European Commission Approves Amgen's IMLYGIC™ (talimogene laherparepvec) As First Oncolytic Immunotherapy In Europe

December 18, 2015

Pivotal Trial Showed IMLYGIC Significantly Increased Durable Response Rates in Patients With Unresectable Melanoma That is Regionally or Distantly Metastatic

IMLYGIC is Approved in the European Union Specifically for Early Stage Metastatic Patients

THOUSAND OAKS, Calif., Dec. 17, 2015 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the European Commission has approved the use of IMLYGIC ™(talimogene laherparepvec) for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a), with no bone, brain, lung or other visceral disease. IMLYGIC is the first oncolytic immunotherapy to demonstrate therapeutic benefit for patients with metastatic melanoma in a Phase 3 clinical trial.

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IMLYGIC is derived from the herpes simplex type 1 virus (HSV-1) , commonly called the cold sore virus. IMLYGIC has been modified to replicate within tumors and to produce the immune stimulatory protein human granulocyte-macrophage colony-stimulating factor (GM-CSF). Administered via intralesional injection, IMLYGIC is designed to cause the death of tumor cells and initiate an anti-tumor immune response.

"As the first oncolytic immunotherapy authorized in the European Union, the approval of IMLYGIC is an important milestone for this new class of drugs, bringing patients with a rare and deadly form of skin cancer a much needed new treatment option," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "By igniting the body's own immune system IMLYGIC can initiate an anti-tumor immune response, providing meaningful and durable response rates in the early stage metastatic melanoma patient."

Melanoma remains a significant public health concern in the European Union (EU), with an estimated 22,000 deaths from the disease in 2012.[1,2] While melanoma is curable when detected in the early stages, metastatic melanoma continues to be one of the most difficult-to-treat cancers because it is highly aggressive and complex.[3] Even with recent new options in immune-oncology, a large number of patients with metastatic melanoma still do not respond to treatment.[4]

The European approval included a review of exploratory subgroup analyses of Study 005/05, referred to as OPTiM. The durable response rate (DRR) in patients with Stage IIIB, IIIC and IVM1a disease was 25.2 percent compared to 1.2 percent in those treated with GM-CSF. In the study, patients with Stage IIIB, IIIC and IVM1a disease achieved an overall response rate (ORR) of 40.5 percent when treated with IMLYGIC compared to 2.3 percent with GM-CSF. The median overall survival (OS) for IMLYGIC patients with Stage IIIB, IIIC and IVM1a disease was 41.1 months compared to 21.5 months for patients treated with GM-CSF. While the pivotal study was not powered to evaluate efficacy in these individual subgroups, patients with no visceral disease derived greater benefit from IMLYGIC treatment than those with more advanced disease. Due to the exploratory nature of the analysis and based on the current evidence, it has not been established that IMLYGIC is associated with an effect on OS.

The most commonly reported treatment-related adverse events were fatigue, chills, pyrexia, nausea, influenza-like illness and injection-site pain. Overall, 98 percent of these adverse reactions reported were mild or moderate in severity. The most common grade 3 or higher adverse reaction was cellulitis. No fatal treatment-related adverse events occurred.[5]

This approval grants a centralized marketing authorization in the 28 countries that are members of the EU. Norway, Iceland and Liechtenstein, as members of the European Economic Area (EEA), will take corresponding decisions on the basis of the decision of the EC.

About the OPTiM Study

OPTiM was a global, randomized, open-label Phase 3 trial evaluating the safety and efficacy of IMLYGIC in patients with Stage IIIB, IIIC or IV melanoma when resection was not recommended compared to GM-CSF. In the 436-patient study, IMLYGIC significantly improved DRR, the primary endpoint of the trial, in the intent-to-treat population. DRR is defined as the percent of patients with complete response (CR) or partial response (PR) maintained continuously for a minimum of six months. In the study, 16.3 percent of patients treated with IMLYGIC achieved a DRR compared to 2.1 percent of patients treated with GM-CSF (p<0.0001) in the intent-to-treat population. Of the patients who experienced a durable response, 29.1 percent had a durable CR and 70.8 percent had a durable PR. In the study, the median time to response was 4.1 months (range: 1.2 to 16.7) in the

IMLYGIC arm.

