NIH-sponsored Trial Finds EYLEA® (aflibercept) Injection Reduced Vision-threatening Complications by 68% after Two Years in Diabetic Retinopathy Patients

March 30, 2021

TARRYTOWN, N.Y., March 30, 2021 /PRNewswire/ --

Protocol W trial data confirm results from PANORAMA trial showing EYLEA significantly reduced vision-threatening complications and improved anatomic measures of diabetic retinopathy

Although patients' overall vision was similar in the EYLEA and sham groups at two years in Protocol W, a new analysis from PANORAMA shows that delaying EYLEA treatment (sham group) was associated with prolonged periods of vision loss

Two diabetic retinopathy trials (Protocol W and PANORAMA) have now shown the benefit of EYLEA every 16 weeks following an initial dosing period; Regeneron to discuss 16-week dosing interval with U.S. FDA

Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced *JAMA Ophthalmology* has published initial results from the National Institutes of Health-sponsored Protocol W trial assessing EYLEA® (aflibercept) Injection in patients with moderate to severe non-proliferative diabetic retinopathy (NPDR), without center-involved diabetic macular edema (CI-DME). At two years, the primary outcome of the trial showed a 68% reduced risk of developing vision-threatening complications (either proliferative diabetic retinopathy [PDR] or CI-DME with vision loss) in patients who received the EYLEA every-16-weeks dosing regimen. In comparison, patients receiving sham injections were almost five times more likely to experience disease progression requiring EYLEA rescue therapy.

Although at the two-year time point of Protocol W, preventive EYLEA treatment did not confer a significant difference in visual acuity versus delayed EYLEA treatment following vision-threatening complications (i.e., sham), a recent Regeneron follow-up analysis in the similarly designed PANORAMA trial found that delaying EYLEA treatment resulted in three times as many patients suffering prolonged vision loss, compared to those receiving preventive EYLEA treatment, during a two-year period. A similar analysis has not yet been conducted for Protocol W.

"Blindness is one of the most feared consequences of diabetic retinopathy, and we thank the National Eye Institute and the DRCR Retina Network for conducting a well-controlled trial that provides useful information to guide treatment in these patients," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer at Regeneron. "Protocol W confirms the landmark results of the similarly-designed PANORAMA trial, underscoring the importance of early and regular diabetic retinopathy treatment and the ability of EYLEA to substantially reduce vision-threatening complications and improve disease severity. Importantly, these results were obtained with an every-16-weeks EYLEA dosing regimen, confirming the efficacy with EYLEA seen in the PANORAMA trial."

In Protocol W, patients were randomly assigned to receive either EYLEA (2 mg, n=200 eyes) every 16 weeks, after receiving four initial doses at weeks 0, 4, 8 and 16, or sham (n=199 eyes). Patients had excellent vision when they entered the trial, with more than three-quarters of eyes having 20/20 visual acuity or better (78% EYLEA, 81% sham). Rescue therapy (primarily EYLEA) was administered to patients if they developed either PDR or CI-DME.

Compared to sham, EYLEA-treated patients were:

- **68% less likely to develop CI-DME with vision loss or PDR**, the primary outcome measure at two years (p<0.001).
  - The cumulative probability of developing PDR or CI-DME with vision loss was 16% with EYLEA versus 44% with sham. EYLEA patients were 66% less likely to develop PDR (p<0.001) and 64% less likely to develop CI-DME with vision loss (p=0.002).
- **Three times more likely to experience at least a two-step improvement in their DR severity score (DRSS)**. In total, 69 (45%) EYLEA patients experienced at least a two-step improvement, versus 22 (14%) of those in the sham group (adjusted odds ratio [OR]: 5.91; p<0.001).
- **Five times less likely to require rescue therapy with EYLEA** due to PDR or DME (4% EYLEA, 19% sham). Other rescue treatments were panretinal photocoagulation (PRP) (<1% EYLEA, 2% sham), vitrectomy for PDR (<1% EYLEA, <1% sham) and focal/grid laser treatment for DME (0% EYLEA, 2% sham).

In the retrospective PANORAMA analysis of vision outcomes over two years, three times more patients in the sham group suffered from prolonged vision loss (range: 6 weeks to 6 months), compared to the EYLEA every-16-weeks dosing group (12 of 135 EYLEA, 38 of 133 sham). Results by loss of letters were as follows (as measured by the Early Treatment Diabetic Retinopathy Study [ETDRS] chart):

- **≥5 letter loss:** 9% EYLEA versus 29% sham, nominal p<0.0001.
- **≥10 letter loss:** 5% EYLEA versus 14% sham, nominal p=0.0212.
- **≥15 letter loss:** 3% EYLEA versus 8% sham, nominal p=0.0672.

