



## **ANNOUNCEMENT OF MARKETING APPROVAL SUBMISSION TO MHLW (JAPAN) FOR LDL CHOLESTEROL-LOWERING MEDICATION EVolocumab**

TOKYO (March 20, 2015) – Astellas Pharma Inc. (Headquarters, Tokyo; President and CEO, Yoshihiko Hatanaka; hereafter referred to as Astellas Pharma) and Amgen Astellas BioPharma K.K. (Headquarters, Tokyo; General Manager and Representative Director, Eiichi Takahashi; hereafter referred to as Amgen Astellas BioPharma) announced that today, Amgen Astellas BioPharma submitted an application for marketing approval of evolocumab (Generic name; Code No., AMG145) for the treatment of hypercholesterolemia to the Ministry of Health, Labour and Welfare (MHLW) in Japan. Evolocumab was jointly developed by both Astellas Pharma and Amgen Astellas BioPharma in Japan.

Evolocumab is an investigational fully human monoclonal antibody developed by Amgen. It inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein that reduces the liver's ability to remove low-density lipoprotein cholesterol (LDL-C), or “bad” cholesterol, from the blood.<sup>1</sup>

The Phase 3 YUKAWA-2 (Study of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk) study evaluating evolocumab in combination with statin therapy in Japanese patients with high cholesterol whose cardiovascular risk are high met its co-primary endpoints: the percent reduction from baseline in LDL-C at week 12 and the percent reduction from baseline in LDL-C at weeks 10 and 12. Both percent reductions in LDL-C were statistically significant.

In the United States, Amgen submitted a Biologics License Application (BLA) for evolocumab for the treatment of hypercholesterolemia to the Food and Drug Administration (FDA) last August. In Europe, Amgen submitted a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for evolocumab through the centralized procedure last September.

High cholesterol, particularly elevated LDL-C, is the most common form of dyslipidemia, which is an abnormality of cholesterol and/or fats in the blood.<sup>2,3</sup> Elevated LDL-C is recognized as a major risk factor for cardiovascular disease.<sup>4,5</sup> It is also known that Familial hypercholesterolemia (FH), an inherited condition caused by genetic mutations, indicates abnormal LDL-C<sup>2</sup>.

This submission is an important step in the strategic partnership between Astellas Pharma and Amgen Astellas BioPharma, focused on meeting unmet medical needs for Japanese patients

## **ANNOUNCEMENT OF MARKETING APPROVAL SUBMISSION TO MHLW (JAPAN) FOR LDL CHOLESTEROL-LOWERING MEDICATION EVOLOCUMAB**

Page 2

through delivering innovative human therapeutics. The companies hope to provide a new treatment option in high cholesterol in the future.

### **About Familial Hypercholesterolemia**

Familial hypercholesterolemia (FH) is an inherited condition caused by genetic mutations which lead to high levels of LDL-C at an early age,<sup>6</sup> and it is estimated that less than one percent of people with FH (heterozygous and homozygous forms) in Japan are diagnosed.<sup>7</sup>

Patients can have either one of two types of FH, heterozygous FH (HeFH) and homozygous FH (HoFH). Patients with HeFH have only one altered copy of a cholesterol-regulating gene, and patients with HoFH have two altered copies of cholesterol-regulating genes inherited from each parent.<sup>6</sup> Heterozygous FH is the more common type of FH and in Japan, occurs in approximately 1/900 individuals.<sup>7,9</sup> It can cause LDL-C levels approximately twice as high as normal (e.g., >180 mg/dL).<sup>8</sup> Homozygous FH is the rare, more severe form, occurring in approximately one in a million individuals.<sup>10</sup> It can cause the levels LDL-C levels more than six times as high as normal (e.g., 500-1,000 mg/dL).<sup>11,12</sup>

### **About Amgen Astellas BioPharma**

Amgen Astellas BioPharma K.K. is a Japanese company that began operations on October 1, 2013, to provide breakthrough-science-based medicines to help address unmet medical needs of patients in Japan. The company is a joint venture between Amgen, the world's largest independent biotechnology company, and Astellas Pharma Inc., a leading Tokyo-based R&D-oriented global pharmaceutical company. The joint venture will become a wholly-owned Amgen affiliate as soon as 2020. Amgen Astellas BioPharma leverages the capabilities of both companies – Amgen's science and pipeline candidates coupled with Astellas' deep knowledge of Japanese patient and physician needs, long-term commercial and regulatory experience, and strong presence as a leading company in Japan – to contribute to the creation of a healthy society.

