Long-Term Data for bluebird bio's Gene Therapy for β-thalassaemia Show Patients Across Ages and Genotypes Achieve Transfusion Independence and Remain Free from Transfusions Up to Six Years

Of the 10 patients enrolled in the ongoing long-term study (LTF-303) from the Phase 3 programme, 9/10 (90%) were transfusion independent (TI) and all these patients remain transfusion independent*[1]

87% (13/15) of patients younger than 18 years in Phase 3 studies achieved TI with median weighted average Hb of 11.3 (9.4 – 12.8) g/dL and remain transfusion free[2]

In long-term follow-up, 53% (9/17) of patients who achieved TI and restarted iron chelation have since stopped; 30% (7/23) who achieved TI now receive phlebotomy to reduce iron levels[1]

ZUG, Switzerland—Dec. 5, 2020— bluebird bio, GmbH. (Nasdaq: BLUE) today presented updated long-term efficacy and safety results reflecting up to six years of data for betibeglogene autotemcel gene therapy (beti-cel; formerly LentiGlobin™ for β-thalassaemia) in patients with transfusion-dependent β-thalassaemia (TDT). The company also presented results from patients <18 years of age in the Phase 3 HGB-207 (Northstar-2) and HGB-212 (Northstar-3) studies. These data were presented at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition, taking place virtually from December 5-8, 2020.

"Our vision for gene therapy for TDT is that a one-time therapy would enable life-long, stable production of functional haemoglobin at sufficient levels to allow patients with TDT to stop and remain free of blood transfusions," said David Davidson, M.D., chief medical officer, bluebird bio. "All of the patients in our Phase 3 studies who achieved transfusion independence have maintained it, with the durability of the treatment effect underscored by patients from our earlier studies reaching their five-year anniversaries of freedom from transfusions. Moreover, transfusion independence has been observed in paediatric, adolescent and adult patients and across genotypes – suggesting outcomes with this gene therapy may be consistent regardless of age or genotype."

TDT is a severe genetic disease caused by mutations in the β-globin gene that result in reduced or significantly reduced haemoglobin (Hb).[3,4] In order to survive, people with TDT require chronic blood transfusions to maintain adequate Hb levels.[4] These transfusions carry the risk of progressive multi-organ damage due to unavoidable iron overload if not treated optimally with chelation to remove excess iron from the body.[4]

Beti-cel is a one-time gene therapy designed to add 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).[5] 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 Hb, at levels that may eliminate or significantly reduce the need for transfusions.[5] In studies of this gene therapy, 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.[1,2,6,7]

**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*

As of March 3, 2020, a total of 60 paediatric, adolescent and adult patients, including 10 patients with at least five years of follow-up and one with at least six years, across genotypes of TDT have been treated with this gene therapy in the Phase 1/2 HGB-204 (Northstar) and HGB-205 studies, and the Phase 3 HGB-207 (Northstar-2) and HGB-212 (Northstar-3) studies.[1]

Long-term follow-up study LTF-303: Efficacy
After participating in and completing the two years of follow-up in either Phase 1/2 studies (HGB-204, HGB-205), or in the Phase 3 studies (HGB-207, HGB-212), patients treated with this gene therapy were invited to enroll in the 13-year long-term follow-up study, LTF-303.[1] As of March 3, 2020, 32 patients were enrolled in LTF-303 (22 treated in Phase 1/2 studies, 10 treated in Phase 3 studies) with a median post-infusion follow-up of 49.1 months (min-max: 23.3 – 71.8 months).[1]

Of the 32 patients enrolled in LTF-303, TI was achieved in 14/22 (64%) patients treated in Phase 1/2 and in 9/10 (90%) patients treated in Phase 3. All patients who achieved TI remained free from transfusions [median duration of ongoing TI is 39.4 months (min-max: 19.4 – 69.4 months)].[1]

Weighted average haemoglobin (Hb) in patients who achieved TI in the Phase 1/2 was 10.4 (min-max: 9.4 – 13.3) g/dL and 12.5 (min-max: 11.9 – 13.5) g/dL in patients who achieved TI in the Phase 3 studies.[1]

Prior to gene therapy infusion, all patients were on iron chelation, which is needed to reduce excess iron caused by chronic blood transfusions. Of the 23 patients who achieved TI following treatment with gene therapy, the majority (65%, n=15) discontinued iron chelation and 30% (7/23) were able to receive phlebotomy (blood removal), which is a preferred method for iron reduction.[1]

Long-term follow-up study LTF-303: Safety
In LTF-303, all patients were alive at last follow up and there were no graft-versus-host disease (GVHD), no cases of replication-competent lentivirus, insertional oncogenesis or clonal dominance were observed.[1] No drug-related AEs were reported >2 years post-infusion.[1] Serious AEs during LTF-303 unrelated to this gene therapy included gonadotropic insufficiency, ectopic pregnancy, gall bladder wall thickening/polyp, bacteraemia, neutropaenia and major depression (n=1 for each).[1]

Phase 3 Paediatric Patients: Efficacy
As of March 3, 2020; 24 paediatric patients (<12 years: n=13; ≥12 to <18 years: n=11) were treated and had a median follow-up of 15.5 months (min-max: 1.1 – 29.5 months) in Phase 3 studies HBG-207 (Northstar-2) and HGB-212 (Northstar-3).[2]

In these Phase 3 studies, the median age at which the children under 12 received their first transfusion was 11 months of age; for the adolescents between the ages of 12 and 18 the median was eight months of age.[2]

Following treatment with gene therapy, 87% (13/15) of evaluable patients under the age of 18 years, including four patients under age 12, achieved TI.[2] As of March 3, 2020, these patients continue to be free of transfusions for a median duration of 14.9 months (min-max: 12.2 – 21.6 months), with median weighted average total haemoglobin levels of 11.3 g/dL (min-max: 9.4 – 12.8 g/dL).[2]

Phase 3 Paediatric Patients: Safety
Drug-related AEs in paediatric patients during the HGB-207 and HGB-212 trials were non-serious and included tachycardia (Grade 1, n=1) and abdominal pain (Grade 1, n=2) on the day of infusion, and Grade 3 thrombocytopaenia in one patient post-infusion.[2] There were no deaths, no graft failures, and no cases of replication-competent lentivirus, insertional oncogenesis or clonal dominance were observed.[2]

Post-infusion non-haematologic Grade ≥3 AEs in ≥3 patients <18 years of age (N=24) included stomatitis (n=14), febrile neutropaenia (n=12), decreased appetite (n=5), epistaxis (n=4), alanine aminotransferase increase (n=3), hypoxia (n=3), and pyrexia (n=3).[2]

Betibeglogene autotemcel (beti-cel) Safety
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.

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.[5] 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.[5]

The CMA 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).[5] 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 is not approved in the United States.

▼ 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 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-thalassaemia and multiple myeloma using three gene and cell 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; Paris, France; and Athens, Greece.

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Media:
Åsa Josefsson, +41 79 679 1217
ajosefsson@bluebirdbio.com

Investors:
Ingrid Goldberg, +1 410-960-5022
igoldberg@bluebirdbio.com

Elizabeth Pingpank, +1 617-914-8736
epingpank@bluebirdbio.com

[1] Kwiatkowski J et al. Long-Term Efficacy and Safety of Betibeglogene Autotemcel Gene Therapy for the Treatment of Transfusion-Dependent β-Thalassemia: Results in Patients with up to 6 Years of Follow-up. Oral presentation (Abstract #153). 62st American Society of Hematology (ASH) Annual Meeting; 2019 Dec 5-8; Virtual Congress.
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