Repatha® (Evolocumab) Phase 3 Cognitive Function Study Results Published In The New England Journal Of Medicine

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Study Showed Lowering LDL-C With Repatha Did Not Impair Cognition
Results From One of the Largest Cognitive Function Trials Support Safety Profile of Repatha

THOUSAND OAKS, Calif., Aug. 16, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the *New England Journal of Medicine* (*NEJM*) published results from the Repatha® (evolocumab) cognitive function trial (EBBINGHAUS), which was conducted in a subset of patients enrolled in the randomized, placebo-controlled Repatha cardiovascular outcomes study (FOURIER). The study demonstrated that Repatha was non-inferior to placebo, with no significant difference in cognitive function between the Repatha and placebo-treated groups.

"In the first prospectively designed study of cognitive function with a PCSK9 inhibitor using validated instruments, we showed that there were no significant differences between patients taking evolocumab and those on placebo," said Robert P. Giugliano, M.D., S.M., Brigham and Women's Hospital, Boston and lead study investigator. "These findings are reassuring for both physicians and patients because they show that LDL cholesterol levels can be lowered with evolocumab to levels well below current treatment targets, with no negative effects on memory or other cognitive domains."

The effect of Repatha on executive function (primary endpoint) was non-inferior to placebo, and there was no statistical difference between Repatha and placebo on the other cognitive domains tested: working memory, memory function and psychomotor speed (secondary endpoints).

"Historically, the clinical cardiology community has had concerns that low LDL-C levels may impact cognitive function," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "Across our comprehensive clinical trial program, thousands of patients have been treated with Repatha, which has demonstrated a consistent safety profile, even at very low LDL cholesterol levels. These findings add to the body of evidence supporting the safety of LDL-lowering with Repatha in patients with established cardiovascular disease who need more than statin therapy alone."

In the primary cohort of 1,204 patients, followed for a median of 19 months, the change from baseline raw score of spatial working memory strategy index of executive function was similar in the Repatha and placebo groups (mean baseline score 17.8; mean change from baseline -0.21 versus -0.29, respectively). The primary endpoint was below the pre-specified margin, demonstrating non-inferiority. The primary endpoint was assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory strategy index of executive function. CANTAB is an established, language- and culture-independent, computerized, tablet-based cognitive assessment tool that uses touchscreen neuropsychological tests of cognition specifically designed to assess central nervous system disorders and cognitive function across a range of domains, including episodic and working memory, executive function, psychomotor speed and attention.

Secondary endpoint results in the three cognitive domains of working memory, memory function and psychomotor speed were consistent with the primary endpoint result, and patients treated with Repatha experienced changes from baseline similar to placebo in all three cognitive domains tested. Changes from baseline in the global composite score were also similar between treatment arms.

In an exploratory analysis, results were consistent regardless of achieved low-density lipoprotein cholesterol (LDL-C) levels and did not show an association between LDL-C level and adverse cognitive outcomes, including in the 661 patients with the lowest-achieved LDL-C level (<25 mg/dL).

In the EBBINGHAUS study, neurocognitive adverse event rates were similar between treatment arms (1.9 percent Repatha; 1.3 percent placebo). The adverse events identified in EBBINGHAUS were consistent with the adverse events identified in the 27,564-patient Repatha cardiovascular outcomes study FOURIER.

The results were initially presented at a Late-Breaking Clinical Trial Session at the American College of Cardiology 66th Annual Scientific Session (ACC.17) in March 2017.

Repatha Cognitive Function (EBBINGHAUS) Study Design
EBBINGHAUS (Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in high cardiovascUlar risk Subjects) is a double-blind, placebo-controlled, randomized non-inferiority trial involving 1,974 patients with clinically evident atherosclerotic cardiovascular disease enrolled in the Repatha cardiovascular outcomes study (FOURIER). The primary non-inferiority assessment of the primary endpoint of spatial working memory strategy index of executive function (assessing executive function, or high-level thinking and decision making) was performed on the primary cohort of 1,204 patients who enrolled on or before the first dose of investigational product and had at least one post-baseline CANTAB assessment. The full cohort (1,974 patients) included all randomized patients. The primary endpoint was assessed by comparing the 95 percent confidence interval (CI) with the pre-specified non-inferiority margin for the treatment difference between Repatha and placebo. Secondary endpoints were the CANTAB Spatial Working Memory between-errors score (assessing working memory, or the ability to hold material in mind while that material is being actively processed); the CANTAB Paired Associates Learning Total Errors Adjusted (assessing memory function, or the ability to store and retrieve information by associating an event with a time and place); and the CANTAB Reaction Time Five-Choice Median Reaction Time (assessing psychomotor speed, which is responsible for detecting and responding to a stimulus). For all three secondary endpoints, the 95 percent CI for the estimated treatment difference between Repatha and placebo spanned equivalence.

