European Commission Approves BLINCYTO® (blinatumomab) For Use In Pediatric Patients With Philadelphia Chromosome-Negative Relapsed Or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia

August 29, 2018

Approval Based on Data From the Phase 1/2 '205 Study

THOUSAND OAKS, Calif., Aug. 29, 2018 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the European Commission (EC) has approved an expanded indication for BLINCYTO® (blinatumomab) as monotherapy for the treatment of pediatric patients aged one year or older with Philadelphia chromosome-negative CD19 positive B-cell precursor acute lymphoblastic leukemia (ALL), which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation. The approval is based on results from the Phase 1/2 '205 study, an open-label, multicenter, single-arm trial which evaluated the efficacy and safety of BLINCYTO in pediatric patients with relapsed or refractory B-cell precursor ALL.

"Historically, children with relapsed or refractory ALL have had limited pharmacologic options beyond chemotherapy, resulting in poor outcomes," said David M. Reese, M.D., executive vice president of Research and Development at Amgen. "This approval for BLINCYTO provides physicians across Europe with an important new immunotherapy option for these young, heavily pretreated patients, delivering on Amgen's commitment to making a difference in the lives of cancer patients."

ALL is a rapidly progressing cancer of the blood and bone marrow that occurs in both adults and children.[1,2] In Europe, an estimated 5,000 children are diagnosed with ALL each year.[3]

BLINCYTO is the first-and-only bispecific T cell engager (BiTE®) immunotherapy construct approved globally. It is also the first immunotherapy from Amgen's BiTE® platform, an innovative approach that helps the body's immune system target cancer cells.

Approval via the centralized procedure grants a marketing authorization from the EC, which is valid in all European Union (EU) and European Economic Area (EEA)-European Free Trade Association (EFTA) states (Norway, Iceland and Liechtenstein).

About Study '205
Study '205 evaluated the safety and efficacy of BLINCYTO in a Phase 1/2 open-label, multicenter, single-arm study in 93 pediatric patients with Ph- relapsed or refractory B-cell precursor ALL (second or later bone marrow relapse, any marrow relapse after allogeneic hematopoietic stem cell transplantation [alloHSCT], or refractory to other treatments and had greater than 25 percent blasts in bone marrow). The results were published in the *Journal of Clinical Oncology.*

BLINCYTO was administered as a continuous intravenous infusion. The recommended dose for this study was determined to be 5 µg/m^2/day on days 1-7 and 15 µg/m^2/day on days 8-28 for cycle 1, followed by two weeks off, and 15 µg/m^2/day on days 1-28, followed by two weeks off for subsequent cycles. Dose adjustment was possible in case of adverse events. Patients who responded to BLINCYTO, but later relapsed, had the option to be retreated with BLINCYTO.

Among the 70 patients treated at the recommended dosage, the median age was eight years (range: seven months to 17 years), 40 out of 70 (57.1 percent) had undergone alloHSCT prior to receiving BLINCYTO, and 39 out of 70 (55.7 percent) had refractory disease; the mean number of treatment cycles was 1.5. Twenty out of 70 patients (28.6 percent) achieved a complete response or complete response with partial hematologic recovery within two treatment cycles; with 17 of 20 responses (85 percent) occurring within the first cycle. In general, the adverse reactions in BLINCYTO-treated pediatric patients were similar in type to those seen in adult patients with relapsed or refractory B-cell precursor ALL.

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 effector T cells. BLINCYTO was granted breakthrough therapy and priority review designations by the FDA in 2014, and carries full approval in the U.S. for the treatment of relapsed or refractory B-cell precursor ALL in adults and children. In the U.S., BLINCYTO is also approved under accelerated approval for the treatment of adults and children with B-cell precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1 percent.

In 2015, BLINCYTO was approved 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 novel immune-oncology technology that can be engineered to target any tumor antigen expressed by any type of cancer. The modified antibodies are designed to kill malignant cells using the patient's own immune system by bridging T cells to tumor cells. BiTE® antibody constructs help connect the T cells to the targeted cell, with the intent of causing T cells to inject toxins which trigger cancer cell death (apoptosis). Amgen is developing BiTE® antibody constructs to uniquely (or specifically) target numerous hematologic malignancies and solid tumors.

Important EU BLINCYTO® (blinatumomab) Safety Information

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

BLINCYTO has been evaluated in paediatric patients with relapsed or refractory B-precursor ALL in a phase I/II dose escalation/evaluation study, in which 70 paediatric patients, aged 7 months to 17 years, were treated with the recommended dosage regimen.

The most frequently reported serious adverse events were pyrexia (11.4%), febrile neutropenia (11.4%), cytokine release syndrome (5.7%), sepsis (4.3%), device-related infection (4.3%), overdose (4.3%), convulsion (2.9%), respiratory failure (2.9%), hypoxia (2.9%), pneumonia (2.9%), and multi-organ failure (2.9%).

The adverse reactions in BLINCYTO-treated paediatric patients were similar in type to those seen in adult patients. Adverse reactions that were observed more frequently (≥ 10% difference) in the paediatric population compared to the adult population were anaemia, thrombocytopenia, leukopenia, pyrexia, infusion-related reactions, weight increase, and hypertension.

The type and frequency of adverse events were similar across different paediatric sub-groups (gender, age, geographic region).

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

For more information, follow us on www.twitter.com/amgenoncology.

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 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.

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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