No new safety signals were identified in Protocol W, consistent with the known safety profile of EYLEA. Ocular adverse events (AEs) included endophthalmitis (n=3 EYLEA, n=0 sham). The rate of any cardiovascular/cerebrovascular AEs was not significantly different among the treatment groups (9% of patients treated with EYLEA in one eye, 9% of patients treated with sham in one eye, and 8% of patients treated with both EYLEA [one

eye] and sham [other eye]).

"Diabetic retinopathy is the leading cause of blindness among working adults. However, vision loss is often preventable if proactive measures are taken by patients and their doctors," said Allen C. Ho, M.D., Attending Surgeon and Director of Retina Research at Wills Eye Hospital in Philadelphia, PA. "Past trials have shown that early systemic and ocular intervention in diabetic eye disease can lead to sustained improvements in visual acuity over the long term, while undertreatment can put patients' vision at risk. The latest data from Protocol W and PANORAMA support this treatment philosophy by showing that an every-16-week EYLEA regimen helped patients avoid vision-threatening complications and prolonged periods of vision loss over two years. I look forward to seeing additional Protocol W vision outcomes at four years."

EYLEA is the only vascular endothelial growth factor (VEGF) inhibitor that is U.S. Food and Drug Administration (FDA) approved with two dosing intervals for DR, allowing doctors to customize treatment. In DR, EYLEA may be dosed every eight weeks following five initial monthly injections, or every four weeks. EYLEA is not approved for 16-week dosing as was studied in Protocol W.

About Protocol W
Protocol W is a four-year, randomized, multi-center, controlled Phase 3 trial (n=399 eyes) designed to determine the efficacy of EYLEA compared to sham in preventing vision-threatening complications in high risk patients. The primary outcome at two years was time to development of CI-DME with vision loss or PDR. Key secondary outcomes included development of any PDR or DME criteria based on reading center assessment, as well as development of CI-DME with a ≥10% and ≥25 micron increase in center subfield thickness. Per the trial protocol, Protocol W will continue for another two years, when the second primary outcome will assess visual acuity outcomes between the two groups at four years.

The Clinicaltrials.gov identifier for this trial is NCT02634333. The trial was supported by the National Eye Institute (NEI) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), with funding through the Special Diabetes Program, through a cooperative agreement (EY14231).

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 PDR, a stage of the disease in which abnormal blood vessels grow onto the surface of the retina and into the vitreous cavity, potentially causing severe vision loss. DME can occur at any stage of DR 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 DR without DME.

About EYLEA® (aflibercept) Injection
EYLEA® (aflibercept) Injection 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. In the U.S., EYLEA is the market-leading, FDA-approved anti-VEGF treatment for its approved indications and is supported by a robust body of research that includes eight 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 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, hematology, 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 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 (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 (collectively, "Regeneron's Product Candidates") and research and clinical programs now underway or planned, including without limitation EYLEA® (aflibercept) Injection; uncertainty of 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 study discussed in this press release, on the commercial success of Regeneron's Products (such as EYLEA) and Regeneron's Product Candidates; the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's Product Candidates and new indications or dosing intervals for Regeneron's Products, such as the 16-week dosing interval for EYLEA discussed in this press release; safety issues resulting from the administration of Regeneron's Products (such as EYLEA) 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; the extent to which the results from the research and development programs conducted by Regeneron and/or its collaborators may be replicated in other studies and/or lead to advancement of product candidates to clinical trials, therapeutic applications, or regulatory approval; 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 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, collaboration, or supply 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 with 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, 2020. 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).

Contacts:

Media Relations
Taylor Ramsey
Tel: +1 (914) 409-2381
taylor.ramsey@regeneron.com

Investor Relations
Mark Hudson
Tel: +1 (914) 355-0213
Mark.Hudson@regeneron.com

View original content:http://www.prnewswire.com/news-releases/nih-sponsored-trial-finds-eylea-aflibercept-injection-reduced-vision-threatening-complications-by-68-after-two-years-in-diabetic-retinopathy-patients-301259081.html

SOURCE Regeneron Pharmaceuticals, Inc.