FDA Grants Priority Review For Amgen's BLINCYTO® (blinatumomab) Supplemental Biologics License Application

March 29, 2017

Application Includes Overall Survival Data From Phase 3 TOWER Study to Support Conversion From Accelerated Approval to Full Approval

Acceptance Reinforces Significant Need for Innovative Treatment Options for Patients With Relapsed or Refractory Acute Lymphoblastic Leukemia

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

THOUSAND OAKS, Calif., March 29, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the U.S. Food and Drug Administration (FDA) has accepted for priority review the supplemental Biologics License Application (sBLA) for BLINCYTO® (blinatumomab) to include overall survival (OS) data from the Phase 3 TOWER study. The application also includes new data supporting the treatment of patients with Philadelphia chromosome-positive (Ph+) relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). The application aims to expand BLINCYTO's indication for the treatment of all patients with relapsed or refractory B-cell precursor ALL and supports the conversion of BLINCYTO's accelerated approval to full approval.

"Patients with relapsed or refractory ALL generally have a very poor prognosis. The median overall survival – or OS – on standard of care chemotherapy is just four months," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "BLINCYTO is the first-and-only approved bispecific immunotherapy with superior OS results versus standard of care chemotherapy, nearly doubling the median OS for patients with this form of ALL. We look forward to making this important potential new option available to patients with all forms of relapsed or refractory B-cell ALL."

Priority review is assigned to applications for drugs that treat serious conditions and would, if approved, provide significant improvements in the safety or effectiveness of the treatment, diagnosis or prevention of serious conditions. The Prescription Drug User Fee Act (PDUFA) target action date is Aug. 14, 2017.

BLINCYTO, the first-and-only FDA-approved CD19-directed CD3 bispecific T cell engager (BiTE®) antibody, was previously granted breakthrough therapy designation and accelerated approval. It is also the first single-agent immunotherapy approved to treat patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory B-cell precursor ALL.

The application is based on results from the TOWER study, investigating the efficacy of BLINCYTO versus standard of care (SOC) chemotherapy in adult patients with Ph- relapsed or refractory B-cell precursor ALL, which found that BLINCYTO demonstrated a statistically significant improvement in OS over SOC chemotherapy, almost doubling median OS. The study showed that median OS was 7.7 months (95 percent CI: 5.6, 9.6) for BLINCYTO versus four months (95 percent CI: 2.9, 5.3) for SOC (hazard ratio for death=0.71; *p*=0.012). BLINCYTO more than doubled median OS versus chemotherapy when used early (in first salvage; 11.1 months versus 5.3 months). Per the recommendation of an independent data monitoring committee, Amgen ended the study early for efficacy. These results were presented during the Presidential Symposium at the 21st Congress of the European Hematology Association and published in the *New England Journal of Medicine*.

Safety results among patients who received BLINCYTO were comparable to those seen in the Phase 2 studies in adult patients with Ph- relapsed or refractory B-cell precursor ALL. For the most common adverse events (greater than or equal to 10 percent incidence rate) in the BLINCYTO arm, only three events (cough, pyrexia, cytokine release syndrome) occurred at an incidence rate that was at least five percent higher for BLINCYTO compared to SOC chemotherapy.

The application also includes data from the ALCANTARA study, evaluating the efficacy and tolerability of BLINCYTO in adult patients with Ph+ relapsed or refractory B-cell precursor ALL, which were published today in the *Journal of Clinical Oncology.*

The FDA-approved prescribing information for BLINCYTO includes a boxed warning for cytokine release syndrome and neurologic toxicities. BLINCYTO is also under a REMS program in the US.

ALL is a rare and rapidly progressing cancer of the blood and bone marrow.[1,2] Currently, there is no broadly accepted standard treatment regimen for adult patients with relapsed or refractory ALL beyond chemotherapy.[3] In adult ALL, approximately 75 percent is B-cell precursor ALL, of which 75-80 percent is Ph-, and roughly half will be refractory to treatment or experience relapse.[4]

About the TOWER Study

The TOWER study was a Phase 3, randomized, active-controlled, open-label study investigating the efficacy of BLINCYTO versus SOC chemotherapy in 405 adult patients with Ph- relapsed or refractory B-cell precursor ALL. The study enrolled a difficult-to-treat patient population which included patients from several stages of relapse, 17 percent of whom had relapsed post-allogenic stem cell transplant (alloSCT), and excluded those with late first relapse (≥ 12 months after initial remission). Patients were randomized in a 2:1 ratio to receive BLINCYTO (n=271) or treatment with investigator choice of one of four protocol-defined SOC chemotherapy regimens (n=134). The primary endpoint was OS. Key secondary endpoints included complete remission within 12 weeks, the combined endpoint of complete remission plus complete remission with partial or incomplete hematologic recovery and event-free survival. Other secondary endpoints included remission duration, minimal residual disease (MRD) remission ($<10^{-4}$), alloSCT rate and adverse event rates.

The TOWER study is the confirmatory trial for BLINCYTO. Click here to read about the trial on ClinicalTrials.gov.