### **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](http://www.amgen.com) and follow us on [www.twitter.com/amgen](https://www.twitter.com/amgen).

### **About Astellas**

Astellas Pharma Inc., located in Tokyo, Japan, is a pharmaceutical company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceuticals. Astellas has approximately 17,000 employees worldwide. The organization is committed to becoming a global category leader in Urology, Immunology (including Transplantation) and Infectious diseases, Oncology, Neuroscience and DM Complications and

## **ANNOUNCEMENT OF MARKETING APPROVAL SUBMISSION TO MHLW (JAPAN) FOR LDL CHOLESTEROL-LOWERING MEDICATION EVOLOCUMAB**

Page 3

Kidney diseases. For more information on Astellas Pharma Inc., please visit the company website at [www.astellas.com/en](http://www.astellas.com/en).

### **Forward-Looking Statements**

This news release contains forward-looking statements that are based on management's current expectations and beliefs 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, including Amgen'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'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 March 20, 2015, 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 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 products liability claims. 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 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

## **ANNOUNCEMENT OF MARKETING APPROVAL SUBMISSION TO MHLW (JAPAN) FOR LDL CHOLESTEROL-LOWERING MEDICATION EVOLOCUMAB**

Page 4

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 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 and there can be no guarantee of our 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 recently announced 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.

The scientific information discussed in this news release related to our product candidates is preliminary and investigative. Such product candidates are not approved by the U.S. Food and Drug Administration (FDA), and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidates.

### **Contacts**

Astellas Pharma Inc.  
Corporate Communications (Tel: +81-3-3244-3201)

Amgen Astellas BioPharma K.K.  
Value, Access and Policy (Tel: +81-3-5293-9870)

### **References**

1. Amgen Data on File, Investigator Brochure.
2. World Health Organization. Quantifying Selected Major Risks to Health. In: The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Chapter4: Geneva: World.
3. Merck Manuals website.  
[http://www.merckmanuals.com/professional/endocrine\\_and\\_metabolic\\_disorders/lipid\\_disorders/dyslipidemia.html](http://www.merckmanuals.com/professional/endocrine_and_metabolic_disorders/lipid_disorders/dyslipidemia.html). Accessed August 2014.
4. American Heart Association (2012). Why Cholesterol Matters.  
[http://www.heart.org/HEARTORG/Conditions/Cholesterol/WhyCholesterolMatters/Why-Cholesterol-Matters\\_UCM\\_001212\\_Article.jsp](http://www.heart.org/HEARTORG/Conditions/Cholesterol/WhyCholesterolMatters/Why-Cholesterol-Matters_UCM_001212_Article.jsp). Accessed August 2014.
5. World Health Organization. Global Status Report on Noncommunicable Diseases 2010. Geneva, 2011.
6. National Human Genome Research Institute. Learning About Familial Hypercholesterolemia. <http://www.genome.gov/25520184>. Accessed August 2014
7. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial Hypercholesterolemia is Underdiagnosed and Undertreated in the General Population: Guidance for Clinicians to Prevent Coronary Heart Disease. *Eur Heart J*. 2013;34:3478-3490.

**ANNOUNCEMENT OF MARKETING APPROVAL SUBMISSION TO MHLW (JAPAN) FOR  
LDL CHOLESTEROL-LOWERING MEDICATION EVOLOCUMAB**

Page 5

8. 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.
9. Austin MA, Hutter CM, Zimmern RL., et al. Genetic Causes of Monogenic Heterozygous Familial Hypercholesterolemia: a HuGE Prevalence Review. *Am J Epidemiol.* 2004;160(5):407-420.
10. Daniels SR, Samuel SG, de Ferranti SD. Pediatric Aspects of Familial Hypercholesterolemias: Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipid.* 2011;5(3S):S30-S37.
11. Sjouke B, Kusters DM, Kindt I, et al. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype - phenotype relationship, and clinical outcome. *Eur Heart J.* 2014; Epub ahead of print. doi:10.1093/eurheartj/ehu058. Feb. 28, 2014.
12. Raal FJ and Santos RD. Homozygous familial hypercholesterolemia: Current perspectives on diagnosis and treatment. *Atherosclerosis.* 2012;223(2):262-268.