A key secondary endpoint was OS. In the intent-to-treat population, the median OS was 23.3 months in the group treated with IMLYGIC compared to 18.9 months for those treated with GM-CSF (p=0.0511). These results were not statistically significant. The ORR for patients in the intent-to-treat population was 26.4 percent for those treated with IMLYGIC compared to 5.7 percent in the GM-CSF arm. In an analysis to evaluate the systemic activity of IMLYGIC, 34 percent of patients in the intent-to-treat population had an overall decrease of at least 50 percent in non-visceral lesions that were not injected.

About IMLYGIC™ (talimogene laherparepvec) in the EU
IMLYGIC is an oncolytic immunotherapy that is derived from HSV-1, which is commonly called the cold sore virus. IMLYGIC has been modified to replicate within tumors and to produce the immune stimulatory protein human GM-CSF. IMLYGIC causes the death of tumor cells and the release of tumor-derived antigens. It is thought that, together with GM-CSF, it will promote a systemic anti-tumor immune response and an effector T cell response.

Important EU Product Safety Information

This product is subject to additional monitoring. All suspected adverse reactions should be reported in accordance with the national reporting system.

The safety of IMLYGIC was evaluated in the pivotal study where 292 patients received at least one dose of IMLYGIC (see section 5.1). The median duration of exposure to IMLYGIC was 23 weeks (5.3 months). Twenty six (26) patients were exposed to IMLYGIC for at least one year.

The most commonly reported adverse reactions (≥ 25 percent) in IMLYGIC-treated patients were fatigue (50.3 percent), chills (48.6 percent), pyrexia (42.8 percent), nausea (35.6 percent), influenza-like illness (30.5 percent), and injection site pain (27.7 percent). Overall, ninety eight percent (98 percent) of these adverse reactions reported were mild or moderate in severity. The most common grade 3 or higher adverse reaction was cellulitis (2.1 percent) (see section 4.4).

Please refer to the Summary of Product Characteristics for full European prescribing information.

About IMLYGIC™ (talimogene laherparepvec) in the U.S.
In the U.S., IMLYGIC is indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. IMLYGIC has not been shown to improve overall survival or have an effect on visceral metastases.

Important U.S. Safety Information
Contraindications

- Do not administer IMLYGIC™ to immunocompromised patients, including those with a history of primary or acquired immunodeficient states, leukemia, lymphoma, AIDS or other clinical manifestations of infection with human immunodeficiency viruses, and those on immunosuppressive therapy, due to the risk of life-threatening disseminated herpetic infection.
- Do not administer IMLYGIC™ to pregnant patients.

Warnings and Precautions

- **Accidental exposure to IMLYGIC™**may lead to transmission of IMLYGIC™ and herpetic infection, including during preparation and administration. Health care providers, close contacts, pregnant women, and newborns should avoid direct contact with injected lesions, dressings, or body fluids of treated patients. The affected area in exposed individuals should be cleaned thoroughly with soap and water and/or a disinfectant.
- Caregivers should wear protective gloves when assisting patients in applying or changing occlusive dressings and observe safety precautions for disposal of used dressings, gloves, and cleaning materials. Exposed individuals should clean the affected area thoroughly with soap and water and/or a disinfectant.
- To prevent possible inadvertent transfer of IMLYGIC™ to other areas of the body, patients should be advised to avoid touching or scratching injection sites or occlusive dressings.
- **Herpetic infections:** Herpetic infections (including cold sores and herpetic keratitis) have been reported in IMLYGIC™ treated patients. Disseminated herpetic infection may also occur in immunocompromised patients. Patients who develop suspicious herpes-like lesions should follow standard hygienic practices to prevent viral transmission.
- Patients or close contacts with suspected signs or symptoms of a herpetic infection should contact their health care provider to evaluate the lesions. Suspected herpetic lesions should be reported to Amgen at 1-855-IMLYGIC (1-855-465-9442). Patients or close contacts have the option of follow-up testing for further characterization of the infection.
- IMLYGIC™ is sensitive to acyclovir. Acyclovir or other antiviral agents may interfere with the effectiveness of IMLYGIC™. Consider the risks and benefits of IMLYGIC™ treatment before administering antiviral agents to manage herpetic infection.
- **Injection Site Complications:** Necrosis or ulceration of tumor tissue may occur during IMLYGIC™ treatment. Cellulitis and systemic bacterial infection have been reported in clinical studies. Careful wound care and infection precautions are recommended, particularly if tissue necrosis results in open wounds.
- Impaired healing at the injection site has been reported. IMLYGIC™ may increase the risk of impaired healing in patients with underlying risk factors (e.g., previous radiation at the injection site or lesions in poorly vascularized areas). If there is persistent infection or delayed healing of the injection site, consider the risks and benefits of continuing treatment.

