# Repatha® (Evolocumab) Regresses Atherosclerosis In Patients With Coronary Artery Disease

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**Nearly Two-Thirds of Patients Experienced Plaque Regression With Repatha on Top of Optimized Statin Therapy**
**Detailed Results Simultaneously Published in the Journal of the American Medical Association and Presented at AHA Scientific Sessions 2016**

THOUSAND OAKS, Calif., Nov. 15, 2016 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that adding Repatha® (evolocumab) to optimized statin therapy resulted in statistically significant regression of atherosclerosis in patients with coronary artery disease (CAD). The detailed results from the GLAGOV Phase 3 coronary intravascular ultrasound imaging trial were presented at a Late-Breaking Clinical Trials Session of the American Heart Association (AHA) Scientific Sessions 2016 and simultaneously published in the *Journal of the American Medical Association*.

To view the multimedia assets associated with this release, please click: http://www.multivu.com/players/English/74140513-amgen-repatha-glagov-study.

The GLAGOV study evaluated whether Repatha, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor for the treatment of certain patients with elevated low-density lipoprotein cholesterol (LDL-C), would modify atherosclerotic plaque build-up in the coronary arteries of patients already treated with optimized statin therapy, as measured by intravascular ultrasound (IVUS) at baseline and week 78.

"The cardiovascular community began conducting imaging studies with LDL-C therapies to measure slowing of atherosclerotic disease progression. This study shows that maximal LDL-C reduction with Repatha can actually regress coronary atherosclerotic disease compared to statins alone," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "In fact, nearly two-thirds of patients on Repatha in this trial, the vast majority of whom were already on high to moderate intensity statin therapy at baseline, experienced a reduction in plaque burden."

The study met its primary objective showing that treatment with Repatha resulted in a statistically significant regression from baseline in percent atheroma volume (PAV), which is the proportion of arterial lumen occupied by plaque. Patients in the Repatha arm experienced a 0.95 percent decrease versus baseline in PAV compared with an increase of 0.05 percent versus baseline in patients receiving optimized statin therapy plus placebo (Repatha arm $p<0.0001$; placebo arm $p=0.78$). The difference between the two comparators was statistically significant ($p<0.0001$). In addition, adding Repatha yielded plaque regression in PAV for a greater percentage of patients than for those receiving placebo (64.3 percent versus 47.3 percent, respectively, $p<0.0001$). At baseline, 98 percent of patients in both arms were on high to moderate intensity statin therapy.

Patients in the Repatha arm experienced a mean decrease in normalized total atheroma volume (TAV), which is a measure of plaque volume, of 5.8mm³ compared with 0.9mm³ seen in the placebo arm (Repatha arm $p<0.0001$; placebo arm $p=0.45$). The difference between the two comparators was statistically significant ($p<0.0001$). Additionally, adding Repatha yielded plaque regression in TAV for a greater percentage of patients than placebo (61.5 percent versus 48.9 percent, respectively, $p=0.0002$).

"Based on previous studies, we did not know if GLAGOV would show additional plaque regression at LDL-C levels below 60 mg/dL," said Stephen J. Nicholls, M.D., Ph.D., professor of Cardiology and deputy director, South Australian Health & Medical Research Institute, Adelaide, Australia. "One of the most compelling results from GLAGOV is the continued reduction of plaque at LDL-C levels well below commonly accepted thresholds."

At baseline, patients had a mean LDL-C of 92.5 mg/dL across both treatment arms. During 78 weeks of treatment, the time-weighted mean LDL-C level was 36.6 mg/dL in the Repatha arm, which represents a reduction of 59.8 percent, compared with 93.0 mg/dL in the placebo arm. At week 78, the mean LDL-C in the Repatha arm was 29 mg/dL, which represents a 68.0 percent decrease from baseline, and in the placebo arm was 90 mg/dL.

