FDA Approves Repatha® (evolocumab) In Pediatric Patients Age 10 And Older With Heterozygous Familial Hypercholesterolemia

September 25, 2021

Approval Based on HAUSER-RCT Study Demonstrating a Significant Reduction in LDL-C

THOUSAND OAKS, Calif., Sept. 24, 2021 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the U.S. Food and Drug Administration (FDA) has approved Repatha® (evolocumab) as an adjunct to diet and other low-density lipoprotein cholesterol (LDL-C)-lowering therapies for the treatment of pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH) to reduce LDL-C.

HeFH is an inherited, genetic condition with a prevalence of one in 250 people worldwide.[1] High levels of LDL-C starting at birth accelerate the development of atherosclerotic cardiovascular disease, leading to an overall increased risk of cardiovascular events, including heart attack and other vascular conditions, at an earlier age.[2] Children with familial hypercholesterolemia (FH) can be normal weight, have a good diet, exercise enough and still have high LDL-C.[2,3]

"The approval of Repatha for pediatric patients with FH represents a much-needed adjunct treatment option for these children with genetically high cholesterol who are unable to manage their high LDL-C with other lipid-lowering agents alone," said David M. Reese, M.D., executive vice president of Research and Development at Amgen. "This milestone further reinforces the safety profile of Repatha and aligns with Amgen's commitment to addressing the unmet needs of the high-risk cardiovascular community."

The approval is based on the HAUSER-RCT Phase 3b study evaluating the safety and efficacy of Repatha in pediatric patients, 10 - 17 years of age, with HeFH. Monthly treatment with Repatha reduced LDL-C by mean 38% (95% CI: 45%, 31%; $p < 0.0001$) from baseline compared to placebo, meeting its primary endpoint.[4] Reductions in LDL-C were observed by the first post-baseline assessment at the Week 12 time point and were maintained throughout the trial.[4] Patients treated with Repatha had improved secondary lipid parameters from baseline in comparison to placebo, including a 35% (CI: 42%, 28%) reduction in non-high-density lipoprotein cholesterol (non-HDL-C) at week 24, a 27% (CI: 32%, 21%) reduction in total cholesterol at week 24 and a 32% (CI: 39%, 26%) reduction in apolipoprotein B (ApoB) at week 24.[5] No new safety risks were identified.[5] The most common treatment-emergent adverse events (>5% of patients treated with Repatha and occurring more frequently than placebo) included nasopharyngitis, headache, oropharyngeal pain, influenza and upper respiratory tract infection.[5]

"As pediatric FH is an under-recognized condition that can lead to premature coronary artery disease, it's critically important to have additional treatments that can significantly lower cholesterol," said Katherine Wilemon, founder and chief executive officer at The FH Foundation.

The FDA also approved Repatha as an adjunct to other LDL-C lowering therapies for the treatment of homozygous familial hypercholesterolemia (HoFH) for younger pediatric patients. Repatha was already approved for treatment in HoFH patients aged 13 and older and is now available as a treatment for patients aged 10 and older.

About Familial Hypercholesterolemia

Elevated low-density lipoprotein cholesterol (LDL-C) is an abnormality of cholesterol and/or fats in the blood.[5,6] Familial hypercholesterolemia (FH) is an inherited condition that causes high levels of LDL-C at an early age[7]. It is estimated that 1 million people in the U.S. have FH (heterozygous and homozygous forms), yet less than 10% are diagnosed.[8] Heterozygous FH (HeFH) is the more common type of FH and occurs globally in approximately 1 in 250.[9] People with HeFH have a 50% chance of passing the condition to their children.[8]

About HAUSER-RCT Study Design

HAUSER-RCT was a Phase 3b, multicenter, randomized (2:1), double-blind, placebo-controlled study evaluating the efficacy, safety, and tolerability of 24 weeks of monthly subcutaneous injections of Repatha® (evolocumab) 420 mg (n = 104) versus placebo (n = 53) in patients 10 to 17 years of age with heterozygous familial hypercholesteremia, or HeFH. Randomization was stratified by LDL-C (<4.1 versus ≥4.1 mmol/L) and age (<14 versus ≥14 years of age) at screening. Patients were required to be on a low-fat diet and must have been receiving optimized background lipid-lowering therapy (statin at optimal dose, not requiring up titration).The primary endpoint was percent change in LDL-C from baseline to week 24; secondary endpoints included mean percent change in LDL-C from baseline to week 22 and 24, change in LDL-C from baseline to week 24, percent changes from baseline to week 24 in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/apolipoprotein A1 (ApoA1) ratio. Further safety evaluations included Tanner staging, hormone levels, carotid intimal medial thickness, and computer-based cognitive assessments.

