Amgen Announces Positive Data From Phase 3B Study Of Repatha® (Evolocumab) In Pediatric Patients With Heterozygous Familial Hypercholesterolemia At ESC Congress 2020

August 29, 2020

First Phase 3 Trial Evaluating a PCSK9 Inhibitor When Added to Lipid-Lowering Therapy in Pediatric HeFH Population

Repatha Significantly Reduced LDL-C and Improved All Secondary Lipid Parameters

THOUSAND OAKS, Calif., Aug. 29, 2020 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced positive data from the HAUSER-RCT Phase 3b study evaluating the safety and efficacy of Repatha® (evolocumab) in pediatric patients, 10-17 years of age, with heterozygous familial hypercholesterolemia (HeFH). The study showed that Repatha, in combination with statins and other lipid-lowering therapies, significantly reduced low-density lipoprotein cholesterol (LDL-C) compared to placebo. These data are being presented during an oral presentation at ESC 2020 – The Digital Experience, organized by the European Society of Cardiology, Aug. 29–Sept. 1 and simultaneously published in *The New England Journal of Medicine*.

HeFH is an inherited, genetic condition with a prevalence of one in 250 people worldwide.[1] High levels of low-density lipoprotein cholesterol (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, and decreasing the age at which such events occur.[2] Children with FH can be normal weight, have a good diet, exercise enough, and still have high LDL-C.[2,3] The risk of heart disease in people with FH is about 20 times greater versus the general population.[4]

"Pediatric patients with FH are at increased risk for cardiovascular events from a very early age, making effective management of LDL-C levels in children with HeFH so important," said Daniel Gaudet, M.D., Ph.D., from the Department of Medicine at the Université de Montréal and senior author of the Hauser-RCT study. "This study shows the potential that Repatha offers as a safe and effective treatment option in pediatric HeFH patients already on lipid-lowering therapies who need further LDL-C reduction."

Results from the randomized, double-blind 24-week study show that in pediatric patients with HeFH, monthly treatment with Repatha reduced LDL-C by mean 38.3% from baseline compared to placebo, and absolute reduction in LDL-C was 68.6 mg/dL (mean absolute reduction) meeting its primary endpoint and showing superiority of evolocumab administered on top of statins.[5] Patients treated with Repatha had improved secondary lipid parameters from baseline in comparison to placebo, including a 42.1% reduction in mean LDL-C from weeks 22-24, a 35.0% reduction in non-high-density lipoprotein cholesterol (non-HDL-C) at week 24, a 32.5% reduction in apolipoprotein B (ApoB) at week 24, and 36.4% reduction in ApoB/apolipoprotein A1 (ApoA1) ratio at week 24.[5] No new safety risks were identified.[5] The most common treatment-emergent adverse events (>2%) proportionally higher (>1%) in the Repatha group compared with placebo were headache, oropharyngeal pain, influenza, influenza-type illness, upper respiratory tract infection and constipation.[5]

"Amgen is dedicated to advancing the care and improving the lives of patients with cardiovascular disease. This includes investing in clinical trials and real-world evidence studies to better understand the safety and efficacy of Repatha across various patient populations and those most in need," said David M. Reese, M.D., executive vice president of research and development at Amgen. "This study increases our overall evidence base for Repatha and provides us with a better understanding of cholesterol management in children with genetically high LDL-C, bringing us one step closer to another treatment option for this historically underdiagnosed and undertreated condition."

"As a parent, it can be hard to understand that your child who looks healthy, eats well and is active, is suffering from an invisible condition that can cause an early heart attack or stroke," said Katherine Wilemon, Founder and CEO of The FH Foundation. "The good news is that with early and ongoing treatment, people with FH can greatly reduce cardiovascular risk by lowering their LDL-cholesterol. This trial data gives us hope for new, safe and effective therapies for children living with familial hypercholesteremia."

