ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Zynteglo 1.2-20 × 10^6 cells/mL dispersion for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

A genetically modified autologous $CD34^+$ cell enriched population that contains haematopoietic stem cells (HSC) transduced with lentiviral vector (LVV) encoding the $\beta^{A\text{-}T87Q}$-globin gene.

2.2 Qualitative and quantitative composition

The finished product is composed of one or more infusion bags which contain a dispersion of 1.2-20 × 10^6 cells/mL suspended in cryopreservative solution. Each infusion bag contains approximately 20 mL of Zynteglo.

The quantitative information regarding strength, $CD34^+$ cells, and dose for the medicinal product is provided in the Lot Information Sheet. The Lot Information Sheet is included inside the lid of the cryoshipper used to transport Zynteglo.

Excipient with known effect

Each dose contains 391-1564 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.

A clear to slightly cloudy, colourless to yellow or pink dispersion.

4. CLINICAL PARTICULARS

4.1 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 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 (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Zynteglo must be administered in a qualified treatment centre by a physician(s) with experience in HSC transplantation and in the treatment of patients with TDT.

Patients are expected to enrol in a registry and will be followed long term in the registry in order to better understand the long-term safety and efficacy of Zynteglo.

Posology

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. The minimum recommended dose is the same for adults and adolescents 12 years of age and older.

Zynteglo is intended for autologous use (see section 4.4) and should only be administered once.

Mobilisation and apheresis

Patients are required to undergo HSC mobilisation followed by apheresis to obtain $CD34^+$ stem cells for medicinal product manufacturing (see section 5.1 for a description of the mobilisation regimen used in clinical studies).

The minimum target number of $CD34^+$ cells to be collected is 12×10^6 $CD34^+$ cells/kg. If the minimum dose of Zynteglo of 5.0×10^6 $CD34^+$ cells/kg is not met after initial medicinal product manufacturing, the patient may undergo one or more additional cycles of mobilisation and apheresis, separated by at least 14 days, in order to obtain more cells for additional manufacture.

A back-up collection of $CD34^+$ stem cells of at least 1.5×10^6 $CD34^+$ cells/kg (if collected by apheresis) or $>1.0 \times 10^8$ TNC/kg (if collected by bone marrow harvest) is required. These cells must be collected from the patient and be cryopreserved prior to myeloablative conditioning and infusion with Zynteglo. The back-up collection may be needed for rescue treatment if there is: 1) compromise of Zynteglo after initiation of myeloablative conditioning and before Zynteglo infusion, 2) primary engraftment failure, or 3) loss of engraftment after infusion with Zynteglo (see section 4.4).

Pre-treatment conditioning

The treating physician should confirm that HSC transplantation is appropriate for the patient before myeloablative conditioning is initiated (see section 4.4).

Full myeloablative conditioning must be administered before infusion of Zynteglo (see section 5.1 for a description of the myeloablative regimen used in clinical studies). It is recommended that patients maintain haemoglobin (Hb) ≥11 g/dL for 30 days prior to myeloablative conditioning. Iron chelation should be stopped at least 7 days prior to myeloablative conditioning. Prophylaxis for hepatic veno-occlusive disease (VOD) is recommended. Depending on the myeloablative conditioning agent administered, prophylaxis for seizures should be considered (see section 5.1 for a description of the prophylaxis regimen used in clinical studies.)

Myeloablative conditioning should not begin until the complete set of infusion bag(s) constituting the dose of Zynteglo has been received and stored at the administration site, and the availability of the back-up collection is confirmed.

Zynteglo administration

See Method of Administration below and section 6.6 for details on Zynteglo administration and handling.

After Zynteglo administration

Any blood products required within the first 3 months after Zynteglo infusion should be irradiated.

Restarting iron chelation after Zynteglo infusion may be necessary and should be based on clinical practice (see sections 4.5 and 5.1). Phlebotomy can be used in lieu of iron chelation, when appropriate.

Special populations

Elderly
Zynteglo has not been studied in patients >65 years of age. HSC transplantation must be appropriate for a patient with TDT to be treated with Zynteglo (see section 4.4). No dose adjustment is required.

Renal impairment
Zynteglo has not been studied in patients with renal impairment. Patients should be assessed for renal impairment defined as creatinine clearance ≤70 mL/min/1.73 m^2 to ensure HSC transplantation is appropriate. No dose adjustment is required.

Hepatic impairment
Zynteglo has not been studied in patients with hepatic impairment. Patients should be assessed for hepatic impairment to ensure HSC transplantation is appropriate (see section 4.4.). No dose adjustment is required.

Paediatric population
The safety and efficacy of Zynteglo in children <12 years of age have not yet been established.

Patients seropositive for human immunodeficiency virus (HIV) or human T-lymphotropic virus (HTLV)
Zynteglo has not been studied in patients with HIV-1, HIV-2, HTLV-1, or HTLV-2. A negative serology test for HIV is necessary to ensure acceptance of apheresis material for Zynteglo manufacturing. Apheresis material from patients with a positive test for HIV will not be accepted for Zynteglo manufacturing.

Method of administration

Zynteglo is for intravenous use only (see section 6.6 for full details on the administration process).

After completion of the 4-day course of myeloablative conditioning, there must be a minimum of 48 hours of washout before Zynteglo infusion.

Before infusion, it must be confirmed that the patient's identity matches the unique patient information on the Zynteglo infusion bag(s). The total number of infusion bags to be administered should also be confirmed with the Lot Information Sheet (see section 4.4).

Zynteglo infusion should be completed as soon as possible and no more than 4 hours after thawing. Each infusion bag should be administered in less than 30 minutes. In the event that more than one infusion bag is provided, all infusion bags must be administered. The entire volume of each infusion bag should be infused.

Standard procedures for patient management after HSC transplantation should be followed after Zynteglo infusion.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and breast-feeding (see section 4.6).

Previous treatment with HSC gene therapy.

Contraindications to the mobilisation agents and the myeloablative conditioning agent must be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply.

General

Warnings and precautions of the mobilisation agents and the myeloablative conditioning agent must be considered.

Patients treated with Zynteglo should not donate blood, organs, tissues or cells for transplantation at any time in the future. This information is provided in the Patient Alert Card which should be given to the patient after treatment.

Risks associated with TDT and iron overload

Patients with TDT experience iron overload due to chronic red blood cell (RBC) transfusions that can lead to end organ damage. HSC transplantation with myeloablative conditioning is not appropriate for patients with TDT who have evidence of severely elevated iron in the heart i.e., patients with cardiac T2* <10 msec by magnetic resonance imaging (MRI). MRI of the liver should be performed on all patients prior to myeloablative conditioning. It is recommended that patients with MRI results demonstrating liver iron content ≥15 mg/g undergo liver biopsy for further evaluation. If the liver biopsy demonstrates bridging fibrosis, cirrhosis, or active hepatitis, HSC transplantation with myeloablative conditioning is not appropriate.

Risk of insertional oncogenesis

No cases of leukaemia or lymphoma have been reported in clinical studies with Zynteglo in patients with TDT. There are no reports of LVV-mediated insertional mutagenesis resulting in oncogenesis. Nevertheless, there is a theoretical risk of leukaemia or lymphoma after treatment with Zynteglo.

Patients should be monitored annually for leukaemia or lymphoma (including with a complete blood count) for 15 years post treatment with Zynteglo. If leukaemia or lymphoma is detected in any patient who received Zynteglo, blood samples should be collected for integration site analysis.

Serological testing

All patients should be tested for HIV-1/2 and HTLV-1/2 prior to mobilisation and apheresis to ensure acceptance of the apheresis material for Zynteglo manufacturing (see section 4.2).

Interference with HIV testing

It is important to note that patients who have received Zynteglo are likely to test positive by polymerase chain reaction (PCR) assays for HIV due to LVV provirus insertion, resulting in a false positive test for HIV. Therefore, patients who have received Zynteglo should not be screened for HIV infection using a PCR-based assay.

Engraftment failure as measured by neutrophil engraftment

Treatment with Zynteglo involves the infusion and engraftment of $CD34^+$ HSCs that have been genetically modified *ex vivo* with a LVV. In clinical trials, no patients failed to engraft bone marrow, as measured by neutrophil engraftment (N=42). Neutrophil engraftment occurred on median (min, max) Day 19.5 (13, 38) after medicinal product infusion. Failure of neutrophil engraftment is a short-term but potentially severe risk, defined as failure to achieve 3 consecutive absolute neutrophil counts (ANC) ≥500 cells/µL obtained on different days by Day 43 after infusion of

Zynteglo. Patients who experience neutrophil engraftment failure should receive rescue treatment with the back-up collection (see section 4.2).

