29 May 2019
EMA/263767/2019
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Zynteglo (Autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human *beta* $^{A\text{-}T87Q}$*-globin* gene)
Treatment of beta-thalassaemia intermedia and major
EU/3/12/1091 (EMA/OD/146/12)
Sponsor: bluebird bio (Netherlands) B.V

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact Telephone +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Product and administrative information

Product	
Active substance	Autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human *beta$^{A\text{-}T87Q}$-globin* gene
International Non-Proprietary Name	Autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-globin gene
Orphan condition	Treatment of beta-thalassaemia intermedia and major
Pharmaceutical form	Dispersion for infusion
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	B
Sponsor's details:	bluebird bio (Netherlands) B.V. Stadsplateau 7 WTC Utrecht 3521AZ Utrecht The Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	bluebird bio France
COMP opinion date	06/12/2012
EC decision date	24/01/2013
EC registration number	EU/3/12/1091
Post-designation procedural history	
Transfer of sponsorship	Transfer from bluebird bio France to bluebird bio (Germany) GmbH – EC decision of 25 July 2018 Transfer from bluebird bio (Germany) GmbH to bluebird bio (Netherlands) B.V. – EC decision of 21 February 2019
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	J. H. Ovelgonne/ V. Closson Carella
Applicant	bluebird bio (Netherlands) B.V.
Application submission date	21 August 2018
Procedure start date	04 October 2018
Procedure number	EMA/H/C/003691
Invented name	Zynteglo
Therapeutic indication	Treatment of 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. Further information on Zynteglo can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/zynteglo
CHMP opinion date	28 March 2019

CHMP revision opinion date	26 April 2019
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	I. Barisic / F. Méndez Hermida
Sponsor's report submission date	14 September 2018
COMP discussion	19-21 March 2019
COMP opinion date	1 April 2019

2. Grounds for the COMP opinion (at the designation stage)

2.1. Orphan medicinal product designation

The COMP opinion on the orphan medicinal product designation was based on the following grounds:

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- for the purpose of orphan designation, the COMP considered that the condition should be renamed as "treatment of beta-thalassaemia intermedia and major";
- the intention to treat the condition was supported by preclinical results in a model of beta-thalassaemia intermedia where treatment with the product improved haemoglobin concentration, haematocrit level, red blood cell counts and reticulocyte percentage;
- beta-thalassaemia intermedia and major (hereinafter referred to as "the condition") was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made. The sponsor performed an extensive literature search and calculated the prevalence using a valid methodology;
- the condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these. beta thalassaemia major causes a hypochromic, microcytic anaemia developing in in the first year of life. Without transfusions, ~85% of patients die by five years of age. Bone marrow expansion due to severe ineffective erythropoiesis results in characteristic deformities of the skull and face, and painful periarticular syndrome with microfractures and osteomalacia. Progressive hepatic, cardiac and endocrine disturbances develop, due to the accumulation of iron from transfusion and its deposition in the tissues. Without chelation therapy, iron overload results in death in the second or third decade, usually from cardiac failure;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human *beta$^{A\text{-}T87Q}$-globin* gene may be of significant benefit to those affected by the condition. This appeared justified by the mechanism of action of the product as a gene therapy product, offering the potential of being curative, differently from the currently authorized products which only target the manifestations of the disease, namely iron overload. The significant benefit is supported by preclinical data showing improvement of haemoglobin concentration, haematocrit level, red blood cell counts and reticulocyte percentage. In addition the benefit is supported by one clinical case where transfusion independence and stable haemoglobin levels where obtained 5 years post treatment with the proposed product.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The designated condition is 'beta-thalassaemia intermedia and major'.

The agreed therapeutic indication in the marketing authorisation is 'Zynteglo is indicated for the treatment of 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'. This indication falls within the scope of the designated orphan condition 'beta-thalassaemia intermedia and major'. TDT is defined in clinical trials supporting this application as a history of transfusions of at least 100 mL/kg/year of packed red blood cells (pRBCs) or with ≥8 transfusions of pRBCs per year in the 2 years preceding enrolment. Patients with TDT include those with β-thalassaemia major; and whilst transfusions are usually less frequent in patients with β -thalassaemia intermedia than those with β-thalassaemia major, some patients with β -thalassaemia intermedia may also meet these criteria for TDT and thus this is still within the designated orphan condition.

Patients with the minor form (which is excluded from the designation) are not transfusion-dependent and as such, are not considered part of the therapeutic indication.

