FINOSE Joint HTA
Fimea NoMA TLV

FINOSE joint assessment report

Zynteglo (autologous cd34+ cells encoding βA-T87Q-globin gene)

Dispersion for infusion

Assessed indication
Zynteglo 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

Case number Norwegian Medicines Agency: 19/10874
Case number TLV: 687/2019
Case number Fimea: 004528/12.01.01/2019

FINOSE

The FINOSE is a Nordic collaboration of Finland, Norway and Sweden in HTA (Health Technology Assessment). The collaborating agencies are the Finnish Medicines Agency (Fimea), the Norwegian Medicines Agency (NoMA) and Sweden's Dental and Pharmaceutical Benefits Agency (TLV). The terms of the cooperation are clarified in the Memorandum of Understanding signed by the Director Generals in September 2017.

The agencies aim to make joint assessments of medicines, for both relative effectiveness and health economics.

The FINOSE collaboration is not aiming for joint decision making.

In this FINOSE report, Fimea and TLV acted as authors and NoMA had a reviewer role.

This is a joint assessment for an ATMP with a very small target population. Joint assessments for this type of products with very few patients in each country might potentially facilitate patient access to those products through the following mechanisms:
- A joint view on the products' benefits and costs could facilitate the practical organisation of patients who might need to travel between countries for treatments
- A joint view may also facilitate-potential future joint negotiations. However, procurement is not within the FINOSE team's remit.
- By introducing a new chapter on post launch evidence generation in this FINOSE report, a joint view is established on required follow-up. This could benefit the health care system and patients, as well as the company, by allowing for a more efficient follow-up of the product.
- For smaller companies with limited organisations in each country, a submission for a joint FINOSE assessment could reduce the administrative burden.

Many of these potential benefits of producing joint assessments for products with small target populations also apply to products with larger target populations so we see benefits in assessing those jointly as well of course in order to facilitate access to the patients.

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Clinical experts: Anne Grete Bechensteen, consultant, Oslo University Hospital; Honar Cherif, consultant haematologist, Uppsala University Hospital; Kirsi Jahnukainen, professor, paediatric haematologist and oncologist, Helsinki University Hospital; Olav Klingenberg, consultant, Oslo University Hospital. The clinical experts have been consulted regarding current clinical praxis, characterization of Nordic TDT patients and Zynteglo post launch evidence generation. The FINOSE group is not bound to the statements of the experts, interpretations and opinions on which the cost-effectiveness analysis should be based on.

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Case number Norwegian Medicines Agency: 19/10874
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Summary

- FINOSE has made a joint assessment of the clinical and cost effectiveness of Zynteglo within its marketing authorization "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".
- β -thalassaemia is a rare genetic blood disease that leads to varying degrees of anaemia. Symptoms include tiredness, weakness and shortness of breath. Patients with β^0/β^0 genotype produce no β-globin and usually present with severe disease symptomatology already in early childhood. Patients with non-β^0/β^0 genotype produce some β-globin and present with varying degrees of disease severity. Zynteglo is indicated to patients with non-β^0/β^0 genotype.
- In TDT β-globin production is so reduced that patients need regular red blood cell (RBC) transfusions for survival and to promote normal growth, normal physical activities and adequate health-related quality of life and avoid complications such as enlarged spleen.
- Frequent RBC transfusions cause too much iron to build up in the body. Iron overload leads to complications including liver cirrhosis, and endocrine complications such as diabetes, sterility, and heart failure. Therefore, patients with TDT need regular iron chelation therapy for preventing and treating iron overload.
- FINOSE agrees with the company that blood transfusion with iron chelation is the most relevant comparator for Zynteglo treatment. It is in line with Finnish, Norwegian and Swedish treatment guidelines.
- Zynteglo is an autologous beta-globin gene therapy that comprises a lentiviral vector which inserts functional copies of a beta globin gene, known as βA-T87Q into CD34+ haematopoietic stem cells, ex vivo. Gene therapy with Zynteglo requires myeloablative conditioning as pre-treatment. Zynteglo is a one-time treatment, which has the potential to increase haemoglobin production and eliminate or reduce dependence on chronic RBC transfusions.
- Zynteglo therapy requires qualified care centres and trained health care professionals, and the treatment will be offered in centres in some of the Nordic countries. Travel and prolonged stays for patients and their caregivers are required before, during and after treatment. These costs are not included in this FINOSE report since they are of national character.
- Organisation of long-term follow-up and need to share patients' health care data across national boundaries may pose additional challenges.
- The clinical evidence base for Zynteglo includes three single arm studies (HGB-204, HGB-205, HGB-207). An additional single-arm study (HGB-212) is ongoing. In these studies, total of 32 adult and adolescent patients with TDT and a non-β^0/β^0 genotype have been treated. Of the treated patients 24 (75 %) were evaluable for transfusion independence (TI), the primary end point in Studies HGB-204 and HGB-207.
- The majority of TI-evaluable patients, 20 out of 24 (83.3%), achieved TI and no longer needed regular blood transfusions. Among the 4 patients who did not achieve transfusion independence, the observed reduction in transfusion frequency ranged from 20.7 % to 100 %.
- There is an uncertainty regarding the company assumption whether the effects of Zynteglo (achieved TI) is sustained in the long term. There is, however, little evidence

on the persistence of the treatment effect: 17 patients had more than 2 years of follow-up and 7 patients had more than 4 years of follow-up.

- The benefits of Zynteglo are based on the assumption that complications associated with high iron levels and the impact of regular blood transfusions are reduced. The company claims that transfusion independence and chelation therapy is anticipated to improve patients' health-related quality of life (HRQoL) but the application includes no HRQL data from the clinical trials (HGG-204, HGB-205, HGB-207).
- The price, that the company has applied for Zynteglo is almost 17 million SEK This should be compared to lifelong treatment with blood transfusions and chelation therapy for transfusion dependence totalling almost 7.2 million SEK over a lifetime with a discount rate of 3 percent.
- According to the results of the company base case Zynteglo therapy leads to survival benefits of 4.29 life years and 8.17 quality adjusted life years (QALYs) gained compared to lifelong blood transfusions and iron chelation therapy.
- FINOSE presents two scenarios, with and without survival gains, resulting in 1 761 000 SEK and 2 137 000 SEK per QALY gained. There is an uncertainty whether all patients within the marketing authorization will benefit survival gains as there is a lack of long-term data. Thus, FINOSE presents two scenarios with and without survival gains, to illustrate how the results are affected.
- FINOSE has performed several one-way sensitivity analyses to explore how changes in individual parameter inputs affect the results. The main uncertainties according to FINOSE is the assumption that the success rate (achieved TI) is sustained over a lifetime. If the success rate is, e.g. sustained for ten years the cost per QALY gained rises to 5 372 000 SEK. The cost per QALY gained become even higher if a shorter time horizon is employed.
- FINOSE concludes that the main uncertainties of the economic analyses concern if the success rate (TI) is sustained and whether the survival gains based on the assumption that complications associated with high iron levels are reduced. The model is also very sensitive to the disutility associated with chelation therapy affecting long term quality of life gains.

The conclusions in the report may change if the premises the assessment is based upon will change in an important way.

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1 Scope

This report is a FINOSE joint assessment of Zynteglo 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.

The assessment is primarily based on the documentation presented by Bluebird Bio.

The aim of this FINOSE report is to inform national policy decision regarding the use of Zynteglo in Finland, Norway and Sweden. The primary focus of this report is to assess the relative effectiveness, the safety and the cost effectiveness of Zynteglo.

2 Background

2.1 Transfusion-dependent β-thalassaemia

Beta-thalassaemia (β-thalassaemia) is a genetic blood disease. β-thalassaemia is defined as transfusion-dependent thalassaemia (TDT) if a patient needs regular RBC transfusions. RBC transfusions are needed for survival and to promote normal growth, normal physical activities and adequate health-related quality of life. In clinical trials with Zynteglo, TDT has been defined as a history of transfusions of at least 100 mL/kg/year of red blood cells and at least eight transfusions per year in the two years preceding enrolment.

People with β-thalassaemia have decreased or absent synthesis of the β-globin chains that form part of the normal adult haemoglobin (HbA molecule). Mutations that completely inactivate the β-gene and β-globin production are classified as β^0-mutations, whereas mutations that lead to reduction of the β-globin production are classified as β^+ or β^{++}-mutations [1].

Generally, people with two β^0 mutations (β^0/β^0 genotype) produce no β-globin and usually present with severe disease symptomatology already in early childhood. Patients with other genotype combinations (collectively are known as non-β^0/β^0 genotype) produce some β-globin and present with varying degrees of disease severity[1] [2].

Patients with non-β^0/β^0 genotype are a very heterogeneous patient group. According to the FINOSE clinical experts, some children need to start transfusions due to failure to thrive already in early childhood, while some of the patients have moderate anaemia during childhood but their disease becomes more severe during teenage years and they start receiving regular red blood cell (RBC) transfusions because of diminished exercise tolerance, poor quality of life and for signs of enlarged spleen and skeletal changes.

TDT patients require regular lifelong RBC transfusions to manage the underproduction of β-globin. Without adequate transfusion support, TDT patients would suffer several complications and a short life span. Serious complications may include cardiomyopathy, pulmonary hypertension, osteoporosis, skeletal deformities, arthropathy, hepatosplenomegaly, delayed puberty and gonadal failure. Iron chelation treatment is necessary to prevent iron accumulation in organs such as liver, heart and endocrine system. Even when adequately managed by blood transfusions and chelation treatments, patients with β-thalassaemia might experience organ dysfunction in the long-term, such as cardiomyopathy and hepatic causes [2].

TDT is a rare disease in the Nordic countries. Endemic populations are primarily found in South Asia, the Middle East, North Africa, and Southern Europe. Most of our Nordic patients are immigrants or their descendants from those endemic areas. A Swedish registry study by Hemminki et al covering the years 1997 to 2010 showed that 69,1 percent (325/470) of those diagnosed with β-thalassaemia in Sweden during that period were immigrants and that Iraq, Iran and Thailand are the most common countries of origin for immigrants with thalassaemia [3]. Precise size of Nordic TDT population is not known. Roughly estimated number of TDT patients is 15 in Finland, 30-50 in Norway and 100-400 in Sweden. Approximately 20-40 % of them are expected to be eligible for Zynteglo treatment. These estimates are made by FINOSE clinical experts and by the company.

[1] However, it should be noted that classification of β^0 and non-β^0 mutations may not be always straightforward. An example of this is mutation IVS1-110 (G→A), which is classified as β^+ in e.g. Thein et al 2013 [1] and in clinical trials HGB-204 and HGB-205, but equivalent to β^0 mutations in subsequent trials HGB-207 and HGB-212 (for description of the trials see section 3.1). According to literature, only 10–20 % of the mRNA resulting from transcription of the β-globin gene with this mutation is normal. [1]

2.2 Treatment with Zynteglo

Zynteglo is a gene therapy involving transplantation of modified autologous stem cells. Zynteglo was designated an orphan drug in 2013 and granted conditional market approval in the EU on May 29, 2019 via the centralised procedure. The post-marketing obligations include to submit final results from the clinical trials ongoing at the time of evaluation and to set up a product registry study where the long term safety and efficacy results are compared to registry data of patients undergoing allogeneic human stem cell transplantation for the disease.

2.2.1 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 HSCT is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available [4].

2.2.2 Mechanism of action

Transplanted autologous haematopoietic stem cells, transduced with functional copies of a modified β-globin gene, engraft in the patient's bone marrow and differentiate to produce red blood cells with increased β-globin production.
Intention is to correct the underlying genetic deficiency and production of gene-derived beta-globin with the aim of attaining transfusion-independence

2.2.3 Posology and method of administration

The minimum recommended dose of Zynteglo is 5.0×10^6 CD34+ cells/kg for adults and adolescents 12 years of age and older.

Zynteglo is intended for autologous use and should only be administered once. It 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 [4]. The company has informed FINOSE, that it anticipates making Zynteglo treatment available in two qualified treatment centres in the Nordic countries: one in Sweden and one in Denmark.

The treatment can be divided into six steps. These steps are also illustrated in **figure 1**.

1-2) **Mobilisation and apheresis**: Collection of autologous CD34+ stem cells for medicinal product manufacturing. In clinical studies granulocyte-colony stimulating factor (G-CFS) and plerixafor[2] were used for mobilisation of CD34+ stem cells. Duration of steps 1-2 is five to six days and it will take place approximately two months prior to Zynteglo infusion. [4]

3) **Stem cell processing** in the manufacturing site: cell processing and transduction process takes four days and is followed by extensive quality control testing, which takes six to eight weeks. This will happen in a centralized manufacturing site located in Munich, Germany. [2]

4) **Pre-treatment myeloablative conditioning**: Conditioning can be started when the complete set of infusion bag(s) constituting the dose of Zynteglo has been received and stored at the administration site. In clinical studies busulfan treatment was used for conditioning and patients received also supportive treatment such as prophylaxis for seizures and veno-occlusive disease (VOD). Duration of step 4 is

[2] N.B. "Plerixafor was not authorised in the EU for use in paediatric subjects at the time of MAA review and did not have an indication for use in non-malignant diseases" (Zynteglo EPAR p. 133)

four days + 48 hours of washout and it will take place at least six days prior to Zynteglo infusion. [4]

5) **Zynteglo administration**

6) **After Zynteglo administration**: According to Zynteglo SPC [4], patients are recommended to stay in hospital for 3-6 weeks.

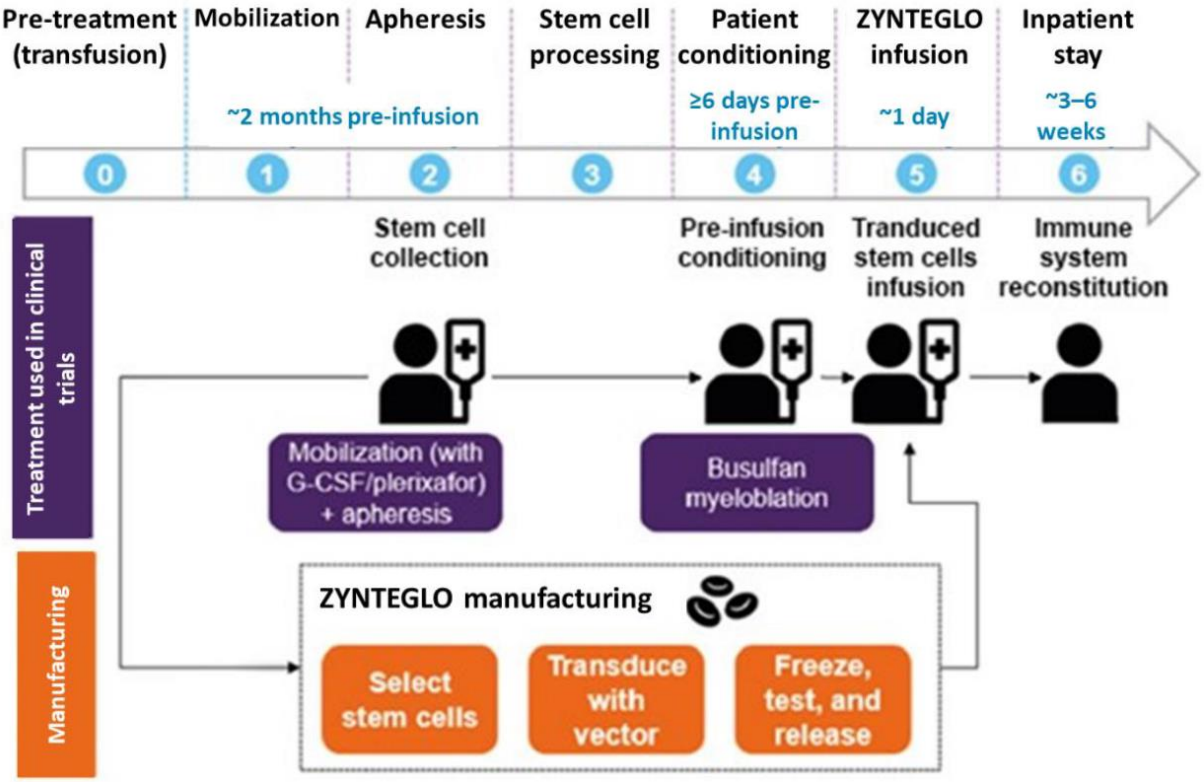


Figure 1 Overview of the Zynteglo manufacturing and treatment pathway (Reference: Company's submission material [2]

2.3 Treatment of transfusion dependent β-thalassaemia

A brief summary of Thalassaemia International Federation (TIF) guidelines for management of TDT [5] is presented below. The following section (2.3.2) includes a summary of the Nordic guidelines.

2.3.1 TIF Guideline for Treatment of TDT

The standard treatment of TDT is lifelong regular RBC transfusions, usually given every two to five weeks. The goal is to maintain pre-transfusion haemoglobin (Hb) level above 9-10.5 g/dL. For some patients a higher pre-transfusion Hb level may be appropriate due to heart disease or other medical conditions. [5]

Due to regular RBC transfusions, iron accumulation is a common problem for TDT patients. Iron chelation therapy is needed to balance the rate of iron accumulation. It is important to start chelation treatment preventively, before toxic levels of iron have accumulated. Once iron has deposited in some tissues, damage is often irreversible. Three different chelators are currently available and they can be used as monotherapy or as different combinations [5]:

- desferrioxamine (DFO), administration as slow (8-12 hours) infusions subcutaneously, intramuscularly or intravenously at least 5 times per week
- deferiprone (DFP), daily oral administration and
- deferasirox (DFX), daily oral administration.

Spleen removal or splenectomy is a treatment option for some of the patients. It is common to the pathophysiology of β-thalassaemia that red blood cells are destroyed by the reticuloendothelial system. This happens particularly in the spleen which results in spleen enlargement (splenomegaly). The rationale for splenectomy is to decrease blood consumption and transfusion requirement associated to enlarged spleen with the ultimate goal of reducing iron overload.

Nowadays splenectomy is not as common as it was some decades ago because Hb level can be controlled more efficiently with current RBC transfusion regimens and adequate intervals between transfusions [5]. According to FINOSE clinical experts, splenectomy is associated with a variety of adverse outcomes in patients with thalassemia including higher risk of venous thromboembolism, pulmonary hypertension, leg ulcers, silent cerebral infarction and post-splenectomy sepsis. Nevertheless, the size of the spleen should be carefully monitored for all TDT patients [5]. A category of patients that still may need of splenectomy is immigrants with a history of suboptimal transfusion treatment.