Delayed platelet engraftment

Platelet engraftment is defined as 3 consecutive platelet values $\geq 20 \times 10^9$/L obtained on different days after Zynteglo infusion, with no platelet transfusions administered for 7 days immediately preceding and during the evaluation period. Patients with TDT treated with Zynteglo who achieved platelet engraftment had a median (min, max) platelet engraftment on Day 41.0 (19, 191) in clinical trials (N=39). No correlation was observed between incidence of bleeding and delayed platelet engraftment. Patients should be made aware of the risk of bleeding until platelet recovery has been achieved. Patients should be monitored for thrombocytopenia and bleeding according to standard guidelines. Platelet counts should be monitored according to medical judgment until platelet engraftment and platelet recovery are achieved. Blood cell count determination and other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise.

Anti-retroviral and hydroxyurea use

Patients should not take anti-retroviral medications or hydroxyurea from at least one month prior to mobilisation until at least 7 days after Zynteglo infusion (see section 4.5). If a patient requires anti-retrovirals following exposure to HIV/HTLV, initiation of Zynteglo treatment should be delayed until an HIV western blot and viral load assay have been performed at 6 months post-exposure.

Sodium content

This medicinal product contains 391-1564 mg sodium per dose equivalent to 20 to 78% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Patients should not take anti-retroviral medicinal products or hydroxyurea from at least one month prior to mobilisation until at least 7 days after Zynteglo infusion (see section 4.4).

Drug-drug interactions between iron chelators and the myeloablative conditioning agent must be considered. Iron chelators should be discontinued 7 days prior to initiation of conditioning. The Summary of Product Characteristics (SmPC) for the iron chelator and the myeloablative conditioning agent must be consulted for the recommendations regarding co-administration with CYP3A substrates.

Some iron chelators are myelosuppressive. After Zynteglo infusion, avoid use of these iron chelators for 6 months. If iron chelation is needed, consider administration of non-myelosuppressive iron chelators (see sections 4.2 and 5.1).

No formal drug interaction studies have been performed. Zynteglo is not expected to interact with the hepatic cytochrome P-450 family of enzymes or drug transporters.

There is no clinical experience with the use of erythropoiesis-stimulating agents in patients treated with Zynteglo.

The safety of immunisation with live viral vaccines during or following Zynteglo treatment has not been studied.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

There are insufficient exposure data to provide a precise recommendation on duration of contraception following treatment with Zynteglo. Women of childbearing potential and men capable of fathering a

child must use a reliable method of contraception (intra-uterine device or combination of hormonal and barrier contraception) from start of mobilisation through at least 6 months after administration of Zynteglo. Consult the SmPC of the myeloablative conditioning agent for information on the need for effective contraception in patients who undergo conditioning.

Pregnancy

A negative serum pregnancy test must be confirmed prior to the start of mobilisation and re-confirmed prior to conditioning procedures and before medicinal product administration.

No clinical data on exposed pregnancies are available.

Reproductive and developmental toxicity studies with Zynteglo were not performed. Zynteglo must not be used during pregnancy because of myeloablative conditioning (see section 4.3). It is unknown whether Zynteglo transduced cells have the potential to be transferred in utero to a foetus.

There is no opportunity for germline transmission of the $\beta^{A\text{-}T87Q}$-globin gene after treatment with Zynteglo, therefore the likelihood that an offspring would have general somatic expression of the $\beta^{A\text{-}T87Q}$-globin gene is considered negligible.

Breast-feeding

It is unknown whether Zynteglo is excreted in human milk. The effect of administration of Zynteglo to mothers on their breast-fed children has not been studied.

Zynteglo must not be administered to women who are breast-feeding.

Fertility

There are no data on the effects of Zynteglo on human fertility. Effects on male and female fertility have not been evaluated in animal studies.

Data are available on the risk of infertility with myeloablative conditioning. It is therefore advised to cryopreserve semen or ova before treatment if possible.

4.7 Effects on ability to drive and use machines

Zynteglo has no influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Zynteglo was evaluated in 42 patients with TDT. The most serious adverse reaction attributed to Zynteglo was thrombocytopenia (2.4%). Given the small patient population and size of cohorts, adverse reactions in the table below do not provide a complete perspective on the nature and frequency of these events.

Tabulated list of adverse reactions

Adverse reactions are listed by MedDRA body system organ class and by frequency. Frequencies are defined as: very common (≥1/10), and common (≥1/100 and <1/10).

Tables 1, 2, and 3 are lists of adverse reactions attributed to mobilisation/apheresis, myeloablative conditioning, and Zynteglo, respectively, experienced by patients with TDT in clinical trials with Zynteglo.

Table 1 Adverse reactions attributed to mobilisation/apheresis

System Organ Class (SOC)	Very Common (≥10%)	Common (≥1% - <10%)
Blood and lymphatic system disorders	Thrombocytopenia	Splenomegaly, Leukocytosis
Metabolism and nutrition disorders	Hypocalcaemia	Hypokalaemia, Hypomagnesaemia
Psychiatric disorders		Agitation
Nervous system disorders	Headache, Peripheral sensory neuropathy	Dizziness, Head discomfort, Paraesthesia
Cardiac disorders		Cardiac flutter
Vascular disorders		Hypotension
Respiratory, thoracic and mediastinal disorders		Hypoxia, Epistaxis
Gastrointestinal disorders	Nausea	Vomiting, Lip swelling, Abdominal pain, Abdominal pain upper, Paraesthesia oral
Skin and subcutaneous tissue disorders		Rash, Hyperhidrosis
Musculoskeletal and connective tissue disorders	Bone pain	Back pain, Musculoskeletal discomfort
General disorders and administration site conditions		Pyrexia, Influenza like illness, Chest discomfort, Chest pain, Injection site reaction, Catheter site haemorrhage, Catheter site bruise, Injection site bruising, Fatigue, Non-cardiac chest pain, Catheter site pain, Injection site pain, Puncture site pain, Pain
Investigations		Blood magnesium decreased
Injury, poisoning and procedural complications		Citrate toxicity, Contusion, Procedural pain

Table 2 Adverse reactions attributed to myeloablative conditioning

SOC	Very Common (≥10%)	Common (≥1% - <10%)
Infections and infestations		Neutropenic sepsis, Systemic infection, Staphylococcal infection, Pneumonia, Lower respiratory tract infection, Urinary tract infection, Mucosal infection, Cellulitis, Vaginal infection, Rash pustular, Folliculitis, Gingivitis
Blood and lymphatic system disorders	Febrile neutropenia, Neutropenia, Thrombocytopenia, Leukopenia, Anaemia	Lymphopenia, Leukocytosis, Monocyte count decreased, Neutrophilia, Mean cell haemoglobin concentration increased
Metabolism and nutrition disorders	Decreased appetite	Hypocalcaemia, Hypokalaemia, Metabolic acidosis, Fluid overload, Fluid retention, Hypomagnesaemia, Hyponatraemia, Hypophosphataemia
Psychiatric disorders	Insomnia	Anxiety
Nervous system disorders	Headache	Dizziness, Lethargy, Dysgeusia

SOC	Very Common (≥10%)	Common (≥1% - <10%)
Eye disorders		Conjunctival haemorrhage
Ear and labyrinth disorders		Vertigo
Cardiac disorders		Atrial fibrillation
Vascular disorders		Hypotension, Haematoma
Respiratory, thoracic and mediastinal disorders	Epistaxis, Pharyngeal inflammation	Hypoxia, Dyspnoea, Pleural effusion, Rales, Upper-airway cough syndrome, Cough, Laryngeal pain, Hiccups
Gastrointestinal disorders	Stomatitis, Vomiting, Nausea, Diarrhoea, Gingival bleeding, Constipation, Abdominal pain, Anal inflammation,	Anal haemorrhage, Gastritis, Gastrointestinal inflammation, Abdominal distension, Abdominal pain upper, Anal fissure, Dyspepsia, Dysphagia, Oesophagitis, Haemorrhoids, Proctalgia. Lip dry
Hepatobiliary disorders	Veno-occlusive liver disease, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased	Cholecystitis, Cholelithiasis, Hepatomegaly, Jaundice, Transaminases increased, Gamma-glutamyltransferase increased
Skin and subcutaneous tissue disorders	Alopecia, Pruritus, Skin hyperpigmentation	Petechiae, Ecchymosis, Pain of skin, Palpable purpura, Petechiae, Pruritus generalised, Purpura, Sweat gland disorder, Urticaria, Dry skin
Musculoskeletal and connective tissue disorders		Bone pain, Myalgia, Pain in extremity, Back pain
Renal and urinary disorders		Haematuria
Reproductive system and breast disorders	Vaginal haemorrhage	Ovarian failure, Menstruation irregular, Premature menopause, Blood follicle stimulating hormone increased, Blood testosterone decreased
General disorders and administration site conditions	Pyrexia, Fatigue	Mucosal inflammation, Face oedema, Hypothermia, Feeling cold, Pain, Xerosis
Investigations		C-reactive protein increased, Aspergillus test positive, Blood potassium decreased, Weight decreased, Blood alkaline phosphatase decreased, Blood magnesium decreased, Forced expiratory flow decreased, Protein total decreased, Blood albumin decreased, Reticulocyte count decreased, Reticulocyte percentage decreased
Injury, poisoning and procedural complications		Transfusion reaction, Skin abrasion