Intention to diagnose, prevent or treat

Zynteglo is a gene therapy medicinal product. The active substance of Zynteglo is an autologous CD34+ cell-enriched population that contains haematopoietic stem cells (HSC) transduced with lentiviral vector encoding the $\beta^{A\,T87Q}$-globin gene. The lentiviral vector (LVV) is a replication-defective, self-inactivating, third-generation, human immunodeficiency virus type-1-based LVV pseudotyped with vesicular stomatitis virus glycoprotein G (VSV-G) envelope protein, carrying the human β-globin gene with a single modification at codon 87 under the transcriptional control of the erythroid-specific human β-globin promoter and erythroid-specific enhancer elements (DNase I hypersensitive sites HS2, HS3, and HS4) of the human β-globin locus control region. The mechanism of action of the product is based on engraftment in the bone marrow of the transduced CD34+ haematopoietic stem cells, followed by their differentiation to produce red blood cells containing biologically active $\beta^{A\text{-}T87Q}$-globin that will combine with α-globin to produce functional haemoglobin (HbA^{T87Q}).

Based on the CHMP assessment, the intention to treat the condition has been justified.

The clinical studies supporting the marketing authorisation (MA) of Zynteglo consisted of two early Phase 1/2 studies (HGB-204 and HGB-205), two confirmatory Phase 3 studies (HGB-207 and HGB-212), and a long-term follow-up study (LTF-303) for all patients treated in the parent studies. Studies HGB-205, HGB-207, HGB-212 and LTF-303 were ongoing at the time of MAA submission and so only interim data contributed to the assessment of efficacy and safety for the marketing authorisation, as well as to the discussion on significant benefit for the purpose of the maintenance of orphan designation. As of December 2018, a total of 38 patients with transfusion-dependent β-thalassaemia

(TDT) with non-β^0/β^0 genotype (the therapeutic indication) were treated, of which 32 were ≥12 years of age.

Chronically debilitating and/or life-threatening nature

There have been no changes in the seriousness of the condition since orphan designation. The condition remains life-threatening and chronically debilitating due to the severe anaemia, the need for regular blood transfusions, and the complications related to these such as iron overload, which requires chelation therapy to manage. Beta-thalassaemia major causes hypochromic, microcytic anaemia developing in the first year of life. Without transfusions, ~85% of patients die by five years of age. Bone marrow expansion due to severe ineffective erythropoiesis results in characteristic deformities of the skull and face, and painful periarticular syndrome with microfractures and osteomalacia. Progressive hepatic, cardiac and endocrine disturbances develop, due to the accumulation of iron from transfusion and its deposition in the tissues. Without chelation therapy, iron overload results in significant organ damage and in death in the second or third decade, usually from cardiac failure.

Number of people affected or at risk

The prevalence estimate was based on published literature. For a number of European member states, the most complete data on β -thalassaemia intermedia and major from the literature are those reported by Modell et al. in 2007 in an article that reported the incidence of the condition across all European countries. For some countries, more recent publications were available and have been used for the prevalence calculations. The most reliable sources of country-specific registry data were considered to be a study reporting on an analysis of the French National Registry for Thalassaemia, already mentioned in the initial orphan designation, which found the cumulative incidence of thalassaemia major to be 0.89 per 100,000 for all live births between 1991 and 2005 (Thuret et al., 2010). Since the orphan designation, the broadest study identified by a wide search was a retrospective cohort study based on Intercontinental Marketing Statistics (IMS) Health hospital and treatment centre audit data, which found 5,748 total prevalent cases of thalassaemia after surveying approximately 660 hospitals in Italy (Angelucci et al., 2016). In addition the sponsor reviewed data from international registries including: the Center for International Blood and Marrow Transplant Research (CIBMTR) registry, the Thalassaemia Longitudinal Cohort (TLC) Study, the European Society for Blood and Marrow Transplantation (EBMT) Registry, the Myocardial Iron Overload in Thalassaemia (MIOT) Study, and the Italian Multiregional Thalassaemia Registry (HTA-Thal). However, most pan-EU Registries include only a limited number of patients with β-thalassaemia intermedia or major, for instance only those eligible for allo-HSCT. Therefore, the sponsor also reviewed country-specific Registries and hospital-based medical encounters to support prevalence. Based on these sources, the prevalence resulting from the sponsor's calculation is 0.79 in 10,000, which is not significantly different from the time of orphan designation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Since the indication of Zynteglo is for the treatment of transfusion-dependent β -thalassaemia (TDT), only the existing methods of treatment for this form of thalassaemia are reported here.

