Amgen's Repatha® (Evolocumab) Approved As First PCSK9 Inhibitor In Japan For The Treatment Of High Cholesterol

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Important Milestone for Certain Japanese Patients With Uncontrolled LDL Cholesterol
First Approval for Amgen and Astellas Joint Venture

THOUSAND OAKS, Calif., Jan. 21, 2016 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the Japanese Ministry of Health, Labour and Welfare has approved the cholesterol-lowering medication Repatha® (evolocumab) Injection, the first proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to be approved in Japan. Repatha is a human monoclonal antibody that inhibits PCSK9, a protein that reduces the liver's ability to remove low-density lipoprotein cholesterol (LDL-C), or "bad" cholesterol, from the blood.[1] Repatha was developed in Japan by Amgen Astellas BioPharma K.K. (AABP), a joint venture between Amgen and Astellas Pharma Inc., a pharmaceutical company headquartered in Tokyo.

In Japan, Repatha is indicated for the treatment of patients with familial hypercholesterolemia (FH) or hypercholesterolemia who have high risk of cardiovascular events and do not adequately respond to HMG-CoA reductase inhibitors (statins).

"Today's approval of Repatha, the first PCSK9 inhibitor approved in Japan, is an important milestone for patients and physicians who need additional treatment options to lower LDL cholesterol," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "High LDL cholesterol is a modifiable risk factor for cardiovascular disease and many patients are unable to appropriately control their LDL cholesterol with statin therapy alone. We are excited to bring Repatha to patients in Japan and will continue to work with regulatory authorities to make this innovative medicine available to patients worldwide."

"This approval is significant for patients and physicians in Japan and is a testament to the ongoing collaboration between Amgen and Astellas," said Eiichi Takahashi, general manager, AABP. "We are proud of the progress we are making toward our common goal of addressing the critical needs of Japanese patients with high LDL cholesterol who struggle to control their condition."

Results from Phase 3 studies showed that adding Repatha to background lipid-lowering therapy that included statins resulted in intensive reductions in LDL-C. YUKAWA-2, a pivotal Phase 3 study in Japanese patients with high cardiovascular risk and high cholesterol, demonstrated that subcutaneous Repatha 140 mg every two weeks or 420 mg every four weeks, compared to placebo, in combination with daily doses of atorvastatin, reduced LDL-C by 67 to 76 percent from baseline at week 12 and at the mean of weeks 10 and 12.[2] The adverse events that occurred in greater than 2 percent of the Repatha group were nasopharyngitis (16.8 percent Repatha; 17.8 percent placebo), gastroenteritis (3.0 percent Repatha; 1.0 percent placebo) and pharyngitis (2.5 percent Repatha; 2.5 percent placebo).[3] Results from TAUSSIG, a global, open-label, single-arm study in patients with homozygous FH, including patients in Japan, showed Repatha reduced LDL-C by approximately 23 percent.[4] The adverse events that occurred in greater than 5 percent of patients were nasopharyngitis (9.0 percent) and influenza (7.0 percent).[4]

"In Japan, LDL cholesterol levels are not adequately controlled for many patients who are at high risk of cardiovascular events and taking statins, nearly half of whom have not reached their desired LDL cholesterol goal," said Tamio Teramoto, M.D., Ph.D., director of Teikyo Academic Research Center and investigator for the Phase 2 YUKAWA-1 trial. "As the first in a new class of medicines in Japan, Repatha offers physicians an important treatment option for patients who require additional LDL cholesterol reduction."

Elevated LDL-C is an abnormality of cholesterol and/or fats in the blood.[5,6] Familial hypercholesterolemia (FH) is an inherited condition caused by genetic mutations which lead to high levels of LDL-C at an early age, and it is estimated that less than 1 percent of people with FH in Japan are diagnosed.[7,8] Patients can have either one of two types of FH.[7] Heterozygous FH is the more common type of FH and in Japan, occurs in approximately one in 500 individuals.[8,9] It can cause LDL-C levels twice as high as normal (e.g., >180 mg/dL).[9,10] Individuals with heterozygous FH have one altered copy of a cholesterol-regulating gene.[7] Homozygous FH is a rare, more severe form.[7] It can cause LDL-C levels more than six times as high as normal (e.g., 500-1,000 mg/dL).[7,10] Individuals with homozygous FH have two altered copies of cholesterol-regulating genes (one from each parent).[7]

Repatha is also approved in the European Union, United States and Canada.

About Repatha® (evolocumab)
Repatha® (evolocumab) is a human monoclonal antibody that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9).[1] 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.[2]

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 recurrent cardiovascular events in patients with high cholesterol and clinically evident cardiovascular disease, and completed patient enrollment in June 2015. Top-line results from the approximately 27,500-patient event-driven FOURIER study are anticipated in the second half of 2016.

Important Japan Product Information
Repatha is indicated for the treatment of patients with familial hypercholesterolemia (FH) or hypercholesterolemia who have high risk of cardiovascular

events and do not adequately respond to HMG-CoA reductase inhibitors.