Haematopoietic stem cell transplantation (HSCT) is the only treatment that can be considered curative for TDT [5]. According to the company's submission material [2], 25-30 % of patients have an HLA-matched relative donor for HSCT. Age and comorbidities - both related to iron burden - may affect the probability of successful HSCT. It is recommended to perform HSCT at an early age or before complications due to iron overload have developed [5].

2.3.2 Treatment guidelines in Finland, Norway and Sweden

In this section RBC transfusion and chelation treatment guidelines for TDT patients in Nordic countries are described. HSCT, splenectomy and other treatment options are not described because they are not relevant comparators for this assessment.

Finland

In Finland, there are no national guidelines for treatment of TDT. One review article [6] was identified but it is nearly 10 years old. According to this review, treatment and follow-up of thalassaemia major[3] is allocated for haematologists, and paediatric patients should be referred to university hospitals. University hospitals have internal guidelines which are not publicly available.

[3] β-thalassaemia can be also classified as β-thalassaemia minor, intermedia or major. The scope of this assessment is treatment of transfusion dependent thalassaemia (TDT). Definition of TDT is mostly comparable to thalassaemia major but they are not exact synonyms.

According to the Finnish clinical expert, adult and adolescent TDT patients treated in Finland receive RBC transfusions every 3-4 weeks (approximately 15 transfusions per year). The goal is to keep pre-transfusion Hb at reference ranges 90-100 g/L. In Finland, deferasirox is the most commonly used chelation treatment (table 1) and it is currently (in February 2020) the only chelator that is reimbursed and available for TDT patients in Finland.

Norway
Two treatment guidelines for paediatric TDT patients are available online [7, 8]. Regular transfusions are recommended for children who have Hb ≤(6)-7 g/dL at 2-3 measurements at 2-3 week intervals together with clinical symptoms/signs of anaemia. Pre-transfusion Hb level between 9.0 and 10.0 g/dL is recommended. Usually RBC dose is 10-15 mL/kg given every 3-4 weeks. However, there can be individual variation in both RBC dose and transfusion interval. According to Norwegian clinical expert, TDT patients typically receive transfusions every 2 to 5 weeks (i.e. 12-24 transfusions per year).

It is recommended to start chelation treatment after one year of regular transfusions (10-15 transfusions) or if serum ferritin exceeds 1000 µg/L. Chelation treatment therapy should be started before there is clinical signs of iron toxity [8]. Subcutaneous desferrioxamine is the primary option for iron chelation, and other options are deferasirox and deferiprone [7]. They can be used as monotherapy or in different combinations. According to Norwegian clinical expert, deferasirox and desferrioxamine monotherapies are the most commonly used chelation treatments in Norway (table 1).

Sweden
In Sweden, a treatment guideline for paediatric TDT patients is 11 years old [9] but guideline for adult TDT patients has been updated in 2019 [10].

<u>Children and adolescents</u>
For children and adolescents, clinical findings and symptoms are more important criteria for starting RBC transfusions than Hb level. For example, patients with Hb level 70-80 g/L can be followed without transfusions if situation is good with growth, bone, heart and spleen. [9]

For those with regular RBC transfusions, recommended pre-transfusion Hb level is above 95-100 g/L. In early childhood, the recommended dose of RBCs is 15-20 ml/kg every 4 weeks and later on 7.5-10 ml/kg every 2 weeks. Chelation treatment should be started after first 10-15 RBC transfusions or if serum ferritin level is ca. 1000 µg/L. [9]

<u>Adults</u>
RBC is the bedrock of the treatment. The goal is to keep Hb level above 105 g/L and pre-transfusion Hb level above 95-105 g/L. To achieve this, most of the adult patients need 2-3 units of RBC transfusions (erythrocyte concentrate) every 2 to 3 weeks. [10]

Currently available chelators in Sweden are desferrioxamine, deferiprone and deferasirox. They can be used as monotherapy or as combination of two products. According to Swedish clinical expert, combination of deferiprone and deferasirox is the most commonly used chelation treatment in Sweden (Table 1).

There is large individual variation in frequency of transfusions and dose of chelation treatment. Therefore, TDT patients need to be regularly monitored for treatment response, adverse events and iron accumulation in blood, liver and heart. [10]

Table 1: Distribution of iron chelator regimens in each country, estimated by FINOSE clinical experts

Chelator regimen	Mode of Administration	Finland	Norway	Sweden
Deferasirox	Oral	50 %	50 %	20 %
Deferiprone	Oral	5 %	20 %	10 %
Desferrioxamine	s.c.	30 %	30-50 %	10 %
Deferiprone + Desferrioxamine	Oral + s.c.	5 %	30 %	10 %
Deferiprone + Deferasirox	Oral	5 %	<10 %	50 %
Deferasirox + Desferrioxamine	Oral + s.c.	5 %	<10 %	0 %

s.c.: subcutaneous

2.3.3 Comparator

The company uses a combination of RBC transfusions and iron chelation therapy as comparator to Zynteglo. The chosen comparator is in line with Finnish, Norwegian and Swedish treatment guidelines.

FINOSE conclusion: FINOSE agrees with company that RBC transfusions with iron chelation therapy is the relevant comparator as this is the primary treatment according to national guidelines and the clinical experts.

2.4 Severity of the disease

Transfusion dependent β-thalassaemia is a congenital disease that lead to premature death without adequate treatment. The focus of this assessment is in TDT patients with non-$\beta^0\beta^0$ genotype, which is a less severe form of the disease compared to patients with two β^0 mutations (β^0/β^0 genotype).

Until mid-1960's, death before 12 years of age was common among TDT patients [11]. The first iron chelation treatment desferrioxamine was introduced in in late 1960's [11] and prognosis of patients has improved thereafter. Other milestones have been bone marrow transplantations since 1981 and introduction of the first oral iron chelator deferiprone in mid 1990's [12]. Good results have also been achieved with regular blood transfusions and tailor-made chelation treatment in specialist centres [11, 13]. Management of comorbidities such as hepatitis C or diabetes has also improved the survival of these patients [13].

The FINOSE authors did not identify any studies including Nordic β-thalassaemia patients. Some long-term data from European countries such as Cyprus, Greece and Italy are available, and these studies are briefly summarized in appendix 1. For patients born in 1970's, survival rate at age of 20 was 96-99% [14, 15] and at age of 30 years it was 93 % [15]. In a Greek study, the estimated overall survival at age of 50 years was 65% [13]. However, survival estimates of these studies are not directly comparable with our current Nordic TDT population covered by the indication of Zynteglo for the following reasons: The iron chelation regimens have improved over time and the results do not reflect the treatment effects of the most recent iron chelators. For example, in the Greek study, patients who were 50 years old at the time of data collection (year 2009), have lived their childhood in 1960's when no adequate iron chelation treatment was available. Also, the documentation of the earlier studies does not allow comparison of genetic (β^0/β^0, non- β^0/β^0) and other important patient characteristics and of availability and quality of health care.

In the company's submission [2] it is stated that TDT patients have low health-related quality of life (HRQoL) compared with general population norms in Western countries such as US, UK, Italy, and France. However, in TIF guidelines [5] it is stated that "with well-organized care a patient with thalassaemia will live a good quality life into middle age and beyond, including

the possibility of raising a family of their own." According to FINOSE clinical experts, transfusion dependency, chelation treatment, frequent health care visits and complications and stress associated with a life-long chronic disease have substantial impact on patients' quality of life. However, in an assessment of the iron chelating drug Exjade performed by TLV (dnr 2986/2009) the company provided HRQoL data from 274 TDT patients participating in an international clinical trial where the patients switched iron chelation therapy from a subcutaneous to an oral formulation. HRQoL was measured using the SF-36 generic instrument before and after the switch resulting in utility weights of 0,845 for subcutaneous iron chelation therapy and 0,882 for oral iron chelation therapy. This would indicate that the measured HRQoL was close to what is expected for the normal population.

As a substantial share of Nordic β-thalassemia patients are first degree immigrants from Asia and Northern Africa there is a risk that they have not received optimal transfusion and/or iron chelation therapy before coming to the Nordics. Therefore, it is possible that there is a subgroup of patients with more severe morbidities and poorer long-term prognosis compared to those receiving optimal care since the onset of the disease. It is not known how large such a subgroup is, however.

FINOSE conclusion: The FINOSE authors note that the assessment of severity of disease is challenging due to following reasons: TDT patient population is very heterogeneous and no data is available to describe the characteristics of Nordic non-β^0/β^0 TDT patients.

3 Clinical efficacy and safety

The assessment of clinical efficacy and safety is based on the evidence included in the submission dossier [2] prepared by the company. The authoring team has checked the information retrieval included in the company's submission dossier for completeness against

- a search in ClinicalTrials.gov and PubMed
- the studies included in the European public assessment report (EPAR) [16].

3.1 Clinical trials

The evidence on the safety and efficacy of Zynteglo in the treatment of TDT is based on

- two phase 1/2 trials (HGB-204 and HGB-205) [17, 18]
- two ongoing phase 3 trials (HGB-207 and HGB-212) [19-21]
- long term follow-up study (LTF-303), where all subjects who have completed their month 24 post-Zynteglo-infusion-visit in the trials (HGB-204, HGB-205, HGB-207 and HGB-212) will be enrolled (ClinicalTrials.gov identifier: NCT02633943).

In the trials, patients were considered to be transfusion dependent (TD) 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 two years preceding enrolment. The details of the eligibility criteria in the clinical trials are reported in appendix 2.

The four trials are described in figure 2 and table 2. In this assessment report, the results of clinical efficacy (section 3.1.2) are based on 32 treated TDT patients aged ≥12 years with non-β^0/β^0 genotype (HGB-204: n = 10; HGB-205: n = 4; HGB-207: n = 15, HGB - 212: n = 3). The results of clinical safety (section 3.1.3) are based on all patients from these studies irrespective of the genotype and age.

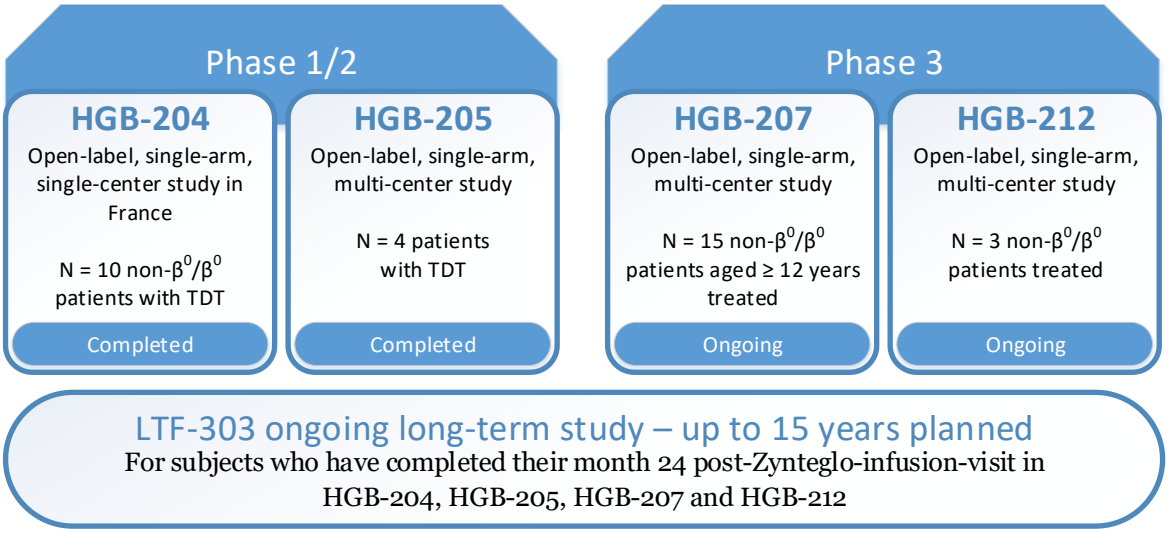


Figure 2: Summary of relevant trials. Modified from: https://www.zynteglo.eu/efficacy

Table 2: Summary of relevant trials

Study NCT-number [primary reference]	**Study design**	**Treated study population**	**Intervention**	**Primary efficacy endpoints**
HGB-204 NCT01745120 [17]	- phase 1/2 - open-label - single-arm - multi-site -	10 patients with non-β^0/β^0 genotype 8 patients with β^0/β^0 genotype	Zynteglo non-commercial manufacturing process	- Proportion of patients with sustained production ≥2.0 g/dL HbA containing $\beta^{A\text{-}T87Q}$-globin for the 6 months between months 18 and 24 post transplant - Transfusion independence (TI) by month 24
HGB-205 NCT02151526 [17, 18]	- phase 1/2 - open-label - single-arm - single- site	4 TDT patients with non-β^0/β^0 genotype	Zynteglo non-commercial manufacturing process	- RBC transfusion requirements per month and year post transplant - number of total inpatient hospital days (post transplant discharge) at 6, 12, and 24 months - Transfusion independence (TI) by month 24
HGB-207 NCT02906202 [19-21]	- phase 3 - open-label - single-arm, - multi-site	15 patients: ≥12 years, non-β^0/β^0 genotype[a] (Cohort 1) 6 patients: <12 years, non-β^0/β^0 genotype[a] (Cohort 2)	Zynteglo commercial manufacturing process	- Transfusion independence (TI)
HGB-212 NCT03207009	- phase 3 - open-label - single-arm, - multi-site	3 patients: ≥12 years, non-β^0/β^0 IVSI-110 genotype 1 patient: <12 years, non-β^0/β^0 IVSI-110 genotype 2 patients: β^0/β^0 genotype	Zynteglo commercial manufacturing process	- Transfusion reduction (TR)

[a] For the purpose of HGB-207 study, the HBB mutation IVS I-110 (G→A) [Human Genome Variation Society (HGVS) nomenclature: HBB:c.93-21G>A] was considered equivalent to a β^0 mutation. For that reason, subjects with the non-β^0/β^0 IVS I-110 (G→A) genotype were excluded from the study.
HbA = Adult Haemoglobin; **RBC** = Red Blood Cells; **TI** = Transfusion independence; **TR** = transfusion reduction.

The phase 3 studies (HGB-207 and HGB-212) are conducted with different Zynteglo manufacturing process compared to non-commercial version of Zynteglo in the phase 1/2 studies

(HGB-204 and HGB-205), resulting in increased average number of functional copies of the transgene (βA-T87Q-globin) integrated in the autologous CD34+ cells. According to the company, the aim was to increase the level of production of the transferred β-globin gene to enable subjects with little or no endogenous β-globing production to achieve TI. However, it is yet to be seen whether the increase in production is sufficient, because the trial HGB-212 with these patients has not yet any results.

3.1.1 Methods

HGB-204

HGB-204 was a single-arm, multi-site, single dose Phase 1/2 study. In total, 10 TDT subjects aged ≥12 years with non-β^0/β^0 genotype were treated with Zynteglo in the study. Patients were enrolled from Australia, Thailand and the United States.

All patients underwent mobilisation with G-CSF and plerixafor prior to apheresis of HSCs. After transduction, cryopreservation, testing, and release of the drug product, patients underwent myeloablative conditioning with intravenous busulfan for four consecutive days. Patients received non-phenytoin prophylactic agents to reduce seizure risk. Zynteglo (≥3.0 × 10^6 CD34+ cells/kg) was infused after a 72-hour washout period, and patients were monitored until their condition was medically stable.

HGB-205

HGB-205 was a single-arm, single site, single dose, Phase 1/2 study. In total, four TDT subjects aged ≥12 years with non-β^0/β^0 genotype were treated with Zynteglo in the study. The study includes one subject with homozygous IVS-I-110 mutation, which was considered equivalent to β^0/β^0 genotype in HGB-207 and HGB-212 because of low levels of endogenous β-globin production. Subjects were enrolled form a single hospital in France (Hôpital Universitaire Necker - Enfants Malades).

Patients received enhanced RBC transfusions for at least three months before stem cell harvesting to maintain Hb above 11.0 g/dL; the aim was to enrich for bona fide HSCs in the harvested CD34+ cell compartment by suppressing the erythroid lineage expansion and skewing that occurs in β-thalassaemia. Zynteglo (≥3.0 × 10^6 CD34+ cells/kg) was infused after a 72-hour washout period after receiving busulfan conditioning, and patients were monitored until their condition was medically stable.

HGB-207

HGB-207 is a phase 3 trial enrolling subjects with TDT with non-β^0/β^0 genotype. For the purpose of the study, the non-β^0/β^0 IVS I-I10 (G→A) genotype was considered equivalent to a β^0/β^0 genotype. For that reason, subjects with the non-β^0/β^0 IVS I-110 (G→A) genotype were excluded from the study.

At the 12 June 2019 data cut, 15 subjects aged ≥12 years (cohort 1) had been treated with Zynteglo. Subjects were recruited from France, Germany, Greece, Italy, Thailand, United Kingdom and United States.

All patients underwent mobilisation with G-CSF and plerixafor prior to apheresis of HSCs. After transduction, cryopreservation, testing, and release of the drug product, patients underwent myeloablative conditioning with intravenous busulfan for four consecutive days. Patients received non-phenytoin prophylactic agents to reduce seizure risk, plus ursodeoxycholic acid or defibrotide to reduce the risk of veno-occlusive disease/hepatic sinusoidal obstruction syndrome.

After at least 48 hours of washout, Zynteglo was administered by intravenous infusion at a dose of ≥5.0 × 10^6 cells/kg (a higher target dosage[4] than in the phase 1/2 trials). Patients were followed up daily in the transplant unit for adverse events (AEs) and laboratory parameters to monitor bone marrow engraftment and were discharged once they were considered medically stable.

HGB-212
HGB-212 is a phase 3 trial enrolling people with TDT who have β^0/β^0 genotypes. For the purpose of the study, the non-β^0/β^0 IVS I-I10 (G→A) genotype was considered equivalent to a β^0/β^0 genotype. Therefore people with the non-β^0/β^0 IVS I-I10 (G→A) genotype are eligible for inclusion.

Planned number of study patients is 18. As of April 12th 2019 (interim data cut) six patients had been treated with Zynteglo. From the six patients three were aged ≥12 years with non-β^0/β^0 IVS-I-110 genotype. None of the patients with the non-β^0/β^0 IVS-I-110 genotype (n = 3) had completed the month 12 follow-up visit.

Long-term follow-up study (LTF-303)
All subjects who have completed their month 24 visit in HGB-204, HGG-205, HGB-207 and HGB-212 studies will be enrolled into the long-term follow-up Study LTF-303, in which subjects will be followed for 13 years (a total of 15 years of follow-up after Zynteglo infusion).