The mainstay of the treatment of TDT in Europe is the one recommended by the 2014 clinical guidelines of the Thalassaemia International Federation (Cappellini et al, 2014). According to the guidelines, standard medical care for patients with TDT is to receive regular red blood cell (RBC) transfusions coupled with an iron chelation regimen. Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is the only potentially curative option for patients with TDT, and it is generally reserved for paediatric patients with a human leukocyte antigen (HLA)-matched related donor.

Lifelong red blood cell (RBC) transfusions are the current standard of care for patients with TDT, usually every 2 to 5 weeks. The goal is to maintain pre-transfusion haemoglobin (Hb) at levels that are considered sufficient for normal growth, physical activity, and to adequately suppress ineffective erythropoiesis in most patients. For most patients, this is a Hb level between 9 to 10.5 g/dL. Transfusions temporarily relieve symptoms of anaemia, but they do not address the underlying causes of the disease. Between transfusions, patients may experience various symptoms of anaemia, and risks associated to chronic RBC transfusions include infections transmitted through the blood product, alloimmunisation, reactions to mismatched blood components, and adverse transfusion reactions. One important consequence of long-term transfusion regimens is also the need of iron chelation therapy.

Chelation therapy is usually started when the patient has received ≥10 transfusions or when serum ferritin is >1000 ng/mL. Three iron chelation agents are currently approved in the EU: desferrioxamine mesylate also known as desferoxamine (Desferal, subcutaneous infusion), deferiprone (Ferriprox, oral solution and film-coated tablets), and deferasirox (Exjade, oral dispersible tablets, film-coated tablets, or granules). Despite iron chelation therapy, 10 to 50% of patients with TDT remain significantly iron overloaded, with iron deposits in different organs leading to increased risk of liver disease, heart failure, diabetes mellitus, osteoarthritis, osteoporosis, metabolic syndrome, hypothyroidism, hypogonadism, as well as potentially accelerating neurodegenerative diseases.

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is the only available potentially curative treatment option for TDT, leading to transfusion independence and thalassaemia-free survival for the large majority of patients who have successful engraftment. Allo-HSCT is associated with significant risks and in a number of cases does not result in transfusion independence, especially in older patients or those with an unmatched donor. In a recent study, the overall survival at 2 years after allo-HSCT in TDT was only 88% and thalassaemia-free survival at 2 years was only 81% (Baronciani et al., 2016). Allo-HSCT is also associated with serious risks of transplant-related mortality, graft failure, and immunological complications such as GVHD. As allo-HSCT is generally only recommended for paediatric patients with a matched donor, this limits its applications.

Significant benefit

The significant benefit of Zynteglo at the time of orphan designation was assumed based on the potential clinically relevant advantage derived from the fact that being a gene therapy, its benefit are expected to be life-long and to eliminate or significantly reduce the need of regular red blood cell transfusions, which constitute a burden for patients and the health care system and are linked to the long-term consequences of iron accumulation. These grounds were discussed during a protocol assistance procedure and it was agreed by the COMP that positive preliminary data from the pivotal trial (see below), showing acceptable levels of haemoglobin (Hb) as well as reduction of the need of chelation therapy would be considered sufficient for demonstration of significant benefit.

RBC transfusion requirements or transfusion independence was the primary efficacy endpoint of the treatment studies performed so far by the applicant (two Phase 1/2 studies [HGB-204 and HGB-205] and two Phase 3 studies [HGB-207 and HGB-212]), apart from the second Phase 1/2 study (HGB-204, completed in February 2018), which was aimed at measuring Hb production for 6 months after

treatment. Data on Hb levels were also collected systematically in the other studies at several time-points, as a secondary endpoint. Patients who do not have a β^0/β^0 genotype were included in all 4 of these treatment studies, which included patients with a non-β^0/β^0 genotype containing the IVS-I-110 mutation in Study HGB-205 as well as Study HGB-212, which is a more recently initiated study.

Below is a table with the clinical studies performed by the applicant (source: CHMP report)

Table 1. **Overview of Clinical Studies Evaluating the Drug Product in Subjects with TDT**

