New England Journal of Medicine Publishes Positive Phase 3 Evinacumab Results in Patients with Severe Inherited Form of High Cholesterol

August 19, 2020

TARRYTOWN, N.Y., Aug. 19, 2020 /PRNewswire/ --

Patients with homozygous familial hypercholesterolemia (HoFH) suffer from a severe form of early cardiovascular disease and are inadequately served by currently available medications

Adding evinacumab to other lipid-lowering therapies cut bad cholesterol levels in half in patients with HoFH, including for the most difficult-to-treat patients who had nearly non-existent LDL-receptor activity

Evinacumab is currently under Priority Review with the FDA; decision expected by February 11, 2021

Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced that the *New England Journal of Medicine* (*NEJM*) published positive results from the Phase 3 trial of evinacumab in 65 patients with homozygous familial hypercholesterolemia (HoFH). Evinacumab is an investigational medicine that binds to and blocks the function of angiopoietin-like 3 (ANGPTL3), and is the first medicine of its kind to show efficacy in patients with HoFH – including patients with little to no low-density lipoprotein (LDL) receptor function.

Patients with HoFH have severely elevated levels of bad cholesterol (low-density lipoprotein cholesterol, or LDL-C), which increases their risk for premature atherosclerotic disease and cardiac events as early as their teenage years. Treatment guidelines recommend early and intensive LDL-C lowering, but patients with HoFH are less responsive (or unresponsive) to standard lipid-lowering therapies, including statins and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors.

As initially announced in a topline press release, the trial met its primary endpoint, showing that patients who added evinacumab to other lipid-lowering therapies (n=43) reduced their LDL-C from baseline by 49% compared to lipid-lowering therapies alone (placebo, n=22) at week 24 (47% reduction evinacumab, 2% increase placebo, p<0.0001). At the same time point, evinacumab-treated patients also decreased LDL-C from baseline by 132 mg/dL compared to placebo (135 mg/dL reduction evinacumab, 3 mg/dL reduction placebo, p<0.0001). As discussed in the *NEJM* publication, genetic loss of ANGPTL3 has been associated with additional lipid-lowering effects, including lowered triglycerides, apolipoprotein B (ApoB), HDL and non-HDL cholesterol, and total cholesterol. Evinacumab treatment mirrored these lipid-lowering effects.

"The vast majority of my patients with HoFH never reach their target LDL-C despite taking multiple lipid-lowering therapies, and they remain at increased risk of premature heart disease because of their persistently high LDL-C levels," 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. "If approved, evinacumab will provide a major step forward for the treatment of patients with HoFH who have significant unmet needs."

Researchers also assessed in a post hoc analysis the effect of evinacumab in patients with nearly non-existent (<2%) LDL-receptor activity, whose mean baseline LDL-C levels were 258 mg/dL (n=10). Among these patients, evinacumab reduced LDL-C by 72% from baseline compared to placebo (54% reduction evinacumab, 19% increase placebo, nominal p=0.005).

During the double-blind treatment period, 66% of evinacumab patients and 81% of placebo patients experienced at least one 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). There were no deaths, major adverse cardiovascular events or discontinuations due to AEs.

"Today's publication further demonstrates how evinacumab, through its novel mechanism of action, was able to reduce LDL-C levels in patients with all forms of HoFH, even those with nearly no LDL-receptor activity," said George D. Yancopoulos, M.D., Ph.D., Co-founder, President and Chief Scientific Officer at Regeneron. "This validates our genetic-based approach, where Regeneron ANGPTL3 genetic research directly led to evinacumab, which we hope can become the standard of care in the treatment of HoFH."

Previous research published in *NEJM* in 2017 by the Regeneron Genetics Center found that people with loss-of-function mutations in their ANGPTL3 gene have significantly lower levels of key blood lipids, including LDL-C. By blocking the ANGPTL3 protein, evinacumab was designed to replicate this loss-of-function mutation effect to lower LDL-C in people with HoFH.

In the U.S., the Biologics License Application (BLA) for evinacumab is currently under Priority Review, with a target action date of February 11, 2021. In 2017, the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy designation to evinacumab for the treatment of hypercholesterolemia in patients with HoFH. Other regulatory submissions are ongoing, including in the European Union, where the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended an accelerated assessment for evinacumab based on the high unmet medical need and therapeutic innovation demonstrated by the product. The safety and efficacy of evinacumab have not been fully evaluated by any regulatory authority.

About evinacumab and the ELIPSE HoFH Trial
Evinacumab is an investigational fully-human monoclonal antibody that binds to and blocks the function of ANGPTL3 and is currently being studied in patients with HoFH (ongoing Phase 3 extension trial), refractory hypercholesterolemia (Phase 2) and severe hypertriglyceridemia (Phase 2).

Regeneron invented evinacumab using the company's *VelocImmune*® technology, 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.

ELIPSE (Evinacumab LIPid StudiEs) HoFH was a multi-national 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 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, 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 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; 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 patients with homozygous familial hypercholesterolemia, refractory hypercholesterolemia, or severe hypertriglyceridemia; 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; safety issues resulting from the administration of Regeneron's Products 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; 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; 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 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; 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), and Praluent® (alirocumab)), 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 and its Form 10-Q for the quarterly period ended June 30, 2020. 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).

Contacts:

Media Relations
Joseph Ricculli
Tel: +1 (914) 418-0405
Joseph.Ricculli@regeneron.com

Investor Relations
Mark Hudson
Tel: +1 (914) 355-0213
Mark.Hudson@regeneron.com

View original content:http://www.prnewswire.com/news-releases/new-england-journal-of-medicine-publishes-positive-phase-3-evinacumab-results-in-patients-with-severe-inherited-form-of-high-cholesterol-301115122.html

SOURCE Regeneron Pharmaceuticals, Inc.