Evkeeza® (evinacumab-dgnb) sBLA for Children with Ultra-rare Inherited Form of High Cholesterol Accepted for FDA Priority Review

November 30, 2022

If approved, Evkeeza would be the first and only treatment of its kind to help children as young as 5 years old control dangerously high levels of LDL cholesterol caused by homozygous familial hypercholesterolemia

TARRYTOWN, N.Y., Nov. 30, 2022 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced the U.S. Food and Drug Administration (FDA) has accepted for Priority Review the supplemental Biologics License Application (sBLA) for Evkeeza® (evinacumab-dgnb) as an adjunct to other lipid-lowering therapies to treat children aged 5 to 11 years with homozygous familial hypercholesterolemia (HoFH). The FDA target action date is March 30, 2023.

HoFH is an ultra-rare inherited condition that affects approximately 1,300 patients in the U.S. and is the most severe form of familial hypercholesterolemia (FH). The disease occurs when two copies of the FH-causing genes are inherited, one from each parent, resulting in dangerously high levels (usually >400 mg/dL) of low-density lipoprotein-cholesterol (LDL-C or bad cholesterol). Those living with HoFH are at risk for premature atherosclerotic disease and cardiac events even in their teenage years.

The sBLA is supported by data from a three-part trial evaluating Evkeeza in children aged 5 to 11 years with HoFH. Efficacy was assessed in 14 children enrolled in the Part B portion of the trial. Despite treatment with other lipid-lowering therapies, these children entered the trial with an average LDL-C level of 264 mg/dL, more than twice the target (<110 mg/dL) for pediatric patients with HoFH. The trial met its primary endpoint, showing children who added Evkeeza to other lipid-lowering therapies reduced their LDL-C by 48% at week 24 on average. Furthermore, 79% (n=11) saw their LDL-C reduced by at least half at 24 weeks following Evkeeza treatment, with an average absolute reduction in LDL-C from baseline of 132 mg/dL.

Among 20 children evaluated for long-term safety across Parts A, B and C of the trial (mean exposure: 52 weeks, range: 42-64 weeks), the most common adverse events (AEs) occurring in ≥15% of patients included COVID-19 (n=15), pyrexia (n=5), headache (n=4), throat pain (oropharyngeal pain, n=4) as well as upper abdominal pain, diarrhea, vomiting, fatigue, nasopharyngitis, rhinitis and cough (all n=3). Most reported AEs were mild or moderate, and none led to study discontinuation. The safety profile of Evkeeza observed in these patients was generally consistent to those seen in adults and pediatric patients aged 12 years and older.

Evkeeza is the first angiopoietin-like 3 (ANGPTL3) targeted therapy approved by the FDA, European Commission and the United Kingdom's Medicines and Healthcare products Regulatory Agency as an adjunct therapy for patients aged 12 years and older with HoFH. The potential use of Evkeeza in HoFH patients aged 5 to 11 years has not been fully evaluated by any regulatory authority.

About the Trial
The three-part, single-arm, open-label trial evaluated Evkeeza in pediatric patients with HoFH aged 5 to 11 years. Part A (n=6) was a Phase 1b trial designed to assess the pharmacokinetics (PK), safety and tolerability of Evkeeza.

Efficacy was evaluated in the 24-week treatment period in the Phase 3 Part B portion, which enrolled 14 patients 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. Patients received Evkeeza 15 mg/kg every four weeks delivered intravenously 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 (i.e., apolipoprotein B, non-high-density lipoprotein cholesterol, lipoprotein[a] and total cholesterol), efficacy by mutation status, safety and tolerability, immunogenicity and PK.

Patients who completed Part A or B were allowed to continue treatment in Part C (n=20), 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. 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 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, develops and commercializes life-transforming medicines for people with serious diseases. Founded and led for nearly 35 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 more information, 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-dgnb); 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 (including potential regulatory approval by the U.S. Food and Drug Administration based on the supplemental Biologics License Application discussed in this press release); uncertainty of the utilization, market acceptance, and commercial success of Regeneron's Products (such as Evkeeza) 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; 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 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 and Bayer (or their respective affiliated companies, as applicable), as well as Regeneron's collaboration with Ultragenyx referenced in this press release, 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, 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 September 30, 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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