European Commission Approves Amgen's BLINCYTO® (blinatumomab) for the Treatment of Adults with Philadelphia Chromosome-Negative Relapsed or Refractory B-precursor Acute Lymphoblastic Leukemia

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BLINCYTO First Bispecific T Cell Engager (BiTE®) Antibody Construct Approved in European Union

THOUSAND OAKS, Calif., Nov. 23, 2015 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the European Commission (EC) has granted conditional marketing authorization for BLINCYTO® (blinatumomab) for the treatment of adults with Philadelphia chromosome-negative (Ph-) relapsed or refractory B-precursor acute lymphoblastic leukemia (ALL).

Experience the interactive Multimedia News Release here: http://www.multivu.com/players/English/7414058-amgen-blincyto-europe-approval/

ALL is a rare and rapidly progressing cancer of the blood and bone marrow.[1,2] For adults with relapsed or refractory ALL, the median overall survival is just three to five months.[3] It is estimated that the incidence of adults with Ph- relapsed or refractory B-precursor ALL in the European Union (EU) is approximately 900 patients per year.[4]

"We are pleased the European Commission granted conditional marketing authorization for BLINCYTO," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "BLINCYTO has demonstrated efficacy in treating relapsed or refractory ALL, a very difficult-to-treat disease for which historically patients had limited therapeutic options. This approval represents an important milestone in immunotherapy research. BLINCYTO is the first clinical validation of the BiTE® platform, a new and innovative approach that helps the body's own immune system fight cancer."

The conditional marketing authorization for BLINCYTO is based on results of two Phase 2 studies, study '211 and '206. In the pivotal '211 trial, 42.9 percent of patients achieved complete remission (CR) or CR with partial hematological recovery (CRh*) with single-agent BLINCYTO.

The most serious adverse reactions that occurred during BLINCYTO treatment in the pivotal '211 trial included infections, neurologic events, neutropenia/febrile neutropenia, cytokine release syndrome and tumor lysis syndrome.

"We tested BLINCYTO in ALL, the most aggressive B-cell malignancy we know, and observed a clinically meaningful remission rate," said Max S. Topp, M.D., professor, Hospital of Wuerzburg, Germany. "This is the first major advance in more than two decades for patients with this hard-to-treat cancer."

"The prognosis for adult patients with ALL who are refractory to treatment or experience relapse is poor, and BLINCYTO constitutes a new treatment option for these patients," said Herve Dombret, M.D., professor, University Paris, Hospital Saint Louis, Paris. "It is important for clinicians and patients to have more treatment options in this acute form of leukemia."

Approval from the EC grants a centralized conditional marketing authorization with unified labeling 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. Conditional license requires the license to be renewed every year and it will be converted to full standard license once post-licensing commitments have been fulfilled.

BLINCYTO was granted orphan drug designation by the European Medicines Agency in 2009 for the treatment of ALL.

About Study '211

Study '211 evaluated BLINCYTO in an open-label, multicenter, single-arm Phase 2 study. Eligible patients were at least 18 years of age with Ph- relapsed or refractory B-precursor ALL relapsed with first remission duration of less than or equal to 12 months in first salvage, or relapsed or refractory after first salvage therapy, or relapsed within 12 months of allogeneic hematopoietic stem cell transplantation (HSCT), and had at least10 percent blasts in bone marrow.

The primary endpoint was the CR/CRh* rate within two cycles of BLINCYTO. Of the 189 patients evaluated in the trial, 42.9 percent (81/189; 95

percent CI, 35.7 - 50.2) achieved CR or CRh* within two cycles of treatment with BLINCYTO with the majority of responses (79 percent [64/81]) occurring within the first cycle of treatment. In a prespecified exploratory analysis, 82.2 percent (60/73) of minimal residual disease (MRD) evaluable patients with CR/CRh* also had an MRD response. The most common adverse reactions (greater than 20 percent) were infusion-related reactions (67.2 percent), infections (63 percent), pyrexia (59.8 percent), headache (34.4 percent), febrile neutropenia (28 percent), peripheral edema (25.9 percent), nausea (24.3 percent), hypokalemia (23.8 percent), constipation (20.6 percent) and anemia (20.1 percent). The most serious adverse reactions that occurred during BLINCYTO treatment included: infections (31.7 percent), neurologic events (16.4 percent), neutropenia/febrile neutropenia (15.3 percent), cytokine release syndrome (0.5 percent) and tumor lysis syndrome (0.5 percent).

