# Regeneron Presents Encouraging Phase 2 Results for High-dose Aflibercept 8 mg in Wet Age-related Macular Degeneration at Angiogenesis Meeting

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**Trial met primary safety endpoint and no new safety signals seen through week 44**

**Results favored aflibercept 8 mg in visual acuity, drying and other anatomical measures through week 44**

**Phase 3 results in wet age-related macular degeneration and diabetic macular edema expected in the second half of 2022**

Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced results from its Phase 2 proof-of-concept trial evaluating an investigational 8 mg high dose of aflibercept compared to the currently-approved 2 mg dose of EYLEA® (aflibercept) Injection in patients with wet age-related macular degeneration (wet AMD). The results will be presented at the Angiogenesis (Angiogenesis, Exudation, and Degeneration) 2022 annual meeting on Saturday, February 12.

As previously announced, more patients treated with aflibercept 8 mg had no retinal fluid at week 16, when the primary efficacy endpoint was assessed. At this timepoint, 43% (n=23/53) had no fluid in the macula compared to 26% for EYLEA (n=14/53) (p=0.0667); and 51% (n=27) had no fluid in the center subfield compared to 34% for EYLEA (n=18) (p=0.0770). At week 16, patients in both treatment groups had received three initial doses (administered at weeks 0, 4 and 8), after which dosing was extended to every 12 weeks. In new results presented for the first time, aflibercept 8 mg continued to show numeric improvements in anatomical and vision outcomes compared to EYLEA through 44 weeks.

"These Phase 2 data in wet AMD demonstrate the exciting potential for aflibercept 8 mg to maintain dryness and improve vision compared to the standard-of-care EYLEA," said Dr. David Brown, Director of Research at Retina Consultants of Texas. "This is the first time we have seen a promising trend towards sustained improved vision over EYLEA in wet AMD. I look forward to seeing the results of the Phase 3 program investigating extended dosing of aflibercept 8 mg."

Eyes treated with aflibercept 8 mg were more likely to be dry in the center subfield on optical coherence tomography (OCT) compared to EYLEA at every timepoint measured throughout the trial after the initial monthly dosing period. At week 44 when the trial ended, key anatomical and vision changes included:

- 40% (n=21/53) of patients treated with aflibercept 8 mg did not have fluid in the center subfield compared to 28% (n=15/53) of patients treated with EYLEA (nominal p=0.2185).
- Twice as many patients treated with aflibercept 8 mg (32%, n=17/53) had no macular fluid compared to patients treated with EYLEA (15%, n=8/53) (nominal p=0.0395), as measured by spectral domain OCT. Measuring macular fluid provides an evaluation of a larger area of the retina compared to the center subfield and may provide a better understanding of the anatomical effects of treatment in wet AMD.
- 7.9 average letter improvement from baseline in the aflibercept 8 mg group, compared to 5.1 letters in the EYLEA group, as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters (nominal p=0.1957).
- Nearly half (47%) of aflibercept 8 mg patients achieved at least a 10-letter gain (2 lines on a vision test) and more than a quarter (28%) achieved more than 15 letters (3 lines on a vision test), compared to 35% and 18% for patients treated with EYLEA, respectively.

Through 44 weeks, adverse events (AEs) in the study eye occurred in 38% (n=20/53) of both aflibercept 8 mg and EYLEA patients. There were no serious AEs of intraocular inflammation (including occlusive retinal vasculitis), and no anti-platelet trialists' collaboration (APTC)-defined arterial thromboembolic events. The most common ocular AEs that occurred more frequently in the aflibercept 8 mg group were vitreous detachment (4 aflibercept 8 mg, 2 EYLEA), conjunctival hemorrhage (3 aflibercept 8 mg, 2 EYLEA) and retinal tear (2 aflibercept 8 mg, 0 EYLEA). There was one patient death in the aflibercept 8 mg unrelated to treatment.

"After more than two decades of following the science in retinal diseases, we are very proud of our legacy helping millions of patients to retain or improve their vision with EYLEA, which has set a very high bar for any new treatment," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer at Regeneron. "The results of this Phase 2 trial for aflibercept 8 mg are promising and we look forward to seeing the results from the Phase 3 program, which we hope will show that aflibercept 8 mg can deliver clinical outcomes that, at a minimum, will be comparable to standard-of-care EYLEA, but allow for extended dosing regimens."

Wet AMD is the leading cause of vision loss among people 50 years and older in the U.S. Existing anti-VEGF treatments including EYLEA have helped change the course of disease for millions of patients worldwide, and efforts to develop new medicines are focused on further enhancing clinical effectiveness while extending the time between treatment doses.

Aflibercept 8 mg is being jointly developed by Regeneron and Bayer. This new, concentrated high-dose aflibercept formulation enables a greater amount of medicine to be administered with each treatment, and could potentially extend the time between doses while retaining the efficacy and safety profile seen with EYLEA. Aflibercept 8 mg is currently under clinical development and its safety and efficacy have not been fully evaluated by

any regulatory authority.

**About the Phase 2 Trial**
The Phase 2 randomized, single-masked CANDELA trial (NCT04126317) enrolled 106 treatment-naïve patients with wet AMD. The trial was designed to investigate the safety, efficacy and tolerability of aflibercept 8 mg compared to the currently-approved 2 mg dose of EYLEA. Patients were randomized into two groups, with one group receiving aflibercept 8 mg (n=53) and the other group receiving EYLEA (n=53). Patients in both groups received three initial intravitreal injections (weeks 0, 4 and 8), before the primary endpoint was assessed at week 16, after which dosing was extended to every 12 weeks, or more frequently if required due to persistent or worsening disease. Efficacy was assessed via the presence of retinal fluid in the center subfield on optical coherence tomography at this timepoint.

Trial participants were at least 50 years of age (mean: 77 years), mean baseline retinal thickness was 502.1 microns, and the best corrected visual acuity (BCVA) ETDRS letter score was between 24 to 78 in the study eye (mean: 59 letters).

**About the Phase 3 Clinical Program**
There are two ongoing pivotal trials to investigate the efficacy and safety of aflibercept 8 mg versus EYLEA. In diabetic macular edema (DME), Regeneron is sponsoring the Phase 2/3 multi-center, randomized, double-masked PHOTON trial (NCT04429503). In wet AMD, Bayer is sponsoring the Phase 3 multi-center, randomized, double-masked PULSAR trial (NCT04423718) in treatment-naïve patients. Across both trials, patients are randomized into one of three treatment groups, testing aflibercept 8 mg with dosing regimens at either 12- or 16-week intervals or EYLEA with an 8-week dosing regimen.

**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), and Diabetic Retinopathy (DR).

**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 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.

**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.
- 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 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, 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 additional information about the company, 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 EYLEA® (aflibercept) Injection and aflibercept 8 mg; the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's Product Candidates (such as aflibercept 8 mg) and new indications for Regeneron's Products; the extent to which the results from the research and development programs conducted by Regeneron and/or its collaborators or licensees (including the aflibercept 8 mg development program and the Phase 2 proof-of-concept trial evaluating aflibercept 8 mg discussed in this press release) may be replicated in other studies and/or lead to advancement of product candidates to clinical trials, therapeutic applications, or regulatory approval; 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; 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; 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 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, 2021. 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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