Study Identifier (Status); Location of CSR or Protocol (as applicable)	**Study Title**	**Number of Subjects with TDT[1] and Genotype**	**Drug Product Characteristics and Recommended Cell Dose**	**Recommended Busulfan Average Daily AUC**	**Primary Efficacy Endpoint(s) from Study Protocol**	**Data Cut Dates**
HGB-205 (ongoing) Module 5.3.5.2 Interim CSR HGB-205 (subjects with TDT only[2])	A Phase 1/2 Open Label Study Evaluating the Safety and Efficacy of Gene Therapy of the β-Hemoglobinopathies (Sickle Cell Anemia and β-Thalassemia Major) by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral β^{A-T87Q}-globin Globin Vector (LentiGlobin BB305 Drug Product)	7 planned (TDT or SCD[2]) 4 TDT treated 4 TDT completed (all non-β^0/β^0)	Original manufacturing process ≥3.0 × 10^6 CD34+ cells/kg	4000 to 5200 μM*min[3]	RBC transfusion requirements (measured in milliliters [mL] per kilogram [kg]) per month and per year post-transplant. Number of total in-patient hospitalization days (post-transplant discharge) at 6, 12, and 24 months.	Interim CSR Data Cut: 11 Oct 2017 Module 2.7.2/2.7.3 Data Cut: 07 Mar 2018 Additional Data Cut: 13 Dec 2018
HGB-204 (completed: 21 February 2018) Module 5.3.5.2 CSR HGB-204	A Phase 1/2 Open Label Study Evaluating the Safety and Efficacy of Gene Therapy in Subjects with 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)	18 planned 18 treated 18 completed (10 non-β^0/β^0; 8 β^0/β^0) 1 discontinued before conditioning	Base manufacturing process ≥3.0 × 10^6 CD34+ cells/kg	3600 to 5000 μM*min[3]	The sustained production of ≥2.0 g/dL of haemoglobin A (HbA) containing β^{A-T87Q}-globin for the 6 months between Month 18 and Month 24 post-transplant.	CSR Data Lock Point: 07 Mar 2018 Module 2.7.2/2.7.3 Data Cut: 07 Mar 2018 Additional Data Cut: 13 Dec 2018
HGB-207 (ongoing) Module 5.3.5.2 Interim CSR HGB-207	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 the β^0/β^0 Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral β^{A-T87Q}-Globin Vector in Subjects ≤50 Years of Age	23 planned (15 for ≥12 and ≤50 years of age; 8 for <12 years of age) 15 treated 0 completed 1 discontinued before conditioning	Refined or commercial manufacturing process ≥5.0 × 10^6 CD34+ cells/kg	3800 to 4500 μM*min[4]	The proportion of subjects who meet the definition of "transfusion independence" (TI). TI is 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 drug product infusion. (Calculation of time period of TI will start when subjects achieve an Hb ≥9 g/dL with no transfusions in the preceding 60 days).	Interim CSR Data Cut: 22 Feb 2018 Module 2.7.2/2.7.3 Data Cut: 22 Feb 2018 Additional Module 2.7.2/2.7.3 Late-Breaking Data Cut: 15 May 2018 Additional Data Cut: 13 Dec 2018
HGB-212 (ongoing) Module 5.3.5.2 Protocol HGB-212	A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent β-Thalassemia, who have a β^0/β^0 Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral β^{A-T87Q}-Globin Vector in Subjects ≤50 Years of Age	15 planned (5 for ≥18 and ≤50 years of age; 10 for <18 years of age) 5 treated 0 completed	Refined or commercial manufacturing process ≥5.0 × 10^6 CD34+ cells/kg	3800 to 4500 μM*min[4]	The proportion of subjects who meet the definition of "transfusion reduction" (TR), defined as demonstration of a ≥60% reduction in volume of packed red blood cell (pRBC) transfusion requirements (in mL/kg) in the post-treatment time period of Months 12 to 24, compared to the average annual transfusion requirements in the 24 months prior to study enrollment	CSR Data Cut: NA Module 2.7.2/2.7.3 Data Cut: 07 Mar 2018 Additional Data Cut: 13 Dec 2018

Table 1. **Overview of Clinical Studies Evaluating the Drug Product in Subjects with TDT**

Study Identifier (Status); Location of CSR or Protocol (as applicable)	Study Title	Number of Subjects with TDT[1] and Genotype	Drug Product Characteristics and Recommended Cell Dose	Recommended Busulfan Average Daily AUC	Primary Efficacy Endpoint(s) from Study Protocol	Data Cut Dates
LTF-303 (ongoing) Module 5.3.5.2 Interim CSR LTF-303 (subjects with TDT only[5])	A Longterm Follow-up of Subjects with Hemoglobinopathies Treated with Ex Vivo Gene Therapy Using Autologous Hematopoietic Stem Cells Transduced with Lentiviral Vector	Long-term follow-up for all subjects with a haemoglobinopathy who received drug product during bluebird bio-sponsored studies[5] 22 treated subjects with TDT enrolled (18 from Study HGB-204; 4 from Study HGB-205)	Not applicable	Not applicable	For subjects with TDT, assessments include, but are not limited to interval transfusions required (pRBC mL/kg), haemoglobin levels, therapeutic phlebotomies, iron chelator use, and measures of iron overload.	CSR Data Cut: 21 Nov 2017 Module 2.7.2/2.7.3 Data Cut: 07 Mar 2018 Additional Data Cut: 13 Dec 2018

