# FDA Approves BLINCYTO™ (Blinatumomab) Immunotherapy for the Treatment of Relapsed or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia

December 3, 2014

**BLINCYTO is the First-and-Only Bispecific CD19-Directed CD3 T-Cell Engager (BiTE®) Immunotherapy to be Approved by the FDA**

**BLINCYTO (Blinatumomab) for Injection Will be Available as a 35 mcg Single use Vial**

THOUSAND OAKS, Calif. and SOUTH SAN FRANCISCO, Calif., Dec. 3, 2014 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the U.S. Food and Drug Administration (FDA) has granted approval of BLINCYTO ™ (blinatumomab) for the treatment of patients with Philadelphia chromosome-negative (Ph-) 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. With this approval, BLINCYTO becomes the first FDA-approved bispecific CD19-directed CD3 T-cell engager (BiTE®) antibody construct product, and the first single-agent immunotherapy to be approved for the treatment of patients with Ph- relapsed or refractory B-cell precursor ALL, a rare and rapidly progressing cancer of the blood and bone marrow.[1-3]

"The FDA's breakthrough therapy designation and accelerated approval of BLINCYTO underscores the critical need for new treatment options for patients with relapsed or refractory B-cell precursor ALL, who are often young adults," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "BLINCYTO is the first clinical and regulatory validation of the BiTE® platform, a new and innovative approach that helps the body's own immune system fight cancer."

The BLINCYTO approval is based on results of Amgen's '211 trial, a Phase 2, multicenter, single-arm open-label study. Eligible patients were ≥ 18 years of age with Ph- relapsed or refractory B-cell precursor ALL. Relapsed or refractory was defined as relapsed with first remission duration of ≤ 12 months in the first salvage, or relapsed or refractory after first salvage therapy, or relapsed within 12 months of allogeneic hematopoietic stem cell transplantation (HSCT), and had ≥ 10 percent blasts in bone marrow. Of the 185 patients evaluated in the trial, 41.6 percent (77/185; 95 percent CI: 34.4-49.1) achieved complete remission or complete remission with partial hematologic recovery (CR/CRh*) within two cycles of treatment with BLINCYTO, which was the primary endpoint of the study. The majority of responses (81 percent [62/77]) occurred within the first cycle of treatment. Among patients who achieved CR/CRh*, 39 percent (30/77) went on to HSCT, and 75.3 percent (58/77 95 percent CI: 64.2-84.4) achieved minimal residual disease (MRD) response, a measure of eradication of residual disease at the molecular level.

"The approval of BLINCYTO represents a significant milestone in immunotherapy research, providing clinicians the opportunity to offer a new single-agent therapy to patients fighting this highly aggressive cancer with previously limited options," said Anthony S. Stein, M.D., clinical professor, Hematology/Oncology at City of Hope.

BLINCYTO has a **BOXED WARNING** in its product label regarding Cytokine Release Syndrome (CRS) and Neurological Toxicities.

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

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

Monitor patients for signs and symptoms of infection and treat appropriately.

Advise patients to refrain from driving and engaging in hazardous occupations or activities such as driving, operating heavy or potentially dangerous machinery while BLINCYTO is being administered.

It is important to strictly follow instructions for preparation (including admixing) and administration to prevent overdose and underdose.

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

The FDA has also approved a risk evaluation and mitigation strategy (REMS) for BLINCYTO. The purpose of the BLINCYTO REMS is to inform healthcare providers of the serious risks of CRS, neurological toxicities, and preparation and administration errors. Additional information about the BLINCYTO REMS program can be found at http://www.BLINCYTOREMS.com.

Please contact Amgen Medinfo at 800-77-AMGEN (800-772-6436) regarding BLINCYTO availability**.**

Amgen and its subsidiary Onyx Pharmaceuticals, Inc., which will commercialize BLINCYTO in the U.S., have announced the availability of Onyx Pharmaceuticals 360 ™ (Onyx 360), to patients receiving BLINCYTO in the U.S. Onyx 360 is a comprehensive patient and caregiver support and services program designed to help patients navigate the treatment journey, including reimbursement and payment support, treatment support and referrals to third-party organizations for day-to-day needs and emotional support. Dedicated Oncology Nurse Advocates are available Monday through Friday from 9 a.m. to 8 p.m. Eastern Standard Time at 1-855-ONYX-360 (1-855-669-9360) to assist patients, caregivers and healthcare providers.

Patients diagnosed with adult ALL are often young adults, with a median age at diagnosis of 34-39.[4] In adult patients with relapsed or refractory ALL, median overall survival is just three to five months.[5]

**About BLINCYTO™ (blinatumomab)**
BLINCYTO is the first BiTE® antibody construct and the first single-agent immunotherapy to be approved by the U.S. Food and Drug Administration (FDA).[3] BLINCYTO was granted breakthrough therapy and priority review designations by the FDA, and is now approved in the U.S. for the treatment of Philadelphia chromosome-negative (Ph-) relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

**About BiTE® Technology**
Bispecific T cell engager (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. For more information, visit www.biteantibodies.com.

**Important U.S. Product Information**
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.

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 are 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 o 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. Follow instructions for preparation (including admixing) and administration in the PI strictly to minimize medication errors (including underdose and overdose).

**Adverse Events**

- 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%) and constipation (20%).

**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 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 the world's largest independent biotechnology company, 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 Onyx Pharmaceuticals, Inc.**
Based in South San Francisco, California, Onyx Pharmaceuticals, Inc., an Amgen subsidiary, is a global biopharmaceutical company engaged in the development and commercialization of innovative therapies for improving the lives of people with cancer. The company is focused on developing novel medicines that target key molecular pathways. For more information about Onyx, visit the company's website at www.onyx.com. Onyx Pharmaceuticals is on Twitter. Sign up to follow our Twitter feed @OnyxPharm at http://twitter.com/OnyxPharm.

**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, we 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. 3, 2014, 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 we and our partners routinely obtain patents for our and 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. Cost savings initiatives may result in us incurring impairment or other related charges on our assets. We may experience difficulties, delays or unexpected costs and not achieve anticipated benefits and savings from our recently announced restructuring plans. 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 common stock.

CONTACT: Amgen, Thousand Oaks
Danielle Bertrand, 650-266-2114 (Media)
Kristen Davis, 805-447-3008 (Media)
Arvind Sood, 805-447-1060 (Investors)

**References**

1. Mayo Clinic. "Acute lymphocytic leukemia." Available at: http://www.mayoclinic.com/health/acute-lymphocytic-leukemia/DS00558. Accessed on October 30, 2014.
2. BLINCYTO™ Draft US Prescribing Information.
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Acute Lymphoblastic Leukemia. Version 1.2014. Available at: https://www.nccn.org/store/login/login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed on November 24, 2014.
4. Seer 2014 data. Available at: http://seer.cancer.gov/statfacts/html/leuks.html. Accessed on November 4, 2014.
5. Advani A.S. New immune strategies for the treatment of acute lymphoblastic leukemia: Antibodies and chimeric antigen receptors. Hematology Am Soc Hematol Educ Program. 2013;2013:131-7. Retrieved from: http://asheducationbook.hematologylibrary.org/content/2013/1/131.long.

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