FDA Approves BLINCYTO® (blinatumomab) To Treat Minimal Residual Disease-Positive B-Cell Precursor Acute Lymphoblastic Leukemia In Adults And Children

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BLINCYTO is the First-and-Only FDA-Approved Therapy for Minimal Residual Disease

Detection of Remaining Cancer Cells After Complete Remission is the Strongest Prognostic Factor for Relapse in Patients With Acute Lymphoblastic Leukemia

Accelerated Approval Based on Data From the Phase 2 BLAST Study, the Largest Prospective Trial in Minimal Residual Disease-Positive Acute Lymphoblastic Leukemia

THOUSAND OAKS, Calif., March 29, 2018 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the U.S. Food and Drug Administration (FDA) has approved the supplemental Biologics License Application (sBLA) for BLINCYTO® (blinatumomab) for the treatment of adults and children with B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1 percent. This indication is approved under accelerated approval based on MRD response rate and hematological relapse-free survival (RFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. BLINCYTO, the first-and-only approved bispecific CD19-directed CD3 T cell engager (BiTE®) immunotherapy, is now also the first-and-only therapy to be FDA-approved for MRD.

MRD refers to the presence of cancer cells that remain detectable, despite a patient's having achieved complete remission by conventional assessment.[1] MRD is only measurable through the use of highly sensitive testing methods that detect cancer cells in the bone marrow with a sensitivity of at least one cancer cell in 10,000 cells — versus about one in 20 with a conventional microscope-based evaluation.[1,2,3]

"Until today, no therapy has been satisfactory in eradicating MRD or approved specifically to treat this high-risk patient population," said David M. Reese, M.D., senior vice president of Translational Sciences and Oncology at Amgen. "This approval not only supports the use of BLINCYTO earlier in the ALL treatment continuum, but represents a paradigm shift in the management of ALL."

"The detection of remaining cancer cells after a complete remission is the strongest prognostic factor for relapse in patients with ALL. It's critical to test for and know your patients' MRD status, because we know that treating to MRD-negativity will help to obtain better possible clinical outcomes for patients," said Elias Jabbour, M.D., associate professor, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston. "In the BLAST study, blinatumomab led to no detectable cancer cells in approximately 80 percent of patients with MRD-positive ALL. This approval provides a much-needed treatment option to destroy the remaining detectable traces of leukemia."

The accelerated approval is based on results from the Phase 2 single-arm BLAST study (n=86), which found that BLINCYTO converted most patients to an MRD-negative state after a single cycle of therapy. BLINCYTO met the primary endpoint, inducing a complete MRD response, which is no detectable MRD, in 81 percent of patients (95 percent CI: 71.6, 89.0). Median hematological RFS was 22.3 months.

Safety results among MRD-positive patients were consistent with the known safety profile of BLINCYTO in relapsed or refractory B-cell precursor ALL. The most common adverse reactions (greater than 20 percent) were pyrexia, infusion related reactions, headache, infections (pathogen unspecified), tremor and chills.

The FDA-approved prescribing information for BLINCYTO includes a boxed warning for cytokine release syndrome and neurologic toxicities. BLINCYTO is also under a risk evaluation and mitigation strategy (REMS) program in the U.S.

About BLINCYTO® (blinatumomab)

BLINCYTO is a bispecific CD19-directed CD3 T cell engager (BiTE®) immunotherapy that binds 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 in 2014, and is now fully approved in the U.S. for the treatment of relapsed or refractory B-cell precursor ALL in adults and children. BLINCYTO is now also approved under accelerated approval for the treatment of adults and children with B-cell precursor ALL in first or second complete remission with MRD greater than or equal to 0.1 percent. This indication is approved under accelerated approval based on MRD response rate and hematological relapse-free survival (RFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

In November 2015, BLINCYTO was granted conditional marketing authorization in the European Union for the treatment of adults with Philadelphia chromosome-negative (Ph-) relapsed or refractory B-cell precursor ALL. Additional regulatory applications for BLINCYTO are underway and have been submitted to health authorities worldwide.

About the BLAST Study

The BLAST study is the largest ever prospective trial in patients with MRD-positive ALL. It is an open-label, multicenter, single-arm, Phase 2 study evaluating the efficacy, safety and tolerability of BLINCYTO in adult patients with MRD-positive B-cell precursor ALL in complete hematologic remission after three or more cycles of intensive chemotherapy. Patients received continuous IV infusion of BLINCYTO 15 $\mu g/m^2/d$ for four weeks, followed by two weeks off. Patients received up to four cycles of treatment and could undergo hematopoietic stem cell transplantation (HSCT) at any time after the first cycle, if eligible. The primary endpoint was the rate of complete MRD response within the first treatment cycle. The key secondary endpoint was RFS at 18 months. Additional secondary endpoints included incidence and severity of adverse events, overall survival (OS), time to hematological remission and duration of complete MRD response.

To evaluate the association between complete MRD response and subsequent RFS and OS, landmark analyses were performed at 45 days (day by which all first cycle MRD responses had been assessed) for patients with and without a complete MRD response in the first cycle. Patients who relapsed, died, or were censored before day 45 were excluded to correct for immortal time bias. Improvement in median RFS was seen for BLINCYTO patients achieving a complete MRD response compared to MRD nonresponses, 23.6 months versus 5.7 months, respectively (p=0.002).

Results from the BLAST study were presented at the 57th Annual Meeting and Exposition of the American Society of Hematology in 2015 and published in *Blood* in 2018.

