bluebird bio Announces Positive Recommendation by PRAC Regarding Article 20 Safety Referral Review of ZYNTEGLO ™ Gene Therapy for Transfusion-Dependent β-thalassaemia and Marketing to Resume in EU

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) confirms favourable benefit-risk balance of ZYNTEGLO

Company has informed EMA of lift of voluntary temporary marketing suspension

ZUG, Switzerland— July 12, 2021 — bluebird bio, Inc. (Nasdaq: BLUE) today announced that the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has concluded based on the review of all available data that the benefit-risk balance of medicinal products containing ZYNTEGLO™ (betibeglogene autotemcel gene therapy) remains favourable. As of today, bluebird bio has informed the EMA that the company is lifting the voluntary suspension.

"Patient safety remains our top priority. To this end, we are grateful to the PRAC for its comprehensive review of the available evidence and positive recommendation for ZYNTEGLO," said Andrew Obenshain, president, severe genetic diseases, bluebird bio. "We are pleased to resume offering ZYNTEGLO to patients living with transfusion-dependent β-thalassaemia, offering the potential to live free from transfusions which is evidenced by our clinical studies where patients are maintaining normal or near-normal haemoglobin levels over the course of up to seven years of follow-up."

No cases of haematologic malignancy have been reported in any patient who has received treatment with ZYNTEGLO. However, because it is manufactured using the same BB305 lentiviral vector used in LentiGlobin for sickle cell disease (SCD; investigational drug product bb1111), bluebird bio decided to temporarily suspend marketing of ZYNTEGLO while the root cause of the safety events reported earlier this year for LentiGlobin for SCD were investigated by the company and assessed by the PRAC.

As previously announced on June 7, 2021, the U.S. Food and Drug Administration (FDA) lifted the clinical holds on the Phase 1/2 HGB-206 and Phase 3 HGB-210 studies of LentiGlobin for SCD following the Agency's review of the data.

The recommendation from the PRAC can be viewed here on the EMA website. As a next step, the recommendation will be forwarded to the Committee for Advanced Therapies (CAT) and Committee for Medicinal Products for Human Use (CHMP) for adoption. The final stage of the review procedure is the adoption by the European Commission (EC) of a legally binding decision applicable in all EU Member States.

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Notes to Editor

About ZYNTEGLO (betibeglogene autotemcel; beti-cel)

betibeglogene autotemcel (beti-cel) is a one-time gene therapy that adds functional copies of a modified form of the β-globin gene ($\beta^{A\text{-}T87Q}$-globin gene) into a patient's own haematopoietic (blood) stem cells (HSCs).[1,2] Once a patient has the $\beta^{A\text{-}T87Q}$-globin gene, they have the potential to produce HbA^{T87Q}, which is gene therapy-derived adult haemoglobin (Hb), at levels that may eliminate or significantly reduce the need for transfusions.[1,2] 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.[1]

beti-cel is manufactured using the BB305 lentiviral vector (LVV), a third-generation, self-inactivating LVV. The promoter, a regulatory element of the LVV that controls the expression of the transgene, selected for BB305 is a cellular (non-viral) promoter that drives gene expression only in the erythroid lineage cells (red blood cells and their precursors).

The European Commission granted conditional marketing authorization (CMA) for beti-cel, marketed as ZYNTEGLO™ gene therapy, for patients 12 years and older with TDT who do not have a β^0/β^0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate, but a human leukocyte antigen (HLA)-matched related HSC donor is not available.[3] Non-serious adverse events (AEs) observed during clinical studies that were attributed to beti-cel included abdominal pain, thrombocytopaenia, leukopaenia, neutropaenia, hot flush, dyspnea, pain in extremity, tachycardia and non-cardiac chest pain. One serious adverse event (SAE) of thrombocytopaenia was considered possibly related to beti-cel.[3]

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.[3] For details, **please see the product information, containing Summary of Product Characteristics (SmPC)**.[1]

bluebird bio is on track to complete its rolling Biologics License Application (BLA) submission to the FDA for beti-cel in mid-2021.[3] This submission is anticipated to include adult, adolescent and children with transfusion dependent β-thalassaemia across all genotypes (including non-β^0/β^0 genotypes and β^0/β^0 genotypes).[3] beti-cel is not approved in the U.S.[3]

beti-cel continues to be evaluated in the ongoing Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies.[3] 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 beti-cel.[3]

About bluebird bio, Inc.

bluebird bio, Inc. (NASDAQ: BLUE) 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 including cerebral adrenoleukodystrophy, sickle cell disease, β-

thalassaemia and multiple myeloma using three gene therapy technologies: gene addition, cell therapy and (megaTAL-enabled) gene editing.

bluebird bio has additional nests in Seattle, Wash.; Durham, N.C.; and Zug, Switzerland. For more information, visit **bluebirdbio.eu**.

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[1] Zynteglo (betibelogene autotemcel) Summary of Product Characteristics; 2020.
[2] European Medicines Agency. Zynteglo. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/zynteglo. November, 2019. Accessed July 2021.
[3] bluebird bio press release, 7 June 2021. bluebird bio Announces the Lifting of FDA Clinical Hold for Sickle Cell Disease and β-Thalassemia Studies. Available at: https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-announces-lifting-fda-clinical-hold-sickle-cell. Last accessed July 2021.