Regeneron Announces American College of Cardiology Presentation of Positive Phase 3 Evinacumab Results in Patients with Severe Inherited Form of High Cholesterol

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Results from separate positive Phase 3 trial of Praluent® (alirocumab) in patients with HoFH also presented; FDA regulatory submission planned for Q2 2020

Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) announced that detailed Phase 3 results of evinacumab were presented today as a late-breaking presentation at the American College of Cardiology's Annual Scientific Session together with World Congress of Cardiology (ACC.20). Evinacumab is an investigational fully-human monoclonal antibody that binds to and blocks the function of angiopoietin-like 3 (ANGPTL3), in patients with homozygous familial hypercholesterolemia (HoFH). Regeneron previously announced topline positive results of this trial in August 2019.

HoFH is an inherited disease in which patients have severely elevated levels of bad cholesterol (otherwise known as low-density lipoprotein cholesterol, or LDL-C) and often experience early atherosclerotic disease, sometimes suffering cardiac events in their teenage years. Most patients with HoFH are less responsive (or unresponsive) to standard lipid-lowering therapies, including statins and PCSK9 inhibitors, which act mainly by inducing LDL receptor function, leaving these patients with high unmet need. Evinacumab acts by a different mechanism than other lipid-lowering therapies, raising the possibility that it might offer patients with HoFH profound LDL-C reductions. Supporting this possibility, genetic research has shown that reduction of ANGPTL3 is associated with decreased LDL-C levels, as well as significantly lower risk of coronary artery disease.

In this Phase 3 trial, patients who added evinacumab to other lipid-lowering therapies reduced their LDL-C by 49% from baseline at 24 weeks compared to the placebo group, who received other lipid-lowering therapies alone, the primary endpoint of the trial ($p<0.0001$). Nearly all (95%) patients in the evinacumab arm entered the trial on statins and 79% were on PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors. Nearly half of evinacumab-treated patients reduced LDL-C to under 100 mg/dL (nominal $p=0.0203$), despite entering the trial with average LDL-C levels of 260 mg/dL on other lipid-lowering therapies.

"As a doctor, it can be heart-wrenching to see HoFH patients struggle to lower their potentially life-threatening LDL-C levels, despite taking every medical treatment available to them," said Professor Derick J. Raal, MMED, Ph.D., principal investigator and Professor & Head, Division of Endocrinology & Metabolism at the University of the Witwatersrand, South Africa. "In this trial, for the first time, evinacumab-treated HoFH patients lowered their LDL-C to previously unattainable levels, with nearly half achieving an LDL-C range that is considered 'normal' for healthy adults."

"Despite medical advances, cardiovascular disease tragically remains the number one cause of death for men and women worldwide. Regeneron remains committed to advance medicines for people who have significant unmet need, including those with HoFH, and we are grateful to the patients and doctors who participated in our trials," said George D. Yancopoulos, M.D., Ph.D., Co-founder, President and Chief Scientific Officer of Regeneron. "Our investments in genetic research and biology enable us to identify completely new ways of targeting diseases. Evinacumab, a first-of-its-kind antibody that works entirely differently to other HoFH medicines, exemplifies the potential of genetic-based research to revolutionize patient treatment."

Also shared today were Phase 3 results from another late-breaking presentation, demonstrating the effect of Praluent® (alirocumab) on patients with HoFH. The trial met its primary endpoint, with Praluent-treated patients reducing their LDL-C by over a third at week 12, compared to placebo ($p<0.0001$). In addition, more than a quarter of patients reduced their LDL-C by at least half ($p=0.0017$), despite entering the trial with average LDL-C levels of 295 mg/dL while being on other lipid-lowering therapies and/or apheresis. No new safety signals were identified in the trial. The use of Praluent in patients with HoFH is investigational and the safety and efficacy have not been evaluated by any regulatory authority.

Detailed ELIPSE HoFH Results
In the Phase 3 ELIPSE HoFH trial, 65 patients were randomized to receive either evinacumab 15 mg/kg intravenously every four weeks (n=43) plus other lipid-lowering therapies, versus lipid-lowering therapies alone (placebo, n=22). At baseline, LDL-C was 260 mg/dL in the evinacumab group and 247 mg/dL in the placebo group.

