Two-year PULSAR Trial Results for Aflibercept 8 mg Demonstrate Durable Vision Gains at Extended Dosing Intervals in Wet Age-related Macular Degeneration

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78% of all aflibercept 8 mg patients maintained ≥12-week dosing intervals throughout the two-year study period

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Visual gains and safety of aflibercept 8 mg remained consistent with the established profile of EYLEA® (aflibercept) 2 mg Injection

TARRYTOWN, N.Y., Aug. 10, 2023 (GLOBE NEWSWIRE) -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced positive, two-year (96 weeks), topline data from the pivotal PULSAR trial investigating aflibercept 8 mg in patients with wet age-related macular degeneration (wAMD). During the trial, aflibercept 8 mg patients were initially randomized to either 12- or 16-week dosing intervals (after three initial monthly doses) and were able to shorten or extend dosing intervals if pre-specified criteria were met. The longer-term data follow the positive two-year results for PHOTON with diabetic macular edema (DME), with PULSAR similarly demonstrating that the vast majority of aflibercept 8 mg patients with wAMD were able to maintain or further extend their dosing intervals. Among those who completed the two-year follow-up:

- 88% were on a ≥12-week dosing interval at the end of two years.
- 78% maintained ≥12-week dosing intervals throughout the two-year study period, compared to 83% throughout the first year of study (48 weeks).
- 71% met the extension criteria for even longer dosing intervals, including 47% for ≥20-week intervals and 28% for 24-week intervals.
- Of those assigned to ≥16-week dosing regimen at baseline, 70% maintained ≥16-week dosing intervals throughout the two-year study period. At the end of two years, 78% were eligible for ≥16-week dosing, with 53% eligible for ≥20-dosing week intervals.

“It is great to see aflibercept 8 mg deliver another set of exciting results,” said Charles C. Wykoff, M.D., Ph.D., Director of Research at Retina Consultants of Texas and a trial investigator. “In the PULSAR trial, aflibercept 8 mg achieved impressive durability, while importantly maintaining visual acuity gains from year one through year two. These data are consistent with the results from the PHOTON trial in diabetic macular edema, with both trials demonstrating a consistent safety profile with substantially fewer treatments than EYLEA. If approved by regulatory authorities, aflibercept 8 mg has the potential to become the new standard of care for diabetic macular edema and wet age-related macular degeneration.”

PULSAR (N= 1,009) is a double-masked, active-controlled pivotal trial evaluating non-inferiority of aflibercept 8 mg 12-week (n=335) and 16-week (n=338) dosing regimens compared to an 8-week dosing regimen for EYLEA® (aflibercept) Injection (n=336). All patients received three initial monthly doses. The PULSAR trial met its primary endpoint last year with aflibercept 8 mg patients achieving clinically equivalent vision gains to EYLEA. Through two years, vision gains were sustained and remained largely consistent with the results at one year.

	Through 48 weeks (one year)			Through 96 weeks (two years)		
	EYLEA 8-week regimen	**aflibercept 8 mg 12-week regimen**	**aflibercept 8 mg 16-week regimen**	**EYLEA 8-week regimen**	**aflibercept 8 mg 12-week regimen**	**aflibercept 8 mg 16-week regimen**
Mean number of injections^	6.9	6.1	5.2	12.8	9.7	8.2
LS mean (SE) change from baseline, letters	7.0 (0.74)	6.1 (0.77)	5.9 (0.72)	6.6 (0.73)	5.6 (0.77)	5.5 (0.75)
Difference in LS mean (95% CI), letters		-0.97* (-2.87, 0.92)	-1.14† (-2.97, 0.69)		-1.01‡ (-2.82, 0.80)	-1.08§ (-2.87, 0.71)

LS: least squares; SE: standard error
^Based on patients completing week 48 or 96 in the trial
*Non-inferiority p-value: p=0.0009
†Non-inferiority p-value: p=0.0011
‡Nominal non-inferiority p-value: p=0.0006
§Nominal non-inferiority p-value: p=0.0007

In PULSAR, the safety of aflibercept 8 mg continued to be similar to EYLEA through two years and remained consistent with the known safety profile of EYLEA from previous clinical trials for wAMD. There were no cases of retinal vasculitis, occlusive retinitis or endophthalmitis in the aflibercept 8 mg group. The rate of intraocular inflammation was 1.3% for the aflibercept 8 mg group and 2.1% for the EYLEA group. Anti-platelet trialists' collaboration-defined arterial thromboembolic treatment-emergent adverse events occurred in 1.8% of patients treated with aflibercept 8 mg and 3.3% of patients

treated with EYLEA.