Table 3 Adverse reactions attributed to Zynteglo

SOC	Very Common (≥10%)	Common (≥1% - <10%)
Blood and lymphatic system disorders		Thrombocytopenia
Vascular disorders		Hot flush
Respiratory, thoracic and mediastinal disorders		Dyspnoea
Gastrointestinal disorders		Abdominal pain
Musculoskeletal and connective tissue disorders		Pain in extremity
General disorders and administration site conditions		Non-cardiac chest pain

Description of selected adverse reactions

Bleeding

Bleeding is a potential complication of thrombocytopenia subsequent to myeloablative conditioning and treatment with Zynteglo. One serious event of hypotension due to epistaxis occurred in a patient, with onset 11 days after Zynteglo treatment. All other bleeding events were nonserious. A risk of bleeding exists before platelet engraftment and may continue after platelet engraftment in patients who have continued thrombocytopenia.

Following platelet engraftment, all patients maintained platelet levels of $\geq 20 \times 10^9$/L in the absence of platelet transfusions. Median (min, max) times to unsupported platelet counts of $\geq 50 \times 10^9$/L and $\geq 100 \times 10^9$/L were 52 (20, 268) days and 63 (20, 1231) days, respectively. (See section 4.4 for guidance on platelet monitoring and management.)

Hepatic veno-occlusive disease

Serious events of hepatic VOD occurred in 11.9% of patients following myeloablative conditioning; 80% of these patients did not receive prophylaxis for VOD. All patients who experienced VOD received treatment with defibrotide and recovered. Patients not receiving prophylaxis for VOD appeared to be at an increased risk for developing VOD. Patients with TDT may be at an increased risk of VOD following myeloablative conditioning compared with other patient populations.

Infusion related reactions to Zynteglo

Pre-medication for infusion reactions was managed at physician discretion. Infusion related reactions to Zynteglo were observed in 11.9% of patients and occurred on the day of Zynteglo infusion. All reactions resolved. Events were mild and included abdominal pain, hot flush, dyspnoea, and non-cardiac chest pain in 9.5%, 2.4%, 2.4%, and 2.4% of patients, respectively.

Paediatric population

According to available data, the frequency, type, and severity of adverse reactions in adolescents 12-17 years of age are similar to adults with the exception of VOD and pyrexia that occurred more frequently in adolescents.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No data from clinical studies are available regarding overdose of Zynteglo.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other haematological agents, ATC code: not yet assigned

Mechanism of action

Zynteglo adds functional copies of a modified β-globin gene into the patients' HSCs through transduction of autologous $CD34^+$ cells with BB305 LVV, thereby addressing the underlying genetic cause of the disease. After Zynteglo infusion, transduced $CD34^+$ HSCs engraft in the bone marrow and differentiate to produce RBCs containing biologically active $\beta^{A\text{-}T87Q}$-globin (a modified β-globin protein) that will combine with α-globin to produce functional Hb containing $\beta^{A\text{-}T87Q}$-globin (HbA^{T87Q}). $\beta^{A\text{-}T87Q}$-globin can be quantified relative to other globin species in peripheral blood using high performance liquid chromatography. $\beta^{A\text{-}T87Q}$-globin expression is designed to correct the β/α-globin imbalance in erythroid cells of patients with TDT and has the potential to increase total Hb to normal levels and eliminate dependence on chronic RBC transfusions. Following successful engraftment and achievement of transfusion independence, the effects of the product are expected to be life-long.

Pharmacodynamic effects

All patients with TDT with a non-β^0/β^0 genotype who received Zynteglo with at least 3 months of follow-up produced HbA^{T87Q} (N=10, HGB-204; N=4, HGB-205; N=14, HGB-207; N=1, HGB-212). For patients with at least 6 months of follow-up, HbA^{T87Q} generally increased steadily after Zynteglo infusion and stabilised by approximately Month 6 to 9 post infusion. Patients had a Month 6 median (min, max) HbA^{T87Q} of 4.90 (1.0, 9.6) g/dL in the Phase 1/2 studies (N=14, HGB-204 and HGB-205) and 9.49 (3.4, 10.6) g/dL in the ongoing Phase 3 study (N=11, HGB-207).

HbA^{T87Q} remained generally stable through Month 24 with a median (min, max) of 6.44 (1.1, 10.1) g/dL (N=14, HGB-204 and HGB-205), and through long-term follow-up in LTF-303, demonstrating stable integration of the $\beta^{A\text{-}T87Q}$-globin gene into long-term HSCs and stable expression of the $\beta^{A\text{-}T87Q}$-globin gene in cells of the erythroid lineage.

Clinical efficacy

Efficacy was based on 32 adult and adolescent patients with TDT and a non-β^0/β^0 genotype treated with Zynteglo (N=10, HGB-204; N=4, HGB-205; N=15, HGB-207; N=3, HGB-212) (see Table 4). Only a few patients have been included in the clinical studies with genotypes characterised by low endogenous β-globin production phenotypically similar to patients with a β^0/β^0 genotype, such as patients homozygous for IVS-I-110 or IVS-I-5.

Table 4 Baseline characteristics for non-β^0/β^0 patients with TDT ≥12 years of age treated with Zynteglo (Studies HGB-204, HGB-205, HGB-207, HGB-212, LTF-303)

	Non-β^0/β^0 patients			
Study	**Total number (adolescents)**	**Age** median (min, max)	**Pre-treatment transfusion volumes** (mL/kg/year) median (min, max)	**Pre-treatment transfusions per year** median (min, max)
HGB-205	4 (2)	17.5 (16, 19)	181.85 (138.8, 197.3)	12.50 (10.5, 13.0)
HGB-204	10 (2)	19.5 (16, 34)	151.28 (140.0, 234.5)	13.75 (10.0, 16.5)
HGB-207	15 (6)	20.0 (12, 34)	192.92 (152.3, 251.3)	17.50 (11.5, 37.0)
HGB-212	3 (1)	21.0 (17, 33)	175.51 (170.7, 209.6)	21.50 (17.50, 39.5)

Transfusion-dependent β-thalassaemia (TDT)

Patients were considered to be transfusion-dependent if they had a history of transfusions of at least 100 mL/kg/year of RBCs or with ≥8 transfusions of RBCs per year in the 2 years preceding enrolment. In the clincal studies, patients received a median (min, max) RBC transfusion volume of 175.7 (139, 251) mL/kg/year and a median (min, max) number of 14.8 (10, 40) RBC transfusions per year.

Adolescents were excluded from Phase 3 studies if they had a known and available HLA-matched related HSC donor. The median (min, max) age in the studies was 19.0 (12, 34) years, 56.3% were females, 59.4% were Asian, and 40.6% White/Caucasian. All patients had a Karnofsky performance score ≥80 and the majority had a performance score of 100 at baseline. Cardiac T2* at baseline was >20 msec. The median (min, max) serum ferritin at baseline was 3778.7 (784, 22517) pmol/L and median (min, max) liver iron concentration was 6.75 (1.0, 41.0) mg/g (N=10, HGB-204; N=4, HGB-205; N=15, HGB-207; N=3, HGB-212).

Mobilisation and apheresis

All patients were administered G-CSF and plerixafor to mobilise stem cells prior to the apheresis procedure. The planned dose of G-CSF was 10 µg/kg/day in patients with a spleen, and 5 µg/kg/day in patients without a spleen, given on Days 1 through 5 of mobilisation in the morning. The planned dose of plerixafor was 0.24 mg/kg/day, given on Days 4 and 5 of mobilisation in the evening. If a third day of collection was needed, plerixafor and G-CSF dosing was extended to Day 6. The dose of G-CSF should be decreased by half if white blood cell (WBC) count is $>100 \times 10^9$/L prior to the day of apheresis. For most patients, the minimum number of $CD34^+$ cells to manufacture Zynteglo was collected with 1 cycle of mobilisation and apheresis.