[1] Number of subjects as of 13 December 2018
[2] Note: subjects with SCD (N=3 treated) were not included in the efficacy analysis for this module or in the interim CSR HGB 205. A final CSR for HGB-205 with data from all subjects will be written after completion of the study.
[3] Changed from 3200 to 4400 µM*min in Protocol HGB-205 Version 7.0 (19 May 2016) and in Protocol HGB-204 Version 3.1 (17 March 2014).
[4] Changed from 4000 to 5000 µM*min in Protocol HGB-207 Version 3.0 (19 June 2018) and in Protocol HGB-212 Version 2.0 (19 June 2018).
[5] Note: subjects with SCD were not included in the efficacy analysis for this module or the interim CSR LTF-303. A final CSR for LTF-303 with data from all subjects will be written after completion of the study

Study HGB-207

The pivotal (Phase 3 study) is Study HGB-207, a single-arm study that is still ongoing. The study is designed to evaluate efficacy and safety of Zynteglo in patients ≤50 years of age with transfusion-dependent β -thalassaemia (TDT) who do not have the β^0/β^0 genotype. The study has a complex design comprising 4 main stages. Firstly, patients are screened to ensure eligibility for treatment. Secondly, each patient undergoes haematopoietic stem cells (HSC) mobilisation with granulocyte colony-stimulating factor and plerixafor, followed by CD34+ cell collection via apheresis. Each patient then undergoes myeloablative conditioning (4 days of conditioning with busulfan, followed by at least 48 hours of washout) before infusion of Zynteglo (Day 1). For this study, patients with TDT must have a history of at least 100 mL/kg/year of pRBCs or be managed under standard thalassemia guidelines with ≥8 transfusions of pRBCs per year in the 2 years preceding enrolment. The treatment effects of Zynteglo are to be compared with historical data of the same patients relating to the two years before the study so that each patient may serve as his/her own control.

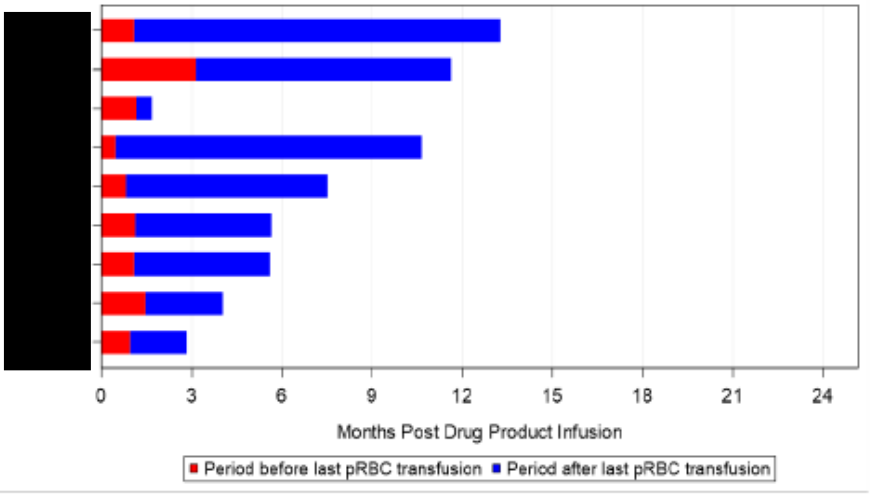
The primary endpoint of this study is the proportion of patients who meet the definition of transfusion independence (TI), with TI defined as a weighted average Hb ≥9 g/dL without any RBC transfusions for a continuous period of ≥12 months at any time during the study after drug product infusion, starting 60 days after last RBC transfusion.

As of February 2018, 10 non-β^0/β^0 patients (6 adults and 4 adolescents) of the 23 planned have been treated, with median follow up of 5.59 months (range 0.8-13.2 mo). The age of start of iron chelation was between 2 and 16 years old and the liver iron content by MRI has a wide range, indicating a patient population with heterogeneous liver iron accumulation, from mild to moderate. Based on the two-year retrospective history, the number of transfusions was approximately 1 to 2 times per month. The weighted average median nadir Hb level preceding transfusion was 9.63 g/dL with a range of 7.5-10.2 g/dL.