As of June 2019 (interim data cut) 17 subjects have been enrolled to the study with the longest follow-up period being 61.3 months post-Zynteglo infusion. Efficacy assessments include (but are not limited to) maintenance of VCN in peripheral blood cells, interval transfusions required (mL/kg pRBCs), therapeutic phlebotomy (blood draw), iron chelator use, and measures of iron overload. Safety assessments include (but are not limited to), physical examinations, documentation of serious and drug-product related adverse events (AEs), complete blood counts, and surveillance for evidence of insertional mutagenesis.

3.1.2 Results for clinical efficacy

The results presented in this report reflect the data cut from June 2019 for all four studies (HGB-204, HGB-205, HGB-207, HGB-212). In comparison, the data that was submitted to EMA as part of marketing authorisation application process and informed the summary of product characteristics (SPC) document, the most recent data is from December 2018 data cut.

Patient disposition and baseline characteristics
Patient disposition in the four studies is described in table 3.

- All treated subjects in the HGB-204 and HGB-205 studies have been followed until the completion of their month 24 visit.
- In the HGB-207 study all 15 treated patients have at least three months follow-up, and 10 patients are TI evaluable with at least 12 months follow-up. Three patients have been followed through completion of their month 24 visit.
- In the HGB-212, three patients have been treated, but due to a limited follow-up time, none are yet evaluable for transfusion independence (TI).

The baseline characteristic of the subjects treated with Zynteglo are reported in appendix 3. In HGB-204, HGB-205 and HGB-207, a total, 24 subjects, between the age of 12–34, were TI evaluable. Their pre-treatment pRBC transfusion frequency ranged from 10 to 24.5 transfusions/year. Pre-treatment baseline liver iron content ranged from 1.2 to 26.4 mg/g, cardiac T2 measurement from 27 to 54 msec and serum ferritin from 349 to 10 020 pmol/L. A detailed

[4] According to the company, improvement of engraftment may be achieved with higher cell doses. In practice, all patients so far have been treated with cell doses higher than 5.0 x 10^6 cells/kg, also in the phase 1/2 trials.

description of iron burden at baseline in ITT-population and comparison by Asian sub-populations are reported in appendix 4.

Table 3: Disposition of transfusion dependent (TDT) patients with a non-β^0/β^0 genotype and age ≥ 12 years by study at the 12 June 2019 data cut.

	HGB-204	HGB-205	HGB-207[a]	HGB-212[b]
Subjects mobilized (ITT), n (%)	11 (100)	4 (100)	16 (100)	3 (100)
Subjects treated with drug product (TP), n (%)	10 (90.9)	4 (100)	15 (93.8)	3 (100)
Subjects with successful engraftment (SEP), n (%)	10 (90.9)	4 (100)	15 (93.8)	3 (100)
TI evaluable subjects	10 (90.9)	4 (100)	10 (62.5)	0
Subjects completing follow-up visit (months post-DPI), n (%)				
Month 3	10 (90.9)	4 (100)	15 (93.8)	3 (100)
Month 6	10 (90.9)	4 (100)	15 (93.8)	3 (100)
Month 9	10 (90.9)	4 (100)	13 (81.3)	1 (33.3)
Month 12	10 (90.9)	4 (100)	11 (68.8)	0
Month 15	10 (90.9)	4 (100)	8 (50.0)	0
Month 24	10 (90.9)	4 (100)	3 (18.8)	0
Month 30	10 (90.9)	4 (100)	0	0
Month 36	10 (90.9)	4 (100)	0	0
Month 42	7 (63.6)	4 (100)	0	0
Month 48	5 (45.5)	2 (50,0)	0	0
Total duration of follow-up post (DPI), months				
N	10	4	15	3
Mean (SD)	46.1 (8.1)	50.1 (11.0)	16.6 (6.3)	7.3 (1.6)
Median	44.6	49.6	16.9	7.8
Min – max	35.8–61.3	40.5–60.6	6.9–26.3	5.6–8.6

[a] cohort 1: patients aged ≥ 12 years, with non-β^0/β^0 genotype.
[b] patients aged ≥ 12 years, with non-β^0/β^0 IVS I-I10 (G→A) genotype.
DPI = drug product infusion, **ITT** = intention to treat, all subjects who initiate any study procedures, beginning with mobilisation by G-CSF and/or plerixafor; **SEP** = successful engraftment population, all subjects who have successful neutrophil engraftment (NE) after Zynteglo infusion; **TI** = transfusion independent; **TP**= transplant population, all subjects who receive Zynteglo treatment.

Transfusion independence

Transfusion independence (TI) requires 12 months without any pRBC transfusion while maintaining a weighted average Hb of ≥9 g/dL. Calculation of time period of TI will start when subjects achieve an Hb ≥9 g/dL with no transfusions in the preceding 60 days. The detailed definition for TI is in appendix 5. The definition was similar across all clinical studies. Of the TI evaluable population 83 % (20/24) met the definition of TI (Table 4).

Table 4: Transfusion independence for non-β^0/β^0 genotype patients in HGB-204, HGB-205 and HGB-207.

Parameter	Static	HGB-204	HGB-205	HGB-207	Overall
Number of TI-evaluable patients	n	10	4	10	24
TI at any time	n	8	3	9	20
	% (95 % CI)	80.0 (44.4 - 97.5)	75.0 (19.4 - 99.4)	90.0 (55.5 - 99.7)	83.3 (62.6 - 95.3)

In the HGB-205 study one subject out of the four did not qualify for TI despite having 12 months without any pRBC transfusion. The subjects weighted average Hb was less than 9 g/dL at least at one time point. The subject is homozygous for the IVS-I-110 mutation and thus had minimal endogenous β-globin production. For this reason, patients with IVS-I-110 mutation in both alleles (and β^0/IVS-I-110) were considered equivalent to β^0/β^0 genotype patients and thus excluded from Study HGB-207 and grouped with the β^0/β^0 subjects in Study HGB-212.

In Study HGB-207, nine out of the ten TI-evaluable patients had become TI. The remaining five patients, who have not been followed long enough for TI-evaluation, appear to be transfusion free as reflected by the five bottom bars in (Figure 3).

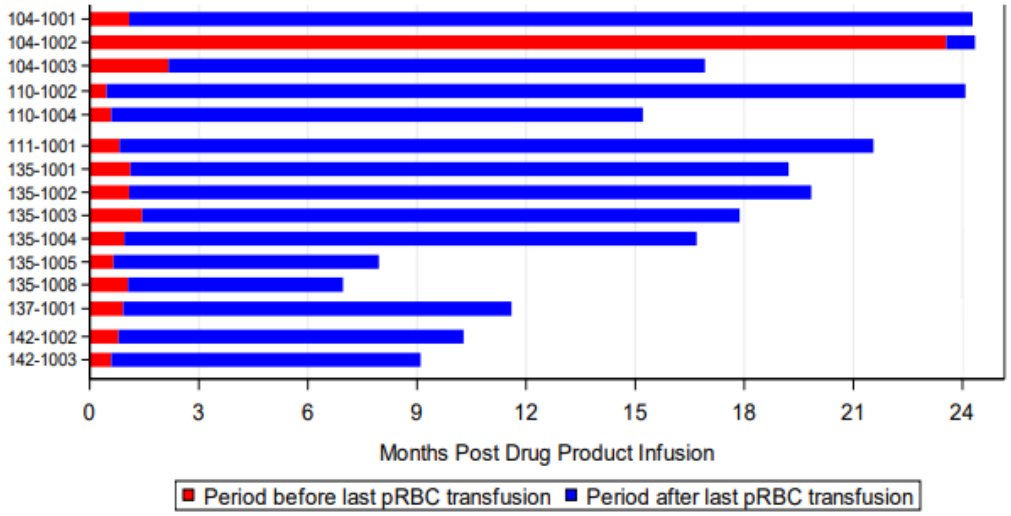
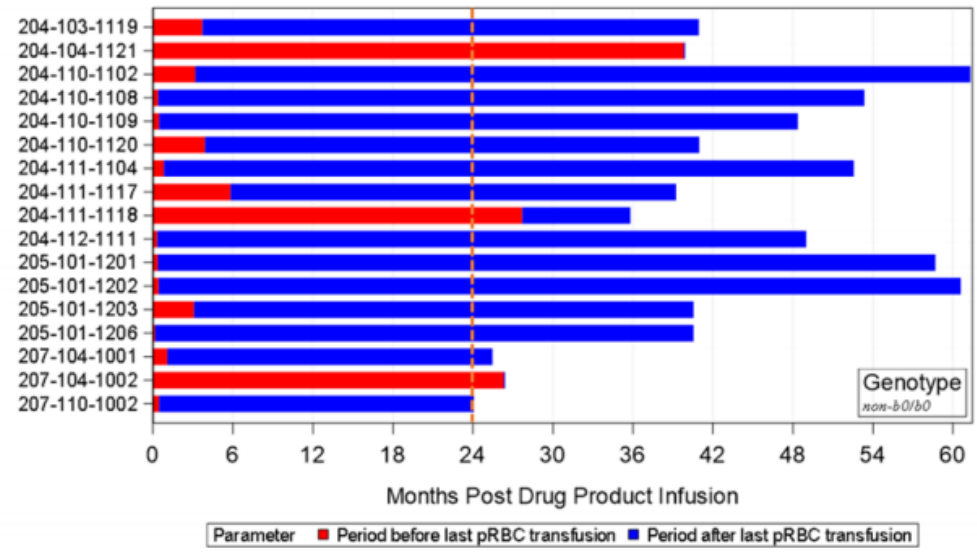


Figure 3: Time since last transfusion in patients in HGB-207 (cohort 1).

Characterisation of subjects achieving TI

All 20 subjects who achieved TI have maintained their TI status through all Hb assessments and none have required transfusion. At the June 2019 data cut, 17 patients had ≥2 years of follow-up and 7 patients had ≥4 years of follow-up (Figure 4).



Source: June 2019 data cut, Interim Clinical Study Report LTF-303 Version 2.0 23 September 2019

Figure 4: Duration of transfusion free periods for non-β^0/β^0 subjects (age ≥ 12 years) with follow-up for ≥24 months. Results from HGB-204 (n = 10), HGB-205 (n = 4) and HGB-207 (n = 3).

For the 20 subjects who achieved TI:

- Half of the subjects had their last pRBC-transfusion within 0.9 months from Zynteglo infusion. The maximum time that passed from Zynteglo infusion to last pRBC-transfusion was 5.8 months (table 5).
- The Hb ≥9g/dL level was reached early in the follow-up and the mean/median total Hb remained stable over time through the follow-up periods in the trials.
- weighted average of nadir Hb during transfusion independence was 11.7 g/dl (Table 5). The formula for calculating weighted average Hb is in appendix 5.

Table 5: Characterisation of non-β^0/β^0 subjects (age ≥ 12 years) achieving TI. Results from HGB-204, HGB-205 and HGB-207.

Parameter	Statistic	HGB-204	HGB-205	HGB-207	Overall
Time from drug product infusion to last pRBC transfusion before becoming TI (months)	N	8	3	9	20
	Mean (SD)	2.3 (2.10)	0.3 (0.13)	1.1 (0.50)	1.5 (1.52)
	Median	2.0	0.4	1.1	0.9
	Min - Max	0.3 - 5.8	0.2 - 0.4	0.5 - 2.2	0.2 - 5.8
Time to reach TI (months)	N	8	3	9	20
	Mean (SD)	17.6 (2.54)	15.1 (0.40)	16.0 (1.00)	16.5 (1.93)
	Median	17.1	14.9	15.9	15.7
	Min - Max	15.0 - 20.9	14.9 - 15.6	15.0 - 17.9	14.9 - 20.9
Weighted average Hb during TI (g/dl)	N	8	3	9	20
	Mean (SD)	10.7 (1.33)	11.6 (1.27)	12.1 (0.49)	11.5 (1.17)
	Median	10.3	11.4	12.2	11.7
	Min - Max	9.3 - 13.3	10.5 - 13.0	11.4 - 12.8	9.3 - 13.3

Characterisation of transfusion reduction for subjects not achieving TI

Three patients from Studies HGB-204 and HGB-205 did not achieve TI (2 out of 10 patients in HGB-204 and 1 out of 4 patients in HGB-205). For these three patients, 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. Reductions in volume and frequency were maintained at last follow-up in LTF303.

From the ten TI-evaluable patients in HGB-207, a single patient did not achieve TI. For this patient, a reduction of 51.5% in transfusion volume requirements and a reduction of 43.4% in transfusion frequency were observed from Month 12 to Month 24 when compared to their pre-study levels of RBC transfusions.

Evaluation of the change in iron burden over time

After Zynteglo infusion, patient iron levels were managed at physician discretion. Of the 14 non-β^0/β^0 patients treated in studies HGB-204 and HGB-205 that completed Month 6,

- nine (64.3 %) reported ongoing chelation use at last follow-up.
- The remaining five subjects (35.7 %) had stopped iron chelation.
- Three out of the 14 subjects (21.4%) received phlebotomy to remove iron.

At 48 months after infusion of Zynteglo for patients who achieved TI,

- the median reduction (min - max) in serum ferritin levels from baseline was 70.0% (39.2 - 84.8) (N=5, HGB-204; N=2, HGB-205).
- the median reduction in liver iron content from baseline was 62.5%, ranging from an 83.3% reduction to a 269.2% increase (N=5, HGB-204; N=2, HGB-205).

Of the 18 non-β^0/β^0 patients treated in studies HGB-207 and HGB-212[5] that completed Month 6,

- five subjects (27.8 %) reported ongoing chelation use at last follow-up.
- the remaining 13 subjects (72.2%) had stopped iron chelation.
- of the 18 subjects, 5 subjects (27.8%; all in study HGB-207) received phlebotomy to remove iron.

For the two patients who completed HGB-207 and achieved TI, the reduction in serum ferritin levels from baseline was 82.1% and 22.4%, respectively, and the change in liver iron content from baseline was a 57.1% increase and a 45.2% decrease, respectively.

Survival and quality of life

From the HTA perspective, it would be important to understand how Zynteglo impacts patients' mortality and health related quality of life (HRQoL). However, the follow-up time in the clinical trials is not sufficient for survival assessment. In addition, no results on HRQL have been reported from HGB-204, HGB-205, HGB-207, or HGB-212.

Estimation of survival benefits in a population that mainly includes children and young adults would require a very long follow-up.

3.1.3 Results for safety

The information presented in this section includes safety data from 60 subjects with TDT (ITT-population) from the studies HGB-204, HGB-205, HGB-207 and HGB-212 (Table 6). The safety review includes all patients from these studies irrespective of the genotype and age. From the 60 subjects 43 (72 %) had a non-β^0/β^0 genotype.

The safety results are from the 12 June 2019 data-cut. The company provided these updated results, and to our knowledge these results have not been published elsewhere.

Table 6: Number of subjects according to study, genotype and age.

Study	HGB-204		HGB-205	HGB-207		HGB-212				Total
Genotype	non-β^0/β^0	β^0/β^0	non-β^0/β^0	non-β^0/β^0		non-β^0/β^0		β^0/β^0		
Age	>12 yrs		>12 yrs	<12 yrs	>12 yrs	<12 yrs	>12 yrs	<12 yrs	>12 yrs	
ITT	11	8	4	7	16	1	4	3	6	60
TP	10	8	4	6	15	1	3	2	5	54

ITT = Intention to treat population includes all patients mobilized; TP = Treated patients (drug product infused)

Patient exposure

For the ITT-population (n = 60), the median (min - max) follow-up time was 19.5 months (0.9 - 61.3) after Zynteglo infusion. For the TP-population (n = 54) the median (min - max) follow-up time was 19.5 (0.9–61.3) after Zynteglo infusion.

All subjects (100 %) had a successful neutrophil engraftment (NE), that occurred on median (min - max) Day 22.0 (13 - 38) after Zynteglo infusion. All subjects also had a successful platelet engraftment (PE), that occurred on median (min - max) Day 47.4 (19 - 191) after Zynteglo infusion.

[5] In HGB-212, three patients aged ≥ 12 years, with non-β^0/β^0 IVS I-I10 (G→A) genotype were treated.

For the treated non-β^0/β^0 population (n = 39) the median (min - max) follow-up time was 19.2 (0.9 - 61.3 months) after Zynteglo infusion.

Summary of adverse events

Adverse events are summarized in Table 7 for the ITT-population (n = 60) and for the non-β^0/β^0-population (n = 43). Treatment emergent adverse event (TEAE) was defined as those events that occur during or after Zynteglo infusion. Adverse event related to drug product (Zynteglo) were determined by the investigator based on pre-defined definitions.

In the ITT-population all but one subject experienced at least one AE, with 90 % experiencing at least one TEAE, and 17 % experiencing at least one AE related to drug product (table 7). The most common treatment emergent adverse events included thrombocytopenia (98.1% of patients), anaemia (81.5%), neutropenia (72.2%), stomatitis (72.2%) and alopecia (61.1%).

Most of the patients (95 %) in the ITT population experienced at least one severe or life threatening (≥grade 3) adverse event during the course of the treatment and safety follow-up. Half of the patients experience at least one serious adverse event.

Table 7: Overall summary of adverse events. Pooled results from HGB-204, HGB-205, HGB-207 and HGB-212. The 12 June 2019 data-cut.

Parameter	non-β^0/β^0 (n = 43)	ITT (n = 60)
Number of subjects with adverse event, n (%)		
At least one AE	42 (97.7)	59 (98.3)
At least one serious AE	22 (51.2)	30 (50.0)
At least one grade 3-4 AE	40 (93.0)	57 (95.0)
At least one AE resulting in death	0 (0)	0 (0)
Number of subjects with treatment emergent adverse event[a], n (%)		
At least one AE	39 (90.7)	54 (90.0)
At least one serious AE	16 (37.2)	23 (38.3)
At least one grade 3-4 AE	39 (90.7)	54 (90.0)
Number of subjects with adverse event related to drug product[b], n (%)		
At least one AE	8 (18.6)	10 (16.7)
At least one serious AE	1 (2.3)	1 (1.7)
At least one grade 3-4 AE	2 (4.7)	2 (3.3)

[a] Treatment emergent adverse event (TEAE) was defined as those events that occur during or after Zynteglo infusion.
[b] The relationship of Zynteglo to an AE was determined by the investigator based on pre-defined definitions

The incidence of adverse events in the ITT-population by study period is presented in table 8. According to these results, half of the patients experienced an adverse event already before the mobilisation with G-CSF and plerixafor had been initiated. All patients who were infused with the drug product reported experiencing at least one grade≥3 adverse events (from Zynteglo infusion to last follow-up). Twenty-three (43 %) of the treated population experienced a serious adverse event (from Zynteglo infusion to last follow-up).

