



## Repatha® (Evolocumab) Reduced Cardiovascular Events In Patients With Baseline LDL-C Levels Below Current Targets

May 20, 2017

### New Analysis From Cardiovascular Outcomes Trial Shows Addition of Repatha in Patients Considered at Goal Further Reduces Cardiovascular Event Risk Separate Analysis Demonstrates Consistent Cardiovascular Risk Reduction in Patients Even on Maximum-Intensity Statin Therapy

THOUSAND OAKS, Calif., May 20, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced new data from the Repatha® (evolocumab) cardiovascular outcomes trial (FOURIER), which showed that Repatha consistently and safely reduced cardiovascular events in patients with established cardiovascular disease regardless of baseline low-density lipoprotein cholesterol (LDL-C) level below or above 70 mg/dL. A separate analysis also demonstrated Repatha reduced cardiovascular events in patients being treated with maximum-intensity statin therapy. These results were presented during a late-breaker session at the 2017 National Lipid Association Scientific Sessions.

"We now have additional evidence of the benefit of evolocumab in reducing cardiovascular event risk, even in patients starting with LDL-C levels below the most aggressive current guideline targets and in patients already on maximum-intensity statin therapy," said Marc S. Sabatine, M.D., M.P.H., 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.

The two analyses compared clinical outcomes in patients stratified by baseline LDL-C above and below 70 mg/dL and in patients on maximum-intensity statin therapy, defined as atorvastatin 80 mg or rosuvastatin 40 mg daily, versus patients on less intense statin therapy.

"These results provide further evidence for patients with established cardiovascular disease who would otherwise be considered as being successfully managed to the most stringent treatment targets," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "Previously, physicians have debated the benefit of treating high-risk cardiovascular patients with baseline LDL-C levels below 70 mg/dL. The Repatha cardiovascular outcomes trial shows that even patients already at lower levels of baseline LDL-C are still at risk for a cardiovascular event, and the addition of Repatha can continue to safely lower these patients' cardiovascular risk by reducing their LDL-C levels beyond current targets."

#### Baseline LDL-C Analysis

In patients with a baseline LDL-C below 70 mg/dL (n=2,034), Repatha reduced the median baseline LDL-C from 65.5 mg/dL to 21.0 mg/dL. Repatha consistently reduced the risk of the composite primary endpoint, which included hospitalization for unstable angina, coronary revascularization, heart attack, stroke or cardiovascular death, regardless of whether baseline LDL-C was below or above 70 mg/dL (20 percent in patients with baseline <70 mg/dL; 14 percent in patients with baseline ≥70 mg/dL, P-interaction=0.65). The results were also consistent for the more robust, secondary composite endpoint of heart attack, stroke or cardiovascular death where patients with a baseline LDL-C less than 70 mg/dL experienced a 30 percent reduction in cardiovascular events and patients with a baseline LDL-C greater than or equal to 70 mg/dL experienced a 19 percent reduction in cardiovascular events (P-interaction=0.44).

#### Background Statin Analysis

In patients on maximum-intensity statins (n=7,533), Repatha reduced the median baseline LDL-C from 93 mg/dL to 32 mg/dL. Additionally, Repatha consistently reduced the risk of major cardiovascular events in patients on maximum-intensity and less intense statin therapy in both the composite primary endpoint (14 percent in patients on maximum-intensity statin therapy; 15 percent in patients on less intense statin therapy, P-interaction=0.88) and the composite secondary endpoint (22 percent in patients on maximum-intensity statin therapy; 19 percent in patients on less intense statin therapy, P-interaction=0.71).

In the two analyses, there were no differences in the rates of adverse events leading to discontinuation between treatment groups in patients who had a baseline LDL-C below 70 mg/dL (4.4 percent Repatha; 4.6 percent placebo) or in patients on maximum-intensity statin therapy (3.9 percent Repatha; 3.7 percent placebo).

#### Primary Analysis

Results from the primary analysis of the 27,564-patient Repatha cardiovascular outcomes study were also presented at the meeting. 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.

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 66<sup>th</sup> Annual Scientific Session (ACC.17) 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  $\geq$ 70 mg/dL or non-high-density lipoprotein cholesterol [non-HDL-C]  $\geq$ 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 effective statin dose. Effective 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 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.<sup>1</sup>

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](http://www.amgen.com) and [www.Repatha.com](http://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.<sup>2</sup> 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](http://www.amgen.com) and follow us on [www.twitter.com/amgen](http://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. 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 the 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**

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2. World Health Organization. Cardiovascular diseases (CVDs) fact sheet. <http://www.who.int/mediacentre/factsheets/fs317/en/> Accessed May 2017.



To view the original version on PR Newswire, visit: <http://www.prnewswire.com/news-releases/repatha-evolocumab-reduced-cardiovascular-events-in-patients-with-baseline-ldl-c-levels-below-current-targets-300461022.html>

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