Primary and secondary endpoints were assessed using a tablet-based tool at baseline, week 24, yearly and at study end. The primary analysis compared the mean change from baseline in patients who had a baseline cognitive assessment on or prior to the first day of study drug.

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 hard major adverse cardiovascular event (MACE) composite endpoint was time to cardiovascular death, myocardial infarction or stroke (key secondary endpoint). The

extended MACE composite endpoint was the time to cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization (primary endpoint).

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 1,300 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 at least 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.[1]

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.

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 current reports on Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those we project. Discovery or identification of new product candidates or development of new indications for existing products cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate or development of a new indication for an existing product will be successful and become a commercial product. Further, preclinical results do not guarantee safe and effective performance of product candidates in humans. The complexity of the human body cannot be perfectly, or sometimes, even adequately modeled by computer or cell culture systems or animal models. The length of time that it takes for us to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and we expect similar variability in the future. Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints we have selected. We develop product candidates internally and through licensing collaborations, partnerships and joint ventures. Product candidates that are derived from relationships may be subject to disputes between the parties or may prove to be not as effective or as safe as we may have believed at the time of entering into such relationship. Also, we or others could identify safety, side effects or manufacturing problems with our products, including our devices, after they are on the market.

Our results may be affected by our ability to successfully market both new and existing products domestically and internationally, clinical and regulatory developments involving current and future products, sales growth of recently launched products, competition from other products including biosimilars, difficulties or delays in manufacturing our products and global economic conditions. In addition, sales of our products are affected by pricing pressure, political and public scrutiny and reimbursement policies imposed by third-party payers, including governments, private insurance plans and managed care providers and may be affected by regulatory, clinical and guideline developments and domestic and international trends toward managed care and healthcare cost containment. Furthermore, our research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. Our business may be impacted by government investigations, litigation and product liability claims. In addition, our business may be impacted by the adoption of new tax legislation or exposure to additional tax liabilities. If we fail to meet the compliance obligations in the corporate integrity agreement between us and the U.S. government, we could become subject to significant sanctions. Further, while we routinely obtain patents for our products and technology, the protection offered by our patents and patent applications may be challenged, invalidated or circumvented by our competitors, or we may fail to prevail in present and future intellectual property litigation. We perform a substantial amount of our commercial manufacturing activities at a few key facilities and also depend on third parties for a portion of our manufacturing activities, and limits on supply may constrain sales of certain of our current products and product candidate development. In addition, we compete with other companies with respect to many of our marketed products as well as for the discovery and development of new products. Further, some raw materials, medical devices and component parts for our products are supplied by sole third-party suppliers. Certain of our distributors, customers and payers have substantial purchasing leverage in their dealings with us. The discovery of significant problems with a product similar to one of our products that implicate an entire class of products could have a material adverse effect on sales of the affected products and on our business and results of operations. Our efforts to acquire other companies or products and to integrate the operations of companies we have acquired may not be successful. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all. We are increasingly dependent on information technology systems, infrastructure and data security. Our stock price is volatile and may be affected by a number of events. Our business performance could affect or limit the ability of our Board of Directors to declare a dividend or our ability to pay a dividend or repurchase our common stock.

The scientific information discussed in this news release relating to new indications is preliminary and investigative and is not part of the labeling approved by the U.S. Food and Drug Administration or European Commission for the products. The products are not approved for the investigational use(s) discussed in this news release, and no conclusions can or should be drawn regarding the safety or effectiveness of the products for these uses.

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

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