



New Virtual Histology Sub-Study Evaluates Impact Of Repatha® (Evolocumab) On Coronary Artery Plaque Composition

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Late-Breaking Clinical Trial Presented at ESC 2017

THOUSAND OAKS, Calif., Aug. 29, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced results from an exploratory virtual histology sub-study of the Repatha® (evolocumab) GLAGOV Phase 3 coronary intravascular ultrasound imaging trial that looked at coronary artery plaque composition. While virtual histology demonstrated an increase in dense calcium in coronary artery plaques in both the statin and Repatha arms, it did not detect a statistically significant difference between the two treatment groups. However, the observed directional trend in increased dense calcium with corresponding reduction in low-density lipoprotein cholesterol (LDL-C) is consistent with findings from previous statin studies.¹ The sub-study also showed reductions in LDL-C and percent atheroma volume (PAV) consistent with the primary GLAGOV results. Detailed results were presented today in a Late-Breaking Clinical Trials session at the European Society of Cardiology (ESC) Congress 2017 in Barcelona, Spain.

"The community has long understood that changes to the individual components of plaque, including an increase in dense calcium, could favorably impact future cardiovascular events, yet we have had limited visibility to how treatment choices may change plaque composition," said Stephen J. Nicholls, M.D., Ph.D., professor of Cardiology and deputy director, South Australian Health & Medical Research Institute, Adelaide, Australia. "As we expected, evolocumab dramatically lowered LDL-C and regressed plaques as assessed by proven measures. In addition, we saw directional changes in plaque composition that we have also seen in prior statin studies. However, the inability of virtual histology to demonstrate an incremental effect with evolocumab suggests that we need to find alternative ways to look at the effects of LDL-C reduction on plaque components."

This sub-study included 331 patients enrolled in the GLAGOV trial and explored whether Repatha produced changes in individual plaque components (dense calcium, fibrous, fibrofatty, necrotic core) compared to placebo using virtual histology. Patients in the Repatha arm experienced a +1.0mm³ absolute change in the primary endpoint of normalized dense calcium volume from baseline at week 78, compared to +0.6mm³ in the placebo arm ($p=0.49$). For the secondary endpoint of absolute change in normalized volume of fibrous, fibrofatty and necrotic core plaque measures, patients in the Repatha arm experienced an absolute change of -3.0mm³ versus -2.4mm³ in the placebo arm ($p=0.49$), -5.0mm³ versus -3.0mm³ ($p=0.49$), and -0.6mm³ versus -0.1mm³ ($p=0.49$), respectively, from baseline to week 78.

"Plaque instability has been linked to rupture and subsequent blood clots associated with atherosclerotic cardiovascular disease and cardiovascular events such as stroke and heart attack," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "The directional data in this Repatha sub-study supports the hypothesis that lowering LDL-C may play a role in changing the composition of the coronary artery plaque."

The primary results from GLAGOV were previously presented at the American Heart Association (AHA) Scientific Sessions 2016 and simultaneously published in the *Journal of the American Medical Association*.

GLAGOV Study Design

GLAGOV (GLobal Assessment of Plaque Regression with a PCSK9 Antibody as Measured by Intravascular Ultrasound) was a Phase 3, multicenter, double-blind, randomized, placebo-controlled trial designed to evaluate the effect of Repatha on the change in burden of coronary artery disease (CAD) in 968 patients undergoing clinically indicated coronary angiogram and on optimized background statin therapy.

Patients were required to have been treated with a stable statin dose for at least four weeks and to have an LDL-C ≥ 80 mg/dL or between 60 and 80 mg/dL with one major cardiovascular risk factor (defined as non-coronary atherosclerotic vascular disease, myocardial infarction or hospitalization for unstable angina in the preceding two years or type 2 diabetes mellitus) or three minor cardiovascular risk factors (defined as current cigarette smoking, hypertension, low levels of high-density lipoprotein (HDL) cholesterol, family history of premature coronary heart disease, high sensitivity C-reactive protein (hs-CRP) ≥ 2 mg/L or age ≥ 50 years in men and 55 years in women).