The most common serious adverse events (SAE ≥5 % of patients) experienced after drug product infusion included veno-occlusive liver disease (9.3% of patients), thrombocytopenia (5.6 %), neutropenia (5.6 %) and pyrexia (5.6%). More details of the most common SAEs and grade 3 - 5 AEs according to the study period is reported in appendix 6.

It should be noted that European Medicines Agency (EMA) has concluded, it is difficult to fully discriminate between adverse effects caused by Zynteglo and those by the concomitant treatment/HSCT procedure, or determine whether Zynteglo exposure may have contributed to the occurrence of AEs. [16]

Table 8: Number of subjects with at least one adverse event according to study period, n (%). The 12 June 2019 data-cut.

	ICF to <MB	MB to <C	C to <NE	NE to M24	D1 to last visit	>M24 to M36	>M36 to M48
Number of subjects at risk	60	60	54	54	54	25	20
Number of subjects with at least one AE, n (%)	35 (58.3)	55 (91.7)	54 (100.0)	51 (94.4)	54 (100.0)	2 (8.0)	0 (0.0)
Number of subjects with at least one serious AE, n (%)	8 (13.3)	5 (8.3)	7 (13.0)	18 (33.3)	23 (42.6)	2 (8.0)	0 (0.0)
Number of subjects with at least one grade 3 AE	9 (15.0)	12 (20.0)	54 (100.0)	32 (59.3)	54 (100.0)	2 (8.0)	0 (0.0)

AE = adverse event; **C** = Initiation of conditioning; **D1** = drug product infusion; **ICF** = informed consent form (date of signature); **MB** = initiation of mobilisation; **M** = months from drug product infusion; **NE** = neutrophil engraftment. **Source:** Market authorization holder

Adverse events of special interest

The pre-specified adverse events of special interest include neutrophil engraftment failure, HIV infection, autoimmune disorders, malignancies, and lack of efficacy.

No cases of neutrophil engraftment failure or autoimmune disorders were noted. No subject experienced graft-versus-host disease (GVHD), graft rejection, or graft failure. One case of HIV infection (wild-type) was reported. It was assessed not to be related to Zynteglo.

No cases of malignancies were noted in the TDT population, however, one case of myelodysplasia was reported in a subject with sickle cell disease participating in Study LTF-303. As no LVV insertion was found in tumour cell-enriched cell population and the cytogenetic analysis revealed a chromosomal abnormality which has been associated with secondary leukaemia, it is considered likely that this event is caused by exposure to busulfan.

According to Zynteglo product information [4] prophylaxis for hepatic veno-occlusive disease (VOD) is recommended in the pre-treatment conditioning. Depending on the myeloablative conditioning agent administered, prophylaxis for seizures should also be considered. VOD occurred in six subjects in the TDT population (10 %). No cases of seizure were reported.

Safety of busulfan

Gene therapy with Zynteglo represents an autologous HSCT and exposes patients to short- and long-term adverse effects of myeloablative busulfan-therapy. Severe short-term consequences of busulfan therapy may, for example, include veno-occlusive disease and infections. Busulfan can impair fertility, and ovarian suppression and amenorrhoea with menopausal symptoms commonly occur in pre-menopausal patients. According to the Finnish clinical expert, fertility impairments are the most important difference between the safety profile of Zynteglo therapy (that included myeloablative busulfan-therapy) and RBC-transfusions and chelation (that did not include myeloablative busulfan-therapy). [22]

For comparison, fertility impairments have also been reported among patients with thalassaemia major [23, 24]. In females with thalassemia, no direct comparison in fertility indicators have been reported between HSC-transplanted and transfusion-dependent groups. Spontaneous pregnancies have, however, been reported in well-chelated and transfused women after spontaneous puberty [25]. After transplant for thalassemia, ovarian failure has been reported with a frequency ranging from 50% to 100% [26]. Risk to ovarian dysfunction after HSCT has reported to increase with the increasing age and it has shown to be hypergonadotropic type. Observation suggest that ovarian damage after HSCT is due to busulfan-related toxicity rather than from iron overload [27]. Fore males with thalassemia direct comparison in fertility indicators have been reported between transplanted and transfusion-dependent groups. Thalassemia patients who had undergone allogeneic HSCT with a myeloablative conditioning regimen including cyclophosphamide and busulfan have significantly lower fertility potential, mainly in sperm parameters compared with patients treated with blood transfusion and chelation. Azospermia, oligospermia, astenospermia, teratospermia and low volume ejaculate were all

significantly more frequent in the post-transplant patients compared to transfusion-dependent group [28].

Busulfan has been classified as a human carcinogen, and a causal relationship between busulfan exposure and cancer has been observed. For example, leukaemia patients treated with busulfan developed many different cytological abnormalities, and some developed carcinomas. [22]

Additional safety information from TDT subgroups, supportive safety data from subjects with sickle cell disease and safety of lentiviral gene therapy vectors is reported in appendix 7.

FINOSE discussion

Effect

The clinical evidence base includes three single-arm trials comprising 32 subjects who are 12 years and older with TDT and with non-β^0/β^0 genotype. Of the treated patients 24 (75 %) were evaluable for transfusion independence (TI). In other words, they had been followed for at least 12 months after their last RBC transfusion. Seventeen subjects (53 %) had been followed for more than two years and seven subjects (22 %) for more than four years after Zynteglo infusion. The maximum duration of follow was 5.1 years (61 months).

The company states that the non-comparative single arm trial design was agreed in a scientific advice because the natural disease course of β-thalassaemia is well known with a clinically stable presentation over time, and patients do not spontaneously start to produce clinically meaningful levels of HbA or become transfusion independent. However, the marketing approval is conditional and EMA requested the company to conduct a study comparing product registry data for Zynteglo (REG-501) with patients treated with transfusions and/or HSCT to contextualize the long-term safety and effect of Zynteglo.

The company argues that data from unmodified allogeneic HSCT provide support for the long-term durability of transplanted stem cells and that there is a growing support for long-term durability in the field of gene therapy. In its assessment of Zynteglo, EMA stated that some level of confidence in the sustainability of the correction of the β-thalassaemia is provided the fact that stem cells are transduced that immunisation against the transgene is unlikely. Moreover, EMA considered the 10 years follow-up of a patient with β-thalassaemia being treated with a similar approach as supportive. EMA concluded that the treatment effect is expected to be life-long [16]. Since comprehensive data is not available, the market approval is conditional as described above.

The company assumes that patients who achieve TI will initially continue iron chelation therapy. When the excess iron is removed, patients would no longer require iron chelation. This, however, has not yet been demonstrated in the clinical trials, where only a subset of patients achieving TI have stopped iron chelation therapy so far. Among patients who have stopped iron chelation, the reduction of baseline iron content has only been partial. The use of iron chelation therapy and reduction of iron load will be evaluated in the follow-up of the clinical trials but for now the effect of Zynteglo on these parameters is uncertain.

The company argues that many β-thalassaemia patients, despite receiving iron chelation therapy, remain substantially overloaded with iron and experience serious complications. The company also argues that independence of transfusions and chelation therapy is anticipated to improve patients' heath related quality of life (HRQoL). While there is a possibility that by eliminating or reducing the need for blood transfusions, Zynteglo treatment may result in reduced iron related morbidity, improvements in HRQoL and even survival benefits, the evidence of these effects is currently missing.

The FINOSE authors agree that dependency of RBC transfusion is likely to have a negative impact on patients' HRQoL due to complications and stress associated with management of a

lifelong chronic disease and practical arrangements associated with frequent RBC transfusions. However, the relative effect on HRQoL of Zynteglo versus treatment with transfusions and iron chelation therapy is unknown. Moreover, the adverse effects of busulfan myeloablation on HRQoL is unknown.

There is no clinical evidence for the relative effects of Zynteglo treatment on mortality and iron related morbidity compared to RBC transfusions and chelation therapy. Some European estimates of TDT patients' survival are available (appendix 1). These results from historical cohorts, however, may not be applicable to the current patient population eligible for Zynteglo treatment in the Nordic countries. Reasons for this include, (i) improvements in the efficacy and quality of chelation therapy during the past two decades (oral iron chelators available since mid 1990's); (ii) historical cohorts do not include information on all important patient characteristics such as genotype. Thus, it is not possible to assess if the patient characteristics are sufficiently similar between the Zynteglo trials and historical cohorts; (iii) availability and quality of health care varies substantially in time and between different parts of the world. Patients that are badly managed in childhood before immigrating to Europe may have irreversible organ damages like diabetes, heart failure, pulmonary hypertension and repeated infections that negatively impact survival. According to the FINOSE clinical experts, in the Nordic and Western Europe the mortality rate is very low but it is still not comparable with non-thalassaemic individuals.

Safety

The limitations of Zynteglo's safety database include limited sample size, single-arm study design and limited long-term follow-up. Due to the short follow-up time, the risk of long-term adverse events has not been evaluated. Also common adverse events might be missed, because of the very limited number of treated subjects. In accordance with the EMA conclusion, the FINOSE authors also state that meaningful conclusions of safety in patient subgroups are not possible, because of the small number of subjects. The updated results from studies HGB-207 and HGB-212 and data from REG-501 are expected to resolve some of the uncertainties related to safety.

Gene therapy with Zynteglo represents an autologous HSCT and exposes patients to adverse events related to Zynteglo but also to adverse events related to mobilisations with G-CFS and plerixafor and conditioning with busulfan. The risks associated with mobilisation and conditioning include secondary malignancies, VOD and impairment of fertility.

It should be noted, however, that subjects treated with Zynteglo are not exposed to many of the risks related to an allogeneic HSCT for TDT. In allogeneic HSCT, the major short-term and long-term risks include development of graft versus host disease (GvHD), either acute or chronic infections and transplant rejection. Patients that receive an allogeneic HSCT are also required to receive immunosuppressive treatment, for some time after the transplant, which brings additional risks for long-term complications. It should also be noted that long term toxicity of myeloablative busulfan-therapy is not expected to differ between allogeneic HSCT and Zynteglo-therapy and thus major treatment related sequelae and infertility will be seen also after Zynteglo-therapy.

Only the patients in the phase 3 trials (HGB-207 and HGB-212) have been treated with the commercial version of Zynteglo, in which the VCN in the transduced cells is higher than with the non-commercial version. It is known that in theory, the risk of insertional mutagenesis increases when VCN increases [29]. However, currently there is no sign of insertional mutagenesis related to commercial or non-commercial version of Zynteglo.

FINOSE conclusion: FINOSE concludes, that the company has demonstrated Zynteglo's benefits on transfusion independence/reduction in three single arm studies, where pooled results showed that 20 out of 24 treated patients achieved transfusion independence and the remaining four patients had reduction in both transfusion volume and frequency. Evaluation of the effects on patients' iron burden is ongoing. No results on iron related morbidity and survival are available due to the limited follow-up time in clinical trials. In addition, no results on health-related quality of life have been reported from the clinical trials. Also, the number of patients treated with Zynteglo is very small, given that there is substantial geographic, ethnic and genetic variation among β-thalassaemia patients.

4 Cost-effectiveness analysis

The following chapter is based on the dossier sent in by the company. All assumptions described are based on the application if not otherwise stated. The conclusions boxes after each section gives a short assessment of the choices related to key parameter inputs, used methods, simplifications and scientific judgements made by the company. The results of the FINOSE scenario analyses are presented in section 5.2.

The conditional approval of Zynteglo, implies that EMA's advisory committee, the CHMP, based its positive opinion on incomplete data indicating that the benefits of the drug outweighed the risks. However, due to the conditional approval, the uncertainty in this case is greater than would normally be the case. The company has submitted a health economic evaluation using a core global model adapted to a Swedish setting to assess both costs and effects of Zynteglo for the treatment of transfusion-dependent β-thalassaemia (TDT) compared to lifelong blood transfusions and iron chelation therapy. The economic evaluation includes patients, 12 years and above, with TDT and non β^0/β^0 genotype for whom hematopoietic stem cell transplantation (HSCT) is appropriate but a human matched related donor is not available. The patient population in the economic evaluation is in line with the authorized indication.

The economic evaluation is based on a discretely integrated condition event (DICE) microsimulation. The DICE approach consists of a sequence of major events during transplant with Zynteglo and acute recovery, post recovery and an ongoing phase to reflect the β-thalassemia management over a lifetime – for patients treated with Zynteglo or lifelong blood transfusions. The model concept is presented in Figure 5 although the conditions are not modelled as traditional Markov health states.

The model concept consists of an initial period of hypertransfusion and mobilization of the stem cells followed by stem cell harvesting in a day case hospital setting, during which the patients are being prepared for the transplant procedure with Zynteglo. During transplant with Zynteglo and acute recovery phase, the patients are hospitalized for the procedure and receive a course of chemotherapy for myeloablative conditioning. This phase includes conditioning, transplant and 90 days of recovery. Engraftment of the gene modified cells occurred at a median of 19 days after transplantation in the clinical studies. Successful engraftment marks the start of the recovery process.

During the post-acute recovery phase, patients who receive Zynteglo are partitioned based on treatment success. A successful transplant results in transfusion independence (TI) or reduced transfusion. The company assumes, based on experience with allogeneic HSCT, that a period of up to four years is required for normalization of iron levels following successful transplant. Patients will receive ongoing chelation and/ or phlebotomy during this period of iron normalization. Patients who become transfusion-independent or have reduced transfusion needs are assumed to remain so for their lifetime. The post-acute recovery phase includes continued blood transfusions, chelation therapy, post-transplant monitoring.

In the ongoing phase, iron overload is expected to be reduced in patients who require substantially fewer transfusions, even if they are not transfusion independent. Patients with substantially reduced transfusion frequency are assumed to continue conventional therapies but with fewer blood transfusions and ongoing iron chelation therapy. These patients are assumed to have reduced iron levels.

Iron levels are assumed to remain at baseline values for patients who are transfusion dependent. Cardiac complications are associated with increased mortality rates compared to other complications.

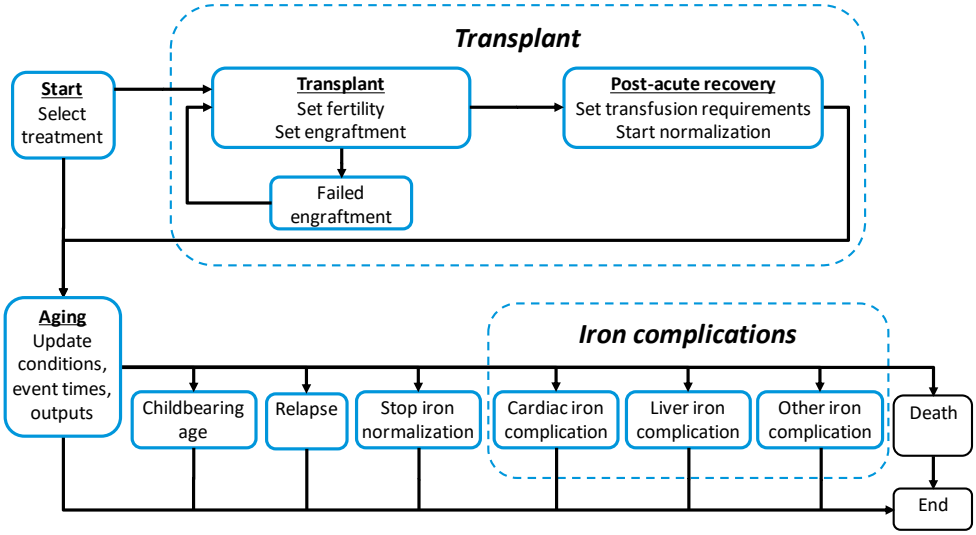


Figure 5: Overview of model concept

A lifetime time horizon was applied in this analysis using a Swedish health care payer perspective. The model was developed for the United Kingdom and was adapted to a Swedish setting. An annual discount rate of three percent was used for both costs and health effects.

FINOSE conclusion: The economic evaluation is based on a discretely integrated condition event (DICE) simulation model and consists of a sequence of major events during transplant with Zynteglo to reflect the β-thalassemia management over a lifetime. The chosen modelling approach implies a greater challenge to critically assess because neither the microsimulation nor the extensive number of programmed conditioned events were always transparent.

4.1 Effectiveness

4.1.1 Clinical effectiveness

The baseline characteristics are based on the patients enrolled in the clinical studies HGB-204, HGB-205 and HGB-207. Twenty-four patients were included in the economic analysis, 59 percent were female. The mean body weight was 50.2 kg. Patient age distribution was based on the three clinical trials and include 33.3 % (age 12-17), 50 % (age 18-23), 8.3% (age 24-29) and 8.3 % (age 30-34). No patients above the age of 34 were included in the economic analysis.

In the model it was assumed that none of the patients had complications related to iron overload at model baseline. The iron distribution levels at the baseline were collected from UK chart review [30]. At the baseline, iron levels for TDT patients were specified as a function of serum ferritin, liver iron concentration (LIC) and myocardial T2. All three variables could be varied independently. Patients with cardiac iron loading were not eligible for Zynteglo therapy and thus their level was assumed to be zero. Patients with severely elevated iron levels in the heart, i.e. patients with cardiac T2* < 10 ms, were excluded in the clinical trials. Therefore, patients with high iron levels in the heart were assumed to be zero in the model.

Table 9: Distribution of iron loading for transfusion-dependent (TDT) patients base case

Iron loading levels	Serum Ferritinin	LIC	Myocardial T2	Source
Low iron	25 %	61 %	88 %	Review of UK thalassaemia patient charts [30]
Moderate iron	39 %	23 %	12 %	Review of UK thalassaemia patient charts [30]
High iron	36 %	16 %	0 %	Review of UK thalassemia patient charts [30] (0% assumed value)

LIC; liver iron concentration.
Serum Ferritin: low iron, ≤1,000 ng/mL; moderate iron, 1,000-2,500 ng/mL; high iron, >2,500 ng/mL
Liver Iron Concentration: low iron, <7 mg/g; moderate iron, 7-15 mg/g; high iron, ≥15 mg/g
Myocardial T2*: low iron, >20 ms; moderate iron, 10-20 ms; high iron, <10 ms

Primary endpoints in the clinical trials is TI or having a reduction in transfusion frequency referred to as transfusion reduced (TR). In the model it is assumed that the patients are considered to be transfusion independent from 12 months. The clinical effectiveness of Zynteglo is based on pooled results in all non-β^0/β^0 genotype subjects from studies HGB-204, 205 and 207. Across the 24 TI evaluable subjects, a total of 20 patients achieved TI (83.3 %). Across the four patients who did not achieve TI, the mean reduction in transfusion frequency was 57.88 percent from six months after infusion of Zynteglo through to the last follow-up visit.

