leak into the retina, causing macular swelling. Fluid in the macula can cause severe vision loss or blindness. The macula is the part of the retina responsible for central, fine vision.

Vascular endothelial growth factor (VEGF), a naturally occurring family of growth factors in the body, appears to play a critical role in the development of DME. Increased VEGF production contributes to the vascular disruptions and leakage that characterize DME, as well as the formation of new blood vessels (a process known as angiogenesis).

About EYLEA® (aflibercept) Injection for Intravitreal Injection
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor formulated as an injection for the eye. EYLEA 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. EYLEA helps prevent VEGF-A and PLGF from interacting with their natural VEGF receptors as shown in preclinical studies.

IMPORTANT PRESCRIBING INFORMATION FOR EYLEA® (aflibercept) INJECTION

EYLEA® (aflibercept) Injection is a prescription medicine approved for the treatment of patients with:

- Wet Age-related Macular Degeneration (AMD): The recommended dose for EYLEA is 2 mg administered by injection in the eye every 2 months (8 weeks) following 3 initial monthly (4 weeks) injections. EYLEA may be dosed once per month, but additional benefit was not seen with this dosing plan.
- Macular Edema following Retinal Vein Occlusion (RVO): The recommended dose for EYLEA is 2 mg administered by injection in the eye monthly (every 4 weeks).
- Diabetic Macular Edema (DME): The recommended dose for EYLEA is 2 mg administered by injection in the eye every 2 months (8 weeks) following 5 initial monthly (4 weeks) injections. EYLEA may be dosed once per month, but additional benefit was not seen with this dosing plan.

IMPORTANT SAFETY INFORMATION FOR EYLEA® (aflibercept) INJECTION

EYLEA® (aflibercept) Injection is a prescription medication administered by injection into the eye. Patients should not use EYLEA if they have an infection in or around the eye, eye pain or redness, or known allergies to any of the ingredients in EYLEA, including aflibercept. As with all medications, EYLEA can cause side effects.

Injection into the eye can result in an infection in the eye and retinal detachment. Inflammation in the eye has been reported with the use of EYLEA.

In some patients, injections with EYLEA may trigger a temporary increase in eye pressure within 1 hour of the injection. Sustained increases in eye pressure have been reported with repeated injections, and doctors may monitor this after each injection.

There is a potential risk of serious and sometimes fatal side effects related to blood clots, leading to heart attack or stroke in patients receiving EYLEA.

Serious side effects related to the injection procedure are rare but can occur including infection inside the eye and retinal detachment.

The most common side effects reported in patients receiving EYLEA are increased redness in the eye, eye pain, cataract, moving spots in the field of vision, increased pressure in the eye, and vitreous (gel-like substance) detachment.

It is important that patients contact their doctor right away if they think they might be experiencing any side effects.

EYLEA is for prescription use only. For additional safety information, please see the full Prescribing Information for EYLEA.

Patients are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1- 800-FDA-1088.

About Regeneron Pharmaceuticals, Inc.
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.

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Forward-Looking Statements

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"), 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; 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 EYLEA® (aflibercept) Injection; 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), such as the comparative effectiveness study in patients with DME discussed in this news release, 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; 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 U.S. Securities and Exchange Commission, including its Form 10-K for the fiscal year ended December 31, 2014. 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.

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