The primary endpoint of TI has not yet been formally analysed versus the historical data of the two years before the study because no patient has sufficient follow-up as of February 2018; the 10 treated patients had been followed for 0.8 to 13.2 months, and time since last transfusion for the 9 patients with available data ranged from 0.53 to 12.19 months (Figure 1). The sponsor presented data from logistic regression models to predict the probability of achieving TI at any time and at Month 24 based

on HbA^{T87Q} levels at Month 6; these models predict that 5 out of 6 patients with Month 6 HbA^{T87Q} data have an approximately 99% or higher probability of achieving TI at any time or at Month 24.

Figure 1 Duration of Transfusion Periods by Subject (TP) (from HGB-207 Interim Study Report)



Source: Figure 14.2.4
Note: Subject [redacted] had a last scheduled visit on Day +8 (Listing 16.2.1.1), and did not have any recorded pRBC transfusions after drug product infusion as of the data lock point, and is therefore not included in the figure.

Due to the limited follow-up time, the majority of secondary endpoints could not be analysed as of February 2018. Using data from the period between hospital discharge and last study visit, the sponsor showed that the 6 patients who completed their Month 6 Visit had not received a pRBC transfusion from before approximately Month 3. Total Hb stabilised at approximately 2 months after last transfusion in patients who have been followed for at least that length of time, and 7/8 patients who had data available after hospital discharge had 100% reduction in annualized transfusion volume as compared to their pre-enrolment data and all patients with 100% reduction in annualised transfusion volume have a weighted average nadir Hb of≥11.1 g/dL, which is greater than the pre-enrolment values.

Study HGB-205

Study HGB-205 was a Phase 1/2 study designed to evaluate patients with either TDT or sickle cell disease; 4 of the 7 patients in the study had TDT and a non-β^0/β^0 genotype. As shown in Table 3 below, 3 out of 4 patients with TDT in the study achieved transfusion independence.

Table 3: Results of Study HGB-205 (from CHMP assessment report)

	Subjects who Achieved TI			Subject who did not achieve TI
Parameter	[redacted]			
Achieved TI	Y	Y	Y	N
Reduction from baseline in pRBC transfusions between M6 to M24	100%	100%	100%	100%
Weighted average Hb (g/dL)	10.6 (during TI)	13.1 (during TI)	11.3 (during TI)	8.5 (during 6 months after DPI through end of study)
Decrease in Liver Iron Content (LIC) (Baseline vs M24)	Y	Y	Y	N
Myocardial T2*>20ms throughout study	Y	Y	Y	Y
Decrease in ferritin (Baseline vs M24)	Y	Y	N	Y
Stopped iron chelation/started phlebotomy	N	Y	Y	N

Time from drug product infusion to last pRBC transfusion prior to becoming TI ranged from 5 to 13 days post-drug product infusion. Transfusion independence was maintained during the observation period of 6 months through Month 24 (i.e., end of study for Study HGB-205), as shown in Table 4.

Table 4: Change in pRBC Transfusion Requirements in Study HGB-205 (from CHMP assessment report)

	Baseline[1]				6 Months (183 days post-infusion) through Month 24 Visit						
					Annualized pRBC Volume			Annualized Number of Transfusions			
Subject	Annualized Volume (mL/kg/year)	Annualized Number of Transfusions	Weighted Average Nadir[2] (g/dL)	Trigger Hb[3] (g/dL)	Volume (mL/kg/ year)	Change from BL (mL/kg/ year)	Percent Change from BL	Number	Change from BL	Percent Change from BL	Weighted Average (g/dL)
[redacted]	138.8	10.5	8.2	8.2	0.0	-138.8	-100.0	0.0	-10.5	-100.0	10.6
	187.7	12.0	10.6	9.5	0.0	-187.7	-100.0	0.0	-12.0	-100.0	13.2
	176.0	13.0	8.1	8.7	0.0	-176.0	-100.0	0.0	-13.0	-100.0	8.5
	197.3	13.0	10.8	9.5	0.0	-197.3	-100.0	0.0	-13.0	-100.0	11.4

Source: Table 14.2.4
Abbrev.: BL, baseline; Hb, hemoglobin; pRBC, packed red blood cell
[1] 2-year period prior to enrollment
[2] Weighted average Hb nadir is defined as an average area under the curve where the Hb closest but within 3 days prior to a transfusion is used as the Hb nadir. Hb values on the day of the transfusion will be considered for nadir calculations.
[3] Hb value that triggered a pRBC transfusion pre-enrollment, as reported by treating physician

Study HGB-204

Study HGB-204 was a single-arm Phase 1/2 study in patients with TDT and treated 10 non-β^0/β^0 patients and 8 β^0/β^0 patients.

