New Repatha® (evolocumab) Analyses Show Efficacy And Safety Across Risk Groups In Results Presented At ESC Congress 2016

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THOUSAND OAKS, Calif., Aug. 28, 2016 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced data presented at the European Society of Cardiology (ESC) Congress 2016 showing Repatha® (evolocumab) consistently reduced low-density lipoprotein cholesterol (LDL-C) in patients across cardiovascular (CV) risk subgroups or with familial hypercholesterolemia (FH).

"These analyses continue to shape the clinical evidence for Repatha and help to advance our understanding of its potential to benefit patients," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "The data at ESC provide further insights into the impact of Repatha on multiple patient populations who are at higher cardiovascular risk and are in need of additional treatment options."

Researchers looking at the "Efficacy of evolocumab in patients across ESC/EAS CV risk subgroups," categorized a total of 2,532 patients from three, 12-week Phase 3 studies by the four ESC/European Atherosclerotic Society (EAS) risk criteria (very high, high, moderate and low). The analysis showed that treatment with Repatha 140 mg every two weeks or 420 mg monthly consistently reduced levels of LDL-C and other lipids from baseline to the mean of weeks 10 and 12 across all risk categories compared to placebo or ezetimibe controls. For example, among very high-risk patients, Repatha reduced LDL-C levels from baseline 65.2 percent more than placebo and 40.7 percent more than ezetimibe. The rates of overall adverse events were similar for the three groups, occurring in 43.1 percent, 50.5 percent and 40.8 percent of patients on Repatha, ezetimibe and placebo, respectively.

In another presentation, researchers looking at the "Long-term safety, tolerability and efficacy of evolocumab in patients with heterozygous familial hypercholesterolaemia," found that treatment with Repatha for 48 weeks resulted in persistent and marked LDL-C reductions in these patients. The analysis showed that Repatha plus standard of care (SoC) reduced LDL-C levels from baseline by 53.6 percent at 48 weeks (n=279), compared to a 2.1 percent increase for SoC alone (n=139). The pooled analysis included 440 patients with heterozygous familial hypercholesterolemia (HeFH) who completed Amgen's RUTHERFORD-1 (Phase 2) or RUTHERFORD-2 (Phase 3) trials and entered open-label extension trials (OSLER-1 or OSLER-2). Patients were randomized in the extension trials to receive SoC alone or Repatha plus SoC. Repatha was well tolerated in the extension studies with no new safety signals. The rates of overall adverse events were similar for the two groups, occurring in 80 percent of patients receiving Repatha and 67 percent of patients receiving SoC.

"These long-term data add to the growing body of evidence supporting Repatha's ability to meaningfully reduce LDL cholesterol levels in patients with familial hypercholesterolemia," said G. Kees Hovingh, M.D., Ph.D., Academisch Medisch Centrum, Vascular Medicine, Amsterdam, the Netherlands. "Familial hypercholesterolemia is an inherited condition that leads to high levels of LDL cholesterol from birth, and these high LDL cholesterol levels can result in increased risk for premature cardiovascular disease in patients with FH. This understanding is important for the HeFH patients in whom adequate control of their cholesterol levels with other currently approved lipid-lowering agents has been troublesome."

Additional data at the Congress included a Rapid Fire Abstract entitled, "Familial Hypercholesterolaemia Diagnosis: A Case of Missed Opportunity," which suggested that as few as 1 in 10 FH patients may be diagnosed. Patient-level data available in the Clinical Practice Research DataLink (CPRD), a UK-based general practice database, indicated a FH prevalence of 1.3 per 1,000 persons, which increased to 11.7 when missed diagnoses were counted.

Elevated LDL-C is an abnormality of cholesterol and/or fats in the blood and is recognized as a major risk factor for CV disease.[1-4] In the U.S., there are approximately 11 million people with atherosclerotic cardiovascular disease (ASCVD) and/or FH who have uncontrolled levels of LDL-C over 70 mg/dL, despite treatment with statins or other cholesterol-lowering therapies.[5,6] More than 60 percent of high-risk patients in Europe are still unable to adequately lower their LDL-C levels with statins or other currently approved lipid-lowering agents. Among very high-risk patients, the percentage is increased to more than 80 percent.[7] It is estimated that less than one percent of people with FH (heterozygous and homozygous forms) in most countries are diagnosed.[8]

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.[9]

GLAGOV, the intravascular ultrasound study, is underway to determine the effect of Repatha on coronary atherosclerosis in approximately 950 patients undergoing cardiac catheterization to test the hypothesis of robust LDL-C reduction leading to a reduction or a change in the build-up of plaque in the arteries. Results from the GLAGOV study are expected in the second half of 2016.

The FOURIER outcomes trial is designed to evaluate whether treatment with Repatha in combination with statin therapy, compared to placebo plus statin therapy, reduces the risk of cardiovascular events in patients with high cholesterol and clinically evident cardiovascular disease, and 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 end point 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 reduction of 15 percent in this endpoint. Top-line results from the approximately 27,500-patient event-driven FOURIER study are anticipated in first quarter of 2017.

Repatha is approved in 44 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 EU Product Information
Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, 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.

Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

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

Important EU 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.

Posology: The recommended dose for adults with primary disease is either 140 mg every two weeks or 420 mg (the contents of three pre-filled syringes) once a month; both doses are clinically equivalent. For adults or children older than 12 years with homozygous familial hypercholesterolemia, the initial recommended dose is 420 mg once a month. If a response is not achieved after 12 weeks of treatment, the dose can be increased up to 420 mg every two weeks. For more information, see the package leaflet.

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 (≥ 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°C – 8°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°C) in the original carton and must be used within 1 week.

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.[10] 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. 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 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. 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. 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. World Health Organization. Quantifying Selected Major Risks to Health. In: The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva. 2002:49-97.
2. Merck Manuals website. http://www.merckmanuals.com/professional/endocrine_and_metabolic_disorders/lipid_disorders/dyslipidemia.html. Accessed August 2016.
3. American Heart Association (2014). Why Cholesterol Matters. http://www.heart.org/HEARTORG/Conditions/Cholesterol/WhyCholesterolMatters/Why-Cholesterol-Matters_UCM_001212_Article.jsp. Accessed August 2016.
4. World Health Organization. Global Status Report on Noncommunicable Diseases 2014. Geneva, 2014.
5. Amgen Data on File.
6. Centers for Disease Control and Prevention. Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol. United States, 1999–2002 and 2005–2008. *MMWR*. 2011;60(4):109–14.
7. Halcox JP, et al. Low Rates of Both Lipid-Lowering Therapy Use and Achievement of Low-Density Lipoprotein Cholesterol Targets in Individuals at High-Risk for Cardiovascular Disease across Europe. *PLoS One*. 2015;10(2).
8. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial Hypercholesterolaemia is Underdiagnosed and Undertreated in the General Population: Guidance for Clinicians to Prevent Coronary Heart Disease. *Eur Heart J*. 2013;34:3478-3490.
9. Repatha® U.S. Prescribing Information. Amgen.
10. World Health Organization. Cardiovascular diseases (CVDs) fact sheet. http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed August 2016.

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