About Study '206

Study '206 evaluated the safety and efficacy of BLINCYTO in an open-label, multicenter, dose-escalation Phase 2 study of 36 patients, who were at least 18 years of age with B-precursor ALL relapsed after at least induction and consolidation or having refractory disease with greater than 5 percent blasts in bone marrow, had an Eastern Cooperative Oncology Group (ECOG) performance status of at most 2, had a life expectancy of at least 12 weeks, and who did not have autologous HSCT within six weeks prior to start of treatment, allogeneic HSCT within three months prior to start of treatment, or previous treatment with BLINCYTO. The CR/CRh* rate was 69.4 percent (25/36) with 15 patients achieving CR (41.7 percent; 95 percent CI, 25.5 percent - 59.2 percent), and 10 patients achieving CRh* (27.8 percent; 95 percent CI, 14.2 percent - 45.2 percent). Of the patients with hematologic CR, 88 percent (22/25) also had MRD responses. Overall safety results from this study were consistent with the known BLINCYTO safety profile.

About Adult ALL in Europe

The incidence of adult ALL in European countries is generally between 0.6 to 0.9 per 100,000 persons per year.[5] In adult ALL, approximately 75 percent is B-precursor ALL, of which between 75-80 percent is Ph- and roughly half of adults will experience relapse or refractory disease.[5] Thus, with a population projection of 416 million adults in the EU,[6] it is estimated that the incidence of adult Ph- relapsed or refractory B-precursor ALL in the EU is approximately 900 patients per year.[4]

About BLINCYTO® (blinatumomab)

BLINCYTO is a bispecific CD19-directed CD3 T cell engager (BiTE®) antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. BLINCYTO was granted breakthrough therapy and priority review designations by the U.S. Food and Drug Administration, and is now approved in the U.S. for the treatment of Ph- relapsed or refractory B-cell precursor ALL. This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit in subsequent trials.

About BiTE® Technology

BiTE® antibody constructs are a type of immunotherapy being investigated for fighting cancer by helping the body's immune system to detect and target malignant cells. The modified antibodies are designed to engage two different targets simultaneously, thereby juxtaposing T cells (a type of white blood cell capable of killing other cells perceived as threats) to cancer cells. BiTE® antibody constructs help place the T cells within reach of the targeted cell, with the intent of allowing T cells to inject toxins and trigger the cancer cell to die (apoptosis). BiTE® antibody constructs are currently being investigated for their potential to treat a wide variety of cancers.

Important EU Product Safety Information

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

The adverse reactions described in this section were identified in the pivotal clinical study (N=189).The most serious adverse reactions that may occur during blinatumomab treatment include: infections (31.7%), neurologic events (16.4%), neutropenia/febrile neutropenia (15.3%) cytokine release syndrome (0.5%), and tumor lysis syndrome (0.5%). The most common adverse reactions were: infusion-related reactions (67.2%), infections (63.0%), pyrexia (59.8%), headache (34.4%), febrile neutropenia (28%), peripheral edema (25.9%), nausea (24.3%), hypokalaemia (23.8%), constipation (20.6%), anaemia (20.1%), cough (18.5%), diarrhea (18.0%), tremor (17.5%), neutropenia (17.5%), abdominal pain (16.9%), insomnia (15.3%), fatigue (15.3%), and chills (15.3%).

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

BLINCYTO® U.S. Product Safety Information

Important Safety Information Regarding BLINCYTO® (blinatumomab) U.S. Indication

This safety information is specific to the current U.S. approved indication.

U.S. INDICATION

BLINCYTO® is indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit in subsequent trials.

U.S. IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO®. Interrupt or discontinue BLINCYTO® as recommended.**
- **Neurological toxicities, which may be severe, life-threatening or fatal, occurred in patients receiving BLINCYTO®. Interrupt or discontinue BLINCYTO® as recommended.**

Contraindications

BLINCYTO® is contraindicated in patients with a known hypersensitivity to blinatumomab or to any component of the product formulation.