About Familial Hypercholesterolemia

Elevated LDL-C is an abnormality of cholesterol and/or fats in the blood.[6,7] FH is an inherited condition that causes high levels of LDL-C at an early age.[8] It is estimated that 1 million people in the U.S. have FH (heterozygous and homozygous forms), yet less than 1% are diagnosed.[9,10] Heterozygous FH (HeFH) is the more common type of FH and occurs globally in approximately 1 in 250.[1] People with FH 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. Key eligibility criteria included fasting LDL-C ≥3.4 mmol/L on a low-fat diet and maximum LLT for ≥4 weeks before screening. 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 and mortality worldwide.[11] 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 high cholesterol 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.

Repatha is approved in more than 70 countries, including the U.S., Japan, Canada and in all 28 countries that are members of the European Union. Applications in other countries are pending.

Important U.S. Product Information

Repatha is a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor antibody indicated:

- to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease.
- as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) to reduce low-density lipoprotein cholesterol (LDL-C).
- as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

The safety and effectiveness of Repatha have not been established in pediatric patients with HoFH who are younger than 13 years old or in pediatric patients with primary hyperlipidemia or HeFH.

Important U.S. Safety Information

Contraindication: Repatha is contraindicated in patients with a history of a serious hypersensitivity reaction to Repatha. Serious hypersensitivity reactions including angioedema have occurred in patients treated with Repatha.

Allergic reactions: Hypersensitivity reactions (e.g. angioedema, rash, urticaria) have been reported in patients treated with Repatha, including some that led to discontinuation of therapy. If signs or symptoms of serious allergic reactions occur, discontinue treatment with Repatha, treat according to the standard of care, and monitor until signs and symptoms resolve.

Adverse reactions: The most common adverse reactions (>5% of patients treated with Repatha and occurring 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.

Allergic reactions occurred in 5.1% and 4.7% of Repatha-treated and placebo-treated patients, respectively. The most common allergic 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%).

The most common adverse reactions in the Cardiovascular Outcomes Trial (>5% of patients treated with Repatha and occurring 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 assigned to Repatha compared with 7.7% in those assigned to placebo.

Homozygous Familial Hypercholesterolemia (HoFH): 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.

Immunogenicity: Repatha is a human monoclonal antibody. As with all therapeutic proteins, there is a 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.

Important EU Product Information

In Europe, Repatha is approved for use in:

Hypercholesterolaemia and mixed dyslipidaemia
Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non–familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL–C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Homozygous familial hypercholesterolaemia
Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

Established atherosclerotic cardiovascular disease
Repatha is indicated in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Posology

Primary hypercholesterolaemia and mixed dyslipidaemia in adults
The recommended dose of Repatha is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent.

Homozygous familial hypercholesterolaemia in adults and adolescents aged 12 years and over
The initial recommended dose is 420 mg once monthly. After 12 weeks of treatment, dose frequency can be up–titrated to 420 mg once every 2 weeks if a clinically meaningful response is not achieved. Patients on apheresis may initiate treatment with 420 mg every two weeks to correspond with their apheresis schedule.

Established atherosclerotic cardiovascular disease in adults
The recommended dose of Repatha is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent.

Important Safety Information

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Special Warnings and Precautions: Renal impairment: There is limited experience with Repatha in patients with severe renal impairment (defined as eGFR < 30 mL/min/1.73 m^2). Repatha should be used with caution in patients with severe renal impairment. Hepatic impairment: In patients with moderate hepatic impairment, a reduction in total evolocumab exposure was observed that may lead to a reduced effect on LDL-C reduction. Therefore, close monitoring may be warranted in these patients. Patients with severe hepatic impairment (Child-Pugh C) have not been studied. Repatha should be used with caution in patients with severe hepatic impairment. Dry natural rubber: The needle cover of the glass pre-filled syringe and of the pre-filled pen is made from dry natural rubber (a derivative of latex), which may cause allergic reactions. Sodium content: Repatha contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'.

