Evkeeza® (evinacumab) Phase 3 Trial Demonstrates 48% LDL-C Reduction in Children with Ultra-rare Form of High Cholesterol

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Children already on other lipid-lowering therapies entered the trial with dangerously high LDL-C (264 mg/dL on average), and 79% saw their LDL-C reduced by at least half at 24 weeks

FDA submission planned by end of 2022

Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced positive results from a Phase 3 trial evaluating Evkeeza® (evinacumab) in children aged 5 to 11 with homozygous familial hypercholesterolemia (HoFH). The trial met its primary endpoint, showing children who added investigational Evkeeza to other lipid-lowering therapies reduced their low-density lipoprotein-cholesterol (LDL-C) by 48% at week 24 on average. Detailed results were presented today at the 5th European Atherosclerosis Society Pediatric Familial Hypercholesterolemia symposium and will form the basis of a regulatory submission to the U.S. Food and Drug Administration (FDA) later this year.

"Children living with HoFH have an incredibly rare and severe disease that causes dangerously high LDL-C levels. On current treatment options alone, many patients don't reach their treatment goals, leaving them with an uncertain future," said M. Doortje Reijman, M.D., Research Associate in Pediatric Metabolic Diseases and Nephrology at the Amsterdam University Medical Center, and a trial investigator. "Evinacumab has already demonstrated significant LDL-C reductions in adolescents and adults with HoFH. This latest Phase 3 trial illustrates the potential of this medicine to be a breakthrough HoFH therapy for children as young as 5-years old, helping them control their LDL-C early in the course of their disease."

Despite treatment with other lipid-lowering therapies, children (n=14) entered the trial with an average LDL-C level of 264 mg/dL, more than twice the target (<130 mg/dL) for pediatric patients with HoFH. After 24 weeks of Evkeeza treatment (15 mg/kg every 4 weeks delivered intravenously [IV]), the Phase 3 trial met its primary endpoint with additional results showing:

- 79% of patients reduced their LDL-C by at least half
- An absolute 132 mg/dL reduction in LDL-C from baseline, on average
- Reductions in levels of all lipid endpoint parameters assessed, which were generally observed within the first 8 weeks of treatment. These lipid parameters were apolipoprotein B, non-high-density lipoprotein cholesterol, lipoprotein(a) and total cholesterol.

Evkeeza was generally well-tolerated with all patients completing the trial. The most common adverse events (AEs) were throat pain (oropharyngeal pain, 21%) as well as upper abdominal pain, diarrhea, headache and nasopharyngitis (all 14%). There were 2 severe AEs (aortic stenosis and tonsilitis), both of which were considered unrelated to treatment.

Evkeeza is the first ANGPTL3-targeted (angiopoietin-like 3-targeted) therapy approved by the FDA (as evinacumab-dgnb) and European Commission as an adjunct therapy for certain patients aged 12 years and older with HoFH.

The potential use of Evkeeza in HoFH patients aged 5 to 11 years is currently under clinical development, and its safety and efficacy have not been fully evaluated by any regulatory authority.

About HoFH

HoFH is an ultra-rare inherited condition, and the most severe form of familial hypercholesterolemia (FH). The disease affects 1 in 160,000 to 300,000 people worldwide and approximately 1,300 in the U.S. HoFH occurs when two copies of the FH-causing genes are inherited, one from each parent, resulting in dangerously high levels (>400 mg/dL) of LDL-C, or bad cholesterol. Those living with HoFH are at risk for premature atherosclerotic disease and life-threatening cardiac events as early as their teen years.

About the trial

The Phase 3 data are the Part B portion of a three-part, single-arm, open-label trial evaluating Evkeeza in pediatric patients with HoFH aged 5 to 11 years. In Part B, 14 patients were enrolled with an average age of 9 years. Among them, 86% were on statins, 93% were on ezetimibe, 50% were on LDL apheresis and 14% were on lomitapide.

During the 24-week treatment period, patients received Evkeeza 15 mg/kg every four weeks via IV alongside their lipid-lowering treatment regimen. The primary endpoint was change in LDL-C at week 24. Secondary endpoints included the effect of Evkeeza on other lipid parameters, efficacy by mutation status, safety and tolerability, immunogenicity and pharmacokinetics (PK).

Part A was a Phase 1b trial designed to assess the PK, safety and tolerability of Evkeeza. Patients who completed Part A or B were allowed to

continue treatment in Part C, an ongoing Phase 3 extension trial. Parts A, B and C were not designed to evaluate the effect of Evkeeza on cardiovascular events.

