Amgen And The Duke Clinical Research Institute Announce Initiation Of First Large-Scale Registry To Evaluate Real-World Lipid Management And The Effectiveness Of PCSK9 Inhibitors

November 15, 2019

New Registry, cvMOBIUS, Will Assess Lipid Therapies and Five-Year Cardiovascular Outcomes in 8,500 High-Risk Patients With a Recent Atherosclerotic Cardiovascular Disease Event

THOUSAND OAKS, Calif., Nov. 15, 2019 /PRNewswire/ -- Amgen (NASDAQ:AMGN) in collaboration with the Duke Clinical Research Institute (DCRI) today announced plans to initiate the Cardiovascular Multi-dimensional Observational Investigation of the Use of PCSK9 inhibitors (cvMOBIUS) study—the first large-scale real-world study to assess lipid management and the impact of PCSK9 inhibitors on cardiovascular (CV) outcomes in clinical practice. While there is strong evidence demonstrating the efficacy of PCSK9 inhibitors from various randomized clinical trial studies, there is less information on the effectiveness of these medicines on cardiovascular outcomes in real-world practice.

The cvMOBIUS study will be conducted across the U.S. and Canada and will begin patient enrollment this month. A prospective observational registry of 8,500 adults eligible for treatment with a PCSK9 inhibitor will be followed for five years. In parallel, an electronic health record (EHR)-based registry will follow a broader population of adults hospitalized with atherosclerotic cardiovascular disease (ASCVD) at participating sites.

"Cardiovascular disease is one of the most significant public health issues facing our country today. Gathering robust, large-scale data from diverse patients will better inform lipid management and help decrease the burden of cardiovascular disease in these high-risk patients," said Ann Marie Navar, M.D., Ph.D., assistant professor of medicine at the Duke University School of Medicine and member of the DCRI. "The clinical evidence supporting the efficacy and safety of PCSK9 inhibitors in patients with cardiovascular disease is well established, but we still have a lot to learn about the benefits of these medicines in the real world."

Patients who have experienced a recent ASCVD event, including a myocardial infarction (MI), are at higher risk of experiencing another CV event, especially within the first year after.[1,2] Lipid lowering is one of the key approaches for reducing a patient's risk for secondary events.[1] Based on large randomized trials, major professional cardiology societies, including the American Heart Association and the American College of Cardiology, acknowledge that lower is better when it comes to low density lipoprotein cholesterol (LDL-C) management in patients who have experienced an MI and other ASCVD events.[3]

"LDL-C is one of the most important modifiable risk factors for cardiovascular disease, so lipid management is an essential element in reducing future CV events and improving clinical outcomes for high-risk patients," said Eric D. Peterson, M.D., MPH, distinguished professor of medicine at the Duke University School of Medicine and member of the DCRI. "This large registry will examine how care is being delivered in clinical practice to patients —whether we are using the right medicines, whether we are reaching guideline-based LDL-C targets, and the degree to which achieving these goals impacts outcomes in real-world practice."

"The cvMOBIUS study is important because it is one of the few instances that researchers will utilize data pulled directly from hospitals' EHR systems for research. This should help set the stage for future big data analyses and pragmatic clinical trials," said Dr. Peterson.

Two large randomized outcomes trials, including the Repatha® (evolocumab) cardiovascular outcomes (FOURIER) study, have demonstrated that innovative therapies like PCSK9 inhibitors lower LDL-C levels and can reduce the risk of heart attacks in high-risk patients with established cardiovascular disease. Additionally, the VESALIUS-CV trial, initiated in March 2019, is an ongoing randomized outcomes trial, designed to evaluate the long-term effects of Repatha in high-risk cardiovascular disease (CVD) patients without a prior heart attack or stroke. The study will be the first to investigate long-term outcomes in this population with Repatha for a minimum of four years.

"Amgen is committed to building a vast body of evidence for Repatha—clinical trial and real-world effectiveness data sets—to advance the knowledge and treatment of cardiovascular disease," said David M. Reese, M.D., executive vice president of Research and Development at Amgen. "This study will generate valuable real-world evidence to help us demonstrate that PCSK9 inhibitors, like Repatha, are an important treatment option for very high-risk patients and can help prevent recurrent cardiovascular events in the real world."

Drs. Navar and Peterson are co-primary investigators of the study.

About cvMOBIUS

cvMOBIUS is a multicenter prospective observational registry in the U.S. and Canada. The study will be comprised of two parallel arms: a multicenter, prospective observational arm that will include 8,500 patients who experienced an ASCVD event within 12 months, from 250 sites; and a parallel EHR-based registry of a larger cohort of patients hospitalized with an ASCVD event treated at participating centers. The primary endpoint includes time to death, any non-fatal MI and any non-fatal ischemic stroke (IS).

About the Duke Clinical Research Institute

The DCRI, part of the Duke University School of Medicine, is the largest academic research organization in the world. It delivers on its mission to develop and share knowledge that improves the care of patients through innovative clinical research by conducting groundbreaking multinational clinical trials, managing major national patient registries, and performing landmark outcomes research. DCRI research spans multiple disciplines, from pediatrics to geriatrics, primary care to subspecialty medicine, and genomics to proteomics. The DCRI also is home to the Duke Databank for Cardiovascular Diseases, the largest and oldest institutional cardiovascular database in the world, which continues to inform clinical decision-making 40 years after its founding.

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.[4]

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.

Repatha Cardiovascular Outcomes (FOURIER) Study Design
FOURIER (Further cardiovascular OUtcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk), a multinational Phase 3 randomized, double-blind, placebo-controlled trial, was designed to evaluate whether treatment with Repatha in combination with statin therapy compared to placebo plus statin therapy reduces cardiovascular events. The primary endpoint was the time to cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary endpoint was the time to cardiovascular death, MI or stroke.

Eligible patients with high cholesterol (LDL-C ≥70 mg/dL or non-high-density lipoprotein cholesterol [non-HDL-C] ≥100 mg/dL) and clinically evident ASCVD at more than 1,300 study locations around the world were randomized to receive Repatha subcutaneous 140 mg every two weeks or 420 mg monthly plus effective statin dose; or placebo subcutaneous every two weeks or monthly plus effective statin dose. Optimized statin therapy was defined as at least atorvastatin 20 mg or equivalent daily with a recommendation for at least atorvastatin 40 mg or equivalent daily where approved. The study was event-driven and continued until at least 1,630 patients experienced a key secondary endpoint.

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.

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.[5] 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.

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 collaboration with any other company, including BeiGene, Ltd., or the acquisition of Otezla® (apremilast), 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 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. 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 or products, and to integrate the operations of companies or in support of products 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.

Any 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.

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