Long-term data of the changes in iron load following Zynteglo treatment is not currently available. For that reason, data on iron levels in patients that have received HSCT were usedfor the expected outcomes with Zynteglo [31, 32]. Elevated levels of iron as measured by serum ferritin, LIC and cardiac T2 are commonly found in patients with TDT following transplantation. Thus, iron chelation therapy and/ or phlebotomy is generally continued following successful transplantation, and patients should be screened for iron overload at various time points during this period. The company assumes a four year iron normalization period following Zynteglo treatment.

In the model, transfusion independent patients remain at risk of complications from iron overload during the normalization period, i.e. four years. After this, they are assumed to achieve normalized iron levels, i.e. chelation therapy is only assumed if iron levels are not normalized. Patients with transfusion reduction were assumed to have low or moderate levels of iron after transplant.

Cardiac complications such as heart failure, arrhythmias and pulmonary hypertension were included in the model and applied for patients with low, moderate and high iron levels. Liver related complications were based on iron levels for patients without hepatitis C and applied to patients with high iron levels.

Adverse events related to chelation therapy were included in the model. Adverse events specifically associated with Zynteglo are not modelled but reportedly captured by the cost impact of e.g. administration, hospitalisation and ongoing monitoring costs. Though transplant related complication due to infertility were included in the model. It was assumed that Zynteglo increases infertility by 24 percent in men and 57 percent in women.

Mortality risk over time in modelled patients without cardiac disease varies with patient age using general population life table data. A standardized mortality ratio (SMR) post-transplant is applied based on transfusion-dependence status. Transfusion-independent patients are assumed to have survival similar to that of an age and sex matched general population informed by Swedish Life Tables. A moderate impairment of survival is included in the base case (SMR 1.25). The value chosen is consistent with SMR values reported for patients with type 2 diabetes [33]. For transfusion dependent patients without cardiac complications an SMR value of 3.9

was applied [34]. Transfusion reduced patients were assumed to have mortality ratio in the midpoint, i.e. SMR of 2.6.

FINOSE conclusion: Achieved primary endpoint, transfusion independence (TI), for patients no longer in need of regular blood transfusions, was based on three single arm clinical trials. Baseline data regarding age were taken from the clinical trials though the iron levels were taken from a review of UK thalassaemia patient charts. The main uncertainties according to FINOSE is the level of achieved TI is and whether it is sustained over the lifetime. Associated survival benefit is based on the risk of complications based on iron overload levels. The benefits of Zynteglo are based on the assumption that complications associated with high iron levels are reduced.

4.1.2 Health related quality of life

According to the company, quality of life is expected to vary over the course of the year in patients receiving Zynteglo - pre-transplant, during the transplant year and post-transplant. According to the company, Zynteglo treatment is an intense process leaving the patient in a compromised state. After Zynteglo has been transfused, patients may require ongoing care and may have reduced social function for the remainder of the year. No studies of utility during the transplant year were identified for patients with thalassaemia.

Thus, due to limited data on quality of life, a vignette study was conducted in a general UK population to inform the assumptions on quality of life made by the company and used in the model. According to the company, the vignette-based methodology may be used for the purpose of capturing attributes in a treatment process.

The vignettes were developed to represent transfusion dependent treatment with ongoing blood transfusions and iron chelation therapy as well as HSCT. The vignettes were drafted based on published literature, clinician interviews, patient/ caregiver interviews, and pilot study. Eight hypothetical health states were presented during the interviews describing patients with transfusion dependent treatment both pre- and post-transplant as well as three path states. The path states describe a series of events during the year in which the patients undergo either an autologous HSCT or allogeneic HSCT.

The utility weights representing each health state were elicited using a time trade off (TTO) approach for five chronic health states and three path states during transplant. A total of 207 participants in the UK completed the interviews. The resulting health state utilities are found in Table 10.

Table 10: Health state utilities (based on Vignette study)

Health states		Utility
Pre transplant, with ongoing blood transfusion and iron chelation	Oral chelation	0.73
	Subcutaneous chelation	0.63
Transplant year, 1 year path states	Gene therapy	0.62
	Allo-HSCT*	0.47
	Allo-HSCT with acute GvHD**	0.39
Post-transplant	Transfusion independent	0.93
	Transfusion reduction (60%)	0.75
	Chronic GvHD	0.51

Allo-HSCT; allogeneic haematopoietic stem cell transplantation ** GvHD; Graft versus host disease

Utility decrements associated with transplantation and adverse events (infertility and complications) are presented in Table 11.

Myeloblative conditioning required for transplantation results in subfertility and infertility. A decrement was assumed for patients in their child bearing years. The company assumes a decrement of 0.07 based on a recent workshop on economic evaluation of infertility conducted by the European Society of Human Reproduction and Embryology. The company has applied this disutility over the ages of 18 to 40.

Table 11: Utility decrements per transfusion status and adverse events

Transfusion status	Utility decrement	Source
Pre transplant	0	Assumption
Transplant	0.31	Vignette study
Post transplant (one year)	0.31	Vignette study
Infertility	0.07	Busnelli (2014)
Cardiac complications	0.11	Karnon (2012)
Liver complications	0.07	Assumption (same as endocrine complications)
Endocrine complications	0.07	Karnon (2012)

FINOSE discussion

According to FINOSE health-related quality of life studies based on TDT patients are preferable for the use in economic evaluations. The FINOSE authors note that utility weights based on 247 TDT patients using the iron chelating drug Exjade (dnr 2986/2009) were provided by the company for patients who switched iron chelation therapy from a subcutaneous to an oral formulation. See section 2.4. Utility weights measured using the SF-36 generic instrument, before and after the switch (0,845 for subcutaneous iron chelation therapy and 0,882 for oral iron chelation therapy) indicating higher utility values than those provided in the application for Zynteglo. Also, a slight difference between the two formulations for iron chelation was shown, the difference between the two formulation are almost the same.

FINOSE conclusion: Health related quality of life (HRQoL) data utilised by the company was based on a vignette study rather than collected from the clinical trials. The company has based their base case on the assumption that the majority of patients (70 %) were treated with subcutaneous chelation therapy. Thus, the utility weights associated with subcutaneous chelation therapy is the main utility parameter affecting the results in the company base case. The main benefits of Zynteglo claimed by the company is eliminating the disutility associated with chelation therapy and disutility of iron related complications. FINOSE conclude that the utility weights collected from the patient group would be preferable and that the utility weights seem low.

4.2 Resource utilisation

4.2.1 Zynteglo

Pre-transplant costs for Zynteglo
Prior to cell harvest, there is a period of hypertransfusion required to maintain a haemoglobin level of 11g/dL. The company assumes one additional blood transfusion in the month preceding transplantation costed at 7 891 SEK. It is assumed that patients will continue with iron chelation therapy and associated monitoring.

Tests in the pre-treatment stage were based on the protocol for HGB-207 and consist of one outpatient visit, blood for several laboratory tests and genotyping, liver biopsy, bone marrow analysis, totaling almost 38 000 SEK.

Additionally, patients will undergo apheresis after mobilisation. Filgrastim, a granulocyte-colony stimulating factor and plerixafor for stem cell mobilisation were used. Each cycle is completed within seven days. These are costed at 4 259 SEK and 135 176 SEK. The hospitalisation cost is assumed to be the same as for autologous HSCT (uncomplicated) costed at 9 524 SEK. An additional cycle of mobilisation and apheresis is assumed for 20 percent of the patient population and a third additional cycle is assumed for 2.9 percent based on the clinical studies. This, in order to obtain more cells for additional manufacture.

Further, patient conditioning includes full myeoablative conditioning with busulfan, which must be administered before infusion of Zynteglo over a period of four days. Assuming a recommended daily dose of 3.2 mg per kg (0.8 mg*4) costed at 28 673 SEK and 19 172 SEK (4 793*4) for administration. Patient conditioning includes 2 follow-up visits with physical examination (2 683*2), prophylaxis using ursodeoxycholic acid (731 SEK) and seizure prophylaxis (707 SEK).

The pre-transplant costs total 217 852 SEK.

Transplant-related costs for Zynteglo
The cost for Zynteglo in patient hospitalisation is based on the aggregated cost for autologous HSCT (uncomplicated) and cost of the drug. For transplant-related costs for Zynteglo see Table 12.

Table 12: Transplant-related costs for Zynteglo, SEK

	Cost (SEK)	Source
In-patient hospitalisation	178 592 kr	Södra regionsvårdsnämnden 2019 [35]
Zynteglo	16 950 000 kr	Bluebirdbio

Post-transplant costs for Zynteglo
Post-transplant monitoring costs were informed by the protocol for Bluebird bio registry (REG-501) following transplantation of Zynteglo. These include monitoring costs for a period of four years. Two follow-up visits with physical examination per year (year 1 and 2) and one visit per year (year 3 and 4). These visits include laboratory blood tests, cardiac MRI, liver MRI, ECG and X-ray totaling 16 014 SEK (year 1 and 2) and 13 270 SEK (year 3 and 4).

4.2.2 Blood transfusions and chelation therapy

The company has based the frequency of transfusions on input from Swedish clinical expert and assumed 20 transfusion with a 2-3 weeks interval. The company assumes that the number

of transfusions of TR patients is reduced by 57.88 percent, corresponding to 8,42 transfusions per annum.

Table 13: Total annual blood transfusion costs, SEK

Patient age	Transfusions per year (transfusion dependence)	Transfusions per year (transfusion reduced)	Unit cost	Annual blood transfusion cost(transfusion reduced)	Annual blood transfusion cost (transfusion dependent)
Patient < 18	20	8.42	7 891 kr	66 474 kr	157 820 kr
Patient ≥ 18	20	8.42	7 891 kr	66 474 kr	157 820 kr

To derive the cost of iron chelation therapy, the company assumes distribution of iron chelation therapy from the Swedish clinical input. The frequency and doses were based on the SmPC for transfusion dependent patients. Desferrioxamine (DFO) (40 mg/kg six times a week), deferasirox (DFX) 20 mg/kg daily and deferiprone (DFP) 25 mg/kg three times a day.

Table 14 Distribution of chelation agents

Iron chelator		UK Chart review	Swedish clinical input
Desferrioxamine (DFO)	s.c.	14 %	70 %
Deferasirox (DFX)	oral	58 %	15 %
Deferiprone (DFP)	oral	7 %	10 %
DFP and DFO	oral and s.c.	11 %	5 %
DFP and DFX	oral	5 %	0 %
DFX and DFO	oral and s.c.	5 %	0 %

s.c.: subcutaneous

Table 15 Unit costs chelation therapy, SEK

Product	Strength (mg)	Adm. Form	Price per pack	Units	Total mg	Cost per unit	Cost per mg
Desferal (desferrioxamine, DFO)	500	s.c.	488.78 kr	10	5 000	48.88 kr	0.0978 kr
Exjade (deferasirox, DFX)	360	oral	5 042.50 kr	90	32 400	222.59 kr	0.6183 kr
Ferriprox (deferiprone, DFP)	500	oral	1 998.02 kr	100	50 000	19.98 kr	0.0399 kr

s.c.; subcutaneous

Table 16: Annual iron chelation therapies costs (transfusion dependent), SEK
Table 16

Patient age	Unit cost	Units per administration	Frequency	Total units per day	Total units per annum	Total cost per annum*	Administration cost
DFO, Patient <18	48.88 kr	25 mg/kg	6 times a week	3.00	939	45 907 kr	19 894 kr
DFO, Patient ≥18	48.88 kr	40 mg/kg	6 times a week	5.00	565	76 512 kr	19 894 kr

DFX	222.59 kr	21 mg/kg	Daily	3.00	1,096	243 901 kr	0 kr
DFP	19.98 kr	25 mg/kg	3 times a day	9.00	3,287	65 680 kr	0 kr

*Based on the mean weight of study population, i.e. 50,2 kg

The annual administration cost for desferrioxamine (DFO) per patient was calculated using a weighted cost for a battery operated pump, porthocath and porthocath surgery. A total of 312 balloon infusers (265 SEK) per patient was assumed by the company. The administration cost was costed at 19 894 SEK.
Transfusion reduced patients were adjusted accordingly.

The total annual treatment costs associated with blood transfusions and iron chelation therapy (drug acquisition, administration and monitoring) for transfusion dependent patients was calculated as 381 863 SEK for patients with oral chelation therapy and 278 124 SEK for patients using subcutaneous chelation therapy. Oral chelation therapy may be used in monotherapy or in combination.

Cost of managing iron overload from chelation therapy include serum ferritin tests, liver function tests, and cardiac MRI

Table 17: Costs for monitoring blood transfusions and iron chelation therapies, SEK

Intervention	Cost of care (year 1)	Unit cost	Total annual cost
Creatine tests	12	20.60 kr	247.20 kr
Liver function tests	12	30.17 kr	362.04 kr
Serum ferritin test	4	42.00 kr	168 kr
Cardiac MRI	1	5 150 kr	5 150 kr
Audiogram	1	476 kr	1 476 kr
Opthalmology review	1	1 193 kr	1 193 kr
For patients on deferiprone			
Full blood count	52	30.17 kr	1 568.84 kr

Table 18: Cost of managing iron overload-related complications, SEK

Complications	Cost of care (year 1)	Cost of care (year 2)
Cardiac	61 666 kr	31 759 kr
Liver	40 873 kr	40 873 kr
Other*	13 971 kr	13 971 kr

*Other complications include diabetes mellitus, hypogonadism, hypoparathyroidism and hypothyroidism

Adverse events associated with Zynteglo were not explicitly modelled and the company assumes that these costs are captured within the administration and monitoring costs.

Adverse events associated with iron chelation therapy included arthralgia/myalgia, neutropenia, abdominal pain, alanine aminotransferase, diarrhea and increase creatinine level and was costed as a health care visit with medical physician at 1 641 SEK per visit.

FINOSE discussion
According to Finnish, Norwegian and Swedish treatment guidelines, iron chelation treatment is recommended after one year of regular transfusions or if serum ferritin exceeds 1000 µg/L. Oral defasirox (DFX) is the primary option for iron chelation in the Nordic countries according to the FINOSE clinical experts. The different chelation treatments can be used as monotherapy or in combination. See section 2.3.2 Table 12.

The distribution of chelator agents estimated by the FINOSE clinical experts should be compared to the company assumption that 70 percent of the patients use subcutaneous desferrioxamine (DFO) in their base case.

FINOSE conclusion: The transplant related costs of Zynteglo is the key cost driver affecting the results of the economic evaluation. Adverse events associated with Zynteglo were not included in the model. These were instead handled as quality of life impairments. Also, the distribution of chelation agents affects the costs in the comparator arm and comprises a substantial part of the costs in the comparator arm.

5 Results

Zynteglo is associated with a one-time upfront cost and the health benefits are expected to be gained over a lifetime. The company proposes five payment over time (4 years) and have also included a component in which payments are tied to value delivered to the patient.

The results are presented without the proposed payment model.

5.1 The company's base case

The company assumes Zynteglo treatment improves both survival and health-related quality of life.

5.1.1 Key assumptions in the base case scenario

- 83.3 % achieved the primary endpoint of treatment success, transfusion independence (TI)
- Patients partitioned at 12 months based on treatment success
- Achieved TI assumed to be maintained, i.e. transfusion free over a lifetime
- 4 year normalisation period after Zynteglo transplant, i.e. use of continued chelation therapy
- Iron overload related complications are permanent once they develop
- Mortality assumed dependent on age and presence of iron overload
- Utility weights: based on Vignette methodology (UK population)
- Lifelong time horizon

According to the company the base case results for Zynteglo versus lifelong blood transfusions and chelation therapy the patient gains more quality adjusted life years, QALYs (8.17) at a higher cost (11 350 000 SEK) (Table 19).

The cost per QALY gained was estimated at 1 389 000 SEK (no payment model).

Table 19: Company base case results (no payment model), SEK

	Zynteglo	Standard treatment (lifelong blood transfusions and chelation therapy)	Diff.
Direct costs			
Transplant			
Pre transplant	217 852 kr	0 kr	217 852 kr
Hospitalisation	178 592 kr	0 kr	178 592 kr
Zynteglo	16 950 000 kr	0 kr	16 950 000 kr
Post transplant monitoring	28 899 kr	0 kr	28 899 kr
Transfusion dependence	741 744 kr	6 819 142 kr	-6 077 398 kr
Transfusion dependent AE	2 597 kr	8 618kr	-6 021 kr
Iron overloading			
(cardiac, liver and other)	179 840 kr	340 004 kr	-160 164 kr
Iron chelation normalization	218 473 kr	0 kr	218 473 kr
Total costs	*18 517 977 kr*	*7 167 765 kr*	*11 350 212 kr*
Life years (LY)	27.57	23.29	4.29
QALYs	21.59	13.42	8.17
Cost per LY gained			2 648 057 kr
Cost per QALY gained			**1 388 918 kr**

The transplant related costs of Zynteglo is the key cost driver affecting the results of the economic evaluation. This should be compared to life-long treatment with blood transfusions and chelation therapy for transfusion dependence totalling almost 7.2 million SEK over a lifetime with a discount rate of 3 percent.

The undiscounted life years gained according to the company is 61.87 years for Zynteglo versus 43.85 years in the comparator arm. This corresponds to 18.02 incremental life years gained over a lifelong time horizon.

5.1.2 Company's sensitivity analyses

The company has performed several one-way sensitivity analyses to explore the sensitivity of individual parameters/ input variables in the deterministic base-case model results. The results were presented as a tornado diagram indicating that the cost of chelation therapies (subcutaneous administered desferrioxamine) and the disutility (decrements) associated with transfusion dependence were the two most important parameters affecting the results of the economic analysis according to the company. The company sensitivity analyses also show that the transplant cost (Zynteglo), discount rates for both costs and effects as well as the time horizon also affect the results. The company notes that the discount rate and proposed payment installments over time have a greater impact on the results than the performed one-way sensitivity analyses.

