Regeneron Announces Positive Topline Results from Phase 3 Trial of Evinacumab in Patients with Severe, Inherited Form of High Cholesterol

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Adding evinacumab reduced LDL cholesterol by 49% in patients with homozygous familial hypercholesterolemia, compared to lipid-lowering therapies alone

Evinacumab was generally well-tolerated, and all evinacumab patients completed the six-month treatment period

Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced positive pivotal Phase 3 results for evinacumab, an investigational angiopoietin-like 3 (ANGPTL3) antibody, in patients with homozygous familial hypercholesterolemia (HoFH). Patients with HoFH have severely elevated levels of bad cholesterol (otherwise known as low-density lipoprotein cholesterol, or LDL cholesterol), and often experience early atherosclerotic disease, sometimes suffering cardiac events as early as their teenage years.

On average, patients entered the trial with LDL cholesterol levels of 255 mg/dL, despite treatment with other lipid-lowering therapies, including maximally-tolerated statins, PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors, ezetimibe, LDL apheresis and lomitapide. The trial met its primary endpoint, showing that adding evinacumab to other lipid-lowering therapies decreased LDL cholesterol by 49% on average, compared to lipid-lowering therapies alone.

"Currently HoFH patients face limited choices in reducing their LDL cholesterol, including therapies that are time-consuming like LDL apheresis, or that may have side effect concerns. Despite recent therapeutic advances, there is still a significant unmet need to lower the LDL cholesterol of many patients with HoFH. On average, evinacumab reduced patients' LDL cholesterol in half and was generally well-tolerated in the trial," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer of Regeneron. "These results raise the potential that evinacumab may have value for other patients with severe, refractory hypercholesterolemia, where we have a trial ongoing."

In 2017, the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy designation for evinacumab for the treatment of hypercholesterolemia in patients with HoFH.

Regeneron scientists discovered the angiopoietin gene family more than two decades ago. Human genetics research published in *The New England Journal of Medicine* in 2017 by scientists from the Regeneron Genetics Center found that patients whose ANGPTL3 gene did not function properly (called a "loss-of function mutation") have significantly lower levels of key blood lipids, including LDL cholesterol, and this is associated with a significantly lower risk of coronary artery disease.

"People born with homozygous familial hypercholesterolemia – the rare and most severe form of FH – are in urgent need of additional therapies to lower life-threatening cholesterol levels. HoFH causes aggressive heart disease even in childhood, and today's treatments often are not enough for these individuals," said Katherine Wilemon, Founder and Chief Executive Officer, FH Foundation. "These evinacumab Phase 3 results bring hope to those who need it most. The FH Foundation is grateful to the researchers who advanced this science and the individuals who participated in this clinical trial."

The Phase 3 trial was designed to assess the effect of evinacumab on LDL cholesterol and other lipid-related endpoints. Results from the evinacumab group at week 24 included:

- 49% reduction in LDL cholesterol from baseline, compared to placebo (47% reduction for evinacumab compared to a 2% increase for placebo, $p<0.0001$), the primary endpoint.
- 132 mg/dL absolute change in LDL cholesterol from baseline, compared to placebo (135 mg/dL reduction for evinacumab compared to a 3 mg/dL reduction for placebo, $p<0.0001$).
- 47% achieved LDL cholesterol levels less than 100 mg/dL, compared to 23% for placebo (nominal $p=0.0203$).
- Similar levels of LDL cholesterol-lowering were also observed in the most difficult-to-treat patients who often don't respond to certain other therapies, described as "null/null" or "negative/negative" patients.
- Evinacumab also reduced apolipoprotein B (ApoB), non-HDL cholesterol and total cholesterol compared to placebo.

LDL cholesterol reductions were observed from the first assessment at week 2, and were maintained throughout the 24-week double-blind treatment period.