Patients were randomized 1:1 into two treatment groups to either receive monthly Repatha 420 mg or placebo subcutaneous injections. Optimized statin therapy was defined as at least atorvastatin 20 mg daily or equivalent, titrated to achieve LDL-C reduction per regional guidelines. Highly effective statin therapy (equivalent to atorvastatin 40 mg daily or higher) was recommended for all patients. Those patients with LDL-C >100 mg/dL not taking highly effective statin therapy, required investigators' attestation as to why such doses were not appropriate. The primary endpoint was change in PAV from baseline to week 78 compared to placebo, as determined by intravascular ultrasound (IVUS). IVUS is a high-resolution imaging tool that allows for the quantification of coronary atheroma in the coronary arteries.

Secondary endpoints included PAV regression (any reduction from baseline); change in total atheroma volume (TAV) from baseline to week 78; and regression (any reduction from baseline) in TAV.

About Repatha® (evolocumab)

Repatha® (evolocumab) 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.²

Repatha is approved in more than 50 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.

U.S. Repatha Indication

Repatha® is indicated as an adjunct to diet and:

- Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C)
- 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 effect of Repatha® on cardiovascular morbidity and mortality has not been determined.

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

The safety and effectiveness of Repatha® have not been established 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®.

Allergic reactions: Hypersensitivity reactions (e.g. 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 Repatha®-treated patients and more common than placebo) were: nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions.

In a 52-week trial, adverse reactions led to discontinuation of treatment in 2.2% of Repatha®-treated patients and 1% of placebo-treated patients. The most common adverse reaction that led to Repatha® treatment discontinuation and occurred at a rate greater than placebo was myalgia (0.3% versus 0% for Repatha® and placebo, respectively).

Adverse 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. The proportions of patients who discontinued treatment due to local injection site reactions in Repatha®-treated patients and placebo-treated patients were 0.1% and 0%, respectively.

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%).

Neurocognitive events were reported in less than or equal to 0.2% in Repatha®-treated and placebo-treated patients.

In a pool of placebo- and active-controlled trials, as well as open-label extension studies that followed them, a total of 1,988 patients treated with Repatha® had at least one LDL-C value <25 mg/dL. Changes to background lipid-altering therapy were not made in response to low LDL-C values, and Repatha® dosing was not modified or interrupted on this basis. Although adverse consequences of very low LDL-C were not identified in these trials, the long-term effects of very low levels of LDL-C induced by Repatha® are unknown.

Musculoskeletal adverse reactions were reported in 14.3% of Repatha®-treated patients and 12.8% of placebo-treated patients. The most common adverse reactions that occurred at a rate greater than placebo were back pain (3.2% versus 2.9% for Repatha® and placebo, respectively), arthralgia (2.3% versus 2.2%), and myalgia (2.0% versus 1.8%).

Homozygous Familial Hypercholesterolemia (HoFH): In 49 patients with homozygous familial hypercholesterolemia studied in a 12-week, double-blind, randomized, placebo-controlled trial, 33 patients received 420 mg of Repatha® subcutaneously once monthly. The adverse reactions that occurred in at least 2 (6.1%) Repatha®-treated patients and more frequently than in placebo-treated patients, included upper respiratory tract infection (9.1% versus 6.3%), influenza (9.1% versus 0%), gastroenteritis (6.1% versus 0%), and nasopharyngitis (6.1% versus 0%).

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:

Hypercholesterolemia and mixed dyslipidemia

Repatha is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, 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 hypercholesterolemia

Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia in combination with other lipid-

lowering therapies.

The effect of Repatha on cardiovascular morbidity and mortality has not yet been determined.

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Primary hypercholesterolemia and mixed dyslipidemia 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 hypercholesterolemia 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.

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:** Patients with severe renal impairment (defined as eGFR < 30 mL/min/1.73 m²) have not been studied. 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 ($\geq 1/100$ 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.

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.³ 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 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 one of the world's leading independent biotechnology companies, 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 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 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. 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 acquire other companies or products and to integrate the operations of companies we have acquired may not be successful. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all. We are increasingly dependent on information technology systems, infrastructure and data security. 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.

The scientific information discussed in this news release relating to new indications is preliminary and investigative and is not part of the labeling approved by the U.S. Food and Drug Administration or European Commission 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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2. Repatha® U.S. Prescribing Information. Amgen.
3. World Health Organization. Cardiovascular diseases (CVDs) fact sheet. <http://www.who.int/mediacentre/factsheets/fs317/en/>. Accessed March 2017.

The Amgen logo consists of the word "AMGEN" in a bold, blue, sans-serif font. The letters are closely spaced and have a slight shadow effect. A registered trademark symbol (®) is located at the top right of the letter "N".

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