bluebird bio Provides Updated Findings from Reported Case of Acute Myeloid Leukemia (AML) in LentiGlobin for Sickle Cell Disease (SCD) Gene Therapy Program

Analyses demonstrate lentiviral vector BB305 unlikely to be the cause of AML in clinical study of LentiGlobin for SCD

bluebird bio has initiated process with regulators to resume clinical studies

ZUG, Switzerland — March 10, 2021 — bluebird bio, Inc. (Nasdaq: BLUE) announced today that based on the analyses completed to date, it is very unlikely the Suspected Unexpected Serious Adverse Reaction (SUSAR) of acute myeloid leukemia (AML) reported in its Phase 1/2 (HGB-206) study of LentiGlobin gene therapy for sickle cell disease (SCD) (bb1111) was related to the BB305 lentiviral vector (LVV).

"In addition to our earlier findings of several well-known genetic mutations and gross chromosomal abnormalities commonly observed in AML in this patient, our latest analyses identified the integration site for the vector within a gene called VAMP4. VAMP4 has no known association with the development of AML nor with processes such as cellular proliferation or genome stability. Moreover, we see no significant gene misregulation attributable to the insertion event," said Philip Gregory, chief scientific officer, bluebird bio. "In totality, the data from our assessments provide important evidence demonstrating that it is very unlikely our BB305 lentiviral vector played a role in this case and we have shared with the FDA that we believe these results support lifting the clinical holds on our β-thalassemia and sickle cell disease programs."

As reported by bluebird bio on February 25, 2021, laboratory analyses showed that this patient had significant chromosomal abnormalities and mutations in genes typically associated with the development of AML. Specifically, mutations in the RUNX1 and PTPN11 genes have been detected in the leukemic cells of this patient. Preliminary findings suggested that the BB305 LVV vector was present in the AML blast cells, but there was not sufficient information to determine causality.

Since then, and with the advice of several independent leading academic experts in lentiviral vector gene therapy, bluebird bio has performed additional scientific assessments to determine where in the genome the LVV insertion occurred, and if this integration was responsible for any change in gene regulation or gene expression nearby.

Multiple independent analyses have confirmed that vector insertion in the AML cells from this patient took place in the VAMP4 gene, or vesicle-associated membrane protein 4. VAMP4 itself has no known role in the development of AML or with any cellular process related to cancer.

bluebird bio also assessed if there was any disruption to normal gene regulation or gene expression in and around the site of vector insertion. Based on completed analyses, the insertion into the VAMP4 gene has had no impact on gene expression or gene regulation nor caused any disruption of nearby genes.

Based on the available results to date, bluebird bio believes that the case of AML is very unlikely related to the BB305 LVV. Given this, the company has initiated engagement with regulators to begin the process of resuming clinical studies for sickle cell disease and β-thalassemia.

A second SUSAR of myelodysplastic syndrome (MDS) in a patient from Group C of HGB-206 was reported in early February and is currently being investigated to determine if the clinical findings meet the criteria to be classified as a case of MDS and, if so, if LentiGlobin for SCD had any role. The MDS diagnosis was based on prolonged anemia following LentiGlobin for SCD infusion coupled with the observation of trisomy 8 in a small percentage of the patient's bone marrow cells. However, no blasts or dysplastic cells were seen in an examination of the patient's bone marrow, and while trisomy 8 is associated with myeloid malignancies, this finding is not sufficient for a diagnosis of MDS in the absence of blasts or dysplastic cells.

Regulatory Status
The U.S. Food and Drug Administration (FDA) has placed a clinical hold on the HGB-206 and HGB-210 studies of LentiGlobin for SCD and the HGB-207 and HGB-212 studies of betibeglogene autotemcel for β-thalassemia. The company is in dialogue with the FDA in order to resume all clinical studies currently on clinical hold.

An Article 20 referral procedure was triggered by the European Commission (EC) and will be conducted by the European Medicines Agency (EMA). The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) will begin the process of reviewing the benefit/risk of Zynteglo▼™ (betibeglogene autotemcel) for the treatment of transfusion-dependent β-thalassemia, during its March 8 – 11 session. The committee will determine whether any additional pharmacovigilance measures are necessary. The EMA has paused the renewal procedure for Zynteglo's conditional marketing authorization (CMA) while the PRAC review is ongoing.

No cases of hematologic malignancy have been reported in any patient who has received treatment with betibeglogene autotemcel for transfusion-dependent β-thalassemia, however because it is also manufactured using the same BB305 LVV used in LentiGlobin for SCD, the company decided to temporarily suspend marketing of Zynteglo while the AML case is assessed.

Notes to editor

About HGB-206 and HGB-210

HGB-206 is a Phase 1/2 open-label study designed to evaluate the efficacy and safety of LentiGlobin gene therapy for sickle cell disease (SCD) that includes three treatment cohorts: Groups A, B and C. A refined manufacturing process designed to increase vector copy number (VCN) and further protocol refinements made to improve engraftment potential of gene-modified stem cells were used for Group C. Group C patients also received LentiGlobin for SCD made from HSCs collected from peripheral blood after mobilization with plerixafor, rather than via bone marrow harvest, which was used in Groups A and B of HGB-206.