Interactions: No formal drug-drug interaction studies have been conducted for Repatha. No studies on pharmacokinetic and pharmacodynamics interaction between Repatha and lipid-lowering drugs other than statins and ezetimibe have been conducted.

Fertility, Pregnancy and Lactation: There are no or limited amount of data from the use of Repatha in pregnant women. Repatha should not be used during pregnancy unless the clinical condition of the woman requires treatment with evolocumab. It is unknown whether evolocumab is excreted in human milk. A risk to breastfed newborns/infants cannot be excluded. No data on the effect of evolocumab on human fertility are available.

Undesirable Effects: The following common (≥ 1/100 to < 1/10) adverse reactions have been reported in pivotal, controlled clinical studies: influenza, nasopharyngitis, upper respiratory tract infection, rash, nausea, back pain, arthralgia, injection site reactions. Please consult the SmPC for a full description of undesirable effects.

Pharmaceutical Precautions: Store in a refrigerator (2 degrees C – 8 degrees C). Do not freeze. Keep the pre-filled syringe or the pre-filled pen in the original carton in order to protect from light. If removed from the refrigerator, Repatha may be stored at room temperature (up to 25 degrees C) in the original carton and must be used within 1 month.

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 Adaptive Biotechnologies (including statements regarding such collaboration's, or our own, ability to discover and develop fully-human neutralizing antibodies targeting SARS-CoV-2 to potentially prevent or treat COVID-19), BeiGene, Ltd., or the Otezla® (apremilast) acquisition, including anticipated Otezla sales growth and the timing of non-GAAP EPS accretion, 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. 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 relating to new indications for our products is preliminary and investigative and is not part of the labeling approved by the U.S. Food and Drug Administration for the products. The products are not approved for the investigational use(s) discussed in this news release, and no conclusions can or should be drawn regarding the safety or effectiveness of the products for these uses.

CONTACT: Amgen, Thousand Oaks
Trish Rowland, 805-447-5631 (Media)
Jessica Akopyan, 805-447-0974 (Media)
Arvind Sood, 805-447-1060 (Investors)

References

[1] The FH Foundation. Heterozygous vs Homozygous FH. https://thefhfoundation.org/heterozygous-vs-homozygous-fh. Accessed August 2020.

[2] McGowan MP, et al. *JAMA*. 2019;8:e013225.

[3] The FH Foundation. Children with FH. https://thefhfoundation.org/familial-hypercholesterolemia/children-with-fh. Accessed August 2020.

[4] FH Foundation. What are the Risks with FH? https://thefhfoundation.org/familial-hypercholesterolemia/what-are-the-risks-with-fh. Accessed August 2020.

[5] Santos RD, et al. Evolocumab Treatment in Pediatric Patients with Heterozygous Familial Hypercholesterolemia: Primary Results of HAUSER-RCT, a Phase 3B, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study. Presented at ESC Congress 2020. Abstract 9097.

[6] World Health Organization. Quantifying Selected Major Risks to Health. In: The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva. 2002:49-97.

[7] Merck Manuals website. http://www.merckmanuals.com/professional/endocrine_and_metabolic_disorders/lipid_disorders/dyslipidemia.html. Accessed August 2020.

[8] National Human Genome Research Institute. Learning About Familial Hypercholesterolemia. http://www.genome.gov/25520184. Accessed August 2020.

[9] Nordestgaard BG, et al. *Eur Heart* J. 2013;34:3478–3490.

[10] Centers for Disease Control and Prevention. Finding Family Members with Familial Hypercholesterolemia. 2020. https://www.cdc.gov/genomics/disease/fh/finding_FH.htm#:~:text=Although%20more%20than%20one%20million,%2C%20genetic%20testing%2C%20or%20both. Accessed August 2020.

[11] World Health Organization. Cardiovascular diseases (CVDs). http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed August 2020.