In the trial, evinacumab was generally well-tolerated. During the double-blind treatment period, 66% of evinacumab patients and 81% of placebo patients experienced an adverse event (AE). AEs that occurred in at least 5% of patients and more commonly with evinacumab were influenza-like illness (11% evinacumab, 0% placebo) and rhinorrhea (7% evinacumab, 0% placebo). During the double-blind treatment period there was no difference in the incidence of nausea, abdominal pain or diarrhea between treatment groups, and there were no deaths, major adverse cardiovascular events or hepatic disorders.

HoFH is a serious, rare, genetic condition and affects approximately 1,300 people in the U.S. Detailed results from this trial will be presented at a future medical meeting, and data will be submitted to regulatory authorities, starting with the FDA in 2020.

About Evinacumab
Evinacumab is an investigational, fully-human, monoclonal antibody that specifically binds to angiopoietin-like protein 3 (ANGPTL3). ANGPTL3 acts as an inhibitor of lipoprotein lipase and endothelial lipase, and appears to play a central role in lipoprotein metabolism. It is currently being studied in patients with HoFH (Phase 3), refractory hypercholesterolemia (Phase 2) and severe hypertriglyceridemia (Phase 2).

About the ELIPSE HoFH Trial
ELIPSE HoFH is an ongoing Phase 3 randomized, double-blind, placebo-controlled, parallel-group trial evaluating the efficacy and safety of evinacumab 15 mg/kg administered intravenously every four weeks in 65 patients aged 12 years or older with HoFH (43 evinacumab, 22 placebo). The primary endpoint is reduction of LDL cholesterol with evinacumab 15 mg/kg compared to placebo after 24 weeks. Secondary endpoints evaluate safety, tolerability and pharmacokinetics (PK), as well as the efficacy of evinacumab on LDL cholesterol goal attainment and other lipid parameters (including ApoB and non-HDL cholesterol) and whether patients met criteria for needing LDL apheresis. The trial was not powered to evaluate the effect of evinacumab on cardiovascular events.

The average age of patients entering the trial was 42 years (range: 12 to 75). In the evinacumab treatment group, 98% of patients were on statins, 81% were on PCSK9 inhibitors, 75% were on ezetimibe, 33% were on LDL apheresis and 26% were on lomitapide. In addition, 35% of evinacumab patients had the most severe, "null/null" form of HoFH.

The trial has three treatment periods: 1) up to an eight-week run-in period; 2) a 24-week double-blind treatment period (DBTP); 3) and an ongoing, 24-week, open-label treatment period (OLTP). During the OLTP portion of the trial, which is ongoing, all patients receive evinacumab, regardless of treatment assignment in the DBTP.

About Regeneron
Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents life-transforming medicines for people with serious diseases. Founded and led for 30 years by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to seven FDA-approved treatments and numerous product candidates in development, all of which were homegrown in our laboratories. Our medicines and pipeline are designed to help patients with eye disease, allergic and inflammatory diseases, cancer, cardiovascular and metabolic diseases, infectious diseases, pain and rare diseases.

Regeneron is accelerating and improving the traditional drug development process through our proprietary *VelociSuite*® technologies, such as *VelocImmune*® which produces optimized fully-human antibodies, and 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 nature, timing, and possible success and therapeutic applications of Regeneron's products, product candidates, and research and clinical programs now underway or planned, including without limitation evinacumab for the treatment of homozygous familial hypercholesterolemia and other potential indications; the extent to which the results from the research and development programs conducted by Regeneron or its collaborators may be replicated in later studies and lead to therapeutic applications; unforeseen safety issues and possible liability resulting from the administration of products and product candidates in patients, including without limitation evinacumab; serious complications or side effects in connection with the use of Regeneron's products and product candidates (such as evinacumab) in clinical trials; the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's late-stage product candidates (such as evinacumab) and new indications for marketed products; the availability and extent of reimbursement of the Company'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; ongoing regulatory obligations and oversight impacting Regeneron's marketed products, 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, such as evinacumab; 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) 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; 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 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 or collaboration 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 without any further product success; 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, Dupixent® (dupilumab) Injection, and Praluent® (alirocumab) Injection, the ultimate outcome of any such proceedings, 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 United States Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2018 and its Form 10-Q for the quarterly period ended June 30, 2019. 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.

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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