Pre-treatment conditioning

All patients received full myeloablative conditioning with busulfan prior to treatment with Zynteglo. The planned dose of busulfan was 3.2 mg/kg/day for patients ≥18 years as a 3-hour IV infusion daily for 4 days with a recommended target $AUC_{0\text{-}24h}$ of 3800-4500 µM*min. The planned dose of busulfan was 0.8 mg/kg for patients 12-17 years of age as a 2-hour IV infusion every 6 hours for a total of 16 doses with a recommended target of $AUC_{0\text{-}6h}$ of 950-1125 µM*min. The busulfan SmPC was used for information on appropriate method for determination of patient weight-based dosing. Busulfan dose adjustments were made as needed based on pharmacokinetic monitoring.

The median (min, max) busulfan dose was 3.50 (2.5, 5.0) mg/kg/day (N=32). $AUC_{0\text{-}24h}$ was measured on Day 1 and informed the dose for Day 3; the median (min, max) estimated daily AUC was

4417.0 (3030, 9087) μM*min (N=31). All patients with non-β^0/β^0 genotypes received anti-seizure prophylaxis with agents other than phenytoin prior to initiating busulfan. Phenytoin was not used for anti-seizure prophylaxis because of its well understood induction of glutathione-S-transferase and cytochrome P450 and resultant increased clearance of busulfan, and because of the widespread availability of effective anti-seizure medications that do not affect busulfan metabolism.

In HGB-207 and HGB-212 prophylaxis for VOD/hepatic sinusoidal obstruction syndrome was required per institutional practice with ursodeoxycholic acid or defibrotide.

Zynteglo administration

All patients were administered Zynteglo with a median (min, max) dose of 7.80×10^6 (5.0, 19.4) $CD34^+$ cells/kg as an intravenous infusion (N=32).

After Zynteglo administration

A total of 28.6% of patients (12/42; HGB-204, HGB-205, HGB-207, HGB-212) received G-CSF within 21 days after Zynteglo infusion. However, G-CSF use was not recommended for 21 days after Zynteglo infusion in Phase 3 studies.

Studies HGB-204 and HGB-205

HGB-204 and HGB-205 were Phase 1/2 open-label, single-arm 24-month studies that included 22 patients with TDT treated with Zynteglo (N=18, HGB-204; N=4, HGB-205), of whom 14 had a non-β^0/β^0 genotype (N=10, HGB-204; N=4, HGB-205) and 8 had a β^0/β^0 genotype in HGB-204. All patients completed HGB-204 and HGB-205 and enrolled for long-term follow-up in the LTF-303 study. The median (min, max) duration of follow-up was 40.48 (29.3, 58.6) months. All patients remain alive at last follow-up.

The primary endpoint was transfusion independence (TI) by Month 24, 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 of Zynteglo. Of the patients with a non-β^0/β^0 genotype, 11/14 (78.6%, 95% CI 49.2%-95.3%) achieved TI by Month 24 (Table 5). Among these 11 patients, the median (min, max) weighted average Hb during TI was 10.51 (9.3, 13.2) g/dL (Table 5).

All patients who have achieved TI at any time have maintained TI at Month 30 with a min, max duration of TI of 21.2+, 56.3+ months (N=11). The median (min, max) time to last RBC transfusion was 0.46 (0.2, 5.8) months following Zynteglo infusion.

In the 3 patients who did not achieve TI, reductions of 100%, 86.9% and 26.8% in transfusion volume requirements and of 100%, 85.3% and 20.7% in transfusion frequency were observed between Month 6 through Month 24 visit when compared to their pre-study levels of RBC transfusions.

The median (min, max) total Hb at Month 6 for patients who had not received a transfusion for the prior 60 days was 10.60 (7.6, 13.4) g/dL (N=11). Total Hb remained stable at Month 24 with a median (min, max) of 10.60 (8.8, 13.7) g/dL (N=12) and at Month 36 with a median (min, max) of 11.30 (7.8, 13.5) g/dL (N=11).

After Zynteglo infusion, patient iron levels were managed at physician discretion. All patients in HGB-204 restarted iron chelation and continue to use iron chelators. One patient in HGB-205 restarted iron chelation and continues to use iron chelators. Three patients in HGB-205 started phlebotomy.

At 48 months after infusion of Zynteglo for patients who achieved TI, the median reduction (min, max) in serum ferritin levels from baseline was 75.02% (39.2, 84.8) (N=3, HGB-204; N=2, HGB-205). The median reduction in liver iron content from baseline was 67.14%, ranging from an 83.3% reduction to a 269.2% increase (N=3, HGB-204; N=2, HGB-205).

Studies HGB-207 and HGB-212

HGB-207 and HGB-212 are ongoing Phase 3 open-label, single-arm 24-month studies that are planned to include approximately 39 adults, adolescents, and children with TDT (N=23, HGB-207; N=16, HGB-212), of whom 29 have a non-β^0/β^0 genotype (N=23, HGB-207; N=6, HGB-212) and 10 have a β^0/β^0 genotype in HGB-212. These studies are conducted with improved transduction compared to Phase 1/2 studies, resulting in increased average number of functional copies of the transgene ($\beta^{A\text{-}T87Q}$-globin) integrated in the autologous $CD34^+$ cells. Eighteen adults and adolescents with TDT with a non-β^0/β^0 genotype have been treated with Zynteglo in Phase 3 studies (N=15, HGB-207; N=3, HGB-212) and their median (min, max) duration of follow-up was 10.0 (1.3, 22.2) months. All patients remain alive at last follow-up.

The primary endpoint was transfusion independence (TI) by Month 24, 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 of Zynteglo. Five patients are evaluable for assessment of TI. Of these, 4/5 (80.0%, 95% CI 28.4-99.5%) achieved TI at last follow-up. Among these 4 patients, the median (min, max) weighted average Hb during TI was 12.42 (11.5, 12.6) g/dL (Table 5).

All patients who have achieved TI have maintained TI with a min, max duration of TI of 12.0+, 18.2+ months (N=4). The median (min, max) time to last RBC transfusion was 0.95 (0.5, 1.1) months following Zynteglo infusion.

For the only patient who did not achieve TI, a reduction of 75.8% in transfusion volume requirements and a reduction of 74.9% in transfusion frequency were observed between hospital discharge and through last study visit when compared to their pre-study levels of RBC transfusions.

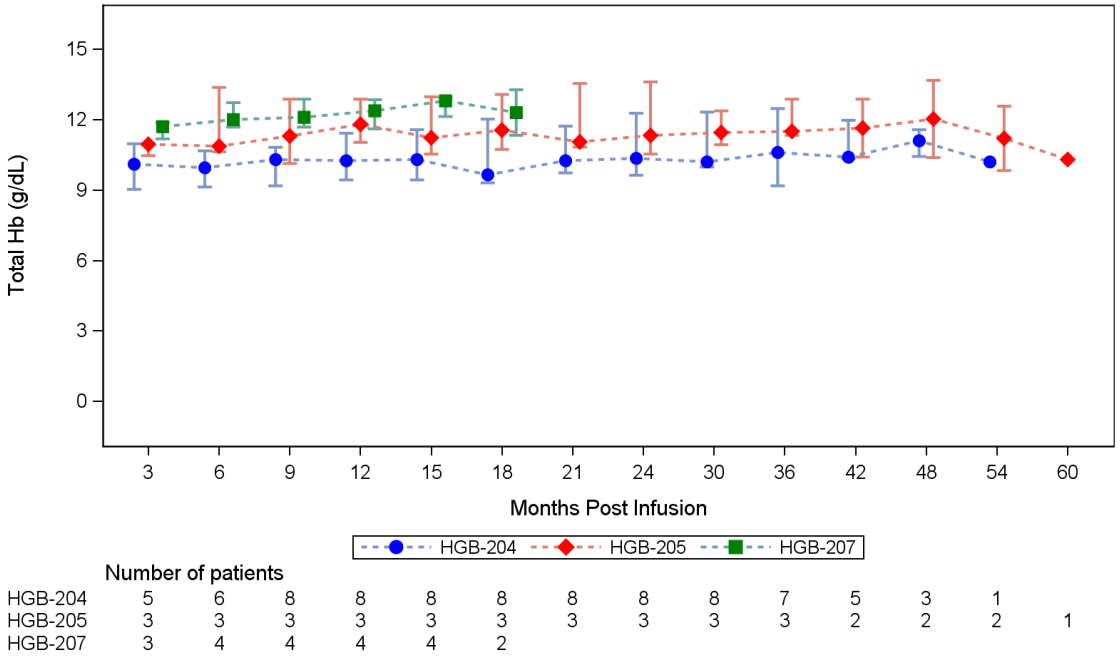
The median (min, max) total Hb at Month 6 for patients who had not received a transfusion for the prior 60 days was 11.90 (8.4, 13.3) g/dL (N=11).

