bluebird bio Announces European Conditional Marketing Authorisation for Zynteglo™ ▼ (autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-globin gene) Gene Therapy for Patients 12 Years and Older with Transfusion-Dependent β-Thalassaemia (TDT) Who Do Not Have a β^0/β^0 Genotype

First gene therapy authorised for a subset of people with TDT

Fastest assessment of an advanced therapy medicinal product (ATMP) as part of the European Medicines Agency's Priority Medicines (PRIME) scheme

bluebird bio's first gene therapy gains regulatory authorisation

BASINGSTOKE, UK— 03 June 2019 — bluebird bio, Inc. announced today that the European Commission (EC) has granted conditional marketing authorisation for Zynteglo™ (autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-globin gene), a 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 haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available. Payer agencies will now begin the country-by-country reimbursement process to help support access to the therapy for appropriate patients.

TDT is a severe genetic condition caused by mutations in the β-globin gene that result in reduced or absent haemoglobin. In order to survive, people with TDT maintain haemoglobin levels through life-long chronic blood transfusions. These transfusions carry the risk of progressive multi-organ damage due to unavoidable iron overload. This one-time gene therapy addresses the underlying genetic cause of TDT and offers patients 12 years and older who do not have a β^0/β^0 genotype the potential to become transfusion independent, which is expected to be life-long once achieved.

The conditional marketing authorisation is supported by efficacy, safety and durability data from the completed Phase 1/2 HGB-205 study and Phase 1/2 Northstar (HGB-204) study as well as available data from the ongoing Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) studies, and the long-term follow-up study LTF-303, as of the data cut-off of 13 December 2018.

- Data from Phase 1/2 HGB-205 showed that 75 percent (n=3/4) of patients without a β^0/β^0 genotype achieved transfusion independence, defined as a weighted average Hb ≥9 g/dL without any RBC transfusions for a continuous period of ≥12 months at any time during the study after infusion.
- In the Phase 1/2 Northstar study, 80 percent (n=8/10) of patients without a β^0/β^0 genotype achieved transfusion independence. These 11 patients (three from HGB-205 and eight from Northstar) continued to maintain transfusion independence for a duration of 21 – 56 months.
- Five patients in the Northstar-2 phase 3 study were evaluable for transfusion independence at the most recent data-cut. Of these five, 80 percent (n=4/5) achieved transfusion independence.
- Non-serious adverse events (AEs) observed during clinical trials that were attributed to this therapy were hot flush, dyspnoea, abdominal pain, pain in extremities and non-cardiac chest pain. One serious adverse event (SAE) of thrombocytopenia was considered possibly related. 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.

The treatment continues to be evaluated in the ongoing Phase 3 Northstar-2 and Northstar-3 studies and the long-term follow-up study LTF-303.

“I’m delighted with today’s news for us as an organisation, but most importantly for families living with this condition. The conditional authorisation is an important milestone as it brings a new treatment option, in the form of the first one-time gene therapy for a subset of people with TDT, one step closer. Our priority now is to ensure reimbursement as quickly as possible by continuing to work together with the patient community, clinicians and NICE, NHS England and stakeholders in the devolved nations, to enable access to this treatment across the UK,” commented Nicola Redfern, General Manager, bluebird bio UK.

In addition to Priority Medicines (PRIME) designation, this therapy received an Orphan Medicinal Product designation from the EC for the treatment of β-thalassaemia intermedia and major, which includes TDT. The evaluation took place via the European Medicines Agency’s (EMA) Priority Medicines (PRIME) and Adaptive Pathways programmes, which support medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. The PRIME and Adaptive Pathway programmes allowed for early and enhanced dialogue and accelerated assessment, which was completed on the shortest timetable for an advanced therapy medicinal product (ATMP) by the EMA to date.

“Using an autologous transplantation approach, this treatment offers clinicians the first gene therapy to tackle the underlying genetic cause in a subset of people with transfusion-dependent β-thalassaemia. It potentially eliminates or reduces the need for red blood cell (RBC) transfusions, using the patient’s own haematopoietic stem cells (HSCs),” said Professor John Porter, Professor of Haematology and Consultant Haematologist at the University College London Hospitals in London, UK and head of the joint Red Cell Unit for UCLH and Whittington Hospitals. “This is a significant development, since previously the only way to address the genetic cause was through an allogeneic haematopoietic stem cell transplant, which is restricted by donor availability, carries serious risks particularly in adults, and is only available to paediatric patients in the UK. As a result, most patients currently require lifelong red blood cell transfusions and iron chelation therapy to manage iron overload.”

The conditional marketing authorisation is valid in all 28-member states of the EU, as well as Iceland, Liechtenstein and Norway.

How the treatment works

The treatment 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). This means there is no need for donor HSCs from another person as is required for allogeneic HSC transplantation (allo-HSCT). A patient’s HSCs are removed from the body through a process called apheresis. These HSCs are taken to a lab where a lentiviral vector is used to insert the $\beta^{A\text{-}T87Q}$-globin gene into the patient’s HSCs. This step is called transduction. Before their modified HSCs are returned through infusion, a patient receives chemotherapy to prepare their bone marrow for the modified HSCs that now carry the $\beta^{A\text{-}T87Q}$-globin gene. 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 significantly reduce or eliminate the need for transfusions. Upon engraftment and achievement of transfusion independence, effects of the treatment are expected to be life-long.

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 by researching cerebral adrenoleukodystrophy, sickle cell disease, transfusion-dependent 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. Our European headquarters are in Zug, Switzerland, and we have offices in France, Germany, Italy, the UK and the Netherlands.

Zynteglo and LentiGlobin are trademarks of bluebird bio.

The full common name for Zynteglo: A genetically modified autologous CD34+ cell enriched population that contains haematopoietic stem cells transduced with lentiviral vector encoding the $\beta^{A\text{-}T87Q}$-globin gene.

Forward-Looking Statements
This release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding the Company's plans and expectations for the commercialisation for Zynteglo™ (autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-globin gene, formerly LentiGlobin™ in TDT) to treat TDT, and the potential implications of clinical data for patients. Any forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to: the risk that the efficacy and safety results from our prior and ongoing clinical trials of Zynteglo will not continue or be repeated in our ongoing or planned clinical trials of Zynteglo; the risk that the current or planned clinical trials of Zynteglo will be insufficient to support regulatory submissions or marketing authorisation in the US, or for additional patient populations in the EU; the risk that the production of HbA^{T87Q} may not be sustained over extended periods of time; and the risk that we may not secure adequate pricing or reimbursement to support continued development or commercialisation of Zynteglo following regulatory authorisation. For a discussion of other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our most recent Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the Securities and Exchange Commission. All information in this press release is as of the date of the release, and bluebird bio undertakes no duty to update this information unless required by law.

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