About ALL and MRD

ALL is a rare and rapidly progressing cancer of the blood and bone marrow that occurs in both adults and children.[4,5] Nearly 50 percent of adult patients and 25 percent of pediatric patients with B-cell ALL eventually relapse or are refractory to treatment.[6,7] Poor outcomes have been observed in patients who relapse after achieving a complete response but have persistent MRD, or disease that remains at the molecular level after treatment.[1,8] Five-year OS rates are as high as 75 percent for patients that achieve MRD-negative status, compared with 33 percent among patients that remain MRD-positive.[8] In pediatric patients, MRD-positive status after treatment is associated with a 15-times higher risk of relapse compared with those with undetectable residual disease.[9] For more information about MRD, please visit AmgenOncology.com.

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 bridge T cells to tumor cells, using the patient's own immune system to eradicate cancer. BiTE® antibody constructs help place the T cells within reach of the targeted cell, with the intent of causing 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.

BLINCYTO® U.S. Product Safety Information

Indication and Important Safety Information, including Boxed WARNINGS, for BLINCYTO® (blinatumomab) for injection, for intravenous use

INDICATION

BLINCYTO is indicated for the treatment of adults and children with:

- B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. This indication is approved under accelerated approval based on MRD response rate and hematological relapse-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
- Relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

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): CRS, which may be life-threatening or fatal, occurred in patients receiving BLINCYTO®. The median time to onset of CRS is 2 days after the start of infusion. Closely monitor patients for signs and symptoms of serious adverse events such as fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased total bilirubin (TBILI), and disseminated intravascular coagulation (DIC). The manifestations of CRS after treatment with BLINCYTO overlap with those of infusion reactions, capillary leak syndrome (CLS), and hemophagocytic histiocytosis/macrophage activation syndrome (MAS). In clinical trials of BLINCYTO, CRS was reported in 15% of patients with relapsed or refractory ALL and in 7% of patients with MRD-positive ALL. Interrupt or discontinue BLINCYTO® as outlined in the PI.
- Neurological Toxicities: Approximately 65% of patients receiving BLINCYTO® in clinical trials experienced neurological toxicities. The median time to the first event was within the first 2 weeks of BLINCYTO® treatment and the majority of events resolved. The most common (≥ 10%) manifestations of neurological toxicity were headache and tremor. Severe, life-threatening, or fatal neurological toxicities occurred in approximately 13% of patients, including encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Manifestations of neurological toxicity included cranial nerve disorders. Monitor patients for signs or symptoms and interrupt or discontinue BLINCYTO® as outlined in the PI.
- Infections: Approximately 25% of patients receiving BLINCYTO® in clinical trials experienced serious infections such as sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site 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), 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 (including, but not limited to, white blood cell count and absolute neutrophil count) 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 19 days. Grade 3 or greater elevations in liver enzymes occurred in approximately 7% 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®.
- Risk of Serious Adverse Reactions in Pediatric Patients due to Benzyl Alcohol Preservative: Serious and fatal adverse reactions including "gasping syndrome," which is characterized by central nervous system depression, metabolic acidosis,

and gasping respirations, can occur in neonates and infants treated with benzyl alcohol-preserved drugs including BLINCYTO® (with preservative). When prescribing BLINCYTO® (with preservative) for pediatric patients, consider the combined daily metabolic load of benzyl alcohol from all sources including BLINCYTO® (with preservative) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known. Due to the addition of bacteriostatic saline, 7-day bags of BLINCYTO® solution for infusion with preservative contain benzyl alcohol and are not recommended for use in any patients weighing < 22 kg.

Adverse Reactions

- The most common adverse reactions (≥ 20%) in clinical trial experience of patients with MRD-positive B-cell precursor ALL (BLAST Study) treated with BLINCYTO® were pyrexia, infusion related reactions, headache, infections (pathogen unspecified), tremor, and chills. Serious adverse reactions were reported in 61% of patients. The most common serious adverse reactions (≥ 2%) included pyrexia, tremor, encephalopathy, aphasia, lymphopenia, neutropenia, overdose, device related infection, seizure, and staphylococcal infection.
- The most common adverse reactions (≥ 20%) in clinical trial experience of patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (TOWER Study) treated with BLINCYTO® were infections (bacterial and pathogen unspecified), pyrexia, headache, infusion-related reactions, anemia, febrile neutropenia, thrombocytopenia, and neutropenia. Serious adverse reactions were reported in 62% of patients. The most common serious adverse reactions (≥ 2%) included febrile neutropenia, pyrexia, sepsis, pneumonia, overdose, septic shock, CRS, bacterial sepsis, device related infection, and bacteremia.
- Adverse reactions that were observed more frequently (≥ 10%) in the pediatric population compared to the adult population were pyrexia (80% vs. 61%), hypertension (26% vs. 8%), anemia (41% vs. 24%), infusion-related reaction (49% vs. 34%), thrombocytopenia (34% vs. 21%), leukopenia (24% vs. 11%), and weight increased (17% vs. 6%).
- In pediatric patients less than 2 years old (infants), the incidence of neurologic toxicities was not significantly different than for the other age groups, but its manifestations were different; the only event terms reported were agitation, headache, insomnia, somnolence, and irritability. Infants also had an increased incidence of hypokalemia (50%) compared to other pediatric age cohorts (15-20%) or adults (17%).

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®.

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

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 current reports on 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. 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. Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints we have selected. 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, including our devices, after they are on the market.

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. 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, including in Puerto Rico, 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. 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. A breakdown, cyberattack or information security breach could compromise the confidentiality, integrity and availability of our systems and our data. 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. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all.

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