The ELIPSE HoFH trial met its primary endpoint, with evinacumab-treated patients reducing their LDL-C from baseline by 49% compared to placebo at week 24 (47% reduction evinacumab, 2% increase placebo, $p<0.0001$). At the same time point, compared to baseline evinacumab-treated patients also experienced:

- Average LDL-C decreased by 132 mg/dL compared to placebo (135 mg/dL reduction evinacumab, 3 mg/dL reduction placebo, $p<0.0001$).
- 47% achieved LDL-C less than 100 mg/dL, compared to 23% in the placebo arm (nominal $p=0.0203$).
- More than three-fourths (84%) reduced their LDL-C by at least 30% and more than half (56%) reduced their LDL-C by at least 50%, compared to 19% and 5% for placebo, respectively ($p<0.0001$ and $p=0.0003$).
- Significant reductions were also observed in other key secondary endpoints including levels of apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol and triglycerides, compared to placebo ($p<0.0001$ for all).
- Similar levels of LDL-C 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.

In the trial, evinacumab was generally well-tolerated. During the double-blind treatment period, 66% of evinacumab patients and 81% of placebo patients experienced at least one adverse event (AE). During the double-blind treatment period, 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). There were no deaths, major adverse cardiovascular events or discontinuations due to AEs.

Detailed results from this trial will be used as the basis of regulatory submissions around the world, with the U.S. Food and Drug Administration (FDA) submission expected to be completed by mid-2020.

Detailed ODYSSEY HoFH Results
In the Phase 3 ODYSSEY HoFH trial, 69 patients were randomized to receive either Praluent (n=45) plus other lipid-lowering therapies, excluding other PCSK9 inhibitors, versus lipid-lowering therapies alone (placebo, n=24). At baseline, LDL-C was 295 mg/dL in the Praluent group and 260 mg/dL in the placebo group; nearly all (>95%) patients were on a statin.

The trial met its primary endpoint, with Praluent-treated patients experiencing a 36% reduction in LDL-C at week 12 compared to placebo (27% reduction Praluent, 9% increase placebo, p<0.0001). At the same time point, compared to baseline Praluent-treated patients also experienced:

- Average LDL-C levels decreased by 72 mg/dL compared to placebo (63 mg/dL reduction Praluent, 9 mg/dL increase placebo).
- More than half (57%) reduced their LDL-C by at least 30% and more than a quarter (27%) reduced their LDL-C by at least half, compared to 4% and 0% for placebo, respectively (p=0.0010 and p=0.0017).

No serious AEs, permanent treatment discontinuations or deaths were reported during the double-blind treatment period. During the double-blind treatment period, the AE that occurred in at least 5% of patients, and more commonly with Praluent, was diarrhea (7% Praluent, 0% placebo). AEs that occurred in at least 5% of patients, and more commonly with placebo, were upper respiratory tract infection (4% Praluent, 8% placebo) and headache (4% Praluent, 8% placebo).

Research into the use of Praluent in patients with HoFH is investigational and the safety and efficacy for this use have not been evaluated by any regulatory authority. Regeneron plans to submit these data as the basis of regulatory submissions with the FDA in the second quarter of 2020.

About evinacumab and the ELIPSE HoFH Trial
Evinacumab is a fully-human antibody that blocks ANGPTL3 and was invented by Regeneron using the company's proprietary *VelocImmune*® technology that utilizes a proprietary genetically-engineered mouse platform endowed with a genetically-humanized immune system to produce optimized fully-human monoclonal antibodies. *VelocImmune* technology has been used to create multiple FDA-approved antibodies including Praluent® (alirocumab), Dupixent® (dupilumab), Libtayo® (cemiplimab-rwlc) and Kevzara® (sarilumab). Regeneron previously used these technologies to rapidly develop a treatment for Ebola virus infection, which is currently under review by the FDA, and is now being used in efforts to create prophylactic and treatment medicines for COVID-19.

Evinacumab is currently being studied in patients with HoFH (Phase 3), refractory hypercholesterolemia (Phase 2) and severe hypertriglyceridemia (Phase 2). In 2017, the 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-C, and this is associated with a significantly lower risk of coronary artery disease.

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 was reduction of LDL-C from baseline with evinacumab compared to placebo at 24 weeks.

