Product: ZYNTEGLO

Proper Name: Betibeglogene autotemcel

Manufacturer: bluebird bio (Netherlands) B.V.

Indication: Zynteglo is indicated for the treatment of patients 12 years and older with transfusion-dependent β-thalassemia (TDT) who do not have a β0/β0 genotype, for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.

Description: Zynteglo is an autologous, advanced therapy medicinal product (ATMP) suitable for infusion and conveys functional copies of the βA-T87Q-globin gene in HSCs to myeloablated patients who have TDT.

EMA Regulatory Milestone:

The applicant bluebird bio (Netherlands) B.V. submitted on 21 August 2018 an application for marketing authorization to the European Medicines Agency (EMA) for Zynteglo, through the centralized procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No. 726/2004. Zynteglo was designated as an orphan medicinal product EU/3/12/1091 on 24 January 2013 in the following condition: treatment of ß-thalassemia intermedia and major. Following the CHMP positive opinion on this marketing authorization, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Zynteglo as an orphan medicinal product in the approved indication. Zynteglo was granted eligibility to PRIME on 15 September 2016 in the following indication: treatment of transfusion-dependent ß-thalassemia.

EMA approval date: May 29, 2019

Package Insert: Zynteglo: EPAR - Product information

European Public Assessment Report: Zynteglo: EPAR - Public assessment report

Manufacturing Platform:

PARAMETER	DATA	REFERENCE
Manufacturer	Bluebird bio (Netherlands) B.V.	
Transgene	βA-T87Q-globin gene	1
Indication	Zynteglo is indicated for the treatment of patients 12 years and older with transfusion-dependent β-thalassemia (TDT) who do not have a β0/β0 genotype, for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.	3
Virus & Serotype	Lentiviral vector (LVV)	2
Cell Substrate	Hematopoietic stem cells (HSCs)	3
Manufacturing platform	**Lentiviral vector**: BB305 LVV is produced by transient transfection. BB305 LVV buds from the production cells, is harvested, purified via chromatography, and formulated prior to frozen storage. The LVV manufacturing process begins with thawing HEK293T cells from the working cell bank (WCB). These cells are transfected with plasmid BB305 and packaging plasmids and incubated at a specified temperature and duration. Subsequently, the supernatants containing the LVV are collected. This crude harvest is clarified by filtration, purified by chromatography, concentrated and formulated. The sterile filtered BB305 LVV is filled in vials. **Transduced autologous cells:** The manufacturing process starts from the starting material, the hematopoietic progenitor cells obtained by apheresis	3

	(HPC-A) and follows a continuous process up to formulation and filling of the FP. HPC-A is subject to a platelet wash and CD34+ cell enrichment. The purpose of the CD34+ cell enrichment step is to separate CD34+ cells from other cells. After enrichment, a pre-transduction stimulation is performed. The purpose of the Pre-Transduction Stimulation Culture process step is to make cells receptive to transduction. The cells are then transduced with BB305 LVV. Cells are then washed and re-suspended. These washed cells constitute the active substance. The process is continuous until formulation of the FP.	
Dose in vial/final container	1.2-20 × 10^6 cells/mL dispersion for infusion	1
Dose / patient	Dose: {N.N} × 10^6 CD34+ cells/kg The minimum recommended dose of Zynteglo is 5.0 × 10^6 CD34+ cells/kg. In clinical studies doses up to 20 × 10^6 CD34+ cells/kg have been administered.	1

1. Package insert: Zynteglo: Product information
2. EPAR full: Zynteglo
3. EPAR quality: Zynteglo: EPAR - Public assessment report

Advisory Committee: -

Clinical Trials:

NCT	TRIAL PHASE	SUBJECTS ENROLLED	STUDY TITLE	COUNTRIES
NCT02151526	1, 2	7	A study evaluating the safety and efficacy of lentiglobin BB305 drug product in β-Thalassemia major (also referred to as Transfusion-dependent β-Thalassemia [TDT]) and Sickle Cell Disease	France
NCT01745120	1, 2	19	A study evaluating the safety and efficacy of the LentiGlobin BB305	United States, Australia, Thailand

			drug product in β-Thalassemia major participants	
NCT02906202	3	23	A study evaluating the efficacy and safety of the LentiGlobin® BB305 drug product in subjects with transfusion-dependent β-Thalassemia, who do not have a β0/β0 genotype	United States, France, Germany, Italy, Thailand, United Kingdom
NCT03207009	3	18	A study evaluating the efficacy and safety of the LentiGlobin® BB305 drug product in subjects with transfusion-dependent β-thalassemia	United States, France, Germany, Greece, Italy, United Kingdom
NCT02633943	-	94	Long-term follow-up of subjects with hemoglobinopathies treated with ex vivo gene therapy	United States, Australia, France, Thailand, Italy, Germany, United Kingdom

EudraCT Numbers:

EUDRACT NUMBER	TRIAL PHASE	SUBJECTS ENROLLED	STUDY TITLE	COUNTRIES
2012-000695-42	1, 2	7	A phase I/II open label study evaluating the safety and efficacy of gene therapy of the β-hemoglobinopathies (sickle cell disease and β-thalassemia major) by transplantation of autologous CD34+ stem cells transduced ex vivo with a lentiviral β-A-T87Q-globin vector (LentiGlobin® BB305 drug product)	France
2015-004122-33	3	23	A phase 3 single arm study evaluating the efficacy and safety of gene therapy in subjects with transfusion-dependent β-thalassemia, who do not have β0/β0 genotype, by transplantation of autologous CD34+ stem cells transduced ex vivo with a lentiviral βA-T87Q-globin vector in subjects ≥12 and ≤50 years of age	France, Italy, Greece, United Kingdom, Thailand, Germany, United States

2016-003611-35	3	15	A phase 3 single arm study evaluating the efficacy and safety of gene therapy in subjects with transfusion-dependent β-thalassemia, who have a β0/β0 genotype, by transplantation of autologous cd34+ stem cells transduced ex vivo with a lentiviral βA-T87Q-globin vector in subjects ≥12 and ≤50 years of age	France, Greece, Italy, Germany, United States, United Kingdom
2013-002245-11		108	Long-term follow-up of subjects with hemoglobinopathies treated with ex vivo gene therapy using autologous hematopoietic stem cells transduced with a lentiviral vector	Australia, Greece, France, Germany, Italy, Thailand, United States, United Kingdom

Publications:

- Schuessler-Lenz, M., Enzmann, H., & Vamvakas, S. (2020). Regulators' Advice Can Make a Difference: European Medicines Agency Approval of Zynteglo for Beta Thalassemia. Clinical pharmacology and therapeutics, 107(3), 492–494. https://doi.org/10.1002/cpt.1639