Table 20: The company base case, SEK

Sensitivity analyses	+/- Δ Costs	+/- Δ LYs	+/- Δ QALYs	Cost/ QALY
The company base case (without payment model)	11 350 213 kr	4.29	8.17	**1 388 918 kr**
The company base case (adjusted)* full payment for treatment success, 83.3% and 20% payment for the remaining 16.7 %)	9 085 713 kr	4.29	8.17	1 111 811 kr
The company base case (including 5 payment installments)**	7 670 486 kr	4.29	8.17	938 631 kr

*Full payment for treatment success, 83.3% and 20% payment for the remaining 16.7 %
**Periodic payments for Zynteglo divided into five equal payments (every 12 months) during four years

5.2 FINOSE scenario analyses

FINOSE presents two scenarios, with and without survival gains, based on the company base case. Three assumptions were adjusted compared to the company base case. According to international and Nordic treatment guidelines 20 blood transfusion a year may be an overestimation. Also, FINOSE has adjusted the parameters associated subcutaneous (SC) chelation therapy as the cost and disutility associated with SC therapy is the main parameter affecting the results according to the company base case.

5.2.1 Key assumptions that differ from the company base case scenario

- 15 blood transfusions a year (instead of 20) for transfusion dependent patients
- No difference in utility between oral and SC iron chelation therapy
- Distribution of oral iron chelation 50 %, subcutaneous iron chelation 50 % (instead of 70 % on SC treatment)
- No difference in mortality between the two comparative treatment arms (scenario 2)

According to FINOSE scenario 1 for Zynteglo versus lifelong blood transfusions and chelation therapy the patients gain more quality adjusted life years, QALYs (6.88) at a higher cost (12 114 000 SEK).

The cost per QALY gained was estimated at 1 761 000 SEK (no payment model).

According to FINOSE scenario 2, no survival gains, for Zynteglo versus lifelong blood transfusions and chelation therapy the patient gains more quality adjusted life years, QALYs (4.88) at a higher cost (12 114 000 SEK).

The cost per QALY gained was estimated at 2 137 000 SEK (no payment model). The FINOSE scenario analyses are presented in Table 21.

Table 21: FINOSE scenario 1 and 2 (no payment model), SEK

Scenario 1 and 2	+/- Costs	+/- Δ LYs	+/- Δ QALYs	Cost/ QALY
FINOSE scenario 1 (15 blood transfusion a year (instead of 20), no difference in utility between oral and SC chelation therapy (0,73 used for both) and same distribution between oral and SC iron chelation	12 114 246 kr	4.29	6.88	1 761 072 kr
FINOSE scenario 2 (same as above and no difference in mortality between the treatment arms)	10 431 006 kr	0	4.88	2 137 246 kr

5.2.2 FINOSE sensitivity analyses

FINOSE has performed several one-way sensitivity analyses to explore how changes in individual parameter inputs affect the results.

A table showing how different discount rates on the acquisition cost of Zynteglo are also presented (Table 22).

Table 22: FINOSE sensitivity analyses based on scenario 1 (no payment model), SEK

Sensitivity analyses		+/- Δ Costs	+/- Δ LYs	+/- Δ QALYs	Cost/ QALY
FINOSE scenario 1 (15 blood transfusion a year (instead of 20), no difference in utility between oral and SC chelation therapy (0,73 used for both) and same distribution between oral and SC iron chelation		12 114 246 kr	4.29	6.88	1 761 072 kr
10 blood transfusions per year (instead of 15 blood transfusions)*		12 966 776 kr	4.29	6.88	1 885 006 kr
Cost of chelation therapy (reduced by 50 %)		12 595 822 kr	4.29	6.88	1 831 080 kr
Cost of blood transfusions (reduced by 50 %)		13 389 095 kr	4.29	6.88	1 946 400 kr
Age at base line	High (100% 24-34 yrs)	12 444 297 kr	4.23s	6.51	1 912 429 kr
	Low (100% 12-23 yrs	12 046 877 kr	4.33	7.02	1 715 285 kr
Iron loading at base line	Low iron loading, all patients	12 116 672 kr	4.07	6.68	1 815 113 kr
	High iron loading, all patients	13 357 754 kr	8.26	9.12	1 465 284 kr
No difference in mortality between the treatment arms		10 431 006 kr	0	4.88	2 137 246 kr

Distribution iron chelation	Oral iron chelation 100%, subcutaneous iron chelation 0%	11 104 216 kr	4.29	6.88	1 614 242 kr
	Oral iron chelation 0%, subcutaneous iron chelation 100%	12 942 976 kr	4.29	6.88	1 881 546 kr
No difference in utility between oral and SC chelation therapy (instead of 0,73)	0.83	12 114 246 kr	4.29	5.04	2 403 327 kr
Success rate (instead of 83.3 %)	90 %	11 852 963 kr	4.55	7.25	1 635 922 kr
	70 %	12 883 556 kr	3.59	5.90	2 184 005 kr
Success rate sustained (instead of lifetime)	10 years	15 512 250 kr	-0.26	2.89	5 371 745 kr
	15 years	14 881 110 kr	0.41	3.51	4 234 025 kr
	20 years	14 317 689 kr	0.86	3.97	3 609 371 kr
Success rate (reduced over time)	90% after 15 years	12 576 110 kr	3.94	6.57	1 913 468 kr
	70% after 15 years	13 204 590 kr	2.80	5.61	2 351 789 kr
	50% after 15 years	13 458 647 kr	2.32	5.22	2 579 417 kr
Discount rate	0% (costs)	7 357 601 kr	4.29	6.88	1 069 952 kr
	0% (effects)	12 112 511 kr	18.00	20.75	583 767 kr
Time horizon	10	15 572 431 kr	0.01	0.96	16 296 091 kr
	20	14 128 322 kr	0.20	2.19	6 443 597 kr
	30	13 219 468 kr	0.88	3.46	3 820 091 kr
	40	12 653 832 kr	1.76	4.59	2 756 083 kr
	50	12 318 830 kr	2.63	5.51	2 236 085 kr

The main parameters affecting the results concern the assumption that achieved TI is sustained over the lifelong time horizon. FINOSE has also performed sensitivity analyses to explore how different success rates affect the results, given the small number of patients included in the clinical trials and the results are based on pooled data. The success rate might be both higher and lower.

The time horizon also show that the main survival gains occur after 30 years according to the assumptions in the model. The benefits of Zynteglo are based on the assumption that complications associated with high iron levels are reduced. Due to lack of data on long-term survival, FINOSE presents two scenarios to illustrate how the results are affected by the inclusion of survival gains.

Also, the disutility associated with chelation therapy, i.e. the benefits of eliminating the disutility associated with chelation therapy affect the results. As stated above, given that there is variation among β-thalassaemia patients, some patients may gain more than others.

Table 23: Sensitivity analyses based on FINOSE scenario 1 (no payment model), SEK

Sensitivity analyses	+/- Δ Costs	+/- Δ LYs	+/- Δ QALYs	Cost/ QALY
FINOSE scenario 1 (full acquisition cost)	12 114 246 kr	4.29	6.88	1 761 072 kr
FINOSE scenario 1 (10 % discount acquisition cost)	10 419 246 kr	4.29	6.88	1 514 667 kr
FINOSE scenario 1 (20 % discount acquisition cost)	8 724 246 kr	4.29	6.88	1 268 261 kr
FINOSE scenario 1 (30 % discount acquisition cost)	7 029 246 kr	4.29	6.88	1 021 856 kr
FINOSE scenario 1 (40 % discount acquisition cost)	5 334 246 kr	4.29	6.88	775 450 kr
FINOSE scenario 1 (50 % discount acquisition cost)	3 639 246 kr	4.29	6.88	529 045 kr
FINOSE scenario 1 (60 % discount acquisition cost)	1 944 246 kr	4.29	6.88	282 639 kr
FINOSE scenario 1 (70 % discount acquisition cost)	249 246 kr	4.29	6.88	36 233 kr
FINOSE scenario 1 (80 % discount acquisition cost)	-	4.29	6.88	Dom

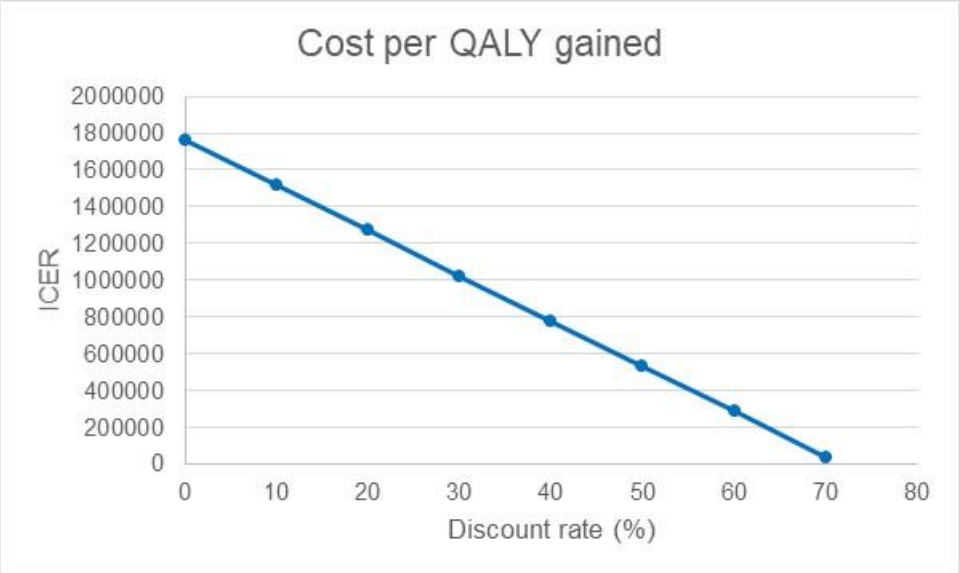


Figure 6: Sensitivity analyses of discount rate on acquisition cost of Zynteglo based on FINOSE scenario 1 (with survival gains), SEK

Table 24: Sensitivity analyses based on FINOSE scenario 2 (no payment model), SEK

Sensitivity analyses	+/- Δ Costs	+/- Δ LYs	+/- Δ QALYs	Cost/ QALY
FINOSE scenario 2 (full acquisition cost)	10 431 006 kr	0	4.88	2 137 246 kr
FINOSE scenario 2 (10 % discount acquisition cost)	8 736 006 kr	0	4.88	1 789 951 kr
FINOSE scenario 2 (20 % discount acquisition cost)	7 041 006 kr	0	4.88	1 442 657 kr
FINOSE scenario 2 (30 % discount acquisition cost)	5 346 006 kr	0	4.88	1 095 362 kr
FINOSE scenario 2 (40 % discount acquisition cost)	3 651 006 kr	0	4.88	748 068 kr
FINOSE scenario 2 (50 % discount acquisition cost)	1 956 006 kr	0	4.88	400 773 kr
FINOSE scenario 2 (60 % discount acquisition cost)	261 006 kr	0	4.88	53 478 kr
FINOSE scenario 2 (70 % discount acquisition cost)	-	0	4.88	Dom

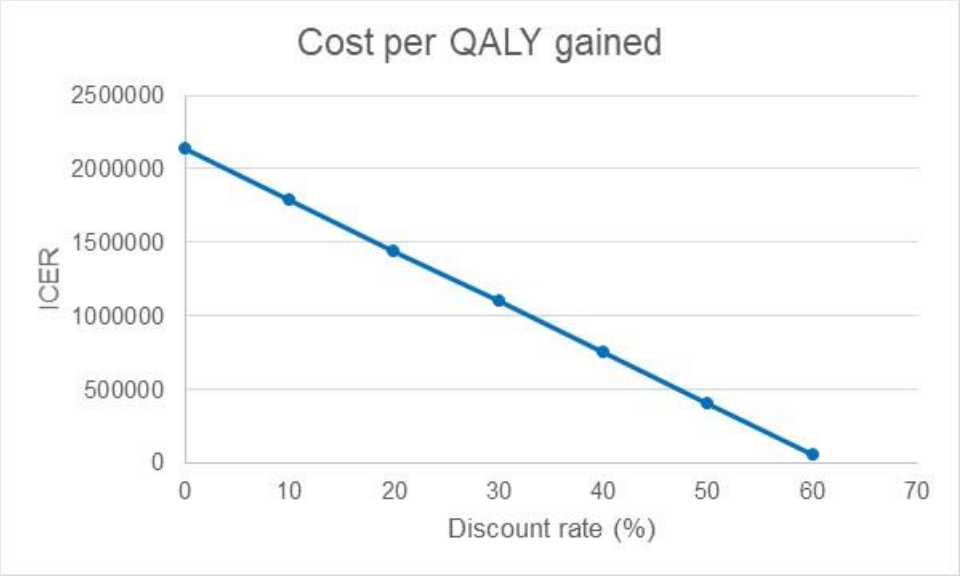


Figure 7: Sensitivity analyses on discount rate on acquisition cost of Zynteglo based on FINOSE scenario 2 (no difference in mortality), SEK

5.3 Budget impact

According to the company the estimated numbers of TDT patients is 15, 30, and 100 in Finland, Norway and Sweden, respectively. The company assumes that a third of the patient population is eligible for Zynteglo treatment. However, the company assumes that not all patients will be treated at once but over the course of several years, e.g. over the course of five years.

If all eligible patients are treated with Zynteglo at once, this would imply that the one time upfront transplant cost of Zynteglo would be 84.8 million SEK in Finland, 167.8 million SEK in Norway and 559.4 million SEK in Sweden. If the patients are treated over the course of five years, the company assumes an annual budget impact of 17 million SEK in Finland, 34 million SEK in Norway and 112 million SEK in Sweden.

FINOSE discussion
The FINOSE clinical experts have estimated that the patient population in the Nordics is almost double the amount stated by the company. Thus, there is an uncertainty regarding the size of the patient population. Also, there is an uncertainty how many additional patients may be expected over the forthcoming years.

FINOSE conclusion: FINOSE concludes that there are uncertainties concerning the size of patients eligible for Zynteglo treatment. More patients may be eligible for Zynteglo treatment than the assumed company estimate.

5.4 Overall summary and conclusion

This is a joint FINOSE assessment of Zynteglo for the treatment of transfusion-dependent β-thalassaemia (TDT) compared to lifelong blood transfusions and iron chelation therapy. The economic evaluation includes patients, 12 years and above, with TDT and non β^0/β^0 genotype for whom hematopoietic stem cell transplantation (HSCT) is appropriate but a human leukocyte antigen matched donor is not available.

FINOSE agrees with the company that blood transfusions with iron chelation is the most relevant comparator for Zynteglo treatment. This in line with Finnish, Norwegian and Swedish treatment guidelines.

The company has applied for a price of Zynteglo of almost 17 million SEK. This should be compared to life-long treatment with blood transfusions and chelation therapy totalling almost 7.2 million SEK over a lifetime using a discount rate of 3 percent. .

According to the results of the company base case, Zynteglo therapy leads to survival benefits of 4.29 life years and 8.17 quality adjusted life years (QALYs) gained compared to life long blood transfusions and iron chelation therapy.

FINOSE presents two scenarios, with and without survival benefits, resulting in 1 761 000 SEK and 2 137 000 SEK per QALY gained. The benefits of Zynteglo are based on the assumption that complications associated with high iron levels are reduced. There is however an uncertainty whether all patients within the marketing authorization will benefit survival gains as there is a lack of long-term data. Thus, FINOSE presents two scenarios with and without survival gains, to illustrate how the results are affected.

FINOSE has performed several one-way sensitivity analyses to explore how changes in individual parameter inputs affect the results. The main uncertainties according to FINOSE is the assumption that the success rate (achieved TI) is sustained over a lifetime. If the success rate is, e.g. sustained for ten years the cost per QALY gained rises to 5 372 000 SEK.

The sensitivity analyses range from1 761 000 SEK to 5 372 000 SEK per QALY gained using a life-long time horizon and even higher if a shorter time horizon was used.

FINOSE concludes that the main uncertainties of the economic analyses concern if the success rate (TI) is sustained and whether the survival gains based on the assumption that complications associated with high iron levels are reduced. The model is also very sensitive to the disutility associated with chelation therapy affecting long term utility gains.

6 Assessments in other countries

The National Institute for Health and Care Excellence (NICE) in the UK were planning a publication of a Health Technology Appraisal of LentiGlobin (Zynteglo) for treating beta thalassaemia major in June 2020. However, the appraisal has not been defined as therapeutically critical and is at present paused due to the current COVID-19 situation.

Institute for Clinical and Economic Review (ICER) in the US are also assessing the product. The appraisal is paused due to the current COVID-19 situation and will be reiterated.

7 Post launch evidence generation

No ongoing randomized trials were identified in the current assessment.

7.1 Regulatory perspective

Zynteglo has been granted a conditional marketing authorization. The EMA has set the following post-authorisation obligations to the company: In order to further characterise and contextualise the long-term safety and efficacy of Zynteglo the company 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 allogeneic HSCT treated patients from an established European registry as a comparator group. The company should also submit interim and final data from Study HGB-207, and from patients with a severe non-β0/β0 genotype such as IVS-I-110 included in Study HGB-212. The company is also obligated to submit interim data and the 5 years follow-up results of the Study LTF-303.

7.2 HTA perspective

The results of the cost-effectiveness analysis (section 5) show that changes in the following parameters have the biggest impact on the model's results:

- treatment success rate (i.e proportion of patients achieving TI after Zynteglo therapy. In the clinical trials, TI requires 12 months without any pRBC transfusion while maintaining a weighted average Hb of ≥9 g/dL)
- sustainability of Zynteglo's treatment effect on patients' haemoglobin production and transfusion requirement
- mortality rate
- HRQoL

It should, however, be noted that probabilistic sensitivity analysis are typically used to quantify the nature and scale of the decision uncertainty. The company has not reported probabilistic sensitivity analysis as part of their cost-effectiveness analysis [36]. In addition, Zynteglo is a

one-time treatment, which make the estimates of cost-effectiveness more sensitive for future changes in market situation and treatment practices.

Collecting real world data (RWD) from the parameters listed above might mitigate the uncertainty regarding Zynteglo's relative-effectiveness and cost-effectiveness at the time of reassessment. It should, however, be noted that the uncertainties related to relative treatment effects and survival benefits will remain with open-label follow-up data. In addition, Zynteglo is indicated to TDT patients who are mainly adolescents or young adults. Observing survival benefits in this population would require decades of follow-up.

In addition to outcome data, descriptive statistics of the patients treated with Zynteglo in the Nordic countries would be needed, including number of treated patients, patient characteristics, and estimates on resource use and costs linked to the treatment of β-thalassaemia. FINOSE team notes, that it would be important to share the national statistics between Finland, Norway and Sweden.