About Praluent and the ODYSSSEY HoFH Trial
Praluent® (alirocumab) inhibits the binding of PCSK9 (proprotein convertase subtilisin/kexin type 9) to the LDL receptor and thereby increases the number of available LDL receptors on the surface of liver cells to clear LDL, which lowers LDL-C levels in the blood. Praluent was developed by Regeneron and Sanofi under a global collaboration agreement and invented by Regeneron using the company's proprietary *VelocImmune*® technology. In December 2019, the companies announced their intent to simplify the Praluent collaboration, with Regeneron expected to gain sole U.S. rights and Sanofi expected to gain sole ex-U.S. rights.

Praluent is approved in more than 60 countries worldwide, including the U.S., Japan, Canada, Switzerland, Mexico, Brazil and the EU. In the U.S., Praluent is approved to reduce the risk of heart attack, stroke and unstable angina requiring hospitalization in adults with established cardiovascular disease. Praluent is also approved as an adjunct to diet, alone or in combination with other lipid lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce LDL-C.

Research into the use of Praluent in patients with HoFH remains investigational, and the safety and efficacy for this use have not been evaluated by any regulatory authority.

In the Phase 3 ODYSSEY HoFH trial, patients on maximally-tolerated stains and/or apheresis were randomized to receive either Praluent 150 mg subcutaneously every 2 weeks (n=45) or placebo (n=24). The primary endpoint was reduction of LDL-C from baseline with Praluent compared to placebo at 12 weeks.

Important Praluent Safety Information for the U.S.
Do not use Praluent if you are allergic to alirocumab or to any of the ingredients in Praluent.

Before you start using Praluent, tell your healthcare provider about all of your medical conditions, including allergies, and if you are pregnant or plan to become pregnant or if you are breastfeeding or plan to breastfeed.

Tell your healthcare provider or pharmacist about any medicines you take, including prescription and over-the-counter medicines, vitamins or herbal supplements.

Praluent can cause serious side effects, including allergic reactions that can be severe and require treatment in a hospital. Stop using Praluent and call your healthcare provider or go to the nearest hospital emergency room right away if you have any symptoms of an allergic reaction including a severe rash, redness, hives, severe itching, trouble breathing or swelling of the face, lips, throat, or tongue.

The most common side effects of Praluent include: redness, itching, swelling, or pain/tenderness at the injection site, symptoms of the common cold, and flu or flu-like symptoms. Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

Talk to your doctor about the right way to prepare and give yourself a Praluent injection and follow the "Instructions For Use" that comes with Praluent.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Praluent is an injectable prescription medicine used:

- in adults with cardiovascular disease to reduce the risk of heart attack, stroke, and certain types of chest pain conditions (unstable angina) requiring hospitalization.
- along with diet, alone or together with other cholesterol-lowering medicines in adults with high blood cholesterol levels called primary hyperlipidemia (including a type of high cholesterol called heterozygous familial hypercholesterolemia), to reduce low-density lipoprotein cholesterol (LDL-C) or bad cholesterol.

It is not known if Praluent is safe and effective in children.

Please click here for the 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 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 diseases, allergic and inflammatory diseases, cancer, cardiovascular and metabolic diseases, pain, 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, suppliers, and other third parties on which Regeneron relies, Regeneron's ability to continue to conduct its research and clinical programs and manage its supply chain, net product sales of products marketed 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 Regeneron's product candidates and research and clinical programs now underway or planned, including without limitation evinacumab and Praluent® (alirocumab); 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 evinacumab for the treatment of homozygous familial hypercholesterolemia (HoFH), refractory hypercholesterolemia, and severe hypertriglyceridemia as well as Praluent for the treatment of HoFH; unforeseen safety issues resulting from the administration of Regeneron's Products (such as Praluent) and product candidates (such as evinacumab) in patients, including serious complications or side effects in connection with the use of Regeneron's Products and product candidates in clinical trials; 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; ongoing regulatory obligations and oversight impacting Regeneron's Products (such as Praluent), 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, including without limitation Praluent and evinacumab; 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 Regeneron's Products and product candidates; the extent to which the results from the research and development programs conducted by Regeneron or its collaborators may be replicated in other studies and lead to therapeutic applications; 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 Dupixent® (dupilumab) and Praluent), 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, 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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