The primary efficacy endpoint per protocol was the proportion of patients with sustained production of ≥2.0 g/dL of HbA^{T87Q} between Month 18 and Month 24. HbA^{T87Q} is the adult haemoglobin (HbA) with a T87Q amino acid substitution (HbA^{T87Q}) that is generated after infusion with Zynteglo, and it is a fully functional Hb. Sixteen out of the 18 patients were producing ≥2.0 g/dL of HbA^{T87Q} at their Month 18 visit, and all of them maintained this production through Month 24. Transfusion independence was achieved by 8 patients with non-β^0/β^0 genotype and 1 patient with the β^0/β^0 genotype during this study (see table 5 below). The β^0/β^0 genotype is out of the focus of this report and of the current marketing authorisation and will not be discussed.

Table 5: Transfusion Independence in Study HGB-204

Parameter	Statistic	Non-β^0/β^0 (N=10)	β^0/β^0 (N=8)	Overall (N=18)
TI at any time [a]	n (%)	8 (80.0)	1 (12.5)	9 (50.0)
	Lower 1-sided 95% CI	49.3	0.6	29.1
Subjects with TI at 24 Months	n (%)	8 (80.0)	0	8 (44.4)
Subjects with TI, sensitivity failure analysis [b]	n (%)	8 (80.0)	0	8 (44.4)
Duration of TI (months) *(TI at any time subjects only)*	N	8	1	9
	Mean (SD)	18.78 (2.587)	16.13 (--)	18.49 (2.576)
	Median	18.91	16.13	17.28
	Min, Max	15.2, 21.4	16.1, 16.1	15.2, 21.4
Time from Drug Product infusion to Last pRBC Transfusion before becoming TI (months) *(TI at any time subjects only)*	N	8	1	9
	Mean (SD)	2.33 (2.098)	1.81 (--)	2.27 (1.970)
	Median	2.00	1.81	1.81
	Min, Max	0.3, 5.8	1.8, 1.8	0.3, 5.8
Weighted average Hb during TI (g/dL) *(TI at any time subjects only)*	N	8	1	9
	Mean (SD)	10.44 (1.277)	10.11 (--)	10.41 (1.200)
	Median	9.99	10.11	10.11
	Min, Max	9.3, 12.8	10.1, 10.1	9.3, 12.8

Source: Table 14.2.5.1

[a] Transfusion independence (TI) is defined as a weighted average Hb ≥9 g/dL without any pRBC transfusions for a continuous period of ≥12 months at any time during the study after LentiGlobin BB305 Drug Product infusion. Time period of TI will start when subjects achieve an Hb ≥9 g/dL with no transfusions in the preceding 60 days.

[b] Subjects who achieved TI and then discontinued early or received any pRBC transfusions are considered failures

Study LTF-303

This study is a multi-centre, long-term safety and efficacy follow-up study in which patients are enrolled after approximately 2 years of follow-up after Zynteglo infusion in the parent studies described above. Once enrolled in LTF-303, patients are followed every 6 months until 5 years post-Zynteglo infusion and then annually for a total of 13 years of follow-up in LTF-303 and a total of 15 years of follow-up post-Zynteglo infusion. The study started in January 2014 and is ongoing, with 22 patients with TDT (18 from Study HGB-204 and 4 from Study HGB-205) enrolled as of December 2018, with median (min, max) follow-up time of 40.74 (29.3, 58.6) months post-Zynteglo treatment.

Out of the 14 non-β^0/β^0 patients with TDT enrolled in LTF-303 as of December 2018, 11 patients had achieved transfusion independence (TI). The median (min, max) duration of TI for these 11 patients was 38.00 (21.2, 56.3) months as of December 2018. The weighted average Hb during TI of these 11 patients ranged from 9.3 to 13.2 g/dL, maintaining the levels reached during the parent studies.

Overall discussion on significant benefit

The efficacy results presented by the sponsor showed durable production of haemoglobin up to approximately 5 years in patients treated in Phase 1/2 studies as of the latest data, which was provided during the procedure based on a December 2018 data cut. Hb levels remained stable during the long-term follow-up Study LTF-303. Similarly, 11/14 non- β^0/β^0 patients treated in these Phase 1/2 studies achieved transfusion independence (TI) apart from 3 patients (3/14). Two of the 3 patients who did not achieve TI, did nonetheless achieve >60% reduction in both annualised transfusion volumes and annualised number of transfusions. As of the most recent data cut for Study HGB-207 (December 2018) for the non-β^0/β^0 patients 12 years and older (N=15), the median time to reach TI in the 4/5 patients who were eligible for assessment of TI was 15.15 months post-infusion, with median (min, max) observed duration of TI to date of 13.60 (12.0, 18.2) months and median (min, max) weighted average Hb during TI of 12.42 (11.5, 12.6) g/dL.

