Repatha® (Evolocumab) Four-Year Open-Label Follow-Up Study Published In 'JAMA Cardiology'

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Long-Term Study Identified No New Safety Concerns

THOUSAND OAKS, Calif., March 14, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that four-year follow-up results from the Repatha® (evolocumab) OSLER-1 study, the longest PCSK9 inhibitor clinical trial to date, were published in *JAMA Cardiology*. Repatha, when added to standard of care (SOC), achieved median low-density lipoprotein cholesterol (LDL-C) reductions of 57 percent at four years, with no new safety concerns identified and no neutralizing antibodies observed with cumulative exposure.[1]

"For patients with cardiovascular disease, persistent LDL-C reduction is an important component of managing this chronic disease," said Michael J. Koren, M.D., Jacksonville Center for Clinical Research. "These results reinforce that adding Repatha to the cardiovascular standard of care can achieve additional sustained LDL-C reductions over several years with no increased risk of safety concerns for patients who continue to struggle with elevated cholesterol levels."

The OSLER-1 open-label extension (OLE) study enrolled 1,324 of the 1,650 (80.2 percent) eligible patients who completed a Phase 2 parent study. OSLER-1 evaluated the durability of LDL-C reduction and incidence of adverse events (AE) with long-term therapy with Repatha. Once therapy was initiated, 79 percent of patients persisted with Repatha treatment with average exposure duration of 44 months. Patients who reached four years of follow-up achieved a median LDL-C of 60 mg/dL.[1]

"Safely reducing LDL-C over the long term is an important treatment objective given that many patients with elevated cholesterol will experience one or more cardiovascular events in their lifetime," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "These long-term follow-up data reaffirm our conviction that Repatha is a valuable tool in the management of cardiovascular disease."

The analysis found no new safety concerns with prolonged observation and reported that AEs occurred in 52.6 percent of patients treated with Repatha and SOC during year four compared to 79.3 percent during year one. The annualized AE rates in the Repatha and SOC group versus SOC alone were 2.8 percent versus 4.0 percent for new onset diabetes, 0.4 percent versus 0 percent for neurocognitive events, and 4.7 percent versus 8.5 percent for muscle-related events. The percentage of patients who discontinued Repatha due to AEs was 0.5 percent in year four and 2.8 percent in year one. Additionally, no neutralizing antibodies and only four transient binding antibody cases were observed.[1]

Cardiovascular disease is the leading cause of death worldwide.[2] In the U.S., there are approximately 11 million people with atherosclerotic cardiovascular disease (ASCVD) and/or familial hypercholesterolemia (FH) who have uncontrolled levels of LDL-C over 70 mg/dL, despite treatment with statins or other cholesterol-lowering therapies.[3,4]

OSLER-1 Study Design

Open Label Study of Long TERm Evaluation Against LDL-C 1 (OSLER-1) is an open-label extension study with Repatha, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. The study is being conducted across 192 sites in 18 countries.

Patients were eligible to enroll in OSLER-1 study after completing one of the double-blind Phase 2 parent studies without experiencing a serious AE requiring treatment discontinuation. During the first year patients were randomized 2:1 to Repatha 420 mg monthly in addition to SOC or SOC alone. After year one, all patients continuing in the study received Repatha 420 mg monthly in addition to SOC. Lipid parameters, safety and tolerability were assessed every 12 weeks.

The primary objective of this analysis is to evaluate whether LDL-C reductions with Repatha persist across different populations during an extended period of time. The secondary objective included the assessment of AEs, anti-drug antibodies (ADAs), and factors contributing to treatment discontinuation.

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.[5]

Repatha is approved in more than 40 countries, including the U.S., Japan, Canada and in all 28 countries that are members of the European Union. Applications in other countries are pending.

Important U.S. Product Information

Repatha® is indicated as an adjunct to diet and:

- Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C)
- Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C

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

The safety and effectiveness of Repatha® have not been established in pediatric patients with HoFH who are younger than 13 years old.

The safety and effectiveness of Repatha® have not been established in pediatric patients with primary hyperlipidemia or HeFH.

Important U.S. Safety Information

Contraindication: Repatha® is contraindicated in patients with a history of a serious hypersensitivity reaction to Repatha®.

Allergic reactions: Hypersensitivity reactions (e.g. rash, urticaria) have been reported in patients treated with Repatha®, including some that led to discontinuation of therapy. If signs or symptoms of serious allergic reactions occur, discontinue treatment with Repatha®, treat according to the standard of care, and monitor until signs and symptoms resolve.

Adverse reactions: The most common adverse reactions (>5% of Repatha®-treated patients and more common than placebo) were: nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions.

In a 52-week trial, adverse reactions led to discontinuation of treatment in 2.2% of Repatha®-treated patients and 1% of placebo-treated patients. The most common adverse reaction that led to Repatha® treatment discontinuation and occurred at a rate greater than placebo was myalgia (0.3% versus 0% for Repatha® and placebo, respectively).