After Zynteglo infusion patient iron chelation was managed at physician discretion. Of the 11 patients followed for at least 6 months after Zynteglo infusion, 6 patients did not restart iron chelation or receive phlebotomy, 3 patients restarted iron chelation, and 2 patients received phlebotomy to reduce iron levels.

Exploratory analyses were performed to confirm resolution of dyserythropoiesis, the fundamental physiologic characteristic of TDT, in the bone marrow. Bone marrow biopsies taken before treatment were consistent with a diagnosis of TDT, including a low myeloid/erythroid ratio (N=15, HGB-207), reflective of erythroid hyperplasia. For 8 patients who had sufficient on-study follow-up to obtain a 12-month follow-up bone marrow assessment, myeloid/erythroid ratios for 7 patients increased from a range of 0.1 to 0.5 at baseline to a range of 0.6 to 1.9 approximately 12 months after Zynteglo infusion, suggesting that Zynteglo improves erythropoiesis in patients with TDT.

Overall results

Figure 1 **Median total haemoglobin over time in non-β^0/β^0 TDT patients treated with Zynteglo who have achieved transfusion independence (Studies HGB-204, HGB-205, HGB-207, LTF-303)**



Bars represent interquartile ranges.

Table 5 **Efficacy outcomes for non-β^0/β^0 TDT patients treated with Zynteglo (Studies HGB-204, HGB-205, HGB-207, LTF-303)**

HbA^{T87Q} (g/dL) at 6 months n median (min, max)	**HbA^{T87Q} (g/dL) at 24 months** n median (min, max)	**Hb (g/dL) at 6 months*** n median (min, max)	**Hb (g/dL) at 24 months*** n median (min, max)	**TI**** n/N^ (%) [95% CI]	**WA Hb during TI (g/dL)** n median (min, max)	**Duration of TI** (months) n median (min, max)
Study HGB-205						
4 7.543 (4.94, 9.59)	4 8.147 (6.72, 10.13)	4 10.73 (7.6, 13.4)	4 10.91 (8.8, 13.6)	3/4 (75.0%) [19.4, 99.4]	3 11.30 (10.5, 13.0)	3 NR (34.9+, 56.3+)
Study HGB-204						
10 4.153 (1.03, 8.52)	10 5.418 (1.10, 9.60)	7 9.20 (7.7, 13.3)	8 10.35 (9.1, 13.7)	8/10 (80.0%) [44.4, 97.5]	8 10.27 (9.3, 13.2)	8 NR (21.2+, 45.3+)
Study HGB-207						
11 9.494 (3.35, 10.60)	NA***	11 11.90 (8.4, 13.3)	NA***	4/5 (80.0%) [28.4, 99.5]	4 12.42 (11.5, 12.6)	4 NR (12.0+, 18.2+)

*Patients who have not received transfusions in the prior 60 days.
**Transfusion independence (TI): 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 medicinal product infusion.
***No patients are currently evaluable for these endpoints.

^N represents the total number of patients evaluable for TI, defined as patients who have completed their parent study (i.e., 24 months of follow-up), or achieved TI, or will not achieve TI in their parent study.
NR = Not reached. NA = Not applicable. Hb = Total Hb. WA Hb = Weighted average Hb.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Zynteglo in one or more subsets of the paediatric population in β-thalassaemia (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Zynteglo is an autologous gene therapy medicinal product consisting of autologous cells that have been genetically modified *ex vivo*. The nature of Zynteglo is such that conventional studies on pharmacokinetics, absorption, distribution, metabolism, and elimination are not applicable.

5.3 Preclinical safety data

Conventional mutagenicity, carcinogenicity and reproductive and developmental toxicity studies have not been conducted.

The pharmacology, toxicology and genotoxicity of the BB305 LVV used for transduction in the manufacture of Zynteglo were evaluated *in vitro* and *in vivo*. An *in vitro* immortalisation (IVIM) assay conducted with BB305 LVV-transduced mouse bone marrow cells (BMCs) showed minimal mutagenic potential (Fitness Score $\approx 0.1 \times 10^{-4}$). Insertion site analysis (ISA) of pre-transplantation transduced mouse BMCs and human $CD34^+$ HSCs showed no enrichment for insertion in or near cancer-related genes. A pharmacology, biodistribution, toxicity and genotoxicity study was conducted in a mouse model of β-thalassaemia. In this study, there was no evidence of toxicity, genotoxicity or oncogenesis (tumorigenicity) related to BB305 LVV integration, and no toxicity related to production of $\beta^{A\text{-}T87Q}$-globin. ISA of post-transplantation BMCs demonstrated no preferred integration in the proximity of or within genes associated clinically (for gamma retroviral vectors) with either clonal dominance or leukaemia, and no evidence of clonal dominance was observed. Additional studies with human $CD34^+$ HSCs administered to immunodeficient, myeloablated mice demonstrated no toxicity, tumorigenicity or genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cryostor CS5
Sodium chloride

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Frozen: 1 year at ≤-140°C.

Once thawed: maximum 4 hours at room temperature (20°C-25°C).

6.4 Special precautions for storage

Store in the vapour phase of liquid nitrogen at ≤-140°C until ready for thaw and administration.

Keep the infusion bag(s) in the metal cassette(s).

Do not re-freeze after thawing.

6.5 Nature and contents of container

20 mL fluoro-ethylenepropylene infusion bag(s), each packed in a transparent pouch inside a metal cassette.

Zynteglo is shipped from the manufacturing facility to the infusion centre storage facility in a cryoshipper, which may contain multiple metal cassettes intended for a single patient. Each metal cassette contains one infusion bag with Zynteglo. A patient may have multiple infusion bags.

6.6 Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

Precautions to be taken before handling or administering the medicinal product

- This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Zynteglo should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

Preparation for the infusion

- Remove each metal cassette from liquid nitrogen storage and remove each infusion bag from the metal cassette.
- Confirm that Zynteglo is printed on the infusion bag(s).
- Confirm that patient identity matches the unique patient identification information located on the Zynteglo infusion bag(s). Do not infuse Zynteglo if the information on the patient specific-label on the infusion bag does not match the intended patient.
- Account for all infusion bags and confirm each infusion bag is within the expiry date using the accompanying Lot Information Sheet.
- Each infusion bag should be inspected for any breaches of integrity before thawing and infusion. If an infusion bag is compromised, follow the local guidelines and contact bluebird bio immediately.

Thaw and administration

- Thaw Zynteglo at 37°C in a water bath or dry bath. Thawing of each infusion bag takes approximately 2 to 4 minutes. Do not overthaw the medicinal product. Do not leave the medicinal product unattended and do not submerge the infusion ports if thawed in a water bath.
- After thaw, mix the medicinal product gently by massaging the infusion bag until all of the contents are uniform. Expose the sterile port on the infusion bag by tearing off a protective wrap covering the port.
- Access the medicinal product infusion bag and infuse per the administration site’s standard procedures for administration of cell therapy products. Do not use an in-line blood filter or an infusion pump.
- Do not sample, alter, or irradiate the medicinal product.

- Administer each infusion bag of Zynteglo via intravenous infusion over a period of less than 30 minutes. If more than one infusion bag is provided, administer each infusion bag completely before proceeding to thaw and infuse the next bag.
- Infuse Zynteglo as soon as possible and no more than 4 hours after thawing. Flush all Zynteglo remaining in the infusion bag and any associated tubing with at least 50 mL of 0.9% sodium chloride solution to ensure as many cells as possible are infused into the patient.

Precautions to be taken for the disposal of the medicinal product

The medicinal product contains genetically-modified cells. Local biosafety guidelines should be followed for unused medicinal products or waste material. All material that has been in contact with Zynteglo (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local biosafety guidelines.

7. MARKETING AUTHORISATION HOLDER

bluebird bio (Netherlands) B.V.
Stadsplateau 7
WTC Utrecht
3521AZ Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1367/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

{DD month YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu <, and on the website of {name of MS Agency (link)}>.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

apceth Biopharma GmbH
Haidgraben 5
85521 Ottobrunn
GERMANY

Name and address of the manufacturer(s) responsible for batch release

apceth Biopharma GmbH
Haidgraben 5
85521 Ottobrunn
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to special and restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Zynteglo in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational and controlled distribution programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational and controlled distribution programme is aimed at providing information on the safe use of Zynteglo.