The COMP was of the opinion that the significant benefit could be justified by the existing data on the achievement of transfusion independence in the majority of patients in the studies, and by the long duration of such independence (approximately 5 years in the patients from the Phase 1/2 studies as of December 2018). Similarly, the target haemoglobin levels were reached and maintained in all studies, which fulfils the advice given by the COMP at protocol assistance. Transfusion independence is a quantifiable and robust endpoint and the achievement of transfusion independence and stable levels of haemoglobin are considered very relevant from a clinical point of view as well as in terms of contribution to patient care because patients can avoid the repeated intravenous infusions linked to the need of regular red blood cell transfusions.

Exploratory endpoints to measure changes in iron burden, iron chelation therapy and therapeutic phlebotomy use were measured across all Phase 1/2 and Phase 3 clinical studies at approximately 12-month intervals after treatment. Iron burden was assessed whenever possible by MRI or SQUID of the liver and the heart, as these are the most important organs for iron accumulation during transfusion treatment.

It is acknowledged that direct comparisons in iron reduction are difficult to perform early in single-arm clinical trials because it can take multiple years for liver iron levels to return to normal. The results from iron overload measurement in the studies presented by the applicant are inconclusive from the point of view of MRI or SQUID, although reductions in iron overload are suggested by serum biomarkers such as ferritin, transferrin, serum iron, and transferrin saturation. Following treatment with Zynteglo, the use of iron chelation and phlebotomy were at investigator's discretion and in accordance with institutional protocols in Phase 3 Studies HGB-207 and HGB-212 as well as in long-term follow-up Study LTF-303, which created heterogeneity in the measurements of iron chelation treatment and use of therapeutic phlebotomy. Three out of 4 patients in Study HGB-205 were able to start phlebotomy and cease iron chelator use, which constitute an encouraging result. Additionally, for HGB-207, of 11 non-β^0/β^0 patients ≥12 years of age with ≥6 months of follow-up, 8 patients had not reinitiated chelation therapy after drug product infusion, with 2 of these patients having started phlebotomy.

The COMP concluded that the sponsor had sufficiently justified the significant benefit, based on the clinically relevant advantage of achieving transfusion independence in the large majority of patients across the clinical studies and a clinically relevant reduction of transfusion frequency in those patients who did not achieve complete independence, as well as stable acceptable levels of Hb over a prolonged time.

4. COMP list of issues

Not applicable.

COMP position adopted on 1 April 2019

The COMP concluded that:

- the proposed therapeutic indication "Zynteglo is indicated for the treatment of patients 12 years and older with transfusion-dependent β thalassaemia (TDT) who do not have a β0 mutation at both alleles of the β globin gene (i.e., patients with a non-β0/β0 genotype), for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available" falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of beta thalassaemia intermedia and major (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.7 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to severe anaemia which usually requires blood transfusions. Without blood transfusions, the majority of patients affected by the major form die by five years of age. Bone marrow expansion due to severe ineffective erythropoiesis results in bone deformities, and painful periarticular syndrome with microfractures and osteomalacia. Due to routine blood transfusions, patients also develop progressive hepatic, cardiac and endocrine disturbances from the accumulation of iron in the tissues. Without iron chelation therapy, iron overload results in death in the second or third decade, usually from cardiac failure;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Zynteglo may be of potential significant benefit to those affected by the orphan condition is fulfilled. This is based on the achievement of transfusion independence in the majority of patients with non-β0/β0 genotype treated so far in the clinical studies. Among those patients who did not achieve transfusion independence, the majority had reduced frequency of blood transfusions. The Committee considered that this constitutes a clinically relevant advantage for patients with non-β0/β0 genotype compared to the current standard of care because treatment with Zynteglo reduces the risk of iron overload, an unavoidable consequence of frequent blood transfusions.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Zynteglo, autologous CD34+ haematopoietic stem cells transduced with lentiviral vector encoding the human *beta$^{A\text{-}T87Q}$-globin* gene EU/3/12/109 for beta thalassaemia intermedia and major is not removed from the Community Register of Orphan Medicinal Products.