The section 7.4 describe the planned RWD collection to REG-501 product registry. The FINOSE team notes that the outcome measures defined for REG-501 include most of the parameters that were identified as the key sources of uncertainty in the cost-effectiveness analysis. However, since REG-501 is a product registry, outcomes that are linked to RBC transfusions and iron chelation (e.g. disutility associated with chelation therapy) will not be collected. Based on the comments from the FINOSE clinical experts, the Nordic clinical community is currently also considering other measures for RWD collection than REG-501 as described in section 7.5.

The FINOSE team, notes that detailed long-term data collection is resource intensive. For that reason, parallel data collections should be avoided. Strategies that allow conducting multiple secondary analyses on the same data should be prioritised. Using same healthcare data for multiple purposes has the potential to reduce costs and time for research. In addition, β-thalassaemia is a rare disease and only few patients are treated annually in the Nordic countries. For that reason, pooling RWD from Finland, Norway and Sweden would be justified. However, organisation of long-term follow-up and need to share patients' health care data across national boundaries may pose additional challenges.

7.3 Managed entry agreements

Outcome or performance based managed entry agreements (MEAs) also require RWD collection post launch. Assessing managed entry agreements, is not in the mandate of FINOSE collaboration.

7.4 The Zynteglo Registry (REG-501)

REG-501 is a multi-centre, international registry designed to collect longitudinal data on patients with TDT treated with Zynteglo in the post-marketing setting. The registry sponsor is the company (Bluebird bio, Inc).

The primary objectives of the observational study are to assess the long-term safety and effectiveness of Zynteglo treatment in patients with TDT. Secondary and exploratory objectives are to describe healthcare resource utilization and patient reported health related quality of life (HRQL) after treatment with Zynteglo.

Safety outcome measures followed in the REG-501 include the following adverse events occurring during or after infusion with Zynteglo:

- Serious adverse events
- Zynteglo related adverse events
- Adverse events of special interest (see section 3.1.3. for more details)

- Time to neutrophil engraftment and platelet engraftment
- Evidence of clonal expansion or insertional oncogenesis
- Overall survival

Effectiveness outcome measures include:

- Red blood cell (RBC) transfusion-free survival
- RBC transfusion requirements
- β-globin fraction measurements, including βA-T87Qglobin
- Total haemoglobin levels (g/dL)
- Quantified therapeutic phlebotomy
- Chelator use
- Measurement of body iron stores
- Incidence of clinical complications of iron overload
- Healthcare resource utilization
- HRQL questionnaire scores
- Work productivity and activity impairment questionnaire scores

Other measures include:

- Time to hospital discharge post-treatment with LentiGlobin BB305 Drug Product
- Pregnancy
- Peripheral blood VCN

According to the company, they will use the REG-501 study to meet regulatory post-marketing commitments that are required by EMA.

The study plans to enroll approximately 350 patients over a period of five years and follow each patient for 15 years post Zynteglo. According to the register protocol, all patients treated with Zynteglo in the participating sites will be strongly encouraged to enroll in the registry. TDT patients who are not treated with Zynteglo are not included in the registry. In other words, this is a product registry that does not aim to collect data on TDT patients treated with transfusions and/or HLA-matched allogeneic HSCT.

7.5 Data collection from the Nordic countries

According to the FINOSE clinical experts the Nordic clinical community has considered the possibility to join European Rare Blood Disorders Platform (ENROL) to enable systematic collection of register from β-thalassaemia patients.

According to the company they will collaborate with the relevant healthcare professionals in the Nordics to ensure that data from patients treated with Zynteglo are captured quantitatively and to learn more about Zynteglo in the real-world setting.

At the time of this assessment (04/2020), it has not been decided whether health care professionals from Finland, Norway and Sweden would be willing to participate in the data collection

for the REG-501 registry. If Nordic sites will participate, patients will be informed that participation in the registry is voluntary, unless a local health authority requires participation for reimbursement purposes, in which case applicable local regulations will be followed.

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Appendix

Appendix 1. European studies with long-term data about TDT patients

FINOSE authors performed a simple and unsystematic literature review to identify some European studies with long-term survival estimates or prognosis of TDT patients. No studies including Nordic TDT patients were identified. Here is a brief summary about studies from Cyprus, Greece and Italy.

- A study from Cyprus [15] included 284 patients with β-thalassaemia major who were born or diagnosed after 1st January 1974 (this is a date when organized blood donation for transfusions and desferrioxamine treatment became available in Cyprus). Patients who received bone marrow transplantation (BMT) were censored at the time of BMT. In this retrospective study patients were followed up between 1980 and 2005. The estimated survival rates at 10, 20 and 30 years were 100% (95% CI 100%), 98.5% (96.1-99.4) and 92.7% (86.7-96.1).
- An Italian study [12, 14] included 720 patients born 1st January 1970 or later and diagnosed with thalassaemia major (TDT) before age of 3 years. The study included only patients with desferrioxamine as chelator monotherapy treatment (available in Italy since 1975). Patients who started oral chelator deferiprone or received BMT, were censored. The last follow-up was on 31 December 1999. For those who were born between 1975 and 1979, the estimated survival rates at 10, 15 and 20 years were 100%, 98.8% and 95.8%. One fifth (21.8%) of the patients born 1970 or later developed at least one complication. Median age at the complication was 16 years.
- A Greek study [13] included 1044 patients with β-thalassaemia. Most of the patients started transfusions before age of 5 years with an annual pack RBC consumption > 180 mL/kg. Patients who underwent stem cell transplantation (SCT) or did not continue their care were censored at the date of SCT or their last visit (n = 159). Data was collected until end of 2009 and median time of observation was 28.4 years. According to the Kaplan-Meier estimates, the overall survival at the age of 50 years was 65.0% (95% CI 57.0-71.9). Heart disease was the most common cause of death (71.0% of the deaths). Risk of death compared to the general population (standardised mortality ratio, SMR) for age group 20-39 years was 28.9% (95% CI 23.2-36.0) in 1990-1999 and 13.5% (95% CI 10.3-17.7) in 2000-2008. Also the standardised cardiac mortality ratio (SCMR) significantly declined between these two time periods.

Appendix 2. Eligibility criteria in HGB-204, HGB-205 and HGB-207

Appendix table 25.1: Inclusion criteria

HGB-204	HGB-205	HGB-207
- Subjects between 12 and 35 years of age, inclusive, at the time of consent or assent (as applicable), and able to provide written consent (adults, or legal guardians, as applicable) or assent (adolescents). - Diagnosis of β-thalassaemia major and a history of at least 100 mL/kg/year of pRBCs or ≥8 transfusions of pRBCs per year for the prior 2 years. - Documented baseline, or pre-transfusion, Hb level of ≤7 g/dL. - Clinically stable, have a Karnofsky performance status of ≥60, and eligible to undergo HSCT. - Treated and followed for at least the past 2 years in a specialised centre that maintained detailed medical records, including transfusion history.	- Between 5 and 35 years of age, inclusive. ○ Adult subjects (between 18 and 35 years of age, inclusive, at the time of consent) must be able to provide written consent. ○ For paediatric subjects (between 5 and 17 years of age, inclusive, at the time of consent), a competent parent or legal guardian must be able to provide written informed consent. When possible, involvement of the child >7 years of age in the decision is highly recommended, and written assent will be obtained and should be clearly documented. ○ Subjects aged 5 to 14 years require the approval from the Comité de Surveillance prior to enrolment. - Have severe SCD or TDT, regardless of the genotype (e.g., β0/β0, β+/β+, βE/β0, βS/βS, βS/β0, βS/β+), with the diagnosis confirmed by Hb studies. Subjects with TDT must be stable and maintained on an appropriate iron chelation regimen. Transfusion-dependence is defined as requiring at least 100 mL/kg/year of packed RBCs. - Eligible for allo-HSCT based on institutional medical guidelines, but without a matched, related donor. - Willing and able, in the Investigator's opinion, to comply with the studyprocedures outlined in the study protocol. If a paediatric subject, the subject's parent/legal guardian also must be willing and able to comply with the study procedures outlined in the study protocol. - Have been treated and followed for at least the past 2 years in a specialized centre that maintained detailed medical records, including transfusion history.	- Subjects ≤50 years of age at the time of consent or assent (as applicable), and able to provide written consent (adults, or legal guardians, as applicable) or assent (adolescents or children). Provided that the DMC has approved enrolling subjects younger than 5 years of age, subjects younger than 5 years of age may be enrolled if they weigh a minimum of 6 kg and are reasonably anticipated to be able to provide at least the minimum number of cells required to initiate the manufacturing process. - Diagnosis of TDT with a history of at least 100 mL/kg/year of pRBCs in the 2 years preceding enrolment (all subjects), or be managed under standard thalassaemia guidelines (e.g., (Cappellini et al. 2014)) with ≥8 transfusions of pRBCs per year in the 2 years preceding enrolment (subjects ≥12 years (Rachmilewitz and Giardina 2011)). - Clinically stable, have a Karnofsky performance status of ≥80 for adults (≥16 years of age) or a Lansky performance status of ≥80 for adolescents or children (<16 years of age), and eligible to undergo HSCT. - Treated and followed for at least the past 2 years in a specialised centre that maintained detailed medical records on RBC transfusions (including volume and units of RBCs and associated pre-transfusion Hb values, reticulocyte counts and relevant blood bank details as available), in-patient hospitalisation, and iron chelation history.

Exclusion criteria

HGB-204

- Positive for presence of human immunodeficiency virus type 1 or 2 (HIV-1 or HIV-2), hepatitis B virus (HBV), or HCV. (Note that subjects who were positive for anti-HBV antibody [to either core or envelope proteins] or for anti-HCV antibody were eligible as long as they have a negative HBV or HCV viral load by quantitative polymerase chain reaction [qPCR]. Where clinically and/or regionally indicated, one or more of the following tests may be performed, in which case positive results would exclude the subject from participating: human T-lymphotrophic virus-1 (HTLV-1) or HTLV-2, syphilis (RPR), toxoplasmosis, Trypanosoma cruzi, or West Nile Virus).
- Active bacterial, viral, fungal, or parasitic infection.
- A white blood cell (WBC) count <3 × 10^9/L, and / or platelet count <100 × 10^9/L not related to hypersplenism.
- Uncorrected bleeding disorder.
- Any prior or current malignancy or myeloproliferative or immunodeficiency disorder.
- Immediate family member with a known or suspected Familial Cancer Syndrome (including but not limited to hereditary breast and ovarian cancer syndrome, hereditary non-polyposis colorectal cancer syndrome and familial adenomatous polyposis).
- Prior HSCT.
- Advanced liver disease, defined as:
    - Baseline alanine transaminase or direct bilirubin value >3 × the upper limit of normal (ULN), or
    - Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis.
- Baseline estimated glomerular filtration rate (eGFR) <70 mL/min/1.73 m^2, as determined using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation for ≥ 18 years of age, and Bedside Schwartz equation calculator <18 years of age (see http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm).
- Uncontrolled seizure disorder.
- Diffusion capacity of carbon monoxide (DLco) <50% of predicted (corrected for haemoglobin and/or alveolar volume, as clinically indicated).
- A cardiac T2* <10 ms by MRI
- Any other evidence of severe iron overload that, in the investigator's opinion, warrants exclusion.
- Clinically significant pulmonary hypertension, as defined by the requirement for ongoing pharmacologic treatment or the consistent or intermittent use of supplemental home oxygen.
- Participation in another clinical study with an investigational drug within 30 days of screening.
- Failure to obtain appropriate informed consent.
- Any other condition that would render the subject ineligible for HSCT, as determined by the attending transplant physician or investigator. Contraindications to the conditioning regimen.
- Prior receipt of gene therapy.
- Diagnosis of significant psychiatric disorder of the subject that could seriously impede the ability to participate in the study.
- Pregnancy or breastfeeding in a postpartum female or absence of adequate contraception for fertile subjects. Females of child bearing potential are required to use effective contraception from screening through at least 6 months after Zynteglo infusion. Male

subjects are required to use effective contraception (including condoms) from screening through at least 6 months after Zynteglo infusion.
- An assessment by the investigator that the subject would not comply with the study procedures outlined in the protocol.

HGG-205:

- Availability of a willing, 10/10 matched HLA identical sibling haematopoietic cell donor, unless recommendation for enrolment is provided by the Comité de Surveillance following a review of the case.
- Positive for presence of human immunodeficiency virus type 1 or 2 (HIV 1 or HIV 2), human T lymphotrophic virus 1 or 2 (HTLV 1 or HTLV 2), vesicular stomatitis virus glycoprotein (VSV G) antibody (Ab).
- Clinically significant, active bacterial, viral, fungal, or parasitic infection.
- Contraindication to anaesthesia for bone marrow harvesting.
- Any prior or current malignancy, myeloproliferative or immunodeficiency disorder.
- A white blood cell (WBC) count <3 × 10^9/L and/or platelet count <120 × 10^9/L.
- Receipt of an allogeneic transplant.
- Receipt of erythropoietin within 3 months before HSCT harvest.
- Immediate family member with a known or suspected Familial Cancer Syndrome (including but not limited to breast, colorectal, ovarian, prostate, and pancreatic cancers).
- Diagnosis of significant psychiatric disorder of the subject that could seriously impede the ability to participate in the study.
- Active relapsing malaria.
- Pregnancy or breastfeeding in a postpartum female or absence of adequate contraception for fertile subjects. Females of childbearing potential must agree to use a medically acceptable method of birth control such as oral contraceptive, intrauterine device, barrier and spermicide, or contraceptive implant/injection throughout the 27 month study period.
- History of major organ damage including:
    - Liver disease, with transaminase levels >3× upper limit of normal. (This observation will not be exclusionary if a liver biopsy shows no evidence of extensive bridging fibrosis, cirrhosis, or acute hepatitis).
    - Histopathological evidence of extensive bridging fibrosis, cirrhosis, or acute hepatitis on liver biopsy.
    - Heart disease, with a left ventricular ejection fraction <25%
    - Kidney disease with a calculated creatinine clearance <30% normal value.
    - Severe iron overload, which in the opinion of the physician is grounds for exclusion.
    - A cardiac T2* <10 ms by MRI.
    - Evidence of clinically significant pulmonary hypertension requiring medical intervention.
- Any other condition that would render the subject ineligible for HSCT, as determined by the attending transplant physician.
- Participation in another clinical study with an investigational drug within 30 days of Screening.
- Subjects who have the desire to become a parent within the 27-month study period.
- Prior receipt of gene therapy.
- An assessment by the Investigator that the subject or parents of the subject will not comply with the study procedures outlined in the study protocol.
- Hydroxyurea therapy within 3 months before hematopoietic stem cell collection.

HGB-207:

- Presence of a mutation characterised as β^0 on both HBB alleles. For the purpose of this study, the HBB mutation IVS I-110 (G>A) [Human Genome Variation Society (HGVS) nomenclature: HBB:c.93-21G>A] will be considered equivalent to a β0 mutation.
- Positive for presence of human immunodeficiency virus type 1 (HIV-1) or 2 (HIV-2), hepatitis B virus (HBV), or hepatitis C virus (HCV). Syphilis (rapid plasma reagin [RPR]) testing is also required and a positive test for syphilis is exclusionary where mandated by regional drug product manufacturing practices. Note that subjects who have been vaccinated against hepatitis B [hepatitis B surface antibody-positive] who are negative for other markers of prior hepatitis B infection [e.g., negative for hepatitis B core antibody] are eligible. Subjects with past exposure to HBV [HBc Ab positive and/or HBe Ab positive] are also eligible for the study provided they are negative by assessment for HBV DNA. Also note that subjects who are positive for antihepatitis C antibody are eligible as long as they have a negative HCV viral load. Where clinically and/or regionally indicated, other tests may be performed, in which case positive results would exclude the subject from participating: for example, human T-lymphotropic virus-1 (HTLV-1) or -2 (HTLV-2), tuberculosis, toxoplasmosis, Trypanosoma cruzi, West Nile Virus, or Zika Virus.
- Clinically significant and active bacterial, viral, fungal, or parasitic infection as determined by the clinical investigator.
- A white blood cell (WBC) count $<3\times10^9$/L, and/or platelet count $<100\times10^9$/L not related to hypersplenism.
- Uncorrected bleeding disorder.
- Any prior or current malignancy (with the exception of adequately treated cone-biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin) or myeloproliferative or significant immunodeficiency disorder.
- Immediate family member (i.e., parent or siblings) with a known Familial Cancer Syndrome (including but not limited to hereditary breast and ovarian cancer syndrome, hereditary non-polyposis colorectal cancer syndrome and familial adenomatous polyposis).
- Prior HSCT
- Advanced liver disease, defined as:
    - Persistent aspartate transaminase (AST), alanine transaminase (ALT), or direct bilirubin value >3 × the upper limit of normal (ULN), or
    - Baseline prothrombin time or partial thromboplastin time >1.5× ULN, suspected of arising from liver disease, or
    - MRI of the liver demonstrating clear evidence of cirrhosis
    - MRI findings suggestive of active hepatitis, significant fibrosis, inconclusive evidence of cirrhosis, or liver iron concentration ≥15 mg/g require follow-up liver biopsy in subjects ≥18 years of age. In subjects <18 years of age, these MRI findings are exclusionary, unless in the opinion of the investigator, a liver biopsy could provide additional data to confirm eligibility and would be safe to perform. If a liver biopsy is performed based on MRI findings, any evidence of cirrhosis, bridging fibrosis, or significant active hepatitis will be exclusionary.
- Baseline estimated glomerular filtration rate (GFR) <70 mL/min/1.73 m^2, as determined using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation for ≥18 years of age, and Bedside Schwartz equation calculator for <18 years of age (see http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm)
- Uncontrolled seizure disorder
- Diffusion capacity of carbon monoxide (DLco) <50% of predicted (corrected for Hb and/or alveolar volume, as clinically indicated).
- A cardiac T2* <10 ms by MRI.

- Any other evidence of severe iron overload that, in the investigator's opinion, warrants exclusion.
- Participation in another clinical study with an investigational drug within 30 days of Screening.
- Any other condition that would render the subject ineligible for HSCT, as determined by the attending transplant physician or investigator.
- Prior receipt of gene therapy.
- Diagnosis of significant psychiatric disorder of the subject that could seriously impede the ability to participate in the study.
- Pregnancy or breastfeeding in a postpartum female or absence of adequate contraception for fertile subjects. Females of childbearing potential and males are required to use two different effective methods of contraception from Screening through at least 6 months after drug product infusion. If subjects are truly sexually abstinent (where true sexual abstinence is defined as being in line with the preferred and usual lifestyle of the subject), no second method is required.
- An assessment by the investigator that the subject would not comply with the study procedures outlined in the protocol.
- A known and available HLA-matched family donor. If required by regional regulatory authority, patients with a known and available matched unrelated donor will be excluded from the study.
- Any contraindications to the use of G-CSF and plerixafor during the mobilisation of HSCs and any contraindications to the use of busulfan and any other medicinal products required during the myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients.