The MAH shall ensure that in each Member State where Zynteglo is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense and/or use Zynteglo have access to/are provided with the following educational package to be disseminated through professional bodies:

- Physician educational material
- Patient information pack

The physician educational material should contain:
  - The Summary of Product Characteristics
  - Guide for healthcare professionals
  - Guide for handling and method of administration

- **The Guide for healthcare professionals** shall contain the following key elements:
  - Warnings and precautions of the mobilisation agents and the myeloablative conditioning agent must be considered.
  - Treatment with Zynteglo in the clinical trials was associated with delayed platelet engraftment. No correlation was observed between incidence of bleeding adverse events (AEs) and time to platelet engraftment. Precautions regarding bleeding consequences of thrombocytopenia need to be taken. Patients should be made aware of the risk of bleeding events that are not easily identifiable, such as internal bleeding.
  - Treatment with Zynteglo is in theory associated with the risk of insertional mutagenesis, potentially leading to development of malignancy. All patients must be advised on signs of leukaemia and to seek immediate medical attention if these signs are present.
  - A negative serology test for HIV is necessary to ensure acceptance of apheresis material for Zynteglo manufacturing.
  - The potential risk of loss of response to gene therapy may lead to loss of transfusion independence or increase transfusion needs for patients who did not reach transfusion-independence.
  - All patients should receive annual monitoring of complete blood counts and total haemoglobin levels to monitor for leukaemia/lymphoma and maintenance of efficacy, respectively.
  - The short-term potential risk of treatment with Zynteglo represents failure of engraftment, which shall be managed by administration of rescue cells.
  - The need to explain and to ensure that patients understand:
    - potential risks of treatment with Zynteglo
    - signs of leukaemia/lymphoma and what action to take
    - content of patient's guide
    - the need to carry the patient alert card and show it to every healthcare professional
    - enrolment in the drug product Registry
  - Scope of the Registry and how to enrol patients

- **The Guide to handling and method of administration for healthcare professionals** shall contain the following key elements:
  - Instructions on receiving and storing of Zynteglo and how to check Zynteglo prior to administration

- Instructions about the thawing of Zynteglo
- Instructions on protective equipment and treatment of spills.

The patient information pack should contain:

- Package leaflet
- A patient/carer guide
- A patient alert card

- **The patient/carer guide** shall contain the following key messages:
  - Treatment with Zynteglo is in theory associated with the risk of development of malignancy. Signs of leukaemia and the need to obtain urgent medical care if these signs are present.
  - Patient alert card and the need to carry it on their person and tell any treating healthcare professional that they were treated with Zynteglo.
  - The potential risk of loss of response to gene therapy may lead to loss of transfusion independence or increase transfusion needs for patients who did not reach transfusion-independence.
  - The importance of annual check-ups.
  - Treatment with Zynteglo is associated with the risk of delayed platelet engraftment that could lead to an increased tendency for bleeding.
  - Signs and symptoms of bleeding and the need to contact the physician if any signs of unusual or prolonged bleeding or any other relevant signs are present.
  - Enrolment in the drug product Registry.

- **The patient alert card** shall contain the following key messages:
  - Information of risk of delayed platelet engraftment, potentially leading to bleeds, and theoretical risks.
  - Statement that the patient was treated with gene therapy and should not donate blood, organs, tissues, or cells.
  - Statement that the patient was treated with Zynteglo, including LOT number and treatment date(s).
  - Details on reporting of adverse effects.
  - Information on the possibility of false positivity of certain commercial HIV tests because of Zynteglo.
  - Contact details where a health care professional can receive further information.

The MAH shall ensure that in each Member State where Zynteglo is marketed, a system aimed to control distribution to Zynteglo beyond the level of control ensured by routine risk minimisation measures. The following requirements need to be fulfilled before the product is prescribed, manufactured, dispensed and used:

- Zynteglo will only be available through bluebird bio qualified treatment centres to ensure traceability of the patient`s cells and manufactured drug product between the treating hospital and manufacturing site. The selection of the treatment centres will be conducted in collaboration with national health authorities as appropriate.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further confirm the appropriateness of the acceptance criteria, the MAH should re-evaluate the acceptance criteria for attributes related to potency tests using batch release data and clinical results after 6 months follow-up of 20 patients treated with commercial batches.	Interim report: at each annual renewal When 20 patients have been treated with 6 months follow-up
Non interventional post-authorisation safety and efficacy study: In order to further characterise and contextualise the long-term safety and efficacy of Zynteglo in patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β^0/β^0 genotype, the MAH should conduct and submit the results of a study based on data from a product registry (REG-501) and use data on patients treated with transfusions and/or HLA-matched allogenic HSCT treated patients from an established European registry as a comparator group.	Protocol submission: February 2020 Interim results: - at each annual renewal - Dec. 2024 - Dec. 2034 Final results: Q4 2039

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of Zynteglo in patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β^0/β^0 genotype, the MAH should submit interim and final data on Study HGB-207	Interim results: at each annual renewal Final results: December 2021
In order to confirm the efficacy and safety of Zynteglo in patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β^0/β^0 genotype, the MAH should submit interim and final data from patients with a severe non-β^0/β^0 genotype such as IVS-I-110 included in Study HGB-212.	Interim results: at each annual renewal Final results: December 2021
In order to confirm the efficacy and safety of Zynteglo in patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β^0/β^0 genotype, the MAH should submit interim data and the 5 years follow-up results of Study LTF-303.	Interim results: at each annual renewal Final results: December 2024

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING – METAL CASSETTE

1. NAME OF THE MEDICINAL PRODUCT

Zynteglo 1.2-20 × 10^6 cells/mL dispersion for infusion

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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 with a strength of 1.2-20 × 10^6 cell/mL.

3. LIST OF EXCIPIENTS

Also contains Cryostor CS5 and sodium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion

20 mL
See Lot Information Sheet for number of infusion bags and $CD34^+$ cells per kg for this patient.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in the vapour phase of liquid nitrogen at ≤-140°C until ready for thaw and administration. Keep infusion bag(s) in the metal cassette(s). Once thawed do not re-freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains genetically-modified cells. Unused medicine must be disposed of in compliance with the local biosafety guidelines.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

bluebird bio (Netherlands) B.V.
Stadsplateau 7
WTC Utrecht
3521AZ Utrecht
The Netherlands
Tel: +31 (0) 303 100 450
e-mail: medinfo@bluebirdbio.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1367/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Patient ID:
COI ID:
Last Name:
First Name:
Date of Birth:
DIN:
Lot:
Bag ID:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INFUSION BAG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zynteglo 1.2-20 × 10^6 cells/mL dispersion for infusion
Autologous $CD34^+$ cells encoding $\beta^{A\text{-}T87Q}$-globin gene.
For intravenous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Patient ID:
COI ID:
Last Name
First Name:
Date of Birth:
DIN:
Lot:
Bag ID:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

See Lot Information Sheet for number of infusion bags and $CD34^+$ cells per kg for this patient.
20 mL

6. OTHER

For autologous use only.

PARTICULARS TO APPEAR ON THE LOT INFORMATION SHEET INCLUDED WITH EACH SHIPMENT FOR ONE PATIENT

1. NAME OF THE MEDICINAL PRODUCT

Zynteglo 1.2-20 × 10^6 cells/mL dispersion for infusion

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Zynteglo is 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.

3. DONATION AND PRODUCT CODES

PATIENT INFORMATION

Name (Last, First):
Date of Birth (DD/MM/YYYY):
Weight at First Collection (kg):
Patient ID:

4. BATCH NUMBER, CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT, AND EXPIRY DATE

INFORMATION ON SUPPLIED LOT(S)

The following lot(s) was manufactured and included in the shipment:

Lot Number / COI ID	**Number of Infusion Bags**	**Bag ID** (First Infusion Bag)	**Bag ID** (Second Infusion Bag)	**Strength** (× 10^6 cells/mL)	**$CD34^+$ Cells** (× 10^6 $CD34^+$ cells)	**Expiry Date** (DD/MM/ YYYY)

5. DOSE OF THE MEDICINAL PRODUCT

Total Number of Infusion Bags: __
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.

6. OTHER SPECIAL WARNING(S), IF NECESSARY

SAVE THIS DOCUMENT AND PREPARE TO HAVE IT AVAILABLE AT THE TIME OF ZYNTEGLO INFUSION.

