



Amgen Announces Positive Results From Two Phase 3 BLINCYTO® (blinatumomab) Studies In Pediatric Patients With Relapsed Acute Lymphoblastic Leukemia

September 24, 2019

Phase 3 '215 and Children's Oncology Group (COG) Studies Both Stopped Early Due to Treatment Benefit of BLINCYTO Over Chemotherapy

THOUSAND OAKS, Calif., Sept. 24, 2019 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the results of a prespecified interim analysis of an open-label, randomized, controlled global multicenter Phase 3 trial (20120215) showed that the primary endpoint of event-free survival was met. The study evaluated the efficacy, safety and tolerability of BLINCYTO® (blinatumomab) compared to conventional consolidation chemotherapy in pediatric patients with high-risk, B-cell acute lymphoblastic leukemia (ALL) at first relapse. Enrollment was terminated early due to encouraging efficacy in the BLINCYTO arm and was based on a recommendation from the Independent Data Monitoring Committee (DMC). Follow up will continue as prescribed per protocol.

In addition, a randomized, Phase 3 trial (AALL1331) conducted by the Children's Oncology Group (COG) using BLINCYTO in pediatric B-cell ALL patients at first relapse has closed to accrual for the high-risk and intermediate risk-arm based on the recommendation of the COG DMC. The DMC closure decision was based on a strong trend towards improved disease-free survival and improved overall survival, markedly lower toxicity, and better minimal residual disease (MRD) clearance for BLINCYTO compared to chemotherapy. The COG DMC recommended that the AALL1331 low-risk group continue to enroll and randomize patients until enrollment goals are reached. AALL1331 is sponsored by the Cancer Therapy Evaluation Program of the National Cancer Institute (NCI), part of the National Institutes of Health, and is conducted by the NCI-funded COG. Amgen provided BLINCYTO for AALL1331 under a Collaborative Research and Development Agreement between the NCI and Amgen.

"Considered together, the results of these studies are remarkable. Children and adolescents who relapse with acute lymphoblastic leukemia face a poor prognosis and there remains a need for additional treatment options, particularly for those that are identified as high-risk. These data have the potential to be practice-changing and may provide a treatment approach to prevent further relapse that is superior to chemotherapy," said David M. Reese, M.D., executive vice president of Research and Development at Amgen. "We look forward to discussing these data with regulatory authorities."

The BLINCYTO adverse events observed in the Phase 3 20120215 and the COG AALL1331 studies were consistent with the known safety profile of BLINCYTO. These interim data will be submitted to a future medical conference and for publication.

About the 20120215 Study

Study 20120215 is a Phase 3 open-label, multicenter, randomized, controlled trial to evaluate event-free survival after treatment with BLINCYTO compared with standard of care consolidation chemotherapy in pediatric patients with high-risk first relapsed B-cell ALL. Key secondary endpoints included incidence of overall survival and MRD response, AEs, 100-day mortality after alloHSCT, incidence of anti-blinatumomab antibody formation, cumulative incidence of relapse. This is a global study that is being conducted as part of the PIP (Pediatric Investigation Plan) agreed to between Amgen and the EMA. The study is being conducted in Australia and various countries in EU and Latin America. Click [here](#) to read about the trial on ClinicalTrials.gov.

About the COG AALL1331 Study

The COG AALL1331 study is a risk-stratified, randomized, Phase 3 trial of blinatumomab in first relapse of pediatric B-ALL to evaluate disease-free survival (DFS) of high-risk (HR) and intermediate-risk (IR) relapsed B-ALL patients who are randomized following induction block 1 chemotherapy to receive either two intensive chemotherapy blocks or two 5-week blocks of blinatumomab. It also compares the DFS of low risk (LR) relapse B-ALL patients who are randomized following block 1 chemotherapy to receive either chemotherapy alone or chemotherapy plus blinatumomab. Key secondary endpoints include overall survival of HR, IR, and LR relapsed B-ALL patients. This is a global study that is being conducted in Australia, Canada, New Zealand and United States. Click [here](#) to read about the trial on ClinicalTrials.gov.

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.

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.

BLINCYTO was granted breakthrough therapy and priority review designations by the U.S. Food and Drug Administration and is approved in the U.S. for the treatment of:

- relapsed or refractory B-cell precursor ALL in adults and children.

- B-cell precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults and children.

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.

In the EU, BLINCYTO is indicated as monotherapy for the treatment of:

- adults with Philadelphia chromosome negative CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).
- adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.
- paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B-precursor 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

About BiTE® Technology

Bispecific T cell engager (BiTE®) technology is a targeted immuno-oncology platform designed to engage patients' own T cells to any tumor-specific antigen, activating the cytotoxic potential of T cells to eliminate detectable cancer. 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 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® and treat with corticosteroids 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 15% of patients with R/R ALL and in 7% of patients with MRD-positive ALL. The median time to onset of CRS is 2 days after the start of infusion and the median time to resolution of CRS was 5 days among cases that resolved. Closely monitor and advise patients to contact their healthcare professional 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, and hemophagocytic

histiocytosis/macrophage activation syndrome. If severe CRS occurs, interrupt BLINCYTO[®] until CRS resolves. Discontinue BLINCYTO[®] permanently if life-threatening CRS occurs. Administer corticosteroids for severe or life-threatening CRS.

- **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 ($\geq 10\%$) 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, 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 "gaspings 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 (91%), infusion-related reactions (77%), headache (39%), infections (pathogen unspecified [39%]), tremor (31%), and chills (28%). 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 adults with relapsed or refractory B-cell precursor ALL 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 and medication guide for BLINCYTO at www.BLINCYTO.com.

About Amgen Oncology

Amgen Oncology is searching for and finding answers to incredibly complex questions that will advance care and improve lives for cancer patients and their families. Our research drives us to understand the disease in the context of the patient's life – not just their cancer journey – so they can take control of their lives.

For the last four decades, we have been dedicated to discovering the firsts that matter in oncology and to finding ways to reduce the burden of cancer. Building on our heritage, Amgen continues to advance the largest pipeline in the Company's history, moving with great speed to advance those innovations for the patients who need them.

At Amgen, we are driven by our commitment to transform the lives of cancer patients and keep them at the center of everything we do.

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 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 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. We rely on collaborations with third parties for the development of some of our product candidates and for the commercialization and sales of some of our commercial products. 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.

The scientific information discussed in this news release related to our product candidates is preliminary and investigative. Such product candidates are not approved by the U.S. Food and Drug Administration, and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidates. Further, 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.

CONTACT: Amgen, Thousand Oaks
Trish Hawkins, 805-447-5631 (Media)
Jessica Akopyan, 805-447-0974
Arvind Sood, 805-447-1060 (Investors)



 View original content to download multimedia:<http://www.prnewswire.com/news-releases/amgen-announces-positive-results-from-two-phase-3-blincyto-blinatumomab-studies-in-pediatric-patients-with-relapsed-acute-lymphoblastic-leukemia-300924297.html>

SOURCE Amgen