About Evkeeza® (evinacumab)

Evkeeza was invented using Regeneron's *VelocImmune*® technology and is a fully human monoclonal antibody that binds to and blocks the function of ANGPTL3, a protein that inhibits lipoprotein lipase (LPL) and endothelial lipase (EL) and regulates circulating lipids, including LDL-C.

Regeneron scientists discovered the angiopoietin gene family more than two decades ago (see publications from 1996, 1997 and 1999). Human genetics research published in *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 that this is associated with a significantly lower risk of coronary artery disease.

The generic name for Evkeeza in its approved U.S. indications is evinacumab-dgnb, with dgnb the suffix designated in accordance with Nonproprietary Naming of Biological Products Guidance for Industry issued by the U.S. FDA. The safety and effectiveness of Evkeeza have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH). The effect of Evkeeza on cardiovascular morbidity and mortality has not been determined.

Regeneron is responsible for the development and distribution of Evkeeza in the U.S. and is collaborating with Ultragenyx to clinically develop, commercialize and distribute Evkeeza outside of the U.S.

About Regeneron's *VelocImmune* Technology

Regeneron's *VelocImmune* technology utilizes a proprietary genetically engineered mouse platform endowed with a genetically humanized immune system to produce optimized fully human antibodies. When Regeneron's President and Chief Scientific Officer George D. Yancopoulos was a graduate student with his mentor Frederick W. Alt in 1985, they were the first to envision making such a genetically humanized mouse, and Regeneron has spent decades inventing and developing *VelocImmune* and related *VelociSuite*® technologies. Dr. Yancopoulos and his team have used *VelocImmune* technology to create approximately one in five of all original, FDA-approved fully human monoclonal antibodies currently available. This includes Evkeeza® (evinacumab-dgnb), REGEN-COV® (casirivimab and imdevimab), Dupixent® (dupilumab), Libtayo® (cemiplimab-rwlc), Praluent® (alirocumab), Kevzara® (sarilumab) and Inmazeb™ (atoltivimab, maftivimab and odesivimab-ebgn).

IMPORTANT SAFETY INFORMATION FOR EVKEEZA® (evinacumab-dgnb) INJECTION

Who should not use EVKEEZA?

Do not use EVKEEZA if you are allergic to evinacumab-dgnb or to any of the ingredients in EVKEEZA.

Before receiving EVKEEZA, tell your healthcare provider about all of your medical conditions, including if you:

- Are pregnant or plan to become pregnant. EVKEEZA may harm your unborn baby. Tell your healthcare provider if you become pregnant while using EVKEEZA. **People who are able to become pregnant:**
    - Your healthcare provider may do a pregnancy test before you start treatment with EVKEEZA
    - You should use an effective method of birth control during treatment and for at least 5 months after the last dose of EVKEEZA. Talk with your healthcare provider about birth control methods that you can use during this time.
- Are breastfeeding or plan to breastfeed. It is not known if EVKEEZA passes into your breast milk. You and your healthcare provider should decide if you will receive EVKEEZA or breastfeed.

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

What are the possible side effects of EVKEEZA?

EVKEEZA can cause serious side effects, including:
Allergic reactions (hypersensitivity), including a severe reaction known as anaphylaxis. Tell your healthcare provider right away if you get any of the following symptoms: swelling (mainly of the lips, tongue or throat which makes it difficult to swallow or breathe), breathing problems or wheezing, feeling dizzy or fainting, rash, hives, and itching.

The most common side effects of EVKEEZA include symptoms of the common cold, flu-like symptoms, dizziness, pain in legs or arms, nausea, and decreased energy.

Tell your healthcare provider if you have any side effect that bothers you or does not go away. These are not all the possible side effects of EVKEEZA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Please see full Prescribing Information, including Patient 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 or licensees (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 or licensees (collectively, "Regeneron's Product Candidates") and research and clinical programs now underway or planned, including without limitation Evkeeza® (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 Evkeeza for the treatment of children aged 5 to 11 with homozygous familial hypercholesterolemia; 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 study discussed 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 Evkeeza); the ability of Regeneron's collaborators, licensees, 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 (such as Evkeeza) 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 Evkeeza; 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 or licensees 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® (aflibercept) Injection, 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, 2021 and its Form 10-Q for the quarterly period ended March 31, 2022. 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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