Precautions Related to Indications in Japan
(1) Prior to Repatha therapy, patients should have a confirmed diagnosis of familial hypercholesterolemia or hypercholesterolemia by going through assessment.

(2) When administering Repatha to patients with non-familial hypercholesterolemia, it should be considered for patients who have high risk of cardiovascular events based on risk factors (e.g., comorbid conditions including coronary artery heart disease, non-cardiogenic stroke, peripheral arterial disease, diabetes and chronic renal disease or medical history). See 'clinical study' section.

Dosage and Administration in Japan
Heterozygous Familial Hypercholesterolemia and Hypercholesterolemia:

For adults, recommend Repatha (genetical recombination) of 140 mg is administrated every 2 weeks or Repatha of 420 mg is administrated every 4 weeks subcutaneously

Homozygous Familial Hypercholesterolemia:

For adults, recommend Repatha (genetical recombination) of 420 mg is administrated every 4 weeks subcutaneously. Repatha of 420 mg every 2 weeks can be administered when the efficacy is not adequate. If Repatha is administered as adjunctive therapy for patients with LDL apheresis, as starting dose, Repatha of 420 mg every 2 weeks can be administered subcutaneously

Precautions Related to Dosage and Administration in Japan
Repatha should be administered as an adjunct to HMG-CoA reductase inhibitor therapy [Efficacy and safety of Repatha monotherapy in Japanese patients not confirmed].

For more information, please see the latest Japan Prescribing Information.

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.[11] 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 biologics manufacturing 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 Inc. and its subsidiaries (Amgen or us) and are subject to a number of risks, uncertainties and assumptions that could cause actual results to differ materially from those described. 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 (SEC) reports filed by Amgen Inc., including Amgen Inc.'s most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and Form 8-K. Please refer to Amgen Inc.'s most recent Forms 10-K, 10-Q and 8-K for additional information on the uncertainties and risk factors related to our business. Unless otherwise noted, Amgen is providing this information as of Jan. 21, 2016, and expressly disclaims any duty to update information contained in this news release.

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 and our partners to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and we expect similar variability in the future. 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 business may be impacted by government investigations, litigation and product liability claims. 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. We depend on third parties for a significant portion of our manufacturing capacity for the supply of certain of our current and future products and limits on supply may constrain sales of certain of our current products and product candidate development.

In addition, sales of our products (including products of our wholly-owned subsidiaries) are affected by the 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 as well as U.S. legislation affecting pharmaceutical pricing and reimbursement. Government and others' regulations and reimbursement policies may affect the development, usage and pricing of our products. In addition, we compete with other companies with respect to some of our marketed products as well as for the discovery and development of new products. We believe that some of our newer products, product candidates or new indications for existing products, may face competition when and as they are approved and marketed. Our products may compete against products that have lower prices, established reimbursement, superior performance, are easier to administer, or that are otherwise competitive with our products. In addition, while Amgen and its partners routinely obtain patents for their products and technology, the protection of our products offered by patents and patent applications may be challenged, invalidated or circumvented by our or our partners' competitors and there can be no guarantee of our or our partners' ability to obtain or maintain patent protection for our products or product candidates. We cannot guarantee that we will be able to produce commercially successful products or maintain the commercial success of our existing products. Our stock price may be affected by actual or perceived market opportunity,

competitive position, and success or failure of our products or product candidates. Further, 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 integrate the operations of companies we have acquired may not be successful. We may experience difficulties, delays or unexpected costs and not achieve anticipated benefits and savings from our ongoing restructuring plan. Our business performance could affect or limit the ability of our Board of Directors to declare a dividend or their ability to pay a dividend or repurchase our common stock.

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References

1. Amgen Data on File, Investigator Brochure.
2. Data on File: Study 20120122 Phase III in Japanese study report.
3. Kiyosue, A., Honarpour, N., Kurtz, C., Xue, A., Wasserman, S. M., & Hirayama, A. (2016). A Phase 3 Study of Evolocumab (AMG 145) in Statin-Treated Japanese Patients at High Cardiovascular Risk. *Am J Cardiol.* American journal of cardiology, 117(1), 40-47.
4. Data on File: Study 20110271 Global long term study in familial homozygous global long term study report.
5. World Health Organization. Quantifying Selected Major Risks to Health. In: The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Chapter 4: Geneva: World.
6. Merck Manuals website. http://www.merckmanuals.com/professional/endocrine_and_metabolic_disorders/lipid_disorders/dyslipidemia.html. Accessed January 2016.
7. National Human Genome Research Institute. Learning About Familial Hypercholesterolemia. http://www.genome.gov/25520184. Accessed January 2016.
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. Teramoto T, Sasaki J, Ishibashi S, et al. Familial Hypercholesterolemia: Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan – 2012 version. *J Atheroscler Thromb.* 2013;21(1):6-10.
10. Hopkins PN, Toth PP, Ballantyne CM, et al. Familial Hypercholesterolemias: Prevalence, Genetics, Diagnosis and Screening Recommendations From the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipid*. 2011:5(3S):S9-S17.
11. World Health Organization. Cardiovascular diseases (CVDs) fact sheet. http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed January 2016.

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