About Amgen in the Cardiovascular Therapeutic Area

Building on more than three decades of experience in developing biotechnology medicines for patients with serious illnesses, Amgen is dedicated to addressing important scientific questions to advance care and improve the lives of patients with cardiovascular disease, the leading cause of morbidity worldwide.[10] Amgen's research into cardiovascular disease, and potential treatment options, is part of a growing competency at Amgen that utilizes human genetics to identify and validate certain drug targets. Through its own research and development efforts, as well as partnerships, Amgen is building a robust cardiovascular portfolio consisting of several approved and investigational molecules in an effort to address a number of today's important unmet patient needs, such as elevated lipids, including high cholesterol and Lp(a), and heart failure.

About Amgen

Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its biologics manufacturing expertise to strive for solutions that improve health

outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be the world's largest independent biotechnology company, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

For more information, visit www.amgen.com and follow us on www.twitter.com/amgen.

About Repatha® (evolocumab)
Repatha is a human monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9). Repatha binds to PCSK9 and inhibits circulating PCSK9 from binding to the low-density lipoprotein (LDL) receptor (LDLR), preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. By inhibiting the binding of PCSK9 to LDLR, Repatha increases the number of LDLRs available to clear LDL from the blood, thereby lowering LDL-C levels.[11]

Repatha is approved in 75 countries, including the U.S., Japan, China and in all 27 countries that are members of the European Union. Applications in other countries are pending.

Indications

Repatha® is indicated:

- In adults with established cardiovascular disease to reduce the risk of myocardial infarction, stroke, and coronary revascularization
- As an adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)–lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL–C
- As an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C
- As an adjunct to other LDL–C-lowering therapies in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH), to reduce LDL–C

  The safety and effectiveness of Repatha® have not been established in pediatric patients with HeFH or HoFH who are younger than 10 years old or in pediatric patients with other types of hyperlipidemia.

Important Safety Information

- **Contraindication:** Repatha® is contraindicated in patients with a history of a serious hypersensitivity reaction to evolocumab or any of the excipients in Repatha®. Serious hypersensitivity reactions including angioedema have occurred in patients treated with Repatha®.
- **Hypersensitivity Reactions:** Hypersensitivity reactions, including angioedema, have been reported in patients treated with Repatha®. If signs or symptoms of serious hypersensitivity reactions occur, discontinue treatment with Repatha®, treat according to the standard of care, and monitor until signs and symptoms resolve.
- **Adverse Reactions in Adults with Primary Hyperlipidemia:** The most common adverse reactions (>5% of patients treated with Repatha® and more frequently than placebo) were: nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions.

  From a pool of the 52-week trial and seven 12-week trials: Local injection site reactions occurred in 3.2% and 3.0% of Repatha®-treated and placebo-treated patients, respectively. The most common injection site reactions were erythema, pain, and bruising. Hypersensitivity reactions occurred in 5.1% and 4.7% of Repatha®-treated and placebo-treated patients, respectively. The most common hypersensitivity reactions were rash (1.0% versus 0.5% for Repatha® and placebo, respectively), eczema (0.4% versus 0.2%), erythema (0.4% versus 0.2%), and urticaria (0.4% versus 0.1%).
- **Adverse Reactions in the Cardiovascular Outcomes Trial:** The most common adverse reactions (>5% of patients treated with Repatha® and more frequently than placebo) were: diabetes mellitus (8.8% Repatha®, 8.2% placebo), nasopharyngitis (7.8% Repatha®, 7.4% placebo), and upper respiratory tract infection (5.1% Repatha®, 4.8% placebo).

  Among the 16,676 patients without diabetes mellitus at baseline, the incidence of new-onset diabetes mellitus during the trial was 8.1% in patients treated with Repatha® compared with 7.7% in patients that received placebo.
- **Adverse Reactions in Pediatric Patients with HeFH:** The most common adverse reactions (>5% of patients treated with Repatha® and more frequently than placebo) were: nasopharyngitis, headache, oropharyngeal pain, influenza, and upper respiratory tract infection.

- **Adverse Reactions in Adults and Pediatric Patients with HoFH:** In a 12-week study in 49 patients, the adverse reactions that occurred in at least two patients treated with Repatha® and more frequently than placebo were: upper respiratory tract infection, influenza, gastroenteritis, and nasopharyngitis. In an open-label extension study in 106 patients, including 14 pediatric patients, no new adverse reactions were observed.

