New FOURIER Analysis Shows Repatha® (Evolocumab) Reduces Cardiovascular Events In Patients With Diabetes

September 15, 2017

Data Supports Safety and Efficacy of Repatha in Patients With Diabetes
Simultaneously Presented at EASD 2017 and Published in The Lancet Diabetes & Endocrinology

THOUSAND OAKS, Calif., Sept. 15, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that a new analysis of the cardiovascular outcomes study (FOURIER) demonstrated that lowering low-density lipoprotein cholesterol (LDL-C) levels with Repatha® (evolocumab) significantly and consistently reduced cardiovascular events in patients with and without diabetes at baseline.

The analysis showed that diabetes was independently associated with a substantially increased risk of cardiovascular morbidity and mortality in patients with atherosclerotic cardiovascular disease. Patients with diabetes tended to have a greater absolute risk reduction of cardiovascular events with Repatha treatment because of their heightened baseline risk. Consistent with recent trials of more intensive LDL lowering, Repatha has not shown an effect on cardiovascular mortality.[1-5] The analysis also showed that Repatha was not associated with an increased risk of new-onset diabetes or worsening glycemia (increased presence of glucose in the blood) over a median of 2.2 years of follow-up in patients without diabetes or pre-diabetes. Additionally, no new safety concerns were identified in this analysis. The results were presented today at the 53rd Annual Meeting of the European Association for the Study of Diabetes (EASD) in Lisbon, Portugal and simultaneously published in *The Lancet Diabetes & Endocrinology*.

"This analysis further demonstrates the benefits of achieving LDL-C levels well below current targets among atherosclerotic cardiovascular disease patients both with and without diabetes, the former of whom are at significantly greater risk of cardiovascular events and thus tend to enjoy even larger absolute risk reductions," said Marc S. Sabatine, chairman of the TIMI Study Group, the Lewis Dexter, MD, Distinguished Chair in Cardiovascular Medicine at Brigham and Women's Hospital, and Professor of Medicine, Harvard Medical School, Boston, and lead author on the analysis. "Importantly, this analysis also provides additional evidence that evolocumab is equally safe in patients with and without diabetes."

As part of a pre-specified analysis of the Repatha cardiovascular outcomes study, diabetes status was defined on the basis of patient history, clinical events committee review of medical records, or baseline glycated hemoglobin (HbA_{1c}) of 6.5 percent (48 mmol/mol) or greater or fasting plasma glucose (FPG) of 7.0 mmol/L (126 mg/dL) or greater. At study baseline, 40 percent of patients had diabetes (n=11,031) and 60 percent did not have diabetes (n=16,533), of whom 10,344 had pre-diabetes and 6,189 had normoglycemia. In this analysis, compared with placebo, the diabetes subgroup experienced a 57 percent mean reduction in LDL-C levels when treated with Repatha (95 percent confidence interval [CI], 56-58.0; $p<0.0001$), and in the non-diabetes subgroup, patients treated with Repatha experienced a 60 percent mean reduction at 48 weeks (95 percent CI, 60-61; $p<0.0001$), down to 0.8 mmol/L (30 mg/dL) in both groups.

The hazard ratio (HR) of Repatha treatment for the composite primary endpoint, which included hospitalization for unstable angina, coronary revascularization, heart attack, stroke or cardiovascular death, was 0.83 (95 percent CI, 0.75-0.93; $p=0.0008$) for those with diabetes, and 0.87 (95 percent CI, 0.79-0.96; $p=0.0052$) for patients without diabetes. Because of their greater baseline risk of cardiovascular events, patients with diabetes tended to have a greater absolute risk reduction with Repatha treatment than patients without diabetes (2.7 percent [95 percent CI, 0.7-4.8] versus 1.6 percent [95 percent CI, 0.1-3.2]), driven largely by a greater absolute risk reduction in coronary revascularisation (2.7 percent [95 percent CI, 1.1-4.2] versus 1.8 percent [95 percent CI, 0.6-3.1]). The HR of Repatha treatment for the secondary composite endpoint of heart attack, stroke or cardiovascular death was 0.82 (95 percent CI, 0.72-0.93; $p=0.0021$) for those with diabetes and 0.78 (95 percent CI, 0.69-0.89; $p=0.0002$) for those without diabetes. As was seen in the overall trial results, the magnitude of risk reduction in both the primary and secondary endpoints tended to increase over time beyond the first year in patients with and without diabetes.[6]