Read the package leaflet before use.
For autologous use only.

7. SPECIAL STORAGE CONDITIONS

INSTRUCTIONS FOR STORAGE AND USE

Store in the vapour phase of liquid nitrogen at ≤-140°C until ready for thaw and administration. Keep infusion bag(s) in the metal cassette(s). Once thawed do not re-freeze.

8. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains genetically-modified cells. Unused medicine must be disposed of in compliance with the local biosafety guidelines.

9. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MARKETING AUTHORISATION HOLDER AND NUMBER

bluebird bio (Netherlands) B.V.
Stadsplateau 7
WTC Utrecht
3521AZ Utrecht
The Netherlands
e-mail: medinfo@bluebirdbio.com

10. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1367/001

B. PACKAGE LEAFLET

Package leaflet: Information for the patient or carer

Zynteglo 1.2-20 × 10^6 cells/mL dispersion for infusion
Autologous $CD34^+$ cells encoding $\beta^{A\text{-}T87Q}$-globin gene

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

You will be given a **Patient Alert Card** which contains important safety information that you need to know about your treatment with Zynteglo. You should carry the Patient Alert Card with you at all times and show it to your doctor or nurse when you see them or if you are admitted to the hospital.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- Read the Patient Alert Card carefully and follow the instructions on it.

What is in this leaflet

1. What Zynteglo is and what it is used for
2. What you need to know before you are given Zynteglo
3. How Zynteglo is given
4. Possible side effects
5. How to store Zynteglo
6. Contents of the pack and other information

1. What Zynteglo is and what it is used for

Zynteglo is used to treat a serious genetic disease called transfusion-dependent beta-thalassaemia (TDT), which includes the disease commonly known as beta-thalassaemia major, in people 12 years and older. People with this condition cannot make enough haemoglobin, a protein in the blood that carries oxygen. More specifically, people with TDT do not make enough of a part of the haemoglobin called beta-globin, due to a gene defect. Because of this defect, people with TDT are anaemic and need frequent blood transfusions to survive.

Zynteglo is a type of medicine called gene therapy. It is made specifically for each patient, using the patient's own (also called autologous) blood stem cells. Zynteglo works by adding functional copies of the beta-globin gene into these cells, so that the patient can make enough beta-globin to increase total haemoglobin, improve anaemia, and carry more oxygen around their body. This reduces or eliminates the need for blood transfusions.

2. What you need to know before you are given Zynteglo

You must not be given Zynteglo if you:
- are allergic to any of the ingredients of this medicine (listed in section 6)
- are pregnant or breast-feeding
- have previously received gene therapy of your blood stem cells
- are allergic to any of the ingredients in the medicines you will be given for mobilisation and chemotherapy (see section 3).

Warnings and precautions
Talk to your doctor before you are given Zynteglo.

Before treatment with Zynteglo, you will be given medicines know as mobilisation medicine and chemotherapy medicine (see sections 3 and 4 for more information on these medicines, including possible side effects).

Before treatment with Zynteglo, your doctor will perform tests to make sure your heart and liver are functioning properly so you can be treated safely with Zynteglo.

Zynteglo is made specifically for you, using your own blood stem cells.

After you have been treated with Zynteglo, you will not be able to donate blood, organs, or tissues in the future. This is because Zynteglo is a gene therapy medicine.

Adding a new gene into the DNA of your blood stem cells could theoretically cause leukaemia or lymphoma, although no patients have developed leukaemia or lymphoma in clinical trials with Zynteglo. After treatment with Zynteglo, you will be asked to enrol in a registry for at least 15 years in order to better understand the long-term effects of Zynteglo. During the long-term follow-up, your doctor will monitor you for any signs of leukaemia or lymphoma.

Zynteglo is prepared using parts of the human immunodeficiency virus (HIV), which have been altered so that they cannot cause HIV infection. The modified virus is used to insert a functional beta-globin gene into your blood stem cells. Although this medicine will not give you HIV infection, having Zynteglo in your blood may cause a false positive HIV test result with some commercial tests that recognise a piece of HIV used to make Zynteglo. If you test positive for HIV following treatment, please contact your doctor or nurse.

Before receiving Zynteglo you will be given chemotherapy in order to remove your existing bone marrow. If Zynteglo cannot be administered after chemotherapy or if the modified stem cells do not take hold (engraft) in your body, the doctor may give you an infusion of your own original blood stem cells that were collected and stored before the treatment started (see also section 3, How Zynteglo is given).

After you receive Zynteglo, you may have a low number of platelets in your blood. This means that your blood may not be able to clot as well as normal and you may be prone to bleeding. You must get medical attention if you:
- bump your head or have a head injury
- have symptoms that could be from internal bleeding, such as unusual stomach or back pain, or severe headache
- have abnormal bruising or bleeding (such as bruising without injury, blood in your urine, stool, vomit, or cough up blood).

Your doctor will tell you when your platelet count has recovered to normal levels.

Other medicines and Zynteglo
Tell your doctor if you are taking, have recently taken or might take any other medicines.

You should not take hydroxyurea (a medicine for blood disorders) or any medicines for HIV infection from at least one month before you undergo mobilisation until at least 7 days after Zynteglo infusion (see also section 3, How Zynteglo is given).

You should stop taking medicines to remove iron from your body (so-called chelating agents: deferoxamine, deferiprone and/or deferasirox) 7 days before you start the chemotherapy before the infusion of Zynteglo (see section 3, How Zynteglo is given). Your doctor will advise you if and when you should start taking these medicines after Zynteglo infusion.

Talk to your doctor if you need to have any vaccinations.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, tell your doctor before you are given this medicine.

If you are a woman, you will be given a pregnancy test before starting mobilisation, before you are given chemotherapy, and before Zynteglo treatment in order to confirm that you are not pregnant.

Women who could become pregnant and men capable of fathering a child must start using a reliable method of contraception from before their blood stem cells are collected and continue until at least 6 months after receiving Zynteglo. Reliable methods of contraception include intra-uterine device or a combination of oral contraceptive (also know as the pill) and condoms.

The added gene from Zynteglo will not be passed on to your children. Your children are still at risk of inheriting your original beta-globin gene.

You should not be given Zynteglo if you are breast-feeding. It is not known whether the ingredients of Zynteglo can pass into breast milk.

It may no longer be possible for you to become pregnant or father a child after receiving chemotherapy medicine. If you are concerned about having children, you should discuss this with your doctor before treatment. Options may include providing reproductive material for storage in a tissue bank to use at a later time. For men, this may be sperm or testicular tissue. For women, this may be eggs (oocytes) or ovarian tissue.

Driving and using machines
Zynteglo has no influence on the ability to drive or use machines.

Sodium content
This medicine contains 391-1564 mg sodium (main component of cooking/table salt) in each dose. This is equivalent to 20-78% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Zynteglo is given

Zynteglo is given by a drip (infusion) into a vein. It can only be given in a specialised hospital by doctors who are experienced in treating patients with TDT, administering bone marrow transplants, and using gene therapy medicines.

Zynteglo can only be made if enough of the right kind of blood stem cells can be collected from your blood ($CD34^+$ blood stem cells). Approximately 2 months before treatment with Zynteglo, you will be given a mobilisation medicine that will move your blood stem cells from your bone marrow into your blood stream. The blood stem cells can then be collected by a machine that separates blood components (apheresis machine). It may take more than 1 day to collect enough blood stem cells to make Zynteglo and to store as replacement cells if Zynteglo cannot be given or does not work.

Time	What happens	Why
Approximately 2 months before Zynteglo infusion	Mobilisation medicine is given	To move the blood stem cells from your bone marrow into your blood stream.
Approximately 2 months before Zynteglo infusion	Blood stem cells are collected	To make Zynteglo and to serve as replacement cells if needed.
At least 6 days before Zynteglo infusion	A chemotherapy medicine is given for 4 days in a hospital	To prepare your bone marrow for treatment with Zynteglo.
Start of Zynteglo treatment	Zynteglo is given by a drip (infusion) into a vein. This will take place in a hospital and will take less than 30 minutes for each infusion bag. The number of bags will vary by patient.	To add blood stem cells containing functional copies of the beta-globin into your bone marrow.
After Zynteglo infusion	You will remain in the hospital for approximately 3-6 weeks	To recover and be monitored until your doctor is satisfied that it is safe for you to leave the hospital.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects observed in clinical studies with Zynteglo are related to mobilisation and blood stem cell collection or to the chemotherapy medicine used to prepare your bone marrow for treatment with Zynteglo.