HGB-210 is a Phase 3 single-arm open-label study designed to evaluate the efficacy and safety of LentiGlobin gene therapy for SCD in patients between two years and 50 years of age with sickle cell disease.

About LentiGlobin for SCD (bb1111)

LentiGlobin gene therapy for sickle cell disease (bb1111) is an investigational treatment being studied as a potential treatment for SCD. bluebird bio's clinical development program for LentiGlobin for SCD includes the completed Phase 1/2 HGB-205 study, the Phase 1/2 HGB-206 study, and the Phase 3 HGB-210 study.

The U.S. Food and Drug Administration granted orphan drug designation, fast track designation, regenerative medicine advanced therapy (RMAT) designation and rare pediatric disease designation for LentiGlobin for SCD.

LentiGlobin for SCD received orphan medicinal product designation from the European Commission for the treatment of SCD, and Priority Medicines (PRIME) eligibility by the EMA in September 2020.

bluebird bio is conducting a long-term safety and efficacy follow-up study (LTF-307) for people who have participated in bluebird bio-sponsored clinical studies of LentiGlobin for SCD. For more information visit: **clinicaltrials.gov** and use identifier NCT04628585 for LTF-307.

LentiGlobin for SCD is investigational and has not been approved in any geography.

About Zynteglo (betibeglogene autotemcel)

Betibeglogene autotemcel (beti-cel) is a one-time gene therapy that adds functional copies of a modified form of the β-globin gene (βA-^{T87Q}-globin gene) into a patient's own hematopoietic (blood) stem cells (HSCs). Once a patient has the $\beta^{A\text{-}T87Q}$-globin gene, they have the potential to produce Hb^{AT87Q}, which is gene therapy-derived adult Hb, at levels that may eliminate or significantly reduce the need for transfusions. In studies of beti-cel, transfusion independence (TI) is defined as no longer needing red blood cell transfusions for at least 12 months while maintaining a weighted average Hb of at least 9 g/dL.

The European Commission granted conditional marketing authorization (CMA) for beti-cel, marketed as Zynteglo™ gene therapy, for patients 12 years and older with transfusion-dependent β-thalassemia (TDT) who do not have a β0/β0 genotype, for whom hematopoietic stem cell (HSC) transplantation is appropriate, but a human leukocyte antigen (HLA)-matched related HSC donor is not available.

Non-serious adverse events (AEs) observed during clinical studies that were attributed to beti-cel included abdominal pain, thrombocytopenia, leukopenia, neutropenia, hot flush, dyspnea, pain in extremity, tachycardia and non-cardiac chest pain. One serious adverse event (SAE) of thrombocytopenia was considered possibly related to beti-cel.

Additional AEs observed in clinical studies were consistent with the known side effects of HSC collection and bone marrow ablation with busulfan, including SAEs of veno-occlusive disease.

For details, please see the Summary of Product Characteristics (SmPC).

On April 28, 2020, the EMA renewed the CMA for beti-cel. The CMA for beti-cel is valid in the 27 member states of the EU as well as the UK, Iceland, Liechtenstein and Norway. In November 2020, bluebird bio submitted to the EMA an application for renewal of the CMA; this procedure is currently on hold. The CMA is valid while the renewal application review is ongoing and while it is on hold.

The U.S. Food and Drug Administration granted beti-cel Orphan Drug status and Breakthrough Therapy designation for the treatment of TDT. Beti-cel is not approved in the U.S. Beti-cel continues to be evaluated in the ongoing Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies.

bluebird bio is conducting a long-term safety and efficacy follow-up study, LTF-303 for people who have participated in bluebird bio-sponsored clinical studies of ZYNTEGLO.

▼ This medicinal product is subject to additional monitoring

About bluebird bio, Inc.

bluebird bio is pioneering gene therapy with purpose. From our Cambridge, Mass., headquarters, we're developing gene and cell therapies for severe genetic diseases and cancer, with the goal that people facing potentially fatal conditions with limited treatment options can live their lives fully. Beyond our labs, we're working to positively disrupt the healthcare system to create access, transparency and education so that gene therapy can become available to all those who can benefit.

bluebird bio is a human company powered by human stories. We're putting our care and expertise to work across a spectrum of disorders: cerebral adrenoleukodystrophy, sickle cell disease, β-thalassemia and multiple myeloma, using gene and cell therapy technologies including gene addition, and (megaTAL-enabled) gene editing.

bluebird bio has additional nests in Seattle, Wash.; Durham, N.C.; Zug, Switzerland; Munich, Germany; Milan, Italy; Utrecht, the Netherlands; Hampshire, United Kingdom; Paris, France; and Athens, Greece.

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