- **Immune-Mediated events** including glomerulonephritis, vasculitis, pneumonitis, worsening psoriasis, and vitiligo have been reported in patients treated with IMLYGIC™. Consider the risks and benefits of IMLYGIC™ before initiating treatment ir patients who have underlying autoimmune disease or before continuing treatment in patients who develop immune-mediated events.
- **Plasmacytoma at Injection Site:** Plasmacytoma in proximity to the injection site has been reported in a patient with smoldering multiple myeloma after IMLYGIC™ administration in a clinical study. Consider the risks and benefits of IMLYGIC™ in patients with multiple myeloma or in whom plasmacytoma develops during treatment.

Adverse Reactions

- The most commonly reported adverse drug reactions (≥ 25 percent) in IMLYGIC™-treated patients were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain. Pyrexia, chills, and influenza-like illness can occur at any time during IMLYGIC™ treatment, but were more frequent during the first 3 months of treatment.
- The most common Grade 3 or higher adverse reaction was cellulitis.

Please see full U.S. Prescribing Information, including Medication Guide, for IMLYGIC at www.Amgen.com and www.IMLYGIC.com.

About Amgen's Immuno-Oncology Focused Partnerships
Amgen has in place a comprehensive clinical development program investigating oncolytic immunotherapies for their potential in melanoma and in a variety of other cancers.

Amgen's recent immuno-oncology focused partnerships include:

- A collaboration with Merck on developing IMLYGIC (talimogene laherparepvec) and KEYTRUDA® (pembrolizumab) Merck's anti-PD-1 therapy, in melanoma and squamous cell cancer of the head and neck.
- A collaboration with Roche on a Phase 1b study to evaluate the safety and efficacy of IMLYGIC in combination with Roche's investigational anti-PDL1 therapy, atezolizumab (also known as MPDL3280A), in patients with triple-negative breast cancer and colorectal cancer with liver metastases.
- A strategic research collaboration and license agreement to develop and commercialise the next generation of novel Chimeric Antigen Receptor (CAR) T-cell immunotherapies with Kite Pharma.
- A research collaborative agreement focusing on Amgen's bispecific T-cell engager (BiTE®) antibody constructs with MD Anderson's Moon Shots Program.
- A research and license agreement with Xencor to develop and commercialise novel therapeutics in the areas of cancer immunotherapy and inflammation. The research collaboration brings together Amgen's capabilities in target discovery and protein therapeutics with Xencor's XmAb® bispecific technology platform.

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.

About Amgen's Commitment to Oncology
Amgen Oncology is committed to helping patients take on some of the toughest cancers, such as those that have been resistant to drugs, those that progress rapidly through the body and those where limited treatment options exist. Amgen's supportive care treatments help patients combat certain side effects of strong chemotherapy, and our targeted medicines and immunotherapies focus on more than a dozen different malignances, ranging from blood cancers to solid tumors. With decades of experience providing treatments for cancer patients, Amgen continues to grow its portfolio of innovative and biosimilar oncology medicines.

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 Dec. 17, 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 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.

References:

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IMLYGIC®
(talimogene laherparepvec)
INTRALESIONAL INJECTION

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