You should discuss possible side effects due to the mobilisation medicines and chemotherapy medicine with your doctor. You should also read the package leaflets for these medicines.

Mobilisation and blood stem cell collection
Most of these side effects occur during or within a few days after mobilisation and blood stem cell collection but can occur later. Tell your doctor immediately if side effects become severe or serious.

Very common side effects (may affect more than 1 in 10 people)
- a low level of blood platelets, which may reduce the ability of blood to clot
- bone pain
- numbness and pain in hands and feet
- feeling sick (nausea)
- headache
- low blood calcium level

Common side effects (may affect up to 1 in 10 people)
- bleeding
- low oxygen level in blood
- low blood pressure
- abdominal pain
- back pain
- bone or muscle pain
- chest pain or discomfort
- other pain
- agitation
- abnormal blood test results (decrease in magnesium and potassium, too much citrate, or increase in white blood cells)

- abnormal heart rhythm
- bruising, bleeding or pain from catheter or injection site
- injection site reaction
- bruising
- dizziness, tiredness
- head discomfort
- excessive sweating
- flu like illness
- lip swelling
- tingling or numbness of the hands, feet, or mouth
- fever
- rash
- enlarged spleen which may result in pain in your upper left belly or left shoulder
- vomiting

Chemotherapy medicine

Tell your doctor immediately if you get any of the following side effects after receiving chemotherapy medicine. They usually happen within the first few days and several weeks after receiving chemotherapy medicine, but can also develop much later.

Very common (may affect more than 1 in 10 people)

- Pain in the right upper abdomen under the ribs, yellowing of eyes or skin, rapid weight gain, swelling of arms, legs and abdomen, and trouble breathing. These may be signs of a serious liver condition called veno-occlusive disease.
- Prolonged bleeding or bleeding without injury such as nosebleeds, bleeding from gums, or vaginal bleeding.

Other possible side effects

Tell your doctor immediately if side effects become severe or serious.

Very common side effects (may affect more than 1 in 10 people)

- low level of red and white blood cells, sometimes with a fever
- increase of certain enzymes in the blood which may indicate a problem with your liver
- a low level of blood platelets, which may reduce the ability of blood to clot
- unusual hair loss or thinning
- stomach pain, upset stomach, constipation, diarrhoea
- feeling sick (nausea), being sick (vomiting)
- fever
- soreness of the mouth
- inflammation of the throat
- changes in blood chemistry which may indicate low calcium, low potassium, low magnesium, low sodium, low phosphate, decrease in protein, or decrease in albumin
- dark patches on skin
- soreness of the rectum area
- trouble sleeping
- decreased appetite
- headache
- tiredness
- itchy skin

Common side effects (may affect up to 1 in 10 people)

- life-threatening inflammatory response to an infection along with low white blood cell count
- infections which may make you feel warm, chilly, or sweaty

- enlarged abdomen
- enlarged liver
- difficulty breathing
- abdominal pain
- bleeding or bruising
- blood in urine
- small tear in tissue that lines the anus
- dizziness, or sensation of feeling off balance or like the room is spinning
- anxiety
- positive test for Apergillus (lung disease caused by fungus)
- changes and abnormalities in heart rhythm
- pain in back, bone, skin, limbs, anus, or muscles
- heartburn
- inflammation of the gallbladder
- gallstones
- cough
- abnormal sense of taste
- difficulty swallowing
- swelling of the face
- feeling cold
- excess water in the body
- inflammation or infection of hair follicles
- decrease in speed of air leaving your lungs
- stomach discomfort with nausea and vomiting
- inflammation in the digestive tract
- gum disease
- piles (haemorrhoids)
- hiccups
- low blood pressure
- low body temperature
- low oxygen level in blood
- yellowing of skin and eyes
- pain in larynx (voice box)
- lack of energy
- soreness and swelling of the digestive tract lining which runs from the mouth to the anus
- irregular menstruation
- loss of function of your ovaries
- premature menopause
- spots on skin from bleeding under the skin
- skin that is discoloured, blotchy, or darker or lighter than normal.
- fluid in or around the lung
- dry, itchy skin
- dry lips
- rash with lesions, sometimes with pus
- inflamed skin lesions
- skin abrasion/scrape
- sweat gland disorder
- transfusion reaction
- weight decreased
- abnormal liver tests
- increased concentration of haemoglobin in cells
- decrease in magnesium, calcium, potassium, phosphate, albumin, sodium in blood
- excess acid in the body not removed by the kidneys

- increase or decrease in white blood cells
- low number of immature (not fully developed) red blood cells
- increase or decrease in blood protein
- increase in female hormones
- decreased testosterone

Zynteglo
Most side effects occur during or within a few days after treatment with Zynteglo but can occur later. Tell your doctor immediately if side effects become severe or serious.

Common side effects (may affect up to 1 in 10 people)
- low level of blood platelets, which may reduce the ability of blood to clot
- shortness of breath
- chest pain not due to a heart problem
- stomach pain
- flushing (redness and warmth of skin)
- pain in legs

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zynteglo

This information is intended for doctors only.

As this medicine will be given by a qualified doctor, they are responsible for the correct storage of the medicine before and during its use, as well as for its correct disposal.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer container label(s) and infusion bag label(s).

Store at ≤-140°C for up to a year. Do not thaw the product until it is ready to be used. Once thawed store at room temperature (20°C-25°C) and use within 4 hours.

This medicine contains genetically-modified cells. Unused medicine must be disposed of in compliance with the local biosafety guidelines.

6. Contents of the pack and other information

What Zynteglo contains
- The active substance of Zynteglo consists of your own blood stem cells that contain functional copies of the beta-globin gene that can be measured in your blood. The concentration is 1.2-20 × 10^6 $CD34^+$ cells (blood stem cells) per millilitre.
- The other ingredients are a solution used to preserve frozen cells and sodium chloride. See section 2, Sodium content.

What Zynteglo looks like and contents of the pack
Zynteglo is a clear to slightly cloudy, colourless to yellow or pink dispersion of cells that is supplied in one or more clear infusion bags, each packed in a transparent pouch inside a closed metal container.

Your name and date of birth, as well as coded information identifying you as the patient, are printed onto each infusion bag and each metal container.

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This leaflet was last revised in <{MM/YYYY}>
This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu<, and on the website of {name of MS Agency (link)}>.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Zynteglo is shipped from the manufacturing facility to the infusion centre storage facility in a cryoshipper, which may contain multiple metal cassettes intended for a single patient. Each metal cassette contains one infusion bag with Zynteglo. A patient may have multiple infusion bags. The infusion bag(s) must be kept inside the metal cassette(s) until ready to thaw and use.

Confirm that Zynteglo is printed on the infusion bag(s). Confirm that patient identity matches the unique patient information located on the infusion bag(s) and metal cassette(s) prior to infusion. Account for all infusion bags and confirm each infusion bag of Zynteglo is within the expiry date using the accompanying Lot Information Sheet.

Inspect each infusion bag for any breaches of integrity before thawing and infusion. If an infusion bag is compromised, follow the local biosafety guidelines and contact bluebird bio immediately.

Zynteglo is intended solely for autologous use.

After carefully removing the outer metal container, thaw each infusion bag at 37°C in a water bath or dry bath for approximately 2-4 minutes. Do not overthaw the medicinal product. Do not leave the medicinal product unattended and do not submerge the infusion ports if thawed in a water bath. After thaw, mix the medicinal product gently by massaging the infusion bag until all of the contents are uniform. Expose the sterile port on the infusion bag by tearing off the protective wrap covering the port. Access the infusion bag and infuse per the administration site's standard procedures for administration of cell therapy products. Do not use an in-line blood filter or an infusion pump. Do not sample, alter, or irradiate the medicinal product.

Administer each infusion bag via intravenous infusion over a period of less than 30 minutes. If more than one infusion bag is provided, administer each infusion bag completely before proceeding to thaw and infuse the next bag.

Zynteglo must not be re-frozen. Infuse as soon as possible and no more than 4 hours after thawing.

Flush all Zynteglo remaining in the infusion bag and any associated tubing with at least 50 mL of 0.9% sodium chloride solution to ensure as many cells as possible are infused into the patient.

This medicinal product contains genetically-modified cells. Local biosafety guidelines applicable for such products should be followed.

Healthcare professionals handling Zynteglo should take standard precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

Work surfaces and material which have potentially been in contact with Zynteglo must be decontaminated with a viricidal disinfectant according to the manufacturer's instructions. Local biosafety guidelines should be followed for unused medicinal products or waste material.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION AND PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.