- **Immunogenicity:** Repatha® is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity with Repatha®.

Please contact Amgen Medinfo at 800-77-AMGEN (800-772-6436) or 844-REPATHA (844-737-2842) regarding Repatha availability or find more information, including full Prescribing Information, at www.amgen.com and www.Repatha.com.

Amgen Forward-Looking Statements
This news release contains forward-looking statements that are based on the current expectations and beliefs of Amgen. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including any statements on the outcome, benefits and synergies of collaborations, or potential collaborations, with any other company (including BeiGene, Ltd., Kyowa-Kirin Co., Ltd., or any collaboration to manufacture therapeutic antibodies against COVID-19), the performance of Otezla® (apremilast) (including anticipated Otezla sales growth and the timing of non-GAAP EPS accretion), or the Five Prime Therapeutics, Inc. acquisition, as well as estimates of revenues, operating margins, capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes, effects of pandemics or other widespread health problems such as the ongoing COVID-19 pandemic on our business, outcomes, progress, or effects relating to studies of Otezla as a potential treatment for COVID-19, and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including our most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and current reports on Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those we project. Discovery or identification of new product candidates or development of new indications for existing products cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate or development of a new indication for an existing product will be successful and become a commercial product. Further, preclinical results do not guarantee safe and effective performance of product candidates in humans. The complexity of the human body cannot be perfectly, or sometimes, even adequately modeled by computer or cell culture systems or animal models. The length of time that it takes for us to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and we expect similar variability in the future. Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints we have selected. We develop product candidates internally and through licensing collaborations, partnerships and joint ventures. Product candidates that are derived from relationships may be subject to disputes between the parties or may prove to be not as effective or as safe as we may have believed at the time of entering into such relationship. Also, we or others could identify safety, side effects or manufacturing problems with our products, including our devices, after they are on the market.

Our results may be affected by our ability to successfully market both new and existing products domestically and internationally, clinical and regulatory developments involving current and future products, sales growth of recently launched products, competition from other products including biosimilars, difficulties or delays in manufacturing our products and global economic conditions. In addition, sales of our products are affected by pricing pressure, political and public scrutiny and reimbursement policies imposed by third-party payers, including governments, private insurance plans and managed care providers and may be affected by regulatory, clinical and guideline developments and domestic and international trends toward managed care and healthcare cost containment. Furthermore, our research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. Our business may be impacted by government investigations, litigation and product liability claims. In addition, our business may be impacted by the adoption of new tax legislation or exposure to additional tax liabilities. If we fail to meet the compliance obligations in the corporate integrity agreement between us and the U.S. government, we could become subject to significant sanctions. Further, while we routinely obtain patents for our products and technology, the protection offered by our patents and patent applications may be challenged, invalidated or circumvented by our competitors, or we may fail to prevail in present and future intellectual property litigation. We perform a substantial amount of our commercial manufacturing activities at a few key facilities, including in Puerto Rico, and also depend on third parties for a portion of our manufacturing activities, and limits on supply may constrain sales of certain of our current products and product candidate development. An outbreak of disease or similar public health threat, such as COVID-19, and the public and governmental effort to mitigate against the spread of such disease, could have a significant adverse effect on the supply of materials for our manufacturing activities, the distribution of our products, the commercialization of our product candidates, and our clinical trial operations, and any such events may have a material adverse effect on our product development, product sales, business and results of operations. We rely on collaborations with third parties for the development of some of our product candidates and for the commercialization and sales of some of our commercial products. In addition, we compete with other companies with respect to many of our marketed products as well as for the discovery and development of new products. Further, some raw materials, medical devices and component parts for our products are supplied by sole third-party suppliers. Certain of our distributors, customers and payers have substantial purchasing leverage in their dealings with us. The discovery of significant problems with a product similar to one of our products that implicate an entire class of products could have a material adverse effect on sales of the affected products and on our business and results of operations. Our efforts to collaborate with or acquire other companies, products or technology, and to integrate the operations of companies or to support the products or technology we have acquired, may not be successful. A breakdown, cyberattack or information security breach could compromise the confidentiality, integrity and availability of our systems and our data. Our stock price is volatile and may be affected by a number of events. Global economic conditions may magnify certain risks that affect our business. Our business performance could affect or limit the ability of our Board of Directors to declare a dividend or our ability to pay a dividend or repurchase our common stock. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all.

The scientific information discussed in this news release related to our product candidates is preliminary and investigative. Such product candidates are not approved by the U.S. Food and Drug Administration, and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidates.

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