Regeneron Announces ANGPTL3/Evinacumab Publication in New England Journal of Medicine and Positive Phase 2 Data in People with HoFH

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ANGPTL3 genetics publication and evinacumab data presentation highlight Regeneron's integrated drug development process

Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced new data from genetics, preclinical and clinical studies supporting the continued development of evinacumab, its investigational angiopoietin-like 3 (ANGPTL3) antibody.

An analysis published today in the *New England Journal of Medicine* (NEJM) showed that people with inactivating mutations of the *ANGPTL3* gene have significantly reduced risk of coronary artery disease (CAD) and significantly lower levels of key blood lipids including triglycerides and low-density lipoprotein cholesterol (LDL-C, or "bad cholesterol"). Data also included in this publication showed that blocking ANGPTL3 activity with evinacumab exhibited similar lipid-lowering effects in animal models and a first-in-human clinical study.

Separate Phase 2 results presented this past weekend at the National Lipid Association's (NLA) Scientific Sessions showed that, in patients with Homozygous Familial Hypercholesterolemia (HoFH), evinacumab added to current lipid-lowering therapy reduced LDL-C by an additional 49 percent (mean reduction; range 25 percent to 90 percent) at week 4 compared to baseline, the primary endpoint of the study. Mean baseline LDL-C for the nine patients was 376 mg/dL. Data also showed that evinacumab reduced levels of other key lipid parameters including lipoprotein(a) and triglycerides.

People with HoFH have serious genetic mutations that result in highly elevated LDL-C levels and often experience early atherosclerotic disease, sometimes suffering cardiac events as early as their teenage years. These patients generally do not respond well to existing therapies.

In three patients with homozygous null allele mutations in the LDL receptor, the additional LDL-C reduction was 37 percent at week 4 (mean reduction); these patients had a mean baseline LDL-C of 597 mg/dL.

There were no adverse events leading to discontinuation. The most common drug-related adverse events were injection-site reactions (1 patient with 2 events) and hot flush (1 patient with 2 events), which were mild in severity.

"Collectively, these findings confirm that the ANGPTL3 pathway is important in regulating lipids and cardiovascular disease," said Robert Pordy, MD, co-author and Vice President of Cardiovascular and Metabolism Therapeutics at Regeneron. "Evinacumab, our antibody to ANGPTL3, has been designated a Breakthrough Therapy by the U.S. Food and Drug Administration for HoFH, and we plan to move to Phase 3 for this indication. We are also planning to initiate additional studies in people with other severe forms of dyslipidemia."

Regeneron scientists were the first to clone angiopoietin-1 in the mid-1990s and discovered that angiopoietin-like knockouts in mouse models reduced triglycerides and LDL-C. Angiopoietin-like proteins such as ANGPTL3 inhibit an enzyme called lipoprotein lipase (LPL) that breaks down triglycerides, a form of fat derived from food. ANGPTL3 also plays a fundamental role in the regulation of both types of blood cholesterol: LDL-C and high-density lipoprotein cholesterol (HDL-C or "good cholesterol"). Loss of ANGPTL3 function due to genetic mutations is associated with decreased triglycerides, LDL-C and HDL-C levels. A previous Regeneron NEJM publication showed that genetic inactivation of a similar angiopoietin-like protein, ANGPTL4, decreases triglyceride levels and the risk of CAD, and a separate publication involving investigators from the Regeneron Genetics Center showed that loss of function mutations in LPL that increase triglyceride levels also increase risk of CAD.

NEJM Publication Findings
In today's NEJM publication, scientists at the Regeneron Genetics Center and a team of international researchers analyzed genetic data and health records from more than 180,000 participants from five studies -- the Geisinger Health System (DiscovEHR study), three major studies in Copenhagen, the Penn Medicine Biobank, the Duke CATHGEN cohort and the TAIwan MetaboCHIp (TAICHI) consortium. The team identified individuals in those studies who had loss of function mutations for ANGPTL3 and found that those who carried loss of function mutations had lower lipid levels and an approximately 40 percent reduction in the risk of CAD.

