New Data from Phase 3 Studies Support Maintained Transfusion Independence* for Patients Across Genotypes Treated with betibeglogene autotemcel (LentiGlobin for β-thalassaemia) Gene Therapy

89% of evaluable patients (17/19) with transfusion-dependent β-thalassaemia who do not have a β^0/β^0 genotype achieved transfusion independence (TI) with 11.9 g/dL median weighted average total haemoglobin (Hb) level in HGB-207* [1]

Data from exploratory analyses of HGB-207 show improved markers of blood cell production and bone marrow function in patients who achieved TI[1]

85% of patients (11/13) with a β^0/β^0 genotype or IVS-I-110 mutation in Phase 3 Northstar-3 (HGB-212) study have been transfusion free for at least 7 months[2]

ZUG, Switzerland—Jun. 12, 2020— bluebird bio, GmbH. (Nasdaq: BLUE) today announced that new data from ongoing Phase 3 studies of betibeglogene autotemcel (beti-cel; formerly LentiGlobin™ for β-thalassaemia gene therapy) show paediatric, adolescent, and adult patients with a range of genotypes of transfusion-dependent β-thalassaemia (TDT) achieve and maintain TI with significantly improved Hb levels (≥10.5 g/dL). These data are being presented at the Virtual Edition of the 25th European Hematology Association (EHA25) Annual Congress.

"With more than a decade of clinical experience evaluating gene therapy in patients with TDT across a wide range of ages and genotypes, we have built the most comprehensive understanding of treatment outcomes in the field," said David Davidson, M.D., chief medical officer, bluebird bio. "Seeing the patients achieve TI and maintain that positive clinical benefit over time with robust haemoglobin levels reflects our initial vision of beti-cel. The accumulating long-term data demonstrating improvements in bone marrow histology, iron balance and red cell biology support the potential of beti-cel to correct the underlying pathophysiology of transfusion-dependent β-thalassaemia."

A total of 60 paediatric, adolescent and adult patients across genotypes of TDT have been treated with beti-cel in the Phase 1/2 Northstar (HGB-204) and HGB-205 studies, and the Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies as of March 3, 2020.[1,2,3,4]

TDT is a severe genetic disease caused by mutations in the β-globin gene that result in significantly reduced or absent adult Hb.[5,6] In order to survive, people with TDT maintain Hb levels through lifelong, chronic blood transfusions.[1,6] These transfusions carry the risk of progressive multi-organ damage due to unavoidable iron overload if not treated with chelation to remove excess iron from the body.[1,6]

"Patients with TDT do not make enough healthy red blood cells and cannot live without chronic transfusions; for patients that means a lifetime of necessary visits to a hospital or clinic and reliance on an often unreliable blood supply, which compounds the challenges of managing this disease," said presenting study author John B. Porter, MA, M.D., FRCP, FRCPath, University College London Hospital, London, UK. "These results showing patients free from transfusions and maintaining near-normal

**Transfusion independence (TI) is defined by beti-cel study protocols as not receiving a transfusion for at least 12 months and maintaining a weighted average haemoglobin (Hb) level of 9 g/dL or higher*

haemoglobin levels after treatment with beti-cel is a positive outcome for people living with TDT. In addition, we now have more data that provide further evidence that most of these patients have a measurable improvement in markers of healthy red blood cell production."

Beti-cel is a one-time gene therapy designed to address the underlying genetic cause of TDT by adding 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).[7] This means there is no need for donor HSCs from another person, as is required for allogeneic HSC transplantation (allo-HSCT).[8] Once a patient has the $\beta^{A\text{-}T87Q}$-globin gene, they have the potential to produce HbA^{T87Q}, which is gene therapy-derived Hb, at levels that may eliminate or significantly reduce the need for transfusions.[7]

Northstar-2 (HGB-207) Efficacy

As of March 3, 2020, all 23 patients in HGB-207 were treated and have been followed for a median of 19.4 (min.-max.: 12.3 – 31.4) months.[1] These patients ranged in age from four to 34 years. Only 19 patients were evaluable for TI; four additional patients do not yet have sufficient follow-up to be assessed.

89% of evaluable patients (17/19) achieved the primary endpoint of TI, with median weighted average total Hb levels of 11.9 g/dL (min.-max.: 9.4 – 12.9 g/dL).[1] These 17 patients previously required a median of 17.5 transfusions per year (min.-max.: 11.5 – 37).

Improved iron levels, as measured by serum ferritin and hepcidin levels (proteins involved in iron storage and homeostasis), were observed and trends toward improved iron management were seen. Over half of patients stopped chelation therapy, which is needed to reduce iron excess caused by chronic blood transfusions. Seven out of 23 patients began using phlebotomy for iron reduction.[1]

Improvements in dyserythropoiesis, abnormal RBC production, were observed in patients with TDT who were transfusion-free and had reached 12 months of follow-up. Patients who were transfusion-free showed improved bone marrow cellularity and M:E ratio (myeloid to erythroid), indicating an improvement in bone marrow functioning and a trend toward normalisation of soluble transferrin receptor and reticulocyte counts, markers of RBC destruction. These effects demonstrate the disease-modifying potential of beti-cel in patients with TDT.[1]

Northstar-3 (HGB-212) Efficacy

As of March 3, 2020, 15 patients (genotypes: nine β^0/β^0, three β^0/ β+IVS1-110, three homozygous IVS-1-110 mutation) were treated and had a median follow-up of 14.4 months (min.-max.: 1.1 – 24.0 months). Median age at enrolment was 15 years of age (min.-max.: 4 – 33 years).[2]

75% (six of eight) of evaluable patients achieved TI, with median weighted average total Hb levels of 11.5 g/dL (min.-max.: 9.5 – 13.5 g/dL) during TI, and continued to maintain TI for a median duration of 13.6 months (min.-max.: 12.2 – 21.2 months) as of the data cutoff.[2]

85% of patients (11/13) with at least seven months of follow-up had not received a transfusion in more than seven months at time of data cutoff. These 11 patients previously required a median of 18.5 transfusions per year (min.-max.: 11.0 – 39.5 transfusions per year). In these patients, gene therapy-derived HbA^{T87Q} supported total Hb levels ranging from 8.8–14.0 g/dL at last visit.[2]

Betibeglogene autotemcel (beti-cel) Safety
Non-serious adverse events (AEs) observed during the HGB-207 and HGB-212 trials that were considered related or possibly related to beti-cel were tachycardia, abdominal pain, pain in extremities, leukopenia, neutropenia and thrombocytopenia.[1,2] One serious AE (SAE) of prolonged thrombocytopenia was considered possibly related to beti-cel.[1] In HGB-207, SAEs post-infusion in ≥ two patients included three events of veno-occlusive liver disease and two of thrombocytopaenia.[1] In HGB-212, serious events post-infusion in ≥ two patients included two events of pyrexia.[2]

Additional AEs observed in clinical studies were consistent with the known side effects of HSC mobilisation and bone marrow ablation with busulfan, including SAEs of veno-occlusive disease.[1,2]

In both Phase 3 studies, there have been no deaths, no graft failure, no cases of vector-mediated replication competent lentivirus or clonal dominance, no leukaemia and no lymphoma.[1,2]

About betibeglogene autotemcel (beti-cel)
The European Commission granted conditional marketing authorisation (CMA) for betibeglogene autotemcel (beti-cel; formerly LentiGlobin™ gene therapy for β-thalassemia), to be marketed as ZYNTEGLO™ ▼gene therapy, for patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β^0/β^0 genotype, for whom HSC transplantation is appropriate, but a human leukocyte antigen (HLA)-matched related HSC donor is not available.[7] On April 28, 2020, the European Medicines Agency (EMA) renewed the CMA for beti-cel, supported by data from 32 patients treated with beti-cel, including three patients with up to five years of follow-up.[7]

The CMA for beti-cel is valid in the 27 member states of the EU as well as UK, Iceland, Liechtenstein and Norway. For details, please see the Summary of Product Characteristics (SmPC).[7] The U.S. Food and Drug Administration (FDA) granted beti-cel Orphan Drug status and Breakthrough Therapy designation for the treatment of TDT.

Beti-cel continues to be evaluated in the ongoing Phase 3 Northstar-2 and Northstar-3 studies. For more information about the ongoing clinical studies, visit clinicaltrials.gov and use identifier NCT02906202 for Northstar-2 (HGB-207) and NCT03207009 for Northstar-3 (HGB-212).

▼ This medicinal product is subject to additional monitoring.

About bluebird bio
bluebird bio is pioneering gene therapy with purpose. From our Cambridge, Mass., headquarters, we're developing gene 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.; Zug, Switzerland; Munich, Germany; Milan, Italy; Utrecht, the Netherlands; Hampshire, United Kingdom; and Paris, France.

For further information, visit **bluebirdbio.eu**
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