“Through one and two years of treatment, aflibercept 8 mg has repeatedly demonstrated unprecedented durability in maintaining clinically meaningful outcomes with extended dosing regimens for patients with retinal disease,” said George D. Yancopoulos, M.D., Ph.D., Board co-Chair, President and Chief Scientific Officer at Regeneron, and a principal inventor of EYLEA. “Throughout the development of aflibercept 8 mg, we have focused on meaningfully transforming the treatment of retinal disease for patients. With PHOTON and now PULSAR, we are proud to have produced landmark, long-term results that may help to reduce the treatment burden for the millions of people living with wet age-related macular degeneration and diabetic macular edema around the world.”

The two-year data from PULSAR are planned for presentation at an upcoming medical meeting. The two-year data from the pivotal PHOTON trial for aflibercept 8 mg in DME were presented at the American Society of Retina Specialists annual meeting in July 2023.

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

About the Aflibercept 8 mg Clinical Trial Program
PULSAR in wAMD and PHOTON in DME 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. The lead sponsors of the trials were Bayer for PULSAR and Regeneron for PHOTON.

Patients treated with aflibercept 8 mg in both trials had 3 initial monthly doses, and patients treated with EYLEA received 3 initial doses in PULSAR and 5 in PHOTON. 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. Patients in all EYLEA groups maintained a fixed 8-week dosing regimen throughout their participation in the trials.

About wAMD and 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 1.4 million Americans have 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.

About Ophthalmology at Regeneron
At Regeneron, we relentlessly pursue groundbreaking innovations in eye care science to help maintain the eye health of the millions of Americans impacted by vision-threatening conditions. Over a decade ago, our breakthrough scientific research resulted in the development of EYLEA, a vascular endothelial growth factor (VEGF) inhibitor designed to block the growth of new blood vessels and decrease the ability of fluid to pass through blood vessels in the eye. EYLEA has since brought fundamental change to the retinal disease treatment landscape and is supported by a robust body of research that includes eight pivotal Phase 3 trials, 11 years of real-world experience, and more than 64 million EYLEA injections globally.

Regeneron continues to advance our anti-angiogenesis expertise with new solutions with the aim of offering optimal flexibility for a broad group of patients and eye care professionals. This includes aflibercept 8 mg, which has been developed with the aim of extending the time between injections, while maintaining the vision gains, anatomic benefits and safety previously observed with EYLEA.

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) (0.4 mg [0.01 mL]).

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 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, Regeneron's unique ability to repeatedly and consistently translate science into medicine has led to numerous FDA-approved treatments and product candidates in development, almost all of which were homegrown in Regeneron's laboratories. Regeneron's medicines and pipeline are designed to help patients with eye diseases, allergic and inflammatory diseases, cancer, cardiovascular and metabolic diseases, hematologic conditions, infectious diseases, and rare diseases.

Regeneron is accelerating and improving the traditional drug development process through its 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 Regeneron, please visit www.regeneron.com or follow Regeneron on LinkedIn.

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 nature, timing, and possible success and therapeutic applications of products marketed or otherwise commercialized by Regeneron and/or its collaborators or licensees (collectively, "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 (including aflibercept 8 mg) and new indications for Regeneron's Products; uncertainty of the utilization, market acceptance, and commercial success of Regeneron's Products and Regeneron's Product Candidates (such as aflibercept 8 mg) 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 (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; 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 (including, if approved, aflibercept 8 mg) 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; the impact of public health outbreaks, epidemics, or pandemics (such as the COVID-19 pandemic) on Regeneron's business; 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 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 and its Form 10-Q for the quarterly period ended June 30, 2023. 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 (https://investor.regeneron.com) and its LinkedIn page (https://www.linkedin.com/company/regeneron-pharmaceuticals).

Contacts:

Media Relations
Mary Heather
Tel: +1 914-847-8650
mary.heather@regeneron.com

Investor Relations
Mark Hudson
Tel: +1 914-847-3482
mark.hudson@regeneron.com

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