In a related preclinical study, evinacumab was evaluated in animal models of atherosclerosis, resulting in statistically significant reductions in triglyceride levels by 84 percent (p &#60 0.001) and atherosclerotic plaque size by 39 percent (p &#60 0.001).

Confirmatory findings from a Phase 1 human study were also included in the paper, showing that responses to treatment were

dose dependent, with a maximal reduction at the highest IV dose of 76 percent in triglyceride levels four days after treatment. No participants dropped out of the study due to adverse safety events. Headaches were the most frequently reported adverse event, and two subjects experienced transient elevations of liver enzymes.

"The *New England Journal of Medicine* publication demonstrates the incredible power of an integrated approach to translational medicine and clinical development," said Frederick Dewey, MD, co-author and Senior Director and Head of Translational Genetics at the Regeneron Genetics Center, a wholly-owned subsidiary of Regeneron. "Our team of researchers used large-scale human genetic studies and mouse models to demonstrate that inactivation of ANGPTL3 reduces key lipid levels and cardiovascular disease risk. This human genetics and preclinical validation provide important insight to inform our evinacumab clinical development strategy."

About the Regeneron Genetics Center (RGC)
The RGC is a fully integrated genomics program that spans early gene discovery and functional genomics and facilitates drug development. The primary goal of the RGC is to improve patient outcomes by identifying novel drug targets, clinical indications for development programs, and genomic biomarkers for pharmacogenomic applications. The RGC is tackling large scale sequencing and analytical approaches and has established numerous collaborations with leading human genetics researchers. To enable this large-scale sequencing and analysis program, the RGC utilizes fully-automated sample preparation and data processing, as well as cutting-edge cloud-based informatics. Through these efforts, the RGC is currently sequencing de-identified samples from patient volunteers at a rate of almost 200,000 unique exomes per year. The RGC has major collaborations with Geisinger Health System and the UK Biobank supporting the goal of sequencing 1,000,000 individuals linked to their comprehensive digital health records, plus many other major initiatives in disease specific-studies, founder populations and family based-studies.

About Regeneron
Regeneron (NASDAQ: **REGN**) is a leading science-based biopharmaceutical company that discovers, invents, develops, manufactures and commercializes medicines for the treatment of serious medical conditions. All Regeneron commercialized medicines were discovered and developed by our own scientists, including therapies for eye diseases, high LDL cholesterol, atopic dermatitis, rheumatoid arthritis and a rare inflammatory condition. Regeneron also has product candidates in development in other areas of high unmet medical need, including asthma, pain, cancer and infectious diseases. Regeneron invented the leading VelociSuite® technologies, which are a suite of complementary genetics-based technologies that accelerate, improve and disrupt the traditional drug discovery and development process and established the Regeneron Genetics Center, one of the largest genetic 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 news 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 (Regeneron's investigational angiopoietin-like 3 (ANGPTL3) antibody); the likelihood and timing of possible regulatory approval and commercial launch of Regeneron's product candidates, such as evinacumab in patients with Homozygous Familial Hypercholesterolemia or other potential indications; the extent to which the results from Regeneron's research programs or preclinical testing may lead to advancement of product candidates to clinical trials or therapeutic applications; unforeseen safety issues resulting from the administration of products and product candidates in patients, including serious complications or side effects in connection with the use of Regeneron's product candidates in clinical trials, such as evinacumab; 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; ongoing regulatory obligations and oversight impacting Regeneron's marketed products, research and clinical programs, and business, including those relating to patient privacy; 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; coverage and reimbursement determinations by third-party payers, including Medicare and Medicaid; 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 to perform filling, finishing, packaging, labelling, 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 sales or other 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 relating to Praluent® (alirocumab) Injection, the permanent injunction granted by the United States District Court for the District of Delaware that, if upheld on appeal, would prohibit Regeneron and Sanofi from marketing, selling, or commercially manufacturing Praluent in the United States, the outcome of any appeals regarding such injunction, the ultimate outcome of such litigation, 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, 2016 and its Form 10-Q for the quarterly period ended March 31, 2017. 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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