Regeneron Announces Encouraging Topline Phase 2 Data of High-dose aflibercept in Wet Age-related Macular Degeneration

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Phase 3 trials in wet AMD and diabetic macular edema fully recruited, with results expected in the second half of 2022

Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced that an ongoing Phase 2 proof-of-concept trial evaluating an investigational 8 mg dose of aflibercept met its primary safety endpoint, with no new safety signals observed compared to the currently-approved 2 mg dose of EYLEA® (aflibercept) Injection in patients with wet age-related macular degeneration (wet AMD). In this small trial involving 106 patients, a higher proportion of patients in the aflibercept 8 mg group had no retinal fluid (43.4%, n=23/53) compared to patients treated with EYLEA 2 mg (26.4%, n=14/53) (p=0.067) at week 16, the primary efficacy endpoint. At this timepoint patients had received three initial doses (administered at weeks 0, 4 and 8), after which dosing was extended.

Aflibercept 8 mg is currently being evaluated in two large Phase 3 trials in wet AMD and diabetic macular edema (DME), which are expected to report results in the second half of 2022. The trials will assess the safety and efficacy of aflibercept 8 mg for up to two years, with visual acuity as the primary efficacy endpoint at 48 weeks, measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA). Both trials will assess aflibercept 8 mg compared to EYLEA 2 mg, testing dosing intervals of every 12 weeks and every 16 weeks.

"We are cautiously optimistic that these early data suggest that a higher dose of aflibercept may potentially benefit patients with wet AMD, and we look forward to Phase 3 data next year, which will be crucial to understand its overall efficacy and safety," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer of Regeneron. "Having worked for nearly two decades in retinal disease, we know that large, robust data sets are required to fully understand whether a medicine can achieve three critical things: improved visual and anatomic outcomes, convenient dosing, and a safety profile that is consistent with EYLEA."

During the initial 16 weeks of the Phase 2 trial, adverse events (AEs) in the study eye occurred in 17.0% (9 of 53) of aflibercept 8 mg patients and 22.6% (12 of 53) of EYLEA 2 mg patients. Serious ocular AEs occurred in two patients overall, one in the aflibercept 8 mg group (retinal tear) and one in the EYLEA 2 mg group (visual acuity reduced). There were no AEs of intraocular inflammation (including occlusive retinal vasculitis), anti-platelet trialists' collaboration (APTC)-defined arterial thromboembolic events or deaths in either patient group.

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. This new, concentrated high-dose aflibercept formulation enables a greater amount of medicine to be administered with each treatment, potentially extending the time between doses while retaining the efficacy and safety profile seen with EYLEA 2 mg.

Aflibercept 8 mg is being jointly developed by Regeneron and Bayer.

About the Phase 2 Trial
The Phase 2 randomized, single-masked trial (NCT04126317) enrolled 106 treatment-naïve patients with wet AMD. The trial was designed to investigate the safety, efficacy and tolerability of high-dose aflibercept (8 mg) compared to the existing approved dose of EYLEA (2 mg). Patients were randomized into two groups, with one group receiving aflibercept 8 mg (n=53) and the other group receiving EYLEA 2 mg (n=53). Patients in both groups received three initial 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 (OCT) at this timepoint. The trial will continue through week 44.

Trial participants were at least 50 years of age (mean: 77 years), baseline retinal thickness was 502.1 microns, and the 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 2 mg. In 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 2 mg with an 8-week dosing regimen.

EYLEA INDICATIONS AND IMPORTANT SAFETY INFORMATION

- 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.
- Patients may experience temporary visual disturbances after intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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, 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 (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 and high-dose aflibercept; the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's Product Candidates and new indications for Regeneron's Products, such as high-dose aflibercept; 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 high-dose aflibercept); 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; 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 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, including without limitation EYLEA; 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; 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, 2020 and its Form 10-Q for the quarterly period ended June 30, 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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