Warnings and Precautions

- **Cytokine Release Syndrome (CRS):** Life-threatening or fatal CRS occurred in patients receiving BLINCYTO®. Infusion reactions have occurred and may be clinically indistinguishable from manifestations of CRS. Closely monitor patients for signs and symptoms of serious events such as pyrexia, headache, nausea, asthenia, hypotension, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased total bilirubin (TBILI), disseminated intravascular coagulation (DIC), capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). Interrupt or discontinue BLINCYTO® as outlined in the Prescribing Information (PI).
- **Neurological Toxicities:** Approximately 50% of patients receiving BLINCYTO® in clinical trials experienced neurological toxicities. Severe, life-threatening, or fatal neurological toxicities occurred in approximately 15% of patients, including encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. The median time to onset of any neurological toxicity was 7 days. Monitor patients for signs or symptoms and interrupt or discontinue BLINCYTO® as outlined in the PI.
- **Infections:** Approximately 25% of patients receiving BLINCYTO® experienced serious infections, some of which were life-threatening or fatal. Administer prophylactic antibiotics and employ surveillance testing as appropriate during treatment. Monitor patients for signs or symptoms of infection and treat appropriately, including interruption or discontinuation of BLINCYTO® as needed.
- **Tumor Lysis Syndrome (TLS):** Life-threatening or fatal TLS has been observed. Preventive measures, including pretreatment nontoxic cytoreduction and on treatment hydration, should be used during BLINCYTO® treatment. Monitor patients for signs and symptoms of TLS and interrupt or discontinue BLINCYTO® as needed to manage these events.
- **Neutropenia and Febrile Neutropenia,** including life-threatening cases, have been observed. Monitor appropriate laboratory parameters during BLINCYTO® infusion and interrupt BLINCYTO® if prolonged neutropenia occurs.
- **Effects on Ability to Drive and Use Machines:** Due to the possibility of neurological events, including seizures, patients receiving BLINCYTO® are at risk for loss of consciousness, and should be advised against driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO® is being administered.
- **Elevated Liver Enzymes:** Transient elevations in liver enzymes have been associated with BLINCYTO® treatment. The majority of these events were observed in the setting of CRS. The median time to onset was 15 days. Grade 3 or greater elevations in liver enzymes occurred in 6% of patients outside the setting of CRS and resulted in treatment discontinuation in less than 1% of patients. Monitor ALT, AST, gamma-glutamyl transferase (GGT), and TBILI prior to the start of and during BLINCYTO® treatment. BLINCYTO® treatment should be interrupted if transaminases rise to > 5 times the upper limit of normal (ULN) or if TBILI rises to > 3 times ULN.
- **Leukoencephalopathy:** Although the clinical significance is unknown, cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving BLINCYTO®, especially in patients previously treated with cranial irradiation and anti-leukemic chemotherapy.
- Preparation and administration errors have occurred with BLINCYTO® treatment. Follow instructions for preparation (including admixing) and administration in the PI strictly to minimize medication errors (including underdose and overdose).

Adverse Reactions

- The most commonly reported adverse reactions (≥ 20%) in clinical trials were pyrexia (62%), headache (36%), peripheral edema (25%), febrile neutropenia (25%), nausea (25%), hypokalemia (23%), rash (21%), tremor (20%), diarrhea (20%), and constipation (20%).
- Serious adverse reactions were reported in 65% of patients. The most common serious adverse reactions (≥ 2%) included febrile neutropenia, pyrexia, pneumonia, sepsis, neutropenia, device-related infection, tremor, encephalopathy, infection, overdose, confusion, Staphylococcal bacteremia, and headache.

U.S. Dosage and Administration Guidelines

- BLINCYTO® is administered as a continuous intravenous infusion at a constant flow rate using an infusion pump which should be programmable, lockable, non-elastomeric, and have an alarm.
- It is very important that the instructions for preparation (including admixing) and administration provided in the full Prescribing Information are strictly followed to minimize medication errors (including underdose and overdose).
- Please see full U.S. Prescribing Information and medication guide for BLINCYTO at www.BLINCYTO.com.

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 Nov. 23, 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.

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