"Abnormally high lipids are common in patients with diabetes, which increases their risk of cardiovascular disease, and some patients continue to struggle with the critical task of managing their LDL-C levels despite treatment with high-intensity statins, which is the standard of care," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "This analysis provides further evidence of a substantially increased risk of cardiovascular events in patients with diabetes, and reinforces the importance of Repatha as an appropriate treatment option in these higher risk patients by virtue of a greater absolute risk reduction with treatment."

Repatha, compared to placebo, did not increase the risk of new-onset diabetes in patients without diabetes at baseline (8.0 percent [663/8,256] versus 7.6 percent [631/8,254], respectively; HR 1.05, 95 percent CI, 0.94-1.17), including those with pre-diabetes (HR 1.00, 95 percent CI, 0.89-1.13). Levels of HbA_{1c} and FPG were similar between the Repatha and placebo groups over time in patients with diabetes, pre-diabetes or normoglycemia.

The overall rates of adverse events and serious adverse events were similar between Repatha and placebo in patients with and without diabetes. Among patients with diabetes at baseline, the proportions of patients with adverse events were 78.5 percent (4,327 of 5,513 patients) in the Repatha group and 78.3 percent (4,307 of 5,502 patients) in the placebo group. Among patients without diabetes at baseline, the proportions with adverse events were 76.8 percent (6,337 of 8,256 patients) in the Repatha group and 76.8 percent (6,337 of 8,254 patients) in the placebo group.

Primary Analysis of the Repatha Cardiovascular Outcomes Study
The primary analysis included 27,564 patients with established cardiovascular disease. The study was statistically powered around the hard major adverse cardiovascular event (MACE) composite endpoint of first heart attack, stroke or cardiovascular death (key secondary composite endpoint) and found that adding Repatha to optimized statin therapy resulted in a statistically significant 20 percent ($p<0.001$) reduction in these events. The study also found a statistically significant 15 percent reduction ($p<0.001$) in the risk of the extended MACE composite (primary) endpoint, which included hospitalization for unstable angina, coronary revascularization, heart attack, stroke or cardiovascular death.[6]

No new safety concerns were identified in this large clinical trial with roughly 60,000 patient-years of follow-up; this included the assessment of patients who achieved very low levels of LDL-C.

The detailed results from the Repatha cardiovascular outcomes study were initially presented during a Late-Breaking Clinical Trials Session at the American College of Cardiology 66th Annual Scientific Session and simultaneously published in the *New England Journal of Medicine.*

Repatha Cardiovascular Outcomes (FOURIER) Study Design
The 27,564-patient Repatha cardiovascular outcomes study, FOURIER (Further Cardiovascular OUtcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk), was a multinational Phase 3 randomized, double-blind, placebo-controlled trial, 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 time to cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary endpoint was the time to cardiovascular death, myocardial infarction 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 atherosclerotic cardiovascular disease at more than 1,200 study locations around the world were randomized to receive Repatha subcutaneous 140 mg every two weeks or 420 mg monthly plus optimized statin dose; or placebo subcutaneous every two weeks or monthly plus optimized 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 1,630 patients experienced a key secondary endpoint.

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.[7]

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.

Posology
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 m^2) 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 (≥ 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.[8] 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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References:

1. Cannon CP, et al. N Engl J Med. 2004;350:1495-1504.
2. LaRosa JC, et al. N Engl J Med. 2005;352:1425-1435.

3. Pederson TR, et al. JAMA. 2005; 294:2437-2445.
4. Search Collaborative Group Lancet 2010; 376: 1658–69.
5. Cannon CP, et al. N Engl J Med. 2015;372:2387-2397.
6. Sabatine MS, Giugliano RP, Keech AC, et al, for the FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017; 376: 1713–22.
7. Repatha® U.S. Prescribing Information. Amgen.
8. World Health Organization. Cardiovascular diseases (CVDs) fact sheet. http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed March 2017.

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