Adverse reactions from a pool of the 52-week trial and seven 12-week trials:

Local injection site reactions occurred in 3.2% and 3.0% of Repatha®-treated and placebo-treated patients, respectively. The most common injection site reactions were erythema, pain, and bruising. The proportions of patients who discontinued treatment due to local injection site reactions in Repatha® -treated patients and placebo-treated patients were 0.1% and 0%, respectively.

Allergic reactions occurred in 5.1% and 4.7% of Repatha®-treated and placebo-treated patients, respectively. The most common allergic reactions were rash (1.0% versus 0.5% for Repatha® and placebo, respectively), eczema (0.4% versus 0.2%), erythema (0.4% versus 0.2%), and urticaria (0.4% versus 0.1%).

Neurocognitive events were reported in less than or equal to 0.2% in Repatha®-treated and placebo-treated patients.

In a pool of placebo- and active-controlled trials, as well as open-label extension studies that followed them, a total of 1,988 patients treated with Repatha® had at least one LDL-C value <25 mg/dL. Changes to background lipid-altering therapy were not made in response to low LDL-C values, and Repatha® dosing was not modified or interrupted on this basis. Although adverse consequences of very low LDL-C were not identified in these trials, the long-term effects of very low levels of LDL-C induced by Repatha® are unknown.

Musculoskeletal adverse reactions were reported in 14.3% of Repatha®-treated patients and 12.8% of placebo-treated patients. The most common adverse reactions that occurred at a rate greater than placebo were back pain (3.2% versus 2.9% for Repatha® and placebo, respectively), arthralgia (2.3% versus 2.2%), and myalgia (2.0% versus 1.8%).

Homozygous Familial Hypercholesterolemia (HoFH): In 49 patients with homozygous familial hypercholesterolemia studied in a 12-week, double-blind, randomized, placebo-controlled trial, 33 patients received 420 mg of Repatha® subcutaneously once monthly. The adverse reactions that occurred in at least 2 (6.1%) Repatha®-treated patients and more frequently than in placebo-treated patients, included upper respiratory tract infection (9.1% versus 6.3%), influenza (9.1% versus 0%), gastroenteritis (6.1% versus 0%), and nasopharyngitis (6.1% versus 0%).

Immunogenicity: Repatha® is a human monoclonal antibody. As with all therapeutic proteins, there is a potential for immunogenicity with Repatha®.

Please contact Amgen Medinfo at 800-77-AMGEN (800-772-6436) or 844-REPATHA (844-737-2842) regarding Repatha® availability or find more information, including full Prescribing Information, at www.amgen.com and www.Repatha.com.

About Amgen 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.[2] Amgen's research into cardiovascular disease, and potential treatment options, is part of a growing competency at Amgen that utilizes human genetics to identify and validate certain drug targets. Through its own research and development efforts, as well as partnerships, Amgen is building a robust cardiovascular portfolio consisting of several approved and investigational molecules in an effort to address a number of today's important unmet patient needs, such as high cholesterol and heart failure.

About Amgen
Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

For more information, visit www.amgen.com and follow us on www.twitter.com/amgen.

Forward-Looking Statements
This news release contains forward-looking statements that are based on the current expectations and beliefs of Amgen. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins,

capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including our most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those we project. Our results may be affected by our ability to successfully market both new and existing products domestically and internationally, clinical and regulatory developments involving current and future products, sales growth of recently launched products, competition from other products including biosimilars, difficulties or delays in manufacturing our products and global economic conditions. In addition, sales of our products are affected by pricing pressure, political and public scrutiny and reimbursement policies imposed by third-party payers, including governments, private insurance plans and managed care providers and may be affected by regulatory, clinical and guideline developments and domestic and international trends toward managed care and healthcare cost containment. Furthermore, our research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. We or others could identify safety, side effects or manufacturing problems with our products after they are on the market. Our business may be impacted by government investigations, litigation and product liability claims. In addition, our business may be impacted by the adoption of new tax legislation or exposure to additional tax liabilities. If we fail to meet the compliance obligations in the corporate integrity agreement between us and the U.S. government, we could become subject to significant sanctions. Further, while we routinely obtain patents for our products and technology, the protection offered by our patents and patent applications may be challenged, invalidated or circumvented by our competitors, or we may fail to prevail in present and future intellectual property litigation. We perform a substantial amount of our commercial manufacturing activities at a few key facilities and also depend on third parties for a portion of our manufacturing activities, and limits on supply may constrain sales of certain of our current products and product candidate development. In addition, we compete with other companies with respect to many of our marketed products as well as for the discovery and development of new products. Discovery or identification of new product candidates cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate will be successful and become a commercial product. Further, some raw materials, medical devices and component parts for our products are supplied by sole third-party suppliers. 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.

CONTACT: Amgen, Thousand Oaks
Kristen Davis, 805-447-3008 (Media)
Kristen Neese, 805-313-8267 (Media)
Arvind Sood, 805-447-1060 (Investors)

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To view the original version on PR Newswire, visit:http://www.prnewswire.com/news-releases/repatha-evolocumab-four-year-open-label-follow-up-study-published-in-jama-cardiology-300423541.html

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