Appendix 3. Baseline characteristics of transfusion dependent patients with a non-β^0/β^0 genotype by study.

	HGB-204 (n = 10)	HGB-205 (n = 4)	HGB-207 (n = 10)[a]	HGB-207 (n = 15)[b]	HGB-212 (n = 3)[c]
Age at informed consent					
Mean (SD)	22.2 (6.6)	17.5 (1.3)	18.3 (4.3)	19.0 (5.77)	23.7 (8.33)
Median	19.5	17.5	19.0	20	21.0
Min - max	16 - 34	16 - 19	12 - 24	12 - 34	17 - 33
≥18 years. n (%)	8 (80.0)	2 (50.0)	6 (60.0)	9 (60.0)	2 (66.7)
≥12 to <18 years	2 (20.0)	2 (50.0)	4 (40.0)	6 (40.0)	1 (33.3)
Gender, n (%)					
Male	3 (30.0)	2 (50.0)	4 (40.0)	7 (46.7)	2 (66.7)
Female	7 (70.0)	2 (50.0)	6 (60.0)	8 (53.3)	1 (33.3)
Race					
Asian	8 (80.0)	2 (50.0)	6 (60.0)	9 (60.0)	0
White	2 (20.0)	2 (50.0)	4 (40.0)	6 (40.0)	3 (100)
HBB genotype, n (%)					
β^E/β^0	6 (60.0)	3 (75.0)	3 (30.0)	5 (33.3)	0
β^0/β^+	1 (10.0)	0	5 (50.0)	6 (40.0)	1 (33.3)
β^+/β^+	2 (20.0)	1 (25.0)	2 (20.0)	4 (26.7)	2 (66.7)
Other	1 (10.0)	0	0	0	0
Splenectomy					
Yes	3 (30.0)	3 (75.0)	2 (20.0)	4 (26.7)	0
No	7 (70.0)	1 (25.0)	8 (80.0)	11 (73.3)	3 (100)
Age at β-thalassaemia major diagnosis (months)					
Mean (SD)	88.9 (102.4)	9.3 (14.0)	26.8 (27.0)	23.0 (24.47)	4.7 (4.16)
Median	68.5	3.0	12.0	12	6.0
Min - max	0 - 315	1 - 30	3 - 84	3 - 84	0 - 8
Age at first pRBC transfusion (months)					
Mean (SD)	38.5 (42.3)	31.8 (38.1)	28.2 (27.6)	23.5 (25.25)	9.7 (2.08)
Median	30.0	21.0	12.0	10.0	9.0
Min - max	0 - 132	1 - 84	4 - 84	4 - 84	8 - 12
Age at starting regular pRBC transfusions (months)					
Mean (SD)	99.2 (90.6)	52.8 (78.4)	91.9 (71.5)	96.4 (74.29)	23.0 (21.70)
Median	72.0	21.0	84.0	84.0	12.0
Min - max	8 - 312	1 - 168	7 - 216	6 - 216	9 - 48
Age at starting iron chelation (years)					
Mean (SD)	9.7 (7.1)	5.0 (5.0)	6.0 (4.2)	3.5 (1.32)	3.5 (1.32)
Median	7.5	3.5	4.5	3.0	3.0
Min - max	2 - 26	1 - 12	2 - 16	3 - 5	3 - 5
Pre-treatment baseline annualized pRBC transfusion volume (ml/kg/year)					
Mean (SD)	164.1 (30.4)	175.0 (25.6)	204.3 (39.9)	197.83 (35.415)	185.29 (21.210)
Median	151.3	181.9	211.3	192.92	175.51
Min - max	140.0 - 234.5	139 - 197	158.7 - 251.3	152.3 - 251.3	170.7 - 209.6
Pre-treatment baseline annualized pRBC transfusion frequency (#/year)					
Mean (SD)	13.4 (1.8)	12.1 (1.2)	17.8 (4.0)	18.73 (6.433)	26.17
Median	13.8	12.5	17.8	17.50	21.50
Min - max	10.0 - 16.5	10.5 - 13.0	11.5 - 24.5	11.5 - 37.0	17.5 – 39.5
Pre-treatment baseline weighted average nadir Hb that preceded pRBC transfusion (g/dl)					
Mean (SD)	8.7 (1.0)	9.5 (1.5)	9.4 (0.8)	9.49 (0.798)	9.75 (0.931)
Median	9.1	9.4	9.6	9.60	9.75
Min - max	7.0 - 9.8	8.1 - 10.8	7.5 - 10.2	7.5 - 11.0	8.8 - 10.7
Pre-treatment baseline iron burden[d]					
Liver iron content (mg/g)					
Min - max	1.2 - 26.4	3.9 - 14.0	1.0 - 19.6	1 - 41	3.3 - 10.4
Cardiac T2 measurement (msec)					
Min - max	27 - 54	29 - 46	35.3 - 50.9	21 - 51	33 - 53
Serum ferritin (pmol/L)					
Min - max	1643 - 8629	2139 - 7097	349 - 10020	784 - 22517	2510 - 3672

[a] TI-evaluable patients from cohort 1 (cohort 1: patients aged ≥ 12 years and a non-β^0/β^0 genotype).

[b] Subjects treated with drug product from cohort 1 (cohort 1: patients aged ≥ 12 years and a non-β^0/β^0 genotype).
[c] Patients aged ≥ 12 years and non-β^0/β^0 IVS I-I10 (G→A) genotype.

[d]Pre-treatment baseline iron burden values are defined as the last value prior to initiation of conditioning.
Source: Zynteglo EPAR [16] table 23 - 24 and Manufacturer

Appendix 4. Iron burden in ITT-population and in Asian and non-Asian sub-populations (pooled data from treated subjects in HGB-204. HGB-205. HGB-207 and HGB-212)

	ITT-population (n = 32)	Asian sub-population (n = 19)	Non-Asian sub-population (n = 13)
Liver Iron Burden (mg/g)			
Mean (std)	9.1 (8.4)	10.3 (10.1)	7.2 (4.5)
Median	6.8	8.2	6.0
Min–max	1–41	1–41	2–17
Cardiac T2* on MRI (msec)			
Mean (std)	37.2 (7.4)	37.9 (8.1)	36.2 (6.4)
Median	36.5	37.4	36.1
Min–max	21–54	21–54	28–53
Serum ferritin (pmol/L)			
Mean (std)	4869.7 (4110.0)	5903.6 (5068.38)	3358.7 (969.40)
Median	3778.7	5314.6	3411.2
Min–max	784–22517	784–22517	2009–4888

Appendix 5. Definitions

Transfusion independence:

The primary efficacy endpoint is defined as 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 pRBC transfusions for a continuous period of ≥12 months at any time during the study after drug product infusion, where:

- Calculation of time period of TI will start when subjects achieve an Hb ≥9 g/dL with no transfusions in the preceding 60 days.
- To remain in the TI state, the treated subject needs to maintain a weighted Hb of ≥9 g/dL from that point forward, without receiving a pRBC transfusion.
- A transfusion of pRBC for a single acute event (e.g., surgery, trauma, parvovirus infection, or sepsis) will not be counted towards the definition of TI. For the calculation of the weighted Hb when an allowed transfusion has occurred, the Hb that triggered the transfusion would be carried forward for 60 days and Hb values during those 60 days would be imputed by the carried-forward value. Post 60 days, the actual Hb drawn would again be used in the calculation of TI.

Weighted average Hb:

The weighted average Hb will be defined as follows. Let t0, t1, t2.....represent the consecutive time points for assessment of Hb, where t0 denotes the time when Hb is first ≥9 g/dL with no transfusions in the preceding 60 days, and where the ti are continuing as long as no transfusions are given. Further, let h0, h1, h2, ...represent the Hb level at each of these time points. Then the weighted average Hb is defined as:

$$[(t_1-t_0)\times((h_0+h_1)/2)+ (t_2-t_1)\times((h_1+h_2)/2)+...+ (t_k-t_{k-1})\times((h_{k-1}+h_k)/2)]/(t_k-t_0)$$

where tk represents the time point such that (tk-t0) represents at least 12 consecutive months. This calculation is invariant to the metric used for the time points, e.g.. calendar dates or days from drug product infusion, since the consecutive differences in times would always be measured as a number of days. Note that the weighted average may be considered as an average area under the curve calculation for Hb.

Source: company

Appendix 6.

SAEs by system organ class and Occurring in ≥ 10% of Subjects: TDT Pool (ITT)

System Organ Class Preferred Term	ICF to < MB n (%)	MB to < C n (%)	C to < NE n (%)	NE to M24 n (%)	D1 to Last Follow-Up n (%)	> M24 to M36 n (%)
Number of Subjects at Risk	**60**	**60**	**54**	**54**	**54**	**25**
Number of Subjects with at Least 1 SAE	**8 (13.3)**	**5 (8.3)**	**7 (13.0)**	**18 (33.3)**	**23 (42.6)**	**2 (8.0)**
Blood and lymphatic system disorders	**0**	**1 (1.7)**	**2 (3.7)**	**2 (3.7)**	**5 (9.3)**	**1 (4.0)**
Thrombocytopenia	0	1 (1.7)	2 (3.7)	1 (1.9)	3 (5.6)	0
Neutropenia	0	0	2 (3.7)	0	3 (5.6)	1 (4.0)
Febrile neutropenia	0	0	2 (3.7)	0	2 (3.7)	0
Cardiac disorders	**0**	**0**	**1 (1.9)**	**1 (1.9)**	**2 (3.7)**	**0**
Gastrointestinal disorders	**0**	**0**	**2 (3.7)**	**0**	**2 (3.7)**	**0**
General disorders and administration site conditions	**1 (1.7)**	**1 (1.7)**	**0**	**3 (5.6)**	**3 (5.6)**	**0**
Pyrexia	1 (1.7)	0	0	3 (5.6)	3 (5.6)	0
Hepatobiliary disorders	**0**	**0**	**1 (1.9)**	**4 (7.4)**	**5 (9.3)**	**0**
Venoocclusive liver disease	0	0	1 (1.9)	4 (7.4)	5 (9.3)	0
Infections and infestations	**3 (5.0)**	**2 (3.3)**	**4 (7.4)**	**7 (13.0)**	**10 (18.5)**	**1 (4.0)**
Injury. poisoning and procedural complications	**2 (3.3)**	**0**	**0**	**2 (3.7)**	**2 (3.7)**	**0**
Investigations	**0**	**1 (1.7)**	**0**	**0**	**0**	**0**
Metabolism and nutrition disorders	**1 (1.7)**	**1 (1.7)**	**0**	**1 (1.9)**	**1 (1.9)**	**0**
Nervous system disorders	**1 (1.7)**	**0**	**0**	**1 (1.9)**	**1 (1.9)**	**0**
Psychiatric disorders	**0**	**0**	**0**	**1 (1.9)**	**2 (3.7)**	**1 (4.0)**
Reproductive system and breast disorders	**1 (1.7)**	**0**	**0**	**0**	**0**	**0**
Respiratory. thoracic and mediastinal disorders	**0**	**0**	**0**	**1 (1.9)**	**1 (1.9)**	**0**
Vascular disorders	**0**	**0**	**1 (1.9)**	**1 (1.9)**	**2 (3.7)**	**0**

Abbrev.: C; Initiation of conditioning; ICF. informed consent form (date of signature); MB. initiation of mobilisation or bone marrow harvest; NE. date of neutrophil engraftment; TDT. transfusion-dependent thalassaemia.

Study Pool: *TDT* = All subjects with TDT.

Note: If event started in the reporting period and continues into the next reporting period. it will be counted only in the first period. If event starts and stops in the reporting period and then recurs in the next reporting period. it will be counted in both periods.

Note: Number of subjects at risk for each period includes subjects who enter the period. No SAEs have been reported during the >M36 to M48 (N = 20). > M47 to M60 (N = 10). or > M60 to Y7 (N = 2) periods so these columns are not displayed in the table.

Incidence of All Adverse Events ≥ Grade 3 by System Organ Class and Preferred Term: *TDT* Pool (ITT); Incidence ≥ 10 %

System Organ Class Preferred Term	ICF to <MB. n (%)	MB to <C. n (%)	C to <NE. n (%)	NE to M24. n (%)	> M24 to M36 n (%)	D1 to Last Follow-Up. n (%)	ICF to Last Follow-Up. n (%)
Number of Subjects at Risk	**60**	**60**	**54**	**54**	**25**	**54**	**60**
Number of Subjects with at Least 1 ≥Grade 3 AE	**9 (15.0)**	**12 (20.0)**	**54 (100.0)**	**32 (59.3)**	**2 (8.0)**	**54 (100.0)**	**57 (95.0)**
Blood and lymphatic system disorders	**0**	**6 (10.0)**	**54 (100.0)**	**23 (42.6)**	**1 (4.0)**	**54 (100.0)**	**55 (91.7)**
Thrombocytopenia	0	3 (5.0)	50 (92.6)	5 (9.3)	0	51 (94.4)	52 (86.7)
Anaemia	0	0	40 (74.1)	14 (25.9)	0	40 (74.1)	42 (70.0)
Neutropenia	0	1 (1.7)	37 (68.5)	6 (11.1)	1 (4.0)	38 (70.4)	38 (63.3)
Febrile neutropenia	0	0	22 (40.7)	0	0	22 (40.7)	22 (36.7)
Leukopenia	0	0	22 (40.7)	3 (5.6)	0	22 (40.7)	22 (36.7)
Gastrointestinal disorders	**0**	**0**	**36 (66.7)**	**4 (7.4)**	**0**	**35 (64.8)**	**37 (61.7)**
Stomatitis	0	0	33 (61.1)	0	0	32 (59.3)	33 (55.0)
General disorders and administration site conditions	**0**	**2 (3.3)**	**8 (14.8)**	**0**	**0**	**7 (13.0)**	**10 (16.7)**
Hepatobiliary disorders	**1 (1.7)**	**0**	**1 (1.9)**	**5 (9.3)**	**0**	**6 (11.1)**	**7 (11.7)**
Venoocclusive liver disease	0	0	1 (1.9)	4 (7.4)	0	5 (9.3)	5 (8.3)
Infections and infestations	**3 (5.0)**	**1 (1.7)**	**10 (18.5)**	**9 (16.7)**	**1 (4.0)**	**15 (27.8)**	**19 (31.7)**
Injury. poisoning and procedural complications	**3 (5.0)**	**2 (3.3)**	**2 (3.7)**	**1 (1.9)**	**0**	**2 (3.7)**	**6 (10.0)**
Investigations	**1 (1.7)**	**0**	**2 (3.7)**	**5 (9.3)**	**0**	**6 (11.1)**	**6 (10.0)**
Metabolism and nutrition disorders	**1 (1.7)**	**2 (3.3)**	**4 (7.4)**	**1 (1.9)**	**0**	**5 (9.3)**	**8 (13.3)**
Reproductive system and breast disorders	**1 (1.7)**	**0**	**1 (1.9)**	**4 (7.4)**	**0**	**5 (9.3)**	**6 (10.0)**
Respiratory. thoracic and mediastinal disorders	**0**	**0**	**15 (27.8)**	**3 (5.6)**	**0**	**17 (31.5)**	**17 (28.3)**
Pharyngeal inflammation	0	0	9 (16.7)	0	0	9 (16.7)	9 (15.0)
Epistaxis	0	0	5 (9.3)	1 (1.9)	0	6 (11.1)	6 (10.0)

Source: Table 1.2.6.1.1
Abbrev.: C. Initiation of conditioning; ICF. informed consent form (date of signature); MB. initiation of mobilisation; NE. date of neutrophil engraftment; TDT. transfusion-dependent thalassaemia.
Study Pool: *TDT* = All subjects with TDT.
Note: If event started in the reporting period and continues into the next reporting period. it will be counted only in the first period. If event starts and stops in the reporting period and then recurs in the next reporting period. it will be counted in both periods.

Note: Number of subjects at risk for each period includes subjects who enter the period.
No adverse events have been reported during the > M36 to M48 (N = 20). > M48 to M60 (N = 10). or > M60 to Y7 (N = 2) periods so these columns are not displayed in the table.

Appendix 7. Additional safety information

Safety in subgroups

In the EPAR, analysis of the impact of some intrinsic (age, race, gender, genotype) and extrinsic factor (manufacturing process) on the safety profile have been reported. It is noted that population size is too small and there are too many variables to allow any meaningful comparisons. The most remarkable difference might be the fact that most cases of veno-occlusive liver disease (VOD) occurred in the adolescent population. However, it's also noted that the adult population is still rather young (no subjects >35 years were enrolled and median age of overall TDT population is 20 years) and the finding could just as well be attributed to chance. [16]

Supportive safety data from subjects with sickle cell disease (SCD)

Additional safety data is gained from 16 subjects with SCD treated the same BB305 LVV as Zynteglo. The results are reported in the EPAR and the following is concluded "Apart from the events of hospitalisation due to pain crises (attributable to the underlying disease) only numerical differences in AE frequencies were noted. However, no conclusions can be drawn on the differences considered the small populations. Overall the available safety data in the SCD population are generally supportive of that seen in the TDT population."

Safety of lentiviral gene therapy vectors

EMA guideline on lentiviral vectors (EMEA 2005) states that the major concerns related with lentiviral vector manufacture and clinical use are (i) the potential generation of replication competent lentiviruses during lentiviral vector production (ii) *in vivo* recombination with lentiviral polynucleotide sequences and (iii) insertional addition of proviral DNA in or close to active genes, which may trigger tumour initiation or promotion.

In Zynteglo, the potential risk of generation replication competent viruses has been mitigated by vector design, manufacturing process and patient selection (EPAR). No replication competent lentivirus derived from recombination of BB305 LVV sequences was detected in any subjects treated with Zynteglo (analysis includes 51 subjects with TDT).

EPAR recognises insertional mutagenesis as a theoretical safety concern on Zynteglo. This has been noted as an important potential risk in the risk management plan of the marketing authorization of Zynteglo. In addition, the SPC states that patients should be monitored annually for leukaemia or lymphoma for 15 years post treatment with Zynteglo. However, so far no cases of insertional mutagenesis leading to clonal dominance, leukaemia, or lymphoma have been reported in any subjects treated with Zynteglo (analysis of 64 subjects, including 25 with TDT who had at least 2 years of follow-up). Three subjects have been followed for approximately 5 years after drug product infusion.