An exploratory analysis evaluated the level of plaque reduction achieved in the 144 patients with baseline LDL-C levels below 70 mg/dL (the lowest treatment target among the current global guidelines). In this analysis, these patients experienced the greatest decrease in plaque burden from baseline (change in PAV) with Repatha compared with placebo (-1.97 percent versus -0.35 percent, respectively, $p<0.0001$). In addition, more than 80 percent of patients in this subset experienced plaque regression (by change in PAV) with Repatha (81.2 percent Repatha; 48.0 percent placebo, $p<0.0001$).

No new safety concerns were identified in the GLAGOV trial. The incidence of treatment-emergent adverse events was comparable among both groups (67.9 percent Repatha; 79.8 percent placebo). Adverse events of clinical importance reviewed in this study included myalgia (7.0 percent Repatha; 5.8 percent placebo), new diagnosis of diabetes mellitus (3.6 percent Repatha; 3.7 percent placebo), neurocognitive events (1.4 percent Repatha; 1.2 percent placebo) and injection site reactions (0.4 percent Repatha; 0.0 percent placebo). In the GLAGOV study, binding antibodies were rarely observed (0.2 percent [1 patient] in the Repatha-treated arm) and no patients tested positively for neutralizing antibodies.

Although the study was not powered to assess effects on cardiovascular events, an exploratory analysis revealed that positively-adjudicated major cardiovascular events occurred in 12.2 percent of patients receiving Repatha and 15.3 percent in those receiving placebo. The majority of adjudicated events were coronary revascularizations (10.3 percent Repatha; 13.6 percent placebo), followed by myocardial infarction (2.1 percent Repatha; 2.9 percent placebo). All other adjudicated cardiovascular events occurred in ≤0.8 percent of patients in each treatment group.

Harper continued, "The compelling data from GLAGOV remove any scientific doubt about the ability of Repatha to lower LDL-C and the impact it has on the critical underlying disease process. We remain concerned that many patients are experiencing barriers to accessing Repatha, despite their physician's treatment recommendations. We look forward to our outcomes study, FOURIER, and will continue to work with payers to improve access for patients who need additional LDL-C lowering."

**GLAGOV Study Design**
GLAGOV (GLobal Assessment of Plaque ReGression with a PCSK9 AntibOdy as Measured by IntraVascular Ultrasound) is a Phase 3, multicenter, double-blind, randomized, placebo-controlled trial designed to evaluate the effect of Repatha on the change in burden of 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 a 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 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 (2.6 mmol/L) 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 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 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.[1]

The FOURIER outcomes trial is designed to evaluate whether treatment with Repatha or placebo on top of optimized statin therapy, reduces the risk of cardiovascular events in patients with clinically evident atherosclerotic disease. The trial completed patient enrollment in June 2015. The primary endpoint for the FOURIER trial is major cardiovascular events defined as the composite of cardiovascular death, myocardial infarction (MI), stroke, hospitalization for unstable angina or coronary revascularization. The key secondary endpoint is the composite of cardiovascular death, MI or stroke. The trial is planned to continue until at least 1,630 patients experience the secondary endpoint, thereby providing 90 percent power to detect a relative reduction of 15 percent in this endpoint. Top-line results from the approximately 27,500-patient event-driven FOURIER study are anticipated in the first quarter of 2017.

Repatha is approved in more than 40 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 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.

**About Amgen Cardiovascular**
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.[2] 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 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. 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. We or others could identify safety, side effects or manufacturing problems with our products after they are on the market. 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. Discovery or identification of new product candidates cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate will be successful and become a commercial product. Further, some raw materials, medical devices and component parts for our products are supplied by sole third-party suppliers. 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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**REFERENCES**

1. Repatha® U.S. Prescribing Information. Amgen.
2. World Health Organization. Cardiovascular diseases (CVDs) fact sheet. http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed August 2016.

Repatha® (evolocumab) Product Shot

GLAGOV Study Design Fact Sheet

Repatha® (evolocumab) Fact Sheet

Repatha® (evolocumab) Logo