About the ALCANTARA Study

The ALCANTARA study was a Phase 2, single-arm, multicenter, open-label study investigating the efficacy and tolerability of BLINCYTO in 45 adult

patients with Ph+ B-cell precursor ALL, who had relapsed after or were refractory to at least one second-generation or later tyrosine kinase inhibitor (TKI), or were intolerant to second-generation or later TKIs and intolerant or refractory to imatinib. BLINCYTO was administered in 28-day cycles by continuous intravenous infusion. The primary endpoint was complete remission or complete remission with partial hematologic recovery during the first two cycles. Key secondary endpoints included MRD response, rate of alloHSCT, relapsed free survival, OS and adverse events.

Safety results among subjects who received BLINCYTO were comparable to those seen in the Phase 2 studies in adult patients with Ph- relapsed or refractory B-cell precursor ALL.

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 FDA, 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.

In November 2015, BLINCYTO was granted conditional marketing authorization in the EU for the treatment of adults with Ph- relapsed or refractory B-cell precursor 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.

BLINCYTO® U.S. Product Safety Information

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

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): CRS, which may be life-threatening or fatal, 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 64% of patients receiving BLINCYTO® in clinical trials experienced neurological toxicities. The median time to onset of any neurological toxicity was 4 days. The most common (≥ 10%) manifestations of neurological toxicity were headache, tremor, dizziness, and altered state of consciousness. Severe, life-threatening, or fatal neurological toxicities occurred in approximately 17% of patients, including encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. The neurological toxicity profile varied by age group. 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): TLS, which may be life-threatening or fatal, 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 with a median time to onset of 3 days. In patients receiving BLINCYTO®, although the majority of these events were observed in the setting of CRS, some cases of elevated liver enzymes were observed outside the setting of CRS, with a median time to onset of 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.
- Pancreatitis: Fatal pancreatitis has been reported in patients receiving BLINCYTO® in combination with dexamethasone in clinical trials and the post-marketing setting. Evaluate patients who develop signs and symptoms of pancreatitis and interrupt or discontinue BLINCYTO® and dexamethasone as needed.
- 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 antileukemic 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).
- Immunization: Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of BLINCYTO® treatment, during treatment, and until immune recovery following last cycle of BLINCYTO®.

Adverse Reactions

- The most common adverse reactions (≥ 20%) in the safety population studied in clinical trials were pyrexia (66%), headache (34%), nausea (27%), edema (26%), hypokalemia (26%), anemia (25%), febrile neutropenia (24%), neutropenia (22%), thrombocytopenia (20%), and abdominal pain (20%). The safety population included 225 patients weighing 45 kg or more and 57 patients weighing less than 45 kg. For some adverse reactions, there were differences in the incidence rates by age subgroup.
- In patients weighing greater than or equal to 45 kg, serious adverse reactions were reported in 61% of patients. The most common serious adverse reactions (≥ 2%) included febrile neutropenia (9%), pyrexia (6%), sepsis (5%), pneumonia (5%), device-related infection (4%), neutropenia (3%), tremor (3%), overdose (3%), encephalopathy (3%), infection (2%), confusion (3%) and headache (2%).
- In patients weighing less than 45 kg, serious adverse reactions were reported in 51% of patients. The most common serious adverse reactions (≥ 2%) included pyrexia (12%), febrile neutropenia (9%), cytokine release syndrome (4%), convulsion (4%), device-related infection (4%), hypoxia (4%), sepsis (4%), and overdose (4%).

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 Prescribing Information, including **Boxed WARNINGS** and Medication Guide, for BLINCYTO® at www.BLINCYTO.com.

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 malignancies, ranging from blood cancers to solid tumors. With decades of experience providing therapies for cancer patients, Amgen continues to grow its portfolio of innovative and biosimilar oncology medicines.

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 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. 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 reports filed by Amgen, including our most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those we project. Our results may be affected by our ability to successfully market both new and existing products domestically and internationally, clinical and regulatory developments involving current and future products, sales growth of recently launched products, competition from other products including biosimilars, difficulties or delays in manufacturing our products and global economic conditions. In addition, sales of our products are affected by pricing pressure, political and public scrutiny and 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. Furthermore, our research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. 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. In addition, our business may be impacted by the adoption of new tax legislation or exposure to additional tax liabilities. 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. Further, 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, or we may fail to prevail in present and future intellectual property litigation. We perform a substantial amount of our commercial manufacturing activities at a few key facilities and also depend on third parties for a portion of our manufacturing activities, and limits on supply may constrain sales of certain of our current products and product candidate development. In addition, we compete with other companies with respect to many of our marketed products as well as for the discovery and development of new products. Discovery or identification of new product candidates cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate will be successful and become a commercial product. Further, some raw materials, medical devices and component parts for our products are supplied by sole third-party suppliers. Certain of our distributors, customers and payers have substantial purchasing leverage in their dealings with us. 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 acquire other companies or products and to integrate the operations of companies we have acquired may not be successful. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all. We are increasingly dependent on information technology systems, infrastructure and data security. Our stock price is volatile and may be affected by a number of events. 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 our common stock.

The scientific information discussed in this news release relating to new indications for our products is preliminary and investigative and is not part of the labeling approved by the U.S. Food and Drug Administration for the products. The products are not approved for the investigational use(s) discussed in this news release, and no conclusions can or should be drawn regarding the safety or effectiveness of the products for these uses.

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