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bluebird bio Presents New Data Demonstrating Long-Term Transfusion Independence* and Safety for LentiGlobin™ Gene Therapy for β-thalassaemia across genotypes at ASH Annual Meeting[1,2,3]

Long-term results show more than four years of durable transfusion independence (TI), stable total haemoglobin (Hb) levels, and reduced iron concentrations in completed Phase 1/2 Northstar study[1]

90% (9/10) of evaluable patients achieved TI in ongoing Phase 3 Northstar-2 study with median average total Hb levels of 12.2 g/dL and improvements in markers of healthy red blood cell production[2]

100% (2/2) evaluable patients achieved TI in ongoing Phase 3 Northstar-3 study[3]

ZUG, Switzerland—Dec. 9, 2019— bluebird bio, GmbH. (Nasdaq: BLUE) announced updated long-term results from the completed Phase 1/2 Northstar (HGB-204) study and new data from ongoing Northstar-2 (HGB-207) and Northstar-3 (HGB-212) Phase 3 studies of its LentiGlobin gene therapy for patients with transfusion-dependent β-thalassaemia (TDT), at the 61st American Society of Hematology (ASH) Annual Meeting in Orlando, Florida, USA.[1,2,3]

52 paediatric, adolescent and adult patients with TDT, including those with or without a β^0/β^0 genotype or IVS-I-110 mutations, have been treated with LentiGlobin in the Northstar clinical programme.[1,2,3]

"The results from our clinical studies of LentiGlobin for β-thalassaemia support its potential benefits and consistent safety profile across a broad range of TDT genotypes and patient populations, including paediatric patients, with the longest duration of follow-up now extending beyond five years," said David Davidson, M.D., chief medical officer, bluebird bio. "Importantly, patients have achieved and maintained transfusion independence, with improvement in multiple markers of bone marrow red blood cell production, as well as reductions in iron overload. These outcomes demonstrate the long-term disease-modifying potential of LentiGlobin for people living with TDT."

TDT is a severe genetic disease caused by mutations in the β-globin gene that result in reduced or significantly reduced Hb.[4,5] In order to survive, people with TDT maintain Hb levels through life-long chronic blood transfusions.[2,5] Regular transfusions cause iron overload leading to progressive multi-organ damage if not treated with chelation to remove excess iron from the body.[2,5]

LentiGlobin was 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).[6] Once a patient has the $\beta^{A\text{-}T87Q}$-globin gene, they have the potential to produce HbA^{T87Q}, which is gene therapy-derived haemoglobin, at levels that may eliminate or significantly reduce the need for transfusions.[6]

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

Phase 1/2 Northstar (HGB-204) Efficacy
As of June 12, 2019, data from up to five years (median 44.9; min–max: 34.8–61.3 months) of follow-up from the completed Phase 1/2 Northstar study show durable TI and stable HbA^{T87Q} levels in patients across genotypes.[1]

80% (8/10) of patients who did not have a β^0/β^0 genotype, treated with LentiGlobin maintained TI for up to 51.3 months as of the data cutoff, with a median weighted average Hb during TI of 10.3 g/dL. All patients who achieved TI maintained TI.[1] Transfusion volumes were reduced by 79% and 52% in the two patients who did not achieve TI.[1]

In patients who have a β^0/β^0 genotype, 38% (3/8) maintained TI with a duration of up to 30.4 months, and a median weighted average Hb during TI of 9.9 g/dL.[1]

Liver iron content, serum ferritin, and transferrin saturation decreased over time for patients of all genotypes following TI.[1]

Phase 3 Northstar-2 (HGB-207) Efficacy
As of June 12, 2019, 21 of 23 patients were treated and have been followed for a median of 11.6 months.[2] 90% (9/10) of patients evaluable for TI had achieved it, with median weighted average haemoglobin level of 12.2 g/dL (min–max: 11.4–12.8 g/dL) during TI.[2] All nine patients continued to maintain TI for a median duration of 15.2 months (min–max: 12.1–21.3 months) as of the data cutoff.[2]

90% (18/20) of patients with at least five months of follow-up had not received a transfusion for at least 3.5 months and total Hb was near normal in most, with the median total Hb at Months 6, 12, 18, and 24 at 11.5 g/dL (n=17), 12.3 g/dL (n=11), 12.2 g/dL (n=8), 12.5 g/dL (n=3) respectively.[2] HbA^{T87Q} levels were stable over time: 8.7 g/dL at Month 6; 9.3 g/dL at Month 12, 9.4 g/dL at Month 18, and 8.8 g/dL at Month 24.[2]

Improvements in dyserythropoiesis, abnormal RBC production, were observed in patients with TDT who were transfusion-free and had reached 12 months of follow-up.[2] 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.[2] These effects demonstrate the disease-modifying potential of LentiGlobin for patients with TDT.

Northstar-3 (HGB-212) Efficacy
As of September 30, 2019, 13 patients (eight β^0/β^0, two β^0/IVS-I-110, three homozygous IVS-I-110 genotypes) treated with LentiGlobin had a median follow-up of 8.8 months (min–max: 2.5–20 months).[3]

Both evaluable patients for TI – including one paediatric patient – achieved and maintained TI with Hb levels of 13.2 g/dL and 10.4 g/dL, respectively, at last visit.[3] 82% (9/11) patients with at least six months of follow-up did not receive a transfusion for more than three months as of last follow-up, with Hb levels ranging from 8.3–14.2 g/dL at last visit.[3]

LentiGlobin for β-thalassaemia Safety
Non-serious adverse events (AEs) observed during clinical studies that were attributed to LentiGlobin for β-thalassaemia were hot flush, dysplasia, dyspnoea, abdominal pain, pain in extremities and non-cardiac chest pain.[1,2,3] One serious AE (SAE) of prolonged thrombocytopenia was considered possibly related to LentiGlobin for β-thalassemia for TDT.[2]

Additional AEs observed in clinical studies were consistent with the known side effects of haematopoietic stem cell (HSC) mobilisation/collection and bone marrow ablation with busulfan, including SAEs of veno-occlusive disease which all resolved with defibrotide.[1,2,3]

With more than five years of follow-up to date, there have been no deaths, no graft failure, and no cases of vector-mediated replication-competent lentivirus or clonal dominance.[1,2,3] In addition, there have been no new reports of veno-occlusive liver disease (VOD) as of the data cutoff presented at ASH.[1,2,3]

About LentiGlobin for β-Thalassaemia
The European Commission granted conditional marketing authorisation for LentiGlobin for β-thalassaemia, to be marketed as ZYNTEGLO™▼(autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-globin gene) gene therapy, for patients 12 years and older with 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.[6]

The conditional marketing authorisation for ZYNTEGLO is valid in the 28 member states of the EU as well as Iceland, Liechtenstein and Norway. For details, please see the Summary of Product Characteristics (SmPC).[6] The U.S. Food and Drug Administration granted LentiGlobin for β-thalassaemia Orphan Drug status and Breakthrough Therapy designation for the treatment of TDT.

LentiGlobin for β-thalassaemia 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).

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 LentiGlobin for β-thalassaemia. For more information visit clinicaltrials.gov and use identifier NCT02633